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ABSTRACT SUPPLEMENT

2011 ANNUAL SCIENTIFIC MEETING

November 4–9, 2011
Chicago, Illinois

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

WILEY-BLACKWELL

AMERICAN COLLEGE OF RHEUMATOLOGY
ABSTRACT SUPPLEMENT

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS
A DIVISION OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

American College of Rheumatology
75th Annual Scientific Meeting

Association of Rheumatology Health Professionals
46th Annual Scientific Meeting

November 4-9, 2011 Chicago, IL

The printing of the 2011 ACR Annual Scientific Meeting Abstract Supplement was supported by Savient Krystexxa, Inc.

ACR/ARHP 2011 Annual Scientific Meeting Overal Needs Assessment/Practice Gaps

The American College of Rheumatology and the Association of Rheumatology Health Professionals are committed to providing comprehensive education to improve the knowledge and performance of physicians, health professionals and scientists. Through evidence-based educational programs, the organization strives to enhance practice performance and improve the quality of care in those with or at risk for arthritis, rheumatic and musculoskeletal diseases. The 2011 annual meeting program has been developed independent of commercial influence. The following groups were involved in the planning process: the ACR Committee on Education; the ACR Annual Meeting Planning Committee; the ARHP Education Committee and the ARHP Annual Meeting Program Planning Committee.

The program is the result of a planning process that identified educational needs to change or enhance the knowledge, competence or performance of rheumatology professionals. The program's content was derived from both needs assessment and practice gap analysis based on professional activities, practice setting, ABIM recertification requirements and physician attributes.

PROGRAM HIGHLIGHTS

- Educational tracks to help attendees identify content targeted to them. Tracks include: business of rheumatology, clinical, clinical and research, clinical practice, educators, fellow-in-training, pediatrics, pediatrics and clinical, and research;
- Latest science and best-practices presented through peer-reviewed and selected clinical and scientific abstracts, and invited speakers providing clinical, evidence-based and quality focused content;
- Diverse formats of education delivery, including: didactic lectures, debates, and interactive sessions, such as poster tours, Meet the Professors and Workshop sessions;
- A larger forum for discussion of practical management issues such as the Curbside Consults – Ask the Professors session and Medical Aspects lectures;
- Extensive learning opportunities in the basic science of rheumatology, an area of the program developed by a subcommittee of US and internationally prominent basic scientists. Offerings include: Basic Science Symposia, State-of-the-Art Lectures, a series of Immunology Updates for the Clinicians, and a Basic Science pre-meeting course;
- Clinical management sessions, including the Thieves' Market, Curbside Consults – Ask the Professors, The Great Debate and the ACR Knowledge Bowl;
- A specific pediatric rheumatology track plus content integrated throughout the program designed to provide a high-level educational program to pediatric rheumatologists; and relevant updates to adult rheumatologists;
- Formal presentations of new practice guidelines provided to alert the membership and explain, in an open forum, the data supporting the guidelines and propose approaches for implementation;
- Over 40 workshops designed to provide hands-on skills training.

For additional details, refer to the session level learning objectives at www.rheumatology.org/annual.

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The American College of Rheumatology and the Association of Rheumatology Health Professionals, a division of the ACR, are organizations of physicians, health professionals and scientists serving members through programs, including education and research. Through these programs, the ACR and the ARHP foster excellence in the care of people with rheumatic and musculoskeletal diseases. The 2011 ACR/ARHP Annual Scientific Meeting programs have been independently planned by the ACR Committee on Education, the ACR Annual Meeting Planning Committee, the ARHP Annual Meeting Program Committee, and the ARHP Clinical Focus Course Task Force.

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PROGRAM OBJECTIVES

At the conclusion of the 2011 ACR/ARHP annual meeting, participants should be able to:

- identify recent developments in the diagnosis and management of patients with rheumatic diseases
- outline new technologies for the treatment of rheumatologic problems
- describe potential challenges in the delivery of care to patients with rheumatic diseases and to specify possible solutions
- utilize new research data to improve the quality of care of patients with rheumatic diseases
- summarize recent rheumatology research findings

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However, the ACR continues to require that information that goes beyond that contained in the abstract, e.g., discussion of the abstract done as part a scientific presentation or presentation of additional new information that will be available at the time of the meeting, is under embargo until 5:00 PM Eastern Time on Saturday, November 5. Violation of this policy may result in the abstract being withdrawn from the meeting and other measures deemed appropriate.

Authors are responsible for notifying financial and other sponsors about this policy.

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ACR Poster Session A
Antiphospholipid Syndrome
Sunday, November 6, 2011, 9:00 AM–6:00 PM

1

Lupus Anticoagulant at a High-Risk Clinic: Results From a 5-Year Review of 2,169 Patients. Christine A. Clark, Karen A. Spitzer and Carl A. Laskin. University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON

Background/Purpose: The lupus anticoagulant (LAC) Is one of several antiphospholipid antibodies (aPL) that comprise laboratory criteria for the antiphospholipid syndrome (APS). From many studies of recurrent early pregnancy loss (RPL) in the context of aPL, there is a perception that LAC is prevalent in this population. We wanted to determine the distribution of LAC positivity at a large tertiary clinic that sees about 250 new patients with RPL annually in addition to those with SLE and/or APS. We also wanted to identify the most frequent clinical manifestations of APS associated with repeated LAC positivity and to establish any correlations with the number of positive LAC tests in a real world setting.

Methods: We included all patients tested in our laboratory for LAC and anticardiolipin antibodies (aCL IgG and IgM) from 2005 to 2010. We reviewed charts of patients with repeated prolonged LAC to ascertain diagnoses including histories of adverse obstetric and thrombotic events (TE). LAC were measured using a panel of 4 tests according not only to ISTH guidelines (DRVVT and PTT-LA) but also using dilute PT and KCT assays; aCL IgG and IgM were measured using INOVA kits.

Results: Over 5 years we measured 3,446 LAC for 2,169 patients (many had multiple tests). There were 370 (1.1%) positive LAC tests distributed among 138 patients; 31 were positive on only one occasion of many retests, 43 were positive with no subsequent tests, and 64 (3.2%) were positive on $\geq$ 2 occasions. Fifty-nine of 64 charts were available for review: 26 (44.1%) have APS; 19 (32.2%) have SLE/APS; 7 (11.9%) have SLE and 7 (11.9%) have other diagnoses. Twenty-two patients (37.3%) have a history of TE, 7 (11.8%) have had more than 1 TE; 13 patients (22.0%) have had a TE in the absence of a predisposing factor; 4 have had a post-partum TE (6.8%); 9 (15.2%) had a TE while on oral contraception. Twenty-four (40.7%) patients have had $\geq$ 1 stillbirth (SB); 9 (15.3%) have a history of IUGR; 6 (10.2%) had preeclampsia and/or HELLP during a pregnancy; and 3 (5.1%) have a history of early RPL only. Patients were evenly distributed among the number of positive tests in the 4-test LAC panel. There were no differences among distribution of SB, IUGR, preeclampsia or HELLP, early RPL, or live birth ever; however patients with 3 or 4 positive in the LAC panel were significantly more likely to have had a TE than those with 1 or 2 positive (54.8% *vs* 21.4% respectively, p = 0.017, 95% CI: 0.087–0.581). Neither mean values nor increased prevalence of > 40 GPL or MPL aCL IgG or IgM were significantly different among the LAC positive groups.

Conclusion: ISTH guidelines recommend using only 2-test LAC panel, but we found significantly more patients with TE were positive for $\geq$ 3 compared to one or two of the LAC panel. A history of SB was the most common clinical manifestation of repeatedly positive LAC, occurring twice as frequently as idiopathic TE. LAC was found in <3% of patients attending a tertiary clinic restricted to patients with SLE, APS and RPL, and in only 0.2% of patients referred with a history of exclusively early RPL. These findings reinforce the need to redefine APS and validate the proposition that early RPL should be excluded from the classification criteria.

2

Effect of Normal Pregnancy on the Lupus Anticoagulant: No Need to Establish Pregnancy-Specific Reference Ranges. Christine A. Clark, Karen A. Spitzer and Carl A. Laskin. University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON

Background/Purpose: The physiological basis for the hypercoagulability of pregnancy is well understood. Shortened clotting times, especially later in pregnancy, may be a result of increased Factor VIII and fibrinogen levels. Whether alterations in these coagulation and hemostatic mechanisms also result in a change in the normal ranges for the lupus anticoagulant (LAC) remains controversial. Some investigators have reported data indicating no change during pregnancy (Derksen *et al,* 1992) and yet recent ISTH guidelines suggest that specific pregnancy-related reference ranges be used when measuring the LAC during pregnancy (J Thromb Hemost 2009;7:1737–40). We wanted to determine if the LAC varies in healthy women between ante- and post-partum plasma samples.

Methods: We recruited 53 consecutive healthy pregnant women with no history of obstetric, hematologic, or autoimmune abnormalities as part of an ongoing study (PROMISSE). Non-study plasma samples were collected during pregnancy and post-partum and were analysed for the presence of LAC using a panel of 4 tests including dilute Russell's viper venom time (dRVVT), dilute prothrombin time (DPT), a lupus-anticoagulant sensitive PTT (PTT-LA), and kaolin clotting time (KCT). We compared values from samples collected between 20–27 weeks' gestation and again post partum and determined not only if there was a statistical difference between the 2 groups, but also if the values were outside previously established reference ranges from a general population sample.

Results: There was no significant difference between ante- and post-partum PTT-LA [median (range) 38.0 (29.0–56.5) vs. 39.7 (31.2–69.0 sec) respectively, p= 0.27], dRVVT [32.7 (23.3–50.0) vs. 30.8 (20.3–39.1); p = 0.07), or KCT [55.5 (35.0–90.7) vs. 54.4 (33.5–104.2); p = 0.81]. Results for dPT showed a significant decrease during pregnancy [39.0 (22.9–54.1)] compared to post-partum [44.1 (24.5 – 65.0); p < 0.001, (95% CI for the difference of means: 4.4–10.4)]. However, this pregnancy-related difference did not fall outside the non-pregnant reference range for dPT in our laboratory.

Conclusion: Normal pregnancy did not affect the dRVVT, PTT-LA or KCT. Only the dPT showed a pregnancy-related decrease, but although the difference between mean pregnant and non-pregnant clotting times was statistically significant, both pregnant and non-pregnant ranges were within the general population reference range for this assay. Our results support Derksen's earlier findings and we conclude that any changes in LAC levels in normal pregnancy, if present at all, are too small to necessitate the use of pregnancy-specific reference ranges, as suggested in the ISTH guidelines.

3

Association of IgG, IgM, and IgA Isotypes of Anticardiolipin Alone or In Combination In Prediction of Thrombosis In Systemic Lupus Erythematosus. Vinicius Domingues, Hong Fang and Michelle Petri, Johns Hopkins. University School of Medicine, Baltimore, MD

Background/Purpose: The Sydney APS Classification Criteria include medium to high titer anticardiolipin IgG or IgM. We explored the association of all anticardiolipin isotypes, singly or in combination, with thrombosis in SLE.

Methods: There were 1567 SLE patients (92% female, 55% Caucasian, 37% African-American, mean age at entry 39.6±12.9) who participated. There were 668 total thrombotic events (arteral: total 328, TIA 67, stroke 129, myocardial infarction 58, digital gangrene 31, other arterial 45; venous: total 340, DVT or PE 211, superficial 54, other venous 75). Anticardiolipin IgG, IgM, or IgA were assessed at each visit (Inova Diagnostics Inc, San Diego, CA), with cut-offs of 20 for medium positive and 40 for high positive.

Results:

Assay	OR	P-value
Venous Thrombosis		
IgG > 20 ever pos	2.26 (1.70,3.00)	<0.0001
IgG > 40 ever pos	2.34 (1.65,3.34)	<0.0001
IgM > 20 ever pos	1.32 (0.98,1.78)	0.0688
IgM > 40 ever pos	1.46 (1.01,2.11)	0.0432
IgA > 20 ever pos	2.17 (1.42,3.31)	0.0006
IgA > 40 ever pos	2.14 (1.18,3.87)	0.0176
IgG > 20 OR IgM > 20 ever pos	1.79 (1.38,2.32)	<0.0001
IgG > 40 OR IgM > 40 ever pos	1.81 (1.34,2.45)	0.0002
IgG > 20 OR IgA > 20 ever pos	2.06 (1.56,2.71)	<0.0001
IgG > 40 OR IgA > 40 ever pos	2.03 (1.44,2.87)	0.0001
Arterial Thrombosis		
IgG > 20 ever pos	1.95 (1.45,2.620	<0.0001
IgG > 40 ever pos	2.39 (1.67,3.43)	<0.0001
IgM > 20 ever pos	1.42 (1.05,1.93)	0.0264
IgM > 40 ever pos	1.68 (1.16,2.44)	0.0081
IgA > 20 ever pos	1.99 (1.28,3.09)	0.0036
IgA > 40 ever pos	2.75 (1.55,4.98)	0.0013
IgG > 20 OR IgM > 20 ever pos	1.70 (1.30,2.23)	0.0002
IgG > 40 OR IgM > 40 ever pos	1.96 (1.44,2.67)	<0.0001
IgG > 20 OR IgA > 20 ever pos	1.79 (1.34,2.39)	<0.0001
IgG > 40 OR IgA > 40 ever pos	2.49 (1.77,3.52)	<0.0001
Stroke		
IgG > 20 ever pos	1.74 (1.17,2.60)	0.0087
IgG > 40 ever pos	2.19 (1.37,3.51)	0.0025
IgM > 20 ever pos	1.34 (0.89,2.03)	0.1787
IgM > 40 ever pos	1.25 (0.74,2.11)	0.3910
IgA > 20 ever pos	1.54 (0.84,2.84)	0.1528
IgA > 40 ever pos	2.02 (0.93,4.37)	0.772
IgG > 20 OR IgM > 20 ever pos	1.53 (1.06,2.21)	0.0242
IgG > 40 OR IgM > 40 ever pos	1.70 (1.12,2.58)	0.0506
IgG > 20 OR IgA > 20 ever pos	1.51(1.02,2.24)	0.0506
IgG > 40 OR IgA > 40 ever pos	2.00 (1.26,3.17)	0.0045

Conclusion: Analysis of single isotypes found that IgG or IgA, > 20 or > 40 (but not IgM) were associated with venous thrombosis. For arterial thrombosis, all single isotypes were associated. For stroke, only IgG was

associated. Combinations of isotypes surprisingly did not add to the strength of the association nor to the statistical significance. We conclude that: 1) the association depends on whether it is venous thrombosis, arterial thrombosis, or stroke (which is important predictive information for clinicians); 2) IgA anticardiolipin should be added to the classification criteria for APS in SLE, as it performs better than IgM; and 3) combining different isotypes of anticardiolipin does not improve the association.

4

Anti-beta2 Glycoprotein I IgA in Systemic Lupus Erythematosus Versus Controls. Ana-Maria Orbai[1], Hong Fang[1], Joan T. Merrill[2], Graciela S. Alarcón[3], Caroline Gordon[4], Paul R. Fortin[5], Ian N. Bruce[6], David A. Isenberg[7], Daniel J. Wallace[8], Ola Nived[9], Gunnar K. Sturfelt[10], Rosalind Ramsey-Goldman[11], Sang-Cheol Bae[12], John G. Hanly[13], Jorge Sanchez-Guerrero[14], Ann E. Clarke[15], Cynthia Aranow[16], Susan Manzi[17], Murray B. Urowitz[18], Dafna D. Gladman[19], Kenneth C. Kalunian[20], Melissa I. Costner[21], Laurence S. Magder[22], Systemic Lupus International Collaborating Clinics (SLICC)[23] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]University of Alabama at Birmingham, Birmingham, AL, [4]University of Birmingham, Birmingham, United Kingdom, [5]Toronto Western Hospital, Toronto, ON, [6]A, Manchester, United Kingdom, [7]University College London, London WC1E 6JF, United Kingdom, [8]Cedars-Sinai/UCLA, Los Angeles, CA, [9]University Hospital, Lund, Sweden, [10]University Hospital Lund, Lund, Sweden, [11]Northwestern University Feinberg School of Medicine, Chicago, IL, [12]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [13]Dalhousie University, Halifax, NS, [14]University Health Network/Mount Sinai Hospital, Toronto, ON, [15]Research Institute of the McGill Univ. Health, Montreal, QC, [16]Feinstein Institute for Medical Research, Manhasset, NY, [17]Allegheny Singer Research Institute, Pittsburgh, PA, [18]Toronto Western Hospital and University of Toronto, Toronto, ON, [19]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [20]UCSD School of Medicine, La Jolla, CA, [21]North Dallas Dermatology Assoc, Dallas, TX, [22]University of Maryland, Baltimore, MD, [23]Chicago

Background/Purpose: Anti-beta2 glycoprotein I (GPI) is not part of the ACR classification criteria for SLE, and IgA isotypes are omitted from the classification criteria for APS. We studied the prevalence and associations of anti-beta2 glycoprotein I IgA in a large multi-center study.

Methods: The dataset consisted of 1384 patients with both anti-beta2-GPI IgA measured and a consensus physicians diagnosis (657 with SLE and 727 controls with other rheumatologic diseases). Of the 657 SLE patients, 599 (91%) were female, 394 (60%) were Caucasian, 134 (20%) were of African descent, and 76 (12%) were Asian. Their mean age (years) was 37.9±13.3. P-values were calculated based on the chi-square test (SAS Institute, Cary, NC, USA).

Results: The prevalence of anti-beta2-GPI IgA was 14% (94/657) in SLE patients and 7% (49/727) in controls (P-value<0.0001, OR=2.3 (95% CI: 1.6, 3.3)). Eleven percent (73/657) of SLE patients had anti-beta2-GPI IgA alone (no anti-beta2-GPI IgG or IgM).

Table 1. Percentage of SLE Patients with Anti-beta2-GPI IgA, by Demographic Variables

		Percentage with Anti-beta2-GPI IgA	P-value
Ethnicity	African Descent	21.6	0.019
	Caucasian	11.4	
	Asian	18.4	
	Other	11.3	
Gender	Female	14.2	0.78
	Male	15.5	
Age	≤30	20.3	0.0035
	>30	11.7	

Table 2. Percentage of SLE Patients with Various Clinical Conditions, by Anti-beta2-GPI IgA Status

ACR criteria	Anti-beta2-GPI IgA (%)	No Anti-beta2-GPI IgA (%)	P-value	Odds Ratio (95% CI)	Adjusted P-value for Race and Age
Malar Rash	52.1	43.5	0.12	1.4 (0.9, 2.2)	0.16
Discoid Rash	20.2	17.9	0.60	1.3 (0.7, 2.2)	0.42
Photosensitivity	48.9	51.0	0.71	1.0 (0.6, 1.5)	0.91
Oral Ulcers	38.3	41.6	0.55	0.9 (0.6, 1.4)	0.57
Arthritis	66.0	65.9	0.99	1.0 (0.6, 1.6)	0.93
Serositis	38.3	30.9	0.15	1.3 (0.8, 2.0)	0.33
Pleurisy	34.0	25.4	0.08	1.4 (0.9, 2.3)	0.16
Pericarditis	12.8	10.8	0.58	0.9 (0.5, 1.9)	0.86
Renal	39.4	31.1	0.11	1.1 (0.7, 1.8)	0.63
Proteinuria	37.2	30.0	0.16	1.1 (0.7, 1.8)	0.71
Urinary casts	9.6	7.1	0.40	1.1 (0.5, 2.5)	0.73
Neurologic	6.4	7.1	0.80	0.8 (0.3, 2.1)	0.72
Seizure	5.3	5.5	0.94	1.0 (0.4, 2.6)	0.92
Psychosis	3.2	2.0	0.44	1.5 (0.4, 5.8)	0.54
Hematologic lupus	61.7	49.7	0.032	1.5 (0.9, 2.4)	0.09
Leukopenia	35.1	28.4	0.19	1.2 (0.7, 1.9)	0.56
Lymphopenia	29.8	30.9	0.83	0.9 (0.6, 1.5)	0.72
Thrombocytopenia	18.1	14.0	0.30	1.2 (0.7, 2.3)	0.46
Anti-dsDNA	75.5	57.0	0.0007	2.4 (1.4, 4.1)	0.001
Anti-Smith	25.5	23.6	0.69	0.8 (0.5, 1.4)	0.51
Lupus anticoagulant	70.2	48.9	0.0001	2.4 (1.5, 3.9)	0.0003
Anticardiolipin IgG	40.4	16.2	<.0001	3.0 (1.9, 5.0)	<.0001
Anticardiolipin IgM	35.1	11.6	<.0001	4.0 (2.4, 6.7)	<.0001
Anticardiolipin IgA	8.5	0.9	<.0001	10.8 (3.2, 36.8)	0.0001
False positive RPR	9.6	3.4	0.032	3.3 (1.1, 10.1)	0.033

Table 3. Sensitivity and Specificity for SLE, based on Anti-beta2 Glycoprotein I IgA Positivity

	Sensitivity %	Specificity %
Anti-beta2-GPI IgA	14.3	93.3

Conclusion: Anti-beta2 glycoprotein I IgA was more prevalent in SLE patients (14%) than in patients with other rheumatologic diseases (7%) in this international multi-center study. It can occur as the sole isotype of anti-beta2-GPI in SLE. It was strongly associated with age, anti-dsDNA and other antiphospholipid antibodies and was highly specific for SLE. This was the rationale to include anti-beta2 glycoprotein I IgA in the new SLICC classification criteria for SLE.

5

Risk Factors for Rethrombosis In Patients with Primary Antiphospholipid Syndrome Regardless of Their Oral Anticoagulation Status. Gabriela Hernandez-Molina[1], Grissel Espericueta-Arriola[2] and Antonio R. Cabral[3]. [1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubirán, Mexico city, Mexico, [3]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubirán, Mexico, Mexico

Background/Purpose: To ascertain the serological and non-serological factors for rethrombosis in patients with primary antiphospholipid syndrome (PAPS) regardless of their anticoagulation status.

Methods: We retrospectively studied patients with PAPS who had at least one thrombotic episode. Patients were excluded if they had a history of hereditary thrombophilia or SLE. We divided patients in 4 groups. **1:** Patients on oral anticoagulants (OA) that after discontinuation (self decision or medical contraindication) developed a new thrombotic event. **2:** Patients on OA that after discontinuation did not have a new thrombotic event. **3:** Patients on continuous OA that have remained thrombosis-free. **4:** Patients on OA who developed a new thrombotic event. We studied: age at time of thrombosis, time for rethrombosis, BMI, comorbidities (DM2, hypertension, dyslipidemia), pregnancies, bedridden, hormonal contraception, estrogen replacement, perioperative period, infections, tobacco use, prednisone, aspirin, immunosuppresors and INR during thrombosis. We also evaluated the frequency of aCL (IgG-IgM), anti-β_2GP-I (IgG-IgM), lupus anticoagulant (alone or combined) and persistently positive antibody titers. We used ANOVA, X^2, Student's t test and Odds Ratio (95% CI).

Results: We studied 95 patients (70 women, 74%): 32 (group 1), 25 (group 2), 29 (group 3) and 10 (group 4). Their overall mean age at time of study was 41.7 ± 14 years with a median follow-up of 4.5 years (0.3–26). Follow-up time was shorter for group 1 (2.8 years, p= 0.05) than the other groups. LA and triple markers (LA, aCL and anti-β_2GP-I) were more prevalent in group 1 than in group 2: 67 vs. 31%; OR= 4.5; 95% CI= 1.3–14.9; p= 0.01; and 57% vs. 27%; OR= 6.6; 1.7–25.2; p=0.03 respectively. These two variables remained associated with recurrence of thrombosis after comparing groups 1 & 4 with group 2: LA 62% vs. 31%, OR= 3.6; 95% CI= 1.1–11.2, p=0.03; triple marker 75% vs. 27%; OR= 8.0; 95% CI= 2.14–29.8; p= 0.04. Patients from group 2 were more frequently on aspirin than those from group 3 (62.4% vs. 31%; OR= 0.27; 95% CI= 0.08–0.84; p=0.02). We found no significant difference between the INR of our patients on oral anticoagulants (Group 3, INR= 2.7 vs. group 4= 2.3, p=0.2). Neither titers nor persistently positive antibody markers were associated with re-

thrombosis. Other studied clinical variables were not associated with recurrent thrombosis.

Conclusion: Our study showed that LA, alone or combined with aCL and anti-β_2GP-I, is a risk factor for recurrent thrombosis in patients with PAPS regardless of therapeutically effective oral anticoagulation.

6

Risk of Recurrent Stroke in Pregnancies of Patients with Antiphospholipid Syndrome and Previous Cerebral Ischemia. Rebecca Fischer-Betz, Christof Specker and Matthias Schneider. MNR-Klinik, Düsseldorf, Germany

Background/Purpose: Cerebral ischemia is one of the most prominent clinical manifestations of Antiphospholipid Syndrome (APS) and may be present with transient ischemic attacks (TIA) or stroke. There are only rare data on maternal and fetal outcome in pregnancies in women with previous cerebral ischemia.

Methods: We prospectively studied the outcome of 21 pregnancies in women with APS (10 primary and 11 secondary to SLE) and previous cerebral ischemia. 12 patients had previous transient ischemic attacks (TIAs) and 9 had stroke before pregnancy. The mean age at pregnancy was 30.5 years (± 5.08). The time between cerebral ischemia and pregnancy ranged from 14–182 months (median 70 months). All patients received treatment with aspirin 100 mg daily. 17 patients received low molecular weight heparin (LMWH). 4 patients were treated with warfarin before pregnancy and switched to therapeutic doses of LMWH.

Results: There were 18 live births (85.7 %) and 3 (14.3 %) pregnancy losses (1 at 10 weeks, 1 at 22 and 1 at 24 weeks). All together, 7/21 (33.3 %) women developed preeclampsia. 12/18 (66.6 %) deliveries were preterm (mean weeks of gestation 36.1 ± 2.27). 88.2 % underwent ceasarean section. The mean birth weight of the life born children was 2871 (± 563) g. One female child was born with a nasal hypoplasia. 1 patient who switched from warfarin to heparin presented with TIA during her 34th week of pregnancy, despite this, she had a normal pregnancy. 1 pregnancy was complicated by a further cerebral ischemic event at 3 weeks postpartum in a patient who unintentionally discontinued her aspirin medication while she was breast feeding. 1 woman developed a third ischemic event 1 year post partum despite continuous treatment.

Conclusion: Our data suggest that successful pregnancy and delivery is possible in APS patients with a history of cerebral ischemia. Despite the treatment with low-dose aspirin and anticoagulants there is a high risk for preterm deliveries and preeclampsia, but the risk for a recurrent cerebral event seems to be low. A previous episode of cerebral ischemia therefore may not be an absolute contraindication for an APS patient to become pregnant.

7

Utility of the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index for Antiphospholipid Antibody (aPL) Positive Patients. Medha Barbhaiya[1], Doruk Erkan[2], Esther Rodriguez-Almaraz[3], Glendalee Ramon[4], JoAnn Vega[4] and Michael D. Lockshin[4]. [1]Weill Cornell Medical Center, New York, NY, [2]Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, New York, NY, [3]Hospital "12 de Octubre", Madrid, Spain, [4]Barbara Volcker Center for Women and Rheumatic Diseases: Hospital for Special Surgery, New York, NY

Background/Purpose: SLICC/ACR Damage Index (DI) was designed and validated for systemic lupus erythematosus (SLE) patients to capture non-reversible organ damage, not related to active inflammation, lasting at least 6 months. Although aPL-positive patients with or without SLE develop aPL-related organ damage, no DI exists specific for these patients. The purpose of this pilot study was to assess the utility of SLICC/ACR DI in aPL-positive patients.

Methods: We identified two groups of persistently aPL-positive patients (positive LA test, aCL IgG/M/A ≥ 20U, and/or aβ_2GPI IgG/M/A ≥ 20U at least 12 weeks apart) from our aPL-registry: those without other systemic autoimmune diseases (SAIDx) and those only with SLE. All patients are assessed by SLICC/ACR DI and ACR SLE Classification Criteria (CC) at the registry entry. For the purpose of this study, we descriptively analyzed the limitations of SLICC/ACR DI use in aPL-positive patients. We grouped patients as (A) *aPL* only (no history of thrombosis, no SLE), (B) *aPL* with SLE-like Disease (ACR_SLE_CC=3/11), (C) *aPL* with SLE (ACR_SLE_CC>3/11), (D) *APS* (history of thrombosis, no SLE); (E) *APS* with SLE-like Disease, and (F) *APS* with SLE. We used One-Way ANOVA test with Games-Howell post hoc analysis to compare the mean SLICC/ACR DI scores between six groups.

Results: Of 51 patients (mean age at the time of the registry entry 39.5 ± 13.6), 73% were female and 86% were Caucasian. Top two limitations of SLICC/ACR DI use in aPL-positive patients were: a) not being able to record aPL-related "damage" (livedo reticularis/racemosa, adrenal infarcts requiring chronic treatment, diffuse pulmonary hemorrhage resulting in chronic symptoms, permanent inferior vena cava filter placement, multiple sclerosis-like disease, and/or white matter changes); and b) the definition of the two SLICC/ACR DI items ("venous thrombosis with swelling, ulceration, OR venous stasis for at least 6 months"; "skin ulceration [excluding thrombosis] for more than 6 months"). For the purpose of further analysis we created an experimental category for aPL-related damage assigning the above "damage" items one point each. We also scored all venous events and skin ulcers as one point. Table shows mean disease duration since the first positive aPL determination and SLICC/ACR DI using the original as well as the experimental criteria.

Patient Groups (n)**	Mean Disease Duration (y)	Mean SLICC/ACR Damage Index Score (Original)*	Mean SLICC/ACR Damage Index Score (Experimental)*
A. aPL with no SLE (7)	5.72 ± 8.00	1.29 ± 0.95	2.00 ± 1.16
B. aPL with SLE-like (5)	2.15 ± 2.18	1.80 ± 1.64	2.20 ± 2.38
C. aPL with SLE (4)	1.50 ± 0.82	1.00 ± 0.00	1.75 ± 0.96
D. APS with no SLE (19)	2.60 ± 2.81	2.32 ± 1.30	2.79 ± 1.55
E. APS with SLE-like (8)	5.57 ± 5.99	2.88 ± 2.41	3.13 ± 2.70
F. APS with SLE (8)	5.65 ± 3.50	5.50 ± 2.44	6.50 ± 2.93

* $p<0.0005$, One-Way ANOVA. ** $p<0.05$: A vs F, C vs D, C vs F for the original, and A vs F, C vs F, for the experimental SLICC/ACR DI

Conclusion: In persistently aPL-positive patients, the SLICC/ACR Damage Index: a) captures most, but not all, of aPL-related organ damage; and b) increases with additional aPL- and/or lupus-related damage. In persistently aPL-positive SLE patients, the SLICC/ACR Damage Index should be interpreted cautiously as it can overestimate lupus-related, and underestimate aPL-related damage. Our study provides a start point to modify and validate the SLICC/ACR Damage Index for aPL-positive patients.

8

Development and Initial Validation of a Chronic Damage Index in Patients with Antiphospholipid Syndrome. Mary-Carmen Amigo[1], Leonor A. Barile[2], Alberto Barragan[3], Gisela Espinosa-Cuervo[4], Mavis Goycochea[5], Laura Aline Martinez-Martinez[6], Gabriela Medina[7], Angelica Vargas[8] and Luis J. Jara-Quezada[9]. [1]ABC Medical Ctr, Mexico City, Mexico, [2]Hospital Especialidades CMN, Mexico City, Mexico, [3]México, Mexico, [4]Research Unit, Mexican College of Rheumatology, Mexico, Mexico, [5]Instituto Mexicano del Seguro Social and Research Unit, Mexican College of Rheumatology, Mexico City, Mexico, [6]Intituto Nacional de Cardiologia, Mexico, Mexico, [7]Seris/Zachila s/n La Raza, Mexico City, Mexico, [8]Instituto Nac de Cardiologia, Mexico City, Mexico, [9]Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico

Background/Purpose: The antiphospholipid syndrome (APS) is defined by the presence of venous or arterial thrombosis or recurrent pregnancy complications in association with antiphospholipid antibodies. Certain key manifestations are associated with a worse prognosis and permanent organ damage; but, at this time, there is not a comprehensive assessment of accumulative damage APS

Purpose: To describe the development and initial content, criterion and construct validity of a disease specific cumulative Damage Index in APS (DIAPS)

Methods: Phase 1 included generation for index content through an expert panel agreement, a list of items considered to reflect the damage in APS was generated in three rounds. An initial list of 60 manifestations linked with potential irreversible damage were identified by experts, then by an operative definition to report each manifestations was established; finally after independent revision by 3 clinicians experts in methodology and 3 APS experts a consensus round selected 47 items. A second phase was a cross-sectional study conducted in patients with APS diagnosis included in a multicentre electronic registry http://investigacion.colmexreuma.org.mx/saaf/index.html. The output rating was determined by the physician if each manifestation was absent (0), present but without sequel (1), or present with sequel (2). The final score was made adding the output rating reflecting the damage for domains and global index. Quality of life related to health status was evaluated with Euroqol for construct validation, considering that this analysis could reflect a good agreement among the physicians on the

assessment damage in the patients; α Cronbach and correlation with Euroqol scale were calculated with SPSS 18.0, ($p<0.05$)

Results: DIAPS was evaluated in 139 cases, female 76.4% (113), the mean of the age at diagnosis 35.5 ± 12.4 years; primary APS diagnosis in 72.6% (119), APS plus SLE in 22% (36) and APS plus Sjögren in 1.8% (3). The most common comorbidities were obesity 24.3% (36), depression 18.2% (27) and dyslipidemia 14.2% (21). The most frequent manifestations conditioning sequels were: deep venous thrombosis 26.6% (37) and ischemic stroke 11.5% (16). Blindness 5.8% (8); retinal occlusive vessel disease 4.3% (6); myocardial infarction 2.9% (4); Cardiac valve requiring replacement 1.4% (2); sequel of mesenteric thrombosis (including liver, spleen and intestine) 3.6% (5) and renal insufficiency 1.4% (2); The index has a high homogeneity (α Cronbach 0.954). Questionnaire DIAPS showed correlation with Euroqol as follow: pain (r 0.479, p 0.000), mobility (r 0.425, p 0.000), personal care (r 0.344, p 0.000), daily activities (r 0.329, p 0.000), current health status (r 0.249, p 0.003) and anxiety/depression (r 0.192, p 0.025).

Conclusion: The preliminary validation study demonstrated content, criterion and construct validity of a new physician-reported instrument of APS damage. DIAPS has a good correlation with Euroqol. Further studies have to be conducted to examine reliability and psychometric properties in extended populations. DIAPS could be a useful clinical tool and a good instrument in epidemiological and economic evaluations to measure the real impact of this severe disease.

9

Low Vitamin D Levels Are Common in Primary Antiphospholipid Syndrome: A Role in the Pathogenesis of the Disease? Laura Andreoli[1], Silvia Piantoni[1], Flavio Allegri[1], Pier Luigi Meroni[2] and Angela Tincani[1]. [1]Rheumatology Unit, University of Brescia, Brescia, Italy, [2]University of Milan, Milan, Italy

Background/Purpose: Low levels of vitamin D (vit.D) have been described in different systemic autoimmune diseases (SAD). *In vitro* studies and animal models have shown anti-inflammatory properties of vit.D. Therefore, hypovitaminosis D has been claimed to be involved in the pathogenesis of SAD. Primary Antiphospholipid Syndrome (PAPS) is characterized by thrombotic events and/or obstetric disease, whose pathogenesis is mediated by antiphospholipid antibodies. Differently from other SAD, PAPS patients (pts) do not usually have a full-blown disease that requires corticosteroids (and therefore the association of vit.D supplementation as osteoporosis prophylaxis), nor have particular limitations in sun exposure. These factors are relevant to vit.D levels. Thus, pts with PAPS appear to be a good model for studying hypovitaminosis D in SAD. Purpose:To assess the prevalence of hypovitaminosis D in a large cohort of PAPS (in comparison with normal population from the same geographical area) and investigate the association with clinical manifestations.

Methods: We enrolled 115 PAPS (19 m, 96 f, median age: 46 years) and 128 normal healthy donors (NHD) (55 m, 73 f, median age: 34). Vit.D levels were tested by the LIAISON® chemiluminescent immunoassay (DiaSorin, Italy), kindly provided by the manufacturer. The samples were grouped upon the season for statistical analysis.

Results: Vit.D deficiency (<10 ng/ml) was more prevalent in PAPS than NHD (17% *vs.* 5%). Seasonal variability was present in both groups (higher levels in the summer, lower levels during winter). However, median values were lower in PAPS than NHD at all time points, with the greatest difference during summertime (median: 28 vs. 40.1 ng/ml; $p<<0.01$), suggesting that PAPS pts may be somehow prevented from vit.D generation upon sun exposure. PAPS pts may receive specific instructions regarding the use of sunscreens in the presence of positive anti-nuclear antibodies (ANA). Comparing pts with positive (n=63) and negative ANA (n=40), we found comparable Vit.D levels during the summer (median: 27.7 *vs*. 28). PAPS were subdivided upon clinical features (thrombotic vs obstetric). Both groups had lower vit.D levels than NHD. Thrombotic PAPS had significantly lower levels than obstetric PAPS (median value: 20.8 *vs.* 33.3; $p<<0.01$).

Conclusion: Pts with PAPS displayed significantly lower levels of vit.D than NHD. Although these pts have limited inflammatory burden and organ involvement, rarely requiring immunosuppression, these epidemiological data make them similar to pts with SAD such as Systemic Lupus Erythematosus or Rheumatoid Arthritis. Using ANA positivity as a surrogate marker for sun exposure, we suggest that sun avoidance may not be the main reason for low vit.D levels. Hypovitaminosis D may be part of the mosaic of factors that determine autoimmunity, rather than a consequence of chronic disease and its treatment (factors that are poorly represented in PAPS). In particular, this hypothesis may be supported by the observation that pts with thrombotic PAPS, i.e. more aggressive disease, are more deficient than those with exclusive obstetric manifestations. This could fit well with a recent *in vitro* observation of anti-thrombotic properties of vit.D.

10

Thrombin Generation Indicates An Increased Risk for Thromboembolic Events in Lupus and Antiphospholipid Patients. A Prospective Cohort Study. Stephane Zuily[1], Veronique Regnault[2], Francis Guillemin[3], Pierre Kaminsky[4], Thomas Lecompte[5] and Denis Wahl[6]. [1]Vascular Medicine Unit, Vandoeuvre-Les-Nancy, France, [2]INSERM U961, Vandoeuvre, France, [3]Faculte de Medecin/BP 184, Vandoeuvre-les-Nancy, France, [4]Orphan disease Unit, Vandoeuvre, France, [5]Haematology, Vandoeuvre, [6]Nancy University Hospital and INSERM U961, Vandoeuvre-Les-Nancy, France

Background/Purpose: Predicting thrombosis in systemic lupus erythematosus (SLE) and/or antiphospholipid antibodies (aPL)-positive patients is an unsolved issue. Our objective was to perform a prospective cohort study to determine clinical and laboratory risk factors for thrombotic events including a novel thrombin generation (TG)-based activated protein C (APC) resistance assay in this population.

Methods: Ninety-two patients with SLE (n=30) and/or aPL (n=77) without anticoagulant treatment at inclusion were studied. Time to thrombotic event was determined according to clinical and laboratory variables (inherited thrombophilia, aPL profiles) and APCsr-aPL (TG-based APC sensitivity ratio: APCsr > 90th percentile of values from a control population, and persisting aPL positivity).

Results: Ninety two patients (74 women) (median age 40 years [interquartile range IQR: 29–58]) were followed-up during a median duration of 35 months (IQR: 26–62; 320 patient-years). Thrombosis during follow-up occurred in 18 patients: 4 arterial, 11 venous including 7 superficial venous thrombosis (SVT), 3 small vessel thromboses. In survival analyses, the presence of APCsr-aPL was associated with an increased risk of thrombotic events during follow-up (HR, 3.67 [95%CI, 1.31–10.31]) while the risk associated with patients positive for all aPL tests (triple positive) was not significant (HR, 2.32 [95%CI, 0.76–7.13]).

Conclusion: APC-resistance determined by thrombin generation predicts the risk for thromoembolic events in patients with antiphospholipid antibodies.

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Myocardial Global Longitudinal Strain in Primary Antiphospholipid Syndrome. Gabriela Medina, Eduardo Gómez-Bañuelos, Erick Calderón-Aranda and Luis J. Jara. Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico

Background/Purpose: Measurement of myocardial deformation or Global longitudinal strain (GLS) by speckle tracking echocardiography (STE) is useful for detection of microvascular damage and myocardial contractility impairment in patients with diabetes mellitus and ischemic cardiopathy. Primary antiphospholipid syndrome (PAPS) is characterized by thrombosis, endothelial damage, and vascular dysfunction. GLS has not been studied in these patients.

Purpose: To evaluate the GLS from the left ventricle by STE in order to provide the early detection of myocardial dysfunction in patients with PAPS.

Methods: Patients with PAPS older than 16 years of age, without signs and symptoms of heart failure and angina were recruited and matched with healthy controls by age and gender. Patients with uncontrolled thyroid disease, poor echocardiographic window, or pregnancy were excluded. Demographic, clinical data, cardiovascular risk factors and lipid profile were recorded. Standard transthoracic evaluation was done and images from GLS 2, 3 and 4 chambers view were recorded and analyzed with STE and strain imaging. Segmental strain (in17 segments from the left ventricle), GLS2 chambers (represent the segments 4, 7, 10, 13, 15), GLS3 chambers (segments 2, 5, 8, 11, 13, 16), and GLS4 chambers (segments 3, 6, 9, 12, 14, 16), and average GLS were assessed. Mann Whitney U test was used to compare strain values.

Results: Thirty-eight patients and 21 controls were included. Average age was 46.7+/−10 and 42+/−7 years respectively. Only one patient had history of myocardial infarction and 13 had stroke. The prevalence of obesity (50% p=0.012) and dyslipidemia (44.73% p=0.001) was higher in PAPS group than the control. Only 4 patients had arterial hypertension under control. The frequency of other risk factors was similar between groups. Ventricular ejection fraction was normal. In the PAPS group, myocardial segmental strain was lower in apical segments (S13, S14, S16, S17), and in GLS2 (corresponding to inferior and anterior wall segments from the left ventricle)

($p<.0.03$). The average of GLS was significantly lower in comparison with controls ($p=0.01$).

Conclusion: Patients with PAPS without signs and symptoms of heart disease had lower values of myocardial GLS than controls probably due to coronary microcirculation abnormalities. Global longitudinal strain has a potential value in the assessment and treatment of myocardial dysfunction in PAPS patients.

12

C5 Inhibitor rEV576 Ameliorates *In Vivo* Effects of Antiphospholipid Antibodies. Ana Laura Carrera-Marin[1], Zurina Romay-Penabad[1], Samuel Machin[2], Hannah Cohen[2], Wynne Weston-Davies[3] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]University College London, LOndon, United Kingdom, [3]Varleigh Immuno Therapeutics, Ltd, London, United Kingdom

Background/Purpose: Murine models indicate involvement of the complement system in antiphospholipid (aPL)-mediated thrombosis. Complement split products (C5a and C3a) may enhance endothelial cell (EC) activation and pro-infflammatory/procoagulant states including tissue factor (TF) upregulation. rEV576 (coversin) is a recombinant salivary protein from the tick *Ornithodoros moubata* which protects it from attack by the host's complement system (Nunn M A et al., *J Immunol* **174** (4), 2084 (2005)). It is a small protein, which binds C5 inhibiting cleavage to C5a and C5b, the first component in the formation of MAC. Blockade of the complement cascade at the level of MAC generation is advantageous because it prevents the destructive effects of MAC while retaining the immunoprotective role of upstream complement components (e.g. C3b opsonization and phagocytosis).Here we examined the effects of coversin on aPL-mediated thrombosis and upregulation of TF in an *in vivo* murine model.

Methods: C57BL/6J mice were injected i.p. twice with 0.5 mg of IgG from a patient with Antiphospholipid Syndrome (APS) or with control IgG in normal human serum (NHS) preceded by i.p. injection of rEV576 0.2 mg, calculated to totally inhibit C5 cleavage, or phosphate buffer (PBS) control. The size of induced thrombus was measured 72 h after the first injection. TF activity was determined in carotid homogenates. Anticardiolipin (aCL) and anti- $\beta_2$glycoprotein I (anti-β_2GPI) antibodies were determined in the serum of the mice by ELISA.

Results: see table

Treatment	Thrombus size (μm^2)	TF carotid (pM/mg/ml)	aCL (GPL units)	anti-β_2GPI (SGU)
IgG-APS + PBS	2067 ± 693	602.8 ± 119.4	103.9 ± 26.4	96.5 ± 9.4
IgG-APS + rEV576	767 ± 179 (†)	176.7 ± 38.9 (†)	114.2 ± 15.7	104.6 ± 13.9
IgG-NHS + PBS	537 ± 118 (†)	187.1 ± 150.8 (†)	<10	<20
IgG-NHS + rEV576	481 ± 164	110.5 ± 20.3	<10	<20

(†) $p<0.001$ compared to IgG-APS + PBS

IgG-APS + PBS induced significantly larger thrombi and TF activity compared to other groups. Mice treated with rEV576 and APS IgG had significantly less thrombus and TF activity than those treated with PBS and APS IgG. Mice treated with IgG-APS had high titers of aCL and anti-β_2GPI at induction of thrombus.

Conclusion: The data confirm involvement of complement activation in aPL-mediated pathogenesis and suggest that complement inhibition might ameliorate APS clinical manifestations.

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Pathogenic Effects of Antiphospholipid Antibodies Are Ameliorated In Tissue Deficient Mice. Zurina Romay-Penabad[1], Ana Laura Carrera-Marin[1], Nigel Mackman[2] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: Antiphospholipid (aPL) antibodies are associated with thrombosis in patients with the Antiphospholipid Syndrome (APS). APL antibodies are thrombogenic *in vivo* and have been shown to cause upregulation and expression of tissue factor (TF) on cultured endothelial cells and increased procoagulant activity in monocytes *in vitro*. Furthermore, monocytes from patients with aPL antibodies are known to have increased procoagulant activity. However, whether TF plays a role on aPL-mediated thrombosis *in vivo* is unknown. We addressed that question by measuring the thrombogenic potential of aPL antibodies in mice with greatly reduced levels of TF in all tissues (low TF mice, mTF−/−, hTF+), in an established mouse model of induced thrombosis.

Methods: mTF−/−, hTF+ and the corresponding control mTF+/−, hTF+ in groups 5 mice were injected intraperitoneally (i.p.) twice with either IgG from a patient with APS (IgG-APS) (500 μg) or with control IgG (IgG-NHS) (500 μg). Seventy-two hours after the first injection a surgical procedure was performed to study thrombus dynamics. The anticardiolipin (aCL) and anti-β_2 GPI titers in the serum of the mice were determined by ELISA.

Results: Thrombus sizes were significantly larger in mTF+/−, hTF+ mice injected with IgG-APS compared to these mice treated with IgG-NHS (1695 ± 382 μm^2 vs. 546 ± 48 μm^2; $p<.0001$). Importantly, the size of thrombus in mTF−/−, hTF+ mice injected with IgG-APS (712 ± 129 μm^2) was significantly smaller than the mean thrombus size in mTF+/−, hTF+ injected with IgG-APS (1695 ± 382; $p<.0001$). The mean aCL and anti-β_2 GPI titers in the serum of mTF +/−, hTF+ and mTF−/−, hTF+ mice injected with IgG-APS were: 55 ± 14 GPL and 22 ± 6 SGU and 53.3 ± 19.3 GPL and 51 ± 20 SGU at the time of surgery, respectively.

Conclusion: The data show that TF mediates aPL-induced thrombosis *in vivo*. Further studies will be performed to determine the cell types that express TF and are responsible for thrombosis in APS.

14

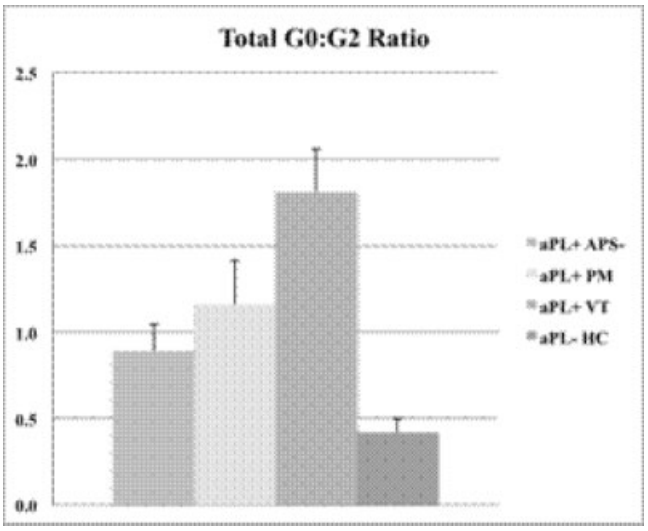
Patterns of Immunoglobulin-G Glycosylation Distinguish Different Clinical Phenotypes of Antiphospholipid Antibody Positivity. Edward Tarelli[1], John S. Axford[1], Ian Giles[2], Charis Pericleous[2], Silvia S. Pierangeli[3], Yiannis Ioannou[4], Anisur Rahman[2] and Azita Alavi[1]. [1]Sir Joseph Hotung centre for Musculoskeletal diseases, St George's University of London, London, United Kingdom, [2]Division of Medicine/Centre for Rheumatology Research, University College London, London, United Kingdom, [3]University of Texas Medical Branch, Galveston, TX, [4]University College London, London, United Kingdom

Background/Purpose: Polyclonal IgG and antiphospholipid (aPL) antibodies from patients with different clinical manifestations of the antiphospholipid syndrome (APS) have been shown to exert differential effects on signalling pathways and tissue factor activity in target cells. Interestingly, these biological effects were not distinguished by their degree of aPL binding which did not differ significantly between the different APS subgroups.

Given that glycosylation is known to influence the biological activity of IgG, and that changes in IgG glycosylation patterns have been shown to predict clinical manifestations for various autoimmune diseases, we examined whether differential glycosylation of IgG may be a factor in determining the observed differences in the mechanism of the effects of IgG from APS patients.

Methods: The glycosylation profile of IgG N-glycans, enzymatically released, from protein G purified IgG from four sets of 8 patients; APS with pregnancy morbidity (PM) alone (aPL+ PM), vascular thromboses (VT) alone (aPL+ VT), aPL+ve patients without APS (aPL+ APS-) and healthy controls (aPL- HC) was examined using Matrix Assisted Laser Desorption Ionisation Time-Of-Flight Mass Spectrometry (MALDI-TOF MS). IgG glycans were divided into three main groups based on the number of galactose residues: G0, G1 and G2. These biantennary complex glycans may be further modified by the presence/absence of fucose (F) and/bisecting N-acetylglucosamine (bis).

Results: There were no significant differences in aPL binding between the different APS and aPL+ groups. In contrast, the glycosylation profile of IgG was found to be significantly different in the 4 groups examined (Figure). IgG from the APS patients had significantly higher ratios of total G0:G2 compared with the aPL+ APS- patients ($p=0.038$) and those from aPL- HC ($p=0.002$). On further, more detailed, analysis, the IgG from patients with VT, which showed the most marked difference in total G0:G2 ratio, could be differentiated from the PM group based on significant differences in the levels of G1F, G2, G2F and G1Fbis ($p<0.05$).



Conclusion: Our findings show that IgG from patients with diverse clinical manifestations of APS and aPL positive healthy controls exhibit differential patterns of glycosylation that were not predicted by differences in aPL binding. Therefore, these glycosylation differences, which include the degree of galactosylation as well as fucosylation, could be used as a biomarker to discriminate between patients with VT and PM, and may provide a better insight into the different mechanistic action of IgG in these patients.

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Role of Apolipoprotein B100 and Oxidized Low-Density Lipoprotein in Anti-beta2 Glycoprotein I Induced Tissue Factor Expression on Monocytes. Kotaro Otomo[1], Tatsuya Atsumi[1], Yuichiro Fujieda[1], Hisako Nakagawa[1], Masaru Kato[1], Olga Amengual[1], Tetsuya Horita[1], Shinsuke Yasuda[1], Masaki Matsumoto[2], Shigetsugu Hatakeyama[3] and Takao Koike[1]. [1]Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Division of Proteomics, Kyusyu University Medical Institute of Bioregulation, Fukuoka, Japan, [3]Department of Biochemistry, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Background/Purpose: To explore plasma molecule involvement in the tissue factor expression induced by beta2 glycoprotein I dependent anticardiolipin antibody (aCL/β2GPI) on monocytes.

Methods: Unknown beta2-glycoprotein I (β2GPI) binding molecules in plasma were screened by a proteomics technique using immunoaffinity chromatography and mass spectrometric analysis. To identify β2GPI binding proteins, FLAG-tagged human β2GPI was constructed. The expression vector encoding FLAG-β2GPI was transfected into HEK293T cells, and the expression of full length FLAG-β2GPI in the culture supernatant was confirmed by immunoblotting. Human serum sample with FLAG-β2GPI was incubated and applied for affinity chromatography with anti -FLAG antibody-conjugated Sepharose beads. The purified fraction was subjected to SDS-PAGE, followed by a silver staining. Immunopurified proteins were analyzed by an online-nanoLC-MS/MS. Obtained MS/MS data were searched against nrNCBI database MASCOT algorithm.

Results: Among many proteins detected in the spectrometry, ApoB100 was the only identified molecule as a candidate plasma protein. Since there was no significant binding between β2GPI and ApoB100 in ELISA, oxidized LDL, containing ApoB100 as well as ox-Lig1 (a known ligand of β2GPI) in its molecule, was considered as a β2GPI-binding molecule in plasma.

The involvement of oxidized LDL was further investigated in aCL/β2GPI induced tissue factor expression on monocytes. RAW264.7, a monocyte cell line, was incubated with a monoclonal aCL/β2GPI, WBCAL-1, in the presence/absence of oxidized LDL. Cells were lysed and TF mRNA was quantitated using Real Time PCR system. The presence of oxidized LDL (100μg/ml) and β2GPI markedly increased TF mRNA expression on RAW264.7 cells induced by WBCAL-1 (Fig). Oxidized LDL upregulated TF mRNA induction as well by purified IgG from APS patients with high titre of aCL/β2GPI.

Conclusion: Oxidized LDL was detected as a major β2GPI binding plasma molecule by proteomics analysis. The presence of oxidized LDL upregulated aCL/β2GPI induced TF expression on monocytes, suggesting the involvement of oxidized LDL in the pathophysiology of thrombosis in patients with APS.

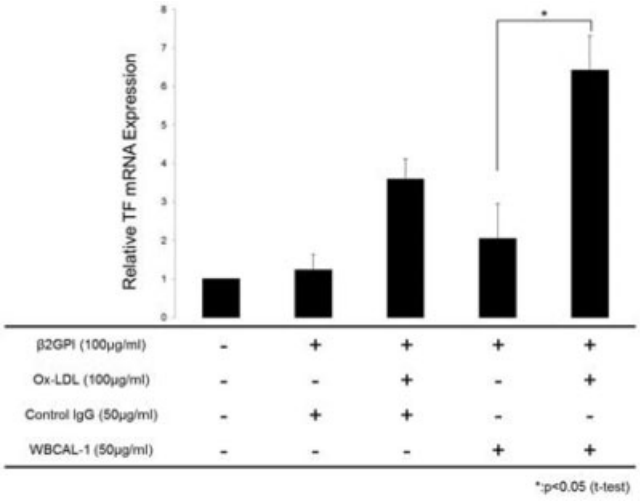

Figure. RAW264.7 cells were incubated with monoclonal aCL/β2GPI (WBCAL-1) in the presence of oxidized LDL. TF mRNA was quantitated by Real Time PCR.

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Circulating B Cells Subpopulations in Patients with Antiphospholip Syndrome. Lorena Alvarez-Rodriguez[1], Marcos Lopez-Hoyos[1], Jaime Calvo-Alen[2], Rafael Barrio del[1], Orlando Pompei[1] and Victor M. Martinez-Taboada[3]. [1]Hospital Universitario Marques de Valdecilla. IFIMAV, Santander, Spain, [2]Hospital Sierrallana, Torrelavega, Spain, [3]Hospital Universitario Marques de Valdecilla-IFIMAV, Santander, Spain

Background/Purpose: Antiphospholipid syndrome (APS) is characterized by arterial and/or venous thrombosis and obstetrical complications together with the production of antiphospholipid autoantibodies. Its pathogenesis remains to be elucidated, but the production of autoantibodies suggests that B cells may have some role in APS. Our aim was to describe the peripheral blood frequency of B cells at different stages of maturation in APS.

Methods: Frequencies of B cells in peripheral blood of 25 APS patients and 11 SLE (without APS) were determined by flow cytometry. As controls, 12 age- and sex-matched healthy subjects (HC) were used. B cell subsets were identified with a combination of monoclonal antibodies (anti-CD5, -CD10, -CD19, -CD24, -CD27, -CD38, -CD138, -IgM and IgD) conjugated to different fluorochromes. Such a panel allowed us to identify the following B cell subsets: immature, naïve, double negative (DN), non-switched memory, switched memory and plasma cells.

Results: A significant decrease of circulating immature ($p=0.006$) and naïve ($p=0.003$) cells in APS than in SLE patients was observed. However, non-switched ($p=0.001$) and switched memory ($p=0.038$) B cells from peripheral blood of APS patients were increased as compared with SLE. No differences in circulating DN and plasma cells were observed between both disorders. In addition, naïve B cells were higher in SLE patients than in HC whereas non-switched memory B cells were lower in SLE patients than in HC. No significant differences were found in B cells between HC and APS patients.

Conclusion: Circulating B cells at a more differentiated stage were higher in APS than in SLE, whereas immature B cells were higher in SLE than in APS. These data point for a higher ability of B cells from SLE to

mature in the periphery and to broad the spectrum of autoantigens they are reactive against. However, our data are only from the peripheral blood compartment and lack confirmation in bone marrow and germinal centres.

The present work was supported by grants from Roche (Spain) and IFIMAV.

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Circulating Cytokine Profile in Patients with Antiphospholipid Syndrome. Lorena Alvarez-Rodriguez[1], Marcos Lopez-Hoyos[1], Jaime Calvo-Alen[2], Rafael Barrio del[1], Orlando Pompei[1] and Victor M. Martinez-Taboada[3]. [1]Hospital Universitario Marques de Valdecilla. IFIMAV, Santander, Spain, [2]Hospital Sierrallana, Torrelavega, Spain, [3]Hospital Universitario Marques de Valdecilla-IFIMAV, Santander, Spain

Background/Purpose: Antiphospholipid syndrome (APS) is characterized by the combination of clinical manifestations (arterial and/or venous thrombosis, and obstetrical complications) and the presence of antiphospholipid antibodies. The role of cellular immunity in the pathogenesis of this syndrome remains unclear, although a shift to a Th1 response, and an increased production of TNFa has been described. The aim of the present study was to determine the peripheral blood cellular phenotype and the circulating cytokine profile in patients with APS.

Methods: Intracellular cytokine production was assessed in T cells (IFN-γ, IL-2, IL-4, IL-10, IL-17) and CD14+ cells (IL-1β, TNF-α, IL-6) by flow cytometry in 27 patients with APS. As control groups we included 17 age- and sex-matched healthy controls (HC) and 11 patients with systemic lupus erythematosus (SLE). Patients with SLE had to be with SLEDAI≤4 (only treatment with antimalarials and/or low-dose corticosteroids were allowed). Circulating cytokines were measured by Cytometric Bead Array (CBA) in 13 patients with APS and 26 HC.

Results: Compared to HC, APS patients were characterized by a decreased frequency of circulating CD3+IFNγ+ *ex vivo* (without stimulus). This decrease in circulating Th1 cells was accompanied by a significant decrease in serum IL-12p70. Although we did not find significant differences in the expression of intracellular proinflammatory cytokines between APS and HC, serum levels of IL-6 were significantly lower in APS patients. Compared to HC, SLE patients were characterized by a decreased frequency of circulating CD3+IL-2+ and CD3+IFNγ+ *ex vivo* (without stimulus). For circulating CD3+IL-2+, these differences were also significant compared to APS. Patients with SLE were characterized by a significant increased frequency of circulating Th17 (CD4+IL17+CCR6+ and CD4+IL17+IFNγ-) cells compared to HC and APS. Circulating CD4+IL17+IFNγ+ cells were also significantly higher in SLE compared to APS patients.

Conclusion: These preliminary results suggest that patients with APS show a distinct functional profile in the peripheral cell compartment. Despite clinical remission or low disease activity, circulating Th17 cells are increased in SLE patients but not APS patients.

The present work was supported by grants from Roche (Spain) and IFIMAV.

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A Systematic Analysis Confirms the Importance of Toll-Like Receptor 4, p38 Mitogen Activated Protein Kinase and Nuclear Factor Kappa-B Activation by Antiphospholipid Antibodies in Multiple Different Cell Types. Katie Poulton, Anisur Rahman and Ian Giles. University College London, London, United Kingdom

Background/Purpose: Diverse experimental evidence exists implicating the activation of various different cell surface receptors and intracellular pathways by antiphospholipid antibodies (aPL). This evidence has been generated using a number of different cell types with varying numbers of aPL from different sources and disease sub-types. This experimental variability has led to uncertainty in their interpretation. Therefore we have undertaken a systematic analysis of this evidence implicating aPL mediated activation of intracellular signalling pathways to interpret their relevance to the pathogenesis of the antiphospholipid syndrome (APS).

Methods: A PubMed search was undertaken from 1966 up until May 2011 using combinations of key signalling pathway words. Each publication was systematically examined to note the following points; antibody type and patient population, outcome measures and use of receptor/signalling pathway inhibitors, and cell type and origin.

Results: We identified 24 original studies implicating the importance of aPL in activation of intracellular signalling pathways. The most convincing evidence from 21 *in vitro* and 3 *in vivo* studies in endothelial cells, monocytes, trophoblasts, platelets, and fibroblasts implicates toll like receptor 4 (TLR4), p38 mitogen activated protein kinases (p38 MAPK) and nuclear factor kappa B (NFkB) in mediating pathogenic intracellular effects of aPL. These consistent responses were confirmed in both thrombotic and obstetric relevant cell types using human monoclonal and polyclonal antibodies and measured by various different outcome measures.

Conclusion: The main finding of our systematic analysis is the striking degree of similarity between the conclusions of studies carried out by many different groups using different methods and cell types. A greater understanding of how aPL activate these intracellular pathways will potentially lead to the development of targeted agents to block these pathways, thus reducing our reliance on anticoagulation as the only current treatment of APS.

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Anti-Phosphatidylserine/Prothrombin Antibody Titers Are Strongly Correlated with Lupus Anticoagulant Assays in Patients with Antiphospholipid Antibodies. Makoto Miyara[1], Laurent Arnaud[1], Laurent Dufat[1], Marie-Claude Diemert[1], Annick Ankri[1], Alexis Mathian[1], Julien Haroche[1], Du Boutin[1], Pascale Ghillani-Dalbin[1], Nathalie Costedoat-Chalumeau[1], Silvia Casas[2], Jean-Charles Piette[1], Lucile Musset[1] and Zahir Amoura[1]. [1]CHU Pitié-Salpêtrière, Paris, France, [2]Instrumentation Laboratory Werfen Group, Lexington, MA

Background/Purpose: Biological criteria for the antiphospholipid syndrome (APS) diagnosis are the detection of either anticardiolipin antibodies (aCL), antib2GPI antibodies (ab2GPI) or lupus anticoagulant (LA). LA is strongly associated with thrombotic events in APS. Detection of LA is complex as it requires several confirmatory steps, which may lead to delayed results. Anti-phosphatidylserine/prothrombin antibodies (aPS/PT) have been recently associated with the presence of LA. However, it is still unclear whether aPS/PT titers correlate with LA assays.

Methods: 504 sera from 101 patients with either definite APS syndrome (n=82) or stable antiphospholipid antibodies (APL, either aCL, ab2GPI or LA; ACL levels >80 UGPL) without clinical APS manifestations (n=19) primarily collected for aCL, b2gPI and/or LA detection, were tested on a aPS/PT (IgG+IgM) ELISA and on individual isotype aPS/PT IgG and aPS/PT IgM ELISA assays (INOVA Diagnostics, San Diego, CA). Correlations between titers of aPS/PT and those of aCL, ab2GPI, with Rosner index, dilute tissue thromboplastin inhibition ratio (dTTI) and dilute Russell's viper venom time ratio (dRVVT) were assessed using Spearman's non-parametric test. According to manufacturer instructions, aPS/PT titers were considered positive when >30 U/mL.

Results: aPS/PT were present in 12 of the 19 patients (63 %) with APL without thrombotic or obstetric events (4 with IgG isotype, 4 with IgM isotype and 4 with both) and in 69 of the 82 patients (84 %) with definite APS (19 with IgG, 11 with IgM and 39 with both isotypes).

Among the 81 patients with positive LA, 74 had aPS/PT (91 %) while 7 did not (9 %). Among the 20 patients without LA, 16 did not have aPS/PT (80 %) while 4 did (20 %). Presence of aPS/PT was significantly associated to the presence of LA ($p<0.0001$ using a chi-square test). 10 of 19 patients without APS had LA among whom 9 had aPS/PT (90%). Among the 9 other patients without LA, 3 had aPS/PT (33%). In the 82 patients with APS, 68 patients had LA, among whom 65 had aPS/PT (96%). Among the 14 other patients without LA, 4 had aPS/PT (28%).

aPS/PT titers strongly correlated with Rosner index ($r=0.72$, $p<0.0001$), dTTI ($r=0.801$, $p<0.0001$) and dRVVT ($r=0.67$, $p<0.0001$). The ROC Curve yielded an excellent sensitivity of 84%, specificity of 98%, and area under the ROC Curve of 0.92 for detecting the presence of LA using an aPS/PT cut-off titer of 53 U/mL.

Conclusion: We confirmed that the presence of aPS/PT antibodies (either IgG isotype, IgM isotype or both) is strongly correlated with the presence of LA. Furthermore, titers of aPS/PT were strongly correlated with Rosner index, dTTI and dRVVT. Our data suggest that aPS/PT (IgG+IgM) ELISA assay could be a good alternative test for the detection of LA.

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Presence of Anti-Phosphatidylserine/Prothrombin Antibodies with Both IgG and IgM Isotypes May Be Associated with the Occurrence of Catastrophic Antiphospholipid Syndrome in Patients with Antiphospholipid Antibodies. Makoto Miyara[1], Laurent Arnaud[1], Laurent Dufat[1], Marie-Claude Diemert[1], Annick Ankri[1], Alexis Mathian[1], Julien Haroche[1], Du Boutin[1], Pascale Ghillani-Dalbin[1], Nathalie Costedoat-Chalumeau[1], Silvia Casas[2], Jean-Charles Piette[1], Lucile Musset[1] and Zahir Amoura[1]. [1]CHU Pitié-Salpêtrière, Paris, France, [2]Instrumentation Laboratory Werfen Group, Lexington, MA

Background/Purpose: Catastrophic antiphospholipid syndrome (cAPS) is a life threatening condition with simultaneous thrombosis in multiple organs that can occur in patients with antiphospholipid antibodies (APL). Predictive biological parameters for cAPS have not been defined yet. Anti-phosphatidylserine/prothrombin antibodies (aPS/PT) of either IgG or IgM isotypes or both have been recently associated with the presence of LA. It has not been determined whether aPS/PT isotypes are correlated to clinical features of antiphospholipid syndrome (APS).

Methods: 157 sera from patients with cAPS (n=29), 58 sera from patients with APS (n=29) and 31 sera from patients with stable antiphospholipid antibodies (APS, either aCL, ab2GPI or LA; ACL levels between 25 and 75 UGPL) without clinical APS manifestations (noAPS; n=19), primarily collected for aCL, b2gPI and/or LA detection, were tested on individual isotype aPS/PT IgG and aPS/PT IgM ELISA assays (INOVA Diagnostics, San Diego, CA). According to manufacturer instructions, aPS/PT titers were considered positive when >30 U/mL.

Results: In noAPS group, 8 patients had aPS/PT IgM (42%) while other patients did not have aPS/PT of IgG or IgM isotype (n=11, 58%). In patients with APS, 3 patients had aPS/PT IgG (10.3%), 6 had aPS/PT IgM (20.7%) and 3 patients had aPS/PT with both isotypes (10.3%) while 17 had no aPS/PT (58.6%). In cAPS group, 4 patients had no aPS/PT (13.8%), 4 patients had aPS/PT IgG (13.8%), 5 had IgM (17.2%) and 15 aPS/PT with both IgG and IgM (51.7%). Proportion of patients with aPS/PT with both isotype was significantly higher in patients with cAPS than in patients with APS without cAPS and patients with stable APL without clinical APS manifestations ($p=0.0014$ and $p<0.0001$ respectively using Fisher's exact test). No difference was observed in the proportion of isolated aPS/PT IgG or IgM between cAPS and APS patients or patients with patients with stable APL without clinical APS manifestations. The 3 patients with APS with aPS/PT with both isotypes developed adrenal insufficiency, cerebral venous thrombosis and Budd-Chiari syndrome.

Conclusion: Our data indicate that presence of aPS/PT of both IgG and IgM isotypes may be associated with severe features of APS, especially cAPS.

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High Antiphospholipid Antibody Levels May Reflect Chronic Endothelial Damage in Non-Autoimmune-Associated Thrombosis. Anna R. Broder[1], Jonathan N. Tobin[2], Jacob H. Rand[3] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Albert Einstein College of Medicine/CDN Network, New York, NY, [3]Montefiore Medical Center, Bronx, NY

Background/Purpose: Persistently elevated antiphospholipid antibodies (aPL Ab) are associated with an increased risk of thrombosis, but factors that may affect aPL Ab levels are poorly understood. While statins have been shown to potentially decrease the risk of aPL Ab - associated thrombosis, the effect of statins on aPL Ab levels has not been studied. It is also not known if aPL Abs represent additional risk for thrombosis in people without autoimmune diseases, or if they reflect previous endothelial damage caused by traditional cardiovascular risk factors: high low-density lipoprotein (LDL), low high-density lipoprotein, hypertension, type 2 diabetes (T2DM), obesity, and smoking (Figure 1). We explored whether elevated aPL Abs were associated both with statin use and with the traditional risk factors in patients without autoimmune diseases hospitalized with a deep vein thrombosis (DVT), pulmonary embolism (PE), or stroke (CVA).

Methods: We included patients hospitalized in a large tertiary care center with a confirmed diagnosis of DVT, PE or CVA, who had lupus anticoagulant (LAC) and aPL Abs measured within 6 months from their index admission.

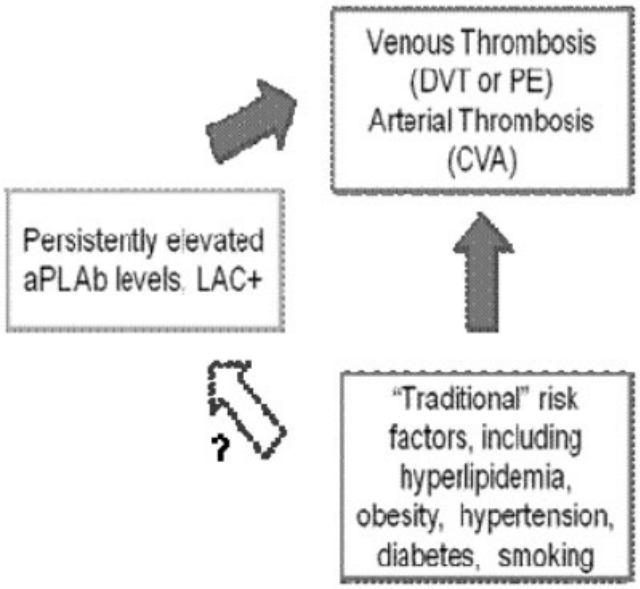

Figure 1. The proposed relationship between thrombosis, aPL Abs/Lac, and traditional cardiovascular risk factors

Results: Among 175 patients included, statin use at the time of aPL Ab measurement was associated with an OR of 7.1 (95% CI 1.1, 43.9, $p = 0.035$) of at least one aPL Ab $\geq$ 40 units, compared with no statin use in a multivariate model adjusted for age, race, gender, history of T2DM, hypertension, smoking and LDL. Furthermore, patients who had LDL < 130 mg/dl and were on statins were 14.5 times more likely to have at least one aPL Ab $\geq$ 40 units, (95% CI 1.1, 186.6, $p = 0.04$), compared with people with LDL < 130 mg/dl and not on statins, adjusted for age, gender, race, history of smoking and history of T2DM. LAC+ was not associated with stain use. None of the traditional risk factors at the time of DVT/PE/CVA was associated with aPL Ab levels $\geq$ 40/LAC+.

Conclusion: In patients without autoimmune diseases, we did not find an association between high aPL Ab levels and any of the traditional risk factors at the time of the thrombotic event. Thus, high aPL Ab levels did not confound the relationship between thrombosis and the traditional risk factors. Statins are associated with elevated aPL Ab levels. Alternatively, if statin therapy reflects the history of prior hyperlipidemia, high levels of aPL Abs may be a marker for prior endothelial damage caused by hyperlipidemia before statin therapy was initiated.

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The Role of Fatty Acid Composition in Antiphospholipid Syndrome and Systemic Lupus Erythematosus. Amaris K. Balitsky[1], Ellie Aghdassi[2], David WL. Ma[3], Stacey Morrison[4], Jiandong Su[4] and Paul R. Fortin[4]. [1]The University of Toronto, Toronto, ON, [2]University Health Network, Toronto, ON, [3]University of Guelph, Guelph, ON, [4]Toronto Western Hospital, Toronto, ON

Background/Purpose: Despite similar traditional Framingham risk scores, systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) patients present with greater thrombovascular disease compared to the general population. APS can occur alone, as primary APS (PAPS), or be associated with SLE, referred to as secondary APS (SAPS). Dietary fat composition and metabolism play an important role in inflammatory reactions. For example, omega-3 polyunsaturated fatty acids (ω-3 PUFA), including alpha-linoleic acid (ALA) and its metabolites, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to have anti-inflammatory and cardioprotective effects. On the other hand, arachidonic acid (AA, ω-6 PUFA), derived from linoleic acid (LA), leads to formation of inflammatory mediators. The purpose of this study was to determine and compare an association between the red blood cell (RBC) FA profile and: the presence of APS, TE and aPL.

Methods: Fifty-nine individuals were selected from the lupus and antiphospholipid outpatient specialty clinics and divided into 4 groups: 1) primary APS (PAPS, n=15) as defined by the revised Sydney criteria, 2) SAPS (n=14), 3) SLE with a previous TE (n=15), and 4) SLE without previous history of TE and no aPL (n=15). All SLE patients met at least four

of the American College of Rheumatology (ACR) classification criteria. Demographics, Framingham risk score and RBC profile including phospholipids, phosphatidylcholine (PC) and phosphatidylethanolamine (PE), and their respective FA compositions were reported. RBC FA compositions were determined using thin-layer and gas chromatography.

Results: The mean (±SD) age (years) of the 4 groups were similar (PAPS: 51.7 ± 16.8; SAPS: 53.0 ± 11.7; SLE+TE: 52.1 ± 10.5; SLE-TE: 53.5 ± 10.3, $p > 0.05$). Framingham risk scores were also similar across the four groups. The PAPS group had less arterial events (40.0%) compared to SAPS (71.4%) and SLE+TE (80.0%). RBC-PC and PE values were similar across PAPS, SAPS, SLE+TE, and SLE-TE. The PAPS group, compared to the three SLE groups, had a higher RBC-PE ALA:DHA+EPA ratio (PAPS: 0.06 ± 0.02; SLE: 0.04 ± 0.02, $p < 0.05$), indicating less efficient conversion of ALA to its anti-inflammatory metabolites, EPA and DHA. In patients with the history of TE, RBC-PE ω-6 PUFA (inflammatory) was higher than the levels of total ω-3 PUFA (anti-inflammatory) (TE: 36.40 ± 3.92; no TE: 34.98 ± 2.26, $p = 0.09$). The presence of aPL tended to be associated with a lower RBC-PC LA:AA ratio, indicating more efficient conversion of LA to its pro-inflammatory metabolite (aPL: 2.40 ± 0.65; no aPL: 2.79 ± 0.97, $p = 0.08$). Those taking ω-3 PUFA supplements had higher levels of RBC-PC EPA+DHA (ω-3: 4.1 ± 1.7 vs. no ω-3: 3.0 ± 1.1; $p = 0.08$).

Conclusion: In patients with APS and SLE, FA composition is in favour of an inflammatory process. Presence of TE, aPL and PAPS were associated with a less favourable FA composition, while those individuals who took ω-3 supplements were associated with a more favourable FA composition.

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Profiling Sub-Types of Anti-β2 Glycoprotein I and Anti-Domain I Antibodies May Distinguish Between Different Clinical Phenotypes of the Antiphospholipid Syndrome. Charis Pericleous[1], Acely Garza-Garcia[2], Lucy Murfitt[2], Paul C. Driscoll[2], David A. Isenberg[1], Silvia S. Pierangeli[3], Ian Giles[1], Yiannis Ioannou[1] and Anisur Rahman[1]. [1]University College London, London, United Kingdom, [2]MRC National Institute of Medical Research, London, London, United Kingdom, [3]University of Texas Medical Branch, Galveston, TX

Background/Purpose: Laboratory classification criteria for the antiphospholipid syndrome (APS) include the quantification of IgG and IgM, but not IgA anticardiolipin (aCL) and anti-β2 glycoprotein I (aβ2GPI) antiphospholipid antibodies (aPL), though recent studies suggest a possible role for IgA. These assays do not reliably differentiate patients with a history of vascular thrombosis (VT) from those with pregnancy morbidity (PM). Of the five domains of β2GPI, pathogenic IgG aPL are considered to target Domain I (DI). We have developed a direct anti-DI ELISA using bacterially expressed DI. Here we investigate whether IgG, IgM and IgA anti-DI levels correlate with IgG, IgM and IgA anti-β2GPI and which of these tests correlate best with clinical phenotypes.

Methods: We used 9 different ELISAs (IgG/IgM/IgA for each of aCL, aβ2GPI and aDI) to test 158 serum samples - 46 from patients with APS (F:M 41:5, mean age 46.4±12.1); 77 with SLE but not APS (F:M 72:5, mean age 38.8±11.3); and 35 healthy controls (HC) (F:M 23:12, mean age 30.8±7.4). Of 46 APS subjects, 21 suffered VT only, 12 PM only, and 13 both. IgG/IgM aCL activity was defined as GPLU/MPLU respectively. For all remaining assays, results were expressed in units of activity by reference to an in-house standard. Univariate analysis was performed using one-way ANOVA to determine which assay(s) best differentiate APS from SLE and HC, and whether any were associated with the VT or PM phenotypes within APS.

Results: 7 of 9 assays gave significantly higher antibody titers in APS compared to SLE and HC ($p<0.0001$ in each case). The exceptions were IgM aCL (high in both APS and SLE) and IgA aDI (few positive samples). For 3 of these 7 assays, titers were raised in SLE compared to HC, thus only 4 assays (IgG/IgM/IgA aβ2GPI and IgG aDI) selectively recognized APS-derived sera. In the APS group, there was a strong correlation between aβ2GPI and aDI for IgG ($p=0.003$, $r=0.5858$) and IgA ($p<0.0001$, $r=0.8603$) but not IgM. In contrast, there were no correlations between aβ2GPI and aDI in the SLE group. Although none of the aβ2GPI assays nor IgG aDI could discriminate between patients with VT compared to PM, IgM aDI was found to be associated with PM ($p<0.0001$) and IgA aDI with VT ($p\leq0.01$).

Conclusion: To our knowledge, this is the first study to measure IgG/IgM/IgA aPL against CL, β2GPI and DI simultaneously. aβ2GPI of all isotypes and IgG aDI were found to be most specific for APS. The correlation between aβ2GPI and aDI in APS, but not non-APS subjects supports the idea that pathogenic aβ2GPI bind specifically to DI. The finding that IgA and IgM aDI show specific associations with VT and PM respectively is interesting but needs to be repeated in larger studies.

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Prevalence of Antibodies to Prothrombin in Solid Phase (aPT) and to Phosphatidylserine/Prothrombin Complex (aPS/PT) in Patients with and without Lupus Anticoagulant (LA). Maria Laura Bertolaccini[1], Savino Sciascia[1], Veronica Murru[1], Giovanni Sanna[2] and Munther A. Khamashta[1]. [1]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [2]Louise Coote Lupus Unit, St. Thomas' Hospital, London, United Kingdom

Background/Purpose: Although aPS/PT has been reported to strongly correlate with the LA, both aPT and aPS/PT have been found in patients with LA. As their clinical diagnostic value and true relationship with the LA remains elusive, we designed this study to evaluate the prevalence and significance of aPT and aPS/PT in a large cohort of patients with and without LA.

Methods: Samples from 263 patients were included. aPT (in-house assay) and aPS/PT (INOVA Diagnostics) were tested by ELISA. LA was tested as per the current criteria from the ISTH Subcommittee on LA-Phospholipid-dependent antibodies.

Results:

	aPS/PT IgG/IgM	aPS/PT IgG	aPS/PT IgM	aPT IgG/IgM	aPT IgG	aPT IgM
LA+ve n/76 (%)	38 (50)	30 (39)	26 (34)	24 (32)	21 (28)	4 (5)
LA-ve samples n/187 (%)	43 (23)	38 (20)	17 (9)	54 (29)	46 (25)	11 (6)

Thrombosis, particularly venous thrombosis was associated with IgG aPT in the LA+ve group (OR7.1 [95% CI 2.2–22.7], $p=0.0006$). aPT was not associated with thrombosis in the LA-ve group. aPS/PT, either IgG/IgM, IgG and IgM were associated with thrombosis in general in the LA+group ($p=0.003$, $p<0.0001$ and $p=0.025$; respectively). After further analysis, this association was only retained for IgG aPS/PT and venous thrombosis (OR8.7 [95%CI 3.0–25.1], $p<0.0001$). In the LA-ve group, aPS/PT was associated with thrombosis ($p=0.026$), particularly, the IgM isotype (OR5.6 [95%CI 1.8–16.7], $p=0.0002$). Titers of IgG aPS/PT were not different between LA+ve and LA-ve (13U±29 vs. 7.5±22, $p=0.9$). Titers of IgM aPS/PT were higher in LA+ve than LA-ve (20.3±30 vs. 6.9±16, $p<0.0001$).

Conclusion: aPS/PT, but not aPT, are more frequently found in patients with LA. Although IgG aPS/PT does not seem to correlate with the LA, the correlation with the IgM isotype deserves further study.

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Antibodies to Phosphatidylserine/Prothrombin (aPS/PT) Are An Independent Risk Factor for Thrombosis in Patients with Systemic Lupus Erythematosus (SLE). Maria Laura Bertolaccini[1], Savino Sciascia[1], Veronica Murru[1], Cesar Garcia-Fernandez[1], Giovanni Sanna[2] and Munther A. Khamashta[1]. [1]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [2]Louise Coote Lupus Unit, St. Thomas' Hospital, London, United Kingdom

Background/Purpose: aPS/PT have been reported to be closely associated with the presence of lupus anticoagulant (LA) in patients with antiphospholipid syndrome. Moreover, aPS/PT has been shown to have a similar diagnostic value to aCL in such patients. We designed this study in an attempt to clarify the role of aPS/PT as risk factors for thrombosis in patients with SLE.

Methods: IgG and IgM aCL, anti-b2GPI, aPT and aPS/PT were tested by ELISA. LA was tested following current criteria from the ISTH. All patients fulfilled at least 4 of the 1982 ACR criteria for SLE. APS patients fulfilled the 1999 Sapporo criteria.

Results: 226 SLE patients (214 female, mean age 42.6±12) were included. Of these, 57 had APS and 82 had a history of thrombosis (35 arterial, 28 venous and 19 both). Miscarriages were recorded in 39 women and fetal death in 36. Univariate analysis showed that aPS/PT were more frequently found in patients with thrombosis than in those without (OR7.0 [95%CI 3.7–13.2], $p=0.025$). IgG and IgM aPS/PT were more frequently found in patients with arterial and venous thrombosis than

in those without ($p<0.001$ for IgG, $p=0.001$ for IgM in arterial and $p<0.001$ for both IgG and IgM in venous thrombosis). aPS/PT were associated with pregnancy morbidity ($p<0.001$ for IgG and IgM), particularly with fetal death ($p<0.001$ for both isotypes) and miscarriages ($p<0.001$ for IgG only; IgM=ns).

Multivariate analysis (including aCL, LA, aPT and anti-b2GPI) confirmed that aPS/PT is an independent risk factor for thrombosis, particularly the IgG isotype that was independently associated with arterial and venous thrombosis ($p=0.002$ and $p=0.003$) and miscarriages ($p=0.03$). IgM aPS/PT was also found to be an independent risk factor for miscarriages ($p<0.001$).

Conclusion: aPS/PT is an independent risk factor for arterial and venous thrombosis and miscarriages in patients with SLE. IgM aPS/PT are also an independent risk factor for miscarriages. Testing for aPS/PT may be warranted in SLE patients.

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The Value of Testing for Antibodies to Phosphatidylethanolamine (aPE) in Patients with Systemic Lupus Erythematosus (SLE). Maria Laura Bertolaccini[1], Veronica Murru[1], Savino Sciascia[1], Giovanni Sanna[2] and Munther A. Khamashta[1]. [1]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [2]Louise Coote Lupus Unit, St. Thomas' Hospital, London, United Kingdom

Background/Purpose: aPE have been reported to be an independent risk factor for idiopathic venous thrombosis and fetal death. However, these findings are the focus of constant debate. The purpose of the present study was to evaluate if testing for aPE has a diagnostic value in patients with SLE.

Methods: This study included 226 patients, all fulfilling the 1982 ACR criteria for SLE. Of these, 214 were women, with a mean age of 42.6 ± 12 and mean disease duration of 12.2 ± 8.8 years. 25% of the patients also fulfilled the 1999 criteria for the antiphospholipid syndrome. aCL, anti-b2GPI, aPT and aPS/PT were tested by in house ELISA. LA was tested according to the ISTH recommendations. aPE were also tested by an in-house ELISA using fetal calf serum. IgG and IgM aPE values were calculated from a sample showing a high binding used as a standard. The cut off value was established on 8U for IgG and 9U for IgM, by the 99th percentile of 140 healthy controls.

Results: aPE were found in 92 patients (41%). Of them, 68 were positive for IgG, 13 for IgM and 11 for both. aPE were more frequently found in patients with thrombosis, particularly the IgG isotype (OR2.0 [95%CI 1.1–3.5], $p=0.01$). When subdividing between venous and arterial thrombosis, only the association with venous thrombosis was retained (OR2.2 [95%CI 1.2–4.6], $p=0.009$). No associations were found between the presence of aPE and pregnancy morbidity in this cohort. The presence of aPE was highly correlated with that of aCL ($R^2=0.61$, $p=0.008$). There were no aPE in the absence of aCL. After multivariate analysis, including all other aPL as variables, clinical associations failed to retain significance.

Conclusion: aPE are frequently seen in SLE. aPE are not an independent risk factor for thrombosis or pregnancy morbidity and their presence is highly associated to that of aCL.

ACR Poster Session A
Cell-cell Interactions and Adhesion
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Steroid Receptor Coactivator-3 and Angiogenesis in Autoimmune Disease Associated Leg Ulcers. Victoria K. Shanmugam[1], Elena Tassi[2], Maram Al-Otaiby[2], Bhaskar Kallakury[1], Mihriye Mete[3], Christopher Attinger[4] and Anton Wellstein[2]. [1]Georgetown University Hospital, Washington, DC, [2]Georgetown University, [3]MedStar Health Research Institute, Hyattsville, MD, [4]Georgetown Universtiy Hosptial, Washington, DC

Background/Purpose: Delayed wound healing is a complication of several autoimmune diseases including scleroderma, rheumatoid arthritis and systemic lupus erythematosus (SLE). While the mechanisms of delayed healing in these patients are not known, we hypothesize that dysregulation of angiogenesis may play a role. Angiogenesis is critical in wound healing. Patients receiving bevacizumab and other vascular endothelial growth factor (VEGF) inhibitors exhibit impaired wound healing, and animal studies of angiogenesis in malignancy support this association.

The purpose of this study was to use immunohistochemistry (IHC) of formalin fixed paraffin embedded (FFPE) biopsy specimens from leg ulcers associated with autoimmune disease, diabetes and bevacizumab use to investigate the distribution of critical angiogenic markers. Steroid receptor coactivator-3 (SRC-3; also named Amplified in Breast Cancer-1) is a p160 steroid receptor coactivator that enhances NF-κB-mediated signaling in inflammatory disease, and modulates angiogenesis in malignancy. Fibroblast growth factor binding protein-1 (FGF-BP1) is another important molecule that is upregulated in wound healing, and acts as an angiogenic switch in malignancy.

Methods: FFPE samples were selected from the following groups: Diabetes Mellitus (n=3), Mixed Connective Tissue Disease (n=4), Systemic Lupus Erythematosus (n=5), Scleroderma (n=5) and bevacizumab use (n=2). The following stains were performed using standard IHC protocol: hematoxylin and eosin (H&E), steroid receptor coactivator-3 (SRC-3), fibroblast growth factor binding protein-1 (FGF-BP1), CD45, CD4, CD8, CD68 and CD34.

Blinded quantitative analysis at $\times200$ magnification using Image-J was used to quantify staining. Representative regions across each specimen were selected moving from intact to ulcerated tissue. Data was analyzed using Stata/IC 11.2 for Windows using linear regression and analysis of variance models to compare cell counts and ratio of blood vessel size between disease groups and across sampling fields.

Results: Total CD34 staining as a measure of blood vessel density was similar across the disease groups. However, the ratio of large to small vessels was significantly lower for autoimmune ulcers and VEGF inhibitor-associated wounds compared to the diabetics ($p=.005$). Pairwise comparisons with Bonferroni adjustment showed that the mean ratio of large to small vessels was significantly greater for diabetics compared to the other group means.

Regression analysis estimating the differences in staining pattern adjusting for location of the sampling field found that steroid receptor coactivator-3 was significantly higher in the SLE group compared to other diseases ($p< 0.001$). We did not find associations with FGF-BP1.

Conclusion: In autoimmune wounds, the ratio of large to small blood vessels was significantly reduced suggesting dysregulation of blood vessel structure or maturation. SRC-3 was significantly higher in SLE-associated ulcers. This study provides preliminary data to support the hypothesis that dysregulation of anigiogenesis and in particular SRC-3 may play a critical role in wound healing in autoimmune disease.

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Differential Regulatory Functions of HIF-1α and HIF-2α During Angiogenesis of Human Microvascular Endothelial Cells (HMECs). Martin Hahne[1], Steffi Luetkecosmann[2], Cam Loan Tran[2], Cindy Strehl[2], Monique Fangradt[2], Manuela Jakstadt[2], Georg Duda[2], Paula Hoff[2], Timo Gaber[2], Gerd-Rüdiger Burmester[3] and Frank Buttgereit[2]. [1]Berlin Brandenburg School for Regenerative Therapies, Berlin, Germany, [2]Charité University Medicine, Berlin, Germany, [3]Charité University Hospital, Berlin, Germany

Background/Purpose: Hypoxia and angiogenesis are features of inflamed and injured tissues. The transcription factors Hypoxia inducible factor (HIF)-1a and (HIF)-2a control cellular metabolic response to decreased oxygen tension thereby promoting angiogenesis and having implications on the pathogenesis of RA. We focused on the effects of HIF-1α and HIF-2α on angiogenesis and developed a human microvascular endothelial cells (HMEC) lentiviral based knockdown system for both transcription factors allowing us to analyze angiogenesis of HMECs under hypoxia in the absence of HIF-1a or HIF-2α, respectively.

Methods: Specific knockdown of HIF-1a or HIF-2α was achieved using lentiviral-based shRNA technology. The reduction of HIF-1a or HIF-2α was confirmed on transcriptional and translational level by realtime RT-PCR and Western blot. Angiogenesis of transduced and non-tronsduced HMECs was studied by investigating both tubuli and node formation under hypoxia (<1% O_2). Expression of hypoxia driven genes *HIF1A*, *HIF2A*, *VEGFA* and *IL8* was quantified by realtime RT-PCR. Multiplex suspension array technology was used to measure the concentrations of secreted VEGF and IL8.

Results: The successful knockdown of HIF-1α and HIF-2α was confirmed by demonstrating considerably reduced gene expression levels of *HIF1A* and *HIF2A* by up to 71% ($p=0.0222$) under normoxic and hypoxic conditions. As a consequence, strongly reduced HIF-1α and HIF-2α protein levels were detected by Western blot. Targeting of HIF-1α led to a significantly decreased node formation (1.6-fold change under hypoxia, $p=0.0067$) with similar effects by trend on tubuli formation. The HIF-2α knockdown also led to a significantly decreased tubuli formation (1.7-fold change, $p=0.0444$) with similar effects by trend on node formation. Furthermore, HIF-1α targeted cells did not show any significant decrease in the gene

expressions of *VEGFA* and *IL8* but surprisingly raised cytokine levels of IL8 under hypoxia (1.4-fold change, p=0.021) compared to the control. In contrast, targeting of HIF-2α gave rise to reduced levels of secreted VEGF and IL8 with a significant suppression of *IL8* gene expression under normoxia (2.1-fold change, p=0.0101).

Conclusion: Our findings show essential and overlapping functions of HIF-1α and HIF-2α with regard to their regulatory potential of angiogenesis in HMECs. Both transcription factors have the same impact on VEGF but differ in their effects on IL8 expression. These findings provide new insights into basic principles of angiogenesis in inflamed tissues and are therefore considered to be of clinical importance.

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Glucocorticoid-Induced Leucine Zipper Inhibits TNF-Induced Endothelial Cell NFκB Activation and Adhesive Function. Eric Morand, Michael Hickey and Qiang Cheng. Monash University, Melbourne, Australia

Background/Purpose: The protein glucocorticoid-induced leucine zipper (GILZ) was recently reported to be expressed in RA synovial tissue, and to exert anti-inflammatory effects in the CIA model of RA (Beaulieu et al, Arthritis Rheum 2010). Strong expression of GILZ was noted in RA synovial endothelial cells, but the function of GILZ in endothelium is unknown. Endothelial cell activation, which is required for leukocyte recruitment into inflamed tissue, is critically dependent upon NFkB and ERK MAP kinase pathways, both of which are reported intracellular targets of GILZ. We tested the hypothesis that GILZ has important regulatory effects on endothelial cell function.

Methods: Primary human umbilical vein endothelial cells (HUVEC) and a human microvascular endothelial cell line (HMEC) were stimulated with TNF. Adhesive function and adhesion molecule expression were examined using flow chamber and flow cytometry respectively.

Results: To determine the functional significance of GILZ in endothelium, we first examined whole blood leukocyte rolling and adhesion interactions with HUVEC. TNF-induced rolling and adhesion, and E-selectin and ICAM 1 expression, were inhibited by GILZ overexpression. No inhibition of HUVEC chemokine expression was observed, and of note, GILZ silencing did not abrogate glucocorticoid inhibition of TNF-induced rolling and adhesion on HUVEC. Overexpression of GILZ in HMEC inhibited TNF-induced NFkB luciferase activity equivalent to the effects of the specific NFkB inhibitor BAY-11–7082. Moreover, chemical NFkB inhibition did not further suppress NFkB activity in GILZ overexpressing cells, indicating that GILZ expression can maximally suppress this pathway. Unexpectedly, we were unable to demonstrate binding interactions of GILZ with NFkB p65, or inhibition of NFkB p65 nuclear translocation or ser-536 phosphorylation. In contrast, we observed that GILZ inhibited TNF-induced activation (phosphorylation) of p38, ERK, and JNK MAP kinases, associated with increased expression of the MAPK inhibitory phosphatase MKP1. TNF-induced NFkB activity was dependent on ERK, but not p38 or JNK, suggesting GILZ effects on NFkB may depend on ERK.

Conclusion: These data demonstrate that GILZ can exert inhibitory effects on endothelial cell function, adhesion molecule expression, NFkB and MAP kinase activation. GILZ inhibition of NFkB may depend on inhibition of ERK MAP kinase. Therapeutic modulation of GILZ may represent a means to modify inflammatory leukocyte recruitment.

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Superoxide Anion Mediates the L-Selectin Down-Regulation Induced by Non-Steroidal Anti-Inflammatory Drugs In Human Neutrophils. M. Jesus Dominguez-Luis[1], Ada Herrera-Garcia[2], M.Teresa Arce-Franco[3], Susana Cardenas[4], Marta Rodriguez-Pardo[5], Manuel Feria[5], Francisco Sanchez-Madrid[4] and Federico Diaz-Gonzalez[3]. [1]Hospital Universitario de Canarias, La Laguna, Spain, [2]Hospital Universitario de Canarias, La Laguna. Tenerife, Spain, [3]Rheumatology Service, La Laguna, Spain, [4]Hospital Universitario La Princesa, Madrid, Spain, [5]University of La Laguna, La Laguna. Tenerife, Spain

Background/Purpose: A group of non-steroidal anti-inflammatory drugs (NSAIDs) are able to induce in neutrophils the shedding of L-selectin, a surface molecule that plays a critical step in the migration of leukocytes to site of inflammation, through a mechanism still not well-understood. The aim of this work was to study both the functional effect of NSAIDs on the neutrophils/endothelial cells dynamic interaction, and the potential implication of reactive oxygen species (ROS) production in the L-selectin down-regulation caused by NSAIDs

Methods: Human neutrophils were isolated from peripheral blood of healthy volunteers and patients with chronic granulomatous disease (CDG) ($p47^{phox}-/-$), a group of hereditary diseases in which cells of the immune system have difficulty forming superoxide radical. The dynamic interaction between neutrophils and activated endothelium was studied in a flow chamber. Surface expression of L-selectin and CD11b were assayed by flow cytometry. Neutrophil-free supernatant L-selectin concentration was determined by ELISA. Intracellular and mitochondrial ROS production was detected by flow cytometry using dihidroethidium (DHE) and MitoSOX Red, respectively. Wilcoxon signed-rank test ($p<0.05$) was used to evaluate the statistical significance.

Results: When human neutrophils were incubated with diclofenac but not with piroxicam, a significant reduction in the number of cells that rolled on activated endothelial cells was observed. Dithiol reducing agents such as, DL-Dithiothreitol (DTT) and 2,3-dimercapto-1-propane-sulfonic acid (DMPS) abrogated the down-regulatory effects of diclofenac, flufenamic acid and meclofenamic acid on neutrophils L-selectin basal expression. Several NSAIDs (n=10) caused variable increases in the mitochondrial and intracellular ROS concentration in neutrophils that were inversely proportional to the change they produced in L-selectin surface expression ($r=-0.8$, $p< 0.01$). The inhibition of NADPH oxidase activity with diphenyleneiodonium (DPI) prevented the down-regulation of L-selectin by diclofenac. The pre-incubation of neutrophils with superoxide dismutase but not with catalase showed both a significant protective effect on the L-selectin down-regulation induced by several NSAIDs and prevented diclofenac's effect on neutrophil rolling ($p<0.05$). Interestingly, neutrophils from CGD patients showed a significant less ability to release L-selectin from neutrophil surface than control in response to diclofenac.

Conclusion: All these data indicate that: 1) a group of NSAIDs is capable of interfering with the ability of neutrophils to interact with endothelial cells by means of the L-selectin-shedding and 2) the generation of superoxide anion by activation of NADPH oxidase at plasma membrane level seems to play a major role in the L-selectin shedding induced by NSAID in neutrophils, suggesting that ROS generation may assume a potentially novel function as regulators of inflammatory response

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A Concerted Dynamic Real Time In Vivo and Static Ex Vivo Analysis of Granulomonocytic Cell Migration in the Collagen Induced Arthritis Model. Ruth Byrne[1], Eva Rath[1], Anastasiya Hladik[1], Birgit Niederreiter[1], Michael Bonelli[1], Sophie Frantal[1], Michael Klimas[1], Josef Smolen[2] and Clemens Scheinecker[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Granulomonocytic cells (GMC) drive the inflammatory process at the earliest stages of rheumatoid arthritis (RA). The migratory behavior and functional properties of GM cells within the synovial tissue are, however, only incompletely understood. This tempted us to study GMC in the murine collagen induced arthritis (CIA) model of RA with the help of multi-photon real time in vivo microscopy together with the subsequent and sequential ex vivo analysis of GMC on tissue sections.

Methods: CIA was induced in LysM-EGFP C57BL/6 transgenic animals that carry the EGFP fluorescence protein under the lysozyme promoter. Individual joints were prepared by surgical microscopy in healthy control and in CIA subjects and $EGFP^+$ GMC were analyzed by 2-photon laser microscopy over 2 hours. One group of animals received one single dose (0.25 mg) of prednisolone i.v. before in vivo imaging. Afterwards the animals were sacrificed and cryo-, and paraffin sections were prepared for immunofluorescence and histomorphological analysis, respectively.

Results: GMC were barely detectable in healthy animals but were abundant in the synovial tissue as soon as clinical arthritis was apparent. GMC were motile and migrated randomly through the synovial tissue with a reduced mean velocity (2.75 ± 1.17 mm/min) of as compared to healthy controls (3.11 ± 1.51 mm/min; $p<0.001$). In CIA subjects the frequent formation of dynamic cell clusters was observed that consisted of both $EGFP^{high}$ neutrophilic granulocytes and $EGFP^{low}$ monocytes. In addition $EGFPI^{ow}$ $F4/80^+$ $TRAP^+$ osteoclast precursor cells were occasionally observed at the synovial-bone junction and areas of bone erosions. Prednisolone treatment reduced the mean velocity of cell migration (2.19 ± 1.06 μm/min; $p<0.001$) and significantly diminished the immigration of GMC into the

synovial tissue, but did not affect GMC allocation within cell clusters or throughout the entire tissue.

Conclusion: The combined application of real time in vivo microscopy together with elaborate static post-mortem analysis of GMC enabled the description of dynamic migratory characteristics of GMC together with their precise allocation in a complex anatomical environment. Moreover this approach was found sensitive enough to detect subtle therapeutic effects within a very short period of time.

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miRNA-126 Regulates Increased VCAM-1 Expression in Muscle Biopsies From Children with Untreated Juvenile Dermatomyositis of Short Disease Duration. Lauren M. Pachman[1], Erin Kim[2], Joan Cook-Mills[1], Gabrielle Morgan[2], Janice Caliendo[1] and Simone Treiger Sredni[1]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Children's Memorial Hospital, Chicago, IL

Background/Purpose: Juvenile dermatomyositis (JDM) is an autoimmune systemic vasculopathy, targeting small blood vessels in both the skin and muscle, in which untreated disease chronicity is accompanied by progressive vascular damage, phenotypic and genotypic alterations. Vascular adhesion molecule, VCAM-1, present on a range of cells, including endothelial cells, aids in the recruitment of leukocytes from the blood to the tissue, and acts as a gatekeeper for the inflammatory process. MicroRNAs are non-coding RNAs that regulate several messenger RNAs simultaneously by mechanisms such as translational repression or cleavage of target messages, potentially offering a new avenue of therapeutic intervention.

Objective: To evaluate the impact of the duration of untreated disease (DUD), disease chronicity, in children with JDM on: 1) expression of VCAM-1 and miRNA in diagnostic muscle biopsies (MBx), and, 2) serum levels of soluble VCAM-1 (sVCAM-1) and TNF-α at the diagnosis of JDM, compared with age-matched controls.

Patients and Methods: After obtaining informed consent, healthy pediatric controls (n=8) and children with definite/probable JDM (n=28) were enrolled. For JDM, short DUD (n=11) was defined as ≤2 months untreated symptoms before diagnostic MBx (mean=1.3±0.4mo); long DUD (n=17) as >2 months (mean=17.1±25.5mo). MBx sections were stained using triple immunoflorescence with antibodies to VCAM-1, α-smooth muscle actin (SMA) and von Willebrand factor (vWF). Total area (microns^2) and total intensity (pixels) of VCAM-1 expression was measured. sVCAM-1 and TNF-α levels (ELISA) were tested in sera from JDM with long (n=8) vs short DUD (n=6). MicroRNA from 6 untreated JDM (3 long DUD, 3 short DUD) was evaluated using Exiqon's miRCURY LNA microRNA Array, v.11.0.

Results: MBx of JDM with short DUD displayed a significantly higher total area and intensity/hpf of VCAM-1 expression than those with long DUD and controls ($p<0.05$). In addition, JDM children with short DUD had sVCAM-1 levels that were significantly higher compared to controls ($p=0.013$). Similar patterns were found in TNF-α levels ($p=0.048$). MicroRNA miR-126, which regulates VCAM-1 expression, was significantly downregulated (FC= −1.92, p-value=0.014) in muscle of untreated JDM with a short DUD.

Conclusion: VCAM-1 protein expression in JDM MBx, regulated by miR-126, is more prominent in JDM with a short DUD (≤2 months) versus long DUD (>2 months), suggesting that VCAM-1 may play a critical role *early* in JDM pathophysiology in response to miRNA-126 control.

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Angiogenic Factors in Early Inflammatory Arthritis. Luana Mancarella[1], Olga Addimanda[1], Lia Pulsatelli[1], Paolo Dolzani[1], Elisa Assirelli[1], Veronica Brusi[1], Stefano Galletti[1] and Riccardo Meliconi[2]. [1]Istituto Ortopedico Rizzoli, Bologna, Italy, [2]Istituto Ortopedico Rizzoli and University of Bologna, Bologna, Italy

Background/Purpose: Angiogenesis is an important event in rheumatoid synovitis, with an increase in immature and destabilized vessels. Fibroblast growth factor-2 (FGF2) and vascular endothelial growth factor (VEGF) play a major role in angiogenesis. PTX3 (long pentraxin-3) is an acute phase glycoprotein produced by several cell types in response to primary inflammatory signals (e.g. Toll-like receptor, TNF, IL-1 but not IL-6). It interacts directly with FGF2 and inhibits its angiogenic activity (1). PTX3 systemic levels have been shown to be elevated in patients with some vascular and inflammatory disorders and seem to correlate with clinical outcome and disease activity (2). The aim of our study was to evaluate the serum concentrations of some angiogenic factors and other biomarkers in patients with early inflammatory arthritis (IA) and their possible relationship with disease activity and ultrasound (US) features.

Methods: We analyzed 37 patients with early inflammatory arthritis (IA) with at least one swollen joint and who had had symptoms for less than one year (except for 4 patients who had had symptoms for more than one year); we compared this group with 24 age- and sex-matched healthy controls (HC). VEGF, vascular cell adhesion molecule-1 (VCAM-1), FGF2, IL-6, and soluble IL-6 receptor and PTX3 levels in peripheral blood samples were determined by ELISA. Demographic (gender, age), clinical (disease duration, tender and swollen joints count, Health Assessment Questionnaire score, 100 mm visual analogue scales for pain and global health status), laboratory (erythrocyte sedimentation rate, C reactive protein, presence or absence of rheumatoid factor and anti-CCP antibodies) data were collected. US scans with 7.5–15 MHz linear array (to assess synovial thickness, power Doppler signal – PDS, and erosions) were carried out and a Disease Activity Score for 28 joints (DAS28) was calculated. Data were analysed using analysis of variance (ANOVA) or the Mann-Whitney U Test (to compare variables not normally distributed). Fisher's exact test was used to compare categorical variables. Pearson's correlation coefficient (*r*) (for linear relationship), otherwise Spearman's rank correlation (*rho*) to assess correlations. The level of significance was $p<0.05$.

Results: A mean age of 57.2 ± 14.5 yrs was found, a disease duration of 32.4 ± 47.7 weeks and a moderate disease activity (DAS28 of 4.8 ± 1.2). 97% of patients had PDS positivity on US examination and 22% had erosive features. VCAM-1 were higher ($p=0.002$), and PTX3 lower ($p<0.0005$) in patients compared to HCs. We found a statistically significant positive correlation between VEGF and IL-6 levels and DAS28 ($r=0.374$, $p=0.03$ and rho= 0.45, $p=0.02$, respectively). At 3rd month of follow up, basal FGF levels had a positive trend with DAS28 ($p=0.08$); patients who continued to show PDS positivity, tended to have higher basal levels of IL-6 and VCAM-1 compared to PDS negative patients ($p=0.06$ and $p=0.07$, respectively).

Conclusion: Our preliminary results show increased VCAM-1 and decreased PTX3 (an anti-angiogenic factor) levels in early IA. Angiogenic factors and IL-6 show a positive trend with disease activity and its persistence.

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Junctional Adhesion Molecule C Regulates the Transendothelial Migration of Murine Synovial Fibroblasts of Human TNFalpha Transgenic Mice. Marianne Heitzmann[1], Adelheid Korb-Pap[1], Christina Wunrau[1], George Kollias[2], Stefan Butz[3], Dietmar Vestweber[3], Hermann Pavenstädt[1] and Thomas Pap[1]. [1]University Hospital Muenster, Muenster, Germany, [2]Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece, [3]University Muenster, Muenster, Germany

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory joint disorder that starts in few single joints and continuously spreads to unaffected ones. Recently, it was demonstrated that RA fibroblast-like synoviocytes (FLS) have the potential to migrate via the bloodstream and invade distant cartilage in the SCID mouse model of disease. The mechanisms of endothelial transmigration of RA-FLS are unknown. In this context, the junctional adhesion molecule C (Jam-C), the third member of Jam family is an interesting candidate molecule because it has been found on RA-FLS and implicated in the transendothelial migration of leukocytes. Here, we used the human TNFalpha transgenic (hTNFtg) mouse as a model for human RA and studied the role of Jam-C in the transmigration of FLS derived from these mice.

Methods: The expression of Jam-C on wildtype and hTNFtg FLS was investigated by Western-blot analysis and immunocytochemistry. The transmigratory capacity of these cells was studied in a transmigration assay using the murine endothelioma cell (bEnd.5) as an endothelial barrier. Murine cartilage tissue treated with IL-1alpha was used as chemoattractant stimulus for the transmigration assays. Functional analyses included the knock down of Jam-C expression by siRNA against murine Jam-C.

Results: We identified the expression of Jam-C on the surface of both wildtype FLS and FLS from hTNFtg mice and found it most prominently on sites of cell-cell interactions. While expression levels of Jam-C were low in wildtype cells, FLS from hTNFtg mice showed a significantly higher expression. Transmigration experiments demonstrated a significantly higher potential of hTNFtg FLS to migrate through the endothelial monolayer than FLS from wildtype mice (+40%, p≤0,05), and cartilage explants pre-treated with IL-1alpha enhanced the migratory capacity of hTNFtg FLS. Interest-

ingly, siRNA-mediated knock down of Jam-C expression reduced the number of transmigrating hTNFtg FLS by 40%.

Conclusion: Our data demonstrate that the inflammatory environment as found in the joints of hTNFtg mice results in an upregulation of Jam-C on FLS in a similar way as described for human RA-FLS. Moreover, they indicate that this environment facilitates the development of a phenotype of FLS that is capable of transmigrating through endothelial barriers. Jam-C appears to be involved functionally in the transmigration and, thus, in extravasation of FLS and, therefore targeting Jam-C may be a promising therapeutic strategy for RA.

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Matrix Effects on Cellular Adhesion of Fibroblasts From Patients with Rheumatoid Arthritis, Osteoarthritis and Systemic Sclerosis. Stephanie Lefevre[1], Simone Benninghoff[1], Angela Lehr[2], Stefan Rehart[2], Henning Stürz[3], Jürgen Steinmeyer[4], Andreas Günther[5], Ulf Müller-Ladner[1] and Elena Neumann[1]. [1]Justus-Liebig-University of Gieβen, Bad Nauheim, Germany, [2]Markus-Hospital, Frankfurt, Germany, [3]University Hospital Gieβen and Marburg, Giessen, Germany, [4]University Hospital Gieβen and Marburg, Gieβen, Germany, [5]Justus-Liebig-University of Gieβen, Giessen, Germany

Background/Purpose: In rheumatoid arthritis (RA), aggressive synovial fibroblasts (SFs) play a central role in cartilage destruction and the spreading of the disease. We recently demonstrated the long-distance migratory potential of RASFs *in vivo* as well as the importance of extracellular matrix (ECM) regarding cellular adhesion with subsequent cartilage invasion. When cartilage was embedded into carrier matrices coated with growth factor-reduced Matrigel® (GFR MG) in the SCID mouse model of RA, a reduced RASF invasion compared to cartilage in Matrigel® (MG)-coated or non-coated carrier matrices was observed. Therefore, matrix-associated growth factors appear to influence migration and adhesion of RASFs. In this study, the effects of ECM-associated growth factors on the adhesion of fibroblasts from different rheumatic diseases as well as healthy individuals were analyzed.

Methods: Multi-well culture plates were coated with MG, GFR MG, or remained untreated, respectively. Cellular adhesion of RASFs (n=4), osteoarthritis (OA) SFs (n=3), RA dermal fibroblasts (n=5), systemic sclerosis (SSc) fibroblasts (n=7), synovial (n=1) and dermal fibroblasts of healthy individuals (n=6) was analyzed after 15 min. For this purpose, the fibroblasts were stained with Calcein-AM and adhesive fibroblasts were quantified using a fluorescence microscope.

Results: In general, an increased adhesion was observed after multi-well plate coating with GFR MG or MG. By using GFR MG, a reduction of cellular adhesion (1.4fold) of RASFs was observed compared to coating with MG. This behaviour was also visible when analyzing RA dermal fibroblasts (1.06 reduction of adhesion to GFR MG compared to MG). Fibroblasts of OA and SSc patients or healthy synovial or dermal fibroblasts showed the opposite reaction, an increased adhesion using GFR MG was observed compared to MG (OA: 1.6fold; SSc: 1.22fold; healthy SFs: 1.8fold; healthy dermal fibroblasts: 1.3fold).

Conclusion: The data show that ECM and its associated components, e.g. growth factors, play a critical role in RASF attraction and adhesion to cartilage. These factors are able to activate different adhesion molecules in RASFs, which are central features of this cell type, as RASFs are characterized by increased surface expression of adhesion molecules. Of note, dermal fibroblasts of RA patients show a similar behaviour but fibroblasts of other diseases or controls do not appear to be influenced by growth factors with respect to an increased expression of adhesion molecules. Therefore, the observed behaviour of RA dermal or synovial fibroblasts regarding adhesion to growth factor-containing matrix appears to be a disease-specific property.

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A Disintegrin and Metalloprotease 10 (ADAM10) Is Overexpressed in Rheumatoid Arthritis Synovial Tissue and Mediates Angiogenesis. Takeo Isozaki[1], Bradley J. Rabquer[1], G. Kenneth Haines III[2] and Alisa E. Koch[3]. [1]University of Michigan, Ann Arbor, MI, [2]Yale University, New Harven, CT, [3]Veteran's Administration and Unversity of Michigan, Ann Arbor, MI

Background/Purpose: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation and joint destruction. Angiogenesis is important in a variety of vasculoproliferatine states in RA. A disintegrin and metalloprotease (ADAM) are a family of proteases that are responsible for the liberation of a variety of types of cell surface expressed proteins. ADAM10 has been shown to cleave a number of inflammatory mediators from the cell surface including CX3CL1 and CXCL16. In this study, we examined the expression of ADAM10 in RA synovial tissue (ST) and the role it plays in angiogenesis.

Methods: ADAM10 expression was determined in ST samples from normal (NL) subjects, osteoarthritis (OA) patients and RA patients using immunohistological staining. To determine whether ADAM10 was expressed by human dermal microvascular endothelial cells (HMVECs) and whether it was regulated by interleukin-17 (IL-17), phorbol 12-myristate 13-acetate (PMA) or lipopolysaccharide (LPS), Western blots and real time polymerase chain reaction (RT-PCR) were performed. In order to confirm the role of ADAM10 in angiogenesis, we did Matrigel assays *in vitro*. To block the expression of ADAM10, HMVECs were transfected with siRNA against ADAM10. After treatment with ADAM10 siRNA, HMVECs were plated on Matrigel and were incubated with phosphate buffered saline (PBS) or basic fibroblast growth factor (bFGF) (positive control) (5nM). Chemotaxis assays were performed to determine the role of ADAM10 in endothelial cell (EC) migration.

Results: ECs within RA ST expressed high levels of ADAM10, while ECs within OA ST and NL ST expressed significantly less ADAM10 (mean ± SEM RA ST 46 ± 6.6% expression of total ECs, OA ST 9 ± 3.29% expression of total ECs and NL ST 0.91 ± 0.61% expression of total ECs). We found that ADAM10 was significantly elevated at the protein level in HMVECs stimulated with proinflammatory mediators such as IL-17, PMA or LPS compared with nonstimulated cells ($p<0.05$). The expression of ADAM10 messenger RNA (mRNA) was induced by stimulation with LPS after 1 hour. ADAM10 siRNA treated HMVECs had decreased EC tube formation compared with control siRNA treated HMVECs (3 ± 1.47 number of tubes formed and 37.3 ± 3.94 number of tubes formed, $p<0.05$). In addition, ADAM10 siRNA treated HMVECs had decreased migration compared with control siRNA treated HMVECs (14.7 ± 0.01 number of cells migrated and 20.5 ± 0.01 number of cells migrated, $p<0.05$).

Conclusion: These data show that ADAM10 is overexpressed in RA and suggest that ADAM10 may play a role in RA angiogenesis. ADAM10 may be a potential target in inflammatory disease like RA.

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Regulation of Synoviocyte Migration by phosphoinositide 3 Kinase (PI3K) Delta. Beatrix Bartok[1], Deepa Hammaker[2], Christian Rommel[3] and Gary S. Firestein[4]. [1]UCSD, La Jolla, CA, [2]Univ of California San Diego, La Jolla, CA, [3]Intellikine, Inc., La Jolla, CA, [4]UCSD School of Medicine, La Jolla, CA

Background/Purpose: Class I phosphoinositide 3 kinase (PI3K) mediate their biological activity through generation of phosphatidylinositol 3, 4, 5 –triphosphate (PIP3) at the cell membrane, which recruits downstream signaling molecules like Akt. One isoform, PI3Kdelta, was originally thought to be expressed mainly in leukocytes but was recently demonstrated in RA synovial tissue and cultured fibroblast–like synoviocytes (FLS). Using a novel selective PI3Kdelta inhibitor INK007, we showed that PI3Kdelta is a major regulator of synoviocytes growth and survival. The goal of current study was to assess role of PI3Kdelta in synoviocyte migration in response to PDGF, a known chemotactic factor for mesenchymal cells.

Methods: FLS were cultured in 6-well plates in presence of medium or PDGF-BB (10 nM) with or without PI3K inhibitors. The selective PI3Kdelta inhibitors INK007 was used for these studies, which has >20 fold selectivity over PI3Kgamma. The cells were wounded by clearing a region with a pipet tip, and the number of cells that migrate into the cleared area at 0 and 24 hour was determined by counting cells with light microscopy. For directed chemotaxis, 24-well modified Boyden transwell with 8.0 μ pore filters were used. Medium was added to the upper chamber and PDGF-BB (10nM) or media were added to the lower chamber. Cells were preincubated with PI3K inhibitors or vehicle for 1 hour prior to the assay and migrating cells were analyzed after 4 hrs. The filters were stained with 1% crystal violet and cells were counted by light microscopy.

Results: The effect of PI3K inhibition on undirected FLS motility in the presence of PDGF was studied using wound healing assay. There was a 2.6 fold increase in the number of migrating cells within the wounded area after 24 hrs in presence of PDGF compared with medium alone ($p<0.03$). The PI3Kdelta inhibitor INK007 significantly decreased number of migrating cells in a concentration dependent manner, with 50±5% inhibition at 1 uM, which is approximately the EC50 for this compound for other functional assays ($p< 0.04$). A pan PI3K inhibitor completely blocked cell migration in response to PDGF, suggesting that other PI3K isoforms also participate. A PI3Kalpha selective inhibitor decreased the number of migrating cells by 60±5% at 1 uM ($p<0.04$). We then studied

effect of PI3K inhibition on PDGF-mediated chemotaxis using a transwell chemotaxis assay. There was a 2.5-fold increase in the number of cells that migrated in response to PDGF compared with medium ($p<0.03$). Preincubation of FLS with PI3Kdelta, or panPI3K inhibitor decreased number of migrated cells by 50±3%. ($p<0.04$ for each).

Conclusion: PI3Kdelta regulates PDGF-mediated FLS migration in addition to its previously defined role in synoviocyte survival and growth. Our findings suggest that targeting PI3Kdelta could be beneficial in RA by modulating synoviocyte function and potentially suppressing joint damage.

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Soluble Junctional Adhesion Molecule-B Inhibits Angiogenesis in Rheumatoid Arthritis. Bradley J. Rabquer[1], Beatrix Balogh[1], Jeffrey H. Ruth[1], Beat A. Imhof[2] and Alisa E. Koch[3]. [1]University of Michigan, Ann Arbor, MI, [2]University of Geneva, Switzerland, [3]Department of Veteran's Affairs and Unversity of Michigan, Ann Arbor, MI

Background/Purpose: Angiogenesis is a highly regulated process of new blood vessel formation that may occur from pre-existing blood vessels. Rheumatoid arthritis (RA) is characterized by synovial hyperplasia, inflammation, and neovascularization. In RA, angiogenesis is regulated by the expression of pro- and antiangiogenic growth factors, cytokines, and adhesion molecules. Junctional adhesion molecule-B (JAM-B) is a recently described adhesion molecule expressed by several cell types, including endothelial cells (ECs). The aim of this study was to determine if JAM-B is found in soluble form (sJAM-B) and if it mediates angiogenesis.

Methods: We designed and performed an ELISA to determine if sJAM-B was present in normal and RA serum, and RA synovial fluid (SF). To determine if sJAM-B mediates *in vivo* angiogenesis, we performed Matrigel plug angiogenesis assays. Matrigel was mixed with sJAM-B or controls and implanted subcutaneously into C57BL/6 mice. After 7 days, the plugs were removed and homogenized for hemoglobin determination, a correlate of vascularity. To determine if sJAM-B mediates *in vitro* angiogenesis, Matrigel EC tube formation assays were performed. Human microvascular endothelial cells (HMVECs) were stimulated with sJAM-B to determine which signaling pathways were activated.

Results: Our results indicate that JAM-B is present in soluble form and that sJAM-B inhibits angiogenesis. sJAM-B was detected in normal serum (n=the number of patients=9, 630 (mean) ± 30 (SEM) pg/ml) and was significantly elevated in RA serum (n=7, 820 ± 80 pg/ml) and RA SF (n=8, 1,090 ± 130 pg/ml) (all $p<0.05$). In an *in vivo* Matrigel plug angiogenesis assay, plugs containing basic fibroblast growth factor (bFGF) (n=the number of mice=7, 1234 (mean) ± 63 (SEM) (μg/ml)/g) had significantly more hemoglobin than those with PBS (n=7, 707 ± 96 (μg/ml)/g) ($p<0.05$), whereas plugs with sJAM-B (n=7, 469 ± 24 (μg/ml)/g) had significantly less hemoglobin than those with PBS ($p<0.05$). *In vitro*, Matrigel EC tube formation assays indicated that when alone sJAM-B (n=the number of experiments=4, 36 (mean) ± 3 (SEM) tubes) induced low levels of tube formation compared to PBS (n=4, 29 ± 2 tubes) ($p<0.05$), but that sJAM-B in combination with bFGF (n=2, 52 ± 2 tubes) resulted in lower levels of tube formation than bFGF alone (n=2, 61 ± 1) ($p<0.05$). Lastly, sJAM-B stimulated the phosphorylation of Erk1/2 and p38 kinases and induced the dephosphorylation of Src kinase in HMVECs.

Conclusion: Our results show that sJAM-B is upregulated in RA serum and SF compared to normal serum. In addition, we show that sJAM-B inhibits *in vivo* angiogenesis. These results suggest that modulation of sJAM-B may provide a novel route for controlling angiogenesis in RA.

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FAAH Inhibition Reverses Glucocorticoid Effects in Synovial Fibroblasts of Patients with Osteoarthritis and Rheumatoid Arthritis. Torsten Lowin[1], Elena Neumann[2], Ulf Muller-Ladner[3] and Rainer H. Straub[1]. [1]University Hospital Regensburg, Regensburg, Germany, [2]Justus-Liebig-University of Gieβen, Bad Nauheim, Germany, [3]Justus-Liebig Universität Gieβen, Kerckhoff-Klinik GmbH, Bad Nauheim, Germany

Background/Purpose: In rheumatoid arthritis, glucocorticoid secretion in relation to inflammation is inadequate. Besides their direct effects on inflammation, GCs induce indirect effects by modulation of the endocannabinoid system, e.g., the production of anandamide after cortisol stimulation of neurons. We hypothesize that cortisol stimulation leads to the generation of endocannabinoids by synovial fibroblasts (SFs) with a distinct profile of action from cortisol. We used *fatty acid amide hydrolase* (FAAH) inhibition to unmask the endocannabinoid effects.

Methods: We performed immunofluorescence analysis and cell-based ELISAs to quantify cannabinoid receptor1 (CB1R) and FAAH levels. Adhesion and proliferation was assessed using the *Xcelligence* system by Roche. Flow cytometry was employed for the detection of integrin $\alpha5$.

Results: Cortisol increased the adhesion of synovial fibroblasts to fibronectin, reaching a maximum at 10^{-8}M. FAAH inhibition plus cortisol reversed cortisol only effects and inhibition of adhesion was maximal at 10^{-8}M cortisol. This effect was partially mediated by modulation of the fibronectin receptor integrin $\alpha5\beta1$. Proliferation of SFs was significantly reduced by cortisol and this effect was reversed when FAAH was blocked. Furthermore, cortisol downregulated levels of FAAH and CB1R but concomitant FAAH inhibition increased levels of both proteins.

Conclusion: FAAH inhibition reversed cortisol effects on adhesion, proliferation and FAAH and CB1r expression. As FAAH inhibition by itself had no influence on SFs it is likely that an endocannabinoid/eicosanoid is synthesized upon cortisol treatment which explains the observed effects.

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Design of Peptides From CD2 to Modulate Protein-Protein Interactions and Immune Response. Ameya Gokhale[1], Veena Taneja[2] and Seetharama Satyanarayanajois[1]. [1]University of Louisiana at Monroe, Monroe, LA, [2]Mayo Clinic, Rochester, MN

Background/Purpose: Cell adhesion molecules play a central role at every step of the immune response. The function of the leukocyte can be regulated by modulating adhesion interactions between cell adhesion molecules to develop therapeutic agents against autoimmune diseases. CD2 and its ligand CD58 are two of the best-characterized adhesion molecules mediating the immune response. To modulate the protein-protein interaction and hence cell adhesion interaction, six peptides with conformational constraints were designed from the discontinuous epitopes of β-strand region of CD2 protein. The purpose is, a) to evaluate the cell adhesion inhibition activity of peptides using cell adhesion assay, b) to evaluate the peptides for immunomodulation in an in vitro assay, and c) to elucidate the three-dimensional structure of the peptides using Nuclear Magnetic Resonance (NMR) and Molecular Dynamics (MD).

Methods: The ability of the CD2-derived peptides to inhibit cell adhesion interaction was studied by E-rosetting assay and lymphocyte epithelial assay using T cells and Caco-2 cells that express CD2 and CD58 proteins respectively. The binding of Peptide 6 to CD58 protein was studied in a competitive binding assay using FITC-antiCD58 by flow-cytometry. Structure of the peptides was studied by NMR spectroscopy, Circular Dichroism Spectroscopy (CD) and MD simulation. In vitro effect of the CD2-derived peptides was done by inhibition of antigen-specific T cell proliferation using HLA-DQ8 (DQA1*0301/DQB1*0302) transgenic mice.

Results: Among the six peptides studied in this series, peptides **6** and **7** inhibit the cell adhesion activity with an IC_{50} value of 7 nM and 11 nM respectively, in lymphocyte-epithelial adhesion assay. These peptides were also able to suppress the antigen-specific T cell response in cells isolated from humanized mice known to be susceptible to inflammatory polyarthritis. The binding of Peptide 6 to CD58 protein was studied in a competitive binding assay using FITC-antiCD58 by flow-cytometry. Peptide 6 inhibited antibody binding to CD58 on Caco-2 and OVCAR cells expressing CD58. NMR and molecular modeling results indicated that peptides **6** and **7** exhibited β-turn structure with a β-hairpin structure in solution.

Conclusion: Peptides designed from the hot-spot region of CD2 protein may form the lead compounds to inhibit immune response and hence may be therapeutically useful for autoimmune diseases such as rheumatoid arthritis.

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Toll-Like Receptor 2 Induced Cell Migration and Invasion Is Mediated Through β1-Integrin Signalling Pathways and Cytoskeletal Dynamics. Trudy McGarry[1], Mary Connolly[2], Jennifer McCormick[1], Douglas J. Veale[1] and Ursula Fearon[1]. [1]Dublin Academic Medical Centre, University College Dublin, Dublin, Ireland, [2]Center of Experimental Rheumatology, University Hospital Zürich, Zurich, Switzerland

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial inflammation and destruction of cartilage and bone. TLR-2 is implicated in the pathogenesis of RA. This study investigates if TLR-2 induced cell migration and invasion is mediated through **β1-integrin** signalling pathways and cytoskeletal dynamics.

Methods: IA patients (n=20) underwent clinical assessment, videoarthroscopy and synovial biopsy pre/post biologic therapy. Macroscopic

synovitis/vascularity was measured by visual analogue scale. Immunohistology/immunoflourescence examined β1 integrin and filamentous actin (F-actin) expression in synovial tissue (ST), primary RA synovial fibroblasts (RASFC) and microvascular endothelial cells (HDEC). Cytoskeletal rearrangement following Pam3CSK4 (1ug/ml)(TLR2-ligand) stimulation was examined by F-actin immunofluorescent staining. Pam3CSK4 induced adhesion, cell migration and invasion was assessed by FACS analysis, wound repair assays and transwell matrigel™ invasion chambers in the presence or absence of anti-β1 integrin (10ug/ml) or IgG control antibody (10ug/ml).

Results: β1 integrin was highly expressed in IA ST compared to osteoarthritis and control tissue. β1 integrin lining and sub-lining layer expression significantly correlated with macroscopic synovitis ($p<0.05$), vascularity ($p<0.05$), and was significantly reduced in biologic responders. β1-integrin and F-actin expression predominantly co-localized to synovial blood vessels and lining layer. Pam3CSK4 induced cell surface expression of ICAM ($p<0.05$). Using RASFC and HDEC, Pam3CSK4 induced cell migration and cytoskeletal disassembly, resulting in filopodia and microspike formation and significantly induced cell invasion through a matrigel ($p<0.05$). Finally, we demonstrated that Pam3CSK4 induced cell migration was inhibited in the presence of anti-β1 integrin, an effect that was also observed for PAM3CSK4 induced cellular invasion ($p<0.05$). No effect was observed for IgG matched control antibody.

Conclusion: b1-integrin is highly expressed in the inflamed joint and mediates cell TLR-2 induced migrational and invasive mechanisms, critical to the pathogenesis of IA.

ACR Poster Session A
Cytokines, Mediators, and Gene Regulation I
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Epigenetically Regulated MicroRNA-126 Influences Migratory Potential and Apoptosis of Synovial Fibroblasts in Rheumatoid Arthritis. Mojca Frank[1], Maria Filkova[1], Joanna Stanczyk[1], Mary Connolly[1], Christoph Kolling[2], Beat A. Michel[1], Blaz Rozman[3], Renate E. Gay[1], Steffen Gay[1] and Astrid Jungel[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]University Medical Centre, Ljubljana, Slovenia

Background/Purpose: Increased migration and decreased apoptosis are main characteristics of the aggressive behaviour of rheumatoid arthritis (RA) synovial fibroblasts (SF). Increased migration has been implicated in spreading RA from affected to unaffected joints, resulting in polyarticular disease. Dysregulation of several microRNAs (miRs) has been found to play a role in cell migration, apoptosis and inflammation.

Objectives: To analyse the expression of most relevant miRs in RA, their regulation by proinflammatory and epigenetic mechanisms in SF and their functional role in shaping the aggressive behaviour of RASF.

Methods: TaqMan Single Assays were used to analyse the expression of 260 miRs in human RASF and osteoarthritis (OA) SF (n=3 each). MiR-126 was further quantified in RASF (n=10), OASF (n=9), RA (n=10), OA (n=6) synovial tissue and RA (n=20) or healthy control sera (n=17) by Taqman Real Time PCR. Let-7a was used as an endogenous control. The regulation of miR-126 expression was investigated in RASF (n=5) treated with TNFα, IL-1β, IFN-β, Poly(I:C) or LPS and in RASF (n=6) exposed to hypoxia (24h, 1% O_2). Additionally, RASF and OASF were treated with 5'azacytidine (5'AZA, 0.1, 0.5 and 1mM, 5 days) or Trichostatin A (TSA, 1mM, 24h). The functional role of miR-126 (migration/scratch and Annexin-V apoptosis assays) was studied in SF following Lipofectamine transfection (48h) with pre-miR-126 (100nM), mature miR-126 (25, 50nM), anti-miR-126 (25, 50nM) or scrambled controls.

Results: MiR-126 was significantly upregulated in RASF (dCt± SE=7.93±2.43) vs. OASF (dCt=9.91±0.81, p=0.022) and in sera from RA patients (dCt=−1.79±1.01) compared to healthy controls (dCt=−1.26±0.61, p=0.031), while no significant difference was found between RA and OA synovial tissue. Proinflammatory cytokines, TLR ligands or hypoxia (1% O_2) had no effect on the expression of miR-126 in RASF. DNA demethylation of RASF (x-fold: 1.78±0.53, n=2) and OASF (1.58±0.21, n=4) with 5-AZA and treatment of OASF (1.50±0.34, n=6, p=0.031) and RASF (1.70±0.34, n=4) with TSA upregulated miR-126. Transfection with pre-miR-126 decreased the migration of SF in the scratch assay by 86±0.05% in all of OA and by 48±16% in 4 out of 6 RA patients. Anti-miR-126 had no significant effect on migration. Apoptosis significantly increased in SF (n=7) transfected with mature miR-126 (2.67±0.43; p=0.008) and anti-miR-126 (1.71± 0.25, p=0.031).

Conclusion: MiR-126 is epigenetically upregulated in synovial fibroblasts by acetylation and demethylation and significantly alters the migration and apoptotic ability of SF. Therefore it may serve as a potential new therapeutic target in RA possibly influencing the spread of RA to unaffected joints.

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Mathematical Modeling of Interleukin-6 Signaling Inhibition: Comparative Efficiency of Different Intervention Strategies. Saroja Ramanujan[1], Daniel Young[1], Peter Maisonpierre[1], Stevan Shaw[2], Jason Chan[1] and Kosmas Kretsos[2]. [1]Entelos, Inc., Foster City, CA, [2]UCB, Slough, United Kingdom

Background/Purpose: A cascade of binding events between IL-6, IL-6R, and gp130 leads to formation of IL-6 signaling complexes in inflammatory conditions.[1] Tocilizumab (TCZ), an anti-IL-6R antibody (Ab), inhibits IL-6 signaling by preventing IL-6+IL-6R dimerization (axis 1 intervention).[2] Axis 1 intervention can also be achieved with anti-IL-6 Abs. Subsequent assembly steps present alternative strategies for IL-6 signal inhibition, including IL-6-targeted agents that prevent trimer formation (IL-6+IL-6R+gp130; axis 2 intervention) or the formation of the $(IL\text{-}6+IL\text{-}6R+gp130)_2$ signaling hexamer (axis 3 intervention).

Methods: We developed a dynamic, mathematical model of IL-6 signaling within a target compartment, with initial steady state IL-6, soluble (s) IL-6R, and sgp130 concentrations. The model encompassed IL-6 interaction with membrane-bound IL-6R (cis) or with both membrane-bound and sIL-6R (cis and trans signaling), including the impact of inhibiting membrane-bound and sgp130 by different targeted strategies. The validity of the model was confirmed by comparison to published PK/PD data for TCZ.[3] Four prototypical intervention strategies were modeled: anti-IL-6R, axis 1; anti-IL-6, axis 1; anti-IL-6, axis 2; and anti-IL-6, axis 3. Simulations compared the sensitivity of drug responses to parameter variations at multiple clinically relevant IL-6, sIL-6R, and sgp130 concentration scenarios. All simulated parameters for interactions and responses were based on a one-compartment linear PK model.

Results: Anti-IL-6 axis 3 intervention was predicted to be the most efficient inhibitor of combined cis + trans IL6 signaling. This advantage held true both when IL-6 concentration was limiting (approximate serum-like RA conditions; Figure 1A), and under conditions of equimolar IL-6 and IL6R (approximate synovial-like RA conditions; Figure 1B).[4] The advantage of anti-IL-6 axis 3 intervention over anti-IL-6R or anti-IL-6 approaches to axis 1 intervention was robust to changes in single parameters, and was lost only in large excess of IL-6 over IL-6R or when multiple conditions coincided, such as a combination of: excess IL-6; inefficient Ab binding to membrane-bound targets; increased IL-6 turnover or slower IL-6R turnover; slow IL-6+IL-6R dimerization kinetics; and low Ab dissociation constant.

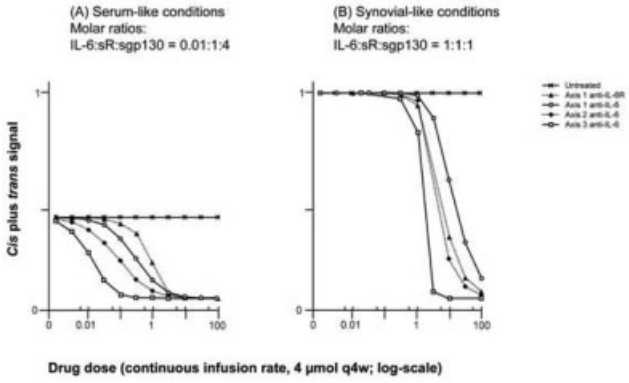

Figure 1. Modeling IL-6 signal inhibition by antibodies targeting different axes of intervention.

Conclusion: Anti-IL-6 intervention at axis 3 may be more efficient at inhibiting IL-6 signaling than axis 1 intervention with an anti-IL-6R Ab, in either serum- or synovial-like conditions. Multiple factors simulating sensitivity of drug responses were required to challenge the advantage of axis 3 intervention.

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Abnormalities in a JAK-STAT Pathway Are Involved in the Aberrant Production of IL-6 by BAFF-Stimulated Peripheral Monocytes of Patients with Primary Sjögren's Syndrome. Keiko Yoshimoto[1], Maiko Tanaka[1], Masako Kojuma[1], Hideko Ogata[1], Hideto Kameda[1], Tohru Abe[2] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Saitama Medical School, Kawagoe-shi Saitama, Japan

Background/Purpose: It has been reported that B cell activating factor belonging to the TNF family (BAFF) and IL-6 are involved in the development of primary Sjögren's syndrome (pSS). BAFF is mainly expressed in monocytes and dendritic cells, and regulates proliferation, differentiation and survival of B cells, which play a pivotal role in the production of autoantibodies and hence in the development of autoimmune diseases. IL-6 is produced by many types of cells including monocytes, and promotes differentiation of B cells. In our previous study, we found that soluble BAFF (sBAFF) abnormally induced the production of IL-6 by peripheral pSS monocytes cultured in vitro.In the present study, we investigated a regulatory mechanism for the production of IL-6 by BAFF-stimulated monocytes and possible abnormalities of pSS monocytes.

Methods: Peripheral monocytes were prepared from pSS patients and age-matched normal individuals. The cells were stimulated in vitro with sBAFF in the presence or absence of inhibitors against several protein kinases, i.e., JAK2, JAK3, p38MAPK and JNK. The production of IL-6 by the cells was measured by ELISA. The expression levels of the kinases were analyzed by quantitative PCR.

Results: pSS monocytes produced substantial amount of IL-6 even in the absence of stimulation, while normal monocytes produced only marginal amount of IL-6. The production of IL-6 by the cells was increased when the cells were stimulated with sBAFF. The increase was especially remarkable for pSS monocytes as compared with normal monocytes. The elevated productions of IL-6 by the cells were significantly suppressed in a dose dependent manner by inhibitors against protein kinases, such as JAK2, JAK3, p38MAPK and JNK, thus far examined. Among the inhibitors, a JAK3 inhibitor showed the highest effect. Quantitative PCR analysis indicated that no significant difference was observed between normal and pSS monocytes in the expression level of JAK3. However, stimulation of pSS monocytes with sBAFF strongly induced the expression of JAK3 while normal monocytes did not significantly respond to the stimulation. Similarly, the expression levels of STAT3 and STAT4 in monocytes were increased upon stimulation with sBAFF, and the increase was higher in pSS monocytes than the control. The increase was remarkable for STAT4 as compared with STAT3.

Conclusion: Our data suggest that a JAK3-STAT4 pathway may be involved in the production of IL-6 by sBAFF-stimulated peripheral monocytes. In addition, abnormalities in the induction of JAK3 and STAT4 may be responsible for the abnormal responses of pSS monocytes to sBAFF. These abnormalities may be involved in the pathogenesis of pSS.

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MiR-451 in Microparticles Derived From Monocytes Influences Gene Expression in Rheumatoid Arthritis Synovial Fibroblasts. Meike Dahlhaus[1], Joanna Stanczyk[1], Mojca Frank[1], Beat A. Michel[1], Christoph Kolling[2], David S. Pisetsky[3], Renate E. Gay[1], Steffen Gay[1], Astrid Jüngel[1] and Diego Kyburz[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Duke University Medical Center, Durham, NC

Background/Purpose: Microparticles (MPs) are small membrane-enclosed vesicles, produced by a variety of cells by budding of cell membranes. It was shown that MPs contain different levels of RNAs, including miRNAs. Here, we investigate the expression of miR-451 in monocyte-derived MPs and its influence on the expression of its target gene *Macrophage Migration Inhibitory Factor* (MIF) in rheumatoid arthritis synovial fibroblasts (RASF).

Methods: MPs were isolated from U937 cells after stimulation with TNFα (10ng/ml) for 16h by differential centrifugation. RASF were cocultured with MPs for 24h. As negative control, MPs were incubated with RNaseA and Triton-X 100 for 60min at 37°C to digest RNA before coculture. To generate miR-451 deficient MPs, U937 cells were transfected 24h before stimulation with an anti-miR451 oligonucleotide (Ambion) with Lipofectamine 2000 (Invitrogen). RNA from cells and MPs were isolated by miRNeasy Kit (Qiagen). Expression of miRNAs (miR-451, miR-144, let7a as endogenous control, cel-39 as spike-in control) and RNAs (MIF, 18S) were determined using semiquantitative Real-time PCR.

Results: MiR-451 is strongly enriched in MP derived from U937 cells without stimulation with TNFα compared to the parental cells (delta Ct: -12.7 (U937) and -6.99 (MPs), $p=0.0313$, $n=6$). After stimulation with TNFα (10ng/ml), miR-451 was strongly enriched in MPs as well (delta Ct: -13.7 (U937) and -8.14 (MPs), $p=0.0313$, $n=6$). MiR-144, located in the same cluster as miR-451, was not enriched in MPs. RASF cocultured with MPs for 24h show an 2-fold increase in miR-451 expression ($p = 0.0156$, $n=6$) and a 30 % decrease in the expression of its target MIF ($p = 0.0156$, $n=6$). Coculture of RASF with RNase A treated MP abolished this effect.

Conclusion: The process of miRNA-transfer by microparticles is a new mechanism of cell-to-cell communication. We show for the first time that miR-451 transferred via MPs influences the gene expression in RASF.

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The Influence of Cigarette Smoke on Expression of Histone Deacetylases in Rheumatoid Arthritis. Anna Loeffler[1], Peter Kunzler[1], Fabienne Niederer[1], Astrid Jungel[1], Christoph Kolling[2], Giovanni Camici[3], Beat A. Michel[4], Renate E. Gay[1], Steffen Gay[1] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Institute of Physiology, University of Zurich, Switzerland, [4]University Hospital, Zurich, Switzerland

Background/Purpose: The superfamily of histone deacetylases comprises HDACs and sirtuins (SIRTs) that regulate many cellular processes by deacetylation of histone and non-histone proteins. Expression and activity of histone deacetylases is altered in rheumatoid arthritis (RA). Smoking is an environmental risk factor for RA. The aim of this study was to examine the influence of cigarette smoke on expression of HDACs and SIRTs in synovial fibroblasts and synovial tissues from RA patients and in joints of mice exposed to cigarette smoke.

Methods: Synovial tissues were obtained from smoking ($n=5$) and non smoking ($n=5$) RA patients undergoing joint replacement surgery. RA synovial fibroblasts (RASF) from non smokers ($n=6$–10) were stimulated with freshly prepared 5% cigarette smoke extract (CSE) for 24 hours. Mice were exposed to room air ($n=8$) or cigarette smoke ($n=6$) in a whole body exposure chamber for 3 weeks, sacrificed and joints were removed. Expression of HDACs and SIRTs was detected at the mRNA level by Real-time TaqMan and SYBR green PCR and at the protein level by immunoblot analysis.

Results: Stimulation of RASF with CSE significantly enhanced the expression of HDAC1 (x-fold: 2.0 ± 0.4; $p=0.04$), HDAC2 (1.9 ± 0.3; $p=0.02$) and HDAC3 (2.4 ± 0.4; $p=0.01$) at the mRNA level while the expression of HDAC 4–11 remained unchanged. However, the protein levels of HDAC1 and HDAC3 were not altered, whereas the expression of HDAC2 protein was decreased. Among all sirtuins examined the transcriptional level of SIRT4 was 4.3-fold ±1.0 ($p=0.01$) and SIRT6 mRNA was 2.7-fold±0.5 increased ($p=0.02$) in CSE stimulated RASF. The elevated expression of SIRT4 and SIRT6 was also detected at the protein level, confirming that stimulation with CSE affects the expression of these two sirtuins in vitro.

Also in joints of mice exposed to cigarette smoke the basal mRNA levels of SIRT4 and SIRT6 were 2.3-fold (DCT smoking 14.6 ± 0.6; DCT control $15.5\ \pm0.7$; $p=0.04$) and 1.8-fold (DCT smoking 13.6 ± 0.9; DCT control 14.7 ± 1.0; $p=0.04$) higher as compared to control mice. In human synovial tissue samples from RA patients, smokers had 3.1-fold (DCT smokers 2.12 ± 0.37; DCT non smokers 3.75 ± 0.48; $p=0.03$) higher mRNA levels of SIRT6 and 2.1-fold higher mRNA levels of HDAC2 (DCT smokers 2.00 ± 0.20; DCT non smokers 3.07 ± 0.34; $p=0.03$) as compared to non smokers.

Conclusion: In the current study we found that the expression of histone deacetylases, in particular SIRT4, SIRT6 and HDAC2 can be altered in

RASF, murine joints and human synovial tissue by environmental factors such as smoking. Since histone deacetylases play an important role in the epigenetic regulation of gene transcription, we suggest that smoking influences gene expression by modification of histone deacetylases.

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A-SAA Induced Angiogenesis and Endothelial Cell Invasion Is Mediated Through NOTCH Signalling Pathways. Peter Rooney[1], Mary Connolly[2], Wei Gao[3], Douglas J. Veale[4] and Ursula Fearon[4]. [1]University College Dublin, Dublin, Ireland, [2]Center of Experimental Rheumatology, University Hospital Zürich, Zurich, Switzerland, [3]St. Vincent's University Hospital, Dublin, Ireland, [4]Dublin Academic Medical Centre, University College Dublin, Dublin, Ireland

Background/Purpose: Acute Serum Amyloid A (A-SAA) is strongly expressed in rheumatoid arthritis (RA) synovial tissue (ST) and is critically involved in regulating cell migration and angiogenesis. Cell migration and EC morphology is dependent on interactions which link NOTCH signalling pathways to cytoskeletal rearrangement and extracellular matrix.

Objectives: To examine if A-SAA induced angiogenesis, cell migration and invasion are mediated by the NOTCH signalling pathways.

Methods: RA whole tissue synovial explants (RAST) and human microvascular endothelial cells (HDEC) were stimulated with A-SAA (10 and 50μg/ml) or TNFα (10ng/ml) for (3–24 hours). NOTCH1 IC, its ligands DLL-4, JAGGED 1 and downstream signalling components HRT1, HRT2 were quantified by Real-time PCR. NOTCH1 IC, and growth factors (VEGF, Angiopoietin-2) were assessed by western blot and/or ELISA. A-SAA induced angiogenesis cell migration and invasion were assessed by Matrigel tube formation, scratch and invasion assay. A-SAA modulation of filamentous actin (F-actin) and focal adhesions (vinculin) was examined by dual immunofluorescence. A-SAA induced angiogenesis, invasion, altered cell shape and migration were performed in the presence or absence of siRNA against NOTCH 1. Pro-inflammatory chemokines IL-8 and Gro-Alpha levels in cultured supernatants were quantified by ELISA.

Results: A-SAA (10μg/ml) increased NOTCH1 IC and VEGF mRNA and protein expression ($p<0.05$). A-SAA induced HRT-1 and JAGGED 1 mRNA ($p<0.05$), with no effect on HRT-2 mRNA. In contrast, A-SAA inhibited DLL-4 mRNA ($p<0.05$), consistent with a negative feedback loop controlling interactions between NOTCH1 IC and DLL-4 in the regulation of EC tip vs. stalk cells development. Alterations in cytoskeletal dynamics in response to A-SAA were observed as early as 15 minutes with maximal effect at 24 hours, where F-actin disassembly and formation of filopodia and microspike protrusions was observed.Finally, A-SAA induced angiogenesis, cell migration and invasion were inhibited in the presence of NOTCH 1 siRNA ($p<0.05$). In contrast A-SAA induced IL-8 and Gro-alpha expression were not altered by NOTCH 1 siRNA.

Conclusion: A-SAA induces the NOTCH signalling pathway, VEGF and cytoskeletal rearrangement which allows temporal and spatial reorganization of cells during cell migratory events and EC morphology. Together these results suggest a critical role for A-SAA in driving cell shape, migration and invasion in the inflamed joint.

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Age-Related Mitochondrial Dysfunction Sensitizes Human Synoviocytes to Inflammatory Response. M. Noa Valcárcel-Ares[1], Romina R. Riveiro-Naveira[1], Carlos Vaamonde-García[1], Laura Hermida-Carballo[1], Francisco J. Blanco[2] and Maria J. López-Armada[1]. [1]Aging and Inflammation Research Lab, INIBIC-CHU A Coruña, A Coruña, Spain, [2]Osteoarticular and Aging Research Lab, INIBIC-CHU A Coruña, A Coruña, Spain

Background/Purpose: Rheumatoid arthritis (RA) is an age-related disease characterized by a marked inflammatory profile. Mitochondrial dysfunction has been widely related with aging and age-related diseases. Evidences support that RA synoviocytes present an increased mitochondrial genome mutagenesis, leading to mitochondrial alterations. However, its role in the inflammatory response of synoviocytes has not been investigated. The purpose of our study was to investigate the role of age-induced dysfunctional mitochondria in the inflammatory response of normal human cultured synovial cells.

Methods: The mitochondrial respiratory chain inhibitor oligomycin (OLI) was used to simulate the aging process in which ROS production is increased and mitochondrial bioenergetics is altered. The cytokines IL-1β and TNFα were employed as they constitute the major pro-inflammatory mediators in the diseased joint. The inflammatory response was measured by cyclooxygenase-2 (COX-2) protein (flow cytometry) and mRNA expression (RT-PCR), and prostaglandin E_2 (PGE_2) and interleukin-8 (IL-8) levels (ELISA). To identify possible pathways NF-kappaB activation was determined by EMSA and BAY was used as an inhibitor of NF-kappaB; also, N-acetylcysteine (NAC) was used as ROS scavenger. Cells were preincubated with the natural antioxidant resveratrol (RSV) to investigate its effect in our mitochondrial dysfunction model.

Results: We found that oligomycin-induced mitochondrial dysfunction per se significantly stimulated the expression of slight levels of COX-2, PGE_2 and IL-8. Oligomicyn-induced mitochondrial dysfunction synergistically intensifies the inflammatory response induced by low concentrations of cytokines. Pre-treatment of synoviocytes with 10μg/ml OLI for 30 minutes significantly increases the IL-1β (0.1ng/ml)-induced COX-2 protein expression (32.5 ± 2.5 OLI+IL-1 vs. 6.5 ± 2.4 IL-1 and 4.5 ± 1.7 OLI, expressed as fluorescence intensity units, $n=3$, $p<0.001$) and COX-2 mRNA expression. Interestingly, the percentage of increase is higher with the lower dosage of cytokines (5ng/ml vs. 0.01ng/ml). When PGE2 production was assessed the synergistic effect was also found (277.0 ± 67.6 OLI+IL-1 vs. 15.4 ± 2.6 IL-1 and 97.5 ± 45.6 OLI, expressed as pg/50,000cells, $n=3$ duplicate, $p<0.005$). Similar results were obtained when IL-8 production was measured (2887 ± 272.6 OLI+IL-1 vs. 1313 ± 201.2 IL-1 and 62.36 ± 15.39 OLI expressed as pg/50,000cells, $n=4$ duplicate, $p<0.005$).

Finally, we demonstrated the involvement of NF-kB and ROS in this process since the inflammatory response was counteracted by the addition of BAY or NAC. NF-kB activation was also shown by EMSA assay. The natural antioxidant resveratrol also proved to significantly reduce inflammatory response.

Conclusion: The present study identifies for the first time mitochondria as organelles implicated in the proinflammatory response in human synoviocytes, since mitochondrial dysfunction sensitizes these cells amplifying the inflammatory response induced by cytokines. This effect is especially relevant in aging, in which a chronic low grade inflammatory state could act as a bridge between normal aging and age-related diseases.

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Regulatory and Anti-Inflammatory Effects of MAP Kinase Phosphatase-1 in Inflammation and Arthritis. Riku Korhonen[1], Riina Nieminen[1], Tuija Turpeinen[1], Ville Taimi[1], Antonis Goulas[2], Andrew R. Clark[3] and Eeva Moilanen[1]. [1]University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland, [2]Aristotle University of Thessaloniki, Greece, [3]Imperial College London, London, United Kingdom

Background/Purpose: MAP kinase phosphatases (MKPs) are protein phosphatases that dephosphorylate and thereby down-regulate the activity of MAP kinases. In the present study, we investigated the effects of MKP-1 on the activation of MAP kinases, on the expression of inflammatory genes and the development of acute inflammatory response in mice.

Methods: The effect of MKP-1 on inflammatory gene expression was investigated by silencing MKP-1 with siRNA in macrophages and chondrocytes, or by using cells and tissues from MKP-1 deficient mice. Also, acute carrageenan-induced paw inflammation was investigated in wild-type and MKP-1 knock-out mice.

Results: MKP-1 deficiency enhanced phosphorylation of p38, but not JNK, and enhanced the expression of inflammation and arthritis associated genes COX-2, IL-6, MMP-3, TNF, and iNOS in macrophages and/or chondrocytes. Also, acute carrageenan-induced paw inflammation was increased in MKP-1 knock-out mice as compared to wild-type mice. The production of IFNγ and IL-2 was increased in splenocytes from MKP-1 knock-out mice. Interestingly, the anti-rheumatic drug aurothiomalate enhanced MKP-1 expression in chondrocytes and in human cartilage, reduced the phosphorylation of p38 MAP kinase, and inhibited the expression of IL6, COX2 and MMP3. Experiments with cartilage from MKP-1 knockout mice confirmed that aurothiomalate decreased inflammatory gene expression via the upregulation of MKP-1.

Conclusion: The data supports that MKP-1 is an endogenous factor that negatively regulates inflammatory gene expression. Compounds that upregulate MKP-1 expression or enhance its function have a promise as novel anti-inflammatory/antirheumatic drugs.

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Critical Role for the IL-23/TNF Axis During TLR2/NOD2 Mediated Acute Joint Inflammation. Ferry Cornelissen[1], Odilia B.J. Corneth[2], Anne-Marie Mus[1], Patrick S. Asmawidjaja[1] and Erik Lubberts[1]. [1]Erasmus MC, University Medical Center, Rotterdam, Netherlands, [2]Erasmus MC, University Medical Center, Rotterdam, Rotterdam, Netherlands

Background/Purpose: IL-23 is essential in the development of chronic autoimmune diseases and supports the maturation of pathogenic Th17 cells. Although the role of IL-23 during adaptive immunity in arthritis has been studied extensively, the role of IL-23 during acute joint inflammation is unknown. Therefore, the purpose of this study is to investigate the role of IL-23 in the development of an acute, macrophage-mediated joint inflammation.

Methods: Peptidoglycan (PG) or streptococcal cell wall fragments (SCW) were intra-articularly injected into the knee joint of naïve wt or IL-23p19-deficient mice. Joint swelling was assessed by measuring joint thickness using a caliper. In addition, synovial expression of different cytokines was measured by specific ELISA and/or Q-PCR. Moreover, synovial explants of wt and IL-23p19-deficient mice were stimulated with SCW and cytokine levels were measured by ELISA.

Results: TLR2/NOD2-mediated streptococcal cell wall (SCW) and peptidoglycan (PG) induced acute joint inflammation in IL-23p19-deficient mice resulted in a profound reduction of local joint inflammation compared to control mice in both these models. Synovial IL-23p19 transcript was detected at 1.5 and 4 hours after arthritis induction and was further increased 1 day after PG injection with a peak at day 2. Interestingly, IL-23p19-deficient mice showed a significant reduction in synovial TNFalpha, but not IL-6 levels 4 hours after TLR2/NOD2-mediated arthritis induction in the knee joint. In line with this, reduced TNFalpha levels were detected in the culture supernatant of SCW-stimulated synovial explants from IL-23p19-deficient mice compared to control mice.

Conclusion: These data show a critical role for IL-23 in the development of a TLR2/NOD2-mediated acute joint inflammation and reveal a novel IL-23/TNFalpha axis in this process.

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T-Cell-Related Cytokines Are Inhibited in Response to Tocilizumab in Patients with Rheumatoid Arthritis in Contrast with TNF-Inhibitor. Jiro Yamana[1], Mitsuyoshi Iwahashi[2], Motoaki Kim[1], Rie Sasaki[1], Keisuke Kobayashi[1], Seizo Yamana[1], Yusuke Sasaki[3], Yasushi Shimonaka[3] and Masahiko Mihara[4]. [1]Higashi-hiroshima memorial Hospital, Hiroshima, Japan, [2]Higashi-Hiroshima Memorial Hospital, Higashi-hiroshima, Japan, [3]Chugai Pharmaceutical Co., Ltd., Kamakura, Kanagawa, Japan, [4]Chugai Pharmaceutical Co., Ltd., Gotemba, Shizuoka, Japan

Background/Purpose: Tocilizumab (TCZ), a humanized monoclonal antibody to the interleukin-6 (IL-6) receptor, inhibits the binding of IL-6 to its receptor, preventing IL-6 signaling. However, the correlation between cytokine profiles and disease activity after TCZ administration in rheumatoid arthritis (RA) has not been clarified. We measured serum concentrations of cytokines in patients received TCZ to identify the mechanisms and predictors of TCZ efficacy in comparison with tumor necrosis factor (TNF) inhibitor.

Methods: In 42 RA patients (27 in the TCZ group, 15 in the TNF-inhibitor group), serum concentrations of IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12(p70), IL-13, IL-17, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage (GM)-CSF, interferon (INF) g, monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein (MIP)-1β, TNFα, chemokine (C-C motif) ligand (CCL)-20, IL-23 and TNF-like weak inducer of apoptosis (TWEAK) before treatment (M0) and after 6 months of treatment (M6) were measured by the multiplex method and ELISA. Clinical response was evaluated with disease activity score 28 using the C-reactive protein (DAS28-CRP) and European League against Rheumatism (EULAR) response criteria.

Results: DAS28-CRP was 4.7 $\pm$ 0.9 (mean $\pm$ SD) in the TCZ group and 5.1 $\pm$ 1.3 in the TNF-inhibitor group (p=0.16) at M0. The ratio of good responders / moderate responders / no responders at M6 was 16/9/2 in the TCZ group and 4/7/4 in the TNF-inhibitor group, respectively. Analysis of the cytokine profiles at M0 and M6 in good responders or moderate responders revealed that T-cell-related cytokines were inhibited mainly in the TCZ group, while chemokines were inhibited mainly in the TNF-inhibitor group (Table). When the cytokines that decreased to less than 40% at M6 were examined in good responders (TCZ group: 16, TNF-inhibitor group: 4), this trend was more pronounced in both groups (Table). Interestingly, the results of a univariate logistic regression analysis showed that M0 cytokines tended to be higher in good responders than in moderate responders.

Difference between TCZ and TNF inhibitor in inhibition of cytokines

	TCZ group	TNF-inhibitor group
Significant inhibition at M6	IL-2, IL-7, IL-8, IL-12, GM-CSF, TNF	IL-6, IL-8, MIP-1β, CCL-20
Among good responders, decrease to $\leq$40% at M6	IL-2, IL-7, IL-10, IL-12, GM-CSF, IFNγ	IL-6, IL-12, CCL-20

* IL-4, IL-5, IL-13, IL-17 and IL-23 were undetectable in more than 50% of RA patients at M0, so they were excluded from the analysis.

Conclusion: Whereas TNF-inhibitor inhibits chemokine type cytokines and might reduce infiltration of inflammatory cells, TCZ inhibits T-cell-related cytokines and might normalize the immunological abnormality. Therefore, it is possible that TCZ can induce a deeper remission than TNF-inhibitors. In patients with high T-cell-related cytokine values before treatment, good response can be expected with TCZ.

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Increased Plasma Levels of IL17F in Rheumatoid Arthritis Patients Are Reduced by Methotrexate and Biologic Agents. Jeffrey D. Greenberg[1], Victoria Furer[1], John Todd[2], Quynh Ann Lu[2], Renita Ramirez[2], Michael Lock[2], Steven B. Abramson[1] and Mukundan Attur[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Singulex, Alameda, California, Alameda, CA

Background/Purpose: A pivotal role of Th17 cells and related cytokines have been recognized in RA. Multiple isoforms of IL17 have been discovered, including IL17A, IL17F and IL17AF, but have not been well characterized in RA patients (pts).

Methods: Using plasma samples from cohorts of RA pts (N= 149) and a knee osteoarthritis (OA) pts (N= 128) serving as controls, we assayed IL17A, IL17F, IL17A/F and a panel including IL1Ra, IL6, IL6R, TNF, sTNFRII, pro-MMP9, MMP9, VEGF, and CRP. The RA cohorts consisted of 78 RA pts off any DMARDs and 71 RA pts with pre/post samples including 33 anti-TNF starts, 27 abatacept starts and 11 methotrexate (MTX) starts.Assays were performed using a fluorescence based, highly sensitive Erenna Immunoassay system (Singulex, Inc). Clinical assessments included DAS28-ESR. Median values between RA vs OA patients were compared using the Wilcoxon rank sum test and adjusted comparisons for age and gender were made using multivariate linear models. Correlations of markers were assessed using Spearman rank correlations. The change in marker value with treatment was assessed by the ratio of the post-drug value to the pre-drug value. Marker and ratio values were log-transformed.

Results: ***RA vs OA (Control) Disease Comparisons:*** Plasma levels of IL17A, IL17A/F and IL17F were all significantly increased in RA vs OA patients, but the magnitude of differences varied. Median IL17F levels in RA (78.0 pg) were approximately 18-fold higher than OA patients (4.4 pg), $p<0.001$ in unadjusted comparisons, and remained significant ($p<0.001$) in adjusted comparisons. The difference between cohorts in IL17A and IL17AF was smaller in magnitude (0.3 vs 0.2 pg, $p<0.001$ and 2.6 vs 2.1 pg, $p=0.004$, respectively), although the latter difference was not significant in adjusted models. Within the RA cohort, correlation between DAS28 and IL17F was weak (rho = 0.32) and almost nonexistent between DAS28 and IL17A (rho = 0.11). RA pts also exhibited statistically significantly higher levels of the following proteins: IL1Ra, IL6, IL6R, pro-MMP9, VEGF, sTNFRII and CRP.

Pre and Post Drug Cohorts: Significant reductions were observed for multiple biomarkers across drug categories (Table), including a consistent reduction of IL17F across drug classes for abatacept ($p<0.001$), anti-TNFs ($p=0.02$) and MTX ($p=0.006$). Neither IL17A nor IL17AF was significant reduced with abatacept, anti-TNFs or MTX.

Table. Change in Plasma Biomarkers with DMARD Interventions

Biomarker	Abatacept (N=27)		Anti-TNF (N=33)		Methotrexate (N=11)	
	Post/Pre Treatment Ratio (Median)	p-value	Post/Pre Treatment Ratio (Median)	p-value	Post/Pre Treatment Ratio (Median)	p-value
CRP	0.88	NS	0.75	0.009	0.56	NS
VEGF	0.82	0.02	0.64	NS	1.05	NS
IL-17A	1.15	NS	0.86	NS	0.77	NS
IL-17F	0.69	<0.001	0.85	0.02	0.47	0.006
IL-17 A/F	0.97	NS	0.76	NS	0.77	NS
IL-6	0.92	NS	0.83	0.04	0.38	0.007
IL-6 R alpha	1.03	NS	0.98	NS	1.06	NS
Total MMP9	0.85	NS	0.70	NS	1.1	NS
pro MMP9	0.69	0.04	0.80	NS	1.22	NS
TNF-alpha	0.91	NS	1.96	<0.001	0.61	NS
sTNF RII	0.90	0.01	1.17	0.03	1.02	NS

Conclusion: 1. Although both IL17A and IL17F plasma levels are increased in RA patients, the magnitude of elevation for IL17F in RA patients was much higher than IL17A.

2. Plasma levels of IL17F but not IL17A were consistently reduced by 3 efficacious drug classes, suggesting that inhibiting IL17F, in addition to IL17A, may relate to RA drug efficacy. Further mechanistic studies are required.

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Decrease of Serum IL-35 Predicts Clinical Improvement in Patients with Very Early RA. Ladislav Senolt[1], Mária Filková[1], Hana Hulejová[1], Lucie Andrés Cerezo[1], Ondrej Pecha[2], Lenka Plestilová[1], Katerina Jarosova[1], Karel Pavelka[1], Jiri Vencovsky[1] and Herman F. Mann[1]. [1]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Institute of Biophysics and Informatics, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic

Background/Purpose: Interleukin-35 (IL-35) is a member of the IL-12 cytokine family. Although IL-35 has been recently described as an anti-inflammatory cytokine in mice (1), recent studies have questioned this finding. We have previously found increased levels of IL-35 in synovial fluids of patients with rheumatoid arthritis (RA) and rather pro-inflammatory properties of IL-35 in humans (2). The aim of this study was to examine serum levels of IL-35 and to evaluate its response to treatment in patients with very early RA (VERA).

Methods: Patients with VERA fulfilling the ACR/EULAR 2010 classification criteria for RA with symptom duration of <6 months were studied. Disease activity was independently assessed using serum levels of CRP, DAS28-ESR and total swollen joint count (SJC) out of 66 joints prior to (n=54), 12 (n=54) and 24 (n=45) weeks after initiation of treatment. A majority of patients were initially given methotrexate and low dose glucocorticoids. Serum levels of IL-35 were measured by ELISA (USCN Life Science) in patients with VERA at baseline and at week 12 and cross-sectionally in 49 healthy controls. If the concentration of IL-35 was bellow detection limit, it was assessed as a minimal detection limit (0.70 pg/ml).

Results: Levels of serum IL-35 were significantly higher in patients with VERA compared with healthy individuals (median [max-min]: 41.51 [0.70–379.70] vs. 32.55 [0.70–238.10] pg/ml; p=0.015) and significantly decreased after the treatment (2.48 [0.70–258.90] pg/ml; p<0.001). The level of IL-35 was bellow detection limit in 9 healthy controls, in 9 patients with VERA at baseline and in 24 patients with VERA after the treatment. IL-35 significantly correlated with disease activity as assessed by CRP (r=0.410, p=0.002), DAS28 (r=0.388, p=0.004) and SJC (r=0.320, p=0.018) at baseline and changes in IL-35 correlated with clinical improvement as assessed by change in CRP (r=0.422, p=0.002), DAS28 (r=0.465, p=0.001) and SJC (r=0.354, p=0.029) after 12 weeks of the treatment. Furthermore, decrease in IL-35 from baseline to week 12 significantly predicted clinical improvement as assessed by change in CRP (r=0.521, p<0.001), DAS28 (r=0.371, p=0.012) and SJC (r=0.345, p=0.020) over 24 weeks. There was no correlation between IL-35 and RF or ACPA serum levels at any time points.

Conclusion: This is the first study to show elevated serum levels of IL-35 in patients with VERA. The decrease of IL-35 levels following treatment and correlation of IL-35 with various disease activity parameters indicate that IL-35 may be a good biomarker of disease activity and may even be considered for early prediction of treatment response in patients with RA.

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Vitamin D Deficient Healthy Individuals Have Decreased Activated T Cells and Altered Lymphocyte Responses to Cytokine Stimulation. Lauren L. Ritterhouse[1], Holden T. Maecker[2], Hongwu Du[3], C. Garrison Fathman[4], Joel Guthridge[1] and Judith A. James[5]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University School of Medicine, Stanford, CA, [3]Stanford University School of Medicine, Stanford, CA, [4]Stanford Univ Medical Center, Stanford, CA, [5]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: Vitamin D has been shown to possess many different immunomodulatory functions. Additionally, epidemiologic evidence has associated vitamin D deficiency with many autoimmune disorders as well as infectious diseases. The objective of this study was to examine the effects of vitamin D deficiency on the immune systems of healthy individuals.

Methods: A cohort of 774 healthy individuals were screened for 25(OH)D levels by ELISA. Twenty vitamin D deficient (25(OH)D < 10.5 ng/mL) and 20 matched vitamin D sufficient (25(OH)D > 30 ng/mL) individuals were selected for further analysis. Sera were measured for 52 cytokines using a multiplex bead-based assay and ELISAs. Immune cell phenotyping and phospho-flow cytometry was performed on peripheral blood mononuclear cells. Unpaired t-tests and Mann Whitney tests were used for statistical analyses.

Results: Vitamin D deficient individuals had significantly increased serum levels of hsCRP, leptin, and GM-CSF (p=0.005, p<0.001, p=0.003, respectively), although the associations with hsCRP and leptin were confounded by BMI. Vitamin D deficient individuals also had decreased percentages of activated CD4+ and CD8+ T cells (HLA-DR+CD38+) (p=0.021 and p=0.028). Vitamin D deficient individuals had decreased pSTAT1 in response to IL-2 and IL-10 stimulation in CD4+ T cells (p=0.007 and p=0.014), and increased pSTAT1 and pSTAT3 in response to IFNγ stimulation in CD4+ T cells (p=0.006 and p=0.033). Deficient individuals had decreased pSTAT1 responses to IL-2, IL-10, and IL-21 stimulation in CD8+ T cells (p=0.018, p=0.049, and p=0.032, respectively). Deficient individuals also had increased pSTAT3 in response to IFNα stimulation in B cells (p=0.043), while they had decreased pSTAT1 in response to IL-2, IL-6, IL-10, and IL-21 stimulation in B cells (p=0.005, p=0.016, p=0.003, and p=0.042, respectively).

Conclusion: The presence of decreased activated T cells in vitamin D deficient individuals as well as altered lymphocyte signaling responses to cytokine stimulation may contribute to systemic autoimmune rheumatic diseases, as well as other vitamin D deficient associated disease states.

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Hypoxia and Inflammation Synergistically Promote Bone Destruction. Shankar Revu[1], Vivekananda Sunkari[2], Akilan Krishnamurthy[3], Ileana R. Botusan[2], Sergiu-Bogdan Catrina[2] and Anca Irinel Catrina[4]. [1]Rheumatology unit, Stockholm, Sweden, [2]Stockholm, Sweden, [3]Karolinska Institute, Karolinska University Hospital, Solna, Stockholm, Sweden, [4]D2:01, Stockholm, Sweden

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial inflammation and consecutive local hypoxia, leading to cartilage and bone destruction. Hypoxia promotes osteoclasts formation in vitro but its role in mediating bone destruction in the presence of chronic inflammation has not previously been investigated. We aimed to investigate the effect of hypoxia on the RANKL/OPG system and bone destruction in the presence of pro inflammatory stimuli

Methods: We investigated the in vitro effect of hypoxia on RANKL/OPG expression in osteoblast-like (Saos2) cells. Cells were cultured in normoxic (21% pO_2) or hypoxic (1% pO_2) conditions with or without TNFα. Expression of RANKL and OPG mRNA was detected by rtPCR. Cellular and soluble forms of RANKL and OPG proteins were determined by Western blot and ELISA respectively. Hypoxia effect on bone resorption was evaluated in a dentine pit formation assay using peripheral blood mononuclear cells from RA patients. Statistical analysis was performed using one-way ANOVA

Results: Exposure to hypoxia induced a significant increase in cellular RANKL mRNA and protein expression, with minimal changes of the cellular OPG. In contrast soluble OPG levels significantly decreased following hypoxia exposure with no changes in the soluble levels of RANKL. Small interfering RNA against HIF2alpha but not HIF1alpha was able to abolish hypoxia effect on cellular RANKL expression. Concomitant exposure to both hypoxia and TNFα had an additive effect resulting in a further increase of the

RANKL/OPG ratio. Hypoxia mimicking by prolyl hydroxylases inhibitors acted synergistically with TNF in inducing pit formation and resorption on synthetic osteologic bone discs

Conclusion: TNF and hypoxia act synergistically to promote bone destruction potentially through a HIF2alpha dependent mechanism. These findings add on the current understanding of bone destruction in the setting of chronic inflammation.

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Anti-TNF Therapy Sensitizes Rheumatoid Arthritis Monocytes to TRAIL-Induced Apoptosis Via Inhibition of Pro-Survival Effects of Soluble TNF. Undine Meusch[1], Manuela Rossol[2], Dagmar Quandt[1], Christoph G. Baerwald[3] and Ulf Wagner[1]. [1]University of Leipzig, Leipzig, Germany, [2]Translationszentrum für Regenerative Medizin (TRM), University of Leipzig, Leipzig, Germany, [3]University Hospital, Leipzig, Germany

Background/Purpose: The autoimmune disease rheumatoid arthritis (RA) is characterized by the production of monocytic cytokines like TNF alpha and IL-1 beta. Both cytokines induce increased survival rates in monocytes. The role of TRAIL in RA has not been intensively studied. Induction of apoptosis by TRAIL is a classic functional consequence, but its effect on primary monocytes has not been investigated. Apoptosis is mediated by the activating TRAIL receptors 1 and 2 and inhibited by receptors 3 and 4. Aim of the study was to analyze TRAIL-induced apoptosis of monocytes from healthy donors and patients with rheumatoid arthritis (RA).

Methods: Monocytes isolated from the peripheral blood of healthy donors (HD) and of RA patients (without or with anti-TNF therapy) were incubated with 100 ng/ml TRAIL for 16h. Subsequently TRAIL induced apoptosis was measured via annexinV/PI staining. Production of different pro-inflammatory cytokines was analyzed by ELISA. Expression levels of all TRAIL receptors and membrane TRAIL (mTRAIL) were detected by flow cytometry. To analyse the influence of sTNF and IL-8 on TRAIL induced apoptosis and IL-8 production, HD monocytes were pre-incubated with 100 pg/ml TNF for 1h before stimulation with TRAIL. Subsequently apoptosis rate, expression of TRAIL receptors and TRAIL induced IL-8 production were analyzed.

Results: Monoctyes of RA patients show resistance to TRAIL-induced apoptosis while HD monocytes undergo apoptosis in response to TRAIL. Interestingly, RA monocytes show decreased expression levels of all TRAIL receptors and mTRAIL. However, TRAIL induces an increased IL-8 production in RA monocytes but not in HD monocytes. Production of IL-1beta, IL-6 and TNF remain unaffected by TRAIL in both analyzed groups. Analysis of TRAIL-induced apoptosis in HD monocytes shows that pre-incubation with soluble TNF or IL-8 has an inhibitory effect on TRAIL-induced apoptosis, pointing to a role of the pro-inflammatory cytokine milieu in influencing monocyte functions. sTNF pre-incubation also led to TRAIL-induced IL-8 production in HD monocytes and decreased expression of TRAIL R1, R2 and R4. Surprisingly, in monocytes from RA patients treated with anti-TNF reagents, TRAIL-induced apoptosis is comparable to HD monocyte apoptosis levels. Additionally, no TRAIL-induced IL-8 production was detectable.

Conclusion: A pro-inflammatory cytokine milieu induces resistance to TRAIL-induced apoptosis in RA monocytes. The treatment with anti-TNF reagents overrides this resistance and sensitizes RA monocytes to TRAIL-induced apoptosis.

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Regulation of Suppressor of Cytokine Signaling-1, -2 and -3 Expression in Patients with Early Arthritis. Ricardo J. Villares[1], Amalia Lamana[2], Coloma Costas[1], Ana M. Ortiz[2], Mercedes López-Santalla[1], Mario Mellado[1] and Isidoro González-Alvaro[2]. [1]Centro Nacional de Biotecnología. CNIC, Madrid, Spain, [2]Hospital Universitario de La Princesa. IIS Princesa, Madrid, Spain

Background/Purpose: Most cytokines involved in the pathogenesis of Rheumatoid Arthritis (RA) act through receptors that trigger several signal transduction pathways that are initiated by JAK/STAT activation. The activation of this system triggers up-regulation of many genes, including those that encode suppressor of cytokine signaling proteins (SOCS). Mice lacking SOCS3 show severe joint inflammation as well as those lacking SOCS1 and IFN-γ. By contrast, SOCS3 overexpression affects T cell responses and prevents development of collagen-induced arthritis. Studies based on SOCS expression in RA patients are very limited and contradictory. Therefore, the objective of our work was to study the expression of SOCS1, SOCS2 and SOCS3 during the follow-up of patients with early arthritis (EA).

Methods: We have studied 144 patients from our EA register (82% female, median age 53 y-o). Demographic, disease related variables, as well as treatment prescribed were systematically recorded and blood samples were obtained at each visit (baseline, 6, 12, 24 and 60 months). The expression levels of SOCS1, SOCS2 and SOCS3 and β-actin as housekeeping was determined through real-time PCR in 223 mRNA samples obtained from the peripheral blood mononuclear cells. RT-PCR data were normalized against β-actin expression and ΔΔCt were determined against the mean expression of SOCS genes in 17 healthy volunteers (53% female, 42.5 y-o). In 45 cases there were two-three samples including the baseline visit (114 samples) allowing us to study the transcriptional regulation of these three genes. To determine the effect of independent variables on levels of SOCS expression, we fitted population-averaged models by generalized linear models, nested by patient and visit, using the *xtgee* command of Stata 10.1 for Windows (StataCorp LP, College Station, TX, USA).

Results: The baseline samples of patients showed significantly lower levels of SOCS1 (median ΔΔCt 0.7 [IQR: 0.365–1.375] vs 1.31 [0.96–1.64]; $p=0.02$) and SOCS3 (0.63 [0.29–1.54] vs 0.95 [0.77–1.97]; $p=0.03$) compared to controls. In addition, all three SOCS showed down-regulation of their levels during the follow-up. The decrease in SOCS expression reached statistical significance only when we compared samples from baseline and 12 months visit ($p=0.05$ for SOCS1 and $p=0.01$ for SOCS2). The decrease of SOCS3 expression did not reach statistical significance at any time. In addition, the multivariable analysis showed that the expression of all three SOCS significantly correlated with the swollen joint count at each visit, but not with tender joint counts, patient global disease assessment or C-reactive protein. In addition, elderly patients showed significantly lower SOCS3 expression.

Conclusion: The expression of SOCS in peripheral blood mononuclear cells from patients with early arthritis seem to be lower than that of healthy controls even at baseline when the expression of these molecules are up-regulated due to a higher disease activity (number of swollen joints).

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Expression Levels of Interleukin-17A, Interleukin-17F and Their Receptors in Synovium of Patients with Rheumatoid Arthritis, Psoriatic Arthritis and Osteoarthritis: A Target Validation Study. Lisa G.M. van Baarsen, Maria C. Lebre, Dennis van der Coelen, Danielle M. Gerlag and PP. Tak. Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Accumulating evidence suggests an important role for interleukin (IL)-17 in the pathogenesis of several inflammatory diseases, including rheumatoid arthritis (RA). IL-17A has been well studied in models of arthritis, but little is known about the relative expression and cellular source(s) of IL-17A, IL-17F, and their receptors in human synovial tissue. The current study is aimed to determine the origin and expression of IL-17A, IL-17F and their receptors IL-17RA and IL-17RC in synovial tissues of patients with RA, psoriatic arthritis (PsA) and inflammatory osteoarthritis (OA).

Methods: Synovial biopsy specimens were obtained by arthroscopy from patients with RA ($n=13$), PsA ($n=15$) and inflammatory OA ($n=14$). For comparison synovial tissues from non-inflammatory controls ($n=7$) were included. Immunohistologic analysis was performed on frozen sections using monoclonal antibodies specific for IL-17A, IL-17F, IL-17RA and IL-17RC. Stained sections were evaluated by digital image analysis. Immunofluorescence analysis was performed using antibodies specific for T cells (CD4, CD8), neutrophils (CD15), macrophages (CD68, CD163), B cells (CD19), endothelial cells (CD31, Von Willebrand Factor, PNAd), lymphatics (Lyve-1) and mast cells (mast cell tryptase). Stained sections were evaluated by confocal microscopy.

Results: Levels of IL-17A, IL-17F, IL-17RA and IL-17RC were abundantly present in synovial tissues of all patient groups and highly variable between patients. Whereas IL-17RA was mostly present in the synovial sublining, IL-17RC was abundantly expressed in the intimal lining layer. Digital image analysis showed a significant increase of IL-17A but not of IL-17F, IL-17RA and IL-17RC in patients with arthritis compared to non-inflamed control tissues (Table 1), while the expression of IL-17A, IL-17F and IL-17RA was similar between the different patient groups. Expression of IL-17RC in the intimal lining layer was significantly increased in PsA compared to OA patients ($p<0.05$). IL-17A was found to be expressed by CD4 and CD8 positive cells, while CD15, CD19 and mast cell tryptase (MCT) positive cells were negative. IL-17F was not expressed by CD4, CD8,

CD15 and MCT positive cells in the synovial tissues of arthritic patients. Interestingly, IL-17A and IL-17F staining was also observed in some macrophages as well as in endothelial cells and lymphatics.

Table 1. IL-17 expression in synovial tissues as determined by immunohistochemistry

	Non-inflammatory controls (n=7)	Inflammatory arthritis (n=42)	p-value
IL-17A	351 (15–8,934)	6,827 (2,131–24,925)	*0.0089*
IL-17F	1,831 (303–4,120)	1,871 (445–4,519)	0.7642
IL-17RA	11,281 (2,564–39,076)	3,067 (332–57,222)	0.5580
IL-17RC in intimal lining layer	13,604 (8,441–63,165)	71,373 (1,292–417,194)	0.3494

Data given as median integrated optical density per mm2 (25th–75th percentile); p-value determined using the appropriate T test.

Conclusion: Increased expression of IL-17A is not restricted to synovial tissues of RA patients but also observed in other forms of inflammatory arthritis. In inflamed synovium various cell types contribute to the production of IL-17A and IL-17F. IL-17 blockade could provide a novel therapeutic approach in a variety of arthritides.

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Type I Interferon and Clinical Phenotype in Idiopathic Inflammatory Myopathies. Louise Ekholm[1], Anna Tjärnlund[1], Clio P. Mavragani[2], Peter J. Charles[3], Leonid Padyukov[1], Mary K. Crow[4] and Ingrid E. Lundberg[5]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [2]Department of Experimental Physiology, School of Medicine, University of Athens, Athens, Greece, [3]Kennedy Institute of Rheumatology, Imperial College, London, United Kingdom, [4]Hospital for Special Surgery, New York, NY, [5]Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are rare autoimmune diseases characterized by proximal muscle weakness and muscle inflammation. Recent studies suggest a pathogenic role for type I interferon (IFN) in IIM patients, particularly within the subgroup dermatomyositis (DM). Expression of type I IFN and IFN-regulated genes, the IFN signature, in muscle tissue and skin biopsies from DM patients have been reported. Studies indicate that an IFN signature in peripheral blood cells of patients correlates to disease activity although results are contradictory. Autoantibodies are a characteristic feature of IIM, and immune complexes have been demonstrated to induce type I IFN expression in target cells. Its effect and correlation with clinical phenotype are, however, poorly understood.

The aim of this study was to examine if the type I IFN activity of sera from IIM patients correlates with disease activity, clinical manifestations, autoantibody profile, or HLA haplotype.

Methods: Clinical, serological, genetic and laboratory data were collected from a cohort of IIM patients with the diagnoses DM, polymyositis (PM), inclusion body myositis (IBM) and juvenile dermatomyositis (JDM). Patient sera were assessed for their type I IFN activity using an *in vitro* system with the WISH epithelial cell line. Expression of IFN-inducible genes, IFIT1, IFI44, and MX1, which are preferentially induced by IFN-alpha, were quantified using real time-PCR. Two groups of patients, IFN+ (N=13) and IFN- (n=119), were categorized based on IFN score, the sum of the individual gene expression scores. Differences between the two groups were assessed for clinical, serological and genetic variables, as well as correlation between IFN score and variables.

Results: The proportion of the IIM subgroups within the IFN+ and IFN- patient groups was equal. No correlation between the type I IFN activity in sera from IIM patients and disease activity was found for any of the IIM subgroups. No significant differences between the two patient categories for any of the assessed clinical or laboratory variables were found. Autoantibody analysis demonstrated that significantly more IFN+ patients were positive for anti-nuclear antibodies (ANA) compared to IFN- patients (p=0.001). HLA-DRB1 typing of patients revealed no differences between the two patients groups. Interestingly, the IFN- patients had a significantly higher prednisolone dose compared to the IFN+ patients (p=0.002). Moreover, a trend for higher self-perceived pain among the IFN+ patients was found.

Conclusion: Our findings show that type I IFN activity in patient sera can be found for all major subgroups of IIM and does not correlate with disease activity. Ability to induce expression of IFN-regulated genes was found to be associated with presence of ANA. This is in line with reports demonstrating nucleic acid containing immune complexes and their interaction with specific TLRs and induction of type I IFNs. In agreement with studies showing suppression of type I IFNs by glucocorticoids, the type I IFN activity in sera was lower for patients receiving higher dose of cortisone treatment.

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Comparative Cytokine Analysis Across a Spectrum of Genetically and/or Clinically Defined Auto-Inflammatory Syndromes. Apostolos Kontzias[1], Yongqing Chen[1], Nicole Plass[1], Damaris Garcia[1], Elizabeth Joyal[1], Robert Wesley[2] and Raphaela T. Goldbach-Mansky[1]. [1]National Institutes of Health Clinical Center, Bethesda, MD, [2]National Insitutes of Health Clinical Center, Bethesda, MD

Background/Purpose: Auto-inflammatory diseases constitute a group of disorders that manifest systemic inflammation in the absence of infection, auto-antibodies or auto-reactive T cells. A specific genetic mutation is identified in some of them, such as in Neonatal Onset Multisystem Inflammatory Disease (NOMID) or Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (CANDLE) syndrome, while in others such as Chronic Recurrent Multifocal Osteomyelitis (CRMO), and Adult onset Still's Disease (AOSD) a specific cause is yet to be elucidated. The rapid response to targeted cytokine blocking therapies suggests that these disorders are mediated by specific cytokines. Herein we investigate whether each disease is characterized by a specific cytokine signature.

Methods: Serum samples, on visits when patients had clinically active disease, were collected and assayed by Luminex for the presence of 43 inflammatory cytokines at 9timepoints. Disease groups (mutation positive and negative NOMID; CANDLE syndrome; CRMO; adult and pediatric Still's disease; rheumatoid arthritis, including juvenile idiopathic arthritis were compared to normal controls whose assays were run at the same time. Ratios of patient values divided by the average of corresponding set of healthy control values were statistically tested for whether they significantly differed from 1 and also among the various disease groups.

Results: A distinct cytokine profile is found in different auto-inflammatory diseases. Specifically, AOSD is characterized by markedly increased levels of Interleukin-18 (p= 0.005, mean= 3.068) and IL-1a (p= 0.032, mean= 1.5687) compared to controls. NOMID mutation positive patients had increased levels of IL-1a (p= 0.00078, mean=1.7819), IL-6 (p 0.001, mean=1.5376) and IL-18 (p= 0.001, mean=1.4924) compared to controls and NOMID mutation negative patients. Il-18 levels in AOSR patients were actually significantly higher than in patients with mutation positive and negative NOMID. CANDLE patients have highly increased IFNg inducing protein 10 (IP-10) levels (p= 0.00053, mean=3.9872) compared to controls and the other autoinflammatory diseases. CRMO patients had low levels of IL-8 (p= 0.005, mean= 0.1697), GM-CSF (p= 0.00684, mean= 0.0969) and MCP-1 (p2=0.002,mean= 0.0687) compared to controls and other diseases. These differences in cytokine profiles disappeared when patients were on effective therapies.

Conclusion: During active disease specific cytokine profiles may allow us to detect dysregulated cytokine pathways that discriminate between clinically different autoinflammatory syndromes. A comprehensive approach of cytokine profiling may be useful to develop a therapeutic plan. Further studies are needed to determine it this approach can be used to monitor therapy and help in the definition of inflammatory disease remission in patients with a number of autoinflammatory disorders.

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PGE2 and FGF-2 Upregulate Activities of the Human F-Spondin Promoter. Mukundan Attur[1], Yang Qing[2], Jinhua Wang[3], Kimberlee Mix[4], Glyn Palmer[1] and Steven B. Abramson[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]New York University School of Medicine, New York, NY, [3]New York University Cancer Institute, New York, NY, [4]Loyola University New Orleans, New Orleans, LA

Background/Purpose: The extracellular matrix protein, F-spondin is a marker of both hypertrophic and osteoarthritic cartilage. Understanding the mechanisms that regulate its expression could therefore identify key pathways that regulate chondrocyte activity in development and disease. In this study we investigated transcriptional regulation of human F-spondin via the cloning and characterization of its 5' regulatory (promoter) region.

Methods: Genomic sequence containing the 5' regulatory region of F-spondin was obtained by PCR of human total genomic DNA (Clontech) using upstream primers designed from F-spondin genomic sequence available at the gene database www.ncbi.nlm.nih.gov, gene ID: 10418. PCR fragments

were cloned into pGL3 Luciferase Reporter Vectors (Promega) for functional analysis. Luciferase assays were performed 36 h after transfection in the human chondrosarcoma cell line, SW1353.

Results: An upstream 2.4 kb genomic sequence of human F-spondin was obtained by PCR, subcloned and sequenced bidirectionally. DNA sequence fidelity was confirmed using the NCBI blast alignment search tool. DNA sequence analysis revealed the presence of TATA box at position -74 and identification of transcription factor binding sites was performed using the JASPAR CORE database (http://jaspar.genereg.net/). High scoring putative binding sites within the 2.4 kb promoter region included NURR1 (NR4A2-nuclear receptor), NFAT, SOX-10 and CREB1. Functional promoter activity was assessed by transient transfection of pGL3 luciferase vectors encoding 2.4 kb (pFS-2.4Luc) and 0.5 kb (pFS-0.5Luc) of F-spondin upstream genomic sequence. In human chondrocytes, both pFS-2.4Luc and pFS-0.5Luc significantly increased luciferase activity above a pGL3 promoterless control vector, 20- and 70-fold, respectively. Since we have previously observed that F-spondin mRNA levels are induced by FGF-2 and PGE2 in OA chondrocytes, we examined their effects on promoter activity. PGE2 (10 uM) stimulated F-spondin luciferase activity 10–20-fold for both 2.4 and 0.5 kb promoter constructs ($p<0.001$) above unstimulated controls. Cotransfection of a cDNA encoding NURR1, a transcription factor induced by PGE2 in human chondrocytes, also increased luciferase activity (100-fold) irrespective of promoter length. This is consistent with the presence of multiple putative NURR1 binding sites (~16) throughout the 2.5 kb promoter region. Conversely, FGF-2 (25 ng/ml) significantly increased luciferase activity of pFS-0.5Luc (2-fold; $p<0.05$) but not pFS-2.4Luc. This finding suggests that regulation of F-spondin via FGF-2 occurs via regulatory regions within its proximal 0.5 kb region.

Conclusion: Our results indicate that both developmental (FGF-2) and proinflammatory (PGE2) factors induce F-spondin expression in chondrocytes via discrete regions in its promoter. Sequence analysis and transfection studies suggest that NURR1 may mediate PGE2 induction of F-spondin via multiple binding sites in the promoter region. The current findings are consistent with previous observations demonstrating overlapping pro-inflammatory/catabolic effects of PGE2, NURR1 and F-spondin in OA chondrocytes.

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Correlation of Vascular Endothelial Growth Factor and Interleukin-6 Levels with Power Doppler Ultrasound of Synovial Joints in Early Inflammatory Arthritis. Joanne Kitchen[1] and David Kane[2]. [1]Adelaide and Meath Hospital, Dublin, Ireland, [2]Adelaide, Meath hospital Dublin (incorporating the National Children's hospital), Dublin 24, Ireland

Background/Purpose: To correlate Power Doppler ultrasound findings in peripheral joints of patients with early inflammatory arthritis with serum levels of IL-1α, IL-1β, IL-2, IL-4, IL6, IL-8, IL-10, VEGF, TNFα, and IFNγ

Methods: Fifty-five patients diagnosed with early inflammatory arthritis completed clinical and serological assessments (DAS 28 CRP, HAQ, EUROQOL, SF-36, ESR and CRP) at baseline (T0), 3 months (T3) and 6 months (T6), with 30 completing a 12 month assessment. Standard greyscale and power Doppler ultrasound examination of the DAS28 joint set plus ankles and metatarsophalangeal joints was performed by a single ultrasonographer (JK) in pre-selected imaging planes [EULAR standardised, MyLab70 XVG system (Esaote, Genoa, Italy)]. Serum samples were analysed for IL-1α, IL-1β, IL-2, IL-4, IL6, IL-8, IL-10, VEGF, TNFα, and IFNγ using the Evidence Investigator™ biochip array (Randox).

Results: There was a significant reduction in greyscale and power Doppler scores from T0 to all subsequent time-points. Both ESR and CRP correlated significantly with both GS and power Doppler scores at baseline ($p < 0.0005$ for all Spearman's rho) but this correlation was reduced following treatment (T3, T6, T12). DAS28 scores correlated significantly with both ultrasound scores but there was less consistent correlation of ultrasound scores with HAQ and SF36. Serum levels of IL-6 correlated significantly with total greyscale ultrasound scores at all time-points during the study. Levels of VEGF correlated significantly with total greyscale scores at T0, T6 and T12 but not at T3. Correlations between each cytokine and the corresponding power Doppler score were evaluated, including data from 26 normal control patients. This resulted in correlation of 198 data sets to determine the overall correlation between power Doppler and each cytokine. The strongest correlation was seen between power Doppler and IL-6 ($r = 0.427$, $p < 0.0005$) and there was a significant correlation between VEGF and power Doppler ($r = 0.203$, $p = 0.004$). Significant correlations were seen between power Doppler and IL-2 ($r = 0.280$, $p < 0.0005$), IL-10 ($r = 0.226$, $p = 0.001$), IL-1α ($r = 0.224$, $p = 0.002$), IL-1β ($r = 0.193$, $p = 0.006$) and MCP-1 ($r = 0.16$, $p = 0.024$).

Conclusion: Power Doppler and greyscale ultrasound correlate significantly with clinical parameters of inflammation and with serum levels of IL-6 and VEGF in patients with early inflammatory arthritis. IL-6 and VEGF are further implicated in the pathogenesis of the power Doppler signal from inflamed synovial joints.

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Preferential Inhibition of IL-6 TRANS-Signaling Shows Potent Anti-Inflammatory Activity *In Vivo*: The Potential of NI-1201, a Novel Fully Human IL-6R Monoclonal Antibody. Florence Guilhot[1], Vanessa Buatois[1], Laurence Chatel[1], Laura Cons[1], Eric Hatterer[1], Greg Elson[1], Suzanne Herren[1], Giovanni Magistrelli[1], Pauline Malinge[1], Simon Jones[2], Manuela Gabler[3], Thomas Kamradt[3], Cristina de Min[1], Marie Kosco-Vilbois[1] and Walter Ferlin[1]. [1]NovImmune S.A., Plan-Les-Ouates, Geneva, Switzerland, [2]Cardiff University, Cardiff, United Kingdom, [3]Institute of Immunology, Jena University Hospital, Jena, Germany

Background/Purpose: Preclinical animal models and successful clinical studies have validated targeting the IL-6 pathway in chronic inflammatory diseases. IL-6 acts via binding to either membrane IL-6-Receptor (mIL-6R), termed CIS-signaling, or soluble IL-6R (sIL-6R) known as TRANS-signaling. TRANS-signaling is characteristically involved in endothelial cell activation and mononuclear cell recruitment, while CIS-signaling in mediating IL-6 effects on hepatocytes and activating naive T cells. With the objective of optimizing the efficacy/safety balance of IL-6 pathway targeting, we aimed to generate a fully human IL-6R monoclonal antibody (mAb) that more efficiently targets TRANS-signaling.

Methods: The fully human mAb, NI-1201, that targets an IL-6R epitope important for binding to the signal-transducing (gp130, CD130) receptor subunit was generated. NI-1201 was tested in synovial explant cultures obtained from RA patients and benchmarked to Tocilizumab. Furthermore, the corresponding mouse surrogate antibody was tested in murine models of inflammatory disease.

Results: Functional *in vitro* assays to measure IL-6 TRANS-signaling, using human-gp130-transfected BAFF-cell proliferation, NI-1201 demonstrated superior neutralization capability when compared to Tocilizumab. Biacore analysis showed high affinity of NI-1201 for soluble IL-6R and IL-6/IL-6R complex (IL-6Rc): 0.06nM and 5.64 nM, respectively. To study and compare the contribution of the different signaling mechanisms *in vivo*, we used the G6PI arthritis model of arthritis and representative anti-mouse mAbs. Administration of 1F7, the NI-1201 mouse surrogate mAb, demonstrated superior efficacy in terms of clinical manifestations as compared to the Tocilizumab-like mAb, 2B10 (area under the curve, for clinical score as measured by paw thickness in mm *versus* days post G6PI immunization, was calculated and demonstrated a significant difference ($p=0.0317$) between 1F7, 10 ± 6 mm.day, and 2B10, 74 ± 22 mm.day). 1F7 also demonstrated improved efficacy when administered therapeutically in the MOG-induced model of Multiple Sclerosis (MS). 1F7 controlled inflammation yet spared CIS-signaling mediated IL-6 effects, such as acute phase protein production by the liver (SAA induction).

Conclusion: NI-1201 is a fully human mAb with high affinity for IL-6R and sIL-6Rc, blocking the latter from binding to gp130. NI-1201 potently blocks IL-6 TRANS-signaling-dependent proliferation *in vitro*. Using the NI-1201-surrogate mAb 1F7 in animal models, we show superiority with improved efficacy in an arthritis and an MS model. Furthermore, while controlling inflammation, 1F7 preserved important physiological functions of IL-6 such as the liver acute phase response.

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Interleukin-22 Promotes Osteoclastogenesis in Rheumatoid Arthritis Through Induction of Receptor Activator of Nuclear Factor-Kb Ligand From Synovial Fibroblasts. Sang-Heon Lee[1], Jung-Hwa Lee[1], Hae-Rim Kim[1] and Kyoung-Woon Kim[2]. [1]Konkuk University Medical Center, Seoul, South Korea, [2]Konkuk University, Institute of Biomedical Science and Technology, South Korea

Background/Purpose: This study aims to determine the regulatory role of interleukin(IL)-22 on the expression of receptor activator of NF-kB ligand(RANKL) and the induction of osteoclastogenesis in rheumatoid arthritis(RA).

Methods: The concentrations of IL-22 and RANKL in sera and synovial fluids(SF) of RA patients were measured using ELISA. After RA synovial

fibroblasts were treated with rhIL-22, the expression of RANKL mRNA and protein was determined using real-time PCR, western blot, and intracellular immunostaining. The IL-22-induced RANKL expression was determined after blockage of intracellular signal molecules. Human monocytes were co-cultured with IL-22-prestimulated RA synovial fibroblasts and monocyte-colony stimulating factor(M-CSF), and then osteoclastogenesis was determined by counting of TRAP-positive multinucleated cells.

Results: SF IL-22 concentration in RA patients was higher than that in osteoarthritis(OA) patients. Serum IL-22 concentration was also higher in RA than OA patients and healthy volunteers. Serum IL-22 concentration was correlated with serum rheumatoid factor titer, and SF IL-22 concentration was correlated with serum anti-cyclic citrullinated peptide antibody titer. When RA synovial fibroblasts were treated with rhIL-22, the expression of RANKL mRNA and protein was increased in a dose-dependent manner. The IL-22-induced RANKL expression was significantly down-regulated by inhibition of p38 MAPK/NF-kB and JAK-2/STAT3. When human monocytes were cultured with IL-22-prestimulated RA synovial fibroblasts in the absence of RANKL, the monocytes were differentiated into osteoclasts, but this osteoclastogenesis was decreased after the inhibition of p38 MAPK/NF-kB and JAK-2/STAT3.

Conclusion: Our results revealed that IL-22 up-regulated RANKL expression in synovial fibroblasts, which facilitated the induction of osteoclastogenesis from precursor cells in rheumatoid joint.

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Leptin Promotes Th17 Responses. Yiyun Yu[1], Yaoyang Liu[1] and Antonio La Cava[2]. [1]UCLA, Los Angeles, [2]Univ of California Los Angeles, Los Angeles, CA

Background/Purpose: Leptin, an adipocyte-derived hormone encoded by the obese (ob) gene, can link nutritional status and immune responses by directly modulating the production of inflammatory mediators and the activation, proliferation and maturation of different immune cell subsets including T cells. The role of leptin in the differentiation and activity of Th17 cells has not been explored, yet this aspect is relevant because of the importance of this T cell population in the promotion of pro-inflammatory and autoimmune responses.

Methods: Th17 cells were compared in the peripheral blood, and IL-17 levels in the plasma, among wilt-type (WT) C57Bl/6J (B6), *ob/ob* leptin-deficient and *db/db* leptin receptor-deficient mice (also on the B6 background). The possibility of direct Th17 cell modulation in the peripheral blood was investigated by administering recombinant leptin to *ob/ob* mice, and the effects of scalar doses of leptin were evaluated on the transcription of the Th17 master regulator RORγt (detected as luciferase activity after retroviral transfection of cells with a reporter construct encoding RORγt). The results were compared to those obtained in (NZB × NZW)F1 (BWF1) lupus-prone mice treated or not with leptin.

Results: Fewer Th17 cells and reduced levels of plasma IL-17 were found in *ob/ob* mice and *db/db* mice as compared with WT mice. Leptin administration in *ob/ob* mice promoted Th17 cell differentiation both *in vivo* and *in vitro*. Leptin upregulated the surface expression of leptin receptor, through which it induced RORγt transcription in $CD4^+$ T cells. In BWF1 lupus mice, leptin facilitated Th17 cell differentiation and expansion, both in vivo and in vitro.

Conclusion: Leptin promotes Th17 response by enhancing RORγt transcription through leptin receptor-mediated signaling. These results suggest that leptin could be targeted for IL-17 modulation in states characterized by autoimmune responses such as in SLE.

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Differential Regulation of Serum Cytokine Profiles In Patients with Rheumatoid Arthritis Treated with Tocilizumab: Possible Involvement of Macrophage Migration Inhibitory Factor. Tsuyoshi Kasama[1], Kuninobu Wakabayashi[1], Takeo Isozaki[2], Hidekazu Furuya[1], Ryo Yanai[1], Kumiko Ohtsuka[1], Michihito Sato[1] and Ryo Takahashi[1]. [1]Showa University School of Med, Shinagawa-ku Tokyo, Japan, [2]University of Michigan Medical School, Ann Arbor, MI

Background/Purpose: To examine the relationship between serum cytokine levels and clinical responsiveness to tocilizumab, a humanized monoclonal antibody specific for the IL-6 receptor, in patients with rheumatoid arthritis (RA) as well as the impact of tocilizumab administration on serum cytokine levels.

Methods: Serum levels of the cytokines TNF-alpha, IL-6, macrophage migration inhibitory factor (MIF), CCL2, CCL3, CXCL8, CXCL10 and CX3CL1 were quantified using double ligand enzyme-linked immunosorbent assays. Measurements were made prior to (i.e., baseline) and after 12 weeks of treatment with tocilizumab (8 mg/kg) in 21 RA patients. The disease status and serum cytokine levels at baseline and 12 weeks after tocilizumab treatment were assessed using the clinical disease activity index (CDAI). The moderate and major responses to tocilizumab were defined as an improvement of greater than 6 and 14 points, respectively, from the baseline CDAI, which is consistent with the improvement criteria proposed by Smolen et al.

Results: At the initiation of therapy, the mean age of patients was 56.1 yrs, mean disease duration was 11.8 yrs, and mean baseline CDAI was 22.4. After 12 weeks of tocilizumab administration, 15 patients achieved a major/moderate response, but there were no significant responses in 6 patients. Although there were no significant correlations between serum levels of any of the cytokines and disease activity (CDAI) at baseline, there was a significant correlation between serum MIF levels and either total tender joint counts or swollen joint counts. Furthermore, there was a significant reduction in MIF, but not other cytokines, in all 21 patients (1857.0 ± 1510.0 to 1401.1 ± 1315.5 pg/ml at week 12, $p = < 0.01$). Basal levels of MIF were significantly higher in the group that responded well to tocilizumab (2065.8 ± 1288.3 pg/ml, $p < 0.01$) than in the unresponsive group (1335.3 ± 818.1). A comparison of patients with lower (<1347 pg/ml; median of MIF levels) and higher (^{3}1347 pg/ml) basal MIF levels revealed no significant differences in CDAI, serum CRP levels or daily prednisolone dosages. However, the percentage of patients with a major/moderate response was statistically higher in patients with higher basal MIF levels compared to those with lower MIF levels. In addition, serum MIF levels were diminished (MIF declined from 2875.5 ± 1407.8 to 1189.7 ± 1070.0, $p < 0.05$) in patients with higher basal MIF levels in response to tocilizumab but not in those with lower basal levels.

Conclusion: Our results suggest that in patients with active RA, serum MIF may be sensitive to tocilizumab therapy and that regulation of MIF via the IL-6/IL-6 receptor plays a crucial role in the pathogenesis of RA.

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Glucosamine Sulphate Reduces the Prostaglandin E_2 Production In Osteoarthritic Cartilage Through the Inhibition of Microsomal Prostaglandin E Synthase-1. Mohit Kapoor, Francois Mineau, Hassan Fahmi, Jean Pierre Pelletier and Johanne Martel-Pelletier. Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC

Background/Purpose: Among the prostaglandins of the E series, PGE_2 is one of the major inflammatory/catabolic mediators involved in cartilage degradation associated with osteoarthritis (OA). Moreover, several of the effects of the catabolic cytokine, IL-1β, are mediated through the stimulation of PGE_2 production. As glucosamine sulfate (GS) has been inferred to have a potential anti-inflammatory effect on OA symptoms, we explored its effect on PGE_2 in human OA chondrocytes and at which level in the PGE_2 pathway its effect takes place. This pathway includes the cyclooxygenases (COX)-1 and -2, the terminal enzyme responsible for PGE_2 synthesis, mPGES-1, as well as its co-factor glutathione and its transcriptional signalling pathway, the early growth response factor (Egr)-1. In addition, as PPAR-g activation inhibits IL-1β induced mPGES-1, we also examined the effect of GS on this factor.

Methods: The effect of GS treatment (0.2, 1, and 2 mM) on human OA chondrocytes ($n = 5–8$) was investigated in the absence or presence of IL-1β (100 pg/ml). The expression levels (real time PCR) and protein production/activity of PGE_2, COX-1, COX-2, mPGES-1, glutathione, Erg-1, and PPAR-g, using specific primers (expression), antibodies or assays (protein), were determined.

Results: Data showed that GS treatment at 1 and 2 mM significantly inhibited ($p \leq 0.03$) the basal endogenous and IL-1β-induced PGE_2 production. GS in both the absence and presence of IL-1β did not significantly modulate COX-1 protein production but, interestingly, GS at 1 and 2 mM demonstrated a decrease in COX-2 activity in that it reduced the molecular mass of COX-2 synthesis from 72–74 kDa to 66–70 kDa. Under IL-1β stimulation, GS significantly inhibited the mPGES-1 mRNA expression and synthesis at 1 and 2 mM ($p \leq 0.02$) as well as the activity of glutathione ($p \leq 0.03$) and the Erg-1 ($p \leq 0.05$) at 2 mM. Finally, data showed that in both the absence and presence of IL-1β, PPAR-g was significantly induced by GS at 2 mM ($p \leq 0.02$).

Conclusion: Our data further documents the potential mode of action of GS at reducing the catabolism of human OA cartilage. GS inhibits PGE_2 synthesis via a reduction in the activity of COX-2 and the production and activity of mPGES-1. These findings may help explain the mechanisms by which this drug exerts its positive effect on OA pathophysiology.

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Role of Transcription Factor Fli-1 in Regulation of Dendritic Cell and Monocyte Development. Eiji Suzuki[1], Sarah Williams[2], Eva Karam[1], Gary S. Gilkeson[3] and Xian Zhang[3]. [1]Medical University of South Carolina, Charleston, SC, [2]Ralph H. Johnson VA Medical Center, Charleston, SC, [3]Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, SC

Background/Purpose: The Fli-1 gene is a member of the *ets* family of transcription factors that is expressed in hematopoietic cells, and has important roles in the immune system. Overexpression of Fli-1 protein in transgenic mice results in the development of a lupus-like disease. Expression of Fli-1 in systemic lupus erythematosus (SLE) patients and animal models of lupus is higher compared to normal controls. Dendritic cell and monocytes have a critical role in immunity and autoimmunity. The molecular mechanisms of Fli-1's role in lupus development are still unclear. In this report, we demonstrate Fli-1 plays an important role in regulating the development of monocytes and dendritic cells.

Methods: C57BL/6 (B6) mutant Fli-1 mice (Fli-$1^{\Delta CTA}$) express a truncated Fli-1 protein that lacks the C-terminal transactivation domain. Removal of this domain of Fli-1 reduces overall in vitro transcriptional activation activity by 40–50%. Fli-$1^{\Delta CTA}$ and wild-type B6 mice were sacrificed at the ages of 8–12 weeks. Bone marrow cells, spleen cells and peripheral blood mononuclear cells were prepared from each mouse and analyzed with Flow cytometery using specific antibodies.To further reveal the molecular mechanisms, Multipotent progenitors (MPP) were sorted from cultured bone marrow cells from both wild-type and Fli-$1^{\Delta CTA}$ mice. The expression of FMS-like tyrosine kinase 3 ligand (Flt3L) in MPP was measured by real-time PCR.

Results: Common dendritic cell precursors population in bone marrow from Fli-$1^{\Delta CTA}$ B6 mice was significantly higher than that from wild-type controls (Fli-$1^{\Delta CTA}$, 0.45±0.061% VS wild-type, 0.25±0.028%, $p<0.05$). The cell number of CD8+ and double negative conventional dendritic cells and macrophages in spleen from Fli-$1^{\Delta CTA}$ B6 mice were significantly higher compared to wild type littermates (for CD8+ dendritic cells, Fli-$1^{\Delta CTA}$, 1.10±0.183 $\times 10^6$ VS wild-type, 0.62±0.060 $\times 10^6$, $p<0.05$; for double negative conventional dendritic cells, Fli-$1^{\Delta CTA}$, 2.77±0.641 $\times 10^6$ VS wild-type, 1.19±0.053 $\times 10^6$, $p<0.05$; for macrophages, Fli-$1^{\Delta CTA}$, 4.60±0.131 $\times 10^6$ VS wild-type, 2.55±0.252 $\times 10^6$, $p<0.01$). Pre-conventional dendritic cells, plasmacytoid dendritic cells and monocytes in peripheral blood from Fli-$1^{\Delta CTA}$ B6 mice were significantly higher compared to wild-type littermates (for pre-conventional dendritic cells, Fli-$1^{\Delta CTA}$, 0.37±0.041% VS wild-type, 0.12±0.014%, $p<0.01$; for plasmacytoid dendritic cells, Fli-$1^{\Delta CTA}$, 0.48±0.044% VS wild-type, 0.27±0.052, $p<0.05$; for monocytes, Fli-$1^{\Delta CTA}$, 2.72±0.637% VS wild-type, 0.92±0.193%, $p<0.05$). The expression of Flt3L in MPP obtained from Fli-$1^{\Delta CTA}$ B6 mice was significantly increased compared to wild-type controls ($p<0.05$).

Conclusion: Our results demonstrate that Fli1 plays an important role in myeloid cell development and the CTA domain in Fli-1 protein negatively regulates the myeloid cell development. We also demonstrated that Fli-1 affects myeloid cell development by directly or indirectly regulating the expression of Flt3L, a key molecule during dendritic cell development.

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Resveratrol Deacetylating Rela/p65 Contributes to Inhibit Transforming Growth Factor-Alpha Induced Inflammation Via a Sirt1 Dependent Manner. Xiaoxia Zhu[1], Meimei Wang[2], Jianhua Qiu[3] and Hejian Zou[1]. [1]Division of Rheumatology, Huashan Hospital, Fudan University, Shanghai, China, [2]Division of Rheumatology, Zhongda Hospital, Dongnan University, Nanjing, China, [3]Neuroscience Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Progressive inflammation is a main mechanism of autoimmune disorders, such as rheumatoid arthritis, systemic sclerosis. Suppression of inflammation is a key resolution to treat the diseases. Sirtuin1 (Sirt1), a NAD^+-dependent deacetylase, plays a role in regulation of inflammation by deacetylating NF-κB subunit RelA/p65. As a potent Sirt1 activator, resveratrol is a natural phytoalexin and has been shown to have anti-inflammation property. However, the mechanism is not fully understood.

Methods: NIH/3T3 cell line (mouse embryonic fibroblast) was treated by TNF-α to induce inflammation. Inflammatory factors and acetylated RelA/p65 were examined by gel zymography, quantitative real-time PCR or immunoblotting. To investigate the role of resveratrol in inflammation, resveratrol was used to treat the cells with TNF-α, inflammatory factors were then examined after treatment. To further explore whether Sirt1 is involved in the anti-inflammation mechanism, Sirt1 was knocked down by siRNA interference before resveratrol treatment.

Results: Upregulation of matrix metalloproteinases 9 (MMP9), interleukin-1beta (IL-1β), IL-6 and inducible nitric oxide synthase (iNOS) were observed in the 3T3 fibroblasts after being treated by TNF-α. Resveratrol suppressed the upregulation of inflammatory factors induced by TNF-α in a dose-dependent manner. However, inflammatory inhibition of resveratrol was largely dependent on Sirt1 expression. Knockdown of Sirt1 caused cell sensitizing to TNF-α stimulation and diminished the inflammatory inhibition of resveratrol. Furthermore, resveratrol inhibited TNF-α-induced RelA/p65 acetylation, which is notably Sirt1 dependent. Resveratrol also attenuated phosphorylation of both mTOR and S6 ribosomal protein while ameliorating inflammation.

Conclusion: Our data suggested that Sirt1 is an efficient target for suppression of inflammation and Sirt1 activator such as resveratrol may be used for anti-inflammatory therapy. This study provides a novel insight or treatment of inflammation-related autoimmune disorders.

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Fasting Expands Regulatory T Cells in Lupus Mice. Yaoyang Liu[1], Yiyun Yu[1] and Antonio La Cava[2]. [1]UCLA, Los Angeles, [2]Univ of California Los Angeles, Los Angeles, CA

Background/Purpose: Caloric restriction has been found beneficial in the prevention and amelioration of the clinical manifestations of systemic lupus erythematosus (SLE), but the mechanisms responsible for these effects remain elusive. Fasting associates with significant changes in the immune response and with significantly reduced levels of circulating leptin. Since recent studies have shown that leptin influences the activity and proliferation of $CD4^+CD25^+Foxp3^+$ regulatory T cells (Tregs)—a subset of lymphocytes with a key role in the maintenance of immune tolerance—we studied whether fasting in (NZB × NZW)F1 (BWF1) lupus-prone mice could modulate Tregs activity in SLE through leptin.

Methods: Cohorts of C57BL6/J wild-type (WT), leptin-deficient ob/ob, leptin receptor-deficient db/db and BWF1 lupus mice were fasted 48 hours during which time they were treated with either leptin or vehicle (PBS). Additional control animals were fed ad libitum and treated with leptin or vehicle. Serum leptin was determined by ELISA and the percentage of Tregs from the periphery blood evaluated by flow cytometry. In vitro suppression assays using thymidine incorporation or CFSE staining in flow cytometry concomitantly addressed Tregs function.

Results: Fasting for 48 hours reduced the serum levels of leptin in all mice, as expected. In both WT and BWF1 lupus mice, 48hr acute starvation significantly expanded the number of functional peripheral Tregs (fasted & PBS vs. fed ad libitum WT mice: 9.80±0.42 vs. 6.32±0.46, $p<0.03$; in BWF1 lupus mice fasted vs fed: 7.69±0.33 vs. 3.85±0.40, $p<0.01$). Specificity of the findings was indicated by the fact that the administration of leptin during starvation reversed the expansion of the Tregs. In the leptin-deficient ob/ob mice, the number of peripheral Tregs was not affected by fasting (P ns vs ob/ob mice fed ad libitum) but significantly deceased when the animals received leptin (fasted & leptin vs. fasted & PBS: 8.64±0.98 vs. 14.50±0.81, $p<0.01$). In leptin receptor-deficient db/db mice, the reduction in serum leptin after starvation had no impact on the number and suppressive function of the Tregs (P ns vs db/db mice fed ad libitum).

Conclusion: This study shows that fasting associates with an expansion of functional Tregs through a reduction of leptin levels in BWF1 lupus mice. This finding advances the understanding of the mechanisms responsible for the beneficial effects of caloric deprivation in SLE. The observed expansion of Tregs that associates with fasting is reversed by the exogenous administration of leptin, suggesting that the link between the nutritional status and immune regulation might represent a new target for the modulation of Tregs activity in SLE.

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Microarray Gene Expression Profiling of Articular Chondrocyte In Patients with Osteoarthritis. Ying-Juan Chen[1], Ci-Bo Huang[1], Su-Ping Niu[1], Ai-Hua Liu, Bei Lai and Chun-Mei Zhang. [1]Beijing Hospital, Beijing, China

Background/Purpose: Osteoarthritis (OA) is characterized by degeneration of articular cartilage which involves complicated multiple gene events. In this study, we used gene microarray technique to investigate the gene expression profiling of articular chondrocyte and the function and pathway of the differentially expressed genes in patients with OA.

Methods: Three patients with OA, three patients with rheumatoid arthritis (RA) and three traumatic controls without arthritis were selected which divided into OA versus RA and OA versus the traumatic control two groups, and their articular cartilage cells were cultivated. The gene expression profiling was performed through human genome oligonucleotide microarray technique. The differences of gene expression of the articular chondrocyte in OA versus RA group and OA versus the traumatic control group were compared respectively by using Significant Analysis of Microarray software. The function and pathway of these differentially expressed genes were analysed by using the biological information database of Molecule Annotation System.

Results: The number of differentially expressed genes was 145 when OA compared the traumatic control, in which 70 were up-regulated and 75 were down-regulated; and the number was 281 when OA compared RA, in which 94 were up-regulated and 187 were down-regulated. The Gene Ontology (GO) functions of differentially expressed genes of OA in each group were related to pathological and immune courses including cellular process, physiological process, cell part, biological regulation and cell signal transduction. The statistically significant pathways of these genes in each group included cell cycle regulation, apoptosis, inflammatory cell, cell signal transduction, cytokine and its receptor pathways ($p<0.05$). There displayed not only marked differences in GO function and gene pathway of differentially expressed genes between OA versus RA group and OA versus the traumatic control group, but also displayed significant overlaping differentially expressed genes and pathways between two groups.

Conclusion: The differentially expressed genes and pathways of articular chondrocyte involved apoptosis, extracellular matrix and cytokines in OA, which contribute to search the early warning genes of OA.

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Progesterone Modulates Interferon-Alpha-Inducible Gene Expression in Human Leukocytes. Michael Cho[1], John Zheng[2] and Grant C. Hughes[2]. [1]Univ of Wash School of Medicine, Seattle, WA, [2]University of Washington, Seattle, WA

Background/Purpose: Interferon-alpha (IFN-a) is a central pathogenic cytokine in systemic lupus erythematosus (SLE). Exposure of leukocytes to IFN-a results in activation of the type 1 IFN receptor, transcription of IFN-a-inducible genes (IIGs) and subsequent leukocyte activation and differentiation. Female sex steroids like estrogen (Es) and progesterone (Pg) modulate SLE autoimmunity. Es is permissive, likely through direct effects on leukocyte activation, maturation and migration. Pg, on the other hand, appears to protect against SLE autoimmunity. Recent data from our lab shows that Pg may do this by suppressing IFN-a production. However, observational data from human tissues indicate transcription of genes involved in IFN-a signaling is under Pg's control—suggesting Pg may also protect against lupus by limiting the immunostimulatory effects of IFN-a. Thus, we hypothesize that Pg inhibits IFN-a signaling in human leukocytes.

Methods: To test our hypothesis, we assessed the effects of Pg treatment on a surrogate measure of IFN-a signaling: induction of IIG expression after IFN-a exposure. Briefly, we isolated peripheral blood mononuclear cells (PBMCs) from healthy donors. PBMCs were cultured in media, ethanol (vehicle), or physiologic concentrations Pg (100 nM), with or without IFN-a stimulation (50 – 100 IU/ml). After 20 h, total RNA was isolated, converted into cDNA, and expression of established IIGs (CXCL10, MX1, IFIT1) was measured by quantitative PCR and normalized to 18s. We recruited healthy donors of both sexes, since expression of Es and Pg receptors is not restricted to female PBMCs.

Results: In a series of 9 independent experiments (4 female, 5 male donors), Pg exposure resulted in variable effects on IIG induction. Pg inhibited to a small degree induction of IFIT1 and MX1, but not CXCL10. Pg alone did not affect IIG expression. Interestingly, Pg appeared to have different effects on IIG induction in female vs. male PBMCs. In female PBMCs, there was a trend toward increased expression of CXCL10 ($p = 0.09$), MX1 ($p = 0.26$) and IFIT1 ($p = 0.40$). In male PBMCs, Pg inhibited induction of MX1 ($p = 0.27$) and IFIT1 ($p = 0.40$), but had no discernable effects on CXCL10.

Conclusion: Pg may regulate IIG induction and IFN-a signaling in human leukocytes. Consistent with our hypothesis, Pg exposure inhibited IIG induction, but this effect was restricted to male PBMCs. In female PBMCs, Pg had the unexpected effect of increasing IIG induction. Thus, inhibition of IFN-a signaling by Pg in leukocytes is unlikely to be involved in protection of women against SLE. However, Pg may inhibit this pathway in men, highlighting a potentially important sexual dimorphism in immune functions related to SLE. This research is supported by NIH grants AR007108 and AI073739.

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Temperature Sensitive Transient Receptor Potential Channels in Human Peripheral Blood Mononuclear Cells Enhance the LPS-Mediated Cytokine Response. Monique Stoffels, Lonneke M. Elders, Heleen D. de Koning, Jos W. M. van der Meer and Anna Simon. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Exposure to cold can induce an exaggerated inflammatory response in a number of disorders. One of these is the hereditary autoinflammatory syndrome cryopyrin-associated periodic syndrome (CAPS), in which NLRP3-mutations cause a very diverse clinical phenotype of inflammation. Particularly patients with the subtype familial cold induced autoinflammatory syndrome (FCAS) are uniquely sensitive to cold exposure. Cold triggers an urticarial rash, fever, joint pain and systemic inflammation. Another example is idiopathic cold urticaria. It is unknown how the inflammatory system senses cold. Neurons are known to sense temperature through certain transient receptor potential (TRP) channels. In the present study we aimed to explore how inflammatory cells sense cold.

Methods: Quantitative real-time polymerase chain reaction assays for mRNA analysis of three known TRP channels, and Western Blot for TRP protein levels were done in several human-derived cell lines and primary cells. Peripheral blood mononuclear cells (PBMCs) were incubated with LPS and menthol, a known stimulus of TRP melastatin subfamily member 8 (TRPM8). Cytokine concentrations in culture supernatants were detected by Enzyme-linked immunosorbent assay (ELISA).

Results: PBMCs express the 'cool' menthol receptor TRPM8 and the noxious cold receptor TRP subfamily A (ankyrin-like) member 1 (TRPA1), as well as the close relative 'hot' capsaicin receptor TRPV1 at the RNA level. TRPM8 protein was detected by western blot in fibroblast and Epstein-Barr virus transformed lymphoblast cell lines. PBMCs preincubated with menthol show increased interleukin-1 beta (IL-1β) secretion in response to LPS, compared to LPS stimulation only. Stimulation with menthol alone did not result in an inflammatory response.

Conclusion: Human PBMCs express the temperature sensitive TRP channels TRPA1, TRPV1 and TRPM8. *Ex vivo* stimulation of PBMCs with menthol results in an increased inflammatory response to LPS. We hypothesize that *in vivo* cold exposure results in a modulated inflammatory response, through activation of temperature sensitive ion channels. Our results suggest that temperature sensing is not only important in the nervous system, but also plays a direct role in innate immunity.

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Synergy Between Adiponectin and Interleukin-1β on the Expression of Interleukin-6, Interleukin-8, and Cyclooxygenase-2 in Fibroblast-Like Synoviocytes. Yeon-Ah Lee[1], Sang-Hoon Lee[2], Hyung-In Yang[2], So Mi Kim[1], Seung-Jae Hong[1], Myung Chul Yoo[3] and Kyoung Soo Kim[1]. [1]Kyung Hee University, Seoul, South Korea, [2]Kyung Hee University Hospital at KANGDONG, Kyung Hee University, Seoul, South Korea, [3]Kyung Hee University Hospital at KANGDONG, Seoul, South Korea

Background/Purpose: To determine whether adiponectin may have synergistic effects in combination with the proinflammatory cytokine interleukin (IL)-1b regarding the production of proinflammatory mediators during arthritic joint inflammation.

Methods: Synovial cells from rheumatoid arthritis (RA) patients were treated with adiponectin, IL-1b, and their combination for 24 hours. Culture supernatant was collected and analyzed by enzyme-linked immunosorbent assay for levels of IL-6, IL-8, prostaglandin E_2 (PGE_2), vascular endothelial

growth factor (VEGF), and matrix metalloproteinases (MMPs). Adiponectin-mediated intracellular signaling pathways were investigated to elucidate the molecular mechanisms underlying their synergy. The association of proinflammatory mediators with adiponectin was investigated in the synovial fluid of arthritis patients.

Results: Adiponectin functioned synergistically with IL-1b to activate IL-6, IL-8, and PGE_2 expression in RA fibroblast-like synoviocytes; Levels of VEGF, MMP-1, and MMP-13 were not synergistically stimulated. Adiponectin appears to activate gene expression through the IkB signaling pathway. However, adiponectin and IL-1b did not synergistically support the degradation of IkB-a or the nuclear translocation of NF-kB. Synergistically increased gene expression was significantly inhibited by MG132, an NF-kB inhibitor. Supporting the in vitro results, IL-6 and IL-8 levels were positively associated with adiponectin in synovial joint fluid from patients with RA, but not osteoarthritis (OA)

Conclusion: Adiponectin and IL-1b may synergistically stimulate the production of proinflammatory mediators through unknown signaling pathways during arthritic joint inflammation. Adiponectin may be more important to the pathogenesis of RA than previously thought.

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The Discordant Impact of IL-1 Signaling on Experimental Uveitis and Arthritis. Holly L. Rosenzweig[1], Stephen R. Planck[1], April L. Woods[1], Jenna S. Clowers[2], Martin J. Nicklin[3] and James T. Rosenbaum[1]. [1]Oregon Health & Science University, Portland, OR, [2]Veterans Affairs Medical Center, Portland, OR, [3]University of Sheffield, United Kingdom

Background/Purpose: Uveitis, or inflammatory eye disease, is an extra-articular manifestation of many systemic autoinflammatory diseases involving the joints. The importance of IL-1 in many arthritic diseases is apparent from the effectiveness of Anakinra (recombinant IL-1 receptor antagonist, IL-1RA) therapy. Yet, very little work has investigated the extent to which IL-1 signaling or IL-1RA influences the onset and/or severity of uveitis. The purpose of this study was to elucidate the impact of IL-1R1 and IL-1RA on murine uveitis.

Methods: The onset and severity of uveitis was monitored by histology and intravital videomicroscopy out to 20 weeks of age and compared to the progression of spontaneous arthritis within the ankles and knees of naïve IL-1RA deficient mice or in mice previously administered an intraperitoneal injection of 25 μg LPS at 8 weeks of age. Expression levels of IL-1R1 and its negative regulators (IL-1RA, IL-1RII, IL-1RAcP, SIGIRR) were analyzed in ocular compared to joint tissues. Differences in uveitis induced by intraocular injection of LPS in mice lacking IL-1R1 or IL-1RA were assessed.

Results: Deficiency in IL-1RA predisposes to arthritis, which is exacerbated by prior systemic LPS exposure. The mouse eye, however, remains unaffected by inflammatory disease despite the progressive arthritis or prior systemic LPS exposure. Tissue-specific expression patterns for IL-1RA and regulators of IL-1R1 were observed in the ankle, knee and eyes and these appear to predict relative disease susceptibility in each tissue in that ankles are most susceptible and eyes are least susceptible. Uveitis in mice does result from locally administered LPS. Interestingly, IL-1RA deficiency markedly exacerbates uveitis induced by locally admininstered LPS whereas IL-1R1 deficiency has no effect on the disease severity.

Conclusion: This study demonstrates discordance between the eyes and joints in the extent to which IL-1RA protects against spontaneous inflammation. Nonetheless, IL-1RA plays an important role in suppressing cellular inflammatory responses to intraocular LPS.

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The Expression of the Receptor for Advanced Glycation End-products in Fibroblast Like synoviocytes From Rheumatoid Arthritis Patients Is Induced by Interleukin-17. Young Ok Jung[1], Mila Cho[2], Hae-Rim Kim[3], Sang-Heon Lee[4], Sung-Hwan Park[5], Hye-Jwa Oh[2] and Ho-Youn Kim[5]. [1]Seoul, South Korea, [2]Catholic Medical Univ, Seoul, South Korea, [3]Konkuk University Medical Center, Seoul, South Korea, [4]Konkuk University Hospital, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul, South Korea

Background/Purpose: Receptor for advanced glycation end-products (RAGE) has been implicated in the pathogenesis of arthritis. We conducted this study to determine the effect of interleukin (IL)-17 on the expression and production of RAGE in fibroblast-like synoviocytes (FLS) from patients with rheumatoid arthritis (RA). The role of nuclear factor-kB (NF-kB) activator 1 (Act1) in IL-17-induced RAGE expression in RA-FLS was also evaluated.

Methods: RAGE expression in synovial tissues was assessed by immunohistochemical staining. RAGE mRNA production was determined by the real-time polymerase chain reaction. Act-1 short hairpin RNA (shRNA) was produced and treated to evaluate the role of Act-1 on RAGE production.

Results: RAGE, IL-17, and Act-1 expression increased in RA synovium compared to osteoarthritis synovium. RAGE expression and production increased by IL-17 and IL-1b (*$P < 0.05$ vs. untreated cells) treatment but not by tumor necrosis factor (TNF)-a in RA-FLS. The combined stimuli of both IL-17 and IL-1b significantly increased RAGE production compared to a single stimulus with IL-17 or IL-1b alone ($P < 0.05$ vs. 10 ng/ml IL-17). Act-1 shRNA added to the RA-FLS culture supernatant completely suppressed the enhanced production of RAGE induced by IL-17.

Conclusion: RAGE was overexpressed in RA synovial tissues, and RAGE production was stimulated by IL-17 and IL-1b. Act-1 contributed to the stimulatory effect of IL-17 on RAGE production, suggesting a possible inhibitory target for RA treatment.

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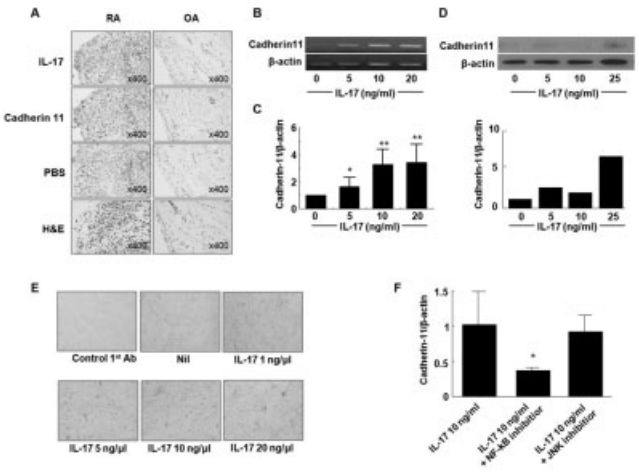
Interleukin 17 Increased Cadherin 11 Expression in rheumatoid Arthritis. Young Eun Park[1], Seong Hu Park[2], Seung Geun Lee[2], Seung Hoon Baek[3], Geun Tae Kim[4], Jun Hee Lee[5], Joung Wook Lee[6], Mi La Cho[7] and Sung Il Kim[1]. [1]Pusan National University Hospital, Busan, South Korea, [2]Pusan Nationl University Hospital, Busan, South Korea, [3]Pusan National University Yangsan Hospital, Yangsan, South Korea, [4]Kosin University Gopsel Hospital, Pusan, South Korea, [5]Ilsin Christian Hospital, Pusan, South Korea, [6]Busan st. Mary's Medical Center, Busan, South Korea, [7]The Rheumatism Research Center, Catholic Research Institute of Medical Science, The Catholic University of Korea, Seoul, South Korea

Background/Purpose: IL-17, produced from Th17 cells, plays important roles in synovial inflammation and joint destruction of autoimmune experimental arthritis model and rheumatoid arthritis (RA). Cadherin 11 is expressed primarily on synovial fibroblasts (FLS) in the synovium, and promotes invasive behavior of FLS in chronic synovitis and rheumatoid arthritis. Cadherin 11 expression is regulated by mediators of inflammation. The purpose of this study was to examine the effect of IL-17 on the expression of cadherin 11 in RA synovium.

Methods: Synovial tissue specimens were isolated from 4 RA and osteoarthritis (OA) patients who were undergoing total knee replacement surgery. IL-17 and Cadherin 11 expressions were examined in synovium of patients with RA and osteoarthritis (OA) by immunohistochemistry. The expression of cadherin 11 were also examined from IL-17 stimulated FLS of RA patients with or without cell signal pathway inhibitors such as parthenolide (NK-kB inhibitor) and SP600125 (JNK inhibitor).

Results: Cahderin 11 and IL-17 expressing cells were more abundantly distributed in RA synovim compared to OA synovium (A). In cultured RA FLS, the mRNA and protein levels of cadherin 11 were measured by RT-PCR (B), real-time PCR (C), western blot (D) and cell stain (E), and increased by IL-17 stimulation. The enhancement of IL-17 expression was blocked by NFkB inhibitor, but not JNK inhibitor (K).



Conclusion: IL-17 induced increases of synovial cadherin 11 expression might be involved in joint inflammation and destruction of RA.

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Type-1 Interferon Does Not Directly Impair Endothelial Cell Function *in Vitro*: Implications for Cardiovascular Models of Systemic Lupus Erythematosus. John A. Reynolds[1], David W. Ray[1], Terence O'Neill[1], M. Yvonne Alexander[1] and Ian N. Bruce[2]. [1]The University of Manchester, Manchester, United Kingdom, [2]A, Manchester, United Kingdom

Background/Purpose: Systemic Lupus Erythematosus (SLE) is associated with a significantly increased risk of cardiovascular disease (CVD). Type-1 interferon (IFN) is the dominant inflammatory cytokine in SLE and IFN treatment can induce endothelial dysfunction in patients with viral hepatitis. Furthermore, IFN impairs the function of endothelial progenitor cells (EPCs) *in vitro*, replicating a phenotype similar to that seen in EPCs from lupus patients. The mechanism by which IFN impairs endothelial cell function is unknown. We aimed to determine the effect of IFN upon endothelial cells in order to establish an *in vitro* endothelial model relevant to SLE.

Methods: Human aortic endothelial cells (HAoECs) were cultured in standard conditions. For proliferation experiments, the effect of IFNα2b was studied either by counting cell nuclei in random fields or by MTT assay. An Affymetrix GeneChip Human Exon 1.0 ST Array was used to determine changes in gene expression at 6 hours following addition of IFNα2b. Nitric oxide bioavailability in the cell culture supernatant was measured using a Griess assay (total nitrate and nitrite) at 6 and 24 hours. The ability of HAoECs to form capillary networks in Matrigel at 18 hours and in type-1 rat tail collagen gels at up to 48 hours was studied in the presence or absence of IFNα2b.

Results: IFNα2b at concentrations of 0.1–100ng/ml had no effect on HAoEC proliferation measured by either cell count or MTT assay at up to 72 hours (n=3 for each). The expression of 164 genes was significantly changed (>2-fold change, q<0.2) by the addition of 10ng/ml IFNα2b at 6 hours. These genes were primarily those previously reported to be regulated by IFNα or those involved in cellular response to virus (e.g. IFIT1, IFI44L, MX1 and CXCL10).

Nitric oxide availability was not changed at up to 24 hours by the addition of IFNα2b (n=3). The formation of 2-dimensional capillary networks in Matrigel was variable and not consistently impaired by the addition of 10ng/ml IFN. Furthermore the development of 3-dimensional networks in collagen was not disrupted by the addition of IFNα2b to either the gel or the culture media.

Conclusion: Interferon-α2b did not affect the function of human aortic endothelial cells *in vitro*. Gene expression was not influenced beyond those genes involved in IFN signalling or in response to virus. We propose therefore, that the reported effects of IFN on EPC function do not extend to mature human endothelial cells. This has implications for the development of *in vitro* endothelial models relevant to SLE and further work should focus upon the role of IFN in EPC differentiation and function.

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Polymyalgia Rheumatica Has a Nocturnal Rise in Serum Interleukin-6 Which Is Almost Completely Suppressed by Nighttime Prednisone. Samy Zakout and John R. Kirwan. University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom

Background/Purpose: Stiffness in polymyalgia rheumatica (PMR) follows a circadian rhythm. In rheumatoid arthritis (RA) morning stiffness is linked to a nocturnal rise in interleukin-6 (IL-6) and converting morning prednisone to a nighttime treatment (modified-release prednisone effective at 2am) led to a significant decrease in morning stiffness [1]. Previous studies of cytokines in PMR collected data only for one time of the day [2] and the possibility of a circadian pattern in IL-6 and the effects of glucocorticoids have not been investigated. The purpose of the study is to determine whether IL-6 follows a circadian rhythm in patients with newly diagnosed untreated PMR, and to compare the effects of morning and nighttime glucocorticoids on overnight IL-6 and morning stiffness.

Methods: 10 patients with newly diagnosed PMR were randomised to two treatment groups with either nighttime prednisone 7mg (Lodotra) or morning prednisolone 7mg. Hourly blood samples over 24-hours were taken before (Night A) and after (Night B) treatment to measure IL-6. Patients were then treated with morning prednisolone 15mg and after 2 weeks a single measurement of IL-6 was performed at 9am (Day C). Duration of morning stiffness was recorded on each occasion.

Results: IL-6 shows a circadian variation in PMR, with a rise during the early hours of the morning (Figure 1, IL-6 pre-treatment). Morning prednisolone 7mg partially suppresses IL-6 and morning symptoms, compared to subsequent treatment with 15mg. Nighttime prednisone 7mg almost completely suppresses IL-6 and morning stiffness (Figures 1 and 2).

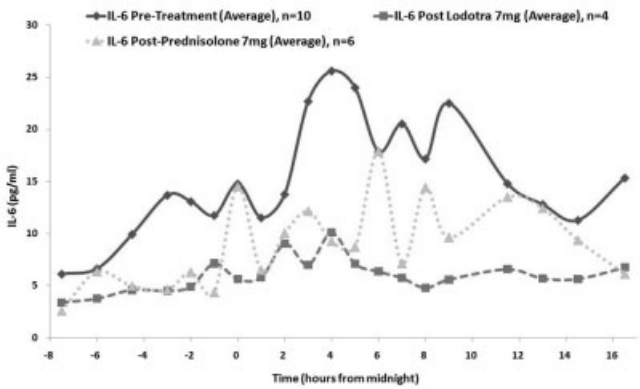

Figure 1

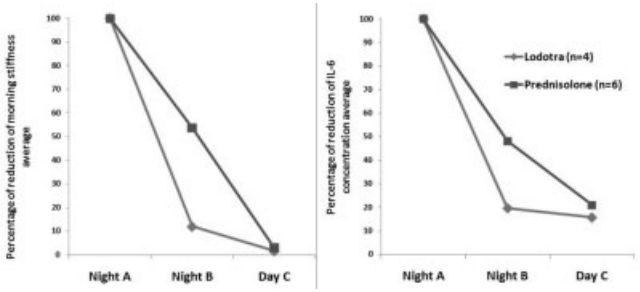

Figure 2

Conclusion: PMR, like RA, has a marked circadian variation in serum IL-6. IL-6 and symptoms of morning stiffness are both suppressed more by nighttime low dose glucocorticoids. This observation raises the possibility that PMR may be controlled by lower doses of glucocorticoids given at night compared to current conventional morning treatment.

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Early Growth Response factor−1 Mediates the Suppressive Effect of Interleukin-1 on Peroxisome proliferator–activated Receptor Gamma Expression in Human Osteoarthritic Chondrocytes. Sarah S. Nebbaki[1], Fatima Ezzahra El Mansouri[2], Nadia Zayed[2], Mohamed Benderdour[3], Johanne M. Pelletier[2], Jean Pierre Pelletier[2] and Hassan Fahmi[2]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Center (CRCHUM), Notre-Dame Hospital, Montreal, QC, [2]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [3]University of Montreal Hospital Research Centre, Sacré-Coeur Hospital, Montreal, QC

Background/Purpose: Peroxisome proliferator-activated receptor gamma (PPARg) gamma is a ligand activated transcription factor and member the nuclear hormone receptor superfamily. Several lines of evidence indicate that PPARg have protective effects in osteoarthritis (OA). Indeed, PPARg has been shown to down-regulate several inflammatory and catabolic responses in articular joint cells and to be protective in animal models of OA. We have previously shown that IL-1 down-regulated PPARg expression in OA chondrocytes. In the present study we will investigate the mechanisms underlying this effect of IL-1.

Methods: Chondrocytes were stimulated with IL-1, and the level of PPARg and Egr-1 protein and mRNA were evaluated using Western blotting

and real-time reverse-transcription polymerase chain reaction, respectively. The PPARg promoter activity was analyzed in transient transfection experiments. Egr-1 recruitment to the PPARg promoter was evaluated using chromatin immunoprecipitation (ChIP) assays. Small interfering RNA (siRNA) approaches were used to silence Egr-1 expression.

Results: We demonstrated that the suppressive effect of IL-1 on PPARg expression requires de novo protein synthesis and was concomitant with the induction of the transcription factor Egr-1. ChIP analyses revealed that IL-1 induced Egr-1 recruitment at the PPARg promoter. IL-1 inhibited the activity of PPARg promoter and overexpression of Egr-1 potentiated the inhibitory effect of IL-1, suggesting that Egr-1 may mediate the suppressive effect of IL-1. Finally, Egr-1 silencing with small interfering RNA blocked IL-1-mediated down-regulation of PPARg expression.

Conclusion: These results indicate that Egr-1 contributes to IL-1-mediated down-regulation of PPARg expression in OA chondrocytes and suggest that this pathway could be a potential target for pharmacologic intervention in the treatment of OA and possibly other arthritic diseases.

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Circulating cytokines in Patients with Hidradenitis Suppurativa: is there a Clue for new Therapeutic Options? Orlando Pompei[1], Lorena Álvarez-Rodríguez[1], Ricardo Blanco[1], Ignacio Villa[2], Marcos López-Hoyos[1], Marcos González López[1], Hector Fernandez-Llaca[1], M. del Carmen Gonzalez Vela[1], Carmen Bejerano[1], Inés Pérez-Martín[1] and Victor M. Martinez-Taboada[1]. [1]Hospital Universitario Marqués de Valdecilla-IFIMAV, Santander, Spain, [2]Hospital Sierrallana, Torrelavega, Spain

Background/Purpose: Hidradenitis suppurativa (HS) is a debilitating chronic disease with a pathogenesis that remains largely unknown. Most treatments remain empiric, are usually supportive and do not prevent the progression of the disease. More recently, treatment with TNF antagonists has shown promising results, that should be confirmed in well-designed clinical trials. As new treatment options for inflammatory conditions are rapidly appearing, the aim of the present study was to determine the cellular phenotype and the circulating cytokine profile in patients with HS.

Methods: Intracellular cytokine production was assessed in T cells (IFN-g, IL-2, IL-4, IL-10, IL-17) and monocytes (IL-1b, TNF-a, IL-6) by flow cytometry in 22 patients with active HS and 18 age- and sex-matched healthy controls (controls). Circulating cytokines (IL-12p70, IL-10, IL-8, IL-1b, TNF-a, IL-6) were measured by Cytometric Bead Array (CBA) in 26 patients with HS and 37 controls. Four HS patients were also assessed after treatment with TNF antagonists.

Results: No significant differences between patients and controls were found for circulating levels of IL-12p70, IL-10, IL-8, IL-1b, and TNF-a. IL-6 was the only circulating cytokine significantly increased in patients with active disease ($p=0.001$). Using flow cytometry technology, we examined whether circulating monocytes were a major source of proinflammatory cytokines in patients with HS. The percentage of proinflammatory cytokine-producing cells *ex vivo* in patients with HS was similar to the percentage in controls. *In vitro* stimulation with LPS showed a clear response of circulating CD14+ cells, especially in controls. The percentage of IL-6, IL-1b and TNFa-producing cells after *in vitro* stimulation was significantly lower in patients with active HS. Compared to controls, HS patients were characterized by a decreased frequency of circulating CD3+IFNg+ *ex vivo* ($p=0.03$). Disease control with treatment was followed by a further decrease of circulating CD3+IFNg+ ($p=0.015$). Patients with active HS showed a non-significant increased frequency of circulating Th17 (CD4+IL17+CCR6+ and CD4+IL17+IFN-) cells compared to controls. Disease control with treatment was also followed by a tendency to decrease circulating Th17 cells ($p=0.06$).

Conclusion: To the best of our knowledge, this is the first report that demonstrate an increase in serum levels of IL6 in patients with HS. We hypothesize that the increased levels of IL6 found in patients with HS are not the result of IL6 production by circulating monocytes, and it is reasonable to assume that the major production of this proinflammatory cytokine is located at the site of the inflammatory process or in other cell types that predominantly produce IL6.

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Differential Production of Angiopoietins-1 and -2 in Synovial Tissue of Rheumatoid Arthritis and Psoriatic Arthritis Patients Is Associated with Expression of Specific Putative Transcription Factors. M. Frleta, L.G.M. van Baarsen, A.M. Grabiec, D. de Launay, M. Garrelfs, D. Gerlag, PP. Tak and K.A. Reedquist. Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: The angiogenic factors angiopoietin (Ang)-1 and -2 are differentially expressed in the serum and synovial fluid of patients with different forms of arthritis. Ang-1 and -2 contribute to inflammation and joint destruction in rheumatoid arthritis (RA), but the underlying mechanisms for their differential expression and their consequences for synovial Tie2 activation are unknown. Here we conducted *in silico* studies to define transcription factors (TFs) potentially involved in the regulation of Ang-1/-2 expression, and investigated the expression of candidate TFs in correlation with Ang-1/-2 in RA and PsA synovial tissue.

Methods: *In silico* analysis was conducted to identify possible TF candidates in the Ang-1/-2 promoter region, using four different TF binding site prediction programs. RA synovial expression of TF and Ang-1/-2 was examined in publicly available gene expression data sets obtained from synovial tissue biopsies of 62 RA patients. Candidate TF and Ang-1/-2 expression was characterized by quantitative PCR arrays (qPCR) in synovial tissue samples obtained from 6 RA and 6 PsA patients.

Results: The *in silico* study identified 74 candidate TFs that might bind to Ang-1/-2 promoting regions. Analyzing correlations with Ang-1/-2 mRNA expression in publicly available gene expression data sets revealed 34 TFs potentially involved in Ang-1 expression and 22 TFs related to Ang-2 regulation. Further analysis by qPCR arrays identified 3 TFs significantly downregulated in PsA compared to RA (more than 2-fold), including ESR1 ($p=0.015$), SOX5 ($p=0.004$), and SOX9 ($p=0.014$). In RA synovial tissue, significant correlations were observed between expression of Ang-1 and 8 TFs: FOXJ2 ($r=0.94$, $p=0.017$), HLF ($r=0.94$, $p=0.017$), LMO2 ($r=1.0$, $p=0.0028$), NR3C1, TCF4, HOXA4, MEF2A and YY1 (all $r=0.94$, $p=0.017$). Ang-2 expression in RA correlated with HLF ($r=0.88$, $p=0.033$), TCF4 ($r=0.88$, $p=0.033$), ESR1 ($r=1.0$, $p=0.0028$), GATA2 ($r=0.88$, $p=0.033$), and JUN ($r=0.88$, $p=0.033$).

Conclusion: We have observed significant upregulation of a number of TFs involved in Ang-1/-2 regulation in RA compared to PsA synovial tissue. Further analyses of the cellular mechanisms driving expression and activation of these TFs in synovial tissue may provide a greater understanding of stimuli responsible for initiating angiogenesis in RA and PsA.

ACR Poster Session A
Education: Medical Education
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Development of a Collaborative Rheumatology and Orthopedic Musculoskeletal Ultrasound Training Program. Minna J. Kohler[1], John S. Reach[1], Janine Evans[1], Lawrence D. Weis[1], Joseph E. Craft[2] and Liana Fraenkel[1]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [2]Yale University School of Medicine, New Haven, CT

Background/Purpose: Interest in musculoskeletal ultrasound (MUS) training by rheumatologists has grown as a tool to facilitate personalized point-of-care diagnostic testing and treatment. Over the past decade, MUS training has been popular in Europe, and there is now increasing demand by American rheumatologists to obtain training. At this time, no formal training curriculum is required in U.S. rheumatology fellowship programs, and lack of MUS-trained rheumatology faculty often impedes the ability for fellows to become proficient in using MUS.

Methods: We describe the development and implementation of a novel, collaborative rheumatology/orthopedic MUS training program at a single academic medical center. The program was developed in conjunction with an orthopedist with advanced training in MUS, access to an ultrasound (US) machine, and clinics that provide care for patients with osteoarthritis and soft tissue rheumatism.

Results: The training program consists of 1) weekly, ½ to 1 day faculty-mentored MUS injection clinic, 2) instructional didactic sessions, 3) monthly hands-on didactic practice sessions, and 4) options to participate in a web-based fellows ultrasound training program (USSONAR) and the American College of Rheumatology MUS course for further training in rheumatology-focused MUS applications. In the MUS clinic, rheumatology fellows and orthopedic residents consecutively evaluate patients referred for musculoskeletal pain, willing to seek a corticosteroid injection if clinically indicated. All patients are evaluated by a fellow/resident under direct faculty supervision by our MUS expert. The clinic consists of half hour appointments in which the patient is clinically evaluated and diagnostic US or US-guided injection is performed. Instructional didactic sessions review basic physics

principles of US, function of basic controls on an US machine, and methods to optimize an US image. Monthly hands-on didactic training sessions review anatomy and ultrasound scanning protocols. Fellows/residents also practice US needle-guidance training with phantom models. The program additionally supports clinical research projects. To allow adequate mentored, hands-on ultrasound time, two fellows/residents per clinic can be trained over a year.

Conclusion: Development and implementation of a MUS clinic is feasible with an ultrasound expert, ultrasound machine, and patients who benefit from MUS point-of-care. The collaborative MUS program is beneficial to the education of both rheumatology fellows and orthopedic residents.

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Educational Efficacy and Durability of Knowledge Gained From a Module on Gout. Bernadette C. Siaton[1], John S. Sundy[1], Sanjay Garg[2], Christopher G. Meyer[3] and Lisa G. Criscione-Schreiber[1]. [1]Duke University Medical Center, Durham, NC, [2]Center for Arthritis and Rheumatism, Fayetteville, NC, [3]Asheville Arthritis Ctr, Asheville, NC

Background/Purpose: With the projected shortage of rheumatologists, primary care providers will be expected to manage patients with common rheumatologic disorders. We aimed to create a validated educational product including a pre- and post-test about gout, assess the efficacy of this product in improving knowledge, and test the durability of acquired knowledge. We compared the efficacy of this educational product when delivered in live didactic sessions vs. on-line as a PowerPoint presentation. The test was designed to assess both knowledge gained and learners' confidence in their knowledge.

Methods: We obtained IRB exemption to perform this study that included Internal medicine (IM) and family medicine (FM) trainees at Duke University. We validated the pre- and post-test questions for relevance and clarity. Baseline knowledge was assessed via a pre-test on Blackboard, followed by the educational intervention, a module about gout. The module was either attended as a live lecture or the PowerPoint presentation was viewed online. The educational module included gout pathophysiology, clinical presentation, and therapeutic management. Immediate post-testing was performed. To assess knowledge durability, participants took the same post-test 6 months after the educational intervention. Six-month scores were compared to pre- and post-test scores. We also measured confidence in test answers at all time points. Data regarding method of didactic delivery (live vs. on-line), post-graduate year (PGY), and training program (IM vs. FM) was collected, and subgroup analyses were performed. The students' t-test was used to compare groups. ANOVA testing was used for PGY subgroup analysis; all other subgroup comparisons used Wilcoxon-Rank sum tests.

Results: Sixty-two learners completed paired pre- and post-tests for analysis. 28 learners completed the 6 month post-test. Test results from participants with incomplete data were eliminated from analysis. Post-test scores were significantly higher than pre-test scores (210.0 out of 260 possible points (pts) vs. 147.3 pts, $p<0.001$). The delivery method (live vs. on-line) did not affect scores. PGY3 had higher baseline knowledge and lower knowledge gains than PGY1 trainees ($p=0.02$). While IM trainees' baseline scores were higher than FM trainees' (151.4 pts vs. 119.7pts, $p<0.002$) both groups had similar score increases ($p=0.60$). Six-month test scores (177.3 pts) were lower than post-test scores ($p<0.001$), and higher than pre-test scores ($p<0.001$). Subgroup analysis showed higher knowledge retention for PGY3 trainees compared to PGY1 (-16.8 pts vs. -45.6 pts, $p=0.03$). IM and FM trainees demonstrated similar decreases in scores ($p=0.63$). Impact of didactic delivery on durability of knowledge was not analyzed. Attrition rate at 6 months was 55%.

Conclusion: Test scores significantly increased after the educational intervention, and increases persisted for 6 months with some decline. Higher PGY level was associated with higher knowledge retention. The mode of presentation did not appear to impact knowledge gained. We are enhancing the module for further on-line distribution. Testing how successful completion of this module informs clinical practice is a topic for future study.

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Twitter and Rheumatology Based Medical Education – Analysis of the First 100 Followers. Christopher E. Collins. Washington Hospital Ctr, Washington, DC

Background/Purpose: Twitter is a social networking and microblogging service which enables its users to send and read messages called tweets (text-based posts of 140 characters or less). Users can "follow" a particular person or group and subscribe to their Twitter feed. Numerous groups utilize Twitter as a means of communicating with interested individuals and the emergence of Twitter in the world of healthcare is gaining popularity. Users range from professional medical organizations, healthcare advocacy groups, individual healthcare providers, medical trainees and patients. There are numerous Twitter accounts specific to the field of rheumatology as well as to medical education, however there are few profiles dedicated to both. @RheumPearls was created in March of 2011 to tweet rheumatology based medical "pearls of wisdom" geared towards medical trainees and physicians interested in rheumatology. In order to understand who was following @RheumPearls as well as ascertain if the target audience (medical trainees and physicians) was being reached, an analysis of the first 100 followers was conducted.

Methods: The first 100 followers of @RheumPearls was analyzed for the nature of the account (individual, patient, medical trainee, physician, medical organization, or healthcare advocacy group) and the geographic location of the user. Since one of the methods for attracting followers to a particular Twitter feed is through the phenomenon of "I follow you, you follow me", and given that several of the followers of @RheumPearls were likely obtained through this method, a second analysis was conducted just on the followers which discovered @RheumPearls through other means ($n=75$).

Results: The largest group of followers was physicians (23%) of whom 61% where rheumatologists. Patients with self identified rheumatic conditions were next representing 20% of the followers (lupus and rheumatoid arthritis being the most common diagnosis). Professional medical organizations accounted for 18% and self identified medical trainees (medical students and residents) 11%. The remaining identified groups were healthcare advocacy groups, individuals with interests in medical education and healthcare, and unknown individuals representing 9%, 7%, and 12% respectively. When looking just at followers who @RheumPearls did not follow first ($n=75$), the percentages of medical trainees, patients, and individuals all increased whereas physicians and medical organizations decreased. Geographically, followers from North American (predominately US) represented 65.5% of the cohort with Europe being the next most common (14.5%). Africa, South America, Australia, and Asia were also represented (3%, 1%, 3%, and 5.5% respectively).

Conclusion: @RheumPearls is a Twitter feed broadcasting rheumatology based medical education directed towards medical trainees and physicians, but available to everyone. An analysis of the first 100 followers suggests that with medical trainees and physicians representing 34% of the cohort, this goal is being achieved. The diversity of the followers as well as an extensive geographic distribution also suggests a wide appeal for rheumatology based education.

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Arthrocentesis Training Using a Knee Simulation Model. Jordan E. Brodsky, Erin P. Patton and Harry D. Fischer. Albert Einstein College of Medicine at Beth Israel Medical Center, New York, NY

Background/Purpose: Arthrocentesis training is a necessary part of the skill set required for Internal Medicine residents. The American Board of Internal Medicine requires that all candidates demonstrate competency in the performance of this procedure. Unfortunately, residents may have limited exposure to patients requiring this procedure and alternative training methods may be needed. The ACGME supports the use of simulation models for the training of Internal Medicine residents. We studied the benefit of using a specialized knee mannequin for simulation training of arthrocentesis.

Methods: We developed a program for simulation training in arthrocentesis. The goal was to assess whether such a program is beneficial in acquiring the skills needed to perform the procedure. Internal Medicine residents were given a didactic lecture on the principles of joint aspiration. This was followed by hands on training by all participants using a simulated knee joint (Sawbones – Pacific Research Labs Inc, Vashon Island, WA). This knee model is equipped with an electric buzzer. When the procedure is correctly performed, the buzzer provides immediate feedback. All participants completed an anonymous questionnaire on arthrocentesis before and after the training session.

Results: 41 Internal Medicine residents, PGY1–13, PGY 2–10, PGY 3–8, PGY 4-1 as well as 9 medical students, participated. 64.4% were male and 36.4% were female. Only 9.8% of those surveyed felt that they were adequately trained in medical school in arthrocentesis. Preparedness to perform arthrocentesis was measured on a scale of 1, being the least prepared, to 10, being the most prepared. Preprogram preparedness averaged 3.36 and post program preparedness rose to 6.95 ($p<0.001$). Similarly, preprogram confidence in performing arthrocentesis measured 2.75 and post program confidence rose to 6.82 ($p<0.001$). Prior to simulation training, 56.1% felt

reluctant to perform a needed arthrocentesis, which decreased to 31.7% following the training (p-value=0.0124).

Conclusion: The use of a knee simulation model to train Medical Students and Internal Medical residents in the performance of arthrocentesis was studied. This training increased the participants' confidence, preparedness, and comfort in performing the procedure. When there are a limited number of patients requiring arthrocentesis available to train residents in this procedure, the use of a simulation knee model appears to be a valuble alternative.

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Evaluation of a Novel Educational Method: The Rheumatology Toolbox. Richard Conway[1], John J. Carey[1], Ronan Kavanagh[2] and Robert J. Coughlan[1]. [1]Galway University Hospitals, Galway, Ireland, [2]Galway Clinic, Galway, Ireland

Background/Purpose: Management guidelines for many rheumatic diseases are published in specialty rheumatology literature but rarely in general medical journals. Musculoskeletal disorders comprise 14% of all consultations in primary care. Formal post-graduate training in rheumatology is limited or absent for many primary care practitioners. Demand for rheumatology care exceeds supply in many countries, a problem expected to increase in the coming decades. Primary care practitioners can be trained to effectively treat complex diseases and have expressed a preference for interactive educational courses.

Our aim was to evaluate a novel educational method for disseminating current knowledge on rheumatology disorders to primary care practitioners.

Methods: The Rheumatology Family Practice Toolbox is designed as an intensive 1/2 day course designed to offer up to date information to primary care practitioners on the latest diagnostic and treatment guidelines for common rheumatic diseases including early inflammatory arthritis, gout, ankylosing spondylitis, back pain, osteoporosis, fibromyalgia and osteoarthritis. The course structure involved a short lecture on each topic and 3 short practical workshops on arthrocentesis, joint injection and DXA interpretation. Participants evaluated their knowledge and educational experience before, during and after the course rating aspects on a 5-point Likert scale.

Results: 32 primary care practitioners attended, who had a mean of 15 years experience in their specialty. 66% completed all 3 course assessments. The mean number of educational symposia they attended in the previous 5 years was 15, with and average of <1 in rheumatology. 100% of respondents agreed believed course participation had significantly changed their practice. Participants stated the toolbox improved their knowledge of, and confidence in diagnosing and managing common rheumatologic disorders, and would improve the quality of their care and referrals, Table 1.

Table 1. Comparison of the pre and post course confidence of course participants for diagnosing and managing common rheumatic disorders.

Diagnosis			Management		
Condition	**Pre-course**	**Post-course**	**Condition**	**Pre-course**	**Post-course**
Osteoarthritis	80%	95%	Osteoarthritis	60%	95%
Fibromyalgia	20%	57%	Fibromyalgia	16%	52%
Gout	72%	95%	Gout	68%	100%
Inflammatory Arthritis	52%	86%	Inflammatory Arthritis	16%	76%
Osteoporosis	80%	95%	Osteoporosis	68%	86%
Back Pain	64%	90%	Back Pain	56%	86%
Ankylosing Spondylitis	12%	86%	Ankylosing Spondylitis	8%	67%

Conclusion: Post-graduate training in rheumatic diseases is uncommon in primary care. The Rheumatology Toolbox is an effective educational method for disseminating current knowledge in rheumatology to primary care physicians and improved participant's self-assessed competence in diagnosis and management of common rheumatic diseases. Further studies are needed to determine whether this improves the quality of patient care and rheumatology referrals.

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The Gait, Arms, Legs & Spine Exam: An Effective Screening Tool for Rheumatoid Arthritis When Used by Family Physicians and Nurse Practitioners. Karen A. Beattie, Norma J. MacIntyre and Alfred A. Cividino. McMaster University, Hamilton, ON

Background/Purpose: Early referral to a rheumatologist for diagnosis of rheumatoid arthritis (RA) and initiation of appropriate treatment is critical. However, recognition of RA signs and symptoms in primary care remains a major challenge. The purpose of this study was to evaluate the sensitivity and specificity of the GALS (gait, arms, legs & spine) examination when used by family physicians and nurse practitioners to screen for signs and symptoms of RA.

Methods: Participating healthcare professionals (HCP), including 2 rheumatologists, 3 family doctors (FDs) and 3 nurse practitioners (NPs), were trained to perform the GALS exam and record their findings by viewing an instructional GALS DVD and attending a hands-on training workshop. One week after training, HCP performed the GALS on 41 study participants recruited through local rheumatology practices. Twenty participants had previously been diagnosed with RA while the remaining 21 participants had never been diagnosed with RA. Study participants were divided into two groups (A & B) such that approximately half of the participants in each group had RA. Those in Group A were assessed by 1 rheumatologist, 1 FD and 2 NPs while those in Group B were assessed by 1 rheumatologist, 2 FDs and 1 NP. HCPs recorded gait abnormalities, abnormalities of the movement or appearance of the arms, legs and spine and, ultimately, whether a diagnosis of RA was suspected. HCP were blinded to the medical history of the participants and were unaware that half of the study participants had previously been diagnosed with RA. Sensitivity and specificity were calculated for each HCP to determine the ability of the FDs and NPs to screen for RA signs and symptoms using the GALS when compared to the rheumatologists' screen on the study day.

Results: When compared to the rheumatologists' suspected diagnosis of RA based on the GALS examination findings on the study day, sensitivity for each of the 3 FDs was 60%, 80% and 100% while the specificity for each was 82%, 82% and 70%, respectively. Sensitivity for each of the 3 NPs was 60%, 80% and 90% while the specificity was 100%, 80% and 73%, respectively.

Conclusion: These results suggest that the GALS exam may be a useful screening tool for RA when used by FDs and NPs working in the primary care setting. Differences in level and type of clinical experience may contribute to the variations observed. The merits of introducing the GALS exam into primary care curricula should be explored.

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Effects of Simulated Joint Aspiration Training on Self-Confidence. Jefferson R. Roberts[1], Jess D. Edison[2], Elizabeth A. Mewshaw[2] and Jeffrey Mikita[3]. [1]Walter Reed Army Medical Ctr, Chevy Chase, MD, [2]Walter Reed Army Medical Ctr, Washington, DC, [3]Senior Author, Washington, DC

Background/Purpose: Musculoskeletal problems encompass 23% of primary care visits and affects 43 million people in the United States. Arthrocentesis among medical providers is on the decline with 74% practicing this procedure in 1986 compared to 54% in 2006. Many medical training programs require three joint procedures for graduation, a requirement recently recommended by the American Board of Internal Medicine. In the setting of this requirement, only 15% of graduating trainees report confidence with arthrocentesis. Joint aspiration and injection are traditionally taught on an informal basis to medical providers during training. Our objective is to determine if the educational tool of joint simulation for needle aspiration improves self-confidence scores among medical providers.

Methods: A pre and post elective, anonymous survey was administered to medical providers who attended a one hour joint simulation workshop during a regional American College of Physicians annual scientific meeting. Knee and shoulder simulators were utilized as educational tools. Using a 10-point Likert type scale, respondents indicated their self-confidence in performing needle aspiration of the knee and shoulder. Medicine internists, subspecialists and trainees were surveyed. Data were compared using Wilcoxon rank sum test. The protocol for this study was approved by the department of clinical investigation at our institution.

Results: Twenty-five pre-joint simulation surveys and 23 post-joint simulation surveys were completed. Approximately half of the respondents were internal medicine staff and trainees and the other half encompassing various internal medicine subspecialists. Self-confidence in performing shoulder aspiration pre and post joint simulation improved significantly (mean scores 4.6+/−2.8 and 7.3+/−2.0 respectively; p<0.001). Self-confidence in performing knee aspiration pre and post joint simulation did not improve significantly (mean scores 6.5+/−3.0 and 8.0+/−1.6 respectively; p=0.14). The need for additional shoulder simulation training pre and post shoulder joint simulation improved significantly (mean scores 7.9+/−2.6 and 5.6+/−2.2 respectively; p<0.001). The need for additional knee simulation training pre and post knee joint simulation training did not improve significantly (mean scores 6.3+/−3.4 and 4.9+/−2.4 respectively; p=0.14). All

participants scored joint simulation as a useful teaching tool with a mean score of 9.0+/−.80.

Conclusion: Simulated arthrocentesis training improves procedural confidence and proves useful among internal medicine staff and trainees. Among participants of a one hour joint simulation workshop, shoulder training significantly improved self-confidence scores, where there was a trend towards improved self-confidence in knee arthrocentesis. Musculoskeletal simulation training proves useful as a teaching tool among internal medicine staff and trainees.

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Increasing Rheumatology Exposure to Internal Medicine Residents in the Setting of Limited Resources: Evaluation of A Web-Based Image of the Month. Steven J. Katz. University of Alberta, Edmonton, AB

Background/Purpose: Previous studies have demonstrated poor musculoskeletal abilities of internal medicine residents when compared to other medical subspecialties. Further, a lack of rheumatology exposure is associated with this ability, with increased exposure being linked with improved ability. However, rheumatology manpower and resources remain limited to facilitate this.The internet may provide a solution to improve rheumatology exposure while using available resources efficiently.

Methods: An Image of the Month webpage was established in July 2010 on the www.EdmontonRheumatology.com website, a site representing rheumatologists in Edmonton, Alberta, Canada. Each month, a rheumatologist was responsible for posting a new image with a question which could be answered and submitted online by University of Alberta Internal Medicine residents. At the end of each month, a token book prize was awarded randomly to a correctly submitted respondent. One year data was analyzed to determine the change in rheumatology exposure for internal medicine residents and the resources required to implement this program.

Results: The Image of the Month webpage has posted images monthly for 12 months. There was no cost to implement the program as the website already existed and there was pre-existing funding for the book prize. The rheumatologist required no more than 15 minutes monthly to administer the contest. The webpage had over 700 unique visits. Out of 80 internal medicine residents, 46 participated at least once out of 12 possible images, with 34 having multiple entries. The average participation per resident was 3.6 times (range 1–11). 25 residents completed a rheumatology rotation over this time, of which 13 submitted an answer at least once. This means 33 residents received rheumatology exposure over the twelve months that may not have otherwise.

Conclusion: The Image of the Month webpage successfully improves rheumatology exposure with minimal resources required. Further study is necessary to determine the impact this exposure may have on MSK abilities of internal medicine residents.

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Advocacy in Rheumatology: Implications for Medical Education Based on a Focused Literature Review. Jellena Wong and Mala Joneja. Queen's University, Kingston, ON

Background/Purpose: Advocacy in healthcare is a critical element of social accountability and a key competency in physician training as defined by the CanMEDS roles. Patient advocacy can be defined as the use of the physician's resources and expertise to enhance the patient's quality of life. Few models for teaching advocacy skills to physicians in training are available. The history and development of patient advocacy in rheumatic disease can serve as the basis for the development of a teaching model for residents and medical students. With this in mind, the purpose of this review was to: 1) Review the literature with respect to advocacy and rheumatic disease 2) Describe connections in the literature with respect to teaching advocacy in medical education 3) Based on our findings, propose a model for teaching advocacy skills to medical students and residents.

Methods: Two separate MESH keyword searches were conducted of Ovid Medline. The first search used "Patient advocacy" (MeSH) AND "Arthritis/Rheumatoid/or Arthritis, Psoriatic/ or Arthritis/ or Arthritis, Reaction" (MeSH) with no date restriction. The second Medline search used "Patient advocacy" (MeSH) AND "Education, Medical" (MeSH) with date restriction from 1996 to present. Further articles were obtained from the reference lists of these articles.

Results: Twenty-four relevant articles and one book were identified based on the two literature reviews. The review of literature on patient advocacy and rheumatic disease identified five broad themes including: 1) self-management, 2) the four psychosocial theories of chronic disease, 3) the advocacy group movement, 4) the Patient Education Model, and 5) specific areas unique to rheumatic disease. The review of the literature on advocacy and medical education identified three different themes including: 1) clinical bioethics and medical ethics, 2) social responsibility, and 3) communication. There is overlap in the literature emphasizing the importance of the role of the physician in educating patients in order to empower patients and promote the self-management of disease.

Conclusion: The literature addressing advocacy in rheumatic disease combined with the literature on advocacy in medical education supports a model of advocacy where the physician has a pivotal role in the education of patients about their condition and associated management strategies. Medical students and residents should be trained to speak to patients in non-medical language, facilitate patient education and provide a scaffolding for self-management strategies. Rheumatology, with its history of promoting self-management and the Patient Education Model, can be a leader in educating future physicians in advocacy in health care.

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The Impact of An Intensive Rheumatology Teaching Programme on the Clinical and Diagnostic Skills of Intern House Officers. L.J Durcan[1] and Gaye Cunnane[2]. [1]St James's Hospital,, Dublin, Ireland, [2]St.James Hospital, Dublin, Ireland

Background/Purpose: It has been previously shown that junior doctors lack skill and confidence in rheumatological examination and diagnosis. This has consequences for patient care and for subsequent recruitment to rheumatology training programmes.

Methods: A dedicated 6 week rheumatology teaching programme for Interns was devised, focussing on clinical examination, recognition of common diseases and plain radiology. The effects on clinical skills were evaluated. Twenty interns were assessed by questionnaire before and after the teaching programme.

Results: Before the start of the programme, 70% of interns declared confidence in their clinical examination of the hand while only 10% were confident in foot examination. Thirty percent were confident in interpretation of hand radiology. The mean number of bones they could accurately name was 7.2 (SD 1.9) in the hand and 4.2 (SD 1.9) in the foot. Confidence in diagnosis of nerve entrapment syndrome was 40% for the ulnar nerve and 30% for the median nerve.

All (100%) felt they could diagnose rheumatoid arthritis, 90% acute gout, 40% psoriatic arthritis, 35% chronic gout, 15% scleroderma, while none knew how to diagnose dermatomyositis. However, when shown clinical pictures of these diseases, they reported in the correct diagnosis in 80% for RA, 50% for PsA, 75% for scleroderma, 75% for chronic ankylosing spondylitis and 70% for acute gout.

After the teaching programme, !00% were confident in the examination of the hand, 95% in the foot and 80% were confident in the interpretation of plain films of the hands. They could name a mean of 9 hand bones (SD.96) and 5.8 foot bones (SD.93). They felt 100% confident in the diagnosis of median, ulnar and radial nerve palsies. 95% felt confident in the diagnosis of PsA, 100% in RA, 100% in acute gout, 85% in chronic gout, 65% in dermatomyositis and 85% in scleroderma.

Conclusion: Interns lack confidence in clinical examination, plain film interpretation and diagnosis of common rheumatological conditions. A short training programme resulted in significant improvement in all modalities examined. It is essential to identify such deficiencies in order to develop clinical skills and encourage knowledge of basic rheumatologic competencies at an early stage in training.

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Hospital for Special Surgery Rheumatology Academy of Medical Educators: Planning Retreat Demonstrates a High Degree of Faculty Interest in Teaching, a Teaching Career and Formalized Education to Increase Competency. Jessica Berman[1], Juliet Aizer[1], Anne R. Bass[1], William L. Cats-Baril[2], Mary K. Crow[3], Edward J. Parrish[1], Laura Robbins[3], Jane E. Salmon[1] and Stephen A. Paget[1]. [1]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [2]University of Vermont, Burlington, VT, [3]Hospital for Special Surgery, New York, NY

Background/Purpose: Academic rheumatologists are expected to teach although very little formal educational instruction is given to faculty and financial support and career advancement for time spent is often inadequate. The concept of the Academy, where intellectual and financial resources are made available to academic educators and their research, is not new, having

been successfully implemented at UCSF and several other institutions. At the Hospital for Special Surgery (HSS) an Education Retreat was recently convened to discuss the feasibility of, faculty interest in and institutional support for the formation of a Rheumatology Academy.

Methods: Faculty in the division of Rheumatology were surveyed pre- and post-retreat regarding their opinions about education in the division, interest in teaching, time and resources. The retreat was held for one day over 8 hours and was divided into 1) formalized didactics given by invited educators; 2) breakout groups assigned various topics for formalizing recommendations and prioritizing institutional goals; and 3) discussion regarding the feasibility of and financial resources necessary to establish an academy at HSS. Of the 41 individuals surveyed, 34 (83%) completed the survey pre- and 19 (46%) post-retreat. Responses ranged from 1=strongly disagree to 5=strongly agree and were anonymous.

Results: Prior to the retreat, the majority of faculty answered that they agreed strongly or very strongly to the following questions: "I have the interest to be a great teacher" (91%; 4.47) and "I have the commitment to be a great teacher" (94%; 4.47). Most were "satisfied with my performance as a teacher" (71%; 3.74). However there was less confidence that "I am an excellent teacher" (54%; 3.70), and fewer felt that they had an "understanding of the latest pedagogical techniques" (36%; 3.33), "the time to be a great teacher" (pre-retreat 39%; 3.15 and post-retreat 24%; 2.59) and "the resources and tools to teach well" (pre-retreat 32%; 3.00 and post 16%; 2.58). Few agreed that "I have the incentives to be a great teacher" (33%; 2.97), however a majority agreed that "if it did not negatively impact my income, I would like to teach more" (67%; 3.88). *A larger number than expected* agreed or strongly agreed that "I would like to be part of an Education Academy and move along a Clinician-Educator track" pre-retreat (42%; 3.29). Post-retreat interest in participation in the educational activities of an Academy rose further (68%; 3.79).

Conclusion: The HSS Rheumatology Academy aims to create a stimulating academic educational environment that enhances the quality of teaching and promotes teaching careers and education research. While the pre-retreat survey indicated a high degree of faculty interest in teaching and advancement on the Clinician-Scholar-Educator track, lack of formal education and support were reasons given for less participation. However, surveys highlight that enthusiasm is high regarding the ability of the Academy to provide faculty with resources. This emphasizes the clear advantages of such a formalized structure to achieve the rheumatology division's heightened educational goals and raise the importance and quality of teaching to equivalence with clinical care and research.

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Attitudes of Pediatric Residents Regarding Musculoskeletal Evaluation and Complaints. Ricardo Guirola[1], Eyal Muscal[2] and Jennifer L. Arnold[2]. [1]Texas Children's Hospital, Houston, TX, [2]Baylor College of Medicine, Houston, TX

Background/Purpose: Musculoskeletal (MSK) conditions may affect up to 30% of children and adolescents. Adult medicine trainees and general practitioners have expressed poor confidence in MSK knowledge and skills, confidence and comfort level. Similar domains have not been evaluated in US pediatric residency training programs.

The aim of this study was to evaluate attitudes regarding MSK skills and training of pediatric residents at a tertiary care residency program. We hypothesized that pediatric residents, like trainees in adult medicine, would: a) have low levels of comfort performing MSK exams and b) express low confidence in evaluating MSK complaints.

Methods: In January of 2011 pediatric residents at Texas Children's Hospital/ Baylor College of Medicine were sent a 16 question survey via a link in survey monkey. Survey results were compiled over a 5 month period. We analyzed relationships between survey responses and type of trainee (pediatric vs. medicine-pediatric), and post-graduate year (PGY level) using non-parametric tests of association for ordinal variables (Kendal tau-b coefficient, T).

Results: 101 out of 161 (62.7%) pediatric residents at our institution completed the survey. The responders included 31 (30.7%) PGY-1 residents, 36 (35.6 %) PGY-2 residents, 29 (28.7%) PGY-3 residents, and 5 (5.0%) PGY-4 residents (all medicine-pediatric). Fifteen of the survey respondents (14.8%) were medicine-pediatric residents. Eighty-two (82%) of responders believed that MSK medicine was important towards their future career. Medicine-pediatrics training was more strongly associated with this belief ($T = 0.208$, $p = 0.02$). Fifty-seven (56.4%) of the residents expressed discomfort in performing a MSK exam. Comfort levels increased after PGY-1 year and throughout training although these associations were not statistically significant ($T = 0.133$, $p = 0.12$). Seventy (69.3%) of the residents expressed a lack of confidence in making diagnoses for patients with MSK complaints. Confidence levels increased over time (maximum PGY-2 38.9 % [n=29] and PGY-4 80% [n=5]). Associations with PGY status was statistically significant ($T = 0.234$, $p < 0.01$). Higher comfort and confidence levels of medicine-pediatric residents were not statistically significant. Ninety-one residents (89.1%) believed that MSK training was not adequate and indeed only 48.5% stated previous formal MSK training. The acknowledgement of formal training increased throughout training (maximum % in PGY-3 and PGY-4 by 65.5% and 100% respectively, $T = 0.326$, $p = 0.01$). Medicine-pediatric residents (throughout all years of training) were not more likely to describe additional formal MSK training when compared to their categorical pediatric counterparts.

Conclusion: Pediatric trainees expressed low confidence, and discomfort with their MSK skills. Most residents expressed inadequacy of MSK medicine training. These negative perceptions were not ameliorated at the completion of training. Pediatric trainees at our institution were aware of the importance of MSK medicine and may be motivated to improve their skills. Evaluation of the effectiveness of standardized patients and web based modules to improve pediatric resident skills in MSK medicine is needed.

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Anatomical Basis of Rheumatologic Examination: Upper Extremity and Cervical Region. Pablo Villaseñor-Ovies[1], Joseph Biundo[2], Juan J. Canoso[3], Simon Carette[4], Francisco J. de Toro-Santos[5], Cristina Hernández-Díaz[1], Robert A. Kalish[6], Dennis McGonagle[7], Miguel A. Saavedra-Salinas[8] and José E. Navarro-Zarza[9]. [1]Instituto Nacional de Rehabilitación, Mexico City, Mexico, [2]Luisiana State Univesity, USA, Metairie, LA, [3]ABC Medical Center and Tufts University, Mexico City, Mexico, [4]Toronto Western Hospital, Toronto, ON, [5]Complejo Hospitalario Universitario Juan Canalejo, Universidad de la Coruña, La Coruña, Spain, [6]Tufts Medical Center, Boston, MA, [7]University of Leeds and Leeds Teaching Hospitals, Leeds, United Kingdom, [8]Centro Médico Nacional, México, Mexico, [9]Mexican Taskforce for the Advancement of Clinical Anatomy, Mexico, Mexico

Background/Purpose: The rheumatologic examination, which is based on a sound internal medicine examination, focuses predominantly on the musculoskeletal system. However, seasoned rheumatologists recognize the importance of the neurologic and vascular examination as well. The current survey is a group effort at listing musculoskeletal, neural and vascular structures that may be most relevant to a successful training in, and practice of, rheumatology

Methods: The Mexican Task Force on Clinical Anatomy (GMAC) is an officially recognized group of the Mexican College of Rheumatology that is comprised of 6 rheumatologists (one off site, RAK) who have had extensive training in clinical anatomy, combined training sessions with the Mexican School of Ultrasonography and anatomists of the National University of Mexico (UNAM), as well as intragroup certification in clinical anatomy. Members of this group individually listed anatomical items felt to be relevant to the practice of rheumatology. A final items list was circulated to the GMAC members and 4 internationally recognized rheumatologists for a Delphi exercise. Items were rated as unimportant, fairly important, moderately important, important and very important. Consensus was reached when an item was rated important or very important by 8 or more of the 10 participants. The original list went through 2 Delphi rounds and consensus items were subsequently analyzed according to the structure involved, anatomical region and possibility of identification on physical examination.

Results: The initial list had 549 items including 381 (69.3%) musculoskeletal (bone, joint, ligament, tendon, enthesis, fascia, bursa), 75 (13.6%) neural, 14 (2.5%) vascular and 75 (13.6%) classified as other. At the 1st Delphi round consensus was reached in 129 items and at the 2nd round 92 consensus items were added reaching a total of 221 (40.2%) items. Of these 125 (56.5%) were musculoskeletal, predominantly muscles (47), joints (27), bones (23) and tendons (17). Of the items that reached consensus, 62 (28%) pertained to the hand, 53 (23.9%) to the shoulder, 45 (20.3%) to the cervical spine and 43 (19.4%) to the elbow. Finally, 103 (46.6%) items were considered identifiable on physical examination.

Conclusion: Given our interest in clinical anatomy our initial listing was, if anything, over-inclusive. However, most of the participants in this exercise are practicing rheumatologists and it was our hope that our collective experience would be reflected in the findings. While musculoskeletal items understandably prevailed a surprisingly high number of neural items were considered important. This should not be unexpected given the intricate anatomical and clinical relations between both systems.

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Impact of Subspecialty Elective Exposures on Outcomes on the American Board of Internal Medicine Certification Examination. Katina C. Tsagaris[1], Amber Schilling[1], Hong Wang[2], Sameer Desale[2], Michael Adams[1] and Victoria K. Shanmugam[1]. [1]Georgetown University Hospital, Washington, DC, [2]MedStar Research Institute, Washington, DC

Background/Purpose: Medical knowledge is an Accreditation Council for Graduate Medical Education (ACGME) core competency, which can be measured by scores on the American Board of Internal Medicine Certification Examination (ABIM-CE). While formalized elective curricula are known to improve subspecialty scores on the ABIM-CE, no studies have evaluated the impact of individual subspecialty elective exposures on resident medical knowledge as measured by the ABIM-CE.This study was designed to evaluate whether exposures to particular subspecialty electives impact ABIM-CE scores.

Methods: This was a retrospective study of ABIM-CE scores and elective exposures from residents enrolled in the Georgetown University Hospital internal medicine residency program between 2002 and 2010. Total and subspecialty scores (percentage of items correct) on the ABIM-CE were compared to subspecialty elective exposures.

Results: For graduation years 2005 to 2013, 307 categorical residents were enrolled in the Georgetown Internal Medicine residency. Of these, 4 did not complete the residency, 29 were combined internal medicine-pediatrics residents, 144 did not have paired elective and ABIM-CE data and 18 withheld their ABIM-CE scores. Concurrent ABIM-CE scores and elective exposures were available for 111 residents. There were no significant differences in age, gender, or location of medical school between annual cohorts and none of these factors correlated with ABIM-CE scores. Rheumatology elective exposure was correlated with higher ABIM-CE score (77.79 +/− 0.76 compared to 79.96 +/− 0.78, $p=0.048$, table 1) whereas, none of the other subspecialty elective exposures had an association with ABIM-CE scores. There were no significant associations between elective exposures and total or subspecialty scores for any of the other subspecialties. ANOVA analysis comparing ABIM-CE scores in subjects with 0, 1 and more than 1 elective exposure in each subspecialty did not show a significant association between repeated elective exposures and improved performance on the ABIM-CE based either on the total percentage correct or the subspecialty percentage correct.

Table 1. ABIM-CE total and subspecialty scores based on percent correct based on elective exposure. (p values are based on unpaired t-test)

	TOTAL % CORRECT ON ABIM-CE (mean, SEM)			SUBSPECIALTY % CORRECT ON ABIM-CE (mean, SEM)		
	No Elective Exposure	Elective Exposure	*p* value	No Elective Exposure	Elective Exposure	*p* value
RHEUMATOLOGY	77.79+/−0.76 (n=57)	79.96+/−0.78 (n=54)	**0.048**	78.82+/−1.4 (n=57)	82.46+/−1.3 (n=54)	0.06
INFECTIOUS DISEASES	77.17+/−1.25 (n=23)	79.28+/−0.6 (n=88)	0.12	78.87+/−2.59 (n=23)	81.90+/−0.95 (n=88)	0.19
NEPHROLOGY	78.42+/−0.88 (n=45)	79/.14+/ −0.71 (n=66)	0.53	82.29+/−1.8 (n=45)	85.53+/−1.5 (n=66)	0.17
GASTROENTEROLOGY	78,7+/−0.79 (n=46)	78.95+/−0.76 (n=65)	0.82	77.41+/−1.59 (n=45)	79.48+/−1.28 (n=65)	0.31
PULMONARY	78.19+/−1.20 (n=31)	79.10+/−0.61 (n=80)	0.46	77.13+/−1.73 (n=31)	79.00+/−1.22 (n=80)	0.41
CARDIOLOGY	78.67+/−0.97 (n=36)	78.93+/−0.67 (n=75)	0.82	78.64+/−1.35 (n=36)	81.35+/−1.17 (n=75)	0.16
HEMATOLOGY	78.73+/−0.77 (n=60)	78.98+/−0.78 (n=51)	0.82	82.08+/−1.7 (n=60)	80.16+/−1.81 (n=51)	0.44
ENDOCRINOLOGY	78.97+/−0.76 (n=39)	78.78+/−0.75 (n=72)	0.86	77.62+/−1.8 (n=39)	79.07+/−1.3 (n=72)	0.51

Conclusion: This study identified a small but significant association between exposure to the rheumatology elective and score on the ABIM-CE. Repeated elective exposures in a single specialty were not associated with improved ABIM scores. Residents should consider these findings when they are making elective selections.

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Availability of Pediatric Rheumatology Training within Pediatric Residency Programs in Canada. Roman Jurencak, Johannes Roth and Sarah Lawrence. University of Ottawa, Ottawa, ON

Background/Purpose: Musculoskeletal symptoms in children are very common, occurring in up to 30% of children at some point during childhood. However, a recent national survey from the United States found that only 18% of pediatricians believed they were adequately trained to diagnose and treat arthritis in children[1]. This may be at least partially attributable to lack of exposure to pediatric rheumatology during their training as only <60% of pediatric residency programs in the USA have an on-site rheumatologist[2]. The aim of this study was to survey all pediatric residency programs in Canada to determine the availability of pediatric rheumatology training.

Methods: Program directors of all 17 pediatric residencies in Canada were contacted and asked to fill out a questionnaire assessing formal pediatric rheumatology teaching in their program.

Results: Response was so far received from 11/17 programs (65%). There was no formal pediatric rheumatology teaching available on-site at 3 centers as there was no rheumatologist on staff. However, all 3 centers offered an off-site rotation at another university. Overall, 7 centers offered an elective rotation in pediatric rheumatology, while 4 centers had a mandatory rotation. The length of rotation at each centre was 4 weeks and was usually done in PGY 2 or PGY 3. When an elective rotation was available, it was chosen on average by <50% of residents. No university reported higher residents' demand than could be accommodated. Formal large group lectures on rheumatologic disorders were offered at all centers, on average 3 hours per year. Small group lectures (case based learning, problem assisted learning etc) we available at 7 centers, on average 3 hours per year. A formal lecture on MSK exam was a part of the postgraduate training at 9 centers.

Conclusion: There is excellent availability of pediatric rheumatology training for pediatric residents at the pediatric programs surveyed. However, at the majority of programs, rheumatology rotations are elective and are chosen by less than half of the residents in each program. Mandatory large and small group lectures on pediatric rheumatology topics combined account for only 5–6 hours of teaching per year. This indicates a clear need for development of strategies to ensure adequate training in pediatric rheumatology for pediatric residents.

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Publication Outcomes of Abstracts Presented At the ACR/ARHP Annual Scientific Meeting. Gil Amarilyo, Jennifer MP Woo, Daniel E. Furst, Olivia I. Lund, Rotem Eyal, Cindy Piao, Miriam F. Parsa, Ornella J. Rullo, Alice DC Hoftman and Deborah K. McCurdy. University of California, Los Angeles, Los Angeles, CA

Background/Purpose: The American College of Rheumatology (ACR) and the Association of Rheumatology Health Professionals (ARHP) Annual Scientific Meeting (ASM) serves as the primary forum for introducing novel clinical and basic science research in the fields of rheumatology and immunology worldwide. However, unlike published studies in peer-reviewed journals, accepted abstracts are usually filtered by 2–4 reviewers who are exposed solely to the summary of the research study. Formal analyses of the scientific impact of ASM on abstract publication have not been performed to date. We therefore aimed to describe the probability of publication and impact factors of presentations and posters when presented at the ASM.

Methods: We identified all abstracts that were accepted for oral or poster presentation at the 2006 ASM. Using a defined search algorithm, which included first or last authors, we conducted a PubMed search for each accepted abstract. If more than one published article was identified, key terms from the abstract title were compared to titles of published articles. Journal name, journal impact factor and time to publication were analyzed for each published study.

Results: A total of 2161 abstracts were presented at 2006 ASM and analyzed. The publication rates are listed in Table 1. The average time from abstract to publication was 16.7 months, with 39.4% of published presentations being published within 12 months following the 2006 ASM. Overall, studies presented in oral format were significantly more likely to be published compared to poster presentations ($p<0.002$); however this association was seen only in clinical studies ($p<0.001$) and not in basic science studies. The average time to publication was significantly shorter for basic science studies compared to clinical research studies (14.66 vs. 17.89 months; $p<0.001$) in both presentation formats ($p<0.01$ for both). Presented studies were published in 144 individual journals. The five journals with the largest number of publications (incorporating 56.6% of all published abstracts) include *Arthritis and Rheumatism* (186), *Annals of Rheumatic Diseases* (99),

Journal of Rheumatology (86), *Rheumatology* (45), and *Clinical and Experimental Rheumatology* (29). Finally, the average journal impact factor of published studies presented in oral format was significantly higher than those presented as posters, irrespective of clinical or basic science research ($p < 0.002$ for clinical, basic, and overall).

Table 1. Publication Data: ACR/ARHP Annual Scientific Meeting, 2006.

Type (%)	Publication Ratio (%)	Time to Publication (months±SD)	Impact Factor of Journal (mean±SD)
Overall (100%)	36.4	16.7 ± 12.74	5.35 ± 3.35
Clinical (63%)	37.3	17.9 ± 12.41	5.2 ± 3.26
Poster sessions (83%)	35.3	17.4 ± 12.37	4.94 ± 3.11
Oral presentations (17%)	47	19.6 ± 12.61	6.17 ± 3.61
Basic Science (37%)	35	14.7 ± 13.07	5.59 ± 3.49
Poster sessions (82%)	34.7	14.7 ± 13.29	5.07 ± 2.55
Oral presentations (18%)	38.4	14.4 ± 12.27	7.64 ± 5.42

Conclusion: The ASM serves as an important forum for early dissemination of novel ideas. As comparable with other national specialty meetings, 36% of the abstracts are published. Abstracts selected for oral presentation represented studies that are more likely to be published in higher impact journals.

ACR Poster Session A
Epidemiology and Health Services Research I: Rheumatoid Arthritis
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Risk Factors for Positive Rheumatoid Factor Among 31,207 People without Rheumatologic Disorders. Hiromichi Tamaki[1], Yuji Nishizaki[2], Ken-ichi Yamaguchi[3], Toshiko Kawakita[4], Mitsumasa Kishimoto[4] and Masato Okada[5]. [1]University of Hawaii, Honolulu, HI, [2]Juntendo University, Tokyo, Japan, [3]St. Luke's International Hospital, Tokyo, Japan, [4]St Luke's International Hospital, Tokyo, Japan, [5]St. Luke's International Hosptal, Tokyo, Japan

Background/Purpose: Rheumatoid factor is known to be associated with smoking, malignancy, hepatitis B or C as well as many rheumatologic disorders not limited to rheumatoid arthritis. However, there have been no large-scale studies to prove these relationships.

Methods: St. Luke's International Hospital Center for Preventive Medicine performs annual health examinations for more than 30,000 people each year, and rheumatoid factor is checked routinely during these examinations. The data in 2004 was obtained from the St. Luke's Center for Preventive Medicine, including rheumatoid factor, past medical history (hypertension, hyperlipidemia, diabetes, ischemic heart disease, malignancy, hepatitis B or C), pulmonary function test and BMI. The people with known rheumatologic disorders were excluded. This data were analyzed statistically.

Results: A total of 31,207 patients were evaluated. The mean age was 49.1 and men consists of 50.7% of the group and women 49.3%. 6.8% had positive rheumatoid factor. Rheumatoid factor was positive in 2.3% among people in their 20s, 4.3% in their 30s, 7.1% in their 40s, 7.8% in their 50s, 7.8% in their 60s, 8.9% in their 70s, and 14.9% in their 80s. Rheumatoid factor was positive in 9.8% of patients with cancer, 20.7% of patients with hepatitis B, 19.6% with hepatitis C. Among current smokers 7.3% people were rheumatoid factor positive and among remote smokers, 7.1%. Sex was not significantly associated with positive rheumatoid factor but age was. Multivariate logistic regression analysis with age and sex correction revealed smoking, diabetes mellitus, malignancy hepatitis B and hepatitis C were risk factors for positive rheumatoid factor. Each odds ratio was as below. Smoking 1.14 (95% confident interval (CI): 1.07 – 1.21, P value <0.0001), diabetes mellitus 2.14 (95% CI: 1.09 – 4.21, P value 0.0276), malignancy 1.26 (95%CI: 1.09 – 1.54, P value <0.0296), hepatitis B 3.605 (95% CI: 2.52 – 5.15, P value <0.0001), hepatitis C (95% CI: 1.99 – 4.17, P value <0.0001). Hypertension, hyperlipidemia, body mass index, ischemic heart disease, vital capacity as percent of predicted or forced expiratory volume in one second as percent of predicted were not associated with positive rheumatoid factor.

Conclusion: The relationship between positive rheumatoid factor and conventionally estimated risk factors such as smoking, malignancy, hepatitis B, and hepatitis C is confirmed. Diabetes Mellitus is also a risk factor for positive rheumatoid factor among non-rheumatologic patients.

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The Association Between Rheumatoid Factor and Predisposing Factors for Atherogenesis in First-Degree Relatives without Rheumatoid Arthritis: *S*tudies of the *E*tiology of *R*heumatoid *A*rthritis. Jan M. Hughes-Austin[1], Kevin D. Deane[2], Lezlie A. Derber[3], Gary O. Zerbe[1], Dana M. Dabelea[1], Robert H. Eckel[4], Jeremy Sokolove[5], William H. Robinson[6], V. Michael Holers[7] and Jill M. Norris[1]. [1]Colorado School of Public Health/University of Colorado Anschutz Medical Campus, Aurora, CO, [2]University of Colorado School of Medicine, Aurora, CO, [3]University of Colorado AMC, Aurora, CO, [4]Aurora, CO, [5]Stanford University, Palo Alto, CA, [6]Stanford University, Stanford, CA, [7]Univ of Colorado School of Med, Aurora, CO

Background/Purpose: Systemic inflammation and immune dysregulation, which include presence of autoantibodies (Abs) and elevated inflammatory markers, characterize rheumatoid arthritis (RA) and precede the development of clinically-apparent RA by years. These two factors not only mark the future development of RA, but may also contribute to the pathogenesis of atherosclerosis and cardiovascular disease (CVD) in preclinical RA. We sought to investigate the relationships between RA-related Abs and atherogenic risk factors in first-degree relatives (FDRs) at risk for future RA, and whether systemic inflammation explains these relationships.

Methods: From the **SERA** project (a prospective study of preclinical RA), 113 FDRs who had been positive for any of 5 RA-related Abs: rheumatoid factor (RF), RF isotypes – IgM, IgG, IgA, or anti-cyclic citrullinated peptide (anti-CCP2) on at least one of their visits, and 100 FDRs who had never been Ab positive were selected. In samples obtained at 392 FDR visits, the following were measured: 1) lipids/lipoproteins: triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and apolipoprotein B (ApoB) (VAP-II); 2) endothelial activation/injury markers: soluble intracellular adhesion molecule-1, soluble vascular cell adhesion molecule-1 (VCAM-1) and E-selectin (ELISA); and 3) a panel of 25 cytokines/chemokines (bead-based assay) and high-sensitivity C-reactive protein (nephelometry). Cytokines/chemokines were standardized, weighted and summed for a Cytokine Score. Relationships between atherogenic risk factors and RA-related Abs, defined as RF and the high-risk profile (positive for anti-CCP2 and/or 2 RF isotypes), were calculated using a linear mixed model. All analyses were adjusted for age, sex, ethnicity, BMI, pack-years of smoking and statin use. Mediation analysis was performed using accelerated bootstrap confidence intervals to explore the effects of inflammation on the relationship between RA-related Abs and atherogenic risk factors.

Results: ApoB levels were lower by 4 mg/dL ($p=0.029$), and VCAM-1 levels were higher by 97 ng/mL ($p=0.0004$) in RF positive FDRs compared with RF negative FDRs. Inflammatory markers associated with both RF and VCAM-1 included IL-4, IL-6, IL-10, IL-12p70, GM-CSF, Eotaxin, IFN□, IP-10, MCP-1 and the Cytokine Score. When assessed for evidence of mediation, however, none of these inflammatory markers explained the relationship between RF and VCAM-1. No inflammatory markers were associated with both RF and ApoB. Therefore, mediation analysis for this association was not conducted. The high-risk profile was not associated with any of the measured atherogenic risk factors.

Conclusion: RF is associated with low ApoB and elevated VCAM-1 in a population without RA, but at increased risk for its future development. Systemic inflammation is associated with both RF and VCAM-1, but it does not explain the association, and suggests that RF affects VCAM-1 through either a different mechanism or another unmeasured marker of inflammation.As low ApoB and elevated VCAM-1 are predisposing factors for atherogenesis, these findings may indicate CVD development in preclinical RA.

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Exposure to Ultraviolet Light and Risk of Developing Rheumatoid Arthritis Among Women in the Nurses' Health Study. Elizabeth V. Arkema[1], Kimberly Bertrand[1], Francine Laden[1], Abrar A. Qureshi[2], Elizabeth W. Karlson[2] and Karen H. Costenbader[2]. [1]Harvard School of Public Health, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA

Background/Purpose: Previous studies have shown that people living in higher latitudes may be at a greater risk of RA. It has been hypothesized that the association between RA and latitude could be due to cutaneous exposure to ultraviolet (UV) light and production of vitamin D, a hormone with known immunomodulatory effects. We examined the relationship between cumulative average UV-B flux, based on residential location, and risk of RA among women followed in two large prospective cohort studies, the Nurses' Health Studies (NHS).

Methods: We examined the prospective association between cumulative

average UV-B flux exposure and RA risk among 222,792 women followed in the NHS 1976–2008 (born 1921–46, n=107,116) and NHSII 1989–2007 (born 1947–1964, n=115,676). Residential locations of NHS participants were available for 1976, 1986–2006 and for NHSII participants from 1989–2007. Incident RA cases diagnosed from 1976–2008 for NHS and 1989–2007 for NHSII were confirmed by medical record review. Average annual UV-B flux, a composite measure of mean UV-B radiation level based on latitude, altitude, and cloud cover, was estimated for all nurses according to state of residence during cohort follow-up. The relationship between tertile of cumulative average UV-B exposure and risk of RA was estimated using Cox proportional hazards models separately in each cohort, then combined using meta-analysis random effects models. Age- and multivariable-adjusted models, including age, parity, breast feeding, body mass index, pack-years smoking, physical activity, vitamin D intake, alcohol consumption, race, husband's education and oral contraceptive use, were used.

Results: We identified and confirmed 1146 incident RA cases. Although no significant heterogeneity between the two cohorts was found, the results were slightly different in the two cohorts. In the older women, NHS, there was a small but significant decrease in RA risk associated with increased UV-B exposure. In the cohort of younger women, however, this effect was not observed. When meta-analytically combined, cumulative UV-B flux exposure was not significantly associated with RA risk overall (**Table 1**).

Table 1. Cox proportional hazards model results estimating the effect of Cumulative Average UV-B on RA incidence

	RA Cases		Multivariable Cox Proportional Hazards Model*			
	NHS (N=875)	NHSII (N=271)	NHS	NHSII	Combined	p het**
Tertile cutpoints for Cumulative Average UV-B (R-B units***)						
≤109	348	73	1.00 (ref)	1.00 (ref)	1.00 (ref)	
109-≤117	318	79	0.87 (0.84, 1.01)	1.15 (0.84, 1.59)	0.96 (0.74, 1.26)	0.12
117	209	119	0.85 (0.72, 1.02)	1.14 (0.85, 1.53)	0.96 (0.73, 1.27)	0.10
p for trend			**0.05**	0.41	0.73	

* adjusted for age, parity, breast feeding, body mass index, pack-years smoking, physical activity, vitamin D intake, alcohol consumption, race, husband's education and oral contraceptive use
** p for heterogeneity between the two cohorts
*** Robertson-Berger UV-B flux units $\times 10^{-4}$

Conclusion: Results suggested an inverse association between UV-B exposure and incident RA in NHS, but there was no evidence of an association in NHSII or in combined analyses. Limitations include lack of data on time spent outside and sunscreen use, which could vary with nurse age. The overall results do not support an association between cumulative exposure to ambient UV-B light and RA risk; however, statistical power may have been limited to detect a modest association.

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Is Sunlight Exposure and Vitamin D Intake Associated with Rheumatoid Arthritis? Nicole C. Wright[1], Brian T. Walitt[2], Jeffery R. Curtis[1], Mary Pettinger[3], Christine G. Parks[4], Anneclaire J. De Roos[3], Jean Wactawksi-Wende[5], Rachel Mackey[6], Rebecca D. Jackson[7], Michal L. Melamed[8] and Barbara V. Howard[9]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Washington Hospital Center, Washington, DC, [3]Fred Hutchinson Cancer Research Center, WA, [4]NIH/NIEHS, Research Triangle Park, NC, [5]University of Buffalo, Buffalo, NY, [6]University of Pittsburgh, Pittsburgh, PA, [7]Ohio State University, Columbus, OH, [8]Albert Einstein College of Medicine, Bronx, NY, [9]Medstar Research Institute, Washington, DC

Background/Purpose: Dietary vitamin D intake has been studied as a risk factor for incidence of RA in several longitudinal cohort studies; however, only few have evaluated sunlight exposure, the primary source of vitamin D, and the risk of RA.

Methods: Using the Women's Health Initiative Observational Study (WHI-OS), we examined the association between vitamin D exposure on the prevalence and incidence of rheumatoid arthritis (RA). Prevalent RA cases were identified using the combination of self-report and medications at baseline. Incident cases were ascertained using year three data, and the comparison group consisted of women who did not report RA at either time point. Vitamin D exposure was identified in three ways: 1) vitamin D intake from food frequency questionnaire and supplementation sources, 2) previous sunlight exposure, and 3) current sunlight exposure. Previous sunlight exposure was ascertained via questions regarding time spent outdoors during summer and non-summer months as a child, in their teens, and in their thirties. Respondents answering <30 minutes were given a score of 15; respondents answering 30 minutes to 2 hours were given a score of 75, and those responding ≥2 hours were given a score of 180. The scores at each period were summed to create cumulative minutes of previous sunlight exposure. Mean solar irradiance, calculated using the clinical center location and national weather data, was used to ascertain current sunlight exposure. The three exposure variables were categorized and after controlling for several variables, the association with prevalent RA was tested using logistic regression and the association with the incidence of RA was tested using Cox-proportional hazards models.

Results: The study population included 76,743 women without RA, 727 prevalent RA cases, and 190 incident RA cases. Women with RA were significantly older, heavier, and had a larger proportion of African Americans and current smokers than the comparison group. After adjustment, no association between vitamin D exposure and the prevalence of RA was found in the total population; however different trends were observed by race (Table). Though not statistically significant in either group, compared to the highest category of summer sunlight exposure (>500 minutes), White women with the lowest exposure (<300 minutes) were 15% less likely to have prevalent RA [OR (95% CI): 0.85 (0.65, 1.10)] whereas African American women in the lowest category were 17% more likely [1.17 (0.60, 2.28)]. Similar differences in racial trends were found in the other exposure variables. No significant association between vitamin D exposure and the incidence of RA was found.

Table. The Association between Vitamin D Intake, Sunlight Exposure and the Prevalence of Rheumatoid Arthritis by Race

	White		African American	
	N/# cases	OR (95% CI)*	N/# Cases	OR (95% CI)*
Vitamin D Intake (IU/day)				
≥600	13,674/114	1.00	358/4	1.00
<600–400	15,683/143	1.08 (0.85, 1.39)	849/16	1.64 (0.54, 4.96)
<400–200	10,527/76	0.85 (0.64, 1.14)	589/8	1.17 (0.35, 3.91)
<200	18,440/125	**0.75 (0.58, 0.97)**	2,084/35	1.32 (0.47, 3.75)
Sunlight Exposure—summer (mins)				
>500	15,028/126	1.00	1,073/17	1.00
500–400	17,574/143	0.95 (0.75, 1.21)	1,308/17	0.87 (0.44, 1.71)
400–300	12,100/91	0.89 (0.68, 1.17)	750/14	1.22 (0.59, 2.49)
<300	14,124/101	0.85 (0.65, 1.10)	1,030/18	1.17 (0.60, 2.28)
Sunlight Exposure—other seasons (mins)				
>400	15,722/149	1.00	1,471/23	1.00
400–300	8,112/58	0.78 (0.57, 1.05)	551/11	1.34 (0.65, 2.78)
300–200	20,941/151	0.81 (0.64, 1.01)	1,217/17	0.96 (0.51, 1.80)
<200	13,888/97	**0.76 (0.59, 0.99)**	884/14	1.01 (0.52, 1.97)
Solar Irradiance (g-cal/cm^2)				
500–475	11,771/85	1.00	404/10	1.00
430–400	9,550/80	1.18 (0.86, 1.62)	959/17	0.69 (0.31, 1.53)
380-375	6,745/50	1.05 (0.72, 1.52)	1,101/12	0.43 (0.18, 1.00)
350	12,743/77	0.80 (0.58, 1.10)	1,321/19	0.54 (0.25, 1.18)
325-300	18,935/175	1.28 (0.97, 1.68)	538/12	0.88 (0.38, 2.08)

* Adjusted for age, BMI, region at birth, education, smoking, alcohol, weight at birth wearing hat outdoors during thirties, and total recreational physical activity

Conclusion: Self-reported estimates of lifetime and current vitamin D exposure were not associated with incidence or prevalence of RA in the WHI-OS; however, results suggest that race may modify the association between vitamin D exposure and RA.

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Prevalence and Incidence of Rheumatoid Arthritis in South Korea. Yoon-Kyoung Sung[1], Soo-Kyung Cho[1], Chan-Bum Choi[1], Jae Hoon Kim[2], Jin Ju Kim[2], Joo-Hyun Lee[2], Young Bin Joo[2] and Sang-Cheol Bae[1]. [1]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

Background/Purpose: Several studies of rheumatoid arthritis (RA) incidence and prevalence indicate that occurrence of the disease varies significantly among different populations. However, descriptive studies may be difficult to compare due to methodological differences in terms of case identification and ascertainment. We conducted this study to estimate the nationwide prevalence and incidence of RA with comparison of methodologies and results of other populations, and the prescription trend of disease-modifying anti-rheumatic drug (DMARD) use in South Korea.

Methods: Almost 100% of the population of South Korea is automatically registered as insured or qualified for Medicaid using an automated hospital billing system established throughout the country, since 2005. Hence we used Korean National Health Insurance (NHI) claims data to estimate the prevalence of RA from 2007 to 2009 and the incidence of RA in 2008. Changes in the use of DMARDs for RA during those three years were also documented.

Results: Using only the ICD-10 diagnostic code for RA, estimates for the prevalence of RA in 2007, 2008, and 2009 were 1.4%, 1.3%, and 1.2%, respectively. However, using our predefined operational definition of RA (a prescription for any DMARD or biologic drug with an RA diagnostic code in the same claim), the corresponding prevalence estimates were 0.26%, 0.27%, and 0.28%. The incidence of RA in 2008 was estimated at 42/100,000 in the general population of South Korea. The prevalence of biologic drug use for RA patients in 2007 was 0.84% and increased to 1.91% in 2009. During that period the prevalence of leflunomide use increased from 5.85% to 11.48%.

Conclusion: Use of data gathered nationwide through the NHI yielded estimates of RA prevalence and incidence in South Korea that are comparable to values for other countries in Asia. The use of leflunomide and anti-TNF agents is increasing in South Korea.

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Postpartum and the Risk of Developing Rheumatoid Arthritis; Results From the Swedish EIRA Study. Camilla Bengtsson[1], Cecilia Orellana[1], Marie Holmqvist[2], Anita Berglund[1], Sara Wedrén[3], Lars Klareskog[3] and Lars Alfredsson[1]. [1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Clinical epidemiology unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: It has previously been described that the incidence of RA is reduced during pregnancy but increased after delivery. The increased risk has been observed during the first three months[1] up to two years after postpartum[2]. To our knowledge, no previous study has investigated the postpartum period and its effect on risk of the two subsets of RA, characterized by presence/absence of antibodies to citrullinated peptides (ACPA), separately.

Methods: Data from the Swedish population-based EIRA (Epidemiological Investigation of Rheumatoid Arthritis) case-control study encompassing women aged 18–50 years. In total, 547 incident cases and 658 randomly selected controls, matched on age, sex and residency, were analysed. Parous women were compared with nulliparous women according to the risk of developing RA overall, ACPA-positive and ACPA-negative disease, respectively. In a separate analysis, women with partum the year before symptom onset was analysed. Odds ratios (OR) with 95% confidence interval (CI) were calculated using unconditional logistic regression.

Results: In total, 360 (66%) of the cases and 431 (66%) of the controls were parous, meaning that there was no association between parity and the risk of RA overall. However, parity increased the risk of developing ACPA-negative RA (OR=1.5 (95% CI 1.0–2.3)). Women with partum the year before disease onset had more than a two-fold increased risk of ACPA-negative RA (OR=2.4 (95% CI 1.1–5.4)). There was no association between parity and the risk of ACPA-positive RA.

Conclusion: Our results indicate that the postpartum period increases the risk of ACPA-negative RA, but has no association with ACPA-positive RA. Why postpartum is associated only with an increased risk of ACPA-negative RA, and what biologic mechanisms are involved, remains to be elucidated. Finally, our results indicate that the higher RA incidence among women than among men, might to some extent be explained by hormonal/reproductive factors, such as the postpartum period.

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Predictors for Remission in Rheumatoid Arthritis Are Affected by Remission Definition. Cheryl CM Barnabe[1], Joanne Homik[2], Susan G. Barr[1], Walter P. Maksymowych[2] and Liam Martin[1]. [1]University of Calgary, Calgary, AB, [2]University of Alberta, Edmonton, AB

Background/Purpose: The proportion of patients meeting remission criteria for rheumatoid arthritis varies by the definition used. We hypothesize that predictors for remission may thus also vary.

Methods: Our pharmacovigilance protocol captures clinical data on treatment efficacy and safety for patients treated with biologic therapies since July 2000. We calculated the proportion of patients achieving remission within the first year of initiating a new biologic agent, using the following definitions: i) 2011 ACR/EULAR Boolean (all of ≤1 tender joint, swollen joint, patient global and C-reactive protein (mg/dL)); ii) Simplified Disease Activity Index (SDAI) ≤3.3; iii) Clinical Disease Activity Index (CDAI) ≤ 2.8; iv) 1981 ACR Remission Definition; v) DAS28 ≤2.6. Predictors for remission were assessed first in univariate analysis for each remission definition. All significant predictors were then assessed in multivariate models.

Results: Our analysis includes 1,583 patients (70% female, mean disease duration 12 years, mean prior DMARDs=3) with a total of 4,532 visits during the first year of treatment. Remission was identified in 8.4% of the cohort using the 2011 ACR/EULAR Boolean definition, 14.6% using the SDAI score, 12.3% using the CDAI score, 5.2% using the 1981 ACR definition, and 34.5% using the DAS28 score. Correlation was good between SDAI and CDAI definitions (r=0.87), SDAI and new ACR/EULAR criteria (r=0.78) and CDAI and new ACR/EULAR criteria (r=0.76). Correlation values were less for DAS28 remission with SDAI (r=0.52), CDAI (r=0.50) and Boolean definitions (r=0.51), as well as between the 1981 ACR and 2011 ACR/EULAR definitions (r=0.55). In univariate analysis, male sex, seropositivity, and lower baseline values for DAS28 score, HAQ score and inflammatory markers predicted remission for all definitions. The number of prior DMARDs was significant predictor in all definitions except DAS28 remission. Short disease duration at inception was a predictor for remission in the DAS28 definition only. Obesity, smoking status and biologic naïve status did not predict remission by any definition. In multivariate models, a baseline DAS28 score <3.2 was a predictor for remission for all definitions (Table 1). A lower baseline HAQ score was a predictor for all definitions except DAS28 remission, and normal inflammatory markers at baseline was a predictor for remission using the 2011 ACR/EULAR Boolean, SDAI and DAS28 definitions. Additional variables in the multivariate model for DAS28 remission were male sex and seropositivity.

Table 1. Multivariate predictors for achieving remission in the first year of biologic therapy

	DEFINITION Odds Ratio (95% Confidence Interval), p value				
	2011 ACR/EULAR Boolean	SDAI	CDAI	1981 ACR	DAS28
Male sex	NS	NS	NS	NS	1.5 (1.2–1.9), p<0.001
Seropositive	NS	NS	NS	NS	2.2 (1.7–2.7), p<0.001
Baseline DAS > 3.2	0.87 (0.79–0.96), p=0.006	0.82 (0.74–0.91), p<0.001	0.78 (0.72–0.85), p<0.001	0.78 (0.69–0.88), p<0.001	0.56 (0.52–0.62), p<0.001
Baseline HAQ (per unit increase)	0.61 (0.49–0.77), p<0.001	0.60 (0.48–0.75), p<0.001	0.71 (0.59–0.85), p<0.001	0.71 (0.53–0.95), p=0.020	NS
ESR and CRP Normal at Baseline	3.0 (2.4–3.9), p<0.001	1.5 (1.1–1.9), p<0.001	NS	NS	1.9 (1.5–2.3), p<0.001

Legend: NS non-significant

Conclusion: In general, predictors for remission are constant across remission definitions. Additional predictors are identified in less stringent definitions. Similar analysis performed in additional cohorts will help clarify the effect of remission definition on the identification of predictors for remission.

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Expectations of Treatment Goals and Goal-Setting Practices in People with Rheumatoid Arthritis. Vibeke Strand[1], Peter Taylor[2], Tom Sensky[3], Nik Harta[4] and Scott Fleming[5]. [1]Stanford University, Palo Alto, CA, [2]Kennedy Institute of Rheumatology, London, United Kingdom, [3]Imperial College, London, United Kingdom, [4]Opinion Matters, London, United Kingdom, [5]UCB, Slough, United Kingdom

Background/Purpose: A previous survey examining the impact of RA showed that the disease has a negative impact on employment, productivity, emotions, and intimate relationships, and causes women with RA to feel isolated.[1] This second survey was conducted to evaluate the expectations of men and women with RA regarding treatment and outcomes in care, particularly their awareness of targeted treatment and goal-setting practices.

Methods: People with RA from 6 countries (USA, UK, France, Germany, Italy, and Spain) were recruited by an online research panel to complete an Internet survey regarding how RA affects their lives. Eligible people were aged 25–65 years and were required to have a diagnosis of

RA ≥6 months. Respondents were queried on their perceptions of disease management, treatment expectations, as well as personal and health care provider (HCP) goal-setting (personal/social/treatment) for RA. Mean responses to each question were computed for the overall population of respondents.

Results: A total of 1829 people (1242 females and 587 males) were recruited from 6 countries (USA [n=303], UK [n=306], Germany [n=304], Spain [n=304], France [n=306], and Italy [n=306]). The majority of female participants (72%) were aged 25–34 years, whereas the majority of male participants (36%) were aged 55–65 years. When asked to describe the severity of their RA, 54%, 33%, and 13% of people responded with 'moderate,' 'mild,' and 'severe.' When asked about goal-setting practices when starting a new treatment, 81% set personal or social goals, and 91% set treatment goals. Most respondents (87%) agreed that establishing personal treatment targets would have a positive impact on disease management. A total of 63% of respondents agreed that a targeted approach to successful management was setting personal, lifestyle, and treatment goals and monitoring progress to achieve them. However, 61% reported that their HCP did not manage their RA with strict goals and timeframes in place and 73% reported that their HCP did not discuss treating RA with an approach that achieved personal or social targets. Regarding treatment perceptions, 81% of respondents wanted relief of signs and symptoms within 3 months of starting new therapy, yet only 75% expected to feel an improvement. However, 56% of respondents would wait 1 month or less to speak to their HCP if they felt a new treatment was not working. Furthermore, the majority of respondents (60%) shared decisions with their HCP regarding how best to manage their RA.

Conclusion: From the perspective of a person with RA, a targeted approach to successful disease management means setting personal, social, and treatment goals and monitoring progress to achieve these goals. People with RA want help from HCPs in determining and setting these goals to assess for themselves whether their treatment is working. As more treatments become available for RA, these expectations of people with RA are likely to increase.

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Understanding What Motivates Patients with Rheumatoid Arthritis to Escalate Their Care. Liana Fraenkel[1], Meaghan Cunningham[2] and Paul Falzer[3]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, [2]Yale University School of Medicine, New Haven, CT, [3]VA Connecticut Healthcare System, New Haven, CT

Background/Purpose: Current ACR guidelines advocate aggressive care with disease modifying anti-rheumatic agents (DMARDs) to achieve and maintain tight control. However, recent studies have found that patients are reluctant to escalate their treatment regardless of current disease activity and that patient reluctance to change treatment is a barrier towards implementing guideline recommendations. The purpose of this study was to examine the influence of specific factors, chosen by their known associations with patient decision making, on willingness to escalate care.

Methods: N=150 patients with RA, currently on at least one DMARD, reporting at least 3 on an 11-point pain scale, whose self-reported arthritis was either the same or worse compared to 2 months ago were interviewed. Predictors of willingness to change included: disease activity as measured by the RAPID-4, discrepancy between current and desired health state measured on a 1 (very close) to 10 (not very close) scale, the importance of improving pain relative to other DMARD-related benefits and risks (quantified using a conjoint analysis survey), worry about current DMARDs measured on a 1 (not at all) to 4 (a lot) scale, and attitude toward starting a new medication measured on a 7-point scale ranging from extremely worried to extremely hopeful. The dependent variable willingness to change was assessed by composite of three items on 1 to 10 scales a) add a DMARD, b) increase the dosage of the current DMARD, and c) switch to another DMARD. The importance of each predictor was assessed via MANOVA with F computed by Wilks' lambda.

Results: The mean age (SD) of the study sample was 58.8 (12.9); 85% were women; 82% Caucasian; 61% married; and 36% were college educated. In bivariate analyses, age (F=0.008, df=3/146, p=0.99) and the RAPID-4 (F=2.11, df=3/138, p=0.1) were not related to willingness to escalate care. Unadjusted and adjusted relationships between factors known to affect decision making and willingness to escalate care are provided in the table below.

Table. Factors influencing patients' willingness to change treatments

	Unadjusted			Adjusted*		
	F	DF	P	F	DF	P
Discrepancy	3.26	3/146	0.02	3.16	3/140	0.027
Importance of improving pain	4.12	3/146	0.008	3.07	3/140	0.030
Worry	2.34	9/351	0.014	2.02	9/341	0.036
Attitude toward new medication	4.45	3/145	0.005	3.27	3/140	0.023

* Containing all four predictors.

Conclusion: In contrast to the medical model, in which decision making is based on measures of disease activity (such as the RAPID-4), patients willingness to escalate care is explained by the discrepancy they perceive between their current and desired health state, the importance they place on pain reduction (relative to other DMARD-related benefits and risks) and emotions related to DMARDs. Addressing these factors may help improve the quality of decision making in clinical practice and consequently increase the number of patients willing to escalate care in order to improve long-term outcomes.

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Factors Associated with Work Status and Missed Work Days in Patients with Rheumatoid Arthritis. Leslie R. Harrold[1], Mary A. Cifaldi[2], Ying Shan[1], George Reed[1], Katherine C. Saunders[3], Joel M. Kremer[4] and Jeffrey D. Greenberg[5]. [1]UMass Medical School, Worcester, MA, [2]Abbott Laboratories, Abbott Park, IL, [3]CORRONA, Inc., Southborough, MA, [4]Albany Medical College and The Center for Rheumatology, Albany, NY, [5]New York University School of Medicine, New York, NY

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk to be underemployed or not working due to the affects of their illness. Therefore we evaluated factors associated with reported work status and missed work days among RA patients who are participants of a multi-centered observational registry within the United States (the Consortium of Rheumatology Researchers of North America: CORRONA).

Methods: We identified RA patients enrolled between 3/1/06 to 4/30/11 and were aged 18 to 64 years. Outcomes of interest included working full-time or not (includes working part time, at home, student, disabled and retired) as well as missed work days in the prior 3 months due to RA in those working full-time. Covariates of interest included duration of RA (<1 year, 1 to 3 years, 4 to 10 years, and >10 years), education, living arrangement, measures of disease activity and severity, functional status as measured by the modified Health Assessment Questionnaire (mHAQ), receipt of joint surgery, and hospitalizations for RA. Descriptive statistics were conducted. Potential predictors of working full-time as well as missing work days were evaluated using logistic regression.

Results: There were 11,512 patients (44% with ≤ 3 years disease duration). Most were women (79%) and the mean age was 50.5 years. About half (54.5%) were working full time. Patients who were working full time were more likely to be younger (49.3 vs. 51.8 years; p<0.001), male (25.7% vs. 15.1%, p<0.001), have a college education (67.5% vs. 55.3%), be in remission based on the Clinical Disease Activity Index (CDAI) (24.6% vs. 14.7%; p<0.001), and have not needed joint surgeries (p<0.001 for comparisons of hip, knee, foot and hand surgeries) or a hospitalization for RA (1.7% vs. 4.0%, p<0.001). In regression models, increased disease duration (≥ 1year) and mHAQ as well as patient global assessment was associated with a reduced likelihood of working full-time (Table). Among those working full-time, in regression models increased disease duration(>3 years) was protective against missed worked days; in contrast tender joint count, patient global assessment, physician global assessment and mHAQ were all associated with a greater likelihood of missing work (Table).

	Adjusted Odds Ratios of Working Fulltime*	Adjusted Odds Ratios of Missing Work**
Disease duration		
<1	1	1
1–3	0.84 (0.73–0.96)	0.91 (0.72–1.15)
4–10	0.74 (0.64–0.85)	0.77 (0.60–0.98)
11+	0.69 (0.59–0.80)	0.76 (0.58–1.00)
Functional status		
mHAQ	0.45 (0.40–0.51)	2.19 (1.74–2.76)
Clinical Disease Activity Index (CDAI)		
Swollen joint count	0.99 (0.98–1.00)	0.98 (0.97–1.00)
Tender joint count	1.00 (0.99–1.01)	1.03 (1.01–1.05)
Patient global assessment	0.99 (0.99–1.00)	1.02 (1.01–1.02)
Physician global assessment	1.00 (1.00–1.00)	1.00 (1.01–1.01)

* adjusted for age, gender, education, living arrangement, hospitalizations for RA and prior joint surgery.
** adjusted for age, gender, education. living arrangement, hospitalizations for RA, prior joint surgery and erosive disease.

Conclusion: In this working age group of RA patients the likelihood of working full-time diminished early in the disease course. Among those working full time, increased disease activity and functional status were predictive of missed days from work. This suggests that rheumatologists should aggressively treat ongoing disease activity to prevent work loss.

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Do Patients with Elderly-Onset Rheumatoid Arthritis Have Severe Functional Disability? Soo-Kyung Cho[1], Yoon-Kyoung Sung[1], So-Yeon Park[1], Jeeseon Shim[2], Chan-Bum Choi[3], Hoon-Suk Cha[4], Jung-Yoon Choe[5], Won-Tae Chung[6], Seung-Jae Hong[7], Jae Bum Jun[8], Tae-Hwan Kim[9], Tae-Jong Kim[10], Eun-Mi Koh[4], Jisoo Lee[11], Shin-Seok Lee[10], Sung Won Lee[6], Wan-sik Uhm[8], Dae-Hyun Yoo[9], Bo Young Yoon[12], Sang-Cheol Bae[1] and KORONA investigators[13]. [1]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Hanyang University Hospital for Rheumatic Disease, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Catholic university of Daegu, School of mediine, Daegu, South Korea, [6]Dong-A University Hospital, Busan, South Korea, [7]Kyung Hee University Hospital, Seoul, South Korea, [8]Hanyang University Hospital for Rheumatic Disease, Seoul, South Korea, [9]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [10]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [11]Ewha Womans University Mokdong Hospital, Seoul, South Korea, [12]Inje University Ilsan Paik Hospital, Goyang, South Korea, [13]Seoul

Background/Purpose: Elderly-onset rheumatoid arthritis (EORA) has been described as having a different clinical course and features in comparison with younger-onset RA. However, it has not been clearly established whether different outcomes can be expected for EORA patients. Recent studies have suggested that patients with EORA show worse disease-related outcomes than patients with YORA, while in earlier studies, EORA was associated with a more favorable or similar outcome to YORA. EORA patients may have greater disabilities than YORA patients, because of factors influencing disability such as the age-related increase in comorbidities and the increase in disease activity caused by less aggressive treatment. Therefore, it is important to determine whether elderly onset RA has a different disease outcome that YORA, with considering effects of current age and disease duration. Our aim in this study was to identify the clinical features of elderly onset rheumatoid arthritis (EORA) and their impact on disease outcome.

Methods: A total of 3,169 RA patients were recruited as part of the KORean Observational study Network for Arthritis (KORONA), a network of rheumatologists across South Korea. Patients were stratified according to age at disease onset: younger than 40 years (younger-onset RA, YORA), between the ages of 40 years and 60 years (middle aged-onset RA, MORA), older than 60 years (EORA). To evaluate the significance of differences in demographic and clinical features among these three groups, we performed analysis of variance (ANOVA) and the chi-square test. We used multivariable logistic regression analysis to examine the association of onset age with functional disability.

Results: Patients were divided into YORA (n=1,167), MORA (n=1,516) and EORA (n=486) groups. The Health Assessment Questionnaire (HAQ) score was significantly higher in patients in the EORA group than those in the YORA and MORA groups (p=<0.001). Multivariable analysis demonstrated that age (middle age: OR=1.55, CI 1.14~2.11, older age: OR=2.51, CI 1.82~3.45), female sex (OR=2.78, CI 2.01~3.83), high disease activity (OR=6.82, CI 5.38~8.64), disease duration ≥10 years (OR=1.77, CI 1.43~2.20), and cardiovascular disease comorbidity (OR=2.32, CI 1.51~3.57) affected disability, though EORA was not associated with high HAQ score (≥1). However, in a predefined subgroup analysis of patients with a disease duration of less than 10 years, elderly onset was an independent factor influencing the functional disability of RA patients (OR 3.04, CI 1.85~5.67: disease duration of < 5 years, OR 3.07, CI 1.64~5.74: disease duration of 5 to 10 years).

Conclusion: EORA is independently associated with functional disability in RA patients with a disease duration of less than 10 years. This finding suggests that an aggressive management approach is required to treat patients with EORA, as is currently the case for patients with YORA.

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An Increase of Disease-Related Knowledge Improves Adherence to Tight Control. Sofie H.M. Manders[1], Laura T.C. van Hulst[1], Piet LCM Van Riel[1], Liana Fraenkel[2] and Wietske Kievit[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT

Background/Purpose: Rheumatoid arthritis (RA) patients with active disease are often reluctant to change their medications. Educating patients about the importance of tight control may help increase patient willingness to accept additional therapy. However, the relationship between patient knowledge and their beliefs about medicine and treatment preferences has not been clearly established. The objective of this study was to determine whether there is an association between 1) disease-related knowledge and 2) beliefs about medicine and patients' considerations in medication decisions.

Methods: We used a Maximum Difference Scaling (MDS) survey to determine the importance of 58 factors related to the decision to change medications for patients with active RA. Participants answered 24 choice tasks in which they chose the single most important item in their decision from five items. MDS generates a relative importance score for each factor. The factors were divided into eight categories (determined by consensus among three researchers). We also collected demographic characteristics as well as patients' beliefs about medicine and disease-related knowledge. We used multiple linear regression to analyze the relationship between disease-related knowledge and beliefs about medicines and the MDS importance scores of the following four categories: disease activity, risk of treatment, burden of treatment (e.g.: route of administration, frequency of drug administration, need for blood tests, number of medications) and disease progression/prognosis. A forward selection procedure was used to find and correct for confounding factors (age, gender, level of education, health literacy and disease duration). Interaction terms were added in the regression model to examine potential effect modification.

Results: 213 subjects completed the survey. The mean age was 60.0 years (SD=11.6), the median disease duration was 7.0 years (IQ range=12.5) and 69.5% of the participants were female.

After adjusting for patients' highest level of education, we found a negative relationship between disease-related knowledge and patients' ratings related to the burden of treatment (β=−0.348, p=0.008). In addition, data showed that this relationship was even stronger in patients with higher educational degrees (β=−0.246, p= 0.049). No relationships were found between disease-related knowledge and the importance of the remaining categories. In addition, no significant relationships were found between beliefs about medicine and any of the four categories.

Conclusion: Patients with greater disease-related knowledge are less likely to be influenced by the potential burden of treatment in the decision to escalate care. Therefore, educating patients seems to have a positive effect on the adherence to tight control. However further research is needed to determine if improving RA-related knowledge through targeted education programs will increase patient willingness to accept additional treatment.

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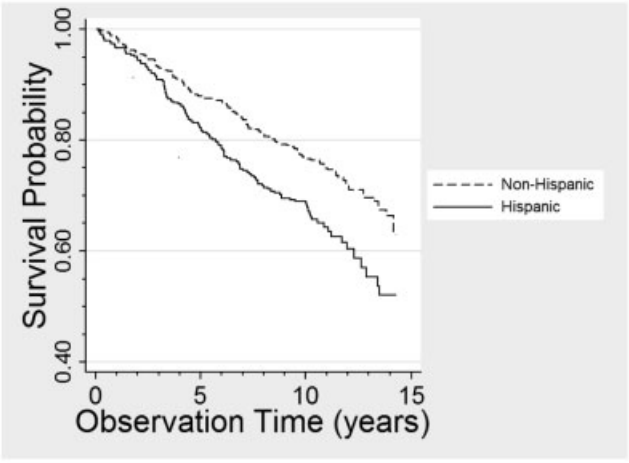
Does the Hispanic Paradox Apply to Mexican Americans With Rheumatoid Arthritis? Antonio E. Mancera[1], Inmaculada Del Rincon[2], Daniel F. Battafarano[3], Jose Felix Restrepo[4] and Agustin Escalante[5]. [1]Univ of Texas HSC San Antonio, San Antonio, TX, [2]UTHSCSA, San Antonio, TX, [3]Brooke Army Medical Ctr, San Antonio, TX, [4]University of Texas. Health Science Center, San Antonio, TX, [5]University of Texas Health Science Center, San Antonio, TX

Background/Purpose: Despite socioeconomic disadvantage and a higher disease burden, all-cause mortality in U.S. Hispanics is equal or lower than that of Non-Hispanic Americans. It is unclear if this "Hispanic Paradox" occurs in rheumatoid arthritis (RA). We compared clinical characteristics and survival between Hispanics and Non-Hispanics in a cohort of RA patients.

Methods: We recruited consecutive RA patients from private and public rheumatology clinics. After a comprehensive baseline evaluation of their clinical and sociodemographic characteristics, we invited them for annual follow-up evaluations. We followed patients until the censoring date of May 31, 2010, unless they died or were lost to follow-up. We learned about deaths from public databases, physicians, relatives, neighbors and obituaries, confirmed by death certificate. We used generalized estimating equations (GEE) to compare clinical characteristics between Hispanics and non-Hispanics, adjusting for confounders and accounting for repeated measures within patients. We used Cox proportional hazards regression to compare survival.

Results: The cohort included 779 patients, who participated in a total of 4,557 observations. Time from enrollment until last follow-up, death or the censoring date was 7,204 patient-years (a median of 10.3 years per patient). There were 434 Hispanic and 345 Non-Hispanic patients. At enrollment, Hispanics were younger on average (52 versus 59 years old) and more were women (74% versus 65%). After adjusting for age and sex, Hispanics had significantly more tender joints (GEE regression coefficient = 4.61, [95% CI = 3.04, 6.20]) more swollen joints (0.58 [0.08, 1.16]), more deformed joints (4.66, [2.97, 6.34]), a higher ESR (10.5 [7.4, 13.5]), and more joint damage, as measured by the modified Sharp score (13.4 [5.1, 21.8]). Hispanics were also significantly more likely to have rheumatoid factor (odds ratio = 1.51, [95% CI = 1.13, 2.03]). There was no significant difference in the frequency of nodules (OR = 1.16 [95 % CI 0.89, 1.52]), or the HLA-DRB1 shared epitope (0.90, [0.65, 1.24]).

237 deaths occurred, for a mortality rate of 3.3 per 100 patient-years [2.9, 3.7]. Among Hispanics, there were 115 deaths in 4,212 patient years for a rate of 2.7 deaths per 100 patient years [2.27, 3.8]. Non-Hispanics had 122 deaths per 2,991 patient years or 4.0 deaths per 100 patient years [95% CI 3.42, 4.88]. The unadjusted hazard ratio for mortality among Hispanics versus Non-Hispanics was 0.65 (0.50, 0.84]). However, after adjusting for age and sex, the difference in survival between Hispanics and Non-Hispanics was no longer significant (age- and sex-adjusted HR 1.07 [1.05, 1.08]).



Conclusion: These findings suggest that despite greater severity in most clinical manifestations among the Hispanics in this RA cohort, their mortality paradoxically was not increased. Further research is needed to understand the mechanisms underlying the Hispanic survival paradox

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Subgroup Analyses of a Novel Baseline Biomarker of Acute-Phase Serum Amyloid A (A-SAA) and Serum Interleukin–2 Receptor Alpha (sIL-2Ra) That Predicted Long-Term (18 to 35 yrs) Mortality in a Cohort of Incident Rheumatoid Arthritis (RA) and Non-RA. Alfonse T. Masi[1], Jean C. Aldag[1] and Jean D. Sipe[2]. [1]University of Illinois College of Medicine at Peoria, Peoria, IL, [2]Boston University School of Medicine, Boston, MA

Background/Purpose: Research on biomarkers of mortality has high priority, especially for cardiovascular causes. A novel biomarker of either elevated serum A-SAA or sIL-2Ra levels predicted total mortality in decades-long follow-up of a prospective cohort (A&R 2010;62:S19). The biomarker is now analyzed for prediction of mortality in cohort subgroups.

Methods: Cohorts in this community-based (n = 21,061 adults) study of risk factors for RA enrolled in 1974. The pre-RA cases had clinical onset, 3 to 20 (mean 12) yrs, after entry (1977 – 1994). Controls (CN) were non-RA cohorts matched at entry (4CN: 1 pre-RA). Biomarker data were available on 192 (44 pre-RA, 148 CN) subjects, who were monitored for mortality, from 1992 thru 2009, excluding 12 pre- 1992 deaths. Baseline stored (−70°C) sera were assayed (ELISA) "blindly" for the combined biomarker. High sensitivity A-SAA was assayed (Hemagen kits) at Boston University (sensitivity 1 μg/ml). The sIL-2Ra was assayed (R & D Systems, high sensitivity kits) at Specialty Laboratories, Santa Monica, CA. Sex- and age - specific upper quartile (UQ) values of A-SAA *and* sIL-2Ra were determined to decrease such covariate confounding. Elevated baseline (1974) A-SAA (p = 0.048) and sIL-2Ra (CD 25), p = 0.036 separately predicted total mortality, from 1992 – 2009. The combined novel predictor is defined as an elevated UQ level of *either* biomarker. All cause, primary cardiovascular (CV) (ICD-9, 390–459 & ICD-10, 00–99), and all other combined mortality (non-CV) was monitored quarterly, from 1992 thru 2009. Subgroup analyses were performed for percentages of deaths, and hazard ratios (HR) of the novel biomarker by Cox regression models.

Results: All causes deaths occurred in 64 (33.3%) of 192 total subjects (biomarker HR = 2.37 (1.44 – 3.90), p = 0.001). Comparative death outcomes in cohort subgroups, percentile mortality, and biomarker predictions (HRs) by the Cox Model are shown in the Table. Mortality was greater in RA (50.0%) vs CN (28.4%), p = 0.017. The biomarker similarly predicted mortality outcomes for RA (HR = 2.50) and CN (HR = 2.32) subgroups. Mortality prediction was significant for females [HR = 3.33 (1.66 – 6.71), p = 0.001], but not for males [HR = 1.54 (0.77 – 3.10), p = 0.225]. Mortality prediction was significant for younger (< 47 yrs) subjects at entry [HR = 3.98 (1.76 – 9.00), p = 0.001], but not for older cohorts [HR = 1.62 (0.85 – 3.10), p = 0.145]. The biomarker strongly predicted CV mortality [HR = 6.38 (2.25 – 18.09), p < 0.001], but not the remainder of deaths [HR = 1.62 (0.90 – 2.94), p = 0.111], as shown in Table.

Cohort Subgroups, Mortality, and Cox Regression Models	Comparative Death Outcomes in Subgroups, and Biomarker Predictions by the Cox Model* Subgroup#1	Subgroup#2
RA (#1) vs CN (#2) Subgroups		
Mortality (%)	22 (50.0%) of 44	42 (28.4%) of 148
Cox Regression Model HR (95% CI) of Deaths:	2.50 (1.02–6.11)	2.32 (1.26–4.27)
p Values (for Biomarker)	p = 0.045	p = 0.007
Females (# 1) vs Males (# 2)		
Mortality (%)	32 (29.1%) of 110	32 (39.0%) of 82
Cox Regression Model HR (95% CI) of Deaths:	3.33 (1.66–6.71)	1.54 (0.77–3.10)
p Values (for Biomarker)	p = 0.001	p = 0.225
Younger (# 1) vs Older (# 2)		
Mortality (%)	26 (19.8%) of 131	38 (62.3%) of 61
Cox Regression Model HR (95% CI) of Deaths:	3.98 (1.76–9.00)	1.62 (0.85–3.10)
p Values (for Biomarker)	p = 0.001	p = 0.145
CV (# 1) vs Non-CV (# 2) Deaths		
Mortality (%)	18 (9.4%) of 192	46 (24.0%) of 192
Cox Regression Model HR (95% CI) of Deaths:	6.38 (2.25–18.09)	1.62 (0.90–2.94)
p Values (for Biomarker)	p < 0.001	p = 0.111

* Includes decades of age covariate

Conclusion: Baseline (1974) UQ levels of either serum A-SAA or sIL-2Ra predicted long-term (18 to 35 yrs) mortality, significantly for females (p = 0.001), younger cohorts (p = 0.001), and circulatory (p < 0.001) deaths. This novel biomarker deserves further testing as a long-term mortality predictor.

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Risk of Cardiovascular Events in Rheumatoid Arthritis Patients Treated with Subsequent-Line Biologic Disease Modifying Antirheumatic Drugs After Switching From First-Line Anti-Tumor Necrosis Factor Agents.
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Background/Purpose: Rheumatoid arthritis (RA) patients frequently switch drug treatments. Little information exists on the risk of cardiovascular events among patients treated with subsequent-line (SL) biologic disease modifying antirheumatic drugs (BIO) after switch from first-line (FL) anti-tumor necrosis factor agents (aTNF). In addition, information is lacking on the relative risk of CV events in patients treated with SL aTNF agents or SL abatacept vs. SL rituximab.

Objectives: Compare the risk of cardiovascular events in RA patients treated with various SL BIO.

Methods: Retrospective analysis of Thomson Reuters MarketScan® Commercial and Medicare databases, a large U.S. administrative claims dataset. RA patients initiating FL anti-TNF therapy from 1/1/2004–3/31/2010 were identified and followed forward in time to capture all SL BIO episodes through 3/31/2010. SL episodes were constructed as time from initiation of a SL BIO until switch to another SL BIO, disenrollment, or 3/31/2010. SL episodes were classified into 1 of 5 SL BIOs: abatacept (ABA); adalimumab (ADA); etanercept (ETN); infliximab (INF); rituximab (RTX). Cardiovascular events, as identified by International Classification of Disease, ninth revision, clinical modification criteria, included the following: acute myocardial infarction, other acute and subacute forms of ischemic heart disease, ventricular arrhythmias, cardiac arrest, and atrial fibrillation/flutter. Multivariable Cox proportional hazards survival models compared the hazard of cardiovascular events across the SL BIOs with RTX as the reference group. The hazard models adjusted for important demographic and clinical confounders identified 12-months prior to initiation of SL BIO.

Results: A total of 4,332 SL episodes were identified: mean age 55 yrs; 80% female. Total person-years exposure by SL BIO were ABA 942, ADA 1,716, ETN 1,349, INF 777, 452 RTX. Average duration of follow-up was similar between SL BIOs (range: 1.1–1.3 yrs). Cardiovascular events occurred in 146 SL BIO episodes overall. The incidence rates of cardiovascular events per 100 person-years of observation were 2.1 INF, 2.4 RTX, 2.7 ADA, 3.0 ETN, 3.3 ABA. As compared to RTX, the adjusted hazard of cardiovascular events was not significantly higher for INF (HR 1.3 95% CI: 0.6–2.8), ABA (HR 1.6 95% CI: 0.8–3.2), ADA (HR 1.8 95% CI: 0.9–3.5), and ETN (HR 1.8 95% CI: 0.9–3.5).

Conclusion: The risk of cardiovascular events did not differ significantly between patients treated with SL aTNF agents or SL abatacept compared to patients treated with SL rituximab. As an observational study, results may be impacted by channeling or residual confounding. Findings are also limited by the infrequency of cardiovascular events.

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Risk of Acute Myocardial Infarction Associated with Arthritis: A Systematic Review of Observational Studies.
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Background/Purpose: Various types of arthritis and rheumatoid arthritis in particular, have been associated with increased cardiovascular morbidity and mortality. However, the cumulative impact of arthritis on the risk of acute myocardial infarction (AMI), as well as potential differences across age groups, sex and between arthritis sub-populations remain unclear. The objective was to perform a systematic review of the risk for incident AMI associated with arthritis; and to compare the relative magnitude of AMI risk across age, gender and type of arthritis.

Methods: A systematic search was performed in MEDLINE, EMBASE and CINAHL databases for controlled population-based prospective/retrospective cohort or case-control studies examining the relationship between arthritis (any arthritis, ankylosing spondylitis (AS), gout, osteoarthritis (OA), psoriatic arthritis (PsA) or rheumatoid arthritis (RA)) and incident AMI (any AMI, fatal or nonfatal AMI) published between January 1980 and February 2011, and stratified or adjusted for at least age and sex. Study quality was assessed with a validated appraisal tool for observational studies; the Newcastle-Ottawa scale. Information on study design, country, funding source, duration of follow-up, crude and adjusted measures of association with 95% confidence intervals were abstracted for each study. All search screening, data abstraction and quality appraisal was performed by 2 independent reviewers.

Results: Nineteen studies met all eligibility criteria and were included in the present review (gout (6), RA (13)). Arthritis was a statistically significant independent risk factor for incident AMI in 17/19 studies. Gout was associated with a significant increased risk of incident AMI in 5/6 studies (Total AMI- RR range: 1.11–1.50; Fatal AMI- RR range; 0.96–1.35; Non-fatal AMI RR range: 1.11–1.59). RA was associated with a significant increased risk of incident AMI in 12/13 studies (Total AMI- RR range: 1.16–2.90; Fatal AMI- RR range; 1.10–2.24; Non-fatal AMI RR range: 1.25–2.17). Eight studies reported stratified estimates for sex and all suggested stronger risks for AMI in women than in men with arthritis, but confidence intervals between groups were wide and overlapped. Similarly, 3 studies included stratified estimates for age and all suggested stronger risks for incident AMI in younger vs. older arthritis populations but confidence intervals overlapped.

Conclusion: Gout and RA were independently associated with increased risks for incident AMI. Increased monitoring and/or enrollment in cardiovascular prevention programs are likely warranted in these patients. As no studies meeting inclusion criteria were identified for patients with AS, PsA and OA there was insufficient evidence to draw conclusions regarding independent risks of incident AMI in these populations. Future analysis including a quantitative synthesis with meta-analysis and meta-regression will help address limitations due to small cell sizes in individual studies and better understand factors contributing to heterogeneity in effect estimates between studies, respectively.

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A Possible Source of Error in the Method of Cancer Risk Estimation in Patients with Rheumatoid Arthritis.
Hasan Yazici[1], Koray Tascilar[1], Yusuf Yazici[2], Gulay Kiroglu[3], Levent Duransoy[3] and Aydin Erar[3]. [1]Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey, [2]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY, [3]Mimar Sinan University School of Science and Letters, Istanbul, Turkey

Background/Purpose: The magnitude of the association of cancer with rheumatoid arthritis, especially after anti-TNF use, remains in dispute. We recently proposed (1) an important selection bias was potentially inherent in the registry data especially when the comparator for the sought cancer incidence in RA was the cancer incidence in the "mother population", the population from which the registry is derived from. In a mother population within a given time there would be many patients with cancer who would not have the chance to develop RA since a. a sizeable fraction would die from their disease before having the chance to develop RA; b. The cancer treatment could potentially prevent the development of RA or finally, and particularly in the case of anti-TNF registries, c. If they remained alive and developed cancer the likelihood of them being included in such a registry would be small. All 3 factors could render the incidence ratio (incidence in the registry/ incidence in the mother population) less than unity even if biologically there are no real differences in the cancer frequencies between the 2 populations. Lastly this ratio would decrease in time as was observed in the Taiwan registry (1). We formally surveyed whether the same potential selection bias was present in other manuscripts reporting similar data.

Methods: We conducted a PubMed search with the search terms "registry" "cancer" and "rheumatoid arthritis" among 7 high-impact rheumatology journals between 2001 and May-2011 (inclusive). First, articles that reported cancer incidence in patients with RA were retrieved in full-text. Among these, those manuscripts which reported an incidence ratio at 2 or more time-points were included in this survey. We specifically sought a. whether the comparisons were made between the registry and a "mother population" and b. the changes in the above described ratio between the first and last time points.

Results: We retrieved 36 articles among 1274 search results. In 6/36 the incidence ratio comparisons were made between at least one RA registry and its mother population at more than 1 time point. The number of time-points ranged from 3 to 11. Sampling-period-length ranged from 8 to 40 years. In 5 of the 6 articles when a comparison was made with the mother population there was a reduction over time in the incidence ratio which ranged from 29 to 99%. In the remaining study there was no appreciable change in the incidence ratio.

Conclusion: There are many important methodological issues for a fair assessment of cancer incidence in RA especially with the use of anti-TNF agents (2) We propose that the selection bias we try to highlight here should be included in this list of issues especially when we compare the cancer in a RA cohort with that in the mother population.

Reference:
1)Arthritis Rheum. 2011 doi: 10.1002/art.30447.Epub 2)Pharmacoepidemiol Drug Saf. 2011;20:119–30

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Cancer Screening Rates in Patients with Rheumatoid Arthritis: No Different Than the General Population. Seo Young Kim[1], Sebastian Schneeweiss[2], Jessica E. Meyers[1], Jun Liu[1] and Daniel Hal Solomon[3]. [1]Brigham & Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham & Womens Hospital, Boston, MA

Background/Purpose: Both the U.S. Preventive Services Task Force and American Cancer Society recommend most adults be regularly screened for cervical, breast and colon cancer. Early detection of such cancers can decrease morbidity and mortality. Previous studies suggest that patients with chronic diseases, such as rheumatoid arthritis (RA), do not receive optimal preventive medical services including cancer screening tests, however few evaluated cancer screening in RA patients compared to non-RA.

Methods: Using data from a large US commercial insurance plan (1/2001–6/2008), we examined rates of screening tests for cervical, breast and colon cancer in patients with RA compared with non-RA. RA was defined as ≥ 2 diagnoses of RA and ≥ 1 prescription for a disease-modifying anti-rheumatic drug. Patients who never had an RA diagnosis were selected for the non-RA cohort. We required ≥ 1 year of follow-up. In sensitivity analysis, RA patients were compared to a subgroup of non-RA patients who have ≥ 2 diagnoses of hypertension (HTN), a chronic disease with similar health care utilization patterns.

Results: 13,314 RA patients and 131,989 non-RA patients were identified with a mean follow-up time of 2.38 years. Mean age was 52 for RA patients and 48 for non-RA. Unadjusted rates of cancer screening are shown in Table 1. Both RA and non-RA patients were screened, on average, once every 3 years for cervical cancer and once every two years for breast cancer. In the age-adjusted Cox regression model, women with RA were more likely to receive ≥ 1 Pap smear (HR 1.21, 95% CI 1.17–1.24), mammogram (HR 1.49, 95% CI 1.45–1.53), and colonoscopy (HR 1.69, 95% CI 1.61–1.77) compared to non-RA. Men with RA, compared to non-RA, were also more likely to receive a colonoscopy (HR 1.52, 95% CI 1.40–1.64). There was no significant difference in cancer screening rates between patients with RA and those with HTN (Table 2). These results were robust in multivariate analyses adjusted for age, number of physician visits, percent of visits made to primary care physicians and comorbidity index.

Table 1. Crude rates (95% confidence intervals) per 1,000 person-years for having at least one cancer screening test in RA and non-RA patients.

	RA	Non-RA
Papanicolaou smear	375.5 (365.7–385.5)	350.9 (347.7–354–1)
Mammogram	551.8 (537.7–566.2)	437.5 (433.0–442.0)
Colonoscopy	229.6 (221.9–237.6)	172.2 (169.7–174.8)

Table 2. Age-adjusted hazard ratios (95% confidence intervals) for having at least one cancer screening test in RA compared with a subgroup of non-RA patients with HTN.

	Women	Men
Papanicolaou smear	0.98 (0.95–1.01)	–
Mammogram	0.94 (0.92–0.97)	–
Colonoscopy	0.95 (0.90–1.00)	0.99 (0.91–1.07)

Conclusion: Individuals with RA did not appear to be at risk for receiving fewer cancer screening than either group of non-RA patients. Cancer screening rates in both RA and non-RA patients appeared to be in accordance with recommendations.

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Biological Agents in Rheumatoid Arthritis and Risk of Malignancy—Results From the Nation-Wide Cohort Study in Japan. Masayoshi Harigai[1], Toshihiro Nanki[1], Ryuji Koike[1], Michi Tanaka[1], Kaori Watanabe[1], Yukiko Komano[1], Ryoko Sakai[1], Hayato Yamazaki[1], Takao Koike[2], Nobuyuki Miyasaka[1] and SECURE study investigators group. [1]Tokyo Medical and Dental University, Tokyo, Japan, [2]Sapporo Medical Center NTT EC, Sapporo, Japan

Background/Purpose: Association of anti-tumor necrosis factor (TNF) therapy with development of malignancy has been addressed using meta-analytic and observational approach in Europe and the US. Risk for malignancy, however, varies widely among ethnics and geographical regions because of genetic predisposition and environmental factors. In this study, we investigate the risk for malignancy in Japanese patients with RA treated with biological agents including TNF inhibitors and tocilizumab.

Methods: Japanese RA patients treated with biological agents have been registered from hospitals participating in SECURE (Safety of Biologics in Clinical Use in Japanese Patients with Rheumatoid Arthritis in Long-Term) study, which is a nation-wide cohort study implemented by Japan College of Rheumatology. All data were collected annually using electronic case report form from registration (year 0) to year 5. Data from the start of the first biological agent to year 0 of each patient were collected retrospectively and data after year 0 were collected prospectively. Demographic data, use of biological agents, occurrence of malignancy, and life prognosis were recorded. As of March 2011, data of 11,697 patients from 332 institutions were obtained. Age standardized incidence rate (ASR) and standardized incidence ratios (SIRs) of newly diagnosed malignancy were calculated as measures of relative risk using estimates from Japanese general population as a reference.

Results: Characteristics of the 11,697 patients were as follows: female, 81.1%; mean age at the start of their 1st biological agents, 56.6 y/o; accumulated number of patients who received each biological agent, 5,823 for infliximab, 6,418 for etanercept, 1,547 for adalimumab, and 1,607 for tocilizumab. In total, 207 cases of malignancy were reported; 44 hematopoietic and 163 non-hematopoietic. Hematopoietic malignancy included 41 cases of malignant lymphoma, 2 leukemia, and 1 multiple myeloma while non-hematological malignancy included 29 cases of gastric cancer, 24 colon cancer, 27 lung cancer, 20 breast cancer, and 63 others. ASR (95% confidence intervals [95%CI]) (/100,000 patient-year) of total malignancy were 302 (228–393) for female and 387 (280–522) for male patients, which were significantly lower than the incidence of total malignancy in Japanese general population (female 405, male 577). SIRs (95% CIs) of total malignancy and total non-hematopoietic malignancy were also significantly lower than Japanese general population in both female and male patients. None of SIRs of each site-specific non-hematopoietic malignancy was significantly elevated compared to Japanese general population. SIRs (95% CIs) of malignant lymphoma were 5.08 (3.33–6.98) in female and 3.93 (1.75–6.55) in male patients, but were numerically lower than those of a previous report from a large-scale Japanese cohort study of RA patients (Rheumatol Int 2010, doi 10.1007/s00296-010-1524-0) (6.00 for female and 6.22 for male patients), in which 97.6% of the patients were biologic naïve.

Conclusion: Risk for malignancy was not elevated in Japanese RA patients who received biological agents including TNF inhibitors and tocilizumab.

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Prophylactic Therapy for Latent Tuberculosis Prior to Anti-Tumor Necrosis Factor Therapy in Patients with Rheumatoid Arthritis: A Decision Analysis. Glen S. Hazlewood[1], David Naimark[1], Michael Gardam[1], Vivian Bykerk[2] and Claire Bombardier[3]. [1]University of Toronto, Toronto, ON, [2]Brigham & Women's Hospital, Boston, MA, [3]Institute for Work & Health, Toronto, ON

Background/Purpose: Screening for latent tuberculosis infection (LTBI) prior to anti-TNF therapy is recommended, with patients offered prophylactic therapy if they screen positive. The utility of this in low-risk populations is uncertain, given a low absolute risk of TB reactivation in patients who screen positive and risks associated with prophylaxis. The objective was to determine if prophylactic therapy for LTBI should be initiated in patients with rheumatoid arthritis (RA) who screen positive prior to starting anti-TNF therapy.

Methods: A Markov model with a lifetime horizon and monthly cycles was developed to model the decision of whether to initiate prophylaxis with isoniazid (INH) for 6–9 months prior to starting anti-TNF therapy in a

hypothetical cohort of patients with RA who screen positive for LTBI. The base case was a 50-year old patient, born in a country with a low TB prevalence with a positive tuberculin skin test of 5–10 mm, who had not been vaccinated with BCG and had no other risk factors for TB reactivation outside of RA and anti-TNF therapy. All model inputs were based on literature reviews. The outcome was quality-adjusted life years, which were discounted at 3%/year. Sensitivity analyses were performed across all variables and for several model assumptions.

Results: No prophylaxis was the favoured approach with a gain of 8.1 quality-adjusted life-days. The decision was robust to the range of plausible values of relative risk (RR) of TB reactivation associated with anti-TNF therapy (RR: 1.3–15.5). Prophylaxis was favoured if the RR of TB reactivation associated with RA alone was > 3.2 or if the utility associated with INH prophylaxis was > 0.98. For any given baseline probability of TB reactivation, as age increased, prophylaxis was less favoured (Fig. 1). This occurred because the risk of hepatotoxicity is accrued initially and increases with age, and because older patients have less lifetime risk of TB reactivation and therefore less potential to benefit from prophylaxis. Prior BCG vaccine or the use of 4 months of rifampin instead of INH did not change the favoured decision.

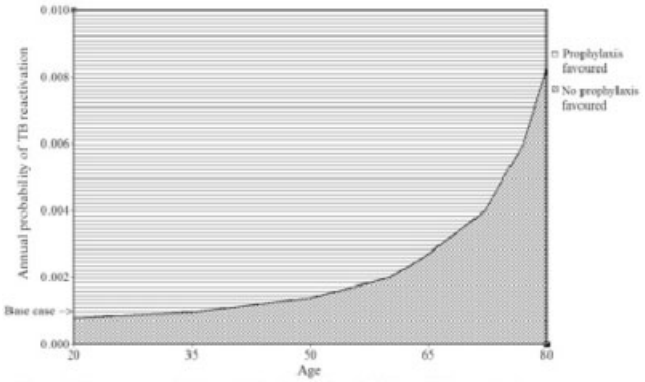

Figure 1: Two-way sensitivity analysis of annual probability of TB reactivation versus age. Prophylaxis is favoured for any patient in the area shaded with horizontal lines.

Conclusion: For RA patients with a low-positive LTBI screen, who are otherwise at low risk of TB reactivation, holding prophylaxis prior to anti-TNF therapy is appropriate. The decision to initiate prophylaxis should be tailored to a patient's age, baseline annual risk of TB reactivation and patient preference for a 9-month course of isoniazid.

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Primary Care Physicians' Attitudes towards Managing Rheumatoid Arthritis: Room for Improvement. Daniel H. Solomon[1], Katie Garneau[1] and Maura D. Iversen[2]. [1]Brigham & Womens Hospital, Boston, MA, [2]Northeastern University, Department of Physical Therapy and Brigham & Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Many people with rheumatoid arthritis (RA) do not receive care from a rheumatologist. We surveyed primary care physicians (PCPs) to better understand their attitudes, knowledge, and practices regarding the optimal treatment of RA.

Methods: Randomly selected PCPs practicing in the US with valid e-mail addresses were surveyed, using a list supplied by the American Medical Association. The survey encompassed their experience with RA, use of disease modifying anti-rheumatic drugs (DMARDs), and experience with rheumatology referrals. Logistic regression analyses described the responses and examined the correlation between physician variables and use of DMARDs.

Results: E-mail invitations were opened by 1,103 PCPs and completed by 267 (25%). Most respondents were men (68%) in practice for over 10 years (64%) who reported 6 or more RA patients under their care in the last year (71%). The majority (59%) reported some RA training after medical school (such as grand rounds or journals), but only 1/3 felt very confident managing this condition. Most (81%) reported prescribing DMARDs, but 37% do not initiate them, with only 9% reporting being very confident starting a DMARD. 35% believe that DMARDs should only be used after a trial of NSAIDs or steroids. A variety of reasons were given for not considering patients appropriate DMARD candidates (see Table). Reasons commonly mentioned include: quiescent disease, too sick to take a DMARD, side effects of DMARDs too great, drug interactions, and monitoring and cost too burdensome. We examined whether PCP characteristics were associated with prescribing DMARDs, but none were significant correlates. Almost half (44%) of PCPs noted that patients report difficulty getting appointments with rheumatologists.

Table Attitudes of 266* PCPs regarding DMARD prescribing for RA

	DMARD Prescribers N = 217	DMARD Non-Prescribers N = 49
Factors that make patients inappropriate candidates for DMARDs		
No need (well controlled without DMARD)	110 (51%)	21 (43%)
Too sick to take a DMARD	78 (36%)	14 (29%)
Side effects of DMARDs too problematic	128 (59%)	20 (41%)
Drug interactions	74 (34%)	9 (18%)
Drug cost and monitoring are too high	115 (53%)	27 (55%)
Cannot get laboratory monitoring	17 (8%)	3 (6%)
Best time to initiate DMARDs		
After a trial of NSAIDs or steroids	75 (35%)	17 (35%)
Within the first 6 months of dx	132 (61%)	27 (55%)
At least 6 months after diagnosis	9 (4%)	4 (8%)
Comfort level starting a DMARD†		
Very comfortable	23 (11%)	0 (0%)
Somewhat comfortable	73 (34%)	6 (12%)
Somewhat uncomfortable	89 (41%)	23 (47%)
Very uncomfortable	30 (14%)	20 (41%)
Comfort level continuing a DMARD§		
Very comfortable	71 (33%)	4 (8%)
Somewhat comfortable	107 (50%)	23 (47%)
Somewhat uncomfortable	37 (17%)	17 (35%)
Very Uncomfortable	1 (0%)	5 (10%)

† 3 missing responses, § 2 missing responses

Conclusion: We found many PCPs are uncomfortable managing RA but perceive poor rheumatology access. Lack of accessibility to rheumatologists and discomfort in prescribing DMARDs for patients with RA are potential barriers to optimal treatment.

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Nudging Patients with Rheumatoid Arthritis towards Accepting ACR Recommendations. Liana Fraenkel[1], Ellen Peters[2] and Valerie Reyna[3]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, [2]Ohio State University, Columbus, OH, [3]Cornell University, Ithica, NY

Background/Purpose: Current American College of Rheumatology (ACR) guidelines "strongly recommend" aggressive care with disease modifying anti-rheumatic drugs (DMARDs) in order to achieve and maintain tight control in rheumatoid arthritis (RA). Despite the widespread endorsement of this approach, data suggest that many RA patients are not effectively treated with DMARDs. There are currently no proven mechanisms in place to effectively inform RA patients and enable them to process the complex information involving decisions related to escalating care. The objective of this study is to develop a decision tool, based on Fuzzy Trace theory, to effectively inform patients and to "nudge" RA patients with ongoing active disease, despite use of traditional DMARDs, to consider biologic therapy.

Methods: We first performed a systematic review to generate the outcome data and risk estimates required for the tool. To ensure equal emphasis on both adverse events (AEs) and benefits, we included the same number of benefits as risks. A Delphi panel of experts was used to determine which AEs should be represented to all subjects to ensure informed consent. Additional information can be accessed through links for those desiring additional information. Probabilistic information was presented using theoretically motivated manipulations: e.g.: bar graphs to emphasize relative benefits and pie charts were used for AEs to emphasize the denominator. Subjects are provided an opportunity to perform a value clarification exercise at the end of the tool. We conducted a pre-post test pilot study to assess the feasibility, acceptability, and preliminary evidence of the tool's efficacy in improving informed choice.

Results: We interviewed104 subjects; mean age (SD) = 62 (12); 84% female, 86% White; median duration of RA =13 years (range 1–61); 72% reported currently using a traditional DMARD and 39% a biologic. Knowledge (as measured by the sum of correct responses to 20 questions) and willingness to take a biologic (as measured on an 11-point numeric rating scale) significantly improved after viewing the tool (mean differences 3.1 and 1.4 respectively, both

$p < 0.0001$). Decisional conflict (informed and value subscales) also significantly decreased (mean differences 20.4 and 20.7, both $p<0.001$). Increased willingness to take a biologic was greater among younger adults and those with a college education. Improvement in knowledge was seen across varying ages and educational backgrounds. Over 90% of participants ratings; related to the quality and quantity of information were very good or excellent. 89% found the tool to be very helpful and all would recommend it for patients with RA.

Conclusion: A tool designed based on the principles of Fuzzy Trace theory to nudge patients towards accepting "strong recommendations" increased knowledge, decreased decisional conflict, and increased patient willingness to escalate care in a pre-post test setting.

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An Analysis of the Use of Lipid Lowering Agents in Rheumatoid Arthritis: A Population Based Cohort Study. Bharath Manu Akkara Veetil, Eric L. Matteson, Sherine E. Gabriel and Cynthia S. Crowson. Mayo Clinic, Rochester, MN

Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular disease and mortality. Lipid lowering therapy to reduce risk for major coronary events and coronary death is reportedly underused in patients with RA, but it is unknown whetheruse of lipid lowering medications in patients with RA differs from the general population.

Methods: A population-based inception cohort of patients who fulfilled 1987 American College of Rheumatology criteria for RA in 1988–2007 and a cohort of non-RA subjects from the same population base were assembled and followed until death, migration, or 12/31/2008. Cardiovascular risk factors, lipid measures and use of lipid-lowering agents were ascertained by review of the medical record. The national cholesterol education program (NCEP) adult treatment panel III (ATP III) guidelines were assessed at the time of each lipid measure throughout follow-up. Time from the first measurement of lipids meeting guidelines for initiation of lipid-lowering agents to initiation of lipid-lowering agents was assessed using Kaplan-Meier methods. Log rank tests were used to compare RA and non-RA cohorts.

Results: The study population included 412 RA and 438 non-RA patients with at least one lipid measure during follow-up and no prior use of lipid-lowering agents (mean age 60 years; 71% female in each cohort). No difference between RA and non-RA cohorts was found in the time from index date to the first lipid measure ($p=0.68$). The rates of lipid testing were lower among patients with RA compared to non-RA subjects, with 2209 lipid tests during 4454 person-years (0.50 per patient per year; 95% CI: 0.48, 0.52) in the patients with RA and 2780 lipid tests during 5119 person-years (0.54 per patient per year; 95% CI: 0.52, 0.56) in the non-RA subjects ($p<0.001$). Overall, patients with RA were less likely to receive lipid-lowering agents than non-RA subjects with 21% of RA and 28% of non RA subjects initiating lipid lowering therapy by 10 years($p=0.02$). The NCEP ATP III cardiovascular disease risk categories were similar in both cohorts ($p=0.48$). Among patients who met NCEP ATP III criteria for lipid lowering therapy during follow-up ($n=106$ RA and $n=120$ non-RA), there was no difference between patients with RA and non-RA in initiation of lipid lowering therapy (27% in RA vs 26% in non-RA, $p=0.36$). In the subset of subjects with LDL$\geq$160 mg/dl, there was no difference between RA and non-RA in initiation of lipid lowering therapy, with 24% of RA and 26% of non-RA patients initiating lipid-lowering agents within 2 years ($p=0.77$).

Conclusion: Patients with RA were less likely to receive lipid-lowering agents than non-RA subjects overall. However, among those who met NCEP ATP III criteria recommending initiation of lipid-lowering agents, the percentage of RA and non-RA patients who initiated lipid-lowering agents was similar. Substantial undertreatment occurred in both the RA and non-RA cohorts.

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Quality of Care for Rheumatoid Arthritis and Osteoporosis: Results From the U.S. Medicare Physician Quality Reporting Program. Jeffrey R. Curtis[1], Pradeep Sharma[2], Tarun Arora[3], Aseem Bharat[3], Michael Morrisey, Kenneth G. Saag[3], Itara Barnes[5] and Elizabeth S. Delzell[3]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Atlanta, GA

Background/Purpose: Quality of care and pay for performance are an increasingly visible facet of medical care. In 2006, Medicare enacted the Physician Quality Reporting Initiative (PQRI) program that allowed physicians to report performance measures for osteoporosis; rheumatoid arthritis (RA) was added in 2008. The objective of this analysis was to describe the number of rheumatologists and other physician specialties participating in the PQRI program and to understand physician-reported reasons why recommended care for individual osteoporosis and RA patients was not provided.

Methods: Using the national random 5% sample of Medicare fee-for-service beneficiaries from 2007–2009, we identified all healthcare providers reporting on 1) PQRI Measure 41: percentage of patients with a physician diagnosis of osteoporosis who were prescribed an osteoporosis medication within 12 months (CPTII 4005F); and/or 2) Measure 108: percentage of RA patients prescribed a biologic or non-biologic DMARD (CPTII 4187F). Modifiers allowed physicians to report on circumstances where there were medical, patient-related, or other reasons why the recommended medications were not prescribed; multiple reasons were allowable.

Results: During 2007–2009, 1–3% of internal medicine and family physicians reported on prescription medication use for approximately 6,000 unique osteoporosis patients (measure 41); 10–12% of rheumatologists reported on this measure. For patients for whom their physicians reported the measure in 2009 ($n=5348$), 7.3% did not receive osteoporosis medication for medical reasons, 4.3% did not receive osteoporosis medication for patient reasons (e.g. refusal), and 15.4% of patients did not receive it for other reasons (e.g. cost). In total, 26% of osteoporosis patients who had their physician report measure 41 did not receive prescription medications due to a reason provided by the physician.

In 2008, a total of 177 (5.7%) out of 3078 rheumatologists reported on DMARD use for RA patients; the proportion of rheumatologists reporting on this measure increased in 2009 to 10.2%. Among unique RA patients in 2009 ($n=1765$), 13.3% of patients had their physician report a medical (6.9%) or other (6.7%) reason why they had not been prescribed a DMARD.

Conclusion: Through 2009, approximately 10% of U.S. rheumatologists were reporting on the quality of care for their rheumatoid arthritis and osteoporosis patients enrolled in Medicare. A substantial fraction of these patients had physician-documented reasons for why recommended care had not been provided. Health plans that report on quality of care that fail to provide a mechanism to allow physicians to provide reasons why care was not provided may misclassify up to 25% of patients for whom care is medically inappropriate, refused, or otherwise not feasible.

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DMARD Underuse in the Medicare Current Beneficiary Survey: Evidence for Socioeconomic Disparities. Daniel H. Solomon[1], John Z. Ayanian[2], Bing Lu[3], M. Alan Brookhart[4], Sebastian Schneeweiss[5], Tamara Shaykevich[1] and Jeffrey N. Katz[1]. [1]Brigham & Womens Hospital, Boston, MA, [2]Brigham and Women's Hospital, [3]Brigham and Women's Hospital, Boston, MA, [4]University of North Carolina, [5]Harvard University, Boston, MA

Background/Purpose: There has been an increased appreciation for the importance of DMARDs for virtually all patients with RA. However, numerous studies have documented that many patients with RA do not appear to receive DMARDs. Our prior work has documented that there racial disparities in who receives DMARDs, but these studies have not examined the role of insurance, income, and education as possible correlates of racial disparities. The goal of these analyses was to determine if racial disparities in DMARD prescribing can be explained by insurance, income, and/or educational differences.

Methods: We examined DMARD use in the Medicare Current Beneficiary Survey (MCBS), a four-year longitudinal US national survey of randomly selected Medicare beneficiaries. This study included data from years 2001–2006. Participants in MCBS with at least one Medicare claim for RA plus a self-report of RA were included in the analyses. DMARD use was based on an in-home assessment of all medications. Variables considered as potential correlates of DMARD use in regression models included race/ethnicity, insurance, income, education, rheumatology visit, region, age, gender, comorbidity index, and calendar year. Because of the repeated measures of DMARD use, each year of follow-up was considered as a separate observation with adjustment for within subject correlation using generalized linear model applying a Generalized Estimating Equation approach.

Results: The cohort consisted of 513 MCBS participants with a mean age of 70 years, of which 72% were female. During follow-up, 42% received a DMARD. In fully adjusted analyses among the whole cohort, the strongest predictor of DMARD use was seeing a rheumatologist (see **Table**). In the total cohort, lower annual income was associated with a reduced probability of DMARD use. This was not observed in the cohort seen by rheumatologists. Among individual not seen by rheumatologists, Black non-Hispanics were much less likely to receive a DMARD (OR 0.16, 95% CI 0.03–0.98)

compared to white, non-Hispanics; this was not the case when these individuals were seen by rheumatologists (OR 0.89, 95% CI 0.12–6.62). Older age was associated with a reduced probability of DMARD use, especially in the cohort not seen by rheumatologists.

Table. Regression models predicting DMARD use in MCBS

Variables	Total Cohort	Among Subjects Without Rheumatology Visits	Among Subjects With Rheumatology Visits
	Odds Ratio (95% confidence interval)		
Age, years			
< 75	1.00	1.00	1.00
75–84	**0.58 (0.37–0.92)**	**0.36 (0.18–0.73)**	**0.83 (0.46–1.51)**
85+	**0.09 (0.02–0.31)**	**0.05 (0.01–0.26)**	**0.15 (0.02–0.89)**
Gender, female	1.04 (0.65–1.67)	0.91 (0.49–1.71)	1.34 (0.71–2.53)
Race			
White, non-Hispanic	1.0	1.0	1.0
Black, non-Hispanic	0.49 (0.14–1.76)	**0.16 (0.03–0.98)**	0.89 (0.12–6.62)
Hispanic	0.99 (0.30–3.22)	0.40 (0.08–2.01)	1.28 (0.22–7.60)
Other, non-Hispanic	1.23 (0.41–3.67)	0.68 (0.17–2.77)	1.56 (0.29–8.22)
Income			
>50K	1.0	1.0	1.0
30–50K	0.89 (0.33–2.40)	0.44 (0.14–1.32)	1.15 (0.40–3.34)
20–30K	0.59 (0.20–1.63)	**0.27 (0.08–0.84)**	0.74 (0.25–2.20)
15–20K	0.58 (0.20–1.71)	**0.28 (0.08–0.95)**	0.75 (0.20–2.61)
< 15K	0.57 (0.21–1.53)	**0.17 (0.05–0.55)**	1.08 (0.36–3.29)
Rheumatology care	**7.74 (5.37–11.1)**	NA	NA

Notes: Bolded findings are statistically significant.NA, not applicable; Models adjusted for variables in the table plus education, region of residence (South, Midwest, Northeast, and West), insurance status (private, HMO, and drug insurance), comorbidity index, as well as year of observation.

Conclusion: We found that less than half of participants diagnosed with RA in MCBS used DMARDs. Among individuals not seeing rheumatologists, Black non-Hispanic ethnicity appears associated with a reduced probability of DMARD use, independent of income, insurance, and education. As has been the results of several other cohort studies, seeing a rheumatologist is the strongest predictor of DMARD use.

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Patients Whose Global Estimates Are Higher Than Their Physician's Global Estimates Are More Likely to Be Female, Have Fewer Years of Formal Education, and Higher RAPID3 (Routine Assessment of Patient Index Data) Scores. Isabel Castrejón[1], Yusuf Yazici[2], Jonathan Samuels[1] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: To analyze levels of agreement of physician global estimates (DOCGL) with patient global estimates (PATGL), and characteristics of patients whose global estimates were higher than versus similar to versus lower than their physicians' global estimates, in patients with different rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and osteoarthritis (OA), seen in usual care.

Methods: A database is maintained on all patients seen at an academic rheumatology clinical setting, which includes demographic, patient self-report MDHAQ (multidimensional health assessment questionnaire), medication, and laboratory data. Each patient completes an MDHAQ at each visit, to score physical function, pain, patient global estimate (PATGL), fatigue, anxiety, depression and quality of sleep. The MDHAQ also queries demographic data including gender, age and formal education level. RAPID3 (routine assessment of patient index data) is a composite index of physical function, pain and PATGL. A physician global estimate (DOCGL) is scored for each patient at each visit by the rheumatologist. One random visit of each patient between July 2005 and April 2011 was selected for analyses of the degree of possible agreement or discordance between PATGL (0–10 scale) and DOCGL (also 0–10). Mean DOCGL levels were classified into 3 groups: "PATGL>DOCGL" (PATGL 2 or more units greater than DOCGL); "PATGL=DOCGL" (differing by <2 units); and "DOCGL>PATGL" (DOCGL 2 or more units greater than PATGL). Analysis of variance (ANOVA) was used to compare differences in MHDAQ measures among the 3 groups.

Results: Overall, 980 patients were studied, including 145 with RA, 57 SLE, 173 OA and 605 with other rheumatic disease; 509 patients (52%) had PATGL=DOCGL (within 2 units on a 0–10 scale), 371 (38%) had PATGL>DOCGL (by 2 units or more), and 100 (10%) had DOCGL>PATGL (by 2 units or more). Patients with PATGL>DOCGL were significantly more likely to be female, have fewer years of formal education, and have higher scores for PATGL, MDHAQ-function, pain, fatigue, RAPID3, sleep, anxiety, depression, and RADAI. Similar, but not identical, patterns were seen in patients with RA, comparable to a published report [Barton JL et al, Arthritis Care Res 2010;62: 857–64].

Table 1. Mean of measures according to comparison of estimate of global status by the physician (DOCGL) and patient (PATGL).

	All Patients N=980	DOCGL>PATGL N=100	PATGL=DOCGL N=509	PATGL>DOCGL N=371	*p*
Age, mean (years)	50.2	51.7	49.3	51.3	0.10
Gender (% female)	68%	64%	64%	74%	0.001
Education (years)	15.5	16.3	15.7	15.0	0.002
DOCGL (0–10)	2.6	4.0	2.5	2.5	<0.001
PATGL (0–10)	4.1	1.2	2.7	6.8	<0.001
MDHAQ-function (0–10)	1.8	1.0	1.3	2.6	<0.001
MDHAQ-pain (0–10)	4.4	3.1	3.3	6.4	<0.001
MDHAQ-fatigue (0–10)	4.0	1.7	3.0	6.0	<0.001
RAPID3 (0–30)	10.3	5.2	7.4	15.7	<0.001
Get a good sleep (0–3)	0.94	0.59	0.80	1.24	<0.001
Anxiety (0–3)	0.58	0.34	0.49	0.76	<0.001
Depression (0–3)	0.48	0.30	0.37	0.70	<0.001
RADAI (0–48)	7.5	4.2	5.7	11.2	<0.001

Conclusion: Among 980 patients, 38% scored global estimates of at least 2 units higher than their physicians' global estimates. These patients were more likely to be female and have higher scores for all MDHAQ components, including depression and anxiety, and a lower formal education level, compared with patients whose physicians estimated global status similarly or worse than the patients' global estimates.

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What Factors Affect Discordance Between Physicians and Patients in Assessments of Global Health in Rheumatoid Arthritis? Soo-Kyung Cho[1], Yoon-Kyoung Sung[1], So-Yeon Park[1], Jeeseon Shim[2], Chan-Bum Choi[3], Hoon-Suk Cha[4], Jung-Yoon Choe[5], Won-Tae Chung[6], Jae Bum Jun[7], Tae-Hwan Kim[8], Tae-Jong Kim[9], Eun-Mi Koh[4], Jisoo Lee[10], Shin-Seok Lee[9], Sung Hoon Park[5], Wan-sik Uhm[7], Dae-Hyun Yoo[8], Bo Young Yoon[11], Sang-Cheol Bae[1] and KORONA investigators[12]. [1]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Hanyang University Hospital for Rheumatic Disease, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Catholic University of Daegu School of Medicine, Daegu, South Korea, [6]Dong-A University, Busan, South Korea, [7]Hanyang University Hospital for Rheumatic Disease, Seoul, South Korea, [8]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [9]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [10]Ewha Womans University Mokdong Hospital, Seoul, South Korea, [11]Inje University Ilsan Paik Hospital, Goyang, South Korea, [12]Seoul, South Korea

Background/Purpose: The agreement of global health (GH) status between patient's reports and physician's assessments is essential to the safe and effective management of rheumatoid arthritis (RA) and improves outcomes. Our study aimed to identify the agreement between patient and physician in assessment of GH and explore influencing factors of discordance between them.

Methods: Total of 3,169 patients with RA were recruited from KORean Observational study Network for Arthritis (KORONA), a database generated by rheumatologist investigators across the Korea. Patients were divided into three subgroups according to their agreement between physician visual analogue scale (VAS) and patients VAS. We defined three groups as positive discordance (≥25mm), concordance (< 25 mm), negative discordance (≤−25) according to difference between patient VAS and physician VAS. The means ± SD of its difference were 43.26 ± 13.69, 1.44 ± 12.26 and −37.11 ± 11.08 in each group. Among them, 2,523 patients were enrolled to evaluate factors influencing on positive discordance. On univariate analysis, we identified association factors for positive discordance group. Then multivariable logistic regression analysis was used to identify predictors of positive discordance.

Results: Of the subjects, 1,901 patients (60.0%) were concordance group

and 225 patients (7.1%), 1,036 patients (32.7%) were negative discordance, positive discordance, respectively. Factors associated with positive discordance were female gender, disease activity, disease duration, comorbid with hypertension (HTN) and gastrointestinal (GI) disease, visual analogue scale (VAS) of fatigue and sleep disturbance in univariate analysis. Multivariable analysis demonstrated comobidity with HTN (OR=1.25, CI 1.01~1.55), comorbidity with GI disease (OR=1.54, CI 1.25~1.89), higher disease activity (OR=2.38, CI 1.75~3.24), higher fatigue VAS (OR=2.41, CI 1.99~2.92), and sleep disturbance VAS (OR=1.56, CI 1.26~1.92) affected on positive discordance. Patients were stratified according to disease activity. In patients with remission or low disease activity, age ≥60 was a protective factor on positive discordance. In moderate or high disease activity group, comorbid with HTN or GI dz. and disease duration of ≥10 were factors influencing on positive discordance.

Conclusion: About 32.7% patients thought their disease more severe than their doctors. Higher disease activity, comorbid with HTN and GI disease, fatigue and sleep disturbance were important factors on discordance between patient and physician.

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Relative Effectiveness of Rituximab and An Alternative TNF Inhibitor in Patients with Rheumatoid Arthritis and An Inadequate Response to a Single Previous TNF Inhibitor: Interim Results From Switch-Rheumatoid Arthritis a Global Comparative-Effectiveness Observational Study. Paul Emery[1], Piercarlo Sarzi-Puttini[2], Robert J. Moots[3], Alexandros A. Andrianakos[4], Thomas P. Sheeran[5], Denis Choquette[6], Axel Finckh[7], Marie-Laetitia Desjuzeur[8], Eric Gemmen[9], Chiedzo Mpofu[8] and Jacques-Eric Gottenberg[10]. [1]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [2]L Sacco University Hospital, Milano, Italy, [3]University of Liverpool, Liverpool, United Kingdom, [4]Hellenic Foundation for Rheumatological Research, Athens, Greece, [5]Cannock Chase Hospital, Cannock, United Kingdom, [6]University of Montreal, Notre-dame Hospital, Montreal, QC, [7]University Hospital of Geneva, Geneva, Switzerland, [8]F. Hoffman-La Roche Ltd, Basel, Switzerland, [9]Quintiles Inc, Rockville, MD, [10]CHU Strasbourg, Strasbourg, France

Background/Purpose: A recent longitudinal cohort study suggested that after an inadequate response to a tumor necrosis factor inhibitor (TNFi), switching to rituximab (RTX) may be more effective than switching to an alternative TNFi.[1] The current study prospectively evaluated the relative effectiveness of RTX vs an alternative TNFi in rheumatoid arthritis (RA) patients with an insufficient response or intolerance to a single previous TNFi in routine clinical practice.

Methods: This is an interim analysis on an ongoing global, multicenter, prospective, observational study in patients with RA who were prescribed RTX or an alternative TNFi following the first TNFi failure. Propensity scores were generated for each patient to reflect the conditional probability of receiving treatment with RTX vs an alternative TNFi. 6-month changes in clinical variables (DAS28-ESR and ESR) following the initiation of the new therapy were compared in the two treatment groups using analysis of covariance; these analyses controlled for baseline value, propensity score, and other covariates found to be statistically different between the two groups at baseline.

Results: Data are presented for 1082 patients enrolled and 660 patients completing 6 months as of Feb 2011 in 9 countries. The 592 RTX and the 490 alternative TNFi patients had a mean (SD) age of 56.4 (12.46) and 54.4 (13.70) yrs, respectively; mean (SD) disease duration 8.9 (7.87) and 7.8 (6.60) yrs; female 77.4% and 80.6%; mean (SD) duration of all previous TNFi therapy 25.2 (25.4) and 25.4 (26.7) months. At the start of the new therapy, mean (SD) DAS28-ESR was significantly higher ($p<0.0001$) in the RTX group (5.57 [1.33]; n=385) vs the alternative TNFi group (4.97 [1.38]; n=272). At 6 months, there was a significantly greater decrease in DAS28-ESR in RTX patients (n=277) than in alternative TNFi patients (n=203): mean improvement at 6 months −1.6 vs −1.2; p=0.047. In addition, there was a significantly greater decrease in ESR (−15.4 vs −9.7; p=0.0219) in the RTX group vs the alternative TNFi group and numerically better results for the other DAS28 components (joint counts, global disease activity assessment).

Conclusion: Following discontinuation of a first TNFi, patients starting treatment with RTX achieved significantly better efficacy at 6 months as measured by DAS28-ESR compared with patients switching to an alternative TNFi.

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Direct and Indirect Effects of Disease Activity on Functional disability in Rheumatoid Arthritis Patients Over Time and the Effect of Increasing Intensive Treatments: Results From Early Utrecht Rheumatoid Arthritis Cohort Study Group. Sandhya C. Nair, P.M.J. Welsing, F.P.J.G. Lafeber and J.W.J. Bijlsma. University Medical Center Utrecht, Utrecht, Netherlands

Background/Purpose: Disease activity influences functional disability in Rheumatiod Arthritis (RA). This influence theoretically constitutes a direct effect (due to current disease activity) and an indirect effect through the effect on joint damage of disease activity over time. It has been found that the direct relation between disease activity and functional disability becomes weaker with higher disease duration, but it has been questioned whether this still is the case with current intensive treatment (1,2). The indirect effect of disease activity on functional disability has not been studied extensively. It is important to understand the relations between these important outcomes and the effect of treatment strategy for the interpretation of disease activity in current tight control treatment strategies. Also with simulation of the progression of the disease in modeling studies as often performed within increasingly performed health-economic studies these relations should be taken into account. The objective of this study was to explore the relation of disease activity with functional disability over time considering indirect and direct associations and also the influence of treatment strategy on these relations.

Methods: Data from consecutive randomized clinical trials and their extension phases performed within the Early Utrecht Rheumatoid Arthritis Cohort study group studying increasing intensive treatment strategies were used. Functional capacity was measured using the HAQ and disease activity with the Disease Activity Score 28 (DAS28) every 12 months. Linear mixed models were used to model the longitudinal relation of DAS28 (current and lagged DAS28) and other variables on functional disability of patients over time. To investigate if the influence of variables changed over time interaction terms were tested in the model. Effect modification by treatment strategy was also studied in the model and in subgroup analyses.

Results: Current DAS28 was as expected positively longitudinally associated with HAQ. Lagged DAS28 was independently associated with HAQ. The longitudinal relation of DAS28 with HAQ decreased over disease duration. Remarkably the longitudinal relation of lagged DAS28 with HAQ increased over disease duration. Both were independent of treatment strategy. Although similar relationships between disease activity and functional disability was observed, HAQ progression was lowest in the high intensity treatment group as compared to low intensity treatment group ($\beta=-0.12$, $p=0.002$).

Conclusion: More intensive combination treatment strategies improve the long-term progression of functional disability. Although the longitudinal relation of disease activity with functional disability decreases the influence of lagged disease activity with functional disability increases with disease duration. This further underpins the importance of disease activity as a treatment target for RA early as well as later in the disease course. These results should be confirmed and be taken into account in studies modeling the progression of RA.

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Rheumatoid Arthritis Continues to Improve in the New Millennium Whilst Use of Medication Change. Findings From a Representative Rheumatoid Arthritis Register Over 15 Years. Cathrine Austad, Tore K. Kvien and Till Uhlig. Diakonhjemmet Hospital, Oslo, Norway

Background/Purpose: During recent years and especially in the new millennium disease severity in patients with rheumatoid arthritis (RA) has been reported improved. It is important to retrieve such information from population based studies and to identify trends over time for this improvement. Purpose: To explore whether observed improved RA severity as measured by patient reported outcomes (PROs) improves over a perspective of 15 years and in the most recent years after introduction of biologic therapies.

Methods: In a population based registry of RA, 868 patients aged 20–79 years (mean (SD) age 59.9 (12.3) years, disease duration 13.0 (10.8) years, 77.1% females, 57.0 % RF+ or CCP+) responded in 2009 to a mailed questionnaire (response rate 60.6%). The PROs included pain, fatigue and patient global assessment of disease impact on 100 mm visual analogue scales, modified HAQ, SF-36 (with calculation of physical (PCS) and mental component summary (MCS) (low scores=poor health),

and SF-6D derived utility). Patients reported use of medications including disease modifying anti-rheumatic drugs (DMARDs).

Results are given with means and 95% confidence intervals (CI), and were compared with outcomes from previous cross-sectional health status surveys using the same instruments in 1994, 1996, 2001, and 2004. Comparisons across these cross-sectional data collections can be performed since the respondents are considered representative for the entire RA population in the geographic area [1]. Non-overlapping CI of a PRO at different time points was considered to represent a true difference. Subanalyses were performed to investigate differences in gender, disease duration ≤ or > 10 years and current use/non-use of DMARDs.

Results: Age, gender and disease duration were similar at all examination points. Use of DMARDs increased from 36.4% in 1994 to 59.6% in 2009, both overall and for genders separately. DMARD users were statistically significant younger than non-users, data not included, with gender distribution equal that of the registry. In 2009 20% of patients used a biological DMARD. A consistent improvement in health status was observed from 1994 to 2009, except for mental health (see table). MHAQ and SF-36 PCS demonstrated a clear improvement from 2004 to 2009. Mean improvements from 1994 to 2009 were in the magnitude of what is considered as minimum clinically important.

	1994	1996	2001	2004	2009
Current DMARD n(%)					
Overall	339 (36.4)	407 (39.6)	373 (45.0)	495 (54.2)	588 (59.6)
MHAQ (1–4)					
Overall	1.68 (1.64; 1.71)	1.65 (1.62; 1.69)	1.58 (1.54; 1.62)*	1.55 (1.51; 1.58)*	1.44 (1.40; 1.47)*
Male	1.48 (1.41; 1.54)	1.52 (1.44; 1.60)	1.44 (1.38; 1.51)	1.49 (1.42; 1.57)	1.38 (1.32; 1.44)
Female	1.74 (1.69; 1.78)	1.69 (1.65; 1.73)	1.62 (1.58; 1.66)*	1.56 (1.52; 1.60)*	1.45 (1.41; 1.48)*
Dis. dur ≤ 10 years	1,53(1.49; 1.57)	1.50 (1.46; 1.54)	1.44 (1.39; 1.48)*	1.43 (1.38; 1.47)*	1.34 (1.30; 1.37)*
Dis. dur >10 years	1,86 (1.79; 1.92)	1.81 (1.75; 1.86)	1.70 (1.65; 1.76)*	1.65 (1.60; 1.70)*	1.50 (1.46; 1.55)*
Use DMARDs	1,64 (1.58; 1.70)	1.64 (1.58; 1.69)	1.55 (1.50; 1.60)	1.53 (1.48; 1.57)*	1.42 (1.38; 1.46)*
No DMARDs	1.70 (1.65; 1.75)	1.67 (1.62; 1.72)	1.61 (1.56; 1.66)	1.57 (1.52; 1.62)*	1.45 (1.40; 1.50)*
VAS patient global (0–100)					
Overall	48.5 (47.0; 50.0)	44.8 (43.5; 46.2)*	39.8 (38.1; 41.6)*	38.2 (36.6; 39.8)*	37.1 (35.4; 38.8)*
Male	50.7 (49.0; 52.4)	40.6 (37.4; 43.7)*	32.2 (28.8; 35.7)*	34.4 (30.9; 37.8)*	34.7 (31.4; 38.0)*
Female	44.4 (40.8; 47.9)	46.0 (44.4; 47.6)	41.9 (39.9; 44.0)	39.2 (37.4; 41.1)	37.4 (35.6; 39.1)*
Dis.dur ≤ 10 years	45.9 (43.7; 48.0)	40.5 (38.5; 42.5)*	34.8 (32.4; 37.3)*	34.0 (31.6; 36.3)*	33.8 (31.4; 36.2)*
Dis.dur >10 years	53.4 (51.1; 55.6)	49.1 (47.1; 51.1)	44.0 (41.6; 46.5)*	41.8 (39.6; 44.0)*	39.1 (37.0; 41.2)*
DMARDs	48.3 (45.6; 50.6)	44.9 (42.8; 47.0)	38.9 (36.4; 41.3)*	37.8 (35.7; 39.9)*	36.9 (34.9; 38.9)*
No DMARDs	49.9 (47.8; 52.0)	45.0 (43.1; 46.9)*	40.6 (38.1; 43.1)*	38.7 (36.2; 41.2)*	36.6 (34.1; 39.1)*
SF-36 MCS (0–100)	46.3 (45.5; 47.2)	45.3 (44.5; 46.0)	47.0 (46.2; 47.9)*	47.5 (46.7; 48.3)	46.9 (46.1; 47.7)*
SF-36 PCS (0–100)	31.4 (30.7; 32.2)	32.0 (31.3; 32.7)	32.7 (31.9; 33.5)	33.7 (32.9; 34.4)*	36.4 (35.6; 37.2)*
SF-6D utility (0–1)	0.616 (0.607; 0.625)	0.617 (0.608; 0.625)	0.639 (0.629; 0.649)*	0.647 (0.638; 0.656)*	0.670 (0.660; 0.680)*
Pain (0–100)	46.0 (44.4; 47.5)*	37.7 (36.2; 39.1)*	35.8 (34.1; 37.4)*	34.5 (33.0; 36.1)*	34.2 (32.6; 35.8)*
Fatigue (0–100)	50.0 (48.2; 51.8)	44.1 (42.3; 45.9)*	46.9 (44.9; 48.9)	46.1 (44.2; 48.1)	44.7 (42.8; 46.6)

* non-overlapping 95% CI with ≥1 other measure

Conclusion: The improvement in physical health and utility observed in 1994–2004 continued until 2009. Improvements were seen in both genders, with short and long disease duration, and independently of DMARD use. RA patients during the last 15 years had consistently reduced disability and better overall health and utility score, indicating that recent investments in health care for patients with RA are justified.

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Perceived Benefits of Intravenous Biologic Therapy Among Patients with Rheumatoid Arthritis. Susan Bolge, Julie Vanderpoel, Helen Eldridge, Samir Mody and Mike Ingham. Janssen Services, LLC, Horsham, PA

Background/Purpose: Currently two modes of administration are available for biologic therapies used to treat rheumatoid arthritis (RA): intravenous infusion (IV) and subcutaneous injection (SQ). Patient preference for mode of administration may be one of many factors influencing choice of biologic therapy. The purpose of the study was to identify perceived benefits of IV biologic therapy among patients with RA who are currently treated with an IV biologic medication.

Methods: In August to September 2010, 209 patients self-reporting a diagnosis of RA and currently receiving IV biologic therapy participated in semi-structured telephone interviews about their experience with IV therapy. Study protocol and questionnaire were approved by an independent institutional review board (IRB). Patients rated their level of satisfaction with their current IV medication on a 7-point Likert scale, where 1=not at all satisfied and 7=very satisfied. Patients were asked to allocate $100 (U.S.) across six features of IV administration and services. Patients also discussed reasons for IV preference.

Results: Mean satisfaction was 6.2 out of 7, and 79% rated satisfaction as a 6 or 7. A mean of $31 out of $100 was allocated to the value of receiving treatment in a healthcare facility where healthcare professionals can assess and monitor the patient. Also highly valued were having a healthcare professional administer medication ($24) and infrequent dosing ($21). Of current IV users, most (83%, n=174) prefer an IV medication to a SQ. The most common reasons for IV preference are not wanting to give self-injections or not liking needles (41%), less frequent dosing (35%), and preference for healthcare professional administration (26%). Additional sub-analyses demonstrated that these results varied by demographics and factors related to treatment.

Conclusion: Patients with RA currently using IV biologic therapy are highly satisfied with their medication. Patients perceive the additional opportunity for healthcare provider interaction at infusion facilities as a benefit of this mode of administration. These results support the need for continued patient access to IV therapeutic options and shared decision-making between patients and physicians when selecting biologic treatment.

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The Effect of Arthritis Self Management Program on Outcome in African-Americans with Rheumatoid Arthritis Served by a Public Hospital. Athan N. Tiliakos[1], Yi Pan[2], Kirk Easley[3], Steven D. Culler[2] and Doyt L. Conn[1]. [1]Emory Univ School of Medicine, Atlanta, GA, [2]Emory University-Rollins School of Public Health, [3]Emory University-Rollins School of Public Health, Atlanta, GA

Background/Purpose: Rheumatoid Arthritis (RA) affects poor people and minority patients more adversely than those who are more economically advantaged and Caucasians. Economically disadvantaged patients have more active disease, more disability, and lower functional status at the presentation of RA. The Arthritis Self Management Program (ASMP) is recognized as an important tool in the management of RA. The purpose of this study was to determine the effect of ASMP on a cohort of RA patients (mostly African-American) served by Grady Memorial Hospital.

Methods: 104 patients with definite RA (based on the 1987 ACR Criteria,) recruited from the rheumatology clinic of Grady Memorial Hospital, were randomized to participate in ASMP versus usual care alone, and were followed for 18 months. The 2 groups were compared with regard to disease activity, functional status, and utilization of health resources. This information was collected at baseline, and at 6, 12, and 18 months. The primary endpoint was clinical improvement, as indicated by the ACR 20.

Results: The percentage of patients achieving ACR 20 was similar in the ASMP (14% at 18 months) and usual care (17% at 18 months) groups (p=0.3.) However, 28% of the 25 ASMP patients who attended at least 4 classes, achieved ACR 20, whereas 5% of the 27 ASMP patients who attended fewer than 4 classes, were able to achieve ACR 20 (p=0.02.) There was a reduction in the total number of tender and swollen joints in both groups throughout the duration of the study, particularly in patient over 60 years of age. At each visit, one third of the patients were not taking their prescribed medications. Influencing adherence was poverty and lack of insurance. There was no difference in healthcare utilization between the two groups.

Conclusion: Although all patients had improvement in the total number of painful and swollen joints, those who attended at least 4 ASMP classes were more likely to achieve ACR 20. ASMP may provide clinical benefit in RA patients served by a Public Hospital. Adherence may be limited by economic and social factors

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Effort-Reward Imbalance in Patients with Rheumatoid Arthritis? Jutta G. Richter, Thomas Muth, Birthe Koerbl, Nicole Hoffmann, Tobias Koch, Johannes Siegrist and Matthias Schneider. Heinrich-Heine-University, Duesseldorf, Germany

Background/Purpose: Working life factors influence patients' (life) satisfaction and their well being. Effort at work is spent as part of a 'social contract' that reciprocates effort by adequate reward. Components of work-related rewards have been shown to matter for health. Research on effort-reward imbalance (ERI) might contribute to the understanding of social and psychological factors related to the well-being of patients (pts) with rheumatoid arthritis (RA). We studied psychosocial stress levels at work measured by the ERI model.

Methods: Within a cross sectional nationwide study a set of standardized self-administered questionnaires was applied to RA pts. The ERI questionnaire assessed the effort-reward imbalance in RA pts capable for work. Effort-reward ratio (ERR) scores > 1 and the upper tertile scores of overcommitment (OCS) reflect relevant values. Data were analyzed in comparison to controls (c) not suffering from a rheumatic disease and recruited by the pts. Ethics committee approval had been obtained.

Results: 275 pts (85.1% female (f)) and 178 c (90.8%f) answered the questionnaire. Pts' mean age was 47.5±10.1 (c 42.8±9.8) years, mean disease duration (dd) 9.1±8.1 years, 83.6% self-reported at least one comorbidity (range 0–8). 74.5% received at least one disease modifying medication (DMARD, range 0–6). 44.0% were on steroids ≤7.5mg, 8.7% on steroids >7.5mg. 60.7% took NSAIDS. Occupational status and self-categorized occupation groups (scog) did not significantly differ between pts and c.

74.5% of the pts (C 5.4%;$p<0.01$) showed an ERR>1, this was consistent in f and male (m) pts ($p>0.05$), see table 1. Age, dd, functional capacity (fc), number of DMARDs, steroid dosages, education, marital status and scog did not significantly differ to those with ERR≤1. In contrast to fulltime (82.1%) or sporadically employed (81.8%), part time employees had significantly less ERR>1 (63.1%,$p<0.05$).

Table 1. Effort&reward and overcommitment scores, ERR>1 and OCS upper tertile in pts and c

	Effort mean±SD	Reward mean±SD	ERR>1 %	Overcommittment mean±SD	OCS upper tertile %
Pts	15.8±5.3	23.5±11.1	74.5	13.9±3.9	33.7
F pts	15.8±5.4	23.7±11.3	74.4	13.9±3.9	34.5
M pts	15.7±4.5	22.1±9.5	75.0	13.7±3.7	29.3
Controls	14.2±4.1	46.8±6.6	5.4	12.8±3.9	25.2
F c	14.0±4.0	47.0±6.5	4.1	12.6±3.8	23.2
M c	16.9±3.9	43.8±7.4	18.8	14.3±4.1	43.8

OCS showed relevant values in 33.7% pts (f 34.5%,m 29.3%; c 25.2% (both $p>0.05$). Age, dd, number of DMARDs, steroid dosages, education, marital status, and scog were not significantly different to those with OCS in lower tertiles. Fc was significantly lower in pts with relevant overcommitment.

Conclusion: This is the first study investigating the ERI in RA pts. Compared to controls a significantly higher proportion of pts reported a relevant ERI. Analysis on direct and indirect mechanisms potentially involved in the relation between psychosocial work characteristics and RA need further evaluations. However, although no cause and effect relationship can be established a reduction of stressful experiences in the framework of the worksites for RA pts seems reasonable.

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Who Are the Patients with Early Arthritis Who Score States "worse Than death" on the EQ-5D? Results From the ESPOIR Cohort. Cécile Gaujoux-Viala[1], Bruno Fautrel[2], Francis Guillemin[3], René-Marc Flipo[4], Patrice Fardellone[5], Pierre Bourgeois[2] and Anne-Christine Rat[3]. [1]1 Nancy-University, Paul Verlaine Metz University, Paris Descartes University, EA 4360 Apemac, Nancy, France, 2 Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [2]Université Pierre et Marie Curie - Paris 6 - Pitie Salpetriere University Hospital, Paris, France, [3]Nancy-University, Paul Verlaine Metz University, Paris Descartes University, EA 4360 Apemac CHU Nancy, Epidémiologie et Evaluation Cliniques, Nancy, France, [4]Rheumatology Department, Lille University Hospital, Lille, France, [5]C.H.U. D'Amiens, Amiens, France

Background/Purpose: Indirect utility measures are increasingly used to assess health benefits in RCTs and to estimate Quality-adjusted life-years (QALYs) gain in cost-effectiveness models. The EQ-5D is a 5-dimensional multi-attribute questionnaire widely used to calculate QALY. It allows negative utility values which theoretically correspond to health state "worse than death".

Objectives: To analyse the patients with EQ-5D <0 ie in states worse than death and to investigate their health status in a large multicenter prospective cohort of patients with EA.

Methods: EQ-5D measures were longitudinally assessed in 813 patients with EA. Clinical outcomes and laboratory measures were also recorded. The characteristics and health status of patients with an EQ-5D<0 were analyzed. Multivariate logistic regression was used to determine which specific aspects of early arthritis were independently associated with states worse than death.

Results: At baseline, 90 (11%) patients were in states worse than death. Mean EQ-5D values were −0.095±0.106 (range −0.594 to −0.003). Patients occupied 16 of the possible 84 health profiles with negative scores, with extreme pain/discomfort being the common characteristic of all these states. Concerning other domains, 40% of patients reporting severe anxiety/depression, 19% severe problems in usual activities, 8% severe problems in self-care, and 3% severe problems in mobility. All patients had at least moderate problems in anxiety/depression domain. Patients with negative EQ-5D scores had higher disease activity, higher HAQ score, more pain, more fatigue, lower mental component of the SF-36 and higher CRP than patients with EQ-5D>=0 (all $p<0.0001$). In the logistic regression model, increasing HAQ score and decreasing mental component of the SF-36 were associated with negative EQ-5D scores (Table). Results were similar at 6 and 12 months with 26 and 24 patients in states worse than death respectively.

Table. Determinants of being in state worse than death

Baseline Variable	EQ5D<0 N=90 (mean± SD)	EQ5D>0 N=723 (mean± SD)	OR [95%CI]
HAQ	1.98 ± 0.44	0.81 ± 0.60	21.3 [10.1;45.1]
Mental component of the SF36	28.2 ± 8.4	39.9 ± 10.6	0.92 [0.89;0.95]
Fatigue	68.3 ± 19.9	45.0 ± 28.0	1.01 [0.99;1.03]
DAS28	6.3 ± 1.2	4.9 ± 1.2	1.15 [0.86;1.54]
Pain	51.1 ± 28.9	35.4 ± 26.9	0.99 [0.98;1.01]

Conclusion: Pain/discomfort was the key domain leading to a state worse than death, scored at the most extreme level in every worse than death EQ-5D profile occupied by the early arthritis patients. In multivariate analysis HAQ and mental component of the SF36 were always associated with state worse than death. Early arthritis patients have specific needs necessitating better management of pain and anxiety.

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An Overview of Health Technology Assessments for Rheumatoid Arthritis Biologics. Floortje Van Nooten[1], Kavita Gajria[2] and Karin Coyne[3]. [1]United Bioscience Corporation, London, United Kingdom, [2]MedImmune LLC, Gaithersburg, MD, [3]United Bioscience Corporation, Bethesda, MD

Background/Purpose: Health Technology Assessments (HTAs) often form the basis for reimbursement decisions and can include medical, economic, social, and ethical implications. The objective of this study was to establish the information assessed, reasons for rejection or restriction, and critiques provided by HTA agencies.

Methods: HTAs for rheumatoid arthritis biologics were searched in Australia, Canada, Germany, Italy, France, the Netherlands, Sweden, the United Kingdom, and the United States. Assessments were included if they contained clinical and health economic information.

Results: Of the 70 HTAs found, 31 were included in this assessment. Twenty-six were single technology assessments (STAs) and 5 were multiple technology assessments (MTAs). No assessments were found for Italy, Germany, France, or the United States. Clinical endpoints included in the STAs were American College of Rheumatology (ACR) scores, Disease Activity Score (DAS)-28, Health Assessment Questionnaire-Disability Index (HAQ-DI), Short Form-36, Sharp score, tender joint count, swollen joint count, proportion of European League Against Rheumatism (EULAR) responders, and Functional Assessment of Chronic Illness Therapy-Fatigue. Comparators were usually other biologics. Economic models included patient level simulation, cost minimization, stepwise, and Markov models. MTAs and STAs were similar in terms of clinical endpoints, models, and comparators. Economic analyses were usually based on cost per quality-adjusted life-years (QALY), with the exception of a Canadian HTA that included cost per ACR-50 response. Decisions for reimbursement varied depending on country-specific requirements. The most common reason for rejection was lack of optimal clinical effectiveness evidence. Additionally, a lack of evidence describing the relative benefit of a new agent against an established standard of care in the standard target population was noted. Criticisms identified by HTA agencies were a need for strong evidentiary support in indirect comparisons, target population not represented in the trial data submitted, preference for country-specific utilities over mapping utilities with HAQ-DI or DAS-28, and cost-effectiveness models not reflective of current medical practice.

Conclusion: Future HTA submissions need to provide clear evidence of clinical effectiveness in the appropriate target population and against established standards of care. Economic models that are reflective of current medical practice, including the use of appropriate comparators, consideration of direct measurement of utilities with an evaluation of time horizon that is 5 years and beyond, and measurement of outcomes using cost-per-QALY approaches, may be more successful with HTA agencies.

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Validation of Diagnostic and Procedural Codes for Identification of Incident Cardiovascular Disease in Subjects with Rheumatoid Arthritis.

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Background/Purpose: The use of International Classification of Diseases, Clinical Modification, Ninth Revision (ICD-9-CM) and Current Procedural Terminology (CPT) codes can be helpful in performing health services research, implementing clinical guidelines, and monitoring health care utilization. However, the accuracy of cardiovascular (CV) event-relevant codes has not been adequately validated for the purpose of identifying incident rather than prevalent CV disease. We examined a population at risk for CV disease (elderly subjects with rheumatoid arthritis) in order to assess the validity of these codes.

Methods: Subjects who are enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) prospective registry were included if their records in either the inpatient or outpatient treatment administrative databases contained a "primary/reason for visit" ICD-9-CM diagnosis code, ICD-9-procedure code, or CPT code relating to myocardial infarction (MI), stroke, coronary artery bypass graft (CABG) surgery, or percutaneous coronary intervention (PCI). For convenience, we limited this study to the Dallas, Omaha, and Denver VA sites. This coding was compared with a gold standard case definition for CV events, determined by medical record review using a structured chart abstraction instrument for incident MI, stroke, PCI, and CABG within a 3 month window of the code being assessed. The positive predictive value (PPV) was calculated for each of the included codes, and any individual diagnostic or procedural code with a PPV >60% was included in a composite coding algorithm for each clinical condition.

Results: We evaluated 158 instances of 21 codes. PPV for the codes for incident disease/procedures varied between 0–100% (see Table). Composite coding algorithms resulted in PPV values ranging from 72–100%. No false positive cases were identified for any of the CABG and PCI procedure codes (33 instances examined).

Table. Positive predictive values for incident cardiovascular event codes

Event	Code	TP (n)	FP (n)	PPV	95% CI	
Acute MI ICD-9-CM						
	410.x	12	3	0.80	0.52	0.96
	411.x	3	4	0.43	0.10	0.82
	412.x	1	8	0.11	0.00	0.48
	413.x	6	4	0.60	0.26	0.88
	414.x	3	19	0.14	0.03	0.35
	429.2	0	4	0.00	0.00	0.60
	v45.81	0	10	0.00	0.00	0.31
Composite MI (410.x, 413.x)		18	7	0.72	0.51	0.88
Stroke ICD-9-CM						
	433.11	1	1	0.50	0.01	0.99
	433.91	0	1	0.00	0.00	0.98
	434.91	9	0	1.00	0.66	1.00
	435.x	5	5	0.50	0.19	0.81
	436.x	3	11	0.21	0.05	0.51
	437.9x	0	2	0.00	0.00	0.84
	438.x	5	5	0.50	0.19	0.81
Composite Stroke(434.91)		9	0	1.00	0.66	1.00
CABG ICD-9-CM procedure						
	36.1x	10	0	1.00	0.69	1.00
PCI						
ICD-9-CM procedure		**20**	**0**	1.00	0.83	1.00
	36.06	1	0	1.00	0.25	1.00
	36.07	10	0	1.00	0.69	1.00
	0.66	9	0	1.00	0.66	1.00
CPT		**3**	**0**	1.00	0.29	1.00
	929.73	1	0	1.00	0.25	1.00
	929.8	1	0	1.00	0.25	1.00
	929.95	1	0	1.00	0.25	1.00
Composite PCI (all codes)		23	0	1.00	0.85	1.00

Key: TP= true positives; FP=false positives; PPV=positive predictive values; 95% CI=95% confidence interval; Acute MI=acute myocardial infarction; CABG=coronary artery bypass graft; PCI=percutaneous coronary intervention; CPT= Current Procedural Terminology; ICD-9-CM International Classification of Diseases, Clinical Modification, Ninth Revision

Conclusion: Validation of diagnostic and procedural codes allows for identification of incident rather than prevalent CV disease in RA patients. Proposed composite algorithms demonstrate improvements over prior attempts to validate diagnostic and procedural codes for this purpose and will lead to the improved detection of incident CV events in RA patients. The ability to detect incident CV events using trustworthy codes may further efforts in health services research, guideline implementation, and health care utilization.

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The 2010 Rheumatoid Arthritis Criteria Versus the 1987 Rheumatoid Arthritis Criteria: Will the Real Criteria Please Stand up!

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Background/Purpose: The 1987 American College of Rheumatology (ACR) classification criteria for Rheumatoid Arthritis (RA) was revised in 2010 by the ACR/European League Against Rheumatism (EULAR) to identify patients with earlier disease and to incorporate anti-cyclic citrullinated peptide (anti-CCP) results. Our aim was to evaluate the usefulness of the 2010 ACR/EULAR RA classification criteria for identification of RA in a large cross-sectional cohort and to determine the characteristics of those that do not fulfill the new criteria.

Methods: We conducted an analysis of the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry (N=606) to determine whether subjects met the 1987 and/or 2010 RA classification criteria. Subjects enrolled in RACER have RA based on the judgment of a treating physician and a second reviewer. Clinical data from the registry including age, sex, race, disease duration, disease activity score-28 joint count (DAS28), clinical disease activity index (CDAI), and laboratory measures (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and anti-CCP) were compared between groups. All variables of each criterion were compared for differences between groups. Statistical analysis was performed with Kruskal-Wallis and Pearson Chi-Square tests.

Results: The majority of RACER subjects met both classification criteria (88.3%) (see Table). The rest met either "1987 only" (4.6%), "2010 only" (4.5%), or neither criteria (1.8%). There were no significant differences between groups in demographics, disease activity (DAS28 and CDAI) and CRP but there were marked differences in disease duration, ESR, RF, and anti-CCP. There were significant differences between the "1987 only" and "2010 only" groups in morning stiffness (85% vs 7%; p=0.0120), having >10 joints affected (0% vs 52%; p<0.0001) and anti-CCP positivity (9% vs 58%; p<0.0001).

Table 1. Group Comparison of Each Domain of the 1987 and 2010 Rheumatoid Arthritis Criteria in RACER subjects (n=606)

	Patients meeting 1987 and 2010 criteria (n=535)	Patients meeting 1987 criteria only (n=33)	Patients meeting 2010 criteria only (n=27)	Patients meeting Neither criteria (n=11)	*P* value
RF, Positive	92%	25%	15%	36%	<0.0001
Mean ±SD	285.1 ± 663.4	13.54 ± 13.2	13.0 ± 13.2	23.3 ± 31.3	<0.0001
Median	84	5	5	5	
CCP, Positive	83%	9%	58%	27%	<0.0001
Mean ±SD	235.9 ± 382.2	3.6 ± 4.8	110.2 ± 218.4	27.7 ± 74.1	<0.0001
Median	100	2	13.5	2	
ESR, Abnormal	59%	32%	39%	20%	0.003
Mean ±SD	38.7 ± 29.8	24.3 ± 26.5	27.8 ± 32.8	23.8 ± 32.6	0.002
Median	33	16	11	12	
CRP, Abnormal	55%	48%	48%	45%	0.73
Mean ±SD	2.56 ± 4.71	1.23 ± 1.8	1.32 ± 2.09	1.24 ± 1.58	0.04
Median	0.90	0.64	0.45	0.70	
2010,1 large joint	64%	64%	59%	64%	0.978
2–10 large joints	59%	61%	52%	73%	0.691
1–3 small joints	100%	100%	93%	73%	<0.0001
4–10 small joints	85%	85%	74%	45%	0.003
>10 joints	38%	0%	52%	0%	<0.0001
≥6 weeks	99%	100%	100%	91%	0.154
1987,≥3 joints	99%	100%	89%	82%	<0.0001
Hand arthritis	99%	97%	89%	55%	<0.0001
Symmetric	98%	100%	85%	73%	<0.0001
Morn.stiffness	37%	85%	7%	27%	0.012
Nodules	14%	0%	0%	0%	<0.0001
Rad. changes	38%	27%	4%	0%	<0.0001

RACER: Rheumatoid Arthritis Comparative Effectiveness Research; SD: standard deviation; RF: rheumatoid factor (IU/ml); CCP: Anti-cyclic citrullinated protein antibody (EU); ESR: erythrocyte sedimentation rate (mm/hr); CRP: C-reactive protein (mg/dL)

Conclusion: Our patients represent a "real world" RA cohort with a wide-range of disease duration and variable disease activity. Patients not fulfilling the 2010 criteria tended to have a low number of joints affected and seronegative disease. The differences between groups are due to the individual features of each

criterion as some domains (morning stiffness, markers of longer disease duration (nodules and x-ray changes)) are not captured in the 2010 criteria and likewise some features are not captured in the 1987 criteria (anti-CCP). Our results support the idea that studies should consider using both criteria since a subset of patients with what would be defined as RA using the 1987 criteria would be missed if the 2010 criteria were used exclusively.

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Sensitivity and Specificity of the American College of Rheumatology and Europe League Against Rheumatism Response Criteria in Rheumatoid Arthritis for Changes Important to Patients: Is An ACR20 Meaningful?

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Background/Purpose: ACR and EULAR response criteria are widely accepted outcomes in rheumatoid arthritis (RA) clinical trials, but many question whether ACR20 responses represent important improvement in RA status, and emphasize ACR50 and ACR70 responses. It is not known how well response criteria correspond to changes that are clinically meaningful to patients. We investigated the sensitivity and specificity of ACR and EULAR responses to reflect patients' subjective assessment of improvement in RA activity.

Methods: In this prospective longitudinal study, we enrolled adults with RA who had active arthritis (evidenced by six or more tender joints and physician judgment) and were either starting a new medication or undergoing a dose escalation of their anti-rheumatic medication. Participants were examined twice, at baseline and at 1 month (for those treated with prednisone) or 4 months later (all others). At each visit we performed joint counts, physician global assessment, ESR, CRP, patient global assessment, HAQ disability index and pain scales. At the follow up visit, we asked patients to report if their overall arthritis status was improved, unchanged or worse, and computed ACR and EULAR responses. We used patient-rated global improvement as the standard.

Results: We enrolled 214 patients (75% women, median duration of RA 6.5 years, mean age 52 years). At entry, the mean swollen joint count was 16, tender joint count 24, CRP 1.9, ESR 39, and DAS28 6.09. 136 (64%) patients reported improvement, 56 (26%) reported no change, and 22 (10%) said they were worse at the follow up visit. ACR20 responses were present in 41%, but only 8% had ACR70 responses (table). Specificity was high for each response criteria, but sensitivity was no higher than 0.55 (table).

	Prevalence	Sensitivity	Specificity	Kappa
ACR 20	41%	.55 (.46, .64)	.83 (.75, .92)	.34 (.22, .46)
ACR 50	16%	.24 (.17, .32)	.97 (.93, 1.0)	.17 (.10, .24)
ACR 70	8%	.11 (.06, .18)	.99 (.96, 1.0)	.08 (.03, .13)
EULAR Moderate	42%	.55 (.46, .64)	.81 (.71, .91)	.31 (.19, .43)
EULAR Good	9%	.11 (.05, .17)	.94 (.88, 1.0)	.04 (0, .10)

Sensitivity and specificity of the ACR20 was similar in subgroups by age, gender, and ethnicity, but sensitivity (0.64) and specificity (0.60) was lower in those with RA of 2 years or less. Many patients who reported improvement but failed to meet ACR20 criteria did so because they lacked 20% improvement in both tender and swollen joint counts.

Conclusion: An ACR20 response has a high specificity to detect changes in RA status rated as important by patients, suggesting that improvements of this degree capture changes that are meaningful to patients. EULAR responses were comparable to ACR responses.

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Can American College of Rheumatology Criteria for Rheumatoid Arthritis Be Assessed Using Self-Report Data?—Comparison of Self-Reported Data with Chart Review.

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Background/Purpose: To measure the agreement between self-report data and chart review to evaluate ACR diagnostic criteria for RA.

Methods: Participants were recruited from a longitudinal study of care for RA. Cases initially identified using administrative data, had agreed to participate in yearly surveys about RA. Complete medical records were obtained from their rheumatologist (rheum.), internist or family physician (FP) (for cases not followed by rheum.) and participants were mailed a self-administered survey designed to elicit specific ACR criteria for RA (presence (ever, for $>$ 6 weeks) of AM stiffness $>$1 hr, specific joint involvement (swelling) on a homunculus, presence of rheumatoid nodules, and RF results). We evaluated whether cases met 1987 ACR criteria for RA, using traditional (4/7 criteria) and "classification tree" schema. Medical records were reviewed by a rheumatologist to determine RA status based on the same criteria. Sensitivity, specificity, positive predictive value (PPV) of self-report compared to chart review (gold standard) were calculated, as well as agreement between self-report and chart review using kappa statistic and percent agreement.

Results: Of the 409 participants in the longitudinal study, permission to access their medical records was granted in 330 (81%), records were successfully obtained in 307 (75%) (165 from rheumatologists, 121 FPs, 21 internists). Response rate to the self-administered questionnaire was 74% (N=302). 216 with both medical records and questionnaire data are included in the analysis (69.8% female; mean (SD) age 65.5 (38); 82% had RA diagnosis according to impression of rheumatologist reviewing the chart). Using ACR criteria from chart review as the "gold standard", ACR criteria from self-reported data had a sensitivity of 68%, PPV of 70%, specificity of 48%, based on traditional ACR criteria. Using the "classification tree" schema, sensitivity improved to 76%, PPV 79%, with specificity of 44%. Agreement in RA diagnosis between self-reported and chart review data was fair using tree criteria (κ=0.238 [95% CI] [0.100–0.375]; 68% perfect agreement), and slight using traditional criteria (κ=0.115 [−0.020–0.25]; 60% agreement). Particularly problematic using self-reported data was eliciting rheumatoid factor (RF) status as 48% reported not knowing the result of their test. A limitation of our study was the large number of cases with records obtained from FPs, who may not routinely record information required to fulfill ACR RA criteria. Thus, we repeated the analysis, using only charts from rheumatologists. For traditional (4/7) criteria, sensitivity improved to 73%, but specificity was lower at 30%, with perfect agreement in 65% and κ=0.025 [−0.14–0.19]. For tree criteria, sensitivity was 81%, specificity 41%, with perfect agreement in 75% and κ=0.18 [0.001–0.37].

Conclusion: Overall, assessing ACR diagnostic criteria for RA using self-report data does not yield similar results to using chart review. Using the "classification tree" version of the criteria, and rheumatologist charts as gold standard, provided the best diagnostic accuracy results and best

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Comparison of the 1987 American College of Rheumatology Criteria and the 2010 American College of Rheumatology/European League Against Rheumatism Criteria in Patients with Established Rheumatoid Arthritis.

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Background/Purpose: The new 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria were developed to improve the ability to classify people with early rheumatoid arthritis (RA). However, the ability of these criteria to classify patients with established RA has not been evaluated widely. If the 2010 criteria are to replace the 1987 criteria in epidemiological studies of RA with mostly prevalent RA cases, it is important to ensure that they accurately classify patients with established as well as early disease. In this study we evaluated the sensitivity and specificity of the 2010 criteria and the agreement between the 1987 and 2010 criteria in a cohort of patients with established RA.

Methods: Participants were recruited from a longitudinal study of care for RA. Prevalent RA cases initially identified using administrative data, had agreed to participate in yearly surveys about RA. Complete medical records were obtained from their rheumatologist, internist or family physician (if not followed by a rheumatologist). Medical records were reviewed by a rheumatologist (MVG) who evaluated whether cases met 1987 ACR criteria for RA, using traditional (4/7 criteria) and "classification tree" schema, and 2010 ACR/EULAR criteria for RA and also recorded her clinical impression from reviewing the chart. Sensitivity, specificity, positive predictive value (PPV) of both criteria compared to study rheumatologist's impression (gold standard) were calculated. Agreement between RA diagnosis using 1987 and 2010 criteria was calculated using kappa statistic (and 95% CI) and percent perfect agreement.

Results: Of the 409 participants in the longitudinal study, 330 gave permission to access their medical records, 307 records were successfully

obtained, but only 203 had adequate information to assess criteria and were included in the analysis (143 from rheumatologists; 54 family physicians; 4 internists and 1 ortho). The sample included 69.8% female; mean (SD) age: 65.5 (9.38) years); mean RA duration: 11 years. Using study rheumatologist impression as the "gold standard", RA diagnosis according to 1987 criteria (either the traditional or tree criteria) had a sensitivity of 83.6%, PPV of 95.9%, and specificity of 92.1%. Using the 2010 criteria, sensitivity was 86.3%, PPV 87.7% and specificity 81.0%. Agreement in RA diagnosis between the 2010 criteria and 1987 criteria was high with 86% perfect agreement and kappa = 0.70 (95% CI: 0.60–0.80).

Conclusion: Our study revealed that the 2010 ACR/EULAR criteria for diagnosis of RA can be used in assessing patients with established RA with sensitivities and PPV comparable to the 1987 criteria.

		1987 RA criteria	
2010 RA criteria		**Yes**	**No**
Yes	117	5	122
No	23	58	81
	140	63	

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Association of Funding Source with Characteristics of Clinical Trials of Rheumatoid Arthritis. Nasim A. Khan[1], Manisha Singh[1], Horace Spencer[2] and Karina D. Torralba[3]. [1]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, [2]University of Arkansas for Medical Sciences, Little Rock, AR, [3]University of Southern California-Los Angeles County Medical Center, Los Angeles, CA

Background/Purpose: A dramatic increase in pharmaceutical industry funding/support for clinical trials (CTs) has occurred in recent decades. The U.S. National Library of Medicine established ClinicalTrials.gov (CTG) registry in 2000 as an Internet-based publicly accessible registry. Funding information is a mandatory data needed for CTG registration. Our aim was a) to determine funding sources of CTs of rheumatoid arthritis (RA), and b) whether funding source is association with characteristics of RA CTs.

Methods: The CTG registry was queried on June 12, 2011 using "Search Term" field for "Rheumatoid Arthritis". CTs with only RA as study condition were eligible. Information on the study title, sponsor, dates (start, registration, completion), type, design, phase, endpoint(s), intervention(s), subject enrollment (planned or completed) and outcome were obtained. Lead sponsors were classified as industry (manufacturer of experimental intervention drug or device) or non-profit (governmental organizations, universities, foundations etc). 47 (6%) studies had both industry and non-profit funding, but for the purpose of analysis we have used lead sponsor as designated by study investigators/sponsors at CTG. Experimental study interventions were categorized as traditional disease modifying anti-rheumatic drugs (DMARD), biologic (alone or in combination with DMARD), small molecule (alone or in combination with DMARD) and others. Chi-square, Fisher's exact, Likelihood ratio test or Mann-Whitney U test were used to analyze results.

Results: Of 1210 CTs, 783 (64.7%) CTs were eligible. Lead sponsorship was by industry in 590 (75.3%) CTs, and 193 (24.7%) by a non-profit source. Industry-funded studies were mostly interventional, with safety and/or efficacy cited as their purpose, and have larger number of study subjects. Among interventional studies, industry funded CTs were more likely to be Phase 1–3, use a biologic or small molecule as the experimental intervention compared to non-profit source studies (Table). A similar proportion of interventional trials had random assignment of subjects, but industry-funded CTs were more likely to be double-blinded. Non-profit funded interventional studies were of significantly longer duration.

Table. Funding source and characteristics of RA clinical trials.

	Lead Study Sponsor		P**
	Industry (N= 590)*	**Non-profit (N = 193)***	
Study type	.	.	.
Interventional	504 (74.1)	143 (85.4)	.
Observational	86 (25.9)	50 (14.6)	<0.001
Subjects enrollment	Median (Q1–Q3)	Median (Q1-Q3)	<0.001
Interventional	160 (56–320)	60 (34–131)	<0.001
Observational	381 (131–1782)	110 (40–382)	
Experimental intervention***	.	.	.
Traditional DMARD	18 (3.6)	12 (8.4)	.
Biologic	361 (71.6)	49 (34.3)	.
Small molecule	72 (14.3)	1 (0.7)	.
Others	53(10.5)	81 (56.6)	<0.001
Study phase***	.	.	.
0 or 1	60 (12)	9 (8.9)	.
1–2 or 2	188 (37.6)	30 (29.7)	.
2–3 or 3	186 (37.2)	19 (18.8)	.
4	66 (13.2)	43 (42.6)	<0.001
Study purpose***	.	.	.
Efficacy	39 (8.7)	60 (48.8)	.
Safety	63 (14)	3 (2.4)	.
Efficacy/safety	309 (68.7)	54 (43.9)	.
Others	39 (8.7)	6 (4.9)	<0.001*
Subject allocation***	.	.	.
Random	379 (75.2)	106 (74.1)	.
Non-random	125 (24.8)	37 (25.9)	0.794
Masking****	.	.	.
Double-blind	322 (85)	65 (61.3)	.
Single-blind	9 (2.4)	18 (17)	.
Open-label	48 (12.6	23 (21.7)	<0.001)
Study duration, months*****	Median (Q1–Q3)	Median (Q1–Q3)	.
Interventional	22 (14–38.5)	29 (19.5–48.5)	<0.001
Observational	32 (15–58.5)	25 (12–70)	0.569

* n (%) unless stated otherwise; ** Using Chi-square test, Fisher's exact test, Likelihood ratio test, or Mann-Whitney U test as appropriate ***For interventional studies only; **** For randomized clinical trials only; *****For studies with "complete" status only.

Conclusion: Funding source was associated with significant differences in study design, duration, subject enrollment and experimental intervention. The balance of funding of clinical trials (industry versus non-profit) has important implications for generation of evidence to guide clinical care.

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Achieving Sustained Remission in Rheumatoid Arthritis Results in Reduced Long-Term Health Care Costs. Cheryl CM Barnabe[1], Nguyen Xuan Thanh[2], Arto Ohinmaa[3], Joanne Homik[3], Susan G. Barr[1], Liam Martin[1] and Walter P. Maksymowych[3]. [1]University of Calgary, Calgary, AB, [2]Institute of Health Economics, Edmonton, AB, [3]University of Alberta, Edmonton, AB

Background/Purpose: Remission status is of functional benefit to individual rheumatoid arthritis (RA) patients. Achieving remission may require a considerable initial investment when considering costs associated with more frequent physician visits, medication titration and ancillary tests. This investment however could result in long-term cost reduction due to decreased RA morbidity over time. We have linked administrative data with a clinical dataset to examine healthcare system costs of achieving various disease remission states.

Methods: We linked data on healthcare utilization (physician visits, outpatient department visits, and hospitalizations) from a provincial administrative database (years 2004–2009) with clinical data from a prospective cohort of biologic treated patients (n=1,086, mean age 54 years). Remission status was classified according to the DAS28 score by the following categories: i) sustained remission (DAS28 score ≤2.6 for >6 months; ii) sustained low disease activity (DAS28 score >2.6 but ≤3.2 for >6 months); iii) brief remission (DAS28 score ≤2.6 for ≤6 months); and iv) never achieving remission (DAS28 ≥2.6). We examined both total healthcare costs and costs directly attributable to RA for each category of clinical response, standardized to 2008 Canadian dollars. A propensity score model and quantile regression was used to account for confounding by individual variables affecting healthcare utilization, including specific therapy received, baseline function, smoking, age, sex, disease duration and medical comorbidities.

Results: Median cost differences between patients in sustained remission, sustained low disease activity, and a brief period of remission were not significantly different over the five year study period (Table 1). Patients in sustained remission had significantly reduced total and RA-attributable healthcare costs relative to those patients never achieving a remission period over the five years, with a savings of $616 (95%CI 90–1141; p<0.001) per patient. Costs directly attributable to RA were constant in all remission categories at approximately 25%.

Table 1. Median Study Period Healthcare Costs per Individual, by Remission Status

	Median Total Cost, 2008 Canadian $	**% of Costs Directly Attributable to RA**
Sustained Remission (n=271)	2575	26.4
Sustained Low Disease Activity (n=87)	2832	25.9
Brief Remission (n=222)	2712	24.3
No Remission (n=470)	3191	25.7

Conclusion: Healthcare system savings are observed in RA patients achieving remission or a low disease activity state. RA-attributable costs are constant across response categories. Ongoing observation of biologic treated patients longitudinally may identify more significant cost savings associated with a reduction in long-term severe morbidity.

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Responsiveness of Health-Related Quality-of-Life Measures in Rheumatoid Arthritis Randomized Controlled Trials. Vibeke Strand[1], Kavita Gajria[2], Paul Williams[3], Amy Barrett[3], Ancilla Fernandes[2] and Fabio Magrini[4]. [1]Stanford University, Portola Valley, CA, [2]MedImmune LLC, Gaithersburg, MD, [3]RTI Health Solutions, Research Triangle Park, NC, [4]MedImmune Ltd, Cambridge, United Kingdom

Background/Purpose: As the number of available rheumatoid arthritis (RA) treatments increases, endpoints that can sufficiently discriminate between active treatments become valuable. Standard disease activity measures, such as the American College of Rheumatology (ACR) criteria, may not be sensitive enough to discriminate between active treatments in comparative randomized controlled trials (RCTs). Therefore, in addition to disease activity measures, health-related quality-of-life (HRQL) measures could be used to discriminate between treatments. We evaluated the responsiveness of HRQL measures in RA RCTs to find those most likely to discriminate between treatments.

Methods: A total of 150 randomized, placebo-controlled trials published between 2000–2010 were identified for potential inclusion. As general health status (measured by Short Form-36 [SF-36]) and fatigue (measured mostly by the Functional Assessment of Chronic Illness Therapy [FACIT-Fatigue] or Fatigue Visual Analog Scale [VAS]) were commonly evaluated in RA clinical trials, responsiveness of these endpoints was assessed by calculating effect size (ES). To allow between-study comparisons, relative responsiveness (RR) for SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) was calculated as a ratio of their ES to that of the Health Assessment Questionnaire (HAQ). Similarly, RR for 8 SF-36 domains was assessed using the SF-36 mental health (MH) domain as a reference. For evaluating RR of fatigue scales, the SF-36 Vitality (VT) scale was used as a reference. Endpoint RR was further compared among 3 subpopulations: disease-modifying antirheumatic drug (DMARD)–naive, DMARD inadequate responders (IR), and anti–tumor necrosis factor (TNF) failures.

Results: For PCS, 40 ESs were calculated from 21 RCTs; median ES was 0.81. PCS ES was greater than HAQ ES in 14 of 25 (56%) comparisons; median RR was 1.06. For MCS, 31 ESs were calculated from 16 RCTs; median ES was 0.27. MCS ES was less than HAQ ES in all 16 comparisons; median RR was 0.18. For each of the 8 SF-36 domains, 20 ESs were calculated from 10 trials. Notably, Bodily Pain (BP; median ES, 1.0) and Role Physical (RP; median ES, 0.76) were most responsive to treatment (RR, >2 compared with MH). VT (median ES, 0.66) and Physical Function (median ES, 0.56) were of intermediate responsiveness (RR, 1.5–2). For Fatigue VAS, 10 ESs were calculated from 6 trials; median ES was 0.68 and median RR was 1.07. For FACIT-Fatigue, 7 ESs were calculated from 6 trials; median ES was 0.64 and median RR was 1.15. RR of all endpoints was comparable across the 3 subpopulations with the exception of MCS, where responsiveness was higher in anti-TNF failure trials but still less than HAQ.

Conclusion: Study results showed that MCS was less responsive, and PCS was generally more responsive, than HAQ. Of the 8 SF-36 domains, BP and RP were the most responsive. Fatigue had comparable responsiveness to SF-36 Vitality. With the exception of MCS, the findings did not appreciably change across DMARD naive, DMARD IR, and anti-TNF failure populations. Future studies should consider SF-36 PCS, BP, RP and fatigue as potential tools for discriminating between active treatments in RCTs.

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A Comparison of RAPID3 Response Criteria and EULAR-DAS28 Response Criteria in the DANCER and REFLEX Rituximab Clinical Trials. Martin J. Bergman[1], Adam Turpcu[2], Pamela Wong[2], Carol Chung[2] and William Reiss[2]. [1]Taylor Hospital, Ridley Park, PA, [2]Genentech, South San Francisco, CA

Background/Purpose: In an effort to improve patient outcomes, an increasing number of physicians are treating Rheumatoid Arthritis (RA) patients to a disease activity target. Targets are typically based on composite indices of core data set measures such as the DAS28 (which is comprised of the TJC, SJC, ESR/CRP, and patient global) and the RAPID3 (which is comprised of the patient pain, patient global, and HAQ). However, there is no consensus as to which index should be used. It is important to understand how different targets compare.

Objectives: To compare EULAR response criteria with proposed RAPID3 response criteria in the REFLEX[1] and DANCER[2] clinical trials.

Methods: Patients treated with rituximab (1000mg) were classified as having EULAR good, moderate or no responses at the time of primary endpoint analysis (week24) in both trials. EULAR response categories[3] are defined in terms of reduction in DAS28-ESR and final DAS28-ESR attained as follows:

Good = decrease >1.2 units AND final <3.2;

Moderate = decrease >1.2 AND final ≥3.2, OR decrease of 0.6–1.2 AND final ≤5.1;

No response = decrease <0.6, OR decrease of 0.6–1.2 AND final >5.1.

Proposed RAPID3 response categories are defined as follows:

Good = decrease >3.6 units AND final <6;

Moderate = decrease >3.6 AND final ≥6, OR decrease of 1.8–3.6 AND final ≤12;

Poor = decrease <1.8, OR decrease of 1.8–3.6 AND final >12.

Responses were pooled across both trials. Comparisons involved cross-tabulations and weighted kappa statistics.

Results: Moderate agreement[4] was observed between the EULAR-DAS28 response criteria and the proposed RAPID3 response criteria (weighted Kappa = 0.50). A greater proportion of patients achieved a good response on the RAPID3 (30.3%) relative to the DAS28 (19.9%) with roughly half (49.6%) of the good RAPID3 responders being defined as moderate responders by the DAS28. A similar proportion of patients were classified as being poor responders by both the DAS28 and the RAPID3.

Table. EULAR Response Criteria vs RAPID3 Response Criteria in the DANCER and REFLEX clinical trials at 24 weeks.

		RAPID3 Good Response	RAPID3 Moderate Response	RAPID3 Poor Response	DAS28 Totals by Response Category
DAS28	Good Response	67 (14.8%)	18 (4.0%)	5 (1.1%)	**90 (19.9%)**
	Moderate Response	68 (15.0%)	117 (25.9%)	47 (10.4%)	**232 (51.3%)**
	No Response	2 (0.4%)	34 (7.5%)	94 (20.8%)	**130 (28.8%)**
RAPID3 Totals by Response Category		**137 (30.3%)**	**169 (37.4%)**	**146 (32.3%)**	**452 (100%)**

Each box displays the number of patients meeting RAPID3 response criteria and the corresponding EULAR-DAS28 response criteria. For example, the top-left box illustrates that 67 patients were classified as good responders by both RAPID3 and EULAR-DAS28 criteria.

Conclusion: Our findings suggest that patients are more likely to be classified as good responders under proposed RAPID3 response criteria relative to the EULAR response criteria. Substantive differences may exist between targets derived from different indices. To enable accurate between-patient and within-patient comparisons, it is important that practices maintain consistent targets where possible.

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Patients' Ratings of Clinically Important Improvement in Pain, Global Assessment, and Physical Function in Rheumatoid Arthritis. Michael M. Ward, Lori C. Guthrie and Maria I. Alba. NIH, NIAMS, Bethesda, MD

Background/Purpose: Criteria for improvement in rheumatoid arthritis (RA) have not emphasized patients' perspectives. We sought to identify the amount of change in measures of pain, global arthritis assessment, and physical functioning that patients with RA consider an important change.

Methods: We enrolled adults with active RA (6 or more tender joints and physician judgment of activity) who were either starting a new anti-rheumatic medication or who were having escalation of their current medication regimen. Patients had physical examinations and completed a pain visual analog scale (0 – 100), global visual analog scale (0 – 100) and the Health Assessment Questionnaire Disability Index (HAQ; 0 – 3). They were reassessed after either 1 month (for those started on prednisone) or 4 months (all others). At the followup visit, patients were asked to report if they had improvement or worsening in each symptom. These judgments were related to measured changes in pain, patient global assessment, and HAQ.

Results: We studied 215 patients (mean age 52; 75% women; median duration of RA 7 years; 74% seropositive). At entry, they had a mean pain score of 59 ± 25, mean global assessment of 55 ± 25, and a mean HAQ score of 1.3 ± 0.7. Fifty-one patients were treated with prednisone, 64 patients were treated with a new disease-modifying medication, and 100 patients had dose escalation of current medications.

At follow-up, 61% reported improvement in pain, 63% reported improvement in global arthritis status, and 56% reported improvement in function. Changes in measured pain scores, global scores, and HAQ differed among patients who reported improvement, no change, or worsening in each aspect of health status.

	Mean (SD) Change in Pain	Mean (SD) Change in Global Assessment	Mean (SD) Change in HAQ
Improved	−26.6 (31.1)	−22.3 (25.4)	−.53 (.59)
No Change	−8.0 (20.6)	−7.0 (20.6)	−.08 (.42)
Worsened	3.5 (22.7)	0.8 (22.7)	.05 (.35)
p	<.0001	<.0001	<.0001

Of those with improvement, 89% rated the improvement as at least "moderately important" for each measure. Areas under receiver operating characteristic curves distinguishing improvement from no change/worsening were.74 for pain,.72 for global assessment, and.75 for HAQ. If the criterion for improvement were required to have a specificity of at least 0.75, an absolute decrease in pain score of 16, an absolute decrease in patient global assessment of 13, and an absolute decrease in HAQ of 0.375 were the cutpoints with maximum sensitivity (0.62, 0.62, and 0.59, respectively).

Conclusion: Patient ratings can accurately distinguish improvement in pain, global assessment, and functioning from no change or worsening. In this sample, decreases in pain score of 16 or more, decrease in global assessment of 13 or more, and decreases in HAQ of 0.375 or more, were specifically associated with clinically important improvement.

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Employability-Adjusted-Life-Years in Patients with Rheumatoid Arthritis Treated with Golimumab Plus Methotrexate or Methotrexate Alone. Chenglong Han[1], Tim Gathany[2], Neeta Tandon[3] and Elizabeth C. Hsia[4]. [1]Johnson & Johnson Pharmaceutical Services, LLC, Malvern, PA, [2]Johnson & Johnson Pharmaceutical Services, LLC, Horsham, PA, [3]Johnson & Johnson North America Pharmaceuticals, Horsham, [4]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC/Univ. of Pennsylvania School of Medicine, Malvern, PA

Background/Purpose: Work disability is a major economic consequence among patients with rheumatoid arthritis (RA). Treatments that inhibit disease progression may delay the time when patients exit from the labor force due to disability. The purpose of this study was to estimate and compare employability-adjusted-life-years (EALYs) over time for RA patients in the GO-FORWARD clinical trial who were treated with GLM + methotrexate (MTX) vs. MTX alone.

Methods: GO-FORWARD was a double-blind, placebo controlled study of adult patients with active RA (>4 tender joints and 4 swollen joints) and inadequate response to MTX. In this analysis, we included patients aged less than 65 years and who received placebo + MTX (MTX Grp) or golimumab (50- or 100mg) q4 wks + MTX (GLM Grp). Self reported employment status and physical function measured by Health Assessment Questionnaire (HAQ) were collected from baseline over 3 years. Employability status was defined as 'unemployable' if a patient was unemployed and felt unable to work even if a job was available or 'employable' if patients were employed or felt well enough to work if a job was available. Long-term employability was estimated using a logistic regression model based on age, gender and HAQ score. HAQ was derived by a progression rate of 0.045 /per year for a person being treated with MTX and by 0 (base case) to 0.025 per year (sensitivity analysis) for a patient on biologics (GLM).[1]

Results: At baseline, the mean (SD) HAQ score was 1.36 (0.67); 61.9% of patients under age 65 were employable, and 44.8% of patients were actually employed. At week 24, the average HAQ score was 1.08 in MTX group and 0.92 in GLM group; 33% of patient unemployable at baseline became employable at week 24 in GLM group compared to 15% in the MTX group (p=0.04). GLM group maintained the HAQ improvement from 0.92 at week 24 to 0.88 at week 160. In the logistic regression model by using the derived HAQ score, age, and gender, in the base case scenarios, over 10 years period for a RA patient cohort with an average of 50 years of age, GLM-treated patients had expected employability adjusted life years of 5.92 for females and 7.15 for males, compared to 4.96 for females and 6.28 for males in MTX-treated patients, an increase of 0.96 years (19.2%) in females and 0.87 years (13.8%) in males. Sensitivity analysis demonstrated an improvement of 0.81 employability adjusted life years in males (16.4%) and 0.74 years (11.8%) in females in GLM-treated patients vs. in MTX-treated patients.

Conclusion: Results of analysis on the employability-adjusted-life-years showed that patients treated with GLM+MTX can realize improvement in employability over time.

Reference:

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Single Item Literacy Screening Questions Are Strongly Associated with Functional Status Among Rheumatoid Arthritis Patients. Liron Caplan[1], Kaleb D. Michaud[2], Frederick Wolfe[3] and Joel M. Hirsh[4]. [1]Denver VA and University of Colorado, Aurora, CO, [2]Univ of Nebraska Med Ctr & National Data Bank for Rheumatic Diseases, Omaha, NE, [3]National Data Bank for Rheumatic Diseases, Wichita, KS, [4]Denver Health Med Ctr, Denver, CO

Background/Purpose: Health Literacy (HL) has been associated with outcomes for a number of conditions and pilot data has linked HL to rheumatoid arthritis (RA) functional status. However, these studies have not adequately accounted for the large number of potential covariates that can influence rheumatoid arthritis outcomes. We examined the association of health literacy with functional status in 5,300 subjects participating in a prospective observational study, controlling for numerous important covariates.

Methods: Using linear regression, we analyzed the cross-sectional association of HL, as measured by two different validated single-item literacy-screening questions (SILS-instruction and SILS-confident), and functional status, assessed by the Health Assessment Questionnaire Disability Index (HAQ). Subjects reported demographics, comorbidities, validated estimates of social support, educational attainment, visual problems, memory problems, as well as prednisone, disease modifying antirheumatic drug, and biologic usage. A stable statistical model was constructed through the use of a backwards stepwise selection procedure with $p<0.25$ required for variable inclusion. The final model retained only those variables with $p<0.05$ and each SILS measure, as the variables of interest, were forced into the final model.

Results: Lower HL was present in 6.3% and 3.9% of subjects (per SILS-instruction and SILS-confident). Results (Table 1) were virtually identical for the two SILS instruments, when entered separately into the final model. When controlling for all covariates, lower HL was associated with a 0.369 greater HAQ score, compared to subjects with adequate HL ($p<0.001$, 95% CI 0.292–0.446). This relationship persisted, even after modeling educational attainment. Visual and memory problems were also associated with more disability, though social support demonstrated no association, after accounting for marital status.

Table 1. Multivariate regression demonstrating variables associated with Health Assessment Questionnaire

	Initial Model				Final Model			
Variable	Coef.	p	95%	CI	Coef.	p	95%	CI
Age (years)	−0.001	0.577	−0.004	0.002				
Sex (male)	−0.345	<0.001	−0.407	−0.283	−0.338	<0.001	−0.383	−0.293
Married	0.117	<0.001	0.052	0.182	0.065	0.003	0.022	0.108
SIMSS score	0.036	0.048	0.000	0.072				
Non-Hispanic White	−0.016	0.779	−0.124	0.093				
Education (years)	−0.019	0.008	−0.032	−0.005	−0.019	<0.001	−0.028	−0.010
Total Income (per $10K US dollars)	−0.048	<0.001	−0.059	−0.036	0.000	<0.001	0.000	0.000
Vision trouble	0.181	<0.001	0.111	0.251	0.174	<0.001	0.125	0.223
Thinking or memory problems	0.202	<0.001	0.141	0.263	0.185	<0.001	0.144	0.226
Comorbidity Index	0.091	<0.001	0.074	0.108	0.103	<0.001	0.091	0.114
Smoking (years)	0.002	0.060	0.000	0.004				
Smoking (ever)	0.131	0.825	−1.027	1.289				
Disease Duration (years)	0.009	<0.001	0.006	0.011	0.009	<0.001	0.007	0.011
Prednisone (current)	0.112	<0.001	0.052	0.171	0.154	<0.001	0.114	0.195
Biologic (ever)	−0.067	0.161	−0.162	0.027				
Biologic (count)*	0.087	<0.001	0.044	0.130	0.060	<0.001	0.035	0.084
DMARD (ever)	−0.050	0.567	−0.222	0.122				
Lifetime DMARD & biologic use (count)*	0.024	0.020	0.004	0.044	0.016	0.009	0.004	0.029
Good adherence to RA medications**	0.067	0.107	−0.015	0.149				
SILS-instruction ***	0.374	<0.001	0.263	0.485	0.369	<0.001	0.292	0.446
SILS-confident ****	0.359	<0.001	0.227	0.491	0.312	<0.001	0.217	0.406

SIMSS=single item measure of social support
DMARD=disease modifying antirheumatic drug
* refers to the number of different medications exposed to from the described class(es)
** Patients who report taking compliance of between 80–120% of their rheumatoid arthritis medication during last month according to the medication adherence self-report inventory (MASRI)visual analogue scale
*** Patients who responded with "often" or "always" to the question: How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?
**** Patients who responded with "a little bit" or "not at all" to the question: How confident are you filling out medical forms by yourself?

Conclusion: Health literacy was more strongly associated with functional status than prednisone use, smoking history, and biologic use, and this effect was independent of educational attainment. Health literacy may play an important role in understanding functional status in RA patients. Single-item questions amenable to use in the clinical setting may identify subjects with lower HL, who are at risk for poor RA outcomes.

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National and Regional Dosing Patterns of Tumor Necrosis Factor Blocker Therapy in Biologic-Naïve Rheumatoid Arthritis Patients in US Health Plans. Amie T. Joyce[1], Shravanthi R. Gandra[2], Kathy M. Fox[3], Timothy W. Smith[1] and Michael Pill[4]. [1]IMS Health, Watertown, MA, [2]Amgen Inc, Thousand Oaks, CA, [3]Strategic Healthcare Solutions, LLC, Monkton, MD, [4]Gemini HealthCare, Westbrook, CT

Background/Purpose: Although research using 2002–2005 data has shown higher rates of dose increases in some TNF blockers than others, the impact of more intensive cost management efforts in recent years on dosing patterns is not clear. This study examined the rates and magnitude of dose increases nationally and regionally among rheumatoid arthritis (RA) patients treated with TNF blockers between 2005–2010, when health plans began to more actively manage this class of drugs.

Methods: Based on a claims database covering approximately 78 million lives, a retrospective cohort study was conducted with commercially-insured adult RA patients who initiated treatment with a TNF blocker (adalimumab [ADA], etanercept [ETN], infliximab [INF]) between 2005–2009. Patients were excluded if they had a diagnosis for other conditions treated with TNF-blockers. Biologic-naïve patients continuously enrolled in the plan for at least 6 months before (baseline) and at least 12 months after start of anti-TNF therapy were followed for 12 months. For ETN and ADA, the maintenance (MTN) dose was the dose of the initial prescription. For INF, the MTN dose was based on the first stable dose (4th dose). Dose increases were assessed among patients using 3 methods 1) Average weekly dose: Dose increase was defined as an average weekly dose (total dispensed quantities in the study period/total days supply) that is ≥ label dose, 2) Average ending dispensing dose: Dose increase was defined as the average ending dispensing dose that is greater than the MTN dose and 3) Average dose after MTN dose: Dose increase was defined as an average dose after the MTN dose that is greater than the MTN dose. The percentages of patients with dose increases were quantified using above 3 definitions. Magnitude of dose escalation was examined by comparing the MTN and ending doses for each patient. Annual cost per patient to the health plan was computed. Statistical testing was performed using Chi-square tests.

Results: Overall, 1,420 ETN, 874 ADA, and 454 INF RA patients were included. Patients initiating ETN therapy had a significantly lower rate of dose escalation using the average weekly dose (3.9% vs. 21.4% ADA and 69.6% INF; $p<0.0001$), average ending dispensing dose method (1.1% vs. 10.6% ADA and 63.0% INF; $p<0.0001$), and average dose after MTN dose (2.8% vs. 15.7% ADA and 69.6% INF; $p<0.0001$). The rates and magnitude of dose escalation were similar for each product among the 4 US census regions. ETN had the lowest cost per treated RA patient ($18,590) compared to ADA ($23,032) and INF ($23,350).

Table 1. Proportion and amplitude of dose escalation overall and by region

	Etanercept (%) n = 1,420			Adalimumab (%) n = 874			Infliximab (%) n = 454		
Geography	Weekly dose	Avg ending	Avg after MTN	Weekly dose	Avg ending	Avg after MTN	Weekly dose	Avg ending	Avg after MTN
Nation (All Pts) (dose escalation rates)	3.9%	1.1%	2.8%	21.4%*	10.6%*	15.7%*	69.6%*	63.0%*	69.6%*
MTN Dose (mg)		50	50		20	20		55	56
Ending Dose (mg)		93	58		40	29		94	80
Magnitude of dose escalation among proportion of patient experiencing dose escalation		86.7%	15.5%		100%	44.9%		75.1%	44.9%
Northeast (dose escalation rates)	1.6%	0.3%	1.3%	20.6%*	12.5%*	15.6%*	69.2%*	65.9%*	69.2%*
MTN Dose (mg)		50	50	20	20	20		53	53
Ending Dose (mg)		100	63	40	40	32		94	80
Magnitude of dose escalation among proportion of patient experiencing dose escalation		100%	25.9%		100%	62.0%		81.7%	52.1%
Midwest (dose escalation rates)	3.2%	0.9%	2.5%	20.6%*	9.3%*	14.8%*	71.0%*	66.5%*	71.0%*
MTN Dose (mg)		50	50		20	20		57	57
Ending Dose (mg)		90	59		40	28		93	82
Magnitude of dose escalation among proportion of patient experiencing dose escalation		80.0%	18.4%		100%	38.2%		65.9%	43.4%
South (dose escalation rates)	5.3%	1.5%	3.5%	24.1%*	12.2%*	18.2%*	67.5%*	55.2%*	67.5%*
MTN Dose (mg)		50	50		20	20		54	55
Ending Dose (mg)		100	59		40	29		97	77
Magnitude of dose escalation among proportion of patients experiencing dose escalation		100%	17.2%		100%	43.8%		85.7%	42.6%
West (dose escalation rates)	6.7%	1.9%	4.8%	15.2%*	6.1%*	9.1%*	72.2%*	70.4%*	72.2%*
MTN Dose (mg)		50	50		20	20		56	57
Ending Dose (mg)		88	53		40	28		89	78
Magnitude of dose escalation among proportion of patient experiencing dose escalation		75.0%	5.4%		100%	41.0%		66.2%	43.3%
Mean annual cost per treated patient		$18,590			$23,032			$23,350	

* $p<0.0001$ compared to ETM, MTN = Maintenance Dose

Conclusion: Similar to previous published results, rates and magnitudes of dose increase differed by anti-TNF therapy. ETN patients had the lowest rates and magnitudes of dose increase across all dose increase calculation methods as compared to ADA and INF patients overall and regionally. Mean annual cost was lowest for patients treated with ETN.

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Patients with Rheumatoid Arthritis Who Are in Remission According to the New ACR/EULAR Criteria Have a Very High Functional Capacity Which Is Comparable to Healthy Subjects. Joachim Listing[1], Anja Strangfeld[1], Joern Kekow[2], Siegfried Wassenberg[3], Thilo Klopsch[4], Thomas Kohlmann[5] and Angela Zink[6]. [1]Deutsches Rheumaforschungszentrum, Berlin, Germany, [2]Univ of Magdeburg, Vogelsang-Gommern, Germany, [3]Evangelisches Fachkrankenhaus, Ratingen, Germany, [4]Rheumatologist, Neubrandenburg, Germany, [5]University Greifswald, Greifswald, Germany, [6]Deutsches Rheumaforschungszentrum and Charité University Medicine, Berlin, Germany

Background/Purpose: New definitions for remission in patients with rheumatoid arthritis (RA) were developed by the ACR and EULAR. The new criteria identify patients with little, if any, disease activity, who should have a good prognosis for their functional outcome. We compared the functional status of RA patients fulfilling those criteria with subjects randomly selected from the normal population.

Methods: Data from two sources were used for the analysis: 4,459 RA patients enrolled in the German biologics register RABBIT at start of therapy with a biologic agent (67%) or with a non-biologic DMARD after at least one DMARD failure (33%) and data from a population based cross-sectional survey of 9,263 subjects [1]. Both sources provide data on functional capacity measured by the Hannover functional status questionnaire (FFbH) which is comparable to the health assessment questionnaire (HAQ). 12 months follow-up data were used for the comparisons. We considered 3 definitions of remission: the new boolean definition (≤1 number of swollen joint, ≤1 tender joint, ≤1 mg/dl CRP, ≤1 patient global assessment (0–10 scale)), the SDAI definition (simplified disease activity index (SDAI) ≤ 3.3) and the DAS28 definition(DAS28 < 2.6).

Results: Mean age of the RA patients was 55 (SD 12) years, the median disease duration 8 years, and the mean DAS28 at start of treatment 5.5 (1.3). After 12 months the stringent new Boolean definition of remission was fulfilled in n=72 (4.9%) of the DMARD treated and n=107 (4.0%) of the biologics treated patients. The remission rates were higher (7.8%, 6.8%) when the SDAI definition or when the "old" DAS28 definition (21.8%, 19.2%) were applied.

RA patients who fulfilled the Boolean or SDAI criterion had a high functional capacity which was fully comparable to age and sex matched subjects from the normal population (tab 1). The functional capacity of DMARD treated patients in remission was even higher. They had shorter disease duration, less joint damage und less treatment failures than patients treated with biologics.

Table 1. Age and sex adjusted mean functional capacity and percentage of patients with almost no limitations in activities of daily living (FFbH >90).

		Mean FFbH	FFbH >= 90 (in % of pts.)
Subjects from normal population		86.6 [86–87]	57.4 [56–59]
RA pts. treated with	RA pts. fulfilling		
DMARDs	Boolean crit. (n=84)	92.1 [88–96]*	66.6 [55–77]
Biologics	Boolean crit. (n=131)	88.8 [86–92]	59.1 [49–68]
DMARDs	SDAI crit. (n=133)	90.6 [88–93]	59.9 [50–69]
Biologics	SDAI crit. (n=212)	85.9 [83–88]	55.2 [48–63]
DMARDs	DAS28 crit. (n=352)	85.7 [84–87]	45.7 [40–51]*
Biologics	DAS28 crit. (n=581)	79.2 [78–81]*	33.8 [30–38]*

Each subgroup: mean age 55 years, (75% female), 95% confidence limits are given in parentheses; * significantly different ($p < 0.05$) from the normal population

62% of the patients in remission according to the new Boolean definition had almost no limitations in activities of daily living defined by a functional capacity > 90% of full function (FFbH >90 or a HAQ score< 0.25). This proportion was again comparable to subjects from the normal population. In contrast, patients in DAS28 remission were more limited in activities of daily living.

Conclusion: In patients with long-standing disease, the new ACR/EULAR remission criteria identify those with a high functional capac ity, comparable to age and sex matched subjects from the general population.

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The Identification of Rheumatoid Arthritis Patients for Comparative Effectiveness Research Using An Electronic Health Record and Mathematical Modeling. Aarat M. Patel[1], Larry W. Moreland[2], Melissa Saul[3], Stephen R. Wisniewski[3] and Marc C. Levesque[4]. [1]Univ of Pittsburgh Med Ctr / Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Univ of Pittsburgh, Pittsburgh, PA, [4]Univ of Pittsburgh Med Ctr, Pittsburgh, PA

Background/Purpose: To develop an electronic search algorithm with a high specificity and sensitivity to accurately identify rheumatoid arthritis (RA) patients in a large health care system linked by an electronic health record (EHR) system.

Methods: Records from the Medical Archival Retrieval System (MARS) at the University of Pittsburgh Medical Center (UPMC) were used to identify potential RA patients. We searched the UPMC MARS system for subjects with a 714.0 International Classification of Diseases, 9th revision (ICD-9) code and used a recursive partitioning method to develop a search algorithm with a high specificity and sensitivity for the identification of RA patients; the recursive partitioning method used the 714.0 ICD-9 code and tested 35 additional variables (serology, inflammatory markers, medications, specific words in physician notes, etc). During the development and validation of the algorithm, patients were classified into those likely or unlikely to have RA and representative sets of these patient records were reviewed to determine if subjects met the 1987 and/or 2010 RA diagnostic criteria.

Results: We initially analyzed records from 2009 to study the effect of clinical setting (inpatient vs. outpatient rheumatology clinic) on the identification of RA patients. For inpatients, there was a low PPV of a 714.0 (39.0%) whereas for outpatient-rheumatology subjects there was a high PPV of a 714.0 for the identification of RA patients (87.3%), (n=95, $p<0.0001$; Fisher's exact test). When the records of subjects with and without a 714.0 ICD-9 code were analyzed (n=400), the sensitivity, specificity, PPV and NPV of a 714.0 among outpatient-rheumatology patients was 98%, 88%, 87% and 98%, respectively. We next used recursive partitioning to test whether other variables besides a 714.0 could be used to create a more specific algorithm for identifying RA patients among outpatient rheumatology patients seen in 2009. We found that a search algorithm with 3 variables 1.) 714.0 ICD-9 code, 2.) ratio of "rheumatoid arthritis" in a physician note per rheumatology visit and 3.) ratio of "RA" in a physician note per rheumatology visit improved the specificity for identifying RA patients. The sensitivity, specificity, PPV and NPV of the algorithm was 93%, 95%, 94%, 95% (n=400). Validation of this algorithm with analysis of an additional 400 subjects produced similar results (95%, 96%, 96%, 95%, respectively). We used this algorithm to analyze records from outpatient-rheumatology patients evaluated in 2010 (n=17,571) to identify 2,610 patients with RA.

Conclusion: The ICD-9 code for RA (714.0) alone was not reliable for identifying RA patients in the inpatient setting and had suboptimal specificity in the outpatient rheumatology setting. We developed and validated a simple algorithm using recursive partitioning that used 3 variables to identify RA patients with a high specificity, sensitivity, PPV and NPV. This simple algorithm represents a substantial improvement in terms of sensitivity and specificity over existing published algorithms. Using an EHR and this electronic search algorithm will enable large-scale comparative effectiveness studies on the treatment and management of RA in "real-world" clinical settings.

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Personal Health Records in Rheumatoid Arthritis: Quality and Adhesion Factors. Sophie Trijau[1], Herve Servy[2], Adam M. Selamnia[2], Vincent Pradel[1], Pierre Lafforgue[1] and Thao Pham[1]. [1]Sainte Marguerite Hospital, Marseille, France, [2]SANOIA, Marseille, France

Background/Purpose: Personal Health Records (PHRs) are patient-controlled repositories, capturing health data entered by individuals and providing information related to the care of those individuals. PHRs include tools to help individuals take a more active role in their own health, and include decision-support capabilities that can assist physician in managing chronic conditions such as rheumatoid arthritis (RA). However, barriers to PHRs adoption exist, including economic and legal concerns. Especially, patients must understand and accept their role and responsibilities related to their own health care. *Objective*: To assess how support measures improve PHRs adoption and to determine factors that influence quality of self recorded data and tool adhesion of RA patients.

Methods: *Design*: controlled randomized study. *PHRs tool*: SANOIA developed PHRs web tool integrated with electronic health records (EHRs). SANOIA tool is a full privacy protection based on innovative anonymization techniques. *Patients:* RA patients fulfilling ACR 1987 criteria, with web access, randomized in 3 groups: Group 1 patients were given a written information about how to create and manage a PHR; Group 2 patients received the written information and a nurse support phone-call 48 hours after inclusion as an PHR filling assistance; Group 3 patients filled PHR with their rheumatologist during the consultation. *Data collected*: demographic data, amount and quality of self recorded data, DAS 28, RAPID 3, ongoing treatment, at baseline and 2 months after. Information quality was compared to rheumatologist medical records (gold standard) and 0–10 scored. Good quality score was defined as >9. Patients were considered as tool adherent if they connected at least twice and as non adherent if they connected once or never. *Statistical analysis*: Khi-2, Mann-Whitney tests.

Results: We included 56 RA patients (20, 19 and 17 in group 1, 2, 3 respectively), 73% female, 57.1 years mean age, 3.04 mean DAS 28 and 2.93 mean RAPID 3. Self reported data quality was significantly higher in group 2 (73.7%) and 3 (82.4%) than in group 1 (45.0%), ($p=0.04$). Moreover, a patient reported tuberculosis history and another neoplasia history that were not reported in the physician medical record. Patient adhesion was higher in group 2 (73.7%) compared to group 1 (55.0%) and 3 (58.8%) ($p=0.45$). Quality was correlated to adhesion ($p<0.0001$). Gender, age, disease duration and activity (DAS 28, RAPID 3) and treatments including biologics and steroids were not correlated to data quality or patient adhesion.

Conclusion: Information quality collected with PHRs was relevant and better when patients were initially assisted either by their physician or by a non-medical phone support. We observed a trend for a better adhesion when using phone call support at 2 months. A follow-up at month 6 is scheduled to confirm these results.

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Evidence for Epistatic Gene-Gene Interactions in Systemic Lupus Erythematosus. Travis Hughes[1], Adam Adler[1], Jennifer A. Kelly[1], Kenneth Kaufman[2], Adrienne Williams[3], Carl D. Langefeld[4], Elizabeth Brown for PROFILE[5], Elena Sanchez[1], Javier Martin[6], Luis M. Vila[7], Gary S. Gilkeson[8], Patrick M. Gaffney[9], Kathy L. Moser[9], J.T. Merrill[1], Judith A. James[10], Timothy J. Vyse[11], Marta E. Alarcon-Riquelme[12], John B. Harley[13], Bruce C. Richardson[14] and Amr H. Sawalha[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [3]Wake Forest University, Winston-Salem, [4]Wake Forest University Health Sciences, Winston-Salem, NC, [5]Univ of Alabama at Birmingham, Birmingham, AL, Birmingham, AL, [6]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [7]University of PuertoRico Medical Sciences Campus, San Juan, PR, [8]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [9]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [10]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [11]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [12]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [13]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [14]University of Michigan, Ann Arbor, MI

Background/Purpose: Several confirmed genetic susceptibility loci for lupus have been described. To date, no clear evidence for genetic epistasis is established in lupus. We test for gene-gene interactions in a number of known lupus susceptibility loci.

Methods: Eighteen SNPs tagging independent and confirmed lupus susceptibility loci were genotyped in a set of 4,250 lupus patients and 3,818 normal healthy controls of European descent. Epistasis was tested using a 2-step approach utilizing both a parametric and non-parametric (multifactor dimensionality reduction) methods. False discovery rate (FDR) was used to correct for multiple testing.

Results: We detected and confirmed gene-gene interactions between *HLA* and *CTLA4*, *HLA* and *IRF5*, *HLA* and *ITGAM*, and *PDCD1* and *IL21* in lupus patients. The most significant interaction detected by parametric analysis was between rs3131379 in the *HLA* region and rs231775 in *CTLA4* ($P = 7.73\times10^{-5}$ (FDR≤0.05), $P_{MDR} = 2.82\times10^{-47}$).

Conclusion: We provide a strong evidence for gene-gene epistasis in systemic lupus erythematosus. These findings support a role for genetic interaction upon the complexity of lupus heritability.

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A Large-Scale Association Study Identified Multiple HLA-DRB1 Alleles Associated with Anti-Citrullinated Peptide Antibody Negative Rheumatoid Arthritis in Japanese. Chikashi Terao[1], Koichiro Ohmura[2], Yuta Kochi[3], Katsunori Ikari[4], Etsuko Maruya[5], Masaki Katayama[2], Kota Shimada[6], Akira Murasawa[7], Shigeru Honjo[8], Kiyoshi Takasugi[9], Keitaro Matsuo[10], Kazuo Tajima[10], Akari Suzuki[5], Kazuhiko Yamamoto[11], Shigeki Momohara[4], Hisashi Yamanaka[4], Ryo Yamada[1], Hiroo Saji[5], Fumihiko Matsuda[1] and Tsuneyo Mimori[2]. [1]Kyoto University, Kyoto, Japan, [2]Kyoto Univ Grad School of Med, Kyoto, Japan, [3]RIKEN, Yokohama, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [5]HLA Laboratory, Kyoto, Japan, [6]Sagamihara, Japan, [7]Niigata, Japan, [8]Honjo Rheumatism Clinic, Kanzaki, Japan, [9]Dohgo Spa Hospital, Matsuyama, Japan, [10]Nagoya, Japan, [11]Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

Background/Purpose: HLA-DRB1 is associated with rheumatoid arthritis (RA). However, it has recently been suggested that HLA-DRB1 is only associated with RA patients with anti-citrullinated peptide/protein antibody (ACPA), an antibody specific to RA. We intended to elucidate whether specific HLA-DR alleles are associated with ACPA-negative RA development.

Methods: HLA-DRB1 typing was carried out in 368 Japanese ACPA-negative RA patients and 1,508 healthy volunteers as the first set, followed by HLA-DRB1 typing of 501 cases and 500 controls as the second set. The HLA-DRB1 allele frequency and diplotype frequency were compared in each group, and the results of the two studies were combined to detect HLA-DRB1 alleles or diplotypes associated with ACPA-negative RA.

Results: HLA-DRB1*12:01 was identified as a novel susceptibility allele for ACPA-negative RA (p=0.000088, OR 1.72, 95%CI: 1.31–2.26). HLA-DRB1*04:05 and *14:03 showed moderate associations with ACPA-negative RA (p=0.0063, OR 1.26, 95%CI: 1.07–1.49 and p=0.0043, OR 1.81, 95%CI: 1.20–2.73, respectively). The shared epitope, including HLA-DRB1*04:05 was weakly associated with ACPA-negative RA, but no dosage effect was detected (p=0.016, OR 1.17, 95%CI: 1.03–1.34). A combination of HLA-DRB1*12:01 and DRB1*09:01 showed a strong association with susceptibility to ACPA-negative RA (p=0.00013, OR 3.62, 95%CI: 1.79–7.30). Homozygosity for HLA-DR8 was significantly associated with ACPA-negative RA (p=0.0070, OR 2.16, 95%CI: 1.22–3.82). We also found that HLA-DRB1*15:02 and 13:02 were protective against ACPA-negative RA (p=0.00010, OR 0.68, 95%CI: 0.56–0.83 and p=0.00059, OR 0.66, 95%CI: 0.52–0.84, respectively).

Conclusion: In our large-scale association study, we found multiple alleles and diplotypes associated with susceptibility to or protection against ACPA-negative RA.

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Polymorphisms in the CCL2 Distal Regulatory Region Are Associated with Rheumatoid Arthritis in a North American Native Population with a High Disease Prevalence. Hani S. El-Gabalawy[1], Konstantin Jilkine[1], David B. Robinson[1], Irene Smolik[2], Donna M. Hart[3], Carol A. Hitchon[1], Christine A. Peschken[1], Charles N. Bernstein[1], Kiem Oen[1], Ye Sun[4] and Katherine A. Siminovitch[4]. [1]University of Manitoba, Winnipeg, MB, [2]University of Manitoba, Winnipeg, [3]Health Sciences Centre, Winnipeg, MB, [4]Mount Sinai Hospital, Toronto, ON

Background/Purpose: North American Native (NAN) populations exhibit a high prevalence of RA and frequent multi-case families, suggesting a strong genetic component to the disease. We have studied the Cree-Ojibway population in Central Canada and have previously shown that the genetic risk is imparted by a high frequency of shared epitope (SE) encoding alleles, with further contributions from TRAF1/C5 and TNFRSF14, the latter demonstrating an interaction with SE in disease risk (PMID:21614018). In addition to RA, this population also has a high burden of atherosclerosis and other chronic inflammatory diseases. MCP-1 plays a key role in the pathogenesis of chronic inflammation, and polymorphisms in the CCL2 locus, which encodes for MCP-1 protein, have been shown in other populations to be associated with increased serum levels of MCP-1 and with an increased risk of several chronic inflammatory diseases, including RA and atherosclerosis. We therefore sought to determine whether the CCL2 polymorphisms are associated with RA disease risk and serum levels of MCP-1 in the NAN population.

Methods: NAN RA patients (n=458), their disease-free FDR (n=300), and unrelated controls (C), (n=715) were recruited from several urban and rural locations in Central Canada. The gender distribution (% females) was RA=82%, FDR=70%, C=59%. All study subjects were genotyped for 3 CCL2 associated SNPs: RS1024610A/T (SNP1), RS1024611C/T (SNP2), RS2857654A/C (SNP3) by sequencing using the Sequenom Mass Array iPLEX platform. MCP-1 levels were tested in a subset of the RA (n=94), FDR (n=249), and C (n=186) by ELISA. Differences between groups were tested using genotypic, allelic, dominant, and recessive models.

Results: Minor allele frequency (MAF) for the CCL2 SNPs in the entire study population was SNP1=0.05, SNP2=0.21, SNP3=0.21, and all were in Hardy-Weinberg equilibrium. SNP2 and SNP3 are known to be in a high degree of linkage disequilibrium. The genotypic analysis indicated that there were significant differences between RA and C for SNP2 (18/168/261 vs. 33/214/457, p=0.04) and SNP3 (18/171/258 vs. 34/218/453, p=0.04). Further analysis indicated a significant difference using a dominant model: SNP2 and SNP3 OR=1.32, p=0.03, while there was no association with SNP1. There were no significant differences in the SNP allele distributions between FDR and C using any of the models. Serum MCP-1 levels for the 3 groups were RA=584±505, FDR=535±436, C=219±108 pg/ml (RA vs. FDR, p=NS; FDR vs. C, p=0.000). Analysis of the allele distribution of the SNPs relative to the serum levels of MCP-1 indicated that there was no clear association between the genotypes and the serum protein level in this population.

Conclusion: In a NAN population that has a high burden of RA, cardiovascular disease, and other chronic inflammatory diseases, there was a significant, albeit weak association of RA with SNPs in the regulatory region

of the CCL2 gene. Despite this, there was no clear association between these SNPs and serum levels of MCP-1. The surprisingly large differences in serum levels of MCP-1 between the disease-free FDR of RA patients and population controls cannot be explained on a genetic basis, and may relate to heretofore unidentified epigenetic effects.

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Is There a Higher Genetic Load of Susceptibility Loci in Familial Ankylosing Spondylitis? Reeti K. Joshi[1], John D. Reveille[2], Matthew A. Brown[3], Michael H. Weisman[4], Michael M. Ward[5], Lianne S. Gensler[6], B. Paul Wordsworth[7], David M. Evans[8] and Shervin Assassi[9]. [1]Washington University in St. Louis, Saint Louis, MO, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]Wellcome Trust Centre, Headington, United Kingdom, [4]Cedars Sinai Med Ctr, Los Angeles, CA, [5]NIH/NIAMS/IRP, Bethesda, MD, [6]UCSF, San Francisco, CA, [7]Bichester, Oxon, United Kingdom, [8]Chesterfield, MO, [9]Univ of Texas Health Science, Houston, TX

Background/Purpose: Several genes have been recently confirmed as genetic susceptibility loci for Ankylosing Spondylitis (AS) in genome wide association studies. The goal of this study is to examine whether the familial AS cases have a higher genetic load of these susceptibility loci.

Methods: Overall, 502 patients with AS were examined, consisting of 312 who had first-degree relatives (FDR) with AS (familial) and 190 who had no FDR with AS or spondyloarthritis (sporadic). All patients and affected FDRs fulfilled the modified New York Criteria for AS. The patients were recruited from North American Spondylitis Consortium (NASC), Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) and United Kingdom- Oxford (UK-Oxford) cohorts.Only one AS case per family was included in the analysis. The frequency of AS susceptibility loci in *IL23R*, *IL1R2, ANTRX2, ERAP1*, two intergenic regions on chromosomes 2 and 21, as well as, a HLA B27 tag single nucleotide polymorphism (SNP), rs4349859 was compared between the familial and sporadic AS patients. Association between SNPs and multiplex status was assessed by logistic regression controlling for sibship size and Eigenstrat derived principal components from a previous genome-wide association study of AS.

Results: The UK –Oxford cohort included 160 familial AS cases with mean age of 47.9 years at enrollment, 60% being male. US cohort included 152 familial AS patients from NASC study with mean age of enrollment 44.4 years, 58% being male. PSOAS group included 190 sporadic AS cases with mean age 47.1 years, 76% being male. The risk allele in HLA-B27 tag SNP, rs4349859 was significantly more prevalent in familial cases ($p=0.002$, OR: 3.69, CI: (1.61, 8.46)). The frequency of AS susceptibility loci in the *ERAP1, IL23R*, *IL1R2*, *ANTXR2* genes in addition to two gene desert regions on 2p15 and 21q22 did not differ significantly between the familial and sporadic cases. However, the susceptibility locus on 21q22 showed a trend toward association ($p=0.054$) with the protective minor allele being less frequent in the familial cases. Further details of the results are shown in Table 1.

Table 1. Comparison of AS susceptibility loci between familial and sporadic AS cases after adjustment for sibship size

SNP	Candidate Gene	Minor Allele	Odds ratio (95% C.I.)	P-value
rs11209026	*IL23R*	A(P†)	0.55 (0.22, 1.36)	0.193
rs10865331	2p15*	A(R‡)	0.85 (0.61, 1.2)	0.365
rs2310173	*IL1R2*	A(R)	1.34 (0.94, 1.9)	0.105
rs4333130	*ANTXR2*	G(P)	0.9 (0.61, 1.32)	0.577
rs27434	*ERAP1*	A(R)	0.96 (0.64, 1.45)	0.855
rs2242944	21q22*	A(P)	0.68 (0.46, 1.01)	0.054
rs4349859	HLA B27 tag SNP	A(R)	3.69 (1.61, 8.46)	0.002

* These SNPs are located in gene deserts
† P: Protective Allele against AS
‡ R: Risk Allele for AS

We also repeated the analysis after restricting the sample to the US cases. The investigation of only US familial and sporadic AS cases showed similar results.

Conclusion: HLA tag SNP, rs4349859 which tracks closely with HLA-B27 is a susceptibility locus for familial AS. This finding confirms higher heritability in HLA-B27 positive subtype of AS. The frequency of the recently described non-MHC susceptibility loci is not markedly different between the sporadic and familial cases of AS.

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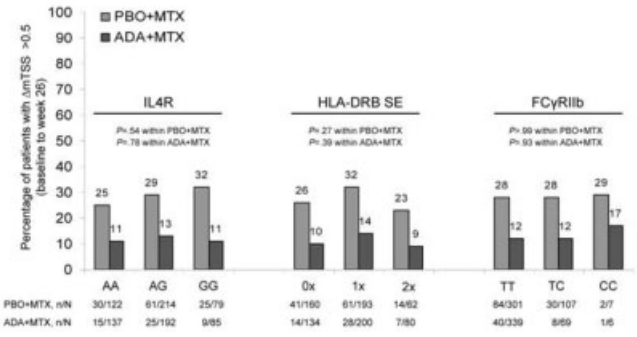
Analysis of Genetic Influence of HLA-DRB1, IL4R, and FcγRIIb on Radiographic Responses to Methotrexate Monotherapy or Adalimumab Plus Methotrexate Through 26 Weeks in Patients with Early Rheumatoid Arthritis. Alla Skapenko[1], Josef Smolen[2], Arthur Kavanaugh[3], Sourav Santra[4], Hartmut Kupper[5], Theresa Peterson[4] and Hendrik Schulze-Koops[1]. [1]University of Munich, Munich, Germany, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [3]University of California San Diego, La Jolla, CA, [4]Abbott, Abbott Park, IL, [5]Abbott, Ludwigshafen, Germany

Background/Purpose: Genetic factors may influence the susceptibility, severity, and radiographic progression of rheumatoid arthritis (RA). Specifically, the IL4R (A→G [I50V]) single nucleotide polymorphism (SNP) has been associated with early joint erosion,[1] and the FcγRIIb (T→C [I232T]) SNP is a candidate factor for rapid radiologic joint damage.[2] Their association with radiographic progression during treatment with anti-TNF agents is unclear. The purpose of this study was to examine radiographic progression through 26 weeks in pts treated with adalimumab plus methotrexate (ADA+MTX) or placebo (PBO)+MTX according to 3 candidate genetic markers: IL4R I50V SNP, HLA-DRB1 shared epitope (SE), and FcγRIIb I232T SNP.

Methods: MTX-naïve pts ≥18 years old with RA <1 year and active disease (DAS28[CRP] >3.2, ESR ≥28 mm/h or CRP ≥1.5 mg/dL), and either >1 erosion, RF+, or anti-CCP+ were randomized to ADA+MTX (n=515) or PBO+MTX (n=517) for 26 wks. This analysis presents radiographic outcomes, including the percentage (%) of pts with progression in modified Total Sharp Score (ΔmTSS >0.5) and rapid radiographic progression (RRP, ΔmTSS >1.5) from baseline (BL) to 26 wks by IL4R I50V SNPs (AA, AG, or GG), HLA-DRB SE copy number (0x, 1x, 2x), and FcγRIIb I232T SNPs (TT, TC, CC). Multiple imputation analyses were used to assess radiographic data.

Results: Genetic data were available for 451 PBO+MTX and 443 ADA+MTX pts. The number (%) of pts with available radiographic data at wk 26 by genotype is lower than that of those genetically analyzed (**Figure**). The distribution of alleles was similar between treatment groups for IL4R and SE; however, the FcγRIIb SNPs were unequally distributed: the PBO+MTX group had more TC and fewer TT pts. BL demographics were similar across alleles, except a higher proportion of anti-CCP+ pts were noted with increasing SE copies. There were no consistent patterns of influence of IL4R SNP, SE copy number, or FcγRIIb SNP on the % of pts with ΔmTSS >0.5 (**Figure**) or RRP at wk 26.

Figure. Percentage of Patients With Radiographic Progression at Week 26



Conclusion: Regardless of genetic background, a higher % of pts in the PBO+MTX group exhibited radiographic progression compared with ADA+MTX. Based on previous studies,[1–2] it is somewhat unexpected that neither the IL4R nor the FcγRIIb SNP influenced radiographic progression. Possible reasons for this difference may be that the study population was pre-selected for pts with risk for aggressive erosive disease, the analysis was performed after a shorter duration of treatment, and the overall increase in mTSS was moderate. Further exploration is warranted to determine any potential interactions in response to anti-TNF agents.

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2. Radstake TR, et al. *Arthritis Rheum* 2006;54:3828–37.

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Characterization of a New Category of Autoinflammatory Disease Associated with Nucleotide Oligomerization Domain2 Gene Mutations: An Expanded Cohort Study. Qingping Yao, Le Chu Su, Lan Zhou, Bijal Jayakar and Bo Shen. Cleveland Clinic, Cleveland, OH

Background/Purpose: Autoinflammatory diseases are characterized by seemingly unprovoked episodes of inflammation, without high titer autoantibodies or antigen specific T cells, and derive from genetic variants of the innate immune system. Clinically, there are patients with autoinflammatory phenotypes of unidentified genetic causes, thus posing diagnostic challenges. Modern molecular and genetic tools would enable a better disease classification. We previously described a small number of patients with autoinflammatory phenotypes associated with nucleotide oligomerization domain (NOD2) gene mutations. Herein, we report a cohort of 17 patients to further characterize this disease entity.

Methods: Seventeen patients with autoinflammatory phenotypes of unknown diagnoses were enrolled and studied between January 2009 and April 2011. The NOD2 gene testing in these patients was performed by sequencing of all 12 coding exons (Center for Genetic Testing in Saint Francis, Oklahoma).

Results: All seventeen patients were non-Jewish Caucasians, with 8 being male. The mean age at disease diagnosis was 39.5 years (range 17–72) and disease duration was 4.7 years (range 1–10). Typical clinical presentations were weight loss (7/17), self limiting fever (10/17), dermatitis (15/17) and inflammatory polyarthritis (14/17), with prominent hip symptoms. There were gastrointestinal symptoms inconsistent with inflammatory bowel disease in 11 patients, granulomas of the skin and gut in 2, and recurrent chest pain in 2, with 1 having pleuritis and pericarditis. Nine had sicca-like symptoms which did not fulfill the diagnostic criteria of Sjogren syndrome. Seven patients had increased acute phase reactants in serum. While the 17 patients had negative tests for autoantibodies for classic connective tissue diseases and systemic vasculitis, all carried the NOD2 gene mutation $IVS8^{+158}$ with 6 having concurrent R702W mutation. Of interest, there was no reported family history in most patients. However, there were 3 female sibs from a single family who presented with similar symptoms and shared $IVS8^{+158}$. Most patients appeared to have mild form of disease which required symptomatic treatment. Dermatitis was primarily treated with topical steroid creams but required small to high dose prednisone in some cases. Arthritis typically did not respond to nonsteroidal anti-inflammatory drugs (NSAIDs). Some patients seemed to respond to sulfasalazine but not to methotrexate. A trial of TNF inhibitors in 3 cases did not improve inflammatory arthritis and abatacept trial in another case did not seem to benefit either. Serositis associated symptoms responded well to a short course of high dose prednisone in 1 case but not to colchicine or NSAIDs.

Conclusion: Our expanded cohort study further supports the new disease category with characteristic clinical phenotypes, which somewhat resembles pediatric Blau syndrome. However, the new entity does not seem rare and may be polygenic. Its association with the NOD2 mutations suggests $IVS8^{+158}$ may be entertained as a genetic marker for the diagnosis of the disease. Further clinical, genetic and etiopathogenic study of the disease is warranted.

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A Putative Functional Polymorphism in the *IL21* 3'-UTR Flanking Region Is Tagged by *IL21* Lupus-Associated Variants and Alters Gene Expression *in Vitro*. Travis Hughes and Amr H. Sawalha Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: We have previously reported, and recently localized, replicated and confirmed the genetic association between *IL21* polymorphisms and the susceptibility to SLE with a genome-wide significance. Two SNPs located within *IL21* and its 3'-UTR flanking region, rs907715 and rs6835457, explain the genetic association in this locus. Herein, we seek to identify putative functional polymorphisms for which the previously observed polymorphisms might serve as a proxy.

Methods: We conducted a scan for genetic polymorphisms in the *IL21* locus that are in LD ($r^2>0.8$) with the two previously reported lupus-associated markers (rs907715 and rs6835457) in Hapmap3 and among polymorphisms in the 1000 Genomes Project. We used luciferase reporter assays to interrogate the *cis*-acting effects of a putative functional polymorphism on *IL21* gene expression.

Results: We identified a total of 9 additional SNPs in high LD with the previously characterized genetic effect within the *IL21* locus using the CEU European-derived samples. The observed LD block formed by these polymorphisms is centered around *IL21* and does not extend to encompass other genes in the region. One polymorphism, rs2175679, is located within a putative regulatory region downstream of *IL21* which is enriched for H3K4me1, H3K4me3, CTCF, and a number of transcription factor binding sites in ENCODE data sets. These data suggest this region to possess enhancer and/or insulator function downstream of *IL21* which might be modified by this non-coding G/T polymorphism. Indeed, luciferase levels using constructs with the G-allele variant are significantly increased relative to those of the T-allele variant in rs2175679 (1.5-fold, $P = 0.007$). The G allele of rs2175679 is the allele which corresponds to the lupus-associated risk allele of both rs907715 and rs6835457.

Conclusion: A common non-coding variant in *IL21* 3'-UTR flanking region might contribute to increased lupus susceptibility by altering the transcriptional regulation of *IL21*.

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Sex-Specific Genetic Architecture of Systemic Lupus Erythematosus. Travis Hughes[1], Adam Adler[1], J.T. Merrill[1], Jennifer A. Kelly[1], Kenneth Kaufman[2], Adrienne Williams[3], Carl D. Langefeld[4], Gary S. Gilkeson[5], Elena Sanchez[1], Javier Martin[6], Elizabeth E. Brown for PROFILE[7], Patrick M. Gaffney[8], Kathy L. Moser[8], Tomothy J. Vyse[9], Marta E. Alarcon-Riquelme[10], Judith A. James[11], Robert H. Scofield[12], John B. Harley[13], Bruce C. Richardson[14] and Amr H. Sawalha[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [3]Wake Forest University, Winston-Salem, [4]Wake Forest University Health Sciences, Winston-Salem, NC, [5]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [6]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [7]University of Alabama at Birmingham, Birmingham, AL, [8]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [9]King's College London, Guy's Hospital, London, United Kingdom, [10]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [11]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [12]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, US Department of Veterans Affairs Medical Center and Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [13]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [14]University of Michigan, Ann Arbor, MI

Background/Purpose: Systemic lupus erythematosus is a sexually dimorphic autoimmune disease which is more common in women, but affected men often experience a more severe disease. The genetic basis of sexual dimorphism in lupus is not clearly defined. Here, we examine sex-specific genetic effects among lupus-susceptibility loci.

Methods: A total of 18 lupus-associated autosomal genetic loci were genotyped in a large set of lupus patients and controls of European descent, consisting of 5,932 female and 1,495 male samples. Sex-specific genetic association analyses were performed. Sex-gene interaction was further validated using both a parametric (logistic regression) and non-parametric (multifactor dimensionality reduction) methods. We examined aggregate differences in sex-specific genetic risk by calculating a cumulative genetic risk score for lupus in each individual and comparing average genetic risk between men and women.

Results: We observe a significantly higher cumulative genetic risk for lupus in men than in women. We report significant sex-gene interaction in the HLA region and *IRF5* genes whereby male lupus patients possess a significantly higher frequency of risk alleles than their female counterparts. We also report that the genetic effect observed in *KIAA1542* is specific to female lupus patients, and does not seem to play a role in lupus in men.

Conclusion: Our data indicate that men require a higher cumulative genetic load to develop lupus compared to women. This observation suggests that the higher prevalence of lupus in women, and the more severe lupus phenotype in men could be related to autosomal genes.

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Recognition of High Risk and Protective HLA-DRB1 Alleles with Respect to Need for Biologic Therapy in a Cohort of 226 Patients with Rheumatoid Arthritis. Surabhi Waghmare[1], Andrew Cairns[2], Clare Matthews[3] and Gary D. Wright[4]. [1]Musgrave Park Hospital-Belfast Health and Social Care Trust, Belfast, BT9 7JB, United Kingdom, [2]Musgrave Park Hospital-Belfast Health and Social Care Trust, Belfast, United Kingdom, [3]Ulster Hospital-South Eastern Trust, Belfast, United Kingdom, [4]Musgrave Park Hospital, Belfast, United Kingdom

Background/Purpose: Studies have shown association of shared epitope (SE) containing HLADRB1 alleles, with increased susceptibility and severity of RA.However their effect on treatment response still remains unexplored. Aim of this study is to identify "treatment prognostic marker" alleles, which are likely to increase the odds of needing biologics and ones rendering a protective effect against their use.

Methods: 226 Caucasion Northern Irish RA patients (mean age 59.3+/−SD13.8y), checked for HLADRB1 haplotype, were treated over 6 years as per standard practice lead by clinical response. Biologics were commenced as per British Society of Rheumatology criteria i.e. active RA in spite of 2 DMARDS trial, measured by disease activity index (DAS28)>5.1 at 2 occasions, monthly apart. Outcome measured at 6 years, was risk of needing biologic therapy; expressed as relative risk and odds ratio. Frequency of each of 30 DRB1 alleles was measured in 2 groups (biologic vs. non-biologic therapy), statistical significance determined by Chi-square test. Differences in the need for biologic therapy in relation to allele types was analysed, statistical significance determined using Chi-square test (when not possible, Fisher's test). Null hypothesis was rejected conventionally with $p<0.05$.

Results: 1. Alleles *401 and *404 were seen more frequently in biologic group (Allele*401:54.9% in biologic vs. 34.9% in non-biologic group, $p=0.010$; Allele*404:17.6% in biologic vs.7.4% in non-biologic group, $p=0.030$). **2**. Allele*1501 occurred more frequently in non-biologic group (21.6% in biologic vs. 36.6% in non-Biologic group, $p=0.045$). **3.** Presence of any one of *401 and *404 allele increased the risk needing biologic therapy, RR 1.89; OR 2.26 (CI 1.17 to 4.39, $p=0.014$) compared to those without them (52.9% vs. 37.7%). *401 and *404 were identified as High Risk Alleles (HRA) for needing biologics. **4.** The above risk increased further, RR 3.63; OR 6.91 (CI 1.70 to 28.09, $p=0.010$) when both alleles are HRA i.e. each allele in the allele pair was either *401 or *404 compared no HRA (9.8% vs. 2.3%). **5.** When patients with any one of the traditional "SE containing alleles" (*101,*401,*404,*405,*408,*1001) were compared to those without them (60.8% vs. 49.7%), an increased risk of needing biologics, RR 2.05; OR 2.42 (CI 1.11 to 5.2868, $p=0.023$) was seen. Of note, HRAs *401 and *404 were included in these SE containing alleles. **6.** In patients with 2 SE alleles, there was a further increased risk of needing biologic therapy, RR 2.6; OR 3.4 (CI 1.24 to 9.3202, $p=0.014$) compared to patients with no SE alleles (2% vs.1.1%) **7.** However, when *401 and *404 was excluded in points 5 and 6, there was no increased risk for biologics (OR 0.8214 and 0 in point 5 and 6, respective p values of 0.23 and 1). **8.** Allele *1501 seemed to offer a protective effect against needing Biologics (RR 0.5537; OR 0.477, CI 0.2288 to 0.9945, $p=0.045$).

Conclusion: Alleles *401 and *404 are dominantly associated with increased risk of needing biologic therapy. This risk is increased further if both alleles are HRA. Although SE containing alleles collectively increased risk, majority of this effect was due to *401 and *404. Presence of *1501 allele may exert protective effect and may reduce the likelihood of needing biologics.

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Investigation of Caucasian Rheumatoid Arthritis Susceptibility Loci in African Patients with the Same Disease. Sebastien Viatte[1], Edward Flynn[1], Mark Lunt[1], Joanne Barnes[1], Madeleine Singwe-Ngandeu[2], Sylvette Bas[3], Anne Barton[1] and Cem Gabay[3]. [1]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]Unit of Rheumatology, Department of Internal Medicine, School of Medicine, University of Yaoundé, Yaoundé, Cameroon, [3]Division of Rheumatology, University Hospitals of Geneva, 26 Avenue Beau-Séjour, 1211 Geneva 14, Switzerland

Background/Purpose: The largest genetic risk to develop rheumatoid arthritis (RA) arises from a group of alleles of the HLA DRB1 locus ("shared epitope", SE). Recent genome wide and candidate gene association studies in Caucasians have identified over 30 confirmed single nucleotide polymorphisms (SNPs) predisposing to disease (susceptibility loci). We previously reported a lower prevalence of the SE in RA patients in Cameroon compared to European patients, despite a similar proportion of anti-CCP positivity. We aimed in the present study to investigate the contribution of United Kingdom (UK) RA susceptibility SNPs to RA susceptibility in Cameroon.

Methods: RA cases and controls from Yaoundé, Cameroon were genotyped for a panel of Caucasian putative RA susceptibility SNPs using Sequenom MassArray technology. Genotype data was also available for 4524 UK cases and 3781 UK controls (reference cohort) and for 500 cases and 500 controls from another UK cohort (validation cohort). Using the reference cohort, a Caucasian cumulative aggregate genetic-risk score (GRS) was calculated, in order to predict RA susceptibility of individuals, as the sum of the weighted risk-allele counts. The ability of the GRS to predict RA in small sample sizes was tested in 200 random samples of the validation cohort.

Results: After genotyping quality control, data on 63 SNPs was available for analysis in 43 Cameroon RA cases and 44 controls. Only 2 SNPs, both mapping to CCL21, were associated with RA: rs951005 (frequency of the A allele in controls: 47%, in cases: 65%, $p=0.01$) and rs2812378 (similar frequencies).

11% of SNPs tested were completely absent in Cameroonian samples, having minor allele frequency (MAF) of over 10% in the UK; these included SNPs mapping to the PTPN22 and ILRA loci. 71% of the remaining SNPs showed a MAF differing by > 10% between the UK and Cameroon.

Among 54 SNPs with data available in the UK reference cohort, 41 showed an association with RA at $p<0.05$. Those SNPs were selected to compute the GRS. The GRS showed a strong association with RA in the UK validation cohort (beta coefficient: 0.80, $p=3.0\times10^{-13}$). In 200 random samples of the validation cohort, 68% showed an association between the GRS and RA at $p < 0.05$. However, the GRS did not predict RA in Cameroon samples (beta coefficient: −0.17, $p=0.77$) and this difference was statistically significant ($p<0.005$).

Conclusion: The MAF of Caucasian RA susceptibility SNPs are different between UK and Cameroon samples. Several confirmed RA susceptibility polymorphisms, including PTPN22, are not detectable in the Cameroon population. The genetic risk of developing RA conferred by a set of 41 SNPs is significantly different in the UK and in Cameroon, despite a similar proportion of anti-CCP positive RA. Taken together, these observations strengthen the hypothesis that RA susceptibility SNPs are at least partially different in different ethnic backgrounds.

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Germinal and Somatic Abnormalities of the *TNFAIP3* Gene Support a Two-Hit Hypothesis of Lymphomagenesis in Autoimmune Diseases. Xavier Mariette[1], Saida Boudaoud[2], Gaetane Nocturne[1], Thierry Lazure[2], Joanne Nititham[3], Kimberly E. Taylor[4], Eric Hachulla[5], Jean Jacques Dubost[6], Jacques-Eric Gottenberg[7], Lindsey A. Criswell[8] and Corinne Miceli-Richard[9]. [1]Bicêtre University Hospital, Le Kremlin Bicetre, France, [2]INSERM U1012 - Université Paris XI, Le Kremlin Bicêtre, France, [3]University of California, CA, [4]University of California, San Francisco, San Francisco, CA, [5]Internal Medicine, Lille CEDEX, France, [6]CHU Gabriel Montpied, Clermont-Ferrand, France, [7]Strasbourg University Hospital, Strasbourg, France, [8]University of California San Francisco, San Francisco, CA, [9]Hopital Bicêtre, Le Kremlin Bicêtre, France

Background/Purpose: The pathophysiology of lymphomas in auto immune disease (AID), particularly primary Sjögren's syndrome (pSS), involves persistent inflammation and activation of autoimmune B cells leading to NF-kB activation. The *TNFAIP3* gene encodes the A20 protein which is a central gatekeeper of NF-kB activation. Germinal abnormalities in *TNFAIP3* have been associated with different AID and somatic mutations of the gene have been observed in several lymphoma subtypes, particularly MALT lymphoma, the lymphoma subtype most frequently associated with pSS. We aimed to investigate whether *TNFAIP3* abnormalities are involved in the lymphomagenesis process in pSS.

Methods: A cohort of 584 pSS patients including 24 patients with lymphoma (ASSESS + KB cohort) and 451 controls of Caucasian ancestry, addressed by 48 AIMs, was used for genetic studies. 3 SNPs encompassing the *TNFAIP3* locus located on 6q23 (rs13192841, rs2230926 and rs6922466) and known to be associated with SLE and/or RA were genotyped. Case control association tests were performed. Quantitative PCR (qPCR) was used for assessing the level of TNFAIP3 mRNA according to genotype. Then complete sequencing of the 9 *TNFAIP3* exons was performed in germinal DNA from 35 pSS patients with lymphoma and in lymphoma DNA extracted from tumoral paraffin sections from 16 of the 35.

Results: The 3 *TNFAIP3* SNPs were not significantly associated with risk of pSS. However, multivariate analysis demonstrated a significant association between the rs2230926 SNP (coding for an amino acid substitution in exon 3) and pSS complicated by lymphoma: OR= 3.36 (95%CI 1.34 – 8.42) p= 0.0097. Complete *TNFAIP3* gene sequencing of germinal DNA from 35 patients with pSS and lymphoma confirmed the presence of the rs2230926 risk variant in 9/35 (25.6%) pSS patients (MAF: 12.8% vs 6% in the 451 controls, OR= 2.3 [95%CI 1.09 – 4.9]; p= 0.04). Based on qPCR, the

expression level of A20 mRNA was significantly decreased in patients carrying the G minor allele (p=0.004). Moreover, we identified a novel germinal abnormality: a deletion of 24 nucleotides in exon 1 that leads to the suppression of a binding site for the Sp1 transcriptional factor in 4/35 patients (11.4%) vs 3/97 (3.1%) in controls and 5/119 (4.2%) in pSS patients without lymphoma (p=0.13). Overall, 11/35 patients (31.4%) with pSS and lymphoma had germinal variants of the *TNFAIP3* gene with potential functional consequences. Based on *TNFAIP3* sequencing, comparison of germinal and tumoral TNFAIP3 DNA among 16 patients with pSS and lymphoma revealed that 4 patients (25%) exhibited the rs2230926 risk variant and 4 other patients (25%) had a loss of heterozygosity in lymphoma DNA for rs2230926, rs661561, rs5029948 and/or rs2307859. This result will be further investigated with FISH. Overall, 8/16 patients (50%) had a functional abnormality of the *TNFAIP3* gene within germinal or lymphoma DNA.

Conclusion: Among patients with pSS and lymphoma, functional abnormalities of the *TNFAIP3* gene were present in germinal and lymphoma DNA of 31% and 50%, respectively. These data strongly support a two-hit process for lymphomagenesis in autoimmunity, in which both germinal and somatic abnormalities of A20 lead to impaired control of NFkB activation and an increased risk of lymphoma.

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Investigation of the Interaction Between Smoking and TRAF1/C5 on Radiological Severity of Inflammatory Polyarthritis. Lily M. Wheeler, Sebastien Viatte, Suzanne Verstappen, Deborah P. Symmons, Jane Worthington and Anne Barton. Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom

Background/Purpose: A number of factors have been identified as contributing to the severity of rheumatoid arthritis (RA), including SNP markers at the TRAF1/C5 region (rs2900180 and rs10760130). The role of smoking in RA disease severity is debated in the literature. We investigated whether smoking status conditions the association of TRAF1/C5 severity variants in patients with recent onset inflammatory polyarthritis (IP).

Methods: Data were collated from the Norfolk Arthritis Register, a prospective inception cohort for recent onset IP recruited from both primary and secondary care. X-rays were taken on patients who satisfied the ACR criteria for RA at one year and on all patients at 5 years follow-up. DNA and X-ray data were available for 1860 patients and X-ray with smoking data for 1789 patients. The interaction between smoking status at baseline and the carriage of polymorphisms at the TRAF1/C5 region with radiological damage, as measured using the Larsen score or the presence of erosions, was investigated longitudinally to include repeat measurements in the same individual at different time points. Interaction was defined as significant departure from a multiplicative model of the individual odds ratios (OR).

Results: Smoking status was not associated with erosions, whilst the carriage of rs2900180 alleles was significantly associated with erosions (OR: 1.82 (95% CI 1.1, 3.0), p-value 0.019). An association was found in ever smokers (OR 3.39 (95% CI 1.7, 6.8), p-value 0.001); when stratified into current smokers and previous smokers, this association was significant in previous smokers (OR: 4.09 (95% CI 1.7, 9.6), p-value 0.001). The OR followed the same direction for current smokers (OR 2.25 (95% CI 0.7, 7.7), p-value 0.196), but not for non-smokers (OR: 0.61 (95% CI 0.2, 1.6), p-value 0.307). The interaction between ever smoker status and the carriage of rs2900180 departed significantly from multiplicativity (interaction OR: 5.56 (95% CI 1.8, 17.6), p value 0.004). The interaction between previous smoker status and the carriage of rs2900180 departed significantly from the multiplicative model (interaction OR: 6.83 (95% CI 2.0, 23.7), p-value 0.003); however the interaction was not significant in current smokers. Consistent results and a significant interaction were also found when using the Larsen score as outcome variable in longitudinal modelling. Total smoking duration and the length of time between smoking cessation and disease onset were, independently, highly significantly correlated with erosions in previous smokers—if the smoking duration is longer, there is a higher the risk of erosive disease. Analysis of rs10760130 showed similar patterns of associations and interactions.

Conclusion: These results demonstrate an interaction between ever smoker status and the carriage of markers at the *TRAF1/C5* region on erosive disease in IP/RA patients. These findings support a model of RA pathogenesis in which smoking prevalence and time prior to disease onset affects the development of erosive disease in genetically predisposed individuals and underlines the importance of gene-environment interactions. We are currently validating these findings in another large data set.

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Identification of Clinical and Genetic Factors That Influence the Response to Methotrexate in Japanese Rheumatoid Arthritis Patients: Genome-Wide Association Study. Taku Suzuki[1], Katsunori Ikari[1], Yoshiaki Toyama[2], Atsuo Taniguchi[1], Nao Nishida[3], Katushi Tokunaga[3], Hisashi Yamanaka[1] and Shigeki Momohara[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Keio University, Tokyo, Japan, [3]Department of Human Genetics, Graduate School Of Medicine, University of Tokyo, Tokyo, Japan

Background/Purpose: Methotrexate (MTX) is the anchor drug for the treatment of rheumatoid arthritis (RA).The aim of this study was to identify clinical and genetic factors that influence the response to MTX in Japanese RA patients.

Methods: The present study is part of IORRA (Institute of Rheumatology RA cohort) project with an enrollment of nearly 5000 RA patients. Of these, 2244 patients, who received MTX therapy, were enrolled in this study. Efficacy of MTX treatment at six months after the first administration was evaluated using European League Against Rheumatism (EULAR) response criteria. First, the association between clinical factors and EULAR response of MTX treatment was studied using multiple regression analysis (independent variable: MTX dose, sex, age of onset and rheumatoid factor status). The analysis was performed using the R software package. Then, we performed a genome-wide association study (GWAS) to define genetic factors that influence response to MTX treatment in 132 RA patients using the detected clinical factors as covariates. Affymetrix Genome-Wide Human SNP Array 6.0 that included more than 906,600 single nucleotide polymorphisms (SNPs) was used for GWAS (Filtering criteria: genotype call rate 0.9 per SNP and per individual, minor allele frequency 0.05, P value for Hardy-Weinburg equilibrium test 0.0001). Logistic regression analysis implemented in PLINK was used to test the association.

Results: Initial dose of MTX had a significant impact on EULAR response of MTX treatment (P=0.0002), while the other factors did not show any association. There were 580,254 autosomal SNPs from 132 patients that met filtering criteria. Twenty-six SNPs associated with the response to MTX treatment at $P<1\times10^{-4}$, but none of them could reach genome-wide significance levels.

Clinical factors associated with response to MTX treatment

	estimate	P
MTX dose	0.082	0.0002
gender	−0.046	0.71
age of onset	0.001	0.81
RF	0.000	0.13

Conclusion: While initial MTX dose was significantly associated with EULAR response of MTX treatment in Japanese RA patients, our GWAS demonstrated that the SNPs did not have any significant effect on the response to MTX treatment.

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Genome-Wide Association Study of Rheumatoid Arthritis, Stratified by Smoking Status. Darren Plant[1], Deborah P. Symmons[1], Jane Worthington[1], David Strachan[2] and Anne Barton[1]. [1]University of Manchester, Manchester, United Kingdom, [2]St George's, University of London, London, United Kingdom

Background/Purpose: Tobacco smoking is well recognised as a major preventable risk factor for the development of rheumatoid arthritis (RA); however the mechanism of action remains unclear. Cigarette smoke condensates induce proinflammatory cytokine expression from lung epithelial cells, whilst deimination of the amino acid arginine to citrulline in alveolar macrophages occurs in individuals who smoke. Interestingly, the most compelling genetic risk factor for RA development is conferred by human leukocyte antigen *(HLA)-DRB1*, with the greatest risk seen in smokers who have a positive titre for autoantibodies to citrullinated peptide (anti-CCP). These data support gene environment interactions in RA patients. We hypothesised that non-HLA genetic risk markers for RA may also be modified by smoking status. In order to test this, we conducted genome-wide association (GWA) analyses in UK individuals, stratified by smoking habits.

Methods: 1,312 UK RA patients (never smoked (n=492), past smoker

(n=558) and current smoker (n=262)) along with 1,480 controls (never smoked (n=426), past smoker (n=712) and current smokers (n=342)) were genotyped for a total of 459,446 single nucleotide polymorphisms (SNPs), using the affymetrix 500k array (www.wtccc.org). GWA analyses were performed within each of the three smoke status groups. Markers with minor allele frequency >5% and demonstrating moderate association ($p < 10^{-5}$) with RA susceptibility in the initial analyses were selected for replication. The replication dataset comprised 715 UK RA patients (never smoked (n=260), past smoker (n=340) and current smoker (n=115)), genotyped using the Sequenom MassArray platform; and 5,016 UK 1958 birth cohort controls (www.b58cgene.sgul.ac.uk; never smoked (n=1,448), past smoker (n=2,365) and current smokers (n=1,203)), genotyped using the illumina 550k array. Anti-CCP data were available for 1,307 (81% positive) patients in the discovery and 643 (81% positive) patients in the validation sample.

Results: 14 SNP markers were included in a Sequenom plex for replication. One SNP failed to genotype successfully, leaving 13 markers available for analysis. The major allele of the marker rs1733717, mapping to the mannan binding lectin *(MBL)-2* gene, correlated with a reduced risk of RA development in all smoking groups in the discovery sample. This finding was replicated in past smokers (OR 0.50 (95%CI 0.15, 0.86)) $p=1.9E^{-6}$). The marker rs6679677 mapping to *PTPN22* was correlated with RA risk in all smoking groups in the discovery and replication sample. No other marker replicated convincingly. Results remained qualitatively the same following stratification by anti-CCP status.

Conclusion: These data support a role for *MBL2* as a modifier of RA susceptibility irrespective of smoking status and suggest that the increase in risk of RA conferred by *PTPN22* is not modified by smoking history. Larger sample sizes are likely to be required to exclude further gene-smoking interactions as modifiers of RA susceptibility risk.

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Genome-Wide Association Analysis of Rheumatoid Arthritis Patients Treated with Anti-TNF Medication. Marieke J.H. Coenen[1], Masha Umicevic-Mirkov[1], Judith A. Wessels[2], Sita H. Vermeulen[1], Erik J. Toonen[1], Annette T. Lee[3], Remco R. Makkinje[1], Wietske Kievit[1], Hans Scheffer[1], Tim L. Jansen[4], Ellen A. Dutmer[5], Timothy R.D. Radstake[6], Mart A.F. van de Laar[7], Pilar Barrera[1], Piet L.C. van Riel[1], Henk-Jan Guchelaar[2], Peter K. Gregersen[8] and Barbara Franke[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Feinstein Institute Med Rsch, Manhasset, NY, [4]Medical Centre Leeuwarden, Netherlands, [5]Gelderse Vallei Hospital, Ede, Netherlands, [6]Radboud University Nijmegen Medical Centre, Nymegen, Netherlands, [7]Medisch Spectrum Twente & Twente University, Enschede, Netherlands, [8]Feinstein Institute Medical Reschearch, Manhasset, NY

Background/Purpose: Treatment strategies blocking tumour necrosis factor (anti-TNF) have proven very successful in patients with rheumatoid arthritis (RA). However, a relevant subset of patients does not respond for reasons that are unknown. Although there is some indication that genetic variants may influence the response to TNF blockers, there are currently no means of identifying these patients prior to treatment start.We aimed at identifying genetic factors predicting anti-TNF treatment outcome in patient with RA using a genome-wide association approach. We aimed at identifying genetic factors predicting anti-TNF treatment outcome in patient with RA using a genome-wide association approach.

Methods: We selected patients with RA treated with antibodies directed against TNF from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry and the database of Apotheekzorg, which facilitates the Dutch distribution of adalimumab. Disease activity scores (DAS) 28 at baseline and after 14 weeks were available of 872 patients. Single nucleotide polymorphisms (SNPs) were genotyped using the Illumina HumanHap550-Duo BeadChip or the Human660W-Quad. Association analysis using the DAS28 change as outcome was performed (co-variates DAS28 at baseline and methotrexate as co-medication) using the whole genome association analysis toolset in PLINK.

Results: 516168 SNPs passed quality control. No findings passed the threshold for genome-wide significance (p-value $\leq 1\times10^{-8}$). Eight SNPs showed suggestive association with DAS28 change with a p-value$<10^{-6}$. Seven of these were located in genes (*ALK, NKAIN3, CETP, CICP10, L3MBTL3, PBX3, RPL18P1*). The top associated gene *ALK* ($p=8.11\times10^{-7}$) is involved in apoptosis one of the working mechanisms of anti-TNF. Pathway analysis, including all SNPs with a p-value $<10^{-4}$, was performed using Ingenuity. This resulted in the identification of four gene networks, two of these could be linked to apoptosis. In addition the second largest network linked the genes to TNF and its downstream signalling pathway. Replication of the top 50 associated SNPs in ~1500 RA patients treated with anti-TNF is ongoing.

Conclusion: The GWA approach is a potent tool for the identification of new candidate biomarkers predicting anti-TNF response. Suggestive findings will be replicated in larger, independent patient cohorts to prove whether the identified SNPs are associated with treatment outcome.

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An Insertion Mutation in the MDFIC (MyoD Family Inhibitor Domain Containing) Gene Defines a Novel Autoinflammatory Syndrome Associated with Lymphedema. Ahmet Gul[1], Duran Ustek[2], Gulen Hatemi[3], Hulya Azakli[2], Zeliha Emrence[2], Fulya Cosan[2], Aris Cakiris[2], Neslihan Abaci[2], Muzaffer Arikan[2], Atilla Cakar[2], Nil Arisoy, Ozgur Kasapcopur[3] and Huri Ozdogan[3]. [1]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Istanbul University, Istanbul, Turkey, [3]Rheumatology, Istanbul, Turkey

Background/Purpose: Autoinflammatory syndromes encompass an expanding spectrum of disorders characterized by seemingly unprovoked inflammatory attacks resulting from inborn errors of the innate immune system. We previously described two patients, who were second degree cousins with shared features of recurrent inflammatory attacks lasting 3–10 days since the first year of life. These attacks are characterized by fever, erythematous/urticarial rash with hyperesthesia, serositis and edema on the face and extremities. The latter feature did not resolve completely between the attacks later in the course of the disease, and both patients eventually developed a lymphedema symmetrically affecting lower extremities and genitalia. Because of autosomal recessive inheritance pattern and availability of 3-generation family members, we aimed to identify the responsible gene using a homozygosity mapping approach.

Methods: Genomic DNA was isolated from 18 family members including two index patients; and all were genotyped using the human 370CNV SNP chip of Illumina. Homozygosity mapping was carried out to identify the candidate genomic regions using the SNP Variation Suite v7 of the Golden Helix. A targeted 385K Capture Array was prepared using the genomic DNA of four family members by NimbleGen for the mapped region; and all coding regions of the known genes were then deep sequenced using the GS-FLX 454 Titanium system (Roche Diagnostics). Confirmation of the identified variation and screening of healthy controls were done by using the classical DNA sequencing method.

Results: All individuals were successfully genotyped using the Illumina 370CNV chips. The homozygosity mapping revealed a 7.8Mb-long region in the long arm of chromosome 7 that was homozygous only in 2 patients and heterozygous in their parents; and a smaller homozygous segment was also identified in chromosome 14. We searched the mapped Chr7q31.1 region by exon sequencing of the all known 24 genes using the GS-FLX 454 system in the two index patients, one parent and one sibling. A homozygous insertion mutation in the exon 3 of the MyoD family inhibitor domain containing gene (MDFIC) was identified only in two index patients. MDFIC is a 247 amino acid long protein, and this insertion causes an amino acid changes at position 131 and 132 (p.131 M>N, p.132 H>A) and a frameshift at position 133, which inhibits the translation of its functional cysteine-rich C-terminal domain. This variation was confirmed by sequencing of genomic DNA of all the available family members. None of the screened 200 regionally matched healthy individuals was carrying this variation.

Conclusion: MDFIC gene was identified as the gene responsible for the manifestations of these two patients, who show features of autoinflammatory disorders and a later onset lymphedema. The gene is reported to be expressed in immune cells without a known function, and recent studies have indicated a role in the regulation of wnt/beta-catenin pathway. We suggest that this is a novel type of autoinflammatory disorder, and a loss-of-function mutation in the MDFIC gene may be associated with a dysregulated inflammatory response affecting the wnt/beta-catenin pathway, which may also be responsible for the development of lymphedema.

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Polygenic Modeling of Genome-Wide Association Study Data Reveals Hidden Heritability of Rheumatoid Arthritis Risk. Eli A. Stahl[1], Daniel Wegmann[2], Peter Kraft[3], Henrik Kallberg[4], Fina Kurreeman[5], Peter K. Gregersen[6], Lars Alfredsson[7], Katherine A. Siminovitch[8], Jane Worthington[9], Paul de Bakker[1], Soumya Raychaudhuri[1] and Robert M. Plenge[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Department of Ecology and Evolutionary Biology, University of California, Los Angeles, CA, [3]Department of Biostatistics, Harvard School of Public Health, Boston, MA, [4]Rheumatology Unit, Department of Medicine, Karolinska Institutet at Karolinska University Hospital Solna, Stockholm, Sweden, [5]Division of Rheumatology Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [6]Feinstein Institute Medical Reschearch, Manhasset, NY, [7]Institute of Environmental Medicine, Unit of Cardiovascular Epidemiology, Karolinska Institutet, Stockholm, Sweden, [8]Mount Sinai Hospital, Toronto, ON, [9]University of Manchester, Manchester, United Kingdom

Background/Purpose: Genetic studies of rheumatoid arthritis (RA) susceptibility have identified ~40 loci to date that explain approximately 18% of disease liability, whereas >50% is thought to be genetic. We hypothesized that much of the missing heritability is due to causal variants that are tagged by common SNPs on contemporary genome-wide association study (GWAS) arrays.

Methods: We estimated missing heritability and modeled its underlying genetic architecture by analyzing six GWAS datasets totaling 5,485 seropositive rheumatoid arthritis cases and 22,609 controls of European ancestry. After removing known RA risk loci, we assessed whether the remaining >2 million SNPs in aggregate could predict risk in independent case-control collections. We then used polygenic modeling and approximate Bayesian computation to estimate distributions of the number, minor allele frequency and effect size of undiscovered common variants. Heritability analysis using mixed linear model regression analysis was used to corroborate our results. In order to understand whether these undiscovered associations tag rare or common causal variants, we simulated hypothetical case-control datasets using 1000 Genomes Project data.

Results: We found that polygenic risk scores of additive, log-odds weighted risk allele counts at independent SNPs achieving $P<0.05$ in discovery GWAS are consistently associated with RA case-control status in independent validation data ($P = 1\times10^{-9}$). Both methods estimated that an additional 20% of rheumatoid arthritis disease variance is explained by at least hundreds of SNPs in contemporary GWAS. Simulations of causal and marker variants revealed that an underlying genetic model where most of the causal alleles are common is much more consistent with our observations than models where most of causal alleles are rare.

Conclusion: We conclude that hundreds of causal variants, most of which are common in general population but with a small effect on disease risk, explain an additional 20% of variance in RA risk. Many of these causal variants are discoverable by larger GWAS. Our approach can be applied to understand genetic architecture of many complex traits where GWAS data are available.

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DO Carriers of A MEFV Mutation Have Any Selective Advantage to A Pathogen Endemic In the Same Geography? Serdal Ugurlu[1], Aynur Engin[2], Gulen Hatemi[1], Gulay Ozgon[3], Elif Akyayla[3], Mehmet Bakir[2] and Huri Ozdogan[1]. [1]MD, Division of Rheumatology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]MD, Department of of Infectious Diseases, Medical Faculty, University of Cumhuriyet, Sivas, Turkey, [3]Nesiller Genetic Lab, Istanbul, Turkey

Background/Purpose: To explain the high level of MEFV heterozygots in Mediterranean basin, it has been speculated that carriers of FMF mutations might have a selective advantage because of increased resistance to a pathogen endemic to this area. The carrier rate for MEFV gene in Sivas, a city in central Turkey is as high as 1:3. Crimean-Congo Hemorrhagic fever (CCHF) a tick-borne disease caused by an arbovirus, associated with high mortality, is also endemic in the same geographical region. This gave us a unique opportunity to test whether MEFV heterozygotes have any survival advantage in this ongoing CCHF endemic.

Methods: MEFV gene mutations were detected with PCR analysis and direct sequencing of Exon 10 and Exon 2, in 100 patients with a definite diagnosis of CCHF followed in Cumhuriyet University, Sivas / Turkey, (mean age 45.6±17, 58 M: 42 F). All CCHF patients were classified into two groups in terms of disease severity (severe and mild), according to the predictive factors for fatal outcome reported by Swanepoel et al (1). MEFV gene mutations were also analyzed with the same methods in 91 healthy blood donors (HC) living in Sivas.

Results: Among the 100 patients with CCHF, 65 had mild and 35 had severe disease. There were 11 deaths in the severe group. Among the CCHF patients 62 patients carried either an exon 10 or exon 2 mutation compared to 33 in the HC ($p<0.001$). This significant difference was due to the increase in Exon 10 mutations (41/100 vs 10/91, $p<0.001$) which disappeared when only Exon 2 mutations were considered (38/100 vs 26/91, $p>0.1$). The number of patients with 2 mutations were also significantly more common among CCHF group ($p<0.001$). Regarding exon 2 we determined a haplotype of 4 SNPs (at positions: 102, 138, 165, 202) in 32 patients compared to 9 in HC ($p<0.001$), and described 4 new mutations in Exon 10. In the mild group there were 37 and in the severe group 25 carriers ($p>0.1$). 63% of the survivors compared to 54% of those who died carried a MEFV mutation ($p>0.1$). The distribution of mutations with regard to disease severity did not reveal a significant difference. Also there was no difference between the number of mutations among survivors versus non-survivors.

Conclusion: Carrying a MEFV gene Exon 10, but not Exon 2 mutation does seem to increase the risk of developing CCHF infection however does not influence disease severity and outcome.

References:

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Elevated Expression of Inflammatory Mediators Cyclooxygenase-2, Its Product Prostaglandin E2 and Interleukin-1 Beta by Peripheral Blood Leukocytes in Symptomatic Knee Osteoarthritis. Mukundan Attur[1], Alexander Statnikov[2], Constantin F. Aliferis[2], Zhiguo Li[2], Svetlana Krasnokutsky[3], Jonathan Samuels[1], Jeffrey D. Greenberg[4], Jyoti Patel[1], Cheongeun Oh[5] and Steven B. Abramson[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]NYU Langone, New York, NY, [3]NYU Hospital for Joint Disease, New York, NY, [4]New York University School of Medicine, New York, NY, [5]New York University, New York, NY

Background/Purpose: OA is considered a *local* joint disease, with increasing recognition of the involvement of cartilage, bone and synovium. We and others have reported that inflammatory mediators, such as PGE2 and IL-1β, are produced by OA joint tissues, where they may contribute to disease pathogenesis. In the current studies we examined whether inflammatory events occurring within joint tissues could be reflected in the plasma and PBLs of patients with OA.

Methods: Two independent cohorts of patients with OA, and a cohort of healthy control subjects, were studied: 44 patients with tibiofemoral OA and 26 healthy control volunteers comprised the NYUHJD Learning Cohort, and 150 patients with knee OA and 21 health controls were enrolled in the NYUHJD Validation Cohort.

Results: Using support vector machine (SVM) methodology we constructed a combinatorial biomarker of OA based on microarray data of the Learning Cohort. Among these probe sets representing PGE2 synthase and cyclooxygenase could classify the case vs. control with 0.83 mean AUC (95% CI 0.72– 0.95) (AUC: area under ROC curve), as estimated by 10-fold cross-validation procedure. Further cluster analysis also revealed two distinct subclasses among these OA patients: those (OA1) with increased expression (>4-fold) of inflammatory genes (e.g., IL-1β, COX-2) compared to non-OA controls and those OA patients (OA2) with expression comparable to controls. Overexpression of inflammatory genes were validated using QPCR ($p<0.0001$). In association studies, patients in the OA1 group exhibited: a) greater JSW at baseline; b) higher WOMAC pain, stiffness and decreased physical function ($p<0.0001$), c) higher VAS pain ($p<0.001$) than OA2 group. Longitudinal studies indicated that OA1 patients with increased PBL IL-1b gene expression, were at higher risk for disease progression, as measured by change in JSW at 24 months (Table 1), Similarly COX-2 overexpressors had greater JSW 3.57 ± 1.91 mm Vs 3.13 ± 1.69 compared to OA patients with less than 2 fold COX-2 expression and higher WOMAC ($p<0.033$) and VAS ($p<0.041$) pain. To determine whether OA PBLs were "primed", we measured PGE2 production by whole blood PBL cultured (24h) ex vivo. PGE2 in controls did not change, while levels in OA patients increased 300% over baseline ($p<0.01$). In these validation cohort, the mean plasma PGE2 levels in OA patients was two-fold higher than in healthy controls (72 ± 33 vs. 163 ± 64 pg/ml, $p=0.001$).

	Mean (standard deviation)		
NYUHJD Validation Cohort	**OA^{IL-1} (n=74)**	**OA^{nl} (n=100)**	**p-value**
Joint space width (JSW) in mm at baseline	3.01 (2.1)	2.5 (1.94)	0.055
JSW (mm) at 24 months	2.53 (1.96)	2.4 (1.96)	0.614
Change (JSN)	0.48 (0.88)	0.097 (0.91)	0.0079

Conclusion: There is increased inflammatory mediator gene expression (COX-2, IL-1b) in a subset of patients with SKOA, which identifies a cohort of patients with increased pain who are at increased risk for disease progression. The data indicate that inflammatory events within joint tissues of patients with SKOA are reported in peripheral blood. These transcriptome and lipidomic signals of local joint inflammation merit further study as potential biomarkers for OA disease activity and progression.

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Genomic Deletions in *Phospholipase Cγ2* define a New Syndrome of Cold Urticaria, Antibody Deficiency and Susceptibility to Both Autoimmunity and Infection. Michael J. Ombrello[1], Elaine F. Remmers[1], Guangping Sun[2], Hirsh Komarow[2], Ivona Aksentijevich[1], Shrimati Datta[2], Parizad Torabi-Parizi[2], Naeha Subramanian[2], Neil Romberg[3], Tom D. Bunney[4], Rhona W. Baxendale[4], Hun Sik Kim[5], Jason Ho[2], Daniel C. Douek[2], Chhavi Gandhi[6], Alan A. Wanderer[7], Hane Lee[8], Stanley Nelson[8], Eric Long[5], Susan Moir[2], Eric Meffre[3], Matilda Katan[4], Daniel L. Kastner[1], Hal M. Hoffman[6] and Joshua D. Milner[2]. [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [3]Yale University School of Medicine, New Haven, CT, [4]Chester Beatty Laboratories, The Institute of Cancer Research, London, United Kingdom, [5]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD, [6]University of California at San Diego, La Jolla, CA, [7]University of Colorado Health Sciences Center, Aurora, CO, [8]University of California Los Angeles, Los Angeles, CA

Background/Purpose: Immune dysregulation occurs when the balance of finely-tuned immune regulatory networks is altered. Genetic analyses of Mendelian disorders manifesting these seemingly antithetical features may provide new insights into the molecular mechanisms that govern immune responses. We have identified three families with a novel, dominantly-inherited complex of cold-induced urticaria, antibody deficiency, and susceptibility to autoimmunity and infection through whom we sought to better understand the interface between autoimmunity and immunodeficiency.

Methods: Genetic investigations began with SNP genotyping and separate linkage analyses in two of the families. Mutational analysis included conventional and long-range PCR assays of both genomic DNA and cDNA, with direct sequencing of the PCR products. Immunophenotyping of these three families included flow cytometric studies, measurement of serum immunoglobulins and autoantibodies, lymphocyte stimulation assays, enzymatic assays, and confocal microscopic examination.

Results: Cold urticaria was present in all affected members of each family (n=27), and immunologic abnormalities were found in 26 of 27 patients. These included antibody deficiency (72%), recurrent infection (59%), atopy (52%), and autoimmunity (48%), which included the presence of antinuclear or other autoantibodies, autoimmune thyroid disease, vitiligo, inflammatory arthritis, and undifferentiated connective tissue disease. Affected subjects had depressed serum immunoglobulins M and A, decreased numbers of circulating NK and class-switched memory B cells, and impairment of B cell central tolerance. Patients' B cells also had impaired ligand-mediated activation, which was restored at subphysiologic temperatures. Using SNP genotyping and linkage analysis, we identified a single 7Mb candidate interval on chromosome 16q (LOD=4.2) in one family, which overlapped by 3.5Mb a disease-associated haplotype identified in another family. Given its importance in B, NK, and mast cells, *PLCG2* was selected from our candidate interval for mutational screening. Sanger sequencing of *PLCG2* cDNA from purified B-cells revealed heterozygous deletions of exon 19 in two families, and exons 20–22 in the third. Long-range PCR and genomic sequencing found three family-specific deletions in *PLCG2* (4.8–8.2kb) that co-segregated perfectly with cold urticaria, but were not detected in over 400 healthy control chromosomes. Of note, five of the six deletional breakpoints were within Alu or LINE repetitive elements, suggesting a role for repetitive element-mediated recombination in their genesis. The deletions, which are within an autoinhibitory domain of *PLCG2*, caused constitutive phospholipase activity, but paradoxically resulted in diminished activation of downstream signaling pathways.

Conclusion: We describe a novel immunodysregulatory syndrome in which deletions in *PLCG2* cause signaling abnormalities in multiple leukocyte subsets and a pleiotropic phenotype encompassing both excessive and impaired immune function.

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Ferritin and Hemochromatosis Polymorphisms Correlate with Clinical Characteristics in a Symptomatic Osteoarthritis Cohort. Lauren M. Kennish[1], Mukundan Attur[2], Xi Huang[3], Svetlana Krasnokutsky[4], Jonathan Samuels[2], Cheongeun Oh[5] and Steven B. Abramson[2]. [1]Hospital for Joint Diseases, New York, NY, [2]NYU Hospital for Joint Diseases, New York, NY, [3]New York University School of Medicine, New York, NY, [4]NYU Hospital for Joint Disease, New York, NY, [5]New York University, New York, NY

Background/Purpose: Iron may be a contributing risk factor for osteoarthritis (OA) development – increased iron is found in OA synovial fluid and is cytotoxic towards chondrocytes. Additionally, patients with hereditary hemochromatosis develop an OA phenotype that is associated with higher ferritin levels. We examined the hypothesis that serum ferritin correlates with clinical features in patients with symptomatic knee OA compared to controls and that this may be associated with hemochromatosis gene (HFE) polymorphisms.

Methods: 131 patients with symptomatic knee OA (diagnosed by ACR criteria, WOMAC score>125) and 21 controls were enrolled in a 2 year longitudinal study. Patients with inflammatory arthritis, infections, steroid use or major comorbid illnesses were excluded. Baseline clinical (age, gender, BMI, WOMAC pain score) and radiographic characteristics (Kellgren-Lawrence, KL, score) were obtained. Cross sectional peripheral blood samples were analyzed for serum ferritin at baseline and 18months by ELISA. HFE genotyping was performed.

Results: Ferritin was measured in 131 OA patients with mean age 65 years (35% men), BMI 26.5 and 20 controls with mean age 56 years (55% men), and BMI 26.5. Men were found to have higher ferritin than women – 62.5 vs. 38.2 ng/ml, p=0.0002, and ferritin correlated with increasing age (r=0.175, p=0.058). Men with OA had a trend towards higher mean ferritin than those without OA when adjusted for age (67.7 vs. 40.4ng/ml, p=0.068). In the total population, ferritin levels greater than 100ng/ml were observed in 13% of patients with OA versus 0% of controls. There was a trend towards higher ferritin in patients with baseline radiographic incidence of OA (KL 0–1: 42.3 vs. KL 2–4: 63.3ng/ml, p=0.276) and in those with more severe radiographic OA (KL 1–2: 48.1 vs. KL 3–4: 71.3ng/ml, p = 0.236). Those with a higher KL score ranging from 0 to 3 were found to have higher serum ferritin, which may be predictive of severity of OA. Baseline WOMAC pain scores in the total OA population showed a weak positive correlation with serum ferritin levels (r= 0.112, p = 0.0148); this positive correlation between WOMAC pain and ferritin was stronger in males (r=0.215, p = 0.008). OA patients had a higher frequency of homozygous HFE gene polymorphism C282Y/C282Y (2.29%) compared to controls (0%) and published population controls (0.44%), and these subjects (n=3) had higher ferritin compared to wild type (n=98) (47.4 vs 140.1ng/ml, p<0.0008).

Conclusion: Ferritin, a marker for body iron storage, increases with age and male gender. Men with OA exhibit higher ferritin levels than those without OA when adjusted for age and levels of ferritin correlated with radiographic severity and WOMAC pain scores. In selected OA patients, the presence of the C282Y/C282Y HFE gene polymorphism was associated with higher ferritin levels. Our data suggest that increased ferritin levels, possibly in part due to HFE polymorphisms, may promote cartilage damage and pain in patients with knee OA. These findings merit further investigation of ferritin as a biomarker of disease severity and progression in a larger cohort.

ACR Poster Session A
Imaging of Rheumatic Disease I: Ultrasound, Optical and Preclinical Imaging
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Patients with Rheumatoid Arthritis On Anti-TNF Therapy; Responders with Major Reduction In Power Doppler Activity Can Be Identified After One Month. Hilde B. Hammer, Britt Birkelund and Tore K. Kvien. Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

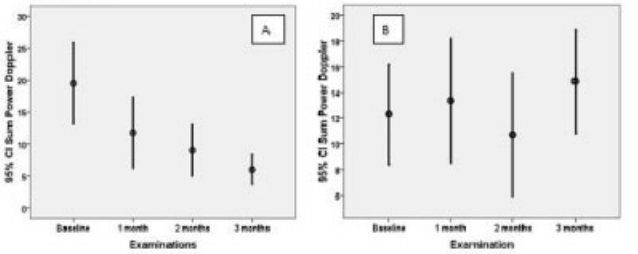
Background/Purpose: Power Doppler (PD) ultrasonography (US) detects inflammatory activity in patients with rheumatoid arthritis (RA) and is highly responsive to anti-TNF treatment. The present objective was to follow RA patients starting anti-TNF treatment with PDUS and clinical assessments to

explore whether any variable could predict a major decrease in PDUS after 3 months.

Methods: Patients with RA starting anti-TNF treatment were consecutively included and examined at baseline and after 1, 2 and 3 months with US of 36 joints and 4 tendons (wrist (radiocarpal, intercarpal and radioulnar), MCP 1–5, PIP 2 and 3, elbow, knee, talocrural, MTP 1–5, extensor carpi ulnaris and posterior tibialis tendons bilaterally). The PD and B-mode (BM) synovitis were scored semi-quantitatively (0–3), and sum scores from all joints and tendons were calculated. In addition, the patients were assessed clinically with DAS28, assessor global VAS (study nurse), ESR and CRP. Patients with at least 40% improvement of sum score PD at the 3 months examination was defined as responders. The results of US, clinical and laboratory assessments at baseline and after 1 month were explored by Mann-Whitney tests to examine for associations with the responders.

Results: A total of 50 patients were included (mean (SD) age 51.7 (13.2) years, disease duration 7.8 (5.8) years, 74% anti-CCP positive and 84% women, with 38% using Remicade, 34% Enbrel, 16% Humira and 12% Simponi). A total of 57% of the patients were defined as PD responders, and they had significantly lower DAS28, assessors global VAS and number of swollen joints ($p=0.023$–0.031) at the 3 months examination. Baseline values of sum scores PD or BM, DAS28, assessors global VAS, ESR or CRP did not separate between responders and non-responders. At 1 month examination the only variable differing between responders and non-responders was the sum score PD, with a significant reduction in sum score PD in the responders versus non-responders 7.4 (8.6) versus −0.5 (7.3) ($p = 0.002$, figure 1A and B).

Figure 1
Error bar plot (with 95% CI) of the sum PD scores in responders (A) vs non-responders (B) during treatment with anti-TNF.



Conclusion: PD activity is associated to erosions in RA patients. However, in the present study more than half of the patients achieved a major decrease in PD scores after starting anti-TNF treatment. It is an advantage to identify responders early, and the present results indicate that a significant reduction of PD activity already after 1 month predicts response to biological treatment.

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New Aspects Concerning the Activity of Established Rheumatoid Arthritis Under a Tocilizumab Therapy. Maria Hoehle. Rheumatology, Hamburg, Germany

Background/Purpose: To determine remission of the rheumatic process, recent publications point out the importance of radiological parameters, besides scores like TJC, SJC, CrP, patient global assessment, or the SDAI. **1)** Since RA is usually a progressing inflammatory disease, native radiological diagnostics is not sufficient for portraying inflammatory activities in grades, and for comparing them with each other during the further course of the disease. Medical imaging by sonography (colour and power Doppler), as well as high-field MRI with contrast medium for the additional assessment of the cartilage/bone oedema, become increasingly important. **2)** Tocilizumab induces a rapid improvement of the patient's health-related QoL and a decrease in CrP and ESR values, but active inflammations may still exist at the joint-related structures. In order to objectify these, the use of sonography (colour and power Doppler) and high-field MRI is indispensible.

Objectives: The course of chronic active inflammatio at the affected joint structures can be quantitatively and qualitatively measured by aforementioned imaging techniques. The aim of the exact inflammation definition is to optimize the cytokine therapy and to determine the time for an OFF therapy.

Methods: 23 RA patients (17 women, 6 men), treated with tocilizumab (8 mg tcz/kg BW), were examined retrospectively. In 7 women and 4 men, tcz was given as monotherapy. At baseline and every 4 weeks DAS 28, CrP, ESR and sonography of a reference joint (wrist joint) were examined, every 6 months, additional high-field MRI. The evaluation was carried out using MRI (RAMRIS) and sonography score.

Results: In all 23 patients, in week 4 DAS value was within the normal range. In 19 patients ESR and CrP value were within the normal range. In 3 further patients (2 of which were men), the ESR and CrP values did not normalize after the second tcz infusion cycle (week 8). In one female patient, the ESR and CrP values normalized after 12 weeks. During the further course of the therapy, the ESR and CrP values in all 23 patients remained in the normal range. At baseline, in all 23 patients the activity score for MRI (RAMIS above 5),and for sonography (PD grade II, synovitis grade II, tenosynovitis grade II) were high. 1 year after the tcz therapy, a normal sonography score and RAMIS score were found in 3 female patients, in further 5 female patients after 2 years. In 16 female patients, a decrease in the score values was found after 3 months (no later than 6 months) for sonography and MRI. However, increased activities could still be seen in imaging diagnostics. The tenosynovitis activity's score value was significantly higher compared to the arthrosynovitis' score. No AE, including SAE, occurred during the observation period – except for two allergic reactions.

Conclusion: The cytokine therapy with tocilizumab leads to a rapid decrease in the inflammation laboratory parameters, and hence to a normalization of DAS 28. However, the inflammation-verifying imaging still showed inflammation at the wrist joints in 70% of the patients. The aforementioned imaging is still highly important for assessing the complete remission in rheumatological practice.

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Metrological Properties of Composite Scoring Systems for Synovitis in Rheumatoid Arthritis: Results From a Randomized, Prospective, Multicentre Study. Peter Mandl[1], Peter V. Balint[2], Yves Brault[3], Marina Backhaus[4], Maria-Antonietta D'Agostino[5], Walter Grassi[6], Désirée van der Heijde[7], Eugenio De Miguel[8], Richard J. Wakefield[9], Isabelle Logeart[3] and Maxime Dougados[10]. [1]Medical University of Vienna, Vienna, Austria, [2]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [3]Pfizer, Paris, France, [4]Charite University Hospital, Berlin, Germany, [5]Versailles-Saint Quentin en Yvelines University- APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, France, [6]Università Politecnica delle Marche, Jesi, Italy, [7]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [8]La Paz University Hospital, Madrid, Spain, [9]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals, Leeds, United Kingdom, [10]Paris-Descartes University, Cochin Hospital, Paris, France

Background/Purpose: To propose different global composite scoring systems for measuring synovitis in rheumatoid arthritis (RA), utilizing information derived from clinical, grey-scale ultrasound (GS) and Power Doppler ultrasound (PD) examination. To evaluate intra-observer reliability, face validity, predictive validity and discriminant capacity as compared to DAS28 and SDAI. To assess the classification of patients according to disease activity using the various composite scoring systems.

Methods: This 52-week, prospective, open-label, randomized, parallel-group, multicenter, outpatient study was conducted in RA subjects with moderate disease receiving etanercept (ETN) combined with methotrexate or various DMARDs. A total of 12 different scoring systems were evaluated, based on clinical, GS and PD-derived data, and calculated according to the DAS28 or SDAI indices. In the composite indices the 28-swollen joint count (SJC) was either replaced by the number of swollen joints showing also signs of synovitis on either GS and/or PD, or supplemented by joints deemed non-swollen on clinical examination in which the presence of synovitis was detected by either GS and/or PD (Table 1). Intra-observer reliability of each proposed synovitis scoring system was calculated by intraclass correlation coefficient and standard error of measurement. Face validity was evaluated as the degree of association between CRP or ESR and each scoring system, and was assessed using Pearson's correlation coefficient. For discriminant capacity the ETN and the conventional DMARD treatment groups were evaluated separately and the difference in standardized response mean was calculated between baseline and week 12.

Results: Data from 62 patients were analyzed. Reliability, face validity and discriminative capacity were found to be similar for the composite indices as compared to their respective, clinical data-based counterparts. Using composite indices in which the SJC was supplemented also by joints in which synovitis was detected by either GS and/or PD, a significantly larger number of patients could be classified as having high disease activity at the screening visit (Table 1).

Table 1.

	LDA (no., % of patients)	MDA (no., % of patients)	HDA (no., % of patients)	Discriminant capacity (SRM, 95% CI)
DAS28 clinical	1 (1.6%)	60 (96.8%)	1 (1.6%)	0.87 (0.28; 1.50)
DAS28 GS[a]	1 (1.6%)	60 (96.8%)	1 (1.6%)	0.85 (0.28; 1.45)
DAS28 PD[b]	1 (1.6%)	60 (96.8%)	1 (1.6%)	0.80 (0.21; 1.43)
DAS28 GS/PD[c]	1 (1.6%)	60 (96.8%)	1 (1.6%)	0.79 (0.20; 1.43)
DAS28 +GS[d]	2 (3.2%)	18 (29%)	42 (67.7%)	0.70 (0.15; 1.44)
DAS28 +PD[e]	2 (3.2%)	32 (51.6%)	28 (45.2%)	0.88 (0.33; 1.61)
DAS28 +GS/PD[f]	2 (3.2%)	17 (27.4%)	43 (69.4%)	0.72 (0.15; 1.44)
SDAI clinical	24 (38.7%)	38 (61.3%)	0 (0%)	1.11 (0.25; 28.73)
SDAI GS[a]	25 (40.3%)	37 (59.7%)	0 (0%)	1.09 (0.21; 51.16)
SDAI PD[b]	31 (50%)	31 (50%)	0 (0%)	1.17 (0.27; 742 4)
SDAI GS/PD[c]	31 (50%)	31 (50%)	0 (0%)	1.17 (0.27; 742.4)
SDAI +GS[d]	6 (9.7%)	37 (59.7%)	19 (30.6%)	0.61 (−0.77; 3.43)
SDAI +PD[e]	11 (17.7%)	43 (69.4%)	8 (12.9%)	0.52 (−0.51; 1.88)
SDAI+GS/PD[f]	6 (9.7%)	36 (58%)	20 (32.3%)	0.84 (−0.24; 3.86)

[a] clinical SJC replaced by swollen joints that also show signs of synovitis on GS (grey-scale ultrasound)
[b] clinical SJC replaced by swollen joints that also show signs of synovitis on PD (Power Doppler ultrasound)
[c] clinical SJC replaced by swollen joints that also show signs of synovitis either on GS and/or PD
[d] clinical SJC supplemented by non-swollen joints showing signs of synovitis on GS
[e] clinical SJC supplemented by non-swollen joints showing signs of synovitis on PD
[f] clinical SJC supplemented by non-swollen joints showing signs of synovitis either on GS and/or PD
LDA: low disease activity (DAS28 <3.2, SDAI ≤11)
MDA: moderate disease activity (DAS28 3.2–5.1; SDAI 11.1–26)
HDA: high disease activity (DAS28>5.1; SDAI>26)
SRM: standardized response mean

Conclusion: Composite scoring systems had similar metrological properties as their clinical counterparts but allowed for a significantly larger number of patients to be reclassified to either high or moderate disease activity at the screening visit, thus influencing eligibility for biologic therapy.

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Ultrasonography Assessment of the Hands As a Measure of Disease Activity in Rheumatoid Arthritis Patients: Correlation with DAS 28 Score. Carla Saucedo[1], Santiago Ruta[1], Javier Rosa[1], David A. Navarta[1], Maria Victoria Garcia[1], Ricardo Garcia Monaco[2] and Enrique R. Soriano[1]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires

Background/Purpose: Disease activity score (DAS) 28 is widely accepted for the assessment of disease activity in rheumatoid arthritis (RA). Ultrasound (US) has become an important tool to monitor inflammatory activity in RA patients. The objective was to correlate different US indexes constructed by the inclusion of different number of joints with the level of disease activity measured by DAS 28 in RA patients.

Methods: RA (2010 ACR/EULAR criteria) consecutive patients > 18 years old attending the outpatient Rheumatology Unit were included. Exclusion criteria were: hands surgery and/or corticosteroid injection within the last 2 months. All patients were clinically assessed by the attending rheumatologist and the level of disease activity was measured using DAS 28 score. In the same day US examination was performed by the same rheumatologist sonographer blinded to clinical data, using a My Lab 70 (Esaote) machine equipped with 6–18 MHz broad band multifrequency linear transducer. US assessment consisted in bilateral examination of the dorsal aspect of wrist, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. The following abnormal US findings were examined and classified as present or absent: joint cavity widening (JCW), due to synovial fluid and/or synovial hypertrophy, and power Doppler (PD) signal. Three different ultrasound indexes were constructed by the sum of JCW and PD scores of individual joints included in each index: index A including both wrists, all bilateral MCP and PIP joints (22 joints) score; index B: including both wrists, both 2nd and 3rd MCP and both 2nd and 3rd PIP (10 joints); and index C: including both wrists and both 2nd and 3rd MCP (6 joints). Correlation between the indexes and DAS28 was performed with Spearman's rho test. Receiver operating characteristic (ROC) analysis was used to evaluate the discriminative utility of each index, and detect the optimal cut off value.

Results: Sixty RA patients (85% female, mean age 59 ± 15 years, 75% were anti CCP positive, 55% were FR positive, mean DAS 28 score 3.69 ± 1.42) were evaluated. All three indexes were significantly higher in patients with active disease (table). Index C had the best correlation with DAS28 (table). Index C showed a very good discriminative value for disease activity defined as a DAS28 score >3.2 and for absence of remission defined by a DAS28 score >2.6 (area under de ROC curve = 0.75 (95% CI: 0.62–0.88) and=0.80 (95% CI:0.67–0.93), respectively). A cut off value of 3 points showed sensitivity of 88.89% and specificity of 66.67% for absence of remission defined by a DAS28 score >2.6.

Table. US indexes and their correlation with DAS28 score.

	Index A: 22 joints (both wrists and all MCP and PIP joints)	Index B: 10 joints (bilateral wrists, 2nd and 3rd MCP and 2nd and 3rd PIP)	Index C: 6 joints (bilateral wrists, and 2nd and 3rd MCP)
Correlation with DAS28 score (Spearman's rho test)	rho= 0.4513 (p=0.0003)	rho= 0.4979 (p=0.0001)	rho= 0.5020 (p<0.0001)
Mean (SD)US score in Active (DAS28>2.6; n=45) vs. inactive disease (DAS28<2.6; n=15)	12.2 (9.8) vs. 5.8 (7.2); p=0.0231	8.3 (5) vs. 3.6 (3.8); p=0.0014	6.4 (3.4) vs. 2.8 (2.6); p=0.0005

Conclusion: US indexes including JCW and PD scores showed moderate to good correlation with DAS28 score. The index with fewer included joints (6 joints) showed the best correlation and discriminative value, perhaps reflecting better clinical assessment of these limited number of joints by the rheumatologist.

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Sensitivity to Change of the 7-Joint Ultrasound (US7) Score Among Patients with Different Musculoskeletal Diseases Under Twelve Months of Therapy. Tina M. Backhaus[1], Sarah Ohrndorf[2], Herbert Kellner[3], Johannes Strunk[4], Wolfgang Hartung[5], Horst Sattler[6], Christof Iking-Konert[7], Gerd R. Burmester[8], Wolfgang A. Schmidt[9] and Marina Backhaus[10]. [1]Berlin, Germany, [2]Charité –University Medicine Berlin,, Berlin, Germany, [3]Centre for Inflammatory Joint Diseases, Munich, Germany, [4]Cologne, Germany, [5]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, [6]Klinikum Ludwigshafen, Ludwigshafen, Germany, [7]University Hospital Hamburg Eppendorf, Hamburg, Germany, [8]Charité - Universitätsmedizin Berlin, Berlin, Germany, [9]Med Ctr Rheumatol Berlin Buch, Berlin, Germany, [10]Charite University Hospital, Berlin, Germany

Background/Purpose: Estimating the US7 score's sensitivity to change throughout a cohort of patients with different musculoskeletal disorders under various therapies (DMARD and Biologics). Comparing US7 score's results with clinical and laboratory parameters over twelve months.

Methods: 506 patients with rheumatoid arthritis (RA; 87.9%), psoriatic arthritis (PsA; 9.7%), ancylosing spondylitis with peripheral arthropathy (1.8%), undifferenciated polyarthritis (0.4%) and juvenile idiopathic arthritis (JIA; 0.2%) with a mean ± SD disease duration of 8.5 ± 9,5 years were set after a baseline examination either on a DMARD or a Biological therapy (single/ combination therapy). Musculoskeletal ultrasonography (US7 score) was done during baseline examination as well as during follow-ups after 3, 6, and 12 months. Furthermore, DAS28, CRP and ESR were assessed. According to their therapy the cohort was divided into four groups: firstline DMARD after new adjustment (26%), therapy switch from DMARD to DMARD (24%), firstline Biological after DMARD therapy (34%), therapy switch from Biological to Biological therapy (12%). One subcohort (12%) did not have any therapy after twelve months.

Results: In both DMARD groups the synovitis score and the tenosynovitis score in GSUS and PDUS as well as ESR, CRP and DAS28 significantly decreased (p<0.05) after twelve months. A significant reduction of erosions could not be detected.

Patients who received a Biological therapy for the first time after DMARD therapy illustrated a decline in the synovitis score as well as in the tenosynovitis score in GSUS and PDUS, and ESR and CRP significantly reduced (p<0.05).

In the group of patients with a switch of therapy from Biological to Biological therapy, erosions decreased significantly from 3.9 ± 4.1 to

3.2 ± 3.7 ($p<0.05$) after one year. No significant reductions in the tenosynovitis score (PDUS), ESR and CRP could be observed.

Patients with first line Biological who switched to another Biological therapy during the study achieved the lowest synovitis score (GSUS and PDUS) at baseline examination.

In the beginning, the highest erosions were detected for patients who changed from DMARD to Biologic. Nevertheless, the US7 erosions score did not decrease significantly in this group.

At baseline, lowest erosion scores had patients who took DMARDs the whole time.

Conclusion: The comparable development of the US7 score data with clinical and laboratory data illustrates its possibility to reflect therapeutic response; therefore the novel US7 score is sensitive to change. Furthermore, patients who switched from Biological to Biological therapy achieved a significant decrease of erosions after twelve months, which could not be detected for patients with only DMARD therapy.

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Impact of the US7 Score for Diagnosis and Prognosis of Rheumatoid Arthritis In Undifferentiated Early Arthritis. Jörg Kaufmann[1], Susanne Seel[2] and Anne-Eve Roske[3]. [1]Rheumatologist, Ludwigsfelde, Germany, [2]Ambulant Centres f. Rheumatology, Ludwigsfelde, Germany, [3]Roche Pharma AG, Grenzach-Wyhlen, Germany

Background/Purpose: Therapy of early RA is characterized by an aggressive DMARD onset to prevent structural joint damage. Treatment decisions with regard to the individual risk of a persistent and/or erosive course of RA are crucial for an appropriate and cost-effective therapy to avoid under- and overtreatment. Some prediction models using clinical factors have been developed to detect RA patients at risk. One limitation of these prediction rules is a lack of inclusion of modern non-incriminating imaging techniques such as joint ultrasound (US).

The US7 score has been established as a routine tool in rheumatology to detect disease activity and for therapy monitoring to ease treatment decisions. In undifferentiated early arthritis joint US could have an impact on identification of those patients in whom persistent and/or erosive RA will develop.The aim was to compare the established prediction models Visser and Helm-van Mil (HvM) as well as the new ACR/EULAR criteria with extent of synovitis and synovial perfusion using joint US.

Methods: 95 patients with early undifferentiated arthritis were initially scored according to Visser, HvM and the new ACR/EULAR criteria. The US7 score was assessed simultaneously containing the synovial thickness (GSUS), the degree of tenosynovitis, early erosions and synovial perfusion with power Doppler (PDUS).

Results:

		Visser_ eRA	Visser_ peRA	HvM_ Pkt	HvM	ACR_ EULAR_ Pkt	Joint_Syn_ GSUS	Joint_Syn_ PDUS	US7_Score
Visser_pRA	Corr Coeff	.857**	.923**	.742**	.780**	.746**	.172	.275**	.290**
	Sig. (2-sided)	.000	.000	.000	.000	.000	.100	.008	.005
Visser_eRA	Corr Coeff		.969**	.669**	.731**	.628**	.165	.320**	.302**
	Sig. (2-sided)		.000	.000	.000	.000	.113	.002	.003
Visser_peRA	Corr Coeff			.723**	.777**	.711**	.170	.311**	.310**
	Sig. (2-sided)			.000	.000	.000	.103	.002	.002
HvM_Pkt	Corr Coeff				.937**	.734**	.308**	.302**	.377**
	Sig. (2-sided)				.000	.000	.003	.003	.000
HvM	Corr Coeff					.774**	.339**	.345**	.424**
	Sig. (2-sided)					.000	.001	.001	.000
ACR_EULAR_Pkt	Corr Coeff						.283**	.292**	.418**
	Sig. (2-sided)						.006	.004	.000
Joint_Syn_GSUS	Corr Coeff							.726**	.829**
	Sig. (2-sided)							.000	.000
Joint_Syn_PDUS	Corr Coeff								.815**
	Sig. (2-sided)								.000

**Significance level 0.01 (2-sided); *Significance level 0.05 (2-sided)

Conclusion: There is a strong correlation between the different prediction models and the joint US results. Synovial thickness as well as perfusion correlates with the risk generated by clinical factors. High US 7 scores as well as the detection of synovial perfusion in early arthritis states could be an additional indicator for persistent and/or erosive RA and helps to identify RA patients at risk who need early aggerssive DMARD therapy.

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Introduction of a New Ultrasound Score for Large Joints: One Year Experience in Daily Rheumatologic Practice. Wolfgang Hartung[1], Herbert Kellner[2], Johannes Strunk[3], Wolfgang A. Schmidt[4], Boris P. Ehrenstein[1], Horst Sattler[5], Marina Backhaus[6] and Martin Fleck[1]. [1]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany, [2]Centre for Inflammatory Joint Diseases, Munich, Germany, [3]Cologne, Germany, [4]Med Ctr Rheumatol Berlin Buch, Berlin, Germany, [5]Klinikum Ludwigshafen, Ludwigshafen, Germany, [6]Charite University Hospital, Berlin, Germany

Background/Purpose: Report of one year experience with a new standardized ultrasound score developed for large joints (**S**onogrpay **O**f **LA**rge joints in **R**heumatology: **SOLAR** score) implemented in daily reumatologic practice.

Methods: An ultrasound score was designed to determine the degree of inflammation in the shoulder, the elbow, the hip and the knee joint in patients with inflammatory joint disease. A scanning protocol has been established for each joint region with well defined planes. Synovitis and synovial vascularity were scored semiquantitatively (grade 0–3) by gray scale (GS) and power Doppler ultrasound (PDUS). The scoring range for GSUS was 0–6 for the shoulder, 0–9 for the elbow, 0–3 for the hip and 0–12 for the knee, depending on the number of defined scanning planes. The scoring range for PDUS was 0–6 for the shoulder, 0–9 for the elbow, 0–3 for the hip and 0–15 for the knee, respectively. In addition, tenosynovitis and erosions were scored for presence. Patients with arthritis were examined at baseline, as well as 3, 6 and 12 months after initiation or modification of disease modifying antirheumatic drugs (DMARD) and/or biologic therapy. C-reactive protein levels (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), anti-citrullinated peptide (anti-CCP) antibodies and the Disease Activity Score in 28 joints (DAS28) were determined. Additionally, radiographs of the affected joints were obtained when clinically indicated.

Results: Six hundred seventeen patients were enrolled. Two hundred fifty three patients already reached the twelve months visit, suffering from rheumatoid arthritis (79%), psoriatic arthritis (14%) and ankylosing spondylitis (7%). DMARD treatment had been initiated or changed in 66% (n = 168) of these patients, whereas, DMARDs plus biologics were utilized in 24% (n = 61), and biologic monotherapy in 10% (n = 24) of patients. The knee joint was examined in 146 patients (58%) as the most affected joint ("target joint"), whereas in 46 patients (25%) the shoulder, in 39 patients (15%) the elbow and in 18 patients (7%) the hip joint were evaluated. At baseline, the mean DAS28 was 4.6 and the synovitis scores were for the knee GS 5.2/PD 3.7, the shoulder GS 2.8/PD 1.7, the elbow GS 5.0/PD 2.4 and the hip GS 2.2/PD 1.1, respectively. After 3 months of therapy, DAS28 scores significantly decreased to 3.6 ($p< 0{,}001$) and the SOLAR scores fell to GS 3.2/PD 2.3 for the knee, GS 2.2/PD 1.1 for the shoulder, GS 3.3/PD 1.5 for the elbow and GS 1.3/PD 0.3 for the hip. This early response even improved within the next 9 months as documented by a further decrease in DAS 28 and the SOLAR scores at six and twelve months (s. Table 1).

		US, clinical and laboratory data (n = 253)#			
Joint region	US score/ disease activity	baseline	after 3 months	after 6 months	after 12 months
knee (n = 148)	GSUS (range 0–12)	5.2 ± 2.9	3.2 ± 2.7**	2.8 ± 2.8**	2.3 ± 2,7**
	PDUS (range 0–15)	3.7 ± 3.1	2.3 ± 2.6**	1.9 ± 2.5**	1.2 ± 2.0**
shoulder (n = 46)	GSUS (range 0–6)	2.8 ± 1.9	2.2 ± 1.6*	1.8 ± 1.4*	1.6 ± 1.6*
	PDUS (range 0–6)	1.7 ± 1.6	1.1 ± 1.5*	1.1 ± 1.4*	0.7 ± 1.2*
elbow (n = 39)	GSUS (range 0–9)	5.0 ± 2.4	3.3 ± 2.7**	2.7 ± 2.8**	2.2 ± 2.7**
	PDUS (range 0–9)	2.4 ± 2.0	1.5 ± 1.9*	1.2 ± 1.6*	0.8 ± 1.2*
hip (n = 18)	GSUS (range 0–3)	2.2 ± 0.6	1.3 ± 0.9**	0.9 ± 0.9**	0.7 ± 0.9**
	PDUS (range 0–3)	1.1 ± 1.2	0.3 ± 0.5	0.3 ± 0.5	0.2 ± 0.5
DAS 28		4.6 ± 1.3	3.6 ± 1.4	3.4 ± 1.3	3.2 ± 1.3
ESR, mm/hour		32.0 ± 22.4	22.9 ± 18.0	21.1 ± 16.2	20.3 ± 16.4

values represent the mean ± SD. US = ultrasound; GSUS = gray scale US; PDUS = power doppler US; DAS 28: Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate. * $P < 0.05$ (2 sided significance by Kruskal-Wallis-test); ** $P < 0.001$ (2 sided significance by Kruskal-Wallis-test).

Conclusion: The SOLAR score is a feasible tool for examining patients with arthritis of large joints in daily rheumatologic practice reflecting therapeutic response within 12 months following modification or initiation of DMARD and/or biologic treatment.

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The Impact of Ultrasonography on the Classification of Rheumatoid Arthritis with 2010 ACR/EULAR Criteria: Ultrasound-Combined Classification with Two Different Definitions of Gray-Scale Synovitis for Joint Involvement. Daiki Nakagomi, Kei Ikeda, Ayako Okubo, Taro Iwamoto, Yoshie Suzuki, Hiroaki Takatori, Kotaro Suzuki, Katsuhiko Takabayashi and Hiroshi Nakajima. Chiba University Hospital, Chiba, Japan

Background/Purpose: 2010 ACR/EULAR rheumatoid arthritis (RA) classification criteria refer to the possible use of new imaging techniques such as ultrasonography (US). However, the impact of US on the classification of RA and the optimal US definition of synovitis for this purpose have not been fully assessed with comprehensive US scanning. Therefore, the purpose of this study is to determine the impact of US assessment for synovitis on the classification of RA with 2010 ACR/EULAR criteria.

Methods: Ultrasonography was performed in cases with possible diagnosis of RA using either LOGIQ E9 (GE Healthcare), Aplio XG (Toshiba Medical Systems) or Avius (Hitachi Medical Corporation). All joint regions included in 2010 ACR/EULAR criteria except hip joints were assessed, and gray scale synovitis (GS) and power Doppler signals (PD) were recorded for each joint with semi-quantitative score (0–3). According to the prevalence of US findings in this cohort, US-synovitis was preliminarily defined either as GS>0 and/or PD>0 (mild-GS definition) or as GS>1 and/or PD>0 (moderate-GS definition). The numbers of cases who clinically fulfilled the ACR/EULAR criteria (CL-RA) were compared with those who fulfilled the criteria after replacing the joint involvement with US synovitis (US-RA).

Results: 117 cases were enrolled. The mean age was 52.1 year-old, 25 patients (21.4%) were male, and median duration of symptom was 6 months. Rheumatoid factor and anti-CCP antibody were positive in 56 cases (47.9%) and 41 cases (35.4%), respectively. The discrepancy between clinical and US assessments was frequent in wrists and knees with both US-synovitis definitions. The numbers of cases with CL-RA (mild-GS definition) and/or US-RA were 47 (40.2%) for CL-RA (+)/ US-RA (+), 12 (10.2%) for CL-RA (+)/ US-RA (−), 11 (9.4%) for CL-RA (−)/ US-RA (+), and 47 (40.2%) for CL-RA (−)/ US-RA (−), respectively (Table 1). On the other hand, the numbers of cases with CL-RA (moderate-GS definition) and/or US-RA were 56 (47.9%) for CL-RA (+)/ US-RA (+), 21 (17.9%) for CL-RA (+)/ US-RA (−), 5 (4.3%) for CL-RA (−)/ US-RA (+), and 35 (29.9%) for CL-RA (−)/ US-RA (−), respectively (Table 2).

Table 1. Classification with mild-GS (> 1) definition of synovitis

	Clinical - RA (−)	Clinical - RA (+)	Total
US - RA (−)	47 cases (40.2%)	12 cases (10.2%)	59 cases (50.4%)
US - RA (+)	11 cases (9.4%)	47 cases (40.2%)	58 cases (49.6%)
Total	58 cases (49.6%)	59 cases (50.4%)	117 cases (100%)

Table 2. Classification with moderate-GS (> 0) definition of synovitis

	Clinical - RA (−)	Clinical - RA (+)	Total
US - RA (−)	56 cases (47.9%)	21 cases (17.9%)	77 cases (65.8%)
US - RA (+)	5 cases (4.3%)	35 cases (29.9%)	40 cases (34.2%)
Total	61 cases (52.2%)	56 cases (47.8%)	117 cases (100%)

Conclusion: The result shows that the combined use of US may alter the RA classification with ACR/EULAR criteria in 19.6–22.2% of the patients assessed, depending on the definition of US-synovitis. In order to further validate the benefit and the optimal definition of US-synovitis in the diagnosis of RA, longitudinal assessment of this cohort is in progress.

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Comparison of the Validity of Synovitis to Predict Structural Damage in Rheumatoid Arthritis (RA) with Regard to the Joint Examination Modality (*e.g.* clinical *versus* ultrasonographic [US]). Maxime Dougados[1], Valerie Devauchelle[2], Jean François Ferlet[3], Jacques Bentin[4], Sandrine Jousse-Joulin[2], E. Maria Atonietta D'Agostino[5], Gérard Chalès[6], Isabelle Chary-Valckenaere[7], Fabien Etchepare[8], Philippe Gaudin[9], Xavier Mariette[10] and Alain Saraux[11]. [1]Paris-Descartes University, Cochin Hospital, Paris, France, [2]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France, [3]RCTS, Lyon, France, [4]CHU-Brugmann, Brussels, Belgium, [5]Rheumatology Department Ambroise Par Hospital, Boulogne-Billancourt, France, [6]CHU RENNES, Rennes, France, [7]CHU NANCY, France, [8]G.H. Pitié-Salpêtrière, Paris, France, [9]Chu A Michallon, Grenoble, France, [10]Université Paris-Sud, Le Kremlin Bicetre, France, [11]CHU de la Cavale Blanche, Brest Cedex, France

Background/Purpose: Longitudinal epidemiological studies have demonstrated the link between the presence of synovitis at a single point of time and a subsequent structural deterioration in RA. In comparison to physical examination, US seems to be more accurate (sensitive) for the detection of synovitis. This study had the objective to compare the predictive validity of synovitis with regard to the joint examination modality (*e.g.* clinical *versus* US).

Methods: *Patients*: Definite RA (1987 ACR criteria), active (necessitating an anti-TNF therapy). *Study design*: Prospective, 2 year follow-up. *Data collected*: For each patient, 32 joints were evaluated (2 wrists, 10 MCP, 10 PIP, 10 MTP). Synovitis was collected before and after 4 months of TNF therapy using a semi-quantitative variable for both the physical examination (from 0=definitively no synovitis to 3=yes obvious and important), US mode B (from 0=absence of synovial thickening to 3=marked synovial thickening) and US Power Doppler (PD) (from 0=absence of signal, no intra-articular flow to 3=marked signal in more than half of the synovial area. US and physical examination were conducted by 2 distinct physicians. Hands and feet X-rays performed at baseline and year 2 were evaluated by another distinct physician unaware of the synovitis findings. For each X-ray, the presence of both erosion and joint space narrowing were evaluated. Moreover, for each joint, the reader noticed whether there was either an occurrence or a worsening in structural damage at year 2 in comparison to baseline. *Analysis*: Measures of association (odds ratio [OR] and 95% confidence intervals [CI] adjusted for within patient correlation and also other age, gender, disease duration, baseline DAS28 and baseline joint structural damage.) were tested between the structural deterioration defined by an occurrence or a worsening of joint space narrowing or bone erosion and the presence of synovitis (grade 0 *vs.* grade 1 or 2 or 3) defined by clinical, US mode B or US PD before and after 4 months of anti TNF therapy.

Results: Of the 77 recruited patients, 59 patients (female: 81%, age: 56±12 years, Rheumatoid Factor Positive: 73%) completed the 4 months of the study and had also a radiologic evaluation at year 2. After 2 years of follow-up, a structural deterioration was observed in 9% of the 1888 evaluated joints (16.2% of the 118 wrists, 7.0% of the 590 MCP, 7.5% of the 590 PIP, and 11.0% of the 590MTP). The increased probability to observe a structural progression in presence of synovitis was confirmed for the different joint examination modalities at baseline (OR = 2.08 [1.39;3.11] $p<0.001$ *vs.* 1.64 [1.08;2.47] $p=0{,}019$ *vs.* 1.80 [1.20;2.71] $p=0{,}005$; but only with a trend (except for US mode B modality) 4 months after anti TNF therapy (OR = 1.63 [0.96;2.76] $p=0{,}069$ *vs.* 2.12 [1.35;3.32] $p=0.001$ *vs.* 1.63 [0.93; 2.86] $p=0.086$; for t he physical examination *versus* US mode B *versus* US PD, respectively.

Conclusion: This study confirms the validity of synovitis to predict subsequent structural deterioration but suggests also that such predictive validity is similar wathever the joint evaluation modality (e.g; clinical or US).

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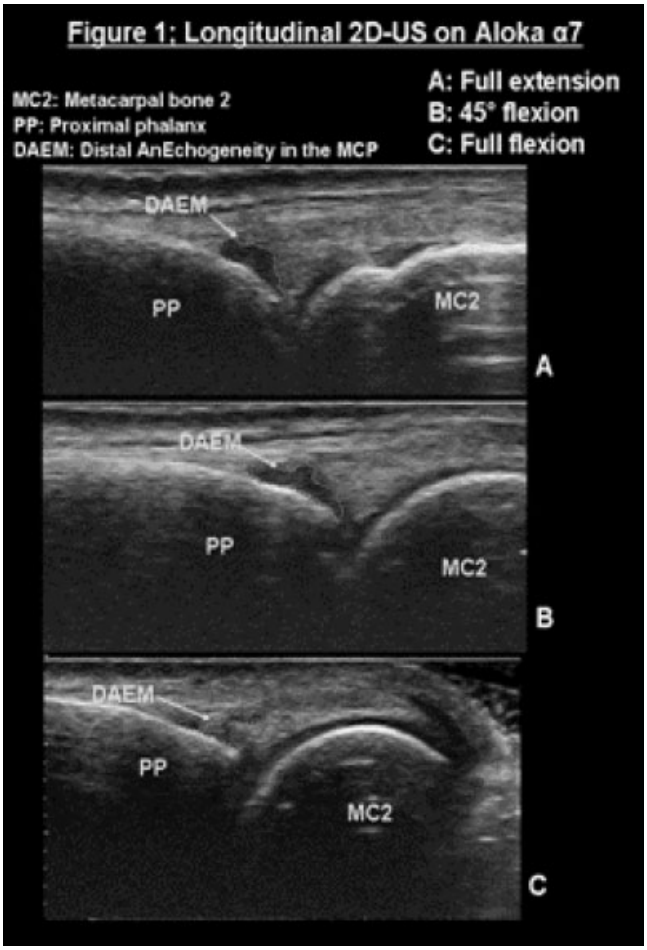
Sonographic Arthritis Remission Criteria Jeopardized by a Physiological Anechogeneity in MCP Joints. David F. Ten Cate[1], Jolanda J. Luime[2], Johanna Hazes[3], G.J. Kleinrensink[2] and Johannes W.G. Jacobs[4]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus MC - University Medical Center, Rotterdam, Netherlands, [3]Erasmus Medical Centre Rotterdam, Rotterdam, Netherlands, [4]UMC Utrecht, Utrecht, Netherlands

Background/Purpose: Ultrasonography (US) of clinically normal joints often reveals a small anechogenic area at the proximal phalanx in MCP joints, being most distinct in MCP 2. Using current US scores, this Distal AnEchogeneity in the MCP joint (DAEM) could be graded as inflammation,[1] but it is also found in healthy joints. The nature of this DAEM is not clear, however. Our aim was to identify the nature of the DAEM.

Methods: MCP2 joints of 10 healthy subjects with a DAEM and 7 RA patients were scanned bilaterally by 2D US (Aloka α7 and GE Logiq E9) and 3D US (GE Logiq E9) scans. Each joint was imaged in extension, 45° flexion and maximal flexion. (Figure 1) The joint space volume was calculated in 4 subjects and the DAEM volume in 3. Two MCP2 joints of 2 cadavers with a DAEM were scanned and injected with Fillopaq™, filling the entire joint space. Then the cadaver joints were dissected.



Results: The DAEM stayed visible when passively flexing the finger, at 45° flexion and in maximal flexion (Figure 1B and 1C, respectively). The 3D US scan showed that the DAEM is a part of the joint space, which was confirmed at dissection. DAEM dimension and volume were similar in the healthy controls and the patients. The median volume of the dorsal joint spaces was 0.09 cm^3 (range 0.04–0.14) and the median volume of the DAEM 0.02 cm^3. So the DAEM volume ranges from 15 to 50 % of the total dorsal joint space volume.

Conclusion: The anechogenic area frequently found distally in MCP2 joints of healthy controls is an extension or distal recess of the joint.[2] Sonographers should be aware of this distal recess and should take it into account, particularly when evaluating patients for remission using current US scoring systems.

References:

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Keywords: Remission, 2D Ultrasound, 3D Ultrasound, Anechogeneity, validation, recess

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No Ultrasound Specific Changes in Trochanter Enthesis in Patients with Greater Trochanter Pain Syndrome and Chronic Arthritis. Julio Ramírez[1], Isaac Pomés[1], Jaume Pomés[1] and Juan D. Cañete[2]. [1]Hospital Clínic, Barcelona, Spain, [2]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain

Background/Purpose: To evaluate sonographic findings in greater trochanter pain syndrome in patients with spondyloarthropathies and two control groups: a first group including patients with rheumatoid arthritis and a second one with patients with degenerative joint disease.

Methods: Case-control study. Patients with unilateral greater trochanter pain syndrome were collected. A rheumatologist and a radiologist experienced in musculoeskeletical ultrasound performed the ultrasound scans of painful greater trochanter and contralateral asymptomatic trochanter (used as controls). We separately explored the gluteus medius tendon enthesis and the gluteus minor tendon enthesis. We specifically searched the following findings suggestive of tendinopathy: changes in tendon structure, cortical bone erosions (scored according to size from 0 to 3), calcifications (also rated according to size from 0 to 3), bursitis and Doppler signal (measured from 0 to 3). Because of the absence of reference measurements in trochanter enthesis, we did not measured the size of gluteus medius and minor tendons.

Results: 100 patients with unilateral greater trochanter pain syndrome were collected. 90 women and 10 men. 33 were diagnosed of seronegative spondylarthropathy according to ASAS criteria, 22 rheumatoid arthritis according to ACR criteria and 45 patients had degenerative disease. The mean age of patients was 61 years. Ultrasound enthesis abnormalities were more common in gluteus minor tendon, regardless of diagnosis (82% had erosions, 61% calcification, 37% bursitis, and 35% had alterations in the tendon structure). The percentage of calcification and bursitis was significantly higher in the symptomatic side than the contralateral in both tendons, but not erosions, equally present bilaterally. Doppler signal was not found in any patient. In subgroup analysis, there were no specific ultrasound findings in patients with spondyloarthropathies. No ultrasound differences were found between spondiloarthropaties patients and rheumatoid arthritis patients. However, when comparing SpA patients with degenerative disease patients, we found a significantly lower rate of bursitis (15% vs 40% in gluteus medius and 21% vs 49% in gluteus minor, $p = 0.024$ and 0.018 respectively). Moreover, although the total percentage of erosions and calcifications in gluteus minor did not differ between the two groups, those found in the degenerative group were larger.

Conclusion: Regardless of the underlying disease, the enthesis of the gluteus minor is the most affected enthesis in greater trochanter pain syndrome by ultrasound examination. Calcifications and bursitis are the most discriminative ultrasound findings. We could not differentiate inflammatory or mechanical origin of greater trochanter pain syndrome because of two reasons; erosions are very common in this area and, because of the depth of trochanter, no Doppler signal was detected in any patient.

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Detection by Ultrasound of Small Calcium Deposits within Cartilage in Patients without Radiographic Chondrocalcinosis. Eric Russell, Humaira Hussain and Angel E. Checa. Drexel University College of Medicine, Philadelphia, PA

Background/Purpose: Musculoskeletal ultrasound (MSKUS) has increasingly been used in the field of rheumatology to evaluate joint pathology and has been shown to be a very sensitive tool in identifying crystalline arthropathies. We describe the sensitivity of MSKUS detection of small deposits of calcium, not visible on conventional radiography, in patients with joint symptoms attributed to other disease process, such as osteoarthritis. In addition, among patients with sonographic evidence of chondrocalcinosis, we measure the degree of cartilage loss using MSKUS, and correlate this to the presence of calcium deposits within the knee cartilage.

Methods: In the cohort of 406 patients who underwent MSKUS from January 2010 to June 2011, thirty patients with chondrocalcinosis were identified by the presence of calcium deposits using a GE LOGIQ e machine equipped with a broadband, 8–13mHz linear transducer. The presence of chondrocalcinosis was sonographically recognized as hyperechoic foci of enhancement, within the joint cartilage. Once aggregates of calcium were identified, the size was measured unless the deposit burden was too large to quantify. In addition, cartilage thickness was measured, on transverse view of a magnified sonographic image of the fully flexed knee, in the lateral femoral compartment, trochlea, and medial femoral compartment of the knee.

Results: We identified 30 patients with MSKUS evidence of aggregates of calcium within the wrist or knee cartilage. Two patients were excluded from the study since prior radiographs of the joint were not available. Of the 28 patients included in the study, 9 (32%) showed radiographic evidence of chondrocalcinosis and 19 (68%) patients had no evidence of chondrocalcinosis on prior radiographs ($p = 0.001$). Those patients with sonographic, but not radiographic chondrocalcinosis, predominately had small calcium deposition. The group with radiographic evidence of chondrocalcinosis in general showed deposits too extensive to measure on ultrasound. Cartilage thickness was not different between patients with or without radiographic chondrocalcinosis [mean (mm) = 1.96 vs. 2.0 respectively, $p = 0.84$] despite a larger calcium burden seen in the group were conventional radiography was able to detect chondrocalcinosis.

Conclusion: Musculoskeletal ultrasound was better than conventional radiography in detecting small calcium deposits in patients with symptoms attributed to other joint pathology. Knee cartilage loss was similar in both groups despite more crystal burden within the group that had evidence of both radiographic and sonographic chondrocalcinosis. Considering the low sensitivity of MRI in detecting chondrocalcinosis and our finding that radiography was insufficient to detect small calcium deposits, we conclude that MSKUS is a very sensitive tool to evaluate for small aggregates of calcium. Future controlled trials, with a larger

patient population, are needed to evaluate whether these small deposits represent a pathologic pattern and have a significant clinical impact.

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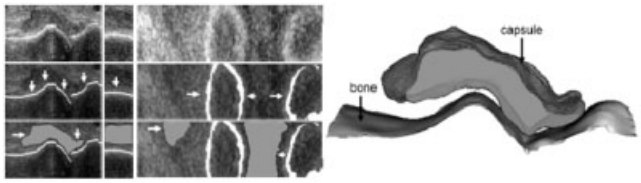
Feasibility of Volumetric Ultrasound and Automated Analysis for Rheumatic Disease. Ralf G. Thiele[1], Kedar Patwardhan[2], Kunlin Cao[2] and David Mills[2]. [1]University of Rochester, Rochester, NY, [2]GE Global Research

Background/Purpose: Two-dimensional (2D) ultrasonography (US) is a cross-sectional imaging modality that is useful for detecting typical changes in rheumatoid arthritis (RA) including synovitis and erosive disease. Inter- and intra-observer variability can be good to excellent if rheumatologists are adequately trained. Nevertheless, 2D sectional imaging can often not sufficiently capture 3D anatomic reality. True volumes of proliferative synovial tissue or erosions in RA may be better measured with 3D imaging. Most 3D US technology is optimized for obstetrical, gynecological, or cardiac indications. Availability of 3D US technology dedicated to assessment of rheumatic disease would be desirable. In addition, automated identification and capture of volumes of interest would facilitate objective and repeatable assessment of rheumatic disease. The aim of this study is to assess the feasibility of development of 3D technology dedicated to the assessment of rheumatic disease.

Methods: In this study, we obtained 31 3D datasets of 11 joints in 9 subjects, at least 6 of whom had rheumatic disease. High-frequency 3D US equipment was used (Voluson-i & RSP-6–16 probe, GE Healthcare, Wauwatosa, WI). Joints examined included MTP joints, n=3; MCP joints, n=6; PIP joint, n=1; and shoulder joint, n=1. All US studies were performed by a rheumatologist certified in musculoskeletal US, with 20 years of US experience (RT). We developed computer algorithms that look for characteristic acoustic responses to automatically identify the bone surface in the US images. This reference surface provides anatomical context to automate other clinically valuable tasks such as identification of the joint capsule.

Results: Despite realistic differences in images from multiple subjects, the majority of the 3D bone surface was successfully identified by our computer algorithm for all 11 joints. Image artifacts, irregular anatomy (e.g. large bone erosions) and areas where the bone surface was far from parallel to the US probe resulted in incorrect identification of small portions of the bone in the images of 5 of the joints. The figure shows (left top-row) 3 views of a 3D US image, automatically identified bone (middle row) and as an example of potential applications, a semi-automatically identified joint capsule over bone is shown (bottom-row).The figure also shows (right) a 3D rendering of the joint capsule and bone.



Conclusion: Development of 3D ultrasound equipment dedicated to rheumatology indications is feasible. Operator independent measurement of volumes of synovitis and erosions can help define disease status more objectively. Serial measurement of volumes of erosions and synovitis could provide valuable information about disease progression or treatment response.

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US Examination of Wrists and Hands: A Comparison Between Rheumatoid Arthritis and Psoriatic Arthritis. Andrea Delle Sedie[1], Niccolò Possemato[2], Elena Sardano[3], Elisa Cioffi[4], Stefano Bombardieri[2] and Lucrezia Riente[2]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy, [3]Immunology Unit, University of Pisa, Italy, [4]School of Medicine, University of Pisa, Pisa, Italy

Background/Purpose: Very little is known about the possible differences in the involvement of joints and periarticular structures in rheumatoid or psoriatic arthritis (PsA). The main pathological features detected by US in rheumatoid arthritis (RA) are synovitis and bone erosion while, in spondyloarthropathies, entheseal inflammation is the common feature. Tendon involvement is particularly frequent and dactylitis is a typical PsA manifestation.

Aim of the study was to investigate the features of wrist and hand involvement in PsA and RA.

Methods: Bilateral ultrasound (US) examination of the wrist and hand was performed, by the same physician, in a group of subjects affected by RA (n=50; F:M=43:7; mean age: 61.3±12.7 years; disease duration: 112.9±85.5 months) and PsA (n=50; F:M=24:26; mean age: 57.4±12.5 years; disease duration: 100.2±97.4 months), using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) with a linear probe operating at 14 MHz. We examined radiocarpal, intercarpal, metacarpophalangeal, proximal interphalangeal and distal interphalangeal (DIP) joints and flexor and extensor tendons (both in wrist and hand). The patients were recruited on a time-criteria (the last 25 patients for each diagnosis who came for an outpatient control) from the whole number of subjects referring to the US unit of our Clinic.

Results: US examination showed joint wrist synovitis in 37/50 (74%) RA and 29/50 (58%) PsA patients, hand synovitis in 33/50 (66%) and in 36/50 (72%) RA and PsA patients respectively. Tendon involvement was present in the 21/50 (42%) and 13/50 (26%) patients in the wrist and 18/50 (36%) in the hand, both in RA and PsA group. Finally, bone erosions were present in 33/50 (66%) and 29/50 (58%) RA and PsA patients respectively.

Conclusion: We did not observed significant differences in wrist or hand involvement (both in joint and tendon structures) between RA and PsA patients, even if a slightly higher frequency of wrist synovitis and tenosynovitis was present in RA group.

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Detection of Inflammation in Early Psoriatic Arthritis by Ultrasound - a Longitudinal Study. Axel P. Nigg[1], Anna M. Malchus[1], Mathias Grünke[1], Matthias Witt[1], Joerg C. Prinz[2] and Hendrik Schulze-Koops[1]. [1]Division of Rheumatology and Clinical Immunology, Med. Poliklinik, University of Munich, Munich, Germany, [2]Department of Dermatology, University of Munich, Munich, Germany

Background/Purpose: By reasons of the phenotypic heterogeneity and the absence of reliable disease-specific biochemical markers in early psoriatic arthritis (PsA) sensitive diagnostic modalities enabling visualization of early inflammatory changes and reliable tools for monitoring the response to therapy are required. We initiated a prospective study to evaluate the utility of US in early PsA. The aims of the study are to analyse the correlation between US findings and clinical parameters, to evaluate the prognostic value of US findings as predictors for clinical outcome and to assess the sensitivity and specificity of US in detection of inflammatory changes on the individual joint level.

Methods: 30 patients with psoriasis suffering from recent onset joint pain were included. Patients were evaluated by US and clinically at baseline and after 3, 6 and 12 months. In each patient a total of 56 joints were examined by US. Grey-Scale (GS) and power doppler (PD) US findings were scored separately on a 0–3 semi-quantitative scale. In addition tendons of fingers and toes and 10 enthesial sites were scanned. Tenosynovitis and enthesitis were registered as being absent (0) or present (1). Total US synovitis/tenosynovits/enthesitis scores were calculated by adding the scores in the GSUS and PDUS modes for all joints/tendons/enthesial sites examined. Clinical assessment included joint count of 68 tender and 66 swollen joints, visual analog scale (VAS) for disease activity (patient/physician), DAS-28, Leeds dactylitis instrument, HAQ, CRP, ESR and demographic data.

Results: When considering each joint individually, a total of 1569 joints were assessed by US and clinically. GSUS detected synovitis in 213 joints (13,5%), PDUS activity was observed in 35 joints (2,2%). Subclinical US synovitis was found in 49% (GSUS) and 20% (PDUS) of all joints with pathologic US findings. With US as reference method clinical examination of joint tenderness had a sensitivity of 49%(GSUS)/71%(PDUS) and a positive predictive value of 55%(GSUS)/13%(PDUS). Joint swelling had a sensitivity of 11% (GSUS)/46%(PDUS) and a positive predictive value of 92%(GSUS)/62%(PDUS). Detection of erosions and proliferative changes in joints of fingers and toes by radiography showed a sensitivity of 3% and positive predictive value of 25% with US as reference method. At baseline the combined US joint score showed a strong and highly significant correlation with TJC68, SJC66, DAS-28 and physician global activity and a moderate significant correlation with HAQ. The US tenosynovits score correlated strongly with Leeds dactylitis instrument (LDI). Longitudinal data showed a moderate to strong correlation between relative changes in the US parameters and changes in clinical parameters through 3 months of follow-up in patients undergoing systemic treatment.

Conclusion: US is a useful instrument in the diagnosis of early PsA. US findings correlate well with clinical disease activity at baseline as well as longitudinally over the treatment course. US detects joint inflammation to a larger extent than clinically expected and confirms the presence of subclinical inflammation.

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Metric Properties of Imaging Methods in Osteoarthritis of the Hand: A Systematic Review. Michael S. Saltzherr, Ruud W. Selles, Sita M.A. Bierma-Zeinstra, Galied S.R. Muradin, J. Henk Coert, Johan W. van Neck and Jolanda J. Luime. Erasmus MC - University Medical Center, Rotterdam, Netherlands

Background/Purpose: To early diagnose and detect response to therapy in hand osteoarthritis (HOA), we need imaging techniques that visualize soft tissue, cartilage and bone in multiple joints with sufficient detail. These techniques should be valid, reliable and responsive. We therefore systematically reviewed the literature on information about validity, reliability and responsiveness of imaging techniques for HOA.

Methods: We systematically searched Pubmed and Embase up to October 2010. Studies were selected if an imaging technique was used to assess HOA and quantitative data was presented on validity, reliability or responsiveness. Articles presenting only data on conventional radiography (CR) were excluded. The methodological quality was assessed by the QUADAS for validity, the QAREL for reliability and the COSMIN for responsiveness.

Results: 13 ultrasound (US), 2 MRI and 7 scintigraphy studies were eligible out of 459 unique records. US validity was evaluated in 11 studies but none used an external criterion (gold standard). Construct validity using CR as comparator (n=6) resulted in: moderate agreement for osteophytes (κ=0.51) and joint space narrowing (JSN) (κ=0.44); sensitivity of 0.72 and specificity of 1.0 for erosions; significantly more ($p<0.05$ and $p=0.01$) erosions and osteophytes on US; and R^2 of 0.62 for cartilage thickness when compared with joint space width. Greyscale synovitis (GS) and power doppler signal (PD) showed no agreement with joint pain (κ=0.10–0.14 and κ=0.06–0.16; n=2), while increased odds ratio's (4–5) were reported in 1 other study. 2 studies compared US findings in HOA patients with healthy controls: significantly more ($p<0.05$) effusion, JSN, osteophytes, GS and PD were found in HOA.

Inter- and intra-observer reliabilities ranged from very poor to very good: cartilage thickness (ICC=0.84–0.96; n=2), JSN (κ=0.64), osteophytes (κ=0.17–0.98; n=3), erosions (κ=0.91), GS (κ=0.17–1.0; n=4), PD (κ=0.09–1.0; n=4), effusion (κ=0.34). Responsiveness on GS and PD after i.m. methylprednisolone was assessed with pain as a comparator, but no significant change was found.

MRI validity of erosions was evaluated in 1 study with CR as comparator. Significantly more erosions were detected on MRI ($p<0.05$). In another study more ($p<0.05$) ligament, tendon and cartilage abnormalities, osteophytes, bone edema and erosions were detected in HOA compared to healthy controls. Inter-reliability of scoring erosions on MRI was good (κ=0.84). Responsiveness has not been assessed on MRI.

Scintigraphy correlated with joint pain (r=0.24–0.35) and CR (r=0.50–0.61; n=2), but detected less pathology than CR. Intra- and inter-observer reliability of scintigraphy were good (κ=0.61–0.84). Responsiveness on scintigraphy without intervention showed no significant change after one year, but did after four years. This correlated with changes on CR (r=0.13).

Conclusion: Limited data is available on the metric properties of imaging techniques in HOA. Scintigraphy seems less sensitive to detect pathology than CR, but US and MRI seem promising. However, there are no data on criterion validity; results on reliability vary greatly for US and are scarce for MRI; and the only study assessing responsiveness found no change.

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New Onset Bilateral Painful Shoulder in Patients with Polymyalgia Rheumatica and Rheumatoid Arthritis: An Ultrasound Study. David A. Navarta[1], Santiago Ruta[1], Javier Rosa[1], Carla Saucedo[1], Ricardo Garcia Monaco[2] and Enrique R. Soriano[1]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires

Background/Purpose: Ultrasound (US) has shown synovial intra-articular and/or periarticular inflammation in painful shoulders from patients with polymyalgia rheumatica (PMR) and rheumatoid arthritis (RA). The feature of different US inflammation patterns may have important pathogenic and therapeutic implications. We compared US inflammatory findings in PMR and RA patients with new onset bilateral painful shoulder.

Methods: Patients with previous diagnosis of PMR (1984 Healey criteria) and RA (2010 ACR/EULAR criteria) complaining of new onset bilateral painful shoulder were included. Subjects without any known inflammatory rheumatic condition with new onset unilateral painful shoulder were assessed as control group. Exclusion criteria were: < 18 years old, oral prednisone dose > 10 mg per day, previous surgery on the shoulder, trauma or corticosteroid injection within the last 2 months. US assessment was performed bilaterally in all patients and unilaterally in controls by the same experienced rheumatologist sonographer who was blinded to clinical data. US examinations were performed with a My Lab 70 (Esaote) machine equipped with 6–18 MHz broad band multifrequency linear transducer and included the detection of subacromial-subdeltoid (SAD) bursitis, long head biceps (LHB) tenosynovitis and/or gleno-humeral (GH) synovitis by a dichotomous evaluation (presence/absence). Standardized scanning method and published reference values were used. Frequency of each feature was calculated and compared between groups by chi2 test. A p value <0.05 was considered significative.

Results: Thirty PMR patients (mean age 74 ± 8 years, 26 female/4 male), 30 RA patients (mean age 64 ± 12 years, 24 female/6 male) and 60 controls (mean age 69 ± 15, 48 female/12 male) were included for a total of 60 shoulders evaluated in each study group. SAD bursitis and LHB tenosynovitis were significantly more frequent in PMR patients than in RA and controls (table). GH synovitis was most common in RA than in PMR and controls (table). Bilateral SAD bursitis was detected in 11 out of 30 (36,6%) patients with PMR and in only 1 out of 30 (3,3%) rheumatoid arthritis patients ($p = 0.0012$) and bilateral LHB tenosynovitis was found in 9 out of 30 (30%) PMR patients in contrast with none (0/30) rheumatoid arthritis patients ($p = 0.0011$). No differences were found on bilateral GH synovitis between PMR and RA patients ($p = 0.3006$).

Table. Frequency of the different shoulder ultrasound findings in the different study groups.

	Polymyalgia rheumatica vs Rheumatoid arthritis	Polymyalgia rheumatica vs control group	Rheumatoid arthritis vs control group
Subacromial-subdeltoid bursitis	33/60 (55%) vs 11/60 (18.3%)	33/60 (55%) vs 15/60 (25%)	11/60 (18.3%) vs 15/60 (25%)
Shoulder affected/Total shoulder examined (%)	*p < 0.0001*	*p = 0.0008*	*p = 0.6576*
Long head biceps tenosynovitis	28/60 (46.6%) vs 14/60 (23.3%)	28/60 (46.6%) vs 12/60 (20%)	14/60 (23.3%) vs 12/60 (20%)
Shoulder affected/Total shoulder examined (%)	*p = 0.0074*	*p = 0.0019*	*p = 0.3754*
Glenohumeral synovitis	7/60 (11.7%) vs 16/60 (26.7%)	7/60 (11.7%) vs 4/60 (6.6%)	16/60 (26.7%) vs 4/60 (6.6%)
Shoulder affected/Total shoulder examined (%)	*p = 0.0369*	*p = 0.3426*	*p = 0.0033*

PMR, RA and controls

Conclusion: We found differences on the inflammation pattern detected by US between PMR and RA. Periarticular involvement was more frequent in PMR and intra-articular involvement was more common in RA. US might be a useful tool to determinate the musculoskeletal structure actually affected during new onset painful shoulder in these rheumatic conditions helping to take a correct therapeutic decision.

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The Role of Color-Doppler-Sonography in the Diagnosis of Giant Cell Arteritis Characterized by Adventitial Inflammation of the Temporal Arteries. Francesco Muratore, Luigi Boiardi, Nicolo Pipitone, Alberto Cavazza, Giovanna Restuccia, Giuseppe Germanò, Pierluigi Macchioni, Gianluigi Bajocchi, Maria Grazia Catanoso, Luca Magnani, Fulvia Rossi, Ilaria Chiarolanza, Lucia Dardani, Andrea Caruso, Alessandra Ghinoi and Carlo Salvarani. Arcispedale S Maria Nuova, Reggio Emilia, Italy

Background/Purpose: The classic histological appearance of inflamed temporal arteries (TA) in giant cell arteritis (GCA) is transmural cell infiltration. However, periadventitial small vessel vasculitis (SVV) surrounding uninflamed TA and/or isolated vasculitis of the TA vasa vasorum (VVV) is found in a minority of patients with GCA. These patients have less frequently cranial manifestations and lower inflammatory markers at diagnosis compared to the patients with classic GCA, whereas the frequency of cranial ischemic events is similar (1).

Color-doppler-sonography (CDS) can demonstrate a hypoechogenic (inflammatory) halo in the TA from patients with GCA in approximately 70% of cases. A study found a correlation between positive CDS findings and trasmural inflammatory cell infiltration in GCA (2).

There are no data on the performance of CDS in the diagnosis of SVV and/or VVV.

The aim of this study was to evaluate the prevalence of the characteristic halo sign in the TA from patients with SVV and/or VVV and to compare it with that found in patients with classic GCA.

Methods: 30 consecutive patients with biopsy-proven SVV and/or VVV GCA who underwent CDS of the TA before TA biopsy were analyzed. Of

this 30 patients, 16 had SVV, 11 isolated VVV, and 3 associated SVV and VVV. The identified patients were randomly matched to 30 biopsy-proven classic GCA patients.

SVV was defined as aggregates of mononuclear inflammatory cells around capillaries located in the connective tissue surrounding the adventitia. VVV was defined as isolated vasculitis of TA vasa vasorum.

A hypoechoic halo > 0.4 mm around the TA lumen on CDS was considered diagnostic of GCA.

For GCA categorization using the 1990 ACR criteria, SVV or isolated VVV were not considered to represent a positive TA biopsy.

Results: Of the 30 patients with SVV and/or VVV-GCA 14 (46.6%) satisfied the ACR criteria for the classification of GCA.

Table 1 shows the comparisons between the patients with SVV/VVV and classic GCA.

Table 1. Characteristics of the patients with SVV and/or VVV versus those with classic GCA

	SVV and/or VVV (N=30)	Classic GCA (N=30)	P
Halo on CDS (%)	6/30 (20%)	23/30 (76.6%)	0,0001
Bilateral Halo on CDS (%)	1/6 (16.7%)	15/23 (65.2%)	0,064
Abnormalities of TA at physical examination (%)	8/24 (33.3%)	18/30 (60%)	0,061

Conclusion: The prevalence of the halo sign on CDS of the TA is significantly lower in patients with SVV/VVV-GCA compared with those with classic GCA.

These results suggest that CDS does not perform well in these two subsets of GCA. TA biopsy is required to confirm the diagnosis of GCA in patients with SVV- and VVV-GCA.

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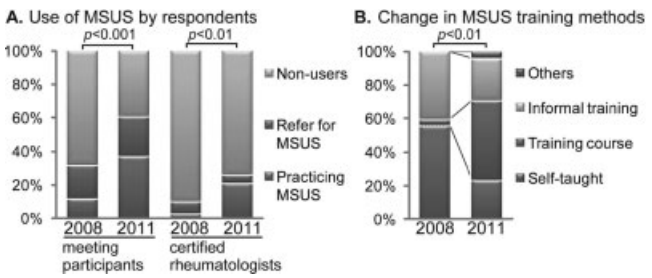
Challenges to Expanding the Clinical Application of Musculoskeletal Ultrasonography Among Rheumatologists in Japan. Maasa Hama, Kaoru Takase, Atsushi Ihata, Mitsuhiro Takeno and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan

Background/Purpose: Our previous survey in 2008 revealed that only 22% of Japanese rheumatologists used musculoskeletal ultrasonography (MSUS) for patient management because of insufficient educational opportunities. The objective of this study is to clarify the current state of MSUS usage which is compared with MRI and to identify further challenges.

Methods: We conducted a second survey between October 2010 through January 2011 by sending questionnaires to 200 randomly selected Japanese rheumatologists, consisting of 100 participants in a meeting in 2009 on imaging in rheumatic diseases and 100 board certified rheumatologists.

Results: Among the respondents, a majority (85% and 67%, respectively) used MRI. MSUS users increased from 32% to 60% of meeting participants and from 11% to 27% of other rheumatologists. The majority of MSUS users had begun using MSUS within the previous 3 years. Whereas most respondents in the previous survey had been self-taught, in the current survey many had attended training courses or had received informal training from skilled users. Despite an increase in skills and equipment ownership, obstacles to implementing MSUS remained, most prominently a lack of time.



Conclusion: Training courses and informal training have contributed to the popularization of MSUS in Japan. To further increase MSUS usage, additional training opportunities and education about the advantages of MSUS will be needed.

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Are Training Sessions Useful for Ultrasound Scan Evaluation of Synovitis In Rheumatoid Arthritis? Andrés Ponce[1], Juan J. Alegre[2], Manuel Castaño[3], Ricardo Gutierrez-Polo[4], Francisco G. Jiménez-Núñez[5], María P. Macarrón[6] and Jesús Garrido[7]. [1]Hospital General de Granollers, Granollers, Spain, [2]Hospital Universitario Dr Peset, Valencia, Spain, [3]Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, [4]C.H. de Navarra, Pamplona, Spain, [5]Hospital Regional Universitario Carlos Haya., Malaga, Spain, [6]Hospital Clínico San Carlos, Madrid, Spain, [7]Facultad de Psicología.Universidad Autónoma de Madrid, Madrid, Spain

Background/Purpose: US is becoming a realistic tool for synovitis assessment in rheumatoid arthritis (RA), although reliability remains as a challenging issue. Therefore, training sessions (TS) are needed to improve the intra and inter-observer reliability. However, the improvement in reliability due to TS has not been quantified. The aim of this study is to measure the reliability of the US evaluation for different joints, both before and after TS.

Methods: 6 rheumatologists expert in US evaluated the presence of synovitis and PD signal in 173 static images of joints from RA patients (45 wrists, 27 metacarpophalangeals, 25 ankles, 36 metatarsophanlangeals, 20 knees, and 20 elbows) recorded in a regular clinical setting by 65 different rheumatologists, with evaluation time limited to 1 minute per image. Fifteen to thirty days later they took a second evaluation of the images of a joint assigned to each researcher (Pre-TS). One month later a 3-hour standardization and training session (TS) took place. Fifteen days after that the rheumatologists evaluated the images following the same procedure, first all the images and, 15–30 days apart, images of assigned joint (Post-TS). Intra and inter-observer kappa were calculated, both pre-TS and post-TS.

Results: The intra- and inter-observer kappa values for each joint, pre-TS and post-TS, are shown in the following table:

	Intra-observer kappa				Inter-observer kappa			
	Power Doppler		Grey scale		Power Doppler		Grey scale	
Joint	Pre-TS	Post-TS	Pre-TS	Post-TS	Pre-TS	Post-TS	Pre-TS	Post-TS
wrist	0.562	0.769	0.319	0.644	0.684	0.760	0.373	0.478
MCP	0.710	0.913	0.578	0.777	0.568	0.699	0.359	0.551
Ankle	0.845	0.930	0.699	0.762	0.685	0.676	0.302	0.588
MTP	0.932	0.904	0.273	0.669	0.762	0.924	0.476	0.485
Knee	0.142	0.824	0.027	0.441	0.479	0.921	0.455	0.533
Elbow	0.434	0.855	0.220	0.806	0.518	0.816	0.359	0.439

After TS the magnitude of the reliability statistic kappa increased mainly for those joints that showed the lowest kappa values at the pre-TS evaluation.

Conclusion: The intra an inter-observer reliability in the evaluation of the static images, taken in regular clinical settings, improve clearly after a training session.

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The Most Reliable Probe Position in An Rheumatoid Arthritis Wrist Is From Lister's Tubercle to Digit III, the Zorro Study. Noelia Dopazo Gonzalez[1], David F. Ten Cate[2], Antonio Mera[3], S.A. Insua Vilariño[4], Nanno Swen[5], E. Perez-Pampin[4], Juan J. Gomez-Reino[6] and Jolanda J. Luime[7]. [1]Erasmus Medical Centre Rotterdam, Rotterdam, Netherlands, [2]Erasmus Medical Center, Rotterdam, Netherlands, [3]General Hospital, Santiago Compostela, Spain, [4]University Clinical Hospital of Santiago de Compostela, Santiago de Compostela, Spain, [5]Medical Center Alkmaar, Alkmaar, Netherlands, [6]Hospital Clinico Universitario, Santiago, Spain, [7]Erasmus MC - University Medical Center, Rotterdam, Netherlands

Background/Purpose: Ultrasound (US) has great potential as an outcome measure in Rheumatoid Arthritis (RA), but is thought to be imperfect and operator dependent. The wrist is often involved but difficult to assess by US. [1] This, with the lack of consensus on probe positioning, has led to little and equivocal clear data on the reliability of US scanning of the wrist.[1–5] Our purpose was to find the most reliable probe position on the wrist, out of 3 probe positions, between 3 examiners.

Methods: 53 RA patients were recruited at the University Clinical Hospital of Santiago de Compostela for a scan of both wrists. Three probe positions using clear anatomical landmarks were examined: Lister's Tubercle to digit II (position 1), Lister's Tubercle to digit III (position 2) and ulnocarpal (position 3), from a lateral orientation. Three examiners (2 experienced and 1 junior ultrasonographer)

scored synovitis following a 0–3 semiquantitative scoring system. Interobserver reliability was expressed using the ICC (A,1), single measure, agreement definition.

Results: The 53 patients had a median disease duration of 57 months [range: 0–354 months] and a heterogeneous disease activity (median DAS28 of 2.83 [range 0.19–6.41]). From table 1 follows that position 2, from Lister's Tubercle to digit III, is slightly more reliable than position 1 in the GSUS examination of the wrist. For PDUS, position 1 and 2 show similar reliability. Position 3 shows poorest reliability of all positions in both GSUS and PDUS.

Table 1. Interobserver reliability, right and left wrist together

	Position 1	Position 2	Position 3
RC (GS)	0.60	0.52	0.35 (UC)
IC (GS)	0.44	0.60	–
RC (PD)	0.52	0.52	0.36 (UC)
IC (PD)	0.40	0.40	–

(RC= radiocarpal joint, IC= intercarpal joint, UC=Ulnocarpal joint, GS= Greyscale, PD= Power Doppler)

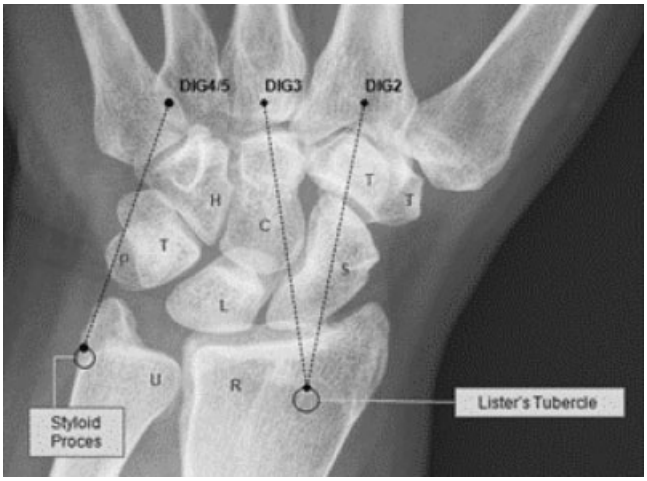

Figure 1. The three probe positions.
R=Radius, U=Ulna, S=Scaphoid, L=Lunatum, T(left)=Triquetrum, P=Pisiforme, H=Hamatum, C=Capitatum, T(middle)=Trapezoideum, T(right)= Trapezium

Conclusion: Position 2 shows the best reliability in scanning the wrist in GSUS. For PDUS position 1 and 2 show similar reliability. The reliability of GSUS and PDUS examination of the wrists of RA patients was poor for position 3 (the ulnocarpal joint). These findings suggest that position 2 should be used in daily practice.

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Meta-Analysis: Improvement In Wrist Pain with US-Guided Glucocorticoid Injections As Compared to Palpation-Guided Injections. Maureen Dubreuil[1], Stephanie Greger[2], Michael P. LaValley[3], Wilmer L. Sibbitt[4] and Eugene Y. Kissin[5]. [1]Boston Medical Center, Boston, MA, [2]Boston University Medical Center, Boston, MA, [3]Boston University School of Public Health, Boston, MA, [4]University of New Mexico HSC, Albuquerque, NM, [5]Boston University, Boston, MA

Background/Purpose: This meta-analysis compares short-term change in wrist pain following ultrasound-guided (US-guided) intra-articular glucocorticoid injections with pain reduction after palpation-guided injections in persons with inflammatory arthritis or osteoarthritis.

Methods: Data sources were MEDLINE, Cochrane, BIOSIS, CINAHL, ACR/AHRP abstracts, ClinicalTrials.gov, hand-search of reviews, and recommendations from experts (USSONAR), and investigators. Studies that assessed change in pain score by Visual Analog Scale (VAS), in direct comparison of US-guided and palpation-guided injections, or with a single relevant treatment arm were included. Subject-level data was sought from authors of relevant studies.

Primary outcome was change in wrist pain at rest, by 0–10 cm (VAS) prior to injection and at 1–4 week follow-up. Mean and 95% confidence intervals (CI) for change in VAS pain were calculated for each group and study. Mean difference was calculated for comparative studies. Secondary outcome was proportion of subjects attaining Minimal Clinically Important Improvement (MCII) in VAS (defined as reduction in VAS of ≥ 20% at follow up); calculated for each group with exact binomial 95% CI. Odds ratios (ORs) of MCII were calculated for comparative studies. Mean differences in VAS pain and ORs for MCII for comparative studies were combined using random effects meta-analysis.

Results: Ten studies were eligible for inclusion, but adequate data was available for only 6 studies; 3 had both US-guided and palpation-guided treatment arms; 3 had a single relevant treatment arm. Rheumatoid Arthritis was the indication for injection in 83.3% of subjects.

Mean VAS reductions ranged from 3.8 to 5.8 for studies of US-guided injections, and from 2.1 to 5.7 for palpation-guided injections. Mean difference in VAS between treatment arms for the 3 direct comparison studies, and ranged from −0.2 to 1.3, with a random effects combined estimate of 1.0 indicating a statistically significant advantage of ultrasound. MCII attainment was 86 to 100% in the US-guided injection arms, and 71 to 96% in palpation arms. The estimated OR for MCII in direct comparison studies was 3.0 (95% CI from 0.9 to 10.1) indicating an increase in odds of MCII with ultrasound that trended toward, but did not reach statistical significance (p=0.07).

Conclusion: Ultrasound-guided glucorticoid injections to the wrist result in greater reductions in pain than palpation-guided injections, and likely provide a clinically important improvement. These data indicate a role for ultrasound guidance in patients who have inadequate reduction in pain after palpation-guided injection. Ultrasound-guidance may be indicated as the initial approach for patients with characteristics that make palpation-guided injection challenging, or for providers with limited experience performing palpation-guided injections.

Table. Mean reductions in wrist rest pain by Visual Analog Scale (VAS) and proportion of subjects attaining Minimal Clinically Important Improvement (MCII) among studies of ultrasound-guided injections and palpation-guided injections.

	Ultrasound-Guided Injections			Palpation-Guided Injections			Ultrasound-Palpation Comparison	
Study	**N**	**VAS Pain Mean Reduction (95% CI)**	**MCII % (95% CI)**	**N**	**VAS Pain Mean Reduction (95% CI)**	**MCII % (95% CI)**	**VAS Pain Mean Difference (95% CI)**	**MCII Odds Ratio (95% CI)**
Luz 2008	30	3.8 (2.9, 4.7)	87 (69, 96)	30	2.7 (2.1, 3.4)	90 (74, 98)	**1.1** (−0.1, 2.2)	**0.7** (0.1, 3.5)
Sibbitt 2009	15	5.5 (4.2, 6.8)	100 (78, 100)	15	5.7 (4.1, 7.3)	93 (68, 100)	**−0.2** (−2.1, 1.7)	**3.2** (0.1, 85.0)
Sibbitt 2011	37	5.8 (5.0, 6.5)	98 (89, 100)	46	4.5 (3.6, 5.4)	78 (62, 90)	**1.3** (0.1, 2.4)	**12.4** (1.5, 100.0)
Filippucci 2004	13	5.7 (4.4, 6.9)	100 (75, 100)					
Lopes 2008				25	4.2 (3.5, 4.9)	96 (80, 100)		
Weitoft 2003				59	2.1 (1.4, 2.8)	71 (57, 83)		
Random Effects Combined Estimate*							**1.0** (0.2, 1.7)	**3.0** (0.9, 10.1)

* For random effects combined estimate, only the 3 comparative studies were included.

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Steroid Injection for Plantar Fasciitis—a Placebo-Controlled Trial. Elisabeth M.A Ball[1], Helen M.A. McKeeman[2], James Burns[3], Wing Hoi Yau[3], Owen Moore[3], Claire Benson[3], Joanne Foo[3], Chris Patterson[4], Gary D. Wright[3] and Allister J. Taggart[3]. [1]Musgrave Park Hospital/Queens' University, Belfast, United Kingdom, [2]Belfast City Hospital, Belfast, United Kingdom, [3]Musgrave Park Hospital, Belfast, United Kingdom, [4]Epidemiology Research Group, Queens University Belfast, United Kingdom

Background/Purpose: Plantar Fasciitis (PF) is a common cause of heel pain and can affect quality of life and work capacity.The aim of this study was threefold - to compare steroid injection with placebo injection, to compare ultrasound-guided with palpation-guided steroid injection and to investigate the role of ultrasonography in the management of plantar fasciitis.

Methods: 65 patients with plantar fasciitis were recruited via Family Practitioner and Podiatric referrals to the Belfast Hospitals Trust between November 2008 and June 2011. Patients with a history of inflammatory arthritis and those who had received a previous steroid injection were excluded. Patients were randomised to one of three groups—ultrasound-guided steroid injection, palpation-guided steroid injection or ultrasound-guided placebo (saline) injection.The 100mm visual analogue scale (VAS) of pain and ultrasonography of the plantar fascia were performed at baseline and at the follow-up visits at 6 and 12 weeks. Blinding was applied to the participants and to the investigators performing the procedures and measuring outcomes. Analysis of covariance was used to analyse the 6 week and 12

week VAS results in the three groups using the baseline VAS levels as a covariate.

Results: The median duration of symptoms was 6 months (range 2.5–60).The mean (standard deviation) thickness of the plantar fascia at the anterior calcaneal border on ultrasound at baseline was 6.05 (1.47) mm. 22 Patients were randomised to ultrasound-guided steroid injection, 21 patients to palpation-guided steroid injection and 22 to ultrasound-guided placebo injection. No adverse events were reported. There was a significant difference in VAS scores between the groups both at 6 weeks and at 12 weeks ($p = 0.021$ and $p = 0.009$ respectively). There was a 20.8 mm (95% CI = 3.3–38.1) difference in mean VAS scores at 6 weeks between the ultrasound guided steroid group and the placebo group and a 22.6mm (95% CI = 5.4–39.8) mean difference between the palpation guided steroid group and the placebo group at 6 weeks. At 12 weeks the mean difference was 23mm (95% CI = 4–42.8) and 27mm (95% CI = 9.2–46) respectively between both groups and the placebo group. There was no significant difference in VAS scores following steroid injection between the ultrasound guided and the palpation guided groups at either time point.

Conclusion: Despite the widespread use of steroid injection only two controlled trials have compared its effect to placebo injection in plantar fasciitis. Blockey[1] showed no benefit over placebo and Crawford et al[2] showed a significant benefit at one month but not subsequently. In our study of 65 patients, steroid injection showed a clear benefit over placebo at 6 weeks and this was sustained at 12 weeks. There were no significant differences in the results achieved using ultrasound-guided or palpation-guided steroid injection.

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Power Doppler Ultrasound Findings and Serum Levels of Pro- and Anti-Inflammatory Cytokines in Normal Joints. Joanne Kitchen[1] and David Kane[2]. [1]Adelaide and Meath Hospital, Dublin, Ireland, [2]Adelaide, Meath hospital Dublin (incorporating the National Children's hospital), Dublin 24, Ireland

Background/Purpose: To determine Power Doppler ultrasound findings in normal peripheral joints and to investigate the relationship between serum levels of IL-1α, IL-1β, IL-2, IL-4, IL6, IL-8, IL-10, VEGF, TNFα, and IFNγ

Methods: Thirty healthy controls (15 male, 15 female, mean age 38.9 yrs, SD 11.7) underwent 2D ultrasound of 40 joints (DAS28 joint set, ankles and metatarsophalangeal joints), with imaging in greyscale and power Doppler modes, resulting in 15,480 images for analysis. Each patient had 58 power Doppler images scored (0–3 score) and recorded, resulting in a potential maximum score of 174 for power Doppler. Serum samples were analysed for an array of pro-inflammatory and anti-inflammatory cytokines using the Evidence Investigator™ biochip array (Randox).

Results: Power Doppler signal >1 was not generally seen in normal joints apart from the wrist (41.7%). The mean total power Doppler score was 4.8 (SEM 0.624, Range 0–13) from a potentially maximum score of 174. There was no significant difference in the power Doppler scores between male and female subjects ($p=0.753$) and no significant correlation between age and power Doppler score ($r= 0.298$, $p= 0.11$). Serum samples were analysed on 26/30 control patients for an array of pro-inflammatory cytokines (IL-2, IL6, IL-8, IL-1α, IL-1β, VEGF, TNFα, IFNγ) and anti-inflammatory cytokines (IL-4, IL-10). There was a significant correlation between the VEGF concentration and the power Doppler score in the normal controls ($r = 0.395$, $p = 0.046$). There was a significant inverse correlation between the TNFα concentration and the power Doppler score ($r = -0.405$, $p=0.04$). There was no correlation with any of the other cytokines and the power Doppler scores.

Conclusion: Power Doppler signals of >1 are an uncommon feature in normal joints apart from the wrist and this study supports the use of >1 score as an appropriate cut-off of clinical abnormality when performing ultrasound assessment. Power Doppler score of the 40 joint set correlated with VEGF levels in serum but not other cytokines providing further evidence of a role for VEGF in synovial neoangiogenesis.

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Lack of Correlation Between Synovial Biology and Ultrasound Features of Synovitis in Osteoarthritis. Jeannie H. Chao[1], Sanna Rosengren[2], Joshua Hillman[2], Kenneth C. Kalunian[2], Scott Ball[1], Brady K. Huang[1], Gary S. Firestein[2] and David L. Boyle[2]. [1]UCSD, La Jolla, CA, [2]UCSD School of Medicine, La Jolla, CA

Background/Purpose: Pain and cartilage degeneration are salient features of osteoarthritis (OA). Synovitis is associated with pain and possibly disease progression, and ultrasound has been proposed as a method to assess disease activity. To identify patients that might benefit from synovitis-targeted therapies and to determine the correlation between inflammatory mechanisms and imaging, we examined the association between power Doppler ultrasound (PDUS) and molecular markers of inflammation in the synovium of end-stage knee OA

Methods: Patients meeting ACR criteria for knee OA and scheduled for arthroplasty were included and assessed using the WOMAC Osteoarthritis Index (n=18). PDUS using a high-frequency linear transducer (12 MHz, GE Logiq E) of the affected knee was performed prior to surgery. Views of the suprapatellar recess as well as lateral and medial parapatellar recesses were collected and semi-quantitatively scored for synovial thickening (ST) and Power doppler activity (PD). Regional measurements were summed to achieve composite scores. Synovium was obtained at time of arthroplasty. A high-sensitivity multiplex Western Blot technique was used to measure signaling proteins. Real-time qPCR was used to determine expression of inflammatory genes.

Results: PDUS features varied widly. Synovial thickening was observed in all patients, mean score 3.56 ± 1.76. PD scores also varied among patients, with a mean of 1.78 ± 1.63. The intraobserver reliability for ST and PD was high (kappa = 0.81 and 1, respectively). Phosphorylated signaling proteins were detectable in all synovia. For example, the mean relative expression of phospho-HSP27 was 0.718 (0.538–0.958) and 1.14 (0.78–1.67) for phospho-Stat1. Strong correlations were observed between phospho-Stat1 and phospho-Stat3 and between phospho-HSP27 and phospho-Erk. mRNA analysis was performed on 13 patients. Examples of mean relative expression of genes of interest include 0.733 (0.40–0.13) for IL1b, and 0.72 (0.38–0.14) for IL8. MMP1 and MMP3 as well as IL1β and IL8 were highly correlated. Correlations between PDUS scores with either qPCR or Western blot did not reach statistical significance. The highest correlation found was between PD and phospho-HSP27 ($R=0.44$, $p=0.0706$). Of note, IL8 expression correlated significantly with WOMAC function ($R=0.717$, $p=0.0058$), and pain subscale scores ($R=0.7044$, $p=.0072$) as well as global scores ($R=0.6399$, $p=0.0185$). CXCL13 also correlated with WOMAC function ($R=0.6863$, $p=0.0096$) and pain (0.5725, $p=0.0409$) subscale scores and global scores ($R=0.5824$, $p=0.0368$).

Conclusion: Ultrasound parameters did not significantly correlate with selected synovial biomarkers related to inflammation. Surprisingly, a clinical assessment of OA (WOMAC) best correlated with molecular measures of synovitis. Alternative imaging measures or technology are needed to improve stratification of patients and define synovitis for clinical trials or clinical decision-making. This observation also has implications for the use of ultrasound in classification criteria, such as the 2010 revised criteria for rheumatoid arthritis.

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Comparison of Optical Coherence Tomography and High Frequency Ultrasound As Measures of Skin Thickness in Systemic Sclerosis; A Pilot Study. Andrea Murray[1], Donna Buckley[2], Graham Dinsdale[1], Tonia Moore[1], Mark Dickinson[2] and Ariane Herrick[1]. [1]School of Translational Medicine, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [2]Photon Science Institute, University of Manchester, Manchester, United Kingdom

Background/Purpose: Accurate, reliable, and non-invasive measures of skin thickness that are sensitive to small but clinically important change are badly required as outcome measures in patients with scleroderma – either localised or related to systemic sclerosis (SSc). At present the gold standard is high frequency ultrasound (HFUS), and yet even this has been relatively little studied. Optical coherence tomography (OCT) is a novel non-invasive light based imaging technique which, due to its high resolution, may provide complementary data to HFUS. HFUS penetrates deeper in skin than OCT (full dermis); however, OCT offers higher resolution (7 μm compared to 40 μm for HFUS) allowing more accurate measurement of epidermal thickness.

Our aim was to carry out a pilot study to validate OCT as a measure of skin thickness by comparison to HFUS measurements in patients with SSc and healthy controls.

Methods: 20 patients with SSc (median 61 (range 28–78) years of age; 80% female, 35% diffuse) and 20 healthy controls (50 (32–70) years of age; 70% female) were recruited. Thickness of the epidermis was assessed at 5 upper limb sites (distal digit [non-dominant, ring], proximal digit, dorsum of hand, forearm, upper arm) using HFUS and OCT. Modified Rodnan skin score (mRSS) was recorded at each site for patients with SSc.

Results: Epidermal skin thickness was significantly higher in patients, as measured by HFUS, at the digits, dorsum and forearm and as measured by OCT at the proximal digit and dorsum (Table 1). The numbers of patients with each mRSS score (0–3) at each site are shown in Table 1. Comparison of patient skin sites split into 2 groups (skin score 0–1 and 2–3) showed significant differences for both HFUS [p<0.001] and OCT [<0.001]). HFUS and OCT showed correlation with skin score when all sites were considered together (R=0.296, p=0.003 and R=0.345, p<0.001 respectively). There was no correlation [Pearson's correlation] between HFUS and OCT results for either the 40 subjects considered together (r=0.157, p=0.090) or for the 20 SSc patients alone (r=0.066, p=0.514).

Table 1.

Site of epidermal thickness (μm) measurement (dorsal aspect)	Controls (N=20)		Patients (N=20)		mRSS			
	HFUS	OCT	HFUS	OCT	0	1	2	3
Distal digit	240(33)	273(41)	264(41)* P=0.023	270(69) P=0.442	0	4	13	3
Proximal digit	244(35)	255(37)	265(41)* P=0.041	290(47)* P=0.007				
Hand	184(37)	213(26)	206(37)* P=0.031	252(35)* P<0.001	4	9	7	0
Forearm	195(35)	208(18)	223(58)* P=0.035	213(20) P=0.174	8	5	6	1
Upper arm	195(42)	215(18)	194(41) P=0.461	225(24) P=0.078	12	4	3	1

mean (SD); *p<0.05 vs control

Conclusion: 1) This preliminary study is the first step in validating the use of OCT as a measurement tool in SSc: OCT epidermal thickness was increased in proximal digit and dorsum. OCT as well as HFUS correlated with mRSS.

2) The higher resolution of OCT, combined with the higher penetration of HFUS (which can therefore also measure dermis thickness), means that the combination of HFUS and OCT gives complementary data.

3) The potential of OCT to incorporate blood flow measurement in individual vessels (optical Doppler tomography [ODT]), is another reason why OCT requires further evaluation in scleroderma: ODT should enable further investigation of the relationship between fibrosis and ischaemia.

4) OCT now needs to be applied in larger cohorts of patients with varying degrees of skin thickening, and in longitudinal studies.

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Sensitivity and Specificity of Indocyanine Green Enhanced Optical Imaging (Xiralite) in Comparison to Magnetic Resonance Imaging and Ultrasonography. Stephanie G. Werner[1], Peter Schott[2], Sarah Ohrndorf[3], Carsten Schwenke[4], Malte Bahner[5], Bernward Kurtz[2], Marina Backhaus[6], Gerd R. Burmester[3] and Hans-Eckhard Langer[7]. [1]RHIO (Rheumatology, Immunology, Osteology) Duesseldorf, Duesseldorf, Germany, [2]Evangelisches Krankenhaus Duesseldorf, Duesseldorf, Germany, [3]Charité University Hospital, Berlin, Germany, [4]SCOSSIS, statistical consulting, Berlin, Germany, [5]mivenion GmbH, Berlin, Germany, [6]Charite University Hospital, Berlin, Germany, [7]Duesseldorf, Germany

Background/Purpose: Indocyanine green (ICG) enhanced fluorescence optical imaging (FOI) with the commercial available Xiralite system (mivenion GmbH, Berlin) is a novel imaging technology to assess inflammatory activity in arthritic conditions. We compared FOI with MRI and ultrasonography in patients with arthritis, arthralgia and healthy controls.

Methods: A total of 125 subjects was examined in 3 comparative studies. Cohort 1: 25 patients with rheumatoid or undifferentiated arthritis with high disease activity (DAS28 >3.2), cohort 2: 20 patients with early arthritis (disease duration≤24months) and cohort 3: 74 patients with arthritis or arthralgia in the hands. Six healthy individuals and 6 subjects with arthralgia without any sign of an inflammatory rheumatic disease served as control group. All patients received clinical examination (CE) and lab testing. In cohort 1 and 2 a contrast enhanced MRI of the clinically leading hand was performed. MRI was evaluated according to the OMERACT-criteria. Ultrasonography in grey-scale mode (GSUS) and power-Doppler Mode (PDUS) of the clinically leading hand was performed in cohort 3. All patients were examined by FOI using ICG as fluorophor (ICG-Pulsion® 0.1 mg/kg/BW bolus i.v., 6 minutes). Image interpretation was done on three defined phases of increased signal intensities (ISI) in the finger tips: early (P1, until strong ISI in the finger tips), intermediate (P2, during ISI in the finger tips), and late phase (P3, after decreasing of ISI in the finger tips) and for an automatically generated composite image (PrimaVista Mode, PVM). Sensitivity and specificity was calculated using MRI, GSUS or PDUS as reference.

Results: With MRI or ultrasonography as reference, FOI was more sensitive than CE (Table 1). FOI had a high sensitivity and high specificity, depending on the evaluated phase. FOI did not detect any positive findings in 97.8%–100% of joints in controls, depending on the evaluated image or phase.

Table 1. Sensitivity and specificity of FOI and clinical examination with ultrasonography or MRI as reference

FOI	MRI cohort 1 sensitivity	MRI cohort 1 specificity	MRI cohort 2 sensitivity	MRI cohort 2 specificity	PDUS cohort 3 sensitivity	PDUS cohort 3 specificity	GSUS cohort 3 sensitivity	GSUS cohort 3 specificity
FOI PVM	51%	81%	55%	92%	67%	54%	56%	57%
FOI P1	27%	94%	34%	95%	33%	90%	22%	95%
FOI P2	72%	56%	83%	69%	72%	44%	68%	50%
FOI P3	47%	89%	60%	92%	60%	69%	51%	78%
Any phase (P1–3)	76%	54%	85%	65%	74%	42%	70%	48%
CE	59%	72%	58%	90%	50%	76%	35%	79%

Abbreviations: FOI: fluorescence optical imaging; PVM: PrimaVista mode; P1: phase 1; P2: phase 2; P3: phase 3; any phase: positive in P1 or P2 or P3; PDUS: ultrasonography in power-Doppler mode (synovitis or tenosynovitis); GSUS: ultrasonography in grey scale mode (synovitis or tenosynovitis); MRI: magnetic resonance imaging (synovitis or tenosynovitis); CE: clinical examination (swollen joints)

Conclusion: FOI appears to be a valuable tool for assessing inflammation in patients with rheumatoid, undifferentiated, early arthritis or arthralgia in the hands. Sensitivity and specificity differed for PVM and P1–3. Therefore an adequate reading of a FOI sequence requires a separate reading of PVM and the phases.

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Indocyanine Green Enhanced Optical Imaging Using for Monitoring of Treatment Response. Stephanie G. Werner[1], Felicitas Spiecker[2], Sabine Mettler[2], Gudrun Lind-Albrecht[2], Carsten Schwenke[3] and Hans-Eckhard Langer[2]. [1]RHIO (Rheumatology, Immunology, Osteology) Duesseldorf, Duesseldorf, Germany, [2]Duesseldorf, Germany, [3]SCOSSIS, statistical consulting, Berlin, Germany

Background/Purpose: Indocyanine green (ICG) enhanced fluorescence optical imaging (FOI) is a novel diagnostic technology for the assessment of inflammation in arthritis. In cross-sectional studies FOI had a good agreement with MRI and US findings (1),(2). The semiquantitative fluorescence optical imaging activity score (FOIAS) correlated with clinical (DAS 28) and MRI (RAMRI) scores of disease activity and a semiquantitative score of swelling and tenderness in the hands (locDAI). This is the first study to use FOI for the measurement of treatment response in DMARD naïve patients and in subjects with inadequate response to non-biologic DMARDs (DMARD-IR) and switch to biologica.

Methods: 33 patients with rheumatoid (RA) and psoriatic (PsA) arthritis were examined before starting treatment with DMARD or biological (visit 1) and at follow-up (visit 2 after ≥3 months). Treatment response was assessed using DAS28, locDAI and FOIAS. For locDAI swelling and tenderness were assessed separately and semiquantitativly for 15 joints of both hands (0 = no, 1 = subtle, 2 = distinct swelling/tenderness, distal interphalangeal joints (DIP) 2–5, interphalangeal joints (IP), proximal interphalangeal joint (PIP) 2–5, metacarpophalangeal joint (MCP) 1–5 and wrist, range 0–60) and a sum score was calculated. The FOI (Xiralite, mivenion GmbH, 0.1 mg/kg/BW of ICG i.v. over 6 minutes) sequences were analyzed for the automatically generated composite image (PVM) and three defined phases of FOI (P1, P2, P3). FOI findings of increased signal intensities were valued as 0=no, 1=low, 2=moderate, and 3=strong increased signal intensities. For FOIAS sum scores over all joints (DIP 2–5, PIP 2–5, IP, MCP 1–5, wrist, both hands, range 0–90) for PVM, the phases P1–3 and all phases were calculated. Standardized response means (SRM) were calculated for measurement of treatment response and Wilcoxon signed rank test was used to assess statistical significant change.

Results: The mean DAS28 at visit 1 was 4.3 and 2.9 at visit 2. All scores (DAS28, locDAI, FOIAS) showed a reduction of disease activity from visit 1 to visit 2. The mean reduction was 34% for DAS28, 47% for locDAI and 22%–34% for FOIAS. The SRMs showed high treatment response (SRM >0.8) for DAS28 (SRM −1.26) and locDAI (SRM −0.95) and moderate response (>0.5–0.8) for FOIAS (SRM −0.57 to −0.76) (3). The change from baseline was stated as statistical significant for all scores except FOIAS P1 ($p<0.05$).

Conclusion: The study suggests that FOI is a suitable tool to assess treatment response in subjects with RA and PsA. Further studies are required to test FOI as a possible additional outcome measure in clinical trails and clinical practice.

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A Comparison of Optical Coherence Tomography and Clinical Assessment of Nail Disease in Psoriasis and Psoriatic Arthritis. Concepcion Castillo-Gallego[1], Sibel Aydin[2], Zoe R. Ash[3], Giusepinna Abignano[3], Paul Emery[3], Helena Marzo-Ortega[3], Francesco Del Galdo[3] and Dennis McGonagle[3]. [1]Hospital Universitario La Paz, Madrid, Spain, [2]Goztepe Training and Research Hospital, Istanbul, Turkey, [3]University of Leeds, Leeds, United Kingdom

Background/Purpose: Nail disease in psoriasis (Pso) is increasingly recognised to be of major clinical and research relevance. Clinical assessment is the only currently available tool and no objective methods have been standardized to image the nails. Optical coherence tomography (OCT) is an analogue of ultrasound, using infrared light instead of acoustic waves and has been used in the clinical setting by ophthalmologists since 1991. The axial resolution is determined by the bandwidth of the light source, which is 1–2 mm in general, limiting its use to very superficial tissues. It has also been widely investigated in dermatology, particularly in non-melanoma skin cancers.

The purpose of this study was to describe nail appearances as seen with OCT and to compare these findings in Pso and psoriatic arthritis (PsA) with clinical assessment.

Methods: A total of 290 finger nails of 17 patients (4 Pso, 13 PsA) and 12 healthy controls (HC) were scanned by OCT with a topical probe "VivoSight" (Michelson Diagnostics) and optics of Swept-source Fourier-Domain type with a laser wavelength of 1305+/− 15 nm. The investigator was blinded to the clinical details.

Signal changes within the nail and contour abnormalities by OCT were documented. Clinical nail abnormalities were independently scored by an assessor blinded to the OCT findings using the mNAPSI scoring system.

Results: OCT showed remarkably high quality images of the nail, the adjacent nail matrix and the subungual epidermis. The most striking finding was that of leukonychia, manifesting as diffuse "white" lines running obliquely along the middle third of the nail. Pits were remarkably superficial and were associated with disorders of the nail matrix keratinisation. Subungual vascularity and subungual epidermis hyperplasia could be delineated.

The mean (SD) age of patients was 54.4 (16.5) and 29.4% of them were female. The overall mean (SD) modified NAPSI scores was 12.8 (10.6) for patients with 94% (16/17) having at least one involved nail by OCT. The number of involved nails by OCT was significantly higher in patients compared to HC (median (range): 7 (0–10) vs. 1 (0–6); $p=0.001$)). When analysed per nail, patients had significantly higher number of involved nails by OCT compared to HC (106/170 (62.4%) vs. 22/120 (18.3%); $p<0.0001$). The absolute agreement between OCT and clinical assessment was 69.3%. Within patient group, OCT detected abnormalities in 33 nails (19.5%) where clinical assessment was normal.

Having a positive OCT (either signal changes or contour abnormalities) had a sensitivity and specificity of 57% and 82%, with a likelihood ratio (LLR) of 3.1 for a diagnosis of Pso. When different findings of OCT were compared, large intra-nail plate linear "calcifications" and superficial hyperkeratinisation of the nail had the highest LLRs (16.2 and 6.4, respectively). None of the HC had clinical nail disease whereas 9/12 (75%) of them had at least one involved nail by OCT.

Conclusion: These preliminary findings clearly show that OCT has great potential for the systematic characterisation of nail changes in Pso and this could have implications for diagnosis, prognosis and monitoring of therapies.

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Adalimumab Improves Endothelial Function and Microcirculation In Rheumatoid Arthritisas Determined by Simultaneous Assessment of Brachial Artery Flow-Mediated Vasodilation and Laser Doppler Flowmetry. György Kerekes, Vanda Pongrácz, Szilvia Szamosi, Gabriella Szücs, Andrea Váncsa, Orsolya Tímár, Zoltán Csiki, Edit Végh, Pál Soltész and Zoltan Szekanecz. University of Debrecen Medical and Health Sciences Center, Debrecen, Hungary

Background/Purpose: Increased cardiovascular morbidity has become a leading cause of mortality in rheumatoid arthritis (RA). Impaired endothelial-dependent, flow-mediated vasodilation (FMD) of the brachial artery has been documented by various groups. Anti-TNF agents have been found to improve FMD in RA. However, there have been neither reports on laser doppler assessments in RA nor the effects of any biologics on laser doppler curves. Here we simultaneously assessed brachial artery FMD and laser doppler curves before and after 12 weeks of adalimumab (ADA) therapy.

Methods: First, we determined microcirculatory parameters during postoocclusive reactive hyperemia (PORH) representing endothelial function in a non-selected population of RA patients (n=46). We assessed FMD of the brachial artery using ultrasound and, simultaneously, laser Doppler PORH curves were recorded. Plasma von Willebrand Factor (vWF) levels were also determined in all patients. Then we assessed the effects of ADA treatment (40mg sc, biweekly) on microcirculatory parameters in 8 patients with early RA (disease duration ≥1 year). Vascular assessment was performed at baseline and then 2, 4, 8 and 12 weeks after the initiation of ADA treatment.

Results: After the comparison of FMD values and vWF levels with laser doppler PORH curves, significant positive correlations were found between FMD and time to max (Tmax, R=0,456, p=0,002), FMD and halftime of deceleration (TH2, R=0,435, p=0,004), and significant negative correlations were detected between vWF and Tmax (R=−0,4, p=0,009) and between vWF and TH2 (R=−0,446, p=0,003). ADA significantly decreased CRP levels ($p=0.04$) and DAS28 ($p<0.0001$). Endothelial function characterized by TH2 times improved in comparison to baseline (34.7 sec vs 26.9 sec; p=0,03), and this effect was prolonged until 8 weeks (40.5 sec; p=0,026) and 12 weeks of treatment (32.1 sec, p=0,013). After 8 weeks of treatment, significant improvement was observed in hyperemic area (AHbaseline= 1599 PUxs vs. AH8weeks =2724 PUxs, p=0,045), in 1 minute postocclusion area (APObaseline = 1469 PUxs vs. APO8weeks = 2462 PUxs, p = 0,019) and in average perfusion until peak (PtoMaxbaseline = 32,2 PU vs. PtoMax8weeks= 46,33, p=0,035).

Conclusion: The PORH test carried out with laser Doppler is a sensitive option to measure endothelial dysfunction, but only the time course of the hyperemia may be accepted as a reliable parameter. Both brachial artery FMD and laser doppler PORH assessments are useful to detect micro- and macrocirculatory endothelial dysfunction in RA patients. Treatment of early RA patients with ADA exerted favorable effects on disease activity, endothelial dysfunction and microcirculation. Early anti-TNF therapy may have important relevance for the prevention and management of vascular comorbidity in RA.

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Development of Early Diagnostic Techniques for Rheumatoid Arthritis Using Carbone Eleven Labeled PK11195 and Carbone Eleven Labeled Ketoprofen. Satoshi Nozaki[1], Sinobu Suzuki[2], Naoko Ozaki[2], Jeffrey Encinas[2], Hisashi Doi[1], Yasuhiro Wada[1], Masaaki Suzuki[1] and Yasuyoshi Watanabe[1]. [1]RIKEN, Center for Molecular Imaging Science, Hyogo, Japan, [2]Nippon Boehringer Ingelheim Co., Ltd, Hyogo, Japan

Background/Purpose: In vivo detection of pathological insults during early stages of rheumatoid synovitis is essential to allow early anti-inflammatory treatment and prevention of joint destruction. Several PET (positron emission tomography) studies have been reported using [^{18}F]fluorodeoxyglucose ([^{18}F]FDG); however, [^{18}F]FDG is not a biomarker specific for inflammation. We undertook this study to investigate whether rheumatoid synovitis pathology and the efficacy of therapies can be visualized by PET tracers specific for the inflammatory process.

Methods: During early stages of a collagen-induced experimental rat model of rheumatoid arthritis, we performed in vivo imaging using the PET tracer (R)-[^{11}C]PK11195, which binds to the translocator protein (TSPO; also known as peripheral-type benzodiazepine receptor (PBR)), and the newly

developed PET tracer [^{11}C]Ketoprofen, used for cyclooxygenase (COX) imaging.

The rat model of arthritis was induced with an emulsion of complete Freund's adjuvant and type II collagen injected intradermally at the base of the tail. Therapy of the disease was carried out with the anti-TNFα blocker ENBREL® (Etanercept, Pfizer Co. Ltd., Japan). Paw swelling was scored as an indicator of disease severity. After three weeks, the rats were injected with 50 MBq (R)-[^{11}C]PK11195 or [^{11}C]Ketoprofen and then scanned for 90 min using a small-animal PET system "microPET®." Regions of interest for each hind paw were drawn on the summed (R)-[^{11}C]PK11195 or [^{11}C]Ketoprofen image and a standardized uptake value (SUV) was calculated. After PET imaging, the hind paws were removed and fixed in formaldehyde for immunostaining.

Results: We observed that (R)-[^{11}C]PK11195 and [^{11}C]Ketoprofen uptake on inflamed paw PET scans was significantly higher than control. The immunostaining intensity for COX-2 and TSPO were especially strong on macrophages and osteoclasts. The resulting data showed a correlation analysis between SUV and paw swelling. As compared with results from a parallel PET study with [^{18}F]FDG, both tracers accumulated much more specifically to the region where inflammation was occurring. However, after treatment of ENBREL, (R)-[^{11}C]PK11195 uptake in inflamed regions did not change compared with the untreated group. Supporting this result, the intensity of immunostaining for TSPO also showed no change in joint sections.

Conclusion: In conclusion, we developed PET imaging techniques for arthritis using (R)-[^{11}C]PK11195 and [^{11}C]Ketoprofen. We speculate that monocyte-lineage cells remain in the inflamed region after anti-TNFα treatment, but reduce their expression of cyclooxygenase, which causes pain. Consequently, by using (R)-[^{11}C]PK11195 and [^{11}C]Ketoprofen, noninvasive in vivo PET imaging for rheumatoid synovitis can provide diagnostic evidence of early synovitis and allow monitoring of inflammatory cell activity during treatment.

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Pre-Clinical Bioimaging in a Mouse Model of Rheumatoid Arthritis. Michelle Ierna[1], Karen Smith[1], Kirsty Ross[2], Gordon Meiklejohn[1], Pasquale Maffia[3], James M. Brewer[3], Iain B. McInnes[3] and Paul Garside[3]. [1]MD Biosciences, Glasgow, United Kingdom, [2]University of Strathclyde, Glasgow, United Kingdom, [3]University of Glasgow, Glasgow, United Kingdom

Background/Purpose: The early detection of changes to molecular pathways underlying Rheumatoid Arthritis (RA) is a key goal in Rheumatology. However, the standard disease scoring methods employed in the standard mouse model of RA, Collagen Induced Arthritis (CIA) cannot adequately quantify cellular or molecular processes. Here, we show that biofluorescence imaging can track in vivo processes contributing to disease and allow comparisons to be made of therapeutic drug efficacy earlier in disease progression.

Methods: The mouse CIA model was induced in 6–8 week old male DBA/1 mice. From Day 17 of the study, n=5 mice per group were administered either PBS, 1mg/kg Dexamethasone or 1 mg/kg Methotrexate intraperitoneally (IP), 5 days per week until the termination of the study on Day 56. Cathepsin activity as measured *in vivo* by administering the protease activatable Near Infra Red Fluorescent probe ProSense 680® (ex/em: 680/700nm), 24 hours prior to biofluorescence imaging on Days 10, 28, 42 and 56. On the selected days, mice were anaesthetised using Hypnoval and Cathepsin activity in all paws was directly visualised and quantified using the Kodak FXPRO In Vivo imaging unit. Regions of interest were applied to each paw for each animal and the mean fluorescence intensity units quantified for each animal using Carestream Molecular Imaging software. The mean MFI units for each group could then be determined. Statistical analysis was performed using ANOVA followed by Tukey post-hoc analysis (Winstat).

Results: We recorded an increase in cathepsin activity in CIA animals treated with PBS (351 MFI units ± 44.2) which was significantly reduced at day 28 in both Dexamethasone (232 MFI units ± 10.5) and Methotrexate treated groups (247 MFI units ± 10.4; $p<0.05$). While both drugs significantly reduced cathepsin activity on days 28, Dexamethasone values were significantly reduced (181 MFI units ± 6.6) compared to those of the Methotrexate-treated mice on day 42 (257 MFI units ± 19.3). Furthermore, biofluorescence demonstrated significant differences between vehicle-treated and drug-treated groups at earlier times than conventional scoring, which did not distinguish significant differences between these groups until day 31.

Conclusion: In vivo biofluorescent imaging is a non-invasive, non-toxic modality which permits us to quantify molecular changes in disease-relevant sites over time in the same animal, thus allowing us to distinguish the effects of drug treatments earlier in disease progression. These studies provided information rich data from all paws in each animal at each time point, in comparison to time consuming procedures such as histological scoring where only a small cross section of tissue can be analysed at the end of the study. In vivo imaging allows researchers to monitor disease progression over time and can inform when the best time point would be to commence drug treatment and ultimately determine which drugs are suitable for movement into clinical trials.

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Development of Contrast Enhanced Ultrasound Imaging and Quantification of Lymphatics in Draining Lymph Nodes of WT and TNF-Tg Mice with Inflammatory Arthritis. Yawen Ju[1], Ronald Wood[2], Lianping Xing[1], Christopher T. Ritchlin[2] and Edward M. Schwarz[1]. [1]University of Rochester, Rochester, NY, [2]University of Rochester School of Medicine and Dentistry, Rochester, NY

Background/Purpose: Lymphatic drainage is an important mechanism to decrease inflammation in arthritis. Studies in mice have demonstrated that efferent lymph nodes (LN) with great draining capacity expand during a prolonged asymptomatic phase, and then suddenly collapse during arthritic flare. Since lymphatic flow and LN dynamics may be important biomarkers of arthritis flare, we developed *in vivo* ultrasound imaging methods to study popliteal lymph nodes (PLN) in normal (WT) and TNF-Tg mice with ankle arthritis. We examined PLNs before and after administration of saline or microbubble ultrasound contrast agents for clinical echocardiography.

Methods: TNF-Tg mice with expanding (4-month-old) or collapsed (8-month-old) PLN, and WT controls were anesthetized, and PLN were evaluated with a high-resolution small-animal ultrasound system (Visualsonics 770 with 704 scanhead). Three-dimensional images of the PLN and surrounding fat pad were acquired before and 7, 30 and 60min after saline or DEFINITY (Lantheus Medical Imaging) injection into the ipsilateral footpad. The mean signal intensity of the fat pad (FPsi) was computed using Amira software (TGS/Mercury Computer Systems). We quantified PLN volume via direct 3D segmentation at all time points. Lymphatic vessels in the PLN were segmented to derive the lymphatic volume (LV) at all time points; vessels were defined as regions with greater signal intensity than FPsi.

Results: In both WT and TNF-Tg mice with expanding PLN <5% change in FPsi was measured within animals, demonstrating the remarkably consistent echogenic signal of this tissue, and its appropriateness for normalization in longitudinal studies. Only a small change in LV signal intensity following DEFINITY injection was observed despite a 4-fold change in LV (0.01 to 0.04mm^3) and a 22% increase in PLN volume in WT; and a 2-fold increase in LV (0.09 to 0.18mm^3) and 34% increase in PLN volume in TNF-Tg mice. While similar increases in PLN volume were observed after saline injections, this treatment resulted in the loss of echogenic signal in PLN such that LV could not be defined. Similarly, collapsed PLN in the older TNF-Tg mice contained no regions with a signal greater than FPsi. Thus, their LV could not be calculated. There was also no change in PLN volume following footpad injection of either DEFINITY or saline, consistent with the known lack of afferent lymph flow to collapsed PLN.

Conclusion: We demonstrate the feasibility of phenotyping the lymphatic drainage function of murine PLN efferent in normal and arthritic joints via *in vivo* 3-D ultrasound imaging. The use of echogenic contrast vs. saline was found to be critical for segmenting the lymphatic vessels within the node, but similar changes in expanding PLN volume are detectible following injection of either agent. Since no changes in collapsed PLN are detected following injection with either agent, we find that dynamic ultrasound imaging following saline injection into afferent tissue is a translational, cost-effective, and minimally invasive approach for phenotyping draining lymph node function. Lymphatic drainage measured with ultrasound serves as a biomarker of erosive inflammatory arthritis progression in mice, and potentially in humans.

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In Vivo Profiling of the Disease-Inducible Promoters Serum Amyloid A3 and S100 Calcium Binding Protein A8 for Personalized Gene Therapy in Arthritis. Eline A. Vermeij, Onno J. Arntz, Peter L.E.M. van Lent, Wim B. van den Berg and Fons A.J. van de Loo. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Local intra-articular gene therapy for arthritis, with the use of disease-inducible promoters, represents a promising alterna-

tive for coping with side effects of the conventional treatments. These disease-inducible promoters react to transcription factors that are released during inflammation and therefore only produce a reporter (luciferase) or therapeutic protein when necessary. Previously, we developed lentiviral based disease-inducible promoter reporters with a computational approach by selecting suitable promoters from endogenous genes differentially regulated in inflamed synovium of collagen-induced arthritis mice (Geurts *et al.,* 2009). Two of those promoters are the *Saa3* and *S100a8. Saa3* stands for Serum Amyloid A3, which is an acute phase protein released during inflammation. *S100a8* is a member of the alarmins, which induces signaling cascades and triggers the immune system. We have elucidated the kinetics of these two promoters in an acute arthritis model to validate the use of these promoters in gene therapy.

Methods: The kinetics of the two promoter reporter constructs were evaluated in-vivo by bioluminescent imaging in the streptococcal cell wall (SCW)–induced arthritis model. An acute joint inflammation was induced 4 days after lentivirus injection by intra-articular injection of *S. pyogenes*. At pre-defined time points after SCW injection, mice were injected with luciferin. The luciferin is converted into visible light by the luciferase that is produced under control of one of the promoters. Using a sensitive CCD camera (IVIS Lumina, Caliper Life Sciences, USA) the visible light was detected and luciferase activity was quantified. Neutrophil elastase activity (neutrophil influx) and cathepsin activity (macrophage activity) at day 1 and 4 after SCW injection was measured in vivo by using an activatable fluorescent probe (PerkinElmer Inc., USA). Histological sections of the knee joints were made and scored for cell influx and synovitis. qPCR was performed on synovial tissue to measure endogenous gene expression of the *Saa3* and *S100a8* genes.

Results: The *Saa3* promoter was strongly upregulated (120 fold) at day one of SCW arthritis, and subsided afterwards, following the course of neutrophil exudation as shown by both histology and fluorescent in vivo imaging (neutrophil elastase activity was 5 times higher at day 1 compared to day 4). The endogenous synovial *Saa3* gene expression showed the same profile. The *S100a8* promoter peaked (20 fold) at day 4 of SCW arthritis, following the course of synovitis (inflammation of the synovium) and cathepsin activity. However, the *S100a8* promoter activity did not follow the endogenous *S100a8* gene expression, which also peaked at day 1 probably due to the infiltration of *S100a8* expressing neutrophils, which are not targeted by the lentivirus.

Conclusion: This study showed that the *Saa3* promoter is a suitable promoter for gene therapy targeting the acute joint inflammatory process, whereas the *S100a8* promoter is a good candidate for gene therapy in immunologically mediated joint inflammation where macrophages play a more dominant role.

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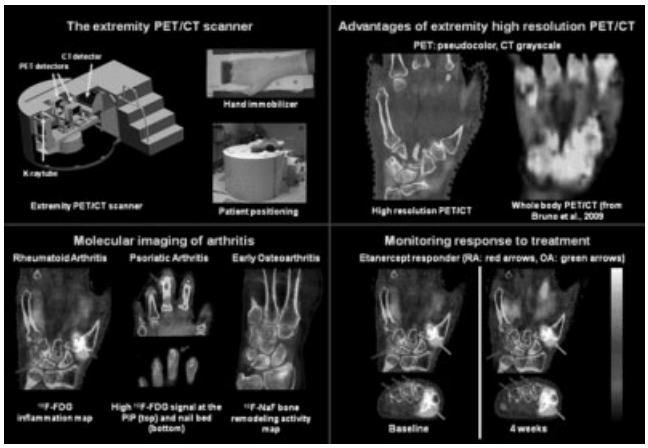
Molecular Imaging of Rheumatoid, Psoriatic and Osteoarthritis in the Hand. Abhijit J. Chaudhari[1], Andrea Ferrero[2], Felipe Godinez[2], Kai Yang[1], John M. Boone[1], Michael H. Buonocore[1], John C. Hunter[1], David K. Shelton[1], Rosalie Hagge[1], Steven W. Falen[3], Ruth D. Tesar[3], Stanley M. Naguwa[1], Nancy E. Lane[1], Siba P. Raychaudhuri[4] and Ramsey D. Badawi[1]. [1]UC Davis School of Medicine, Sacramento, CA, [2]University of California Davis, Davis, CA, [3]Northern California PET Imaging Center, Sacramento, CA, [4]Sacramento VA Medical Center/ UC Davis School of Medicine, Mather, CA

Background/Purpose: An extremity scanner capable of sequentially performing high resolution 3D molecular imaging by positron emission tomography (PET) and 3D anatomical imaging by X-ray computed tomography (CT) has been built by our group. This system is the first of its kind. We report our initial experience in using this system for (1) assessing metabolic activity (hence, inflammation) in Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Osteoarthritis (OA) of the hand, (2) monitoring early response to anti-TNF-alpha therapy in RA, and (3) characterizing bone remodeling (osteoblastic) activity in early OA.

Methods: Eight patients (5 with RA, 2 with PsA, all starting etanercept, and 1 with early OA) were recruited. Three RA patients also had OA. The RA and PsA patients were administered the radiotracer fluorodeoxyglucose (^{18}F-FDG) and were scanned at 80 ± 5 min post-injection. The scan lasted 13 min. All RA patients were scanned at baseline and at 1 month after initiation of etanercept therapy. Changes from baseline in regions of high metabolic activity were documented from PET/CT images. The PsA patients have only been scanned at baseline to date. The patient with early OA was administered the radiotracer sodium fluoride (^{18}F-NaF) and was scanned at 105 min post-injection. Images for all patients were read by consensus by three radiologists.

Results: Detailed 3D quantitative maps of molecular activity and anatomy were produced by the extremity system. Baseline scans in RA patients showed classic symptoms such as inflammation in the carpal synovium, the pisiform-triquetral compartment, at the thumb CMC joint (from OA) and at sites of erosions. In responders to etanercept (3 patients) as determined by a routine 3-month clinical exam, a reduction of >30% in maximum PET signal in the carpal synovium and pisiform-triquetral compartment was observed at 1 month. An increase of >20% at 1 month was observed in clinical non-responders (2 patients). In the PsA patients, enthesitis and inflammatory activity in the nail bed were noted at baseline and can be quantified. In the patient with early OA, high bone remodeling activity was identified at sites of subchondral cysts and the thumb CMC joint, although only very early joint space narrowing was clinically noted.



Conclusion: Our initial studies show that high resolution PET/CT molecular imaging biomarkers can potentially provide novel means for documenting the pathogenesis or RA, PsA and OA in the hand. Extremity PET/CT may prove to be a useful tool for early monitoring of response to anti-TNF-alpha inhibitor or other newer therapies.

ACR Poster Session A
Metabolic and Crystal Arthropathies I: Pathogenesis, Epidemiology, and Diagnosis
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Daily Intake of Skim Milk Powder Enriched with Glycomacropeptide and G600 Milk Fat Extract May Reduce Frequency of Gout Flares; Results From a Randomized, Controlled Trial. Nicola Dalbeth[1], Ruth Ames[1], Gregory Gamble[1], Anne Horne[1], Sumwai Wong[1], Barbara Kuhn-Sherlock[2], Alastair MacGibbon[2], Fiona M. McQueen[1], Ian R. Reid[1] and Kate Palmano[2]. [1]University of Auckland, Auckland, New Zealand, [2]Fonterra Research Centre, Palmerston North, New Zealand

Background/Purpose: Dietary modification is frequently recommended as a strategy for prevention and treatment of gout. Longitudinal observational studies have shown a clear inverse relationship between low fat dairy intake and risk of developing gout. Previous laboratory studies have identified two dairy fractions, glycomacropeptide (GMP) and G600 milk fat extract (G600), with anti-inflammatory effects in models of acute gout. The aim of this proof-of-concept clinical trial was to test the hypothesis that daily intake of skim milk powder (SMP) enriched with GMP and G600 can prevent gout flares.

Methods: This was a three month randomized, double blind controlled trial of milk products for prevention of gout flares. One hundred and twenty patients with recurrent gout flares were randomized to one of three arms; lactose powder control, SMP control, or SMP enriched with GMP and G600 (SMP/GMP/G600). Each intervention was a cream-coloured powder administered daily as a 250ml vanilla flavoured shake. The primary endpoint was change in the frequency of gout flares using a daily flare diary measured monthly for three months.

Results: The frequency of gout flares reduced in all three groups over the three month study period compared with baseline. Over the three month study period there was a significantly greater reduction in gout flares in the SMP/GMP/G600 group (Figure, ANCOVA $p_{group}=0.039$, Tukey post hoc test compared with lactose control $p=0.042$). Following treatment with SMP/GMP/G600 over the three month period, greater improvements were also observed compared with controls in pain and fractional excretion of uric acid, with a trend to greater improvement in tender joint count. Similar adverse event rates and discontinuation rates were observed between the three groups.

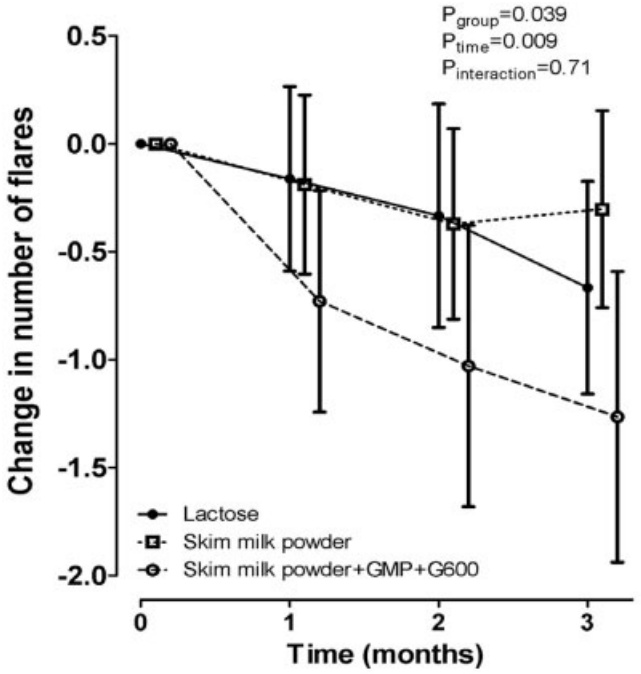

Figure. Primary endpoint: change in number of flares from baseline. ANCOVA analysis includes baseline flare frequency as a covariate. Data are presented as mean (95% CI).

Conclusion: This is the first reported controlled trial of a dietary intervention in patients with gout, and suggests that SMP enriched with GMP and G600 may reduce the frequency of gout flares.

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Validation of the Measurement of Tophi with Magnetic Resonance Imaging As An Outcome Measure for Chronic Gout. Fernando Perez-Ruiz[1], Aranzazu Urresola[2], Diana Gorostiza[3] and Begoña Canteli[4]. [1]Hospital De Cruces, Baracaldo, Spain, [2]Radiology Division. Hospital de Cruces., Baracaldo, Spain, [3]Radiology Division, Hospital de Cruces, Baracaldo, Spain, [4]Radiology Division. Hospital de Cruces, Baracaldo, Spain

Background/Purpose: Magnetic Resonance Imaging (MRI) has not yet fully validated to measure tophi in patients with gout. This study intends to validate MRI for the measurement of tophi in the knee joint fulfilling the OMERACT filter.

Methods: Digital images from 41 RNM procedures of knee joints were stored in a prospective study in 19 patients with tophaceous gout, 28 at baseline (3 bilateral), and 13 during follow-up (1 bilateral) while on urate-lowering therapy in a prospective, open study approved by the Ethics & Investigation Committee. All patients had crystal-proven gout, synovial fluid samples obtained from the knee joints.

After completion of the study, images were retrieved and evaluated twice in a randomized, blinded fashion by two observers, readings being separated by a 3-month period. Lateral-lateral (LL), anterior-posterior (AP) and cranial-caudal (CC) maximal diameters were measured for every tophus from the best imaging sequence. Both baseline and follow-up images were used for intra-reader and inter-reader accuracy. Reduction of tophi was assessed in the LL, AP, and CC diameters, changes being corrected by time exposed to ULT in months, the smallest detectable change (SDC) was estimated as twice the standard deviation of the difference of the averages of the measurements, and effect size with Guyat′s method.

Results: One hundred and four tophi were evaluated, means being 13, 20 and 26 mm for LL, AP, and CC diameters respectively. Concordance for detection of tophi was observed in 101/104 tophi (96.7%). Inter-observer intra-class correlations (ICC) were 0.96, 0.92, and 0.92 for LL, AP, and CC measurements respectively. Intra-reader ICC was 0.98, 0.98, and 0.95 for LL, AP, and CC measurements respectively. SDD were 1.9 mm (14%), 3.3 mm (16%), and 4.0 mm (19%) for LL, AP, and CC maximal diameters respectively. Effect size was 1.52, 0.82, and 0.87 for LL, AP, and CC diameters respectively. Regression models showed that the greater the maximal diameter (LL) at baseline ($R^2 = 0.23$) and the lower the average serum urate while on treatment ($R^2 = 0.31$) were independently associated with greater reductions in measurement (overall model $R^2 = 0.52$).

Conclusion: Measurement of tophi diameters with MRI of the knee joint has shown to be reproducible and sensible to change, especially the LL diameter. MRI deserves further investigation in randomized, controlled clinical trials as an outcome measure for patients with tophaceous gout undergoing urate-lowering therapy.

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Detection of Periarticular Urate Deposits with Dual Energy Computed Tomography in Patients with Acute Gouty Arthritis. Juergen Rech[1], Michael Lell[1], Jochen Wacker[1], Georg Schett[2] and Bernhard Manger[1]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: To evaluate the diagnostic utility of a dual energy CT (DECT) scan in the assessment of periarticular sodium urate depositions in patients with acute arthritis with clinical or laboratory parameters suggestive for a gout attack.

Methods: 14 consecutive patients with signs and symptoms of an acute gout attack were included. DECT using two X-ray tubes with energies of 80 kV and 140 kV of the involved joint regions was performed. The obtained datasets were analysed using a three-dimensional material decomposition algorithm allowing colour coded visualization and differentiation of sodium urate (green) from calcium (purple).

Results: 11 of 14 patients with acute gouty arthritis without any clinical evidence of gout tophi had periarticular or peritendinous sodium urate deposits detectable by DECT. Typical locations of these deposits were ankle joints, metatarsals and at tendon insertion sites (quadriceps, patellar, and Achilles tendons).

Conclusion: A substantial proportion of patients with acute gout attacks have tissue deposits of sodium urate detectable by DECT despite the absence of tophi. This method is helpful for the detection of subclinical tophaceous gout and may be of significant diagnostic value in a setting of undifferentiated mono- or oligoarthritis.

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Effects of Monosodium Urate Crystals on Chondrocyte Viability and Function; Implications for Development of Cartilage Damage in Chronic Gout. Ashika Chhana, Karen E. Callon, Bregina Pool, Dorit Naot, Gregory Gamble, Michael Dray, Fiona M. McQueen, Jillian Cornish and Nicola Dalbeth. University of Auckland, Auckland, New Zealand

Background/Purpose: Chondrocytes are important mediators of cartilage degradation in common arthropathies, including osteoarthritis and rheumatoid arthritis. In gout, focal cartilage damage occurs within the joint at sites of monosodium urate monohydrate (MSU) crystal deposition. We hypothesized that interactions between chondrocytes and MSU crystals contribute to cartilage damage in chronic gout. In this study we investigated the effects of MSU crystals on chondrocyte viability and function.

Methods: MSU crystals were prepared by recrystallisation of uric acid. Cultures of primary human chondrocytes were prepared from macroscopically normal cartilage obtained from patients undergoing knee or hip arthroplasty. These cells were cultured under non-adherent conditions using tissue culture plates coated with poly-(2-hydroxyethyl methacrylate). PicoGreen and alamarBlue assays were used to assess chondrocyte viability following culture with MSU crystals. Quantitative real-time PCR was used to determine changes in gene expression in chondrocytes cultured with MSU crystals. The clinical relevance of our *in vitro* data was further assessed in toluidine blue stained cartilage samples from patients with gout.

Results: MSU crystals reduced chondrocyte viability in a dose-dependent manner (Figure). The reduction of chondrocyte viability was specific to MSU crystals, as soluble uric acid did not alter cell viability. The effects of MSU

crystals on chondrocyte viability were unaltered by the addition of high levels of serum. Culture with MSU crystals reduced mRNA expression of type II collagen and increased mRNA expression of degradative enzymes such as matrix metalloprotease-13 (MMP-13) and A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 and ADAMTS-5. In cartilage samples from patients with gout, cartilage adjacent to tophus was highly disordered with loss of normal architecture and reduced proteoglycan staining.

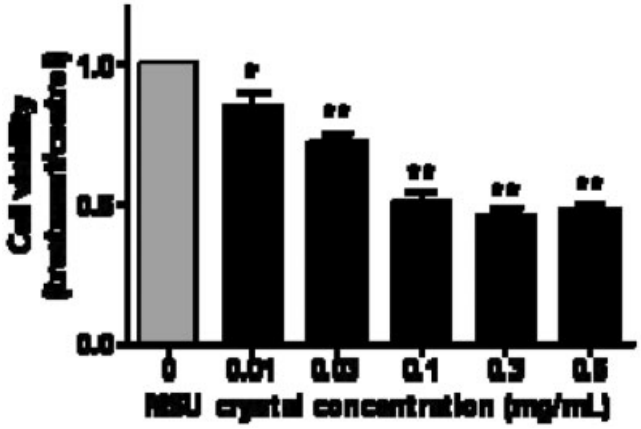

Figure. Effect of MSU crystals on primary human chondrocyte viability. Cell viability was assessed in the alamarBlue assay following 24 hours of culture with MSU crystals. Data shown are mean (SEM); one-way ANOVA ($P<0.0001$) with *post hoc* Dunnett's test *$p<0.05$, **$p<0.001$ versus control (no MSU crystals).

Conclusion: These data indicate that interactions between MSU crystals and chondrocytes may contribute to focal cartilage damage in chronic gout through reduction of chondrocyte viability and promotion of a catabolic state.

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Confirmation of Association of Urate Transporter *SLC17A1* (*NPT1*) with Gout At a Genome-Wide Level of Significance. Tony R. Merriman[1], Amanda Phipps-Green[1], Murray Cadzow[1], Ruth Topless[1], Marilyn E. Merriman[1], Gregory T. Jones[1], Andre M. van Rij[1], Nicola Dalbeth[2], Peter J. Gow[3], Andrew Harrison[4], John Highton[5], Peter B. B. Jones[6], Lisa K. Stamp[7] and Jade E. Hollis-Moffatt[1]. [1]University of Otago, Dunedin, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Middlemore Hospital, Auckland, New Zealand, [4]Hutt Hospital, Lower Hutt, New Zealand, [5]Univ of Otago Med Sch, Dunedin, New Zealand, [6]Waikato Clinical School, Waikato Hospital, Hamilton, New Zealand, [7]University of Otago, Christchurch, Christchurch, New Zealand

Background/Purpose: The major risk factor for gout is hyperuricemia. Two major gout-causing genes have been identified, *SLC2A9* and *ABCG2*, as a consequence of genome-wide association scanning for genetic variants controlling serum urate levels. Genetic variants within *SLC17A1*, which encodes for a renal urate transporter, sodium dependent transporter 1 (NPT1) have also been identified as controlling serum urate levels. Variations within *SLC17A1* have been convincingly associated with serum urate concentrations in Caucasian. Despite this, evidence for association with gout in Caucasian is equivocal, with $P=0.013$ in one study (Yang et al. Cardiovasc Circ Genet 2010;3:523–30) and $P=0.68$ in a second study (Stark K et al. PLoS One. 2009;4:e7729). This may be because of the method of ascertainment of gout, self-report or use of gout drugs (allopurinol, colchicine, probenecid), without exclusion of cases taking diuretics. Here, we aimed to investigate the effect of *SLC17A1* on gout risk in three population groups; Eastern Polynesian (New Zealand Maori and Cook Island), Western Polynesian (Samoa, Tonga, Niue) and Caucasian.

Methods: Genotyping of *rs1183201* was done using TaqMan® SNP genotyping assays, across Caucasian (421 cases, 1228 controls) and Polynesian (combined 551 cases and 518 controls) sample sets. Cases, recruited within New Zealand, were ascertained by American College of Rheumatology criteria, with exclusion of cases taking diuretics. Caucasian genotypes were combined with the publically-available Framingham Heart Study (67 cases, 4712 controls), with cases ascertained by self-report and use of gout medication, and exclusion of cases taking diuretics. Stratification owing to admixture in the Polynesian samples was controlled for using genomic control markers and STRUCTURE/STRAT software.

Results: Association was identified between *rs1183201* and gout in the Caucasian and Eastern Polynesian, but not Western Polynesian, sample sets ($OR = 0.67$, $P = 1.4 \times 10^{-7}$; $OR = 0.65$, $P_{GenomicControl} = 0.02$; and $OR = 0.70$, $P_{GenomicControl} = 0.17$, respectively). Mantel-Haenszel meta-analysis of all sample sets confirmed association of *rs1183201* with gout at a genome-wide level of significance ($OR = 0.67$, $P = 1.4 \times 10^{-11}$).

Conclusion: We have convincingly associated *SLC17A1* with gout in Caucasian, and provide evidence for association in NZ Eastern Polynesian. A *P* by meta-analysis less than the genome-wide cut-off ($P < 5\times10^{-8}$) confirms *SLC17A3* as just the third locus associated with gout, after *SLC2A9* and *ABCG2*.

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Association with Gout of *PDZK1* Variants That Influence Metabolic Traits and Serum Urate Levels. Tony R. Merriman[1], Nicola Dalbeth[2], Jade E. Hollis-Moffatt[1], Amanda Phipps-Green[1], Ruth Topless[1], Marilyn E. Merriman[1], Peter J. Gow[3], Andrew Harrison[4], John Highton[5], Peter B. B. Jones[6], Lisa K. Stamp[7] and Sara Altaf[1]. [1]University of Otago, Dunedin, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Middlemore Hospital, Auckland, New Zealand, [4]Hutt Hospital, Lower Hutt, New Zealand, [5]Univ of Otago Med Sch, Dunedin, New Zealand, [6]Waikato Clinical School, Waikato Hospital, Hamilton, New Zealand, [7]University of Otago, Christchurch, Christchurch, New Zealand

Background/Purpose: Hyperuricemia is an independent risk factor for the development of gout. Gout is associated with obesity, insulin resistance, type 2 diabetes and cardiovascular disease. Genome wide association studies have identified variants in *PDZK1* that regulate serum urate levels (Yang et al. Cardiovasc Circ Genet 2010;3:523–30), and *PDZK1* variants have also been associated with the metabolic syndrome (Junyent M et al. J Nutr 2009;139: 842–8). However, despite influencing serum urate levels at a genome-wide level, there was no evidence for association with gout in 1,100 cases and 27,183 controls (Yang et al. 2010). This may be due to the inclusion of cases taking diuretics. Significantly, the same allele of *PDZK1* variant *rs1967017* that is associated with increased serum urate levels is associated with reduced blood pressure (van der Harst et al. Hum Mol Genet 2010;19:387–92). Our aim was to use a case-control approach to examine the effects of *PDZK1* variants on the risk of gout development in New Zealand (NZ) in sample sets with cases taking diuretics excluded.

Methods: Patients were 328 Caucasians, 280 Eastern Polynesian (NZ Maori and Cook Island), and 249 Western Polynesians (Tonga, Samoa, Niue, Tokelau). Controls were 641 Caucasians, 348 Eastern Polynesians, and 144 Western Polynesians. Cases, recruited within New Zealand, were ascertained by American College of Rheumatology classification criteria, with exclusion of cases taking diuretic medication. Caucasian genotypes were combined with the publically-available Framingham Heart Study (FHS; 67 cases, 4712 controls) and Atherosclerosis Risk in Communities Study (ARIC; 153 cases, 6969 controls), with exclusion of cases taking diuretics with gout ascertained by self-report and use of gout medication for FHS and self-report for ARIC. Three *PDZK1* variants (*rs11576685, rs1284300, rs1967017*) were genotyped using Taqman. The variants were tested for association using the Mantel-Haenszel method of meta-analysis.

Results: All variants were significantly associated with gout: *rs11576685*, OR = 0.53 [0.34–0.82], $P = 0.004$; *rs1284300*, OR = 0.74 [0.59–0.93]. $P = 0.009$; *rs1967017*, OR = 1.23 [1.09–1.40], $P = 0.001$. There was no evidence for heterogeneity – all Breslow-Day *P* values were greater than 0.09.

Conclusion: The direction of association with gout of *rs1967017* is consistent with that previously reported for control of serum urate levels. None of the variants exhibit any intermarker linkage disequilibrium, implying the existence of multiple gout risk variants within the PDZK1 locus. These results suggest that *PDZK1* not only influences metabolic traits and serum urate levels, but also gout.

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Gouty Enthesopathy: An Important Pattern of Uric Acid Deposition in Difficult to Diagnose Gout. Hailong Wang[1], Katrina N. Glazebrook[2], Steven J. Kavros[2], Clement J. Michet[1], Stephen P. Merry[3], Naveen S. Murthy[1], Bharath Manu Akkara Veetil[1], John M. Davis III[1], Thomas G. Mason II[4], Kenneth J. Warrington[1], Nisha J. Manek[1], Tanaz A. Kermani[1], Deana D. Hoganson[1], A. Kirstin Bacani[1], Cynthia H. McCollough[2] and Tim Bongartz[1]. [1]Mayo Clinic, Rochester, MN, [2]Rochester, MN, [3]Mayo Clinic, Rochester, [4]Mayo Clinic Rochester, Rochester, MN

Background/Purpose: One of the major obstacles to effective and timely management of gout is a high error rate in diagnosis, resulting in misdirected investigations and inappropriate treatment. As part of a study which evaluated the diagnostic yield of dual energy computed tomography (DECT) scanning for diagnosing gout, we have establish a cohort of patients with suspected gout based on clinical presentation but negative polarizing microscopy results. In a high number of these patients, we found imaging evidence of monosodium urate (MSU) deposition, supporting a diagnosis of gout. We set out to characterize the locations of MSU deposition in these difficult to diagnose patients in order to understand why initial routine testing (polarizing microscopy of synovial fluid) did not reveal intraarticular MSU crystals.

Methods: We prospectively included patients who had clinically suspected gout but from whom an appropriate specimen for analysis either could not be obtained, or polarizing microscopy was negative for the presence of MSU crystals. All patients underwent dual source, dual energy (80 and 140 kVP) CT scanning of the aspirated joint. Images were classified as positive or negative for MSU deposits and sites of MSU deposition were characterized.

Results: 42 patients in whom gout was considered as a possible diagnosis were included in our cohort. In these individuals, DECT scanning revealed evidence of uric acid deposition in 19 cases (45.2%).Entheses were a common location for uric acid deposition in patients with a previously negative aspiration: overall, 11 (57.9%) of the 19 patients with DECT evidence for gout did have tophaceous deposits seated in the Achilles tendon, plantar fascia, patellar tendon or triceps tendon insertion site. In the majority of patients with gouty enthesopathy, entheseal involvement was either isolated or occurred in combination with pertendinous involvement. Only 3 out of 11 patients with enthesopathy demonstrated additional deposits involving the joint space or capsule.

Conclusion: Gouty enthesopathy is a common pathology in patients whose clinical presentation is suspicious for gouty arthritis but synovial fluid analysis fails to demonstrate MSU crystals. The predominance of entheseal/tendinous MSU deposits and the frequent lack of associated MSU deposition in the actual joint space/capsule may explain the negative aspiration results in these patients. Our findings suggest that gouty enthesitis should be included in the list of differential diagnoses when evaluating patients with clinical inflammatory arthritis/periarthritis who do have risk factors for gout. In these patients, the diagnosis of gout should not be dismissed even if the synovial fluid aspiration is negative for MSU crystals. DECT appears to be a valuable diagnostic test in this subgroup of patients to confirm the presence of MSU deposition in periarticular structures.

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Serum Uric Acid Concentration and Physical Activity: the National Health and Nutrition Examination Survey 2003–2004. Tony Ning[1], Carl Pieper[2], Virginia Byers Kraus[1], William E. Kraus[2] and Kim M. Huffman[1]. [1]Division of Rheumatology, Department of Medicine, Duke University Medical Center, Durham, NC, [2]Duke Pepper Center, Durham, NC

Background/Purpose: Physical activity improves cardiovascular risk and associates with reduced mortality, but the impact of physical activity on hyperuricemia or chronic gout is unclear. Since uric acid and insulin compete for renal excretion and exercise improves insulin resistance, physical activity has the potential to modify hyperuricemia. We hypothesized that amounts of physical activity would be inversely related to uric acid concentrations. Specific Aims: Our aim was to determine the relation between uric acid and objectively-measured physical activity.

Methods: As part of the 2003–4 Continuous National Health and Nutrition Examination Survey (NHANES), serum uric acid concentrations were measured via a colorimetric enzymatic assay, and seven days of physical activity were assessed using Actigraph accelerometers (n=3840; ages 20–85 years). Accelerometer counts, reflecting activity intensity over a one minute epoch, were used to determine bouts of exercise or total accumulated amounts of (metabolic equivalents [met]) physical activity. After accounting for sample weights, Pearson correlations were used to relate uric acid and physical activity with and without adjustments for age, gender, BMI, and creatinine.

Results: Uric acid was not related to moderate ($r=-0.0074$; $p=0.64$) or vigorous-intensity ($r=-0.019$; $p=0.24$) exercise bouts. However, while there was a direct relationship at high intensity [high met/hrs, $r=.160$ ($p<.0001$)], uric acid was inversely related to total physical activity at low and moderate intensities [low met/hrs, $r=-0.17$ ($p<.0001$); moderate met/hrs, $r=-0.056$ ($p=<0.0001$)]. When accounting for age, gender, BMI, and creatinine, these relations were not significant. Male gender ($r=-0.25$, $p<.0001$) a lower BMI ($r=-0.18$, $p<.0001$), as well as being younger in age ($r=-0.33$, $p<.0001$) were predictors of increased time in higher physical activity.

Conclusion: In a nationally representative sample of US adults, uric acid was directly related to total low and moderate intensity physical activity but not bouts of exercise. Disappearance of these relations after adjusting for age, gender, BMI and creatinine suggests that these covariates mediate physical activity and uric acid relationships. These relations might be useful in determining how physical activity can improve gout.

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Serum Procalcitonin Could Be a Useful Serologic Marker for the Differential Diagnosis Between Acute Gouty Attack and Bacterial Infection. Sang Tae Choi and Jung-Soo Song, Chung-Ang. University College of Medicine, Seoul, South Korea

Background/Purpose: Acute gouty attack is an inflammatory condition secondary to a high concentration of uric acid in the blood. It is usually characterized by redness, tenderness, swelling and systemic or localized fever. These features and laboratory findings, including leukocytosis, elevation of serum erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, are similar to those of infectious diseases. Moreover, there were many cases in which serum uric acid levels were not elevated in the acute gouty attack state, which made the differential diagnosis of acute gouty attack difficult. Procalcitonin is the precursor of calcitonin and increases in bacterial or fungal infection. We investigated whether or not procalcitonin levels are elevated in patients with acute gouty attack and the availability of those in differential diagnosis between acute gouty attack and bacterial infection.

Methods: This cross-sectional study included 41 patients with acute gouty attack and 75 age-matched patients with bacterial infection. The serum samples were obtained from patients during the clinically active inflammatory state. The mean duration from the development of acute gouty attack to blood sampling was 2.9 ± 2.3 days. Their serum levels of procalcitonin were measured by enzyme-linked fluorescent assay (ELFA; BioMerieux SA, France). Clinical and laboratory data were collected at the time serum samples were obtained.

Results: Patients with acute gouty attack had significantly lower serum procalcitonin levels than the patients with bacterial infection (0.078 ± 0.066 ng/mL vs 5.401 ± 14.982 ng/mL, $p = 0.003$). However, there were no significant differences between these two groups in serum ESR, CRP levels, white blood cell counts and segmented neutrophil counts. The ranges of serum procalcitonin levels were from 0.05 to 0.33 ng/mL in the acute gouty attack group and from 0.05 to 102.00 ng/mL in the bacterial infection group, respectively. There was a larger number of patients in the acute gouty attack group who had serum procalcitonin levels greater than the reference range than in the bacterial infection group (11/41, 26.8 % vs 63/76, 82.9 %, $p < 0.001$). Serum uric acid levels were statistically elevated in patients with acute gouty attack than those without it (7.50 ± 1.89 mg/dL vs 5.02 ± 1.89 mg/dL, $p < 0.001$); however, the rate of patients whose serum uric acid levels were below 6.0 mg/dL was 22.0% (9/41) among the acute gouty attack group.

Conclusion: Serum procalcitonin levels were lower in the acute gouty attack group than in the bacterial infection group. The serum procalcitonin level could be a useful serologic marker for the differential diagnosis between acute gouty attack and bacterial infection.

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Gout Patient Burden Associated with Flares, Tophi, and Awareness of Uric Acid Levels In US and EU. Puja Khanna[1], Anne-Kathrin Tausche[2], Anna Forsythe[3], Amir Goren[4] and Dinesh Khanna[1]. [1]University of Michigan, Ann Arbor, MI, [2]Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany, [3]Savient Pharmaceuticals, Inc., East Brunswick, NJ, [4]KantarHealth, New York, NY

Background/Purpose: The prevalence of gout is increasing both in men and post-menopausal women. Although serum urate (SUA) levels have been associated with disease burden among gout patients, little research has examined the impact of tophi and the number of acute gout attacks on health-related quality of life (HRQOL), productivity, and healthcare resource utilization.

Methods: Patients with self-reported gout (n = 620) in 2010 US and EU National Health and Wellness Surveys (cross-sectional databases representative of French, German, Italian, Spanish, UK, and US populations) and the Lightspeed Research Ailment panel: n = 338 (US) and 282 (EU) were contacted. Respondents were categorized into mutually-exclusive groups based on number of gout flares in the past 12 months (0, 1–2, 3, 4–5, 6+), current presence of gouty tophus/tophi (yes, no), and SUA level awareness (yes, no). Differences on HRQOL (SF-12v2), resource use (healthcare

provider visits in last 6 months), and work and activity impairment were examined using Chi-square tests and ANOVAs for categorical and continuous variables, respectively.

Results: Majority of patients, 81.3% (n=504) were male, with mean age of 60.9 years; 31.1% were untreated with urate lowering therapy. Of 51.5% (n=319) who were on allopurinol therapy, only 9.1% (n=29) used allopurinol dose > 300mg, and 1.9% (n=6) used febuxostat. 75.6% (n=469) reported experiencing an acute gout flare in the past 12 months, and 12.3% (n=76) reported tophi. Among the 27.7% (n=172) of patients who were aware of their SUA levels (<6mg/dL −10.0%, 6 – 8mg/dL −12.1%, or >8mg/dL −5.6%), these levels correlated with number of flares experienced in the past 12 months (r_s = 0.361) and number of tophi currently present (r_s =0.282), all $p < 0.001$. Patients reported greater HRQOL burden with number of flares (see Table), and patients with tophi vs. without reported lower SF-12v2 mental (MCS) (44.4 vs. 48.6) and physical (PCS) component summary scores (36.9 vs. 41.1), plus lower SF-6D utilities (0.64 vs. 0.71). They experienced greater overall work productivity loss (40.2% vs. 21.2%), activity impairment (48.7% vs. 37.2%), and more provider visits (9.0 vs. 6.5), all $p < 0.05$. Patients aware of SUA levels had higher PCS (42.3 vs. 39.9), $p < 0.05$. In multivariable models, we predicted outcomes after adjusting for the tophi presence, number of flares, age, gender, time since diagnosis, and smoking, presence of flares (4+) were associated with MCS, PCS, and SF-6D decrements, plus activity impairment (all $p < 0.05$).

Table.

	Number of self-reported flares in past 12 months										
	0/Unknown (n=85)		1 to 2 (n=128)		3 (n=44)		4 to 5 (n=50)		6+ (n=31)		
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	*p-value*
HRQOL											
SF-12 MCS	**49.91**	*9.67*	**49.23**	*10.30*	**47.85**	*10.03*	**44.66**	*13.03*	**44.46**	*13.43*	<0.0001
SF-12 PCS	**43.25**	*11.61*	**42.72**	*12.27*	**38.16**	*11.85*	**37.04**	*11.40*	**33.49**	*9.99*	<0.0001
SF-6D Utility	**0.73**	*0.12*	**0.72**	*0.14*	**0.67**	*0.15*	**0.64**	*0.17*	**0.61**	*0.13*	<0.0001
Work Productivity											
% Work missed (n=234)	**6.76**	*23.15*	**5.16**	*16.23*	**4.66**	*17.42*	**1.85**	*5.11*	**8.71**	*14.99*	0.661
% Impairment at work (n=229)	**14.12**	*18.35*	**21.22**	*26.72*	**21.62**	*27.84*	**19.26**	*26.01*	**33.33**	*30.60*	0.056
% Overall work impairment (n=234)	**19.80**	*26.90*	**23.23**	*29.80*	**24.29**	*30.42*	**19.93**	*26.70*	**36.58**	*33.32*	0.197
% Activity impairment	**28.68**	*28.42*	**36.77**	*33.39*	**43.41**	*34.42*	**45.58**	*34.39*	**54.21**	*30.29*	<0.0001
Resource Use											
Number of ER visits	**0.17**	*0.45*	**0.31**	*2.32*	**0.40**	*1.05*	**0.38**	*0.75*	**0.33**	*0.81*	0.779
Number of days hospitalized	**0.44**	*1.73*	**0.65**	*4.45*	**0.82**	*3.82*	**0.38**	*1.61*	**0.68**	*2.81*	0.885
Number of traditional HCP visits	**6.91**	*8.45*	**5.68**	*6.01*	**8.29**	*10.09*	**8.02**	*8.76*	**7.40**	*6.79*	0.032

Note. Total n = 620, except where otherwise noted.

Conclusion: In patients with gout the SUA levels correlate with number of flares experienced in the past 12 months and the presence of tophi. The increase number of acute gout flares and tophi are associated with significant decrements in HRQOL, work productivity, and increased healthcare resource utilization.

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Risk Factors for Incident Psuedogout in the General Population. Young Hee Rho, Yanyan Zhu, Yuqing Zhang and Hyon K. Choi, Boston. University School of Medicine, Boston, MA

Background/Purpose: Pseudogout, a common inflammatory arthritis of the elderly, belongs to a group of related diseases called calcium pyrophosphate deposition diseases (CPPDs), which also includes chondrocalcinosis (CC). While studies have identified the risk factors for CPPD such as osteoarthritis (OA), rheumatoid arthritis (RA), hyperparathyroidism, or use of diuretics (1), no analogous data are available for pseudogout. Although CC and pseudogout are related conditions, not all CC subjects develop pseudogout, so their risk factors may not be identical. We sought to evaluate the association between the known risk factors for CPPD and the risk of incident pseudogout in the general population.

Methods: We conducted a matched case-control study using data from The Health Improvement Network (a UK general population database of 7.3 million individuals), collected between January 1986 and May 2010. An incident case was defined as a first diagnosis of pseudogout by a general practitioner, following at least one year of enrollment in the database. Up to 5 controls were matched on age, sex, follow-up time, and practice site to each case. Purported risk factors, such as OA, RA, gout, hyperparathyroidism, hypertension, diabetes, myocardial infarction, stroke, body mass index (BMI), and diuretics (loop and thiazide) were determined before the index date of pseudogout. We performed conditional logistic regression to determine the independent associations of these factors with the risk of incident pseudogout.

Results: We identified 1527 cases of pseudogout. Among these, 981 cases (mean age: 70 years, 52% male) were matched with 4407 controls (n=5388). Four percent of the cases had pre-existing CC and 20% of the cases had a history of gout. In the final multivariate model, the risk of incident pseudogout was associated with pre-existing CC (OR 19.56, 95%CI 8.47–45.15), hyperparathyroidism (OR 6.91, 95%CI 2.71–17.63), gout (OR 4.39, 95%CI 3.49–5.53), OA (OR 2.60, 95%CI 2.19–3.10), being underweight (vs. normal weight, OR 1.81, 95% CI 1.04–3.15), RA (OR 1.65, 95% CI 1.01–2.69), and loop diuretics (OR 1.36, 95%CI 1.10–1.67) (**Table**). These associations persisted even after patients with gout were excluded to reduce the potential clinical misclassification between gout and pseudogout.

Table. Independent Risk Factors of Incident Pseudogout (n = 5388)

Purported Risk Factors	OR	95% CI	P
BMI: Underweight (<18.5 kg/m^2, 1.7%)	1.81	(1.04–3.15)	0.04
Normal Weight (18.5–24.9 kg/m^2, 25.5%)	1.00	Referent	–
Overweight (25–30 kg/m^2, 30.1%)	0.99	(0.80–1.21)	0.90
Obese (≥30 kg/m^2, 17.1%)	0.92	(0.72–1.18)	0.52
Missing (25.5%)	0.75	(0.59–0.95)	0.02
Hypertension (37.2%)	1.14	(0.93–1.39)	0.22
Diabetes (9.1%)	1.06	(0.82–1.38)	0.66
Myocardial Infarction (6.1%)	1.20	(0.89–1.61)	0.23
Stroke (4.8%)	0.97	(0.69–1.37)	0.87
Hyperparathyroidism (0.46%)	6.91	(2.71–17.63)	<.001
Rheumatoid Arthritis (1.91%)	1.65	(1.01–2.69)	0.04
Osteoarthritis (27.7%)	2.60	(2.19–3.10)	<.001
Gout (7.85%)	4.39	(3.49–5.53)	<.001
Chondrocalcinosis (0.85%)	19.56	(8.47–45.15)	<.001
Thiazides (28.9%)	0.94	(0.75–1.16)	0.55
Loop Diuretics (17.2%)	1.36	(1.10–1.67)	0.004

Conclusion: This general population study provides the first epidemiologic evidence that the risk factors for pseudogout are similar to those for chondrocalcinosis. These findings provide strong support for a common pathophysiology between the two conditions.

1. Zhang W et al. Ann Rheum Dis. 2011 Apr;70(4):563–70.

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Is Calcium Pyrophosphate Deposition Associated with Vitamin D Deficiency? Sophia Li[1], Joshua Baker[1], Janet E. Dinnella[1], Gilda M. Clayburne[2], Joseph R. Perno[2], H. Ralph Schumacher[2] and Sally W. Pullman-Mooar[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]VA Medical Center, Philadelphia, PA

Background/Purpose: Calcium pyrophosphate deposition (CPPD) is the second most common form of crystal-associated arthropathy. Calcium pyrophosphate (CPP) crystals are biologically active particles that can contribute to joint damage and accelerate osteoarthritis. Excess accumulation of extracellular inorganic pyrophosphate (ePPi) can bind calcium and lead to CPP crystal deposition in cartilage and synovium. 25(OH) vitamin D is important for calcium homeostasis although the role of vitamin D in CPPD disease is unknown. This study examined levels of 25(OH) vitamin D in subjects with and without crystal-proven CPPD.

Methods: We performed a cross-sectional study of all patients who had a vitamin D level drawn within the past 6 months at our VA Medical Center and had an arthrocentesis performed with synovial fluid available for microscopic analysis. Synovial fluid was analyzed for presence of calcium pyrophosphate, monosodium urate (MSU), and any other crystals with the technician blinded to diagnosis or vitamin D status. Patient demographics were extracted from the electronic medical record. Non-parametric tests of significance were performed on skewed data. Simple multivariable linear and logistic regression models were performed to adjust for age, race, and renal function.

Results: We identified 11 patients who demonstrated CPP crystals in synovial fluid and 15 patients who had non-CPP containing synovial fluids. 5 of 11 patients (45.5%) with CPP crystals had vitamin D levels <20 ng/mL compared with 2 of 15 patients (13.3%) without CPP crystals. The median (intra-quartile range) vitamin D level in patients with CPPD was 16.1 (9.4, 23.6) ng/mL compared to 26.6 (19.7, 35.7) ng/mL in all other patients (p=0.02). In a multivariable model with a log-transformed

vitamin D variable as the outcome, CPPD was associated with lower vitamin D levels after adjustment for age, race, and creatinine [β: −0.23 (−0.44, −0.022) p=0.03]. Similarly, in multivariable logistic regression, higher vitamin D level (per 1 ng/mL) was independently associated with a lower probability of CPPD [OR 0.90 (0.82–1.00) p=0.04].

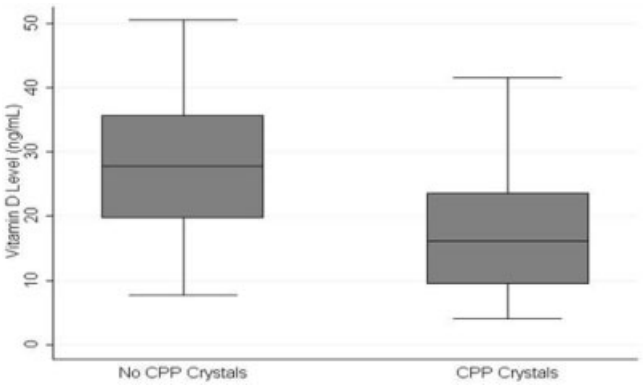

Figure 1.

Conclusion: Our study suggests that vitamin D deficiency may be another metabolic abnormality associated with CPPD. Strengths of this study include the crystal proven diagnosis and blinded assessment of synovial fluid. Limitations of this study include the small numbers which limits controlling for all potential confounders. Further study is warranted to better understand the implications of vitamin D deficiency in CPPD.

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Illness Perceptions Predict Disability After One Year In Patients with Gout. Nicola Dalbeth[1], Keith J. Petrie[1], Meaghan House[1], Jimmy Chong[1], Wingchi Leung[1], Rini Chegudi[1], Anne Horne[1], Gregory Gamble[1], Fiona M. McQueen[1] and William J. Taylor[2]. [1]University of Auckland, Auckland, New Zealand, [2]University of Otago, Wellington, Wellington, New Zealand

Background/Purpose: Illness perceptions are key determinants of behavior directed at managing disease. Although low adherence and suboptimal disease management has been reported in patients with gout, patients' perceptions of illness have not been systematically studied. The aims of this study were to determine the illness perceptions in patients with gout, to understand how patients' perceptions are related to medication beliefs and adherence to urate-lowering therapy, and to examine the influence of illness perception on disease outcomes over time.

Methods: 142 patients with gout for <10 years were recruited from primary and secondary care settings. Participants completed a gout-specific Brief Illness Perception Questionnaire, questionnaires about medication beliefs and adherence to urate lowering therapy (ULT), and had a comprehensive assessment of gout disease activity. Serum urate, flare frequency and Health Assessment Questionnaire (HAQ-II) were recorded at baseline and after one year.

Results: Patients viewed gout as a chronic condition that was responsive to treatment but not strongly influenced by personal actions. Overall, gout was seen as having a moderate impact on their life. Most patients believed that gout was caused by dietary factors. Adherence to ULT was positively associated with a greater perceived understanding of gout, and inversely associated with perceived severity and consequences of disease. Of the clinical factors assessed, pain scores were most strongly associated with negative illness perception scores at baseline. Baseline illness perception scores (perceived severity of symptoms and consequences, lower personal and treatment control) predicted worsening musculoskeletal disability at one year, as determined by the HAQ-II (Table). This relationship was independent of baseline disability scores.

Table. Stepwise linear regression analysis of baseline factors independently associated with change in the HAQ-II score after one year. Variables included in models: age, sex, ethnicity, baseline HAQ-II score, adherence score, B-IPQ item score

Model number	Dependent variable	Predictors	Standardized β	Partial R^2	p	Model
1	Change in HAQ-II score	Baseline HAQ-II score	−0.60	0.20	<0.0001	Adjusted R^2=0.29; F=10.8; p<0.0001
		Age	0.30	0.05	0.007	
		B-IPQ consequences score	0.29	0.08	0.008	
2	Change in HAQ-II score	Baseline HAQ-II score	−0.53	0.20	<0.0001	Adjusted R^2=0.27; F=9.6; p<0.0001
		Age	0.25	0.05	0.02	
		B-IPQ personal control score	−0.23	0.05	0.03	
3	Change in HAQ-II score	Baseline HAQ-II score	−0.47	0.19	<0.0001	Adjusted R^2=0.22; F=10.9; p<0.0001
		B-IPQ treatment control score	−0.24	0.05	0.03	
	Change in HAQ-II score	Baseline HAQ-II score	−0.53	0.20	<0.0001	Adjusted R^2=0.26; F=9.5; p<0.0001
		Age	0.23	0.05	0.03	
		B-IPQ identity score	0.22	0.05	0.04	

Conclusion: Negative illness perceptions are associated with poorly controlled disease, lower adherence to ULT, and progression of musculoskeletal disability in patients with gout. These findings raise the possibility that an individualized intervention programme designed to change behaviour by altering illness perceptions may improve outcome in patients with gout.

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Association of Insuline Resistance with Renal Clearance of Uric Acid In Phenotipically Selected Males with Gout. Fernando Perez-Ruiz. Hospital De Cruces, Baracaldo, Spain

Background/Purpose: Glut9 (SLC2A9) is a renal tubular voltage-driven sugar transporter of uric acid. Genetic studies have associated Glut9 to hyperuricemia and gout. Insulin resistance has also been associated to hyperuricemia and gout due to a reduction of renal clearance of uric acid. A direct link between renal clearance of uric acid and insulin resistance is an attractive physiopathologic hypothesis.

Methods: Consecutive male patients with crystal-proven gout were evaluated at baseline visit in a Gout Clinic. To be included, they should not be on any drug therapy, including urate-lowering therapies but low-dose colchicine for gout prophylaxis, show normal renal function (CKD 1 with no significant proteins or altered urine sediment), fasting glucose < 120 mg/dl, normal diet and alcohol avoidance. HOMA-IR was calculated with fasting serum glucose and insulin determinations. Clearance of uric acid and creatinine were calculated using 24-hour urine collections, inefficient excretion of uric acid being defined as clearance of uric acid < 6 ml/min/1.73 sqm. Hypertension, previous ethanol intake, body mass index, time from onset, age, vascular events, renal lithiasis, total cholesterol, HLD-cholesterol, LDL-cholesterol, triglycerides, glycosilated hemoglobin, number of flares, and presence of tophi were also recorded in the database. Data for numeric variables are expressed as median and inter-quartile range.

Results: Ninety-five male patients were included for analysis. Age was 53 (45–59), time from onset 5.5 (3–11) years, number of flares/year 3 (2–4), 39% polyarticular, and 38% tophaceous. Previous ethanol intake > 15 g/day, hypertension, glycosilated hemoglobin, clearance of creatinine, and HOMA-IR were associated to clearance of uric acid in bivariate regression analysis. Multivariate regression analysis showed that HOMA-IR (p<0.001) and hypertension (p=0.03) were the only variables predictive of the model. ROC curve showed that HOMA-IR cut-off >2.7 showed 81% sensitivity ad 81% specificity for classifying patients with efficient or inefficient renal excretion of uric acid.

Conclusion: Insulin resistance, but also hypertension, was associated with lower clearance of uric acid in a series of phenotype-selected male gout patients, showing a plausible link between glucose metabolism and sugar transporters of uric acid that deserves further investigation.

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Impact of Acute Gout Flares on Health Related Quality of Life (HRQOL) and Productivity in Patients with Chronic Gout. Puja Khanna[1], Cleopatra A. Beaton[2], Jay E. Persselin[3], Ronald D. Hays[4], Daniel E. Furst[5], Harold E. Paulus[6], Robert Terkeltaub[7], Paul Maranian[4] and Dinesh Khanna[1]. [1]University of Michigan, Ann Arbor, MI, [2]West LA VA Medical Ctr, Los Angeles, CA, [3]VA Greater LA Healthcare Sys, Los Angeles, CA, [4]University of California, Los Angeles, [5]UCLA, Los Angeles, CA, [6]University of California, Los Angeles, Los Angeles, CA, [7]VA Medical Ctr, San Diego, CA

Background/Purpose: Acute painful episodes of arthritis are a common feature of chronic gout. We evaluated the impact of acute flares on HRQOL and productivity in patients with chronic gout in an ongoing, prospective, 1-year observational study.

Methods: Patients with chronic gout were recruited at a VA and

University Hospital. Physical exam was performed by rheumatologists and HRQOL was assessed using the SF-36 v2, HAQ-DI and the GAQ 2.0 gout-impact scale (GIS).[1] Home and work productivity was captured using the Work Productivity Survey[2]. Health care utilization was measured by UCSD Healthcare Utilization Questionnaire (HCU). Differences on these measures by acuity of the flare (≤ 4 weeks vs. >4 weeks) was examined using an alpha of 0.05 level of statistically significance.

Results: The mean age of the participants was 66 years, 92% were males, disease duration was 15 years, and mean SUA was 7.7 mg/dl. Patients who experienced a flare within 4 weeks of study visit (n=56) rated their gout as more severe on a 0–10 scale ($p< 0.01$), reported significantly more bodily pain ($p<0.007$), and greater concern on 2 of 5 GIS scales ($p<0.0001$; Table). Other domains of the SF-36 and summary scores were not statistically significant. Patients with recent flares also reported absenteeism from work for 2.6 days per month, 50% reduction in productivity for 3.5 days a month, 4.3 days per month when gout interfered with work, and a loss of 3.7 days from family and social activities due to the acute flares ($p< 0.05$ for all comparisons in patients without recent flares). Primary care visits for gout were significantly higher in those with recent flares ($p<0.03$).

Patient Characteristics	≤4 weeks n=56	> 4 weeks n=58
Age (years), mean (SD)	65.0 (11.5)	67.7 (10.0)
Duration of gout (years), mean (SD)	13.3 (12.2)	16.0 (13.2)
Severity of Gout scale (0–10 cm), mean (SD)	6.9 (2.8)	5.1 (3.4)*
Patients with X-ray evidence of erosions/ tophi n (%)	23 (41%)	15 (26%)
No. of patients with tophi on exam (%)	20 (36%)	18 (32%)
Serum Urate mg/dl, mean (SD)	7.3 (2.2)	7.7 (1.6)
# of Comorbidities (0–22), mean (SD)	4.0 (3.4)	3.7 (4.1)
Patient reported outcome measures		
SF-36 Bodily Pain (0–100), mean (SD)	39.0 (11.5)	45.1 (12.7)*
HAQ-DI (0–3), Mean (SD)	0.8 (0.6)	0.8 (0.7)
GAQ-GIS: (0–100), mean (SD)		
-Gout Concern Overall	74.3 (23.5)	59.0 (27.7)*
-Unmet Gout Treatment Needs	51.6 (19.1)	36.1 (17.8)*
-Gout Medication Side Effects	58.5 (26.2)	54.7 (27.7)
-Well Being During Attack	57.7 (27.2)	53.0 (27.3)
-Gout Concern During Attack	53.9 (26.6)	50.7 (26.5)
Work Productivity: in Days (#) **mean (SD)**		
-Work missed due to gout	2.6 (5.3)	2.5 (7.5)*
-Productivity was reduced by 50% in last month	3.5 (6.6)	2.1 (6.4)*
-Gout interfered with work in last month	4.3 (3.6)	1.5 (2.8)*
-Missed activities with family/social due to gout	3.7 (7.2)	1.3 (4.6)*
- Days requiring outside help	1.1 (4.6)	0.7 (4.1)
HCU: No. of Primary Care Doctor Visits, mean (SD)	2.4 (2.4)	1.5 (1.9)*

* $p<0.05$; Higher scores on the HAQ-DI and GIS denote worse HRQOL.

Conclusion: Acute flares have a significant detrimental impact on HRQOL and productivity in patients with chronic gout. The impact of acute flares on HRQOL may be underestimated and difficult to study in an accurate fashion due to the episodic nature of flares. Our data documents that health status, work productivity and HCU measures are feasible in patients with recent acute flares of gout.

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Subjects with Gout Have a Higher Prevalence of Simple Renal Cysts Than the General Population. Eduardo M. Hasegawa[1], Ricardo Fuller[1], Maria Cristina Chammas[2], Filipe M. Mello[1] and Claudia Goldenstein-Schainberg[1]. [1]Rheumatology Division—University of São Paulo, São Paulo, Brazil, [2]Radiology Division—University of São Paulo, São Paulo, Brazil

Background/Purpose: Gout is a metabolic disease in which a variety of renal disorders may occur. The prevalence of simple renal cysts in gout patients has never been in the scope of any research previously performed. The aim of this study was to determine the prevalence of simple renal cysts in gout patients and evaluate associated risk factors for its development.

Methods: One hundred forty six (146) patients followed at our outpatient Gout Unit and 47 sex and age-matched healthy kidney donors underwent routine renal ultrasonography, using a static grey-scale and real-time B-mode units with a 3.5 or 5.0MHz transducer, to determine the presence of renal cysts. Demographic and clinical characteristics of gout patients were evaluated considering possible risk factors for the occurrence of simple renal cysts.

Results: The prevalence of simple renal cyst was 26.0% in gout patients and 10.6% in control group ($P=0.045$). Gout patients with simple renal cysts presented less renal lithiasis than those without this complication (5.2% vs 25.9%; $P=0.003$) in spite of an overall higher frequency of renal stones in gout patients compared to control group (20.5% vs. 6.3%, $P=0.025$). The presence of simple renal cyst in gout was not associated with previously reported factors such as age ($P=0.296$), male predominance ($P=0.688$), hypertension ($P=0.314$), and renal impairment ($P=0.254$). Moreover, no association with disease duration ($P=0.843$) or tophi ($P=0.616$) was observed.

Conclusion: Gout patients have an increased prevalence of simple renal cysts, and this finding was shown to be associated with a lower occurrence of nephrolithiasis. Whether renal cysts have any protective effect in the development of nephrolithiasis in gout remains to be determined.

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Gout Vs Hyperuricemia As Risk Factors for Coronary Artery Disease – A Pilot Study. Victoria Furer, Rennie N. G. Howard, Jonathan Samuels and Michael H. Pillinger. NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Multiple studies implicate either gout or hyperuricemia is associated with increased coronary artery disease (CAD) risk. However, such studies are often limited by retrospective database methodologies, and often do not distinguish the extent to which CAD risk is associated primarily with gout, hyperuricemia, or both. We conducted a prospectively-enrolled cohort pilot study to assess the relative contributions of asymptomatic hyperuricemia (AH) and gout to CAD.

Methods: Male veterans (N=116) ages 55–85 were recruited during routine visits to the primary care clinic at the NY Harbor VA Health Care System NY Campus. All subjects underwent serum uric acid (UA) determination, gout screening (ACR clinical criteria) and CAD self-assessment. Patients with non-gout inflammatory arthritis/other systemic inflammatory disease were excluded. Enrollees were divided into 3 groups: 55 controls (no gout, UA≤ 6.8 mg/dl), 30 AH (no gout, UA>6.8mg/dl), and 31 gout. Chart review was performed (ICD-9 code identification and review of the primary care and/or cardiology note) to confirm gout, CAD and comorbidities. The primary outcomes were CAD by chart ascertainment and patient self-report. For sub-analysis, patients with AH and gout were further subdivided into equal cohorts with the lowest and highest UA levels. Summary statistics were calculated by disease group. Differences between groups were estimated by Kruskal-Wallis test for continuous measures, Chi-square test or Fisher test for prevalence and categorical measures using SPSS.

Results: The 3 groups were similar in age (controls 68.9±8.3, AH 67.7± 9.1, gout 71.3±8.6 years) and racial/ethnic composition. Serum UA (mg/dL) was higher among AH (8.0±0.9) and gout subjects (7.7±2.4) vs controls (5.6±0.79) ($p<0.05$). BMI in AH (31±7) and gout (31±4.2) subjects were elevated vs controls (28.6±11.2) ($p<0.05$). Diabetes prevalence was similar in all groups (controls 38%, AH 46.7%, gout 42%). Gout subjects had higher rates of hypertension (controls 78%, AH 86.7%, gout 93.5%), hyperlipidemia (controls 71%, AH 73.3%, gout 90.3%) and renal disease (eGFR<60) (controls 11%, AH 13.3%, gout 51.6%, $p=0.00003$), but lower smoking rates (controls 29%, AH, 13.3%, gout, 6.5%, $p=0.03$). CAD was increased among gout but not AH subjects according to both self-report and chart ascertainment (self-report: controls 27%, AH 27%, gout 42%; chart ascertainment: controls 31%, AH 27%, gout 42%). Adjustment for renal disease/smoking status did not alter the results. Gout patients with higher serum UA (≥7.9mg/dL, n=14) had more CAD vs those with lower UA (<7.9 mg/dl, n=17) (53% vs 28.6%), but our data do not permit us to distinguish whether this represents an effect of hyperuricemia or a marker for gout severity. In contrast, AH subjects had similar rates of CAD regardless of UA level.

Conclusion: This well-characterized, prospectively-enrolled cohort study suggests that the presence of gout conveys an additional level of CAD risk beyond that of hyperuricemia. Although larger studies are needed, our pilot study demonstrates the feasibility of using a prospective enrollment strategy to distinguish between hyperuricemia and gout comorbidity.

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One Year Randomised Controlled Trial of SEcond Line Agents in Myositis (SELAM): Late Additional immunosuppression is Ineffective in Patients Who Have Partially Responded to Steroids. Ernest Choy[1], Patrick Gordon[2], Beverley White-Alao[2], Fowzia Ibrahim[2], Anna Kowalczyk[2], Alan Hakim[3], George Kitas[4], David A. Isenberg[5], Bridget Griffiths[6], Bryan Lecky[7], Kuntal Chakravarty[8], John Winer[9], Katalin Danko[10], Robert G. Cooper[11] and David L. Scott[2]. [1]Cardiff University, Cardiff, England, United Kingdom, [2]King's College London, London, United Kingdom, [3]Whipps Cross University Hospital, London, United Kingdom, [4]Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Dudley, West Midlands, UK, Dudley, United Kingdom, [5]University College London, London WC1E 6JF, United Kingdom, [6]Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [7]Walton Centre for Neurology and Neurosurgery (WCNN), Liverpool, [8]Queen's Hospital/BHR NHS Trust, Romford, United Kingdom, [9]The Queen Elizabeth Hospital, Birmingham, United Kingdom, [10]University of Debrecen, Debrecen, Hungary, Debrecan, Hungary, [11]Hope Hospital, Salford, United Kingdom

Background/Purpose: Idiopathic inflammatory myopathies (IIM), which includes dermatomyositis and polymyositis, are conventionally treated with steroids. Immunosuppressives like ciclosporin and methotrexate are often used when patients respond incompletely to steroids. Their efficacies have not been proven in randomised controlled trials (RCTs). SELAM evaluated their benefits in a placebo-controlled factorial RCT of two immunosuppressives.

Methods: A 56 week multicentre factorial-design double-blind placebo-controlled RCT compared steroids alone with added methotrexate (15–25mg weekly), ciclosporin (5mg/kg/day) and both immunosuppressives. Adults with IIM by Bohan and Peter criteria receiving corticosteroids were enrolled if they had active disease (4/5 muscle weakness by manual muscle strength testing (MMT) in 2 or more muscle groups) and functional deficits (one or more activities of daily living). Patients with inclusion body myositis and muscular dystrophies were specifically excluded. MMT at 12 months was the primary outcome. Secondary outcomes included a Functional Rating Scale (FRS), 30 metre walking time (WT), creatine kinase (CK) and ESR. The primary outcome was analysed using a linear mixed model. Paired t-tests identified significant changes between baseline and 12 months in all primary and secondary outcomes.

Results: 58 patients were randomised. They comprised 18 males and 40 females of mean age 50 years and mean disease duration 2 years. 33 (57%) completed 12 months treatment. Full data was collected in 50 (86%). Analysis of all observed data at 12 months showed no evidence any immunosuppressive treatment was more effective than placebo therapy. The mean comparisons of MMT and all secondary outcomes by active/placebo ciclosporin and methotrexate showed no significant treatment effects. The combination of both treatments was also no more effective than placebo (Table). Paired t tests showed the patients improved significantly over 12 months as follows: MMT 15% improvement ($p<0.001$), FRS 11% ($p<0.001$), WT 13% ($p=0.001$) and CK 9%; ($p=0.024$). Only changes in CK were different in early (under 3 months) than established (4–220 months) IIM.

		Placebo n=15	Methotrexate n=12	Ciclosporin n=16	Methotrexate and Ciclosporin n=15
MMT	Baseline	65 (10)	68 (9)	66 (13)	63 (7)
	Change	14 (9)	7 (11)	6 (13)	10 (98)
30 Metre Walk	Baseline	31 (21)	35 (23)	37 (24)	35 (20)
	Change	6 (16)	8 (10)	6 (13)	9 (12)
Functional Rating Scale	Baseline	35 (4)	32 (4)	32 (5)	32 (6)
	Change	2 (4)	3 (3)	3 (5)	4 (6)

Initial and 12 months changes in key observed outcomes by trial group. Means (SD) shown

Conclusion: SELAM – one of the largest RCTs of immunosuppressives in IIM - shows no evidence they give more benefits than corticosteroids alone. Using immunosuppressives in IIM, in line with management of other rheumatic diseases, appears questionable. We need a different therapeutic approach.

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Clinical Features and Treatment of Dermatomyositis Patients with Anti-CADM-140 (melanoma differentiation-associated protein 5: MDA5) Antibody; Recommendation of Combined Immunosuppressive Therapy with Intensive Intravenous Cyclophosphamide. Ran Nakashima, Yuji Hosono, Naoichiro Yukawa, Hajime Yoshifuji, Daisuke Kawabata, Koichiro Ohmura, Takashi Usui, Takao Fujii and Tsuneyo Mimori. Kyoto University Graduate School of Medicine, Kyoto, Japan

Background/Purpose: Recently, it have been reported that anti-CADM-140 (MDA5/IFIH1)-positive dermatomyositis (DM) patients frequently develop acute or subacute progressive interstitial pneumonia (A/SIP) with poor prognosis. In these patients, hyperferritinemia can be a marker for disease activity. To assess the pathophysiology of the disease and improve their survival, we investigated the clinical and laboratory findings including serum cytokine profiles, and assessed the efficacy of combined immunosuppressive therapy.

Methods: We compared anti-CADM-140 (+) patients (n=24) with anti-CADM-140 (−) DM patients (n=23). Serum cytokine levels (IL-1β, IL-6, IL-10, IL-12, IL-22, IFN-β, IFN-γ, TNF-α and M-CSF) were measured by ELISA or Cytometric Bead Array. Anti-CADM-140 (+) patients were divided into two groups, those survived (n=11) and those deceased (n=13), and the differences in their serum ferritin levels and clinical backgrounds were analyzed. We applied an intensive regimen of combined immunosuppressive therapy (high dose prednisolone, oral ciclosporin and intravenous cyclophosphamide (IVCY, 750–1000mg/m^2 in every other week) to anti-CADM-140 (+) patients and assessed the improvement in the survival rate.

Results: Anti-CADM-140 (+) DM patients showed significantly higher serum IL-6 and IL-10 levels and lower serum IL-12 and IL-22 levels than antibody (−) patients. There was no difference between the survived and the deceased patients with anti-CADM-140 in serum ferritin levels before treatment, but the hyperferritinemia in the deceased patients was progressively worsen irrespective of treatment. Those survived were significantly younger than those deceased (49.6 ± 9.6 vs. 58.7 ± 8.1, respectively: $p<0.05$). 14 patients developed respiratory failure and only 2 of them could survive. All patients except for two (one of them received lung transplantation) died who received immunosuppressants after the development of hypoxemia. The period from the onset of skin manifestation to the detection of IP was significantly longer in those survived than in those deceased (3.7 ± 2.9 months vs. 1.2 ± 1.1 months, respectively: $p<0.01$). The survival rate of the intensive regimen group (n=7) was higher than that of the others (n=14) (57.1% vs. 28.6%). The serum ferritin levels tended to go down about 14 days after IVCY, suggesting that IVCY may be a key drug in treatment of anti-CADM-140 (+) A/SIP patients.

Conclusion: Unregulated macrophage activation may be involved in the pathophysiology of anti-CADM-140 (+) DM and A/SIP. These patients should be treated with intensive combined immunosuppressive therapy, especially intensive IVCY, as soon as when they were diagnosed.

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Anti-CADM-140 Autoantibody Titer Correlates with Disease Activity in Patients with Dermatomyositis and Rapidly Progressive Interstitial Lung Disease. Shinji Sato[1], Masataka Kuwana[2], Takashi Fujita[3] and Yasuo Suzuki[1]. [1]Tokai University School of Medicine, Isehara, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Institute for Virus Research and Graduate School of Biostudies, Kyoto University, Kyoto, Japan

Background/Purpose: Anti-CADM-140 autoantibody is specifically detected in patients with dermatomyositis (DM), especially those who have little or no muscle manifestation (clinically amyopathic dermatomyositis: CADM). Its presence is known to have a strong association with rapidly progressive interstitial lung disease (RP-ILD). Despite its diagnostic utility, the relationship between anti-CADM-140 antibody titer and disease activity is still unknown. Here, we have examined this issue using an enzyme-linked immunosorbent assay (ELISA) to measure anti-CADM-140 titers.

Methods: Serum samples from 62 patients diagnosed as having adult DM (46 with classical DM and 16 with CADM) at Keio University Hospital or Tokai University Hospital between 2000–2010 were screened for autoantibody using RNA and protein immunoprecipitation assays. Sera containing anti-CADM-140 antibody were then titered using a previously-established ELISA. Associations between anti-CADM-140 titer and clinical course and outcome were analyzed.

Results: Sera from thirteen of 62 patients with DM were found to contain anti-CADM-140 antibody. Two had classical DM and 11 had CADM. Ten patients had ILD, of whom 9 developed RP-ILD. In the latter, the mean titer of anti-CADM-140 antibody before treatment was significantly lower in those who responded to therapy and survived (responder group, n=3) than in those who did

not respond and died (non-responder group, n=6) (101.6 units vs. 351.4 units, p= 0.018). In the responder group, the mean titer of anti-CADM-140 antibody decreased to below the cut-off level after treatment, in parallel with improved respiratory symptoms (n= 3, 101.6 units vs. 1.5 units, p= 0.041, cut-off level = 8.0 units). In contrast, the mean anti-CADM-140 titer in the non-responder group did not decrease significantly and was maintained at a high level over the disease course (n=4, 364.2 units vs. 198.4 units, p=0.17). Interestingly, the anti-CADM-140 titer remained below the cut-off level after improvement of RP-ILD in the three surviving patients.

Conclusion: These results illustrate the clinical utility of anti-CADM-140 antibody to predict the development of RP-ILD as well as to monitor disease activity and to assess the response to treatment in patients with DM and RP-ILD.

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Anti-CADM-140 Antibody, Ferritin and IL-18 Are Associated with Disease Activity of Interstitial Lung Disease in Anti-CADM-140 Antibody-Positive Dermatomyositis. Takahisa Gono[1], Shinji Sato[2], Yasushi Kawaguchi[1], Masataka Kuwana[3], Yasuhiro Katsumata[1], Masanori Hanaoka[1], Kae Takagi[1], Hisae Ichida[1], Sayumi Baba[1], Yuko Okamoto[1], Yuko Ota[1], Sayuri Kataoka[1] and Hisashi Yamanaka[1]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Tokai University School of Medicine, Isehara, Japan, [3]Keio University School of Medicine, Tokyo, Japan

Background/Purpose: The aim of this study was to investigate the precise clinical characteristics and association between the anti-CADM-140 antibody titer and disease status in patients with anti-CADM-140 antibody-positive dermatomyositis (DM).

Methods: Twenty-seven patients who presented with DM and had the anti-CADM-140 antibody were enrolled. All patients except one had the complication of interstitial lung disease (ILD). The association between clinical manifestations and clinical parameters, including the anti-CADM-140 antibody, was analyzed.

Results: The complication of rapidly progressive (RP)-ILD was revealed in twenty patients (74%). The frequencies of fatal outcome, relapse and malignancy were 33%, 4% and 4%, respectively. All patients who died had the complication of RP-ILD in the present study. Remarkably, a fatal outcome was revealed within the first 6 months after disease onset. Elderly age at onset, severely involved pulmonary function and high levels of serum ferritin were present in twenty RP-ILD patients, compared to six non-RP-ILD patients. Twenty RP-ILD patients with the anti-CADM-140 antibody was divided into the two subsets, eleven patients who died (dead subset) and nine patients who survived (living subset).The ferritin levels were significantly higher ($P = 0.017$) in the dead subset than the living subset, although KL-6, CRP and IL-18 concentrations did not differ significantly between the two subsets. The median value of the anti-CADM-140 antibody titer on admission was higher in the dead subset than the living subset. RP-ILD was refractory and progressive in the dead subset, although almost of these patients received combination therapy, including prednisolone, intravenous cyclophosphamide therapy and calcineurin inhibitor. In addition, $AaDO_2 \geq 32$ mmHg and ferritin $\geq$ 828 ng/ml upon admission were poor prognostic factors in RP-ILD patients with anti-CADM-140 antibody. In addition, we compared clinical parameters upon admission with the parameters after treatment. There was no significant difference ($P = 0.15$) between the living subset and the dead subset in the duration of evaluation after treatment. The anti-CADM-140 antibody titer was significantly lower ($P = 0.0061$) after treatment than on admission in the living subset. The anti-CADM-140 antibody disappeared after treatment in 6 (50%) of 12 living patients. On the other hand, there was no statistical significant difference ($P = 0.16$) in the dead subset between the anti-CADM-140 antibody titer upon admission as compared to the antibody after treatment. The median values of ferritin after treatment were 76 ng/ml and 1987 ng/ml in the living and dead subsets, respectively. Moreover, the levels of IL-18 were significantly lower ($P = 0.031$) after treatment in the living subset. In the dead subset, the levels of IL-18 were not significantly lower after treatment. Sustained high levels of anti-CADM-140 antibody titer, ferritin and IL-18 were present in the dead subset.

Conclusion: The anti-CADM-140 antibody is a disease-activity marker and a disease-specific marker. Serum anti-CADM-140 antibody, ferritin and IL-18 concentrations reflect the response to treatment and the status of ILD in patients with anti-CADM-140 antibody-positive DM.

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Transcription Intermediary Factor (TIF)-1β Is a New Dermatomyositis Autoantigen. Minoru Satoh[1], Jason Y.F. Chan[1], Steven J. Ross[1], Angela Ceribelli[1], Yi Li[1], Yoshioki Yamasaki[2], Hidehiro Yamada[2], Monica Vazquez-Del Mercado[3], Marcelo Petri[4], Eric S. Sobel[1], Westley H. Reeves[1] and Edward K.L. Chan[1]. [1]University of Florida, Gainesville, FL, [2]St. Marianna University, Kawasaki, Japan, [3]Univ de Guadalajara, CUCS, Guadalajara, Mexico, [4]Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, Mexico

Background/Purpose: Each myositis specific autoantibodies (MSA) are associated with unique clinical subset and useful biomarkers in polymyositis/dermatomyositis (PM/DM). Identifying new MSA will help in monitoring PM/DM patients as evidenced recently by reports on anti-p155/140 (transcription intermediary factor-1gamma, TIF-1gamma) associated with malignancy and anti-CADM140/MDA5 associated with clinically amyopathic DM with rapidly progressive lung disease. Although new autoantibody specificities have been added, ~50% of patients with PM/DM are still without known MSA, thus identifying additional MSA is relevant. ~120kD protein recognized by serum from a patient with DM was identified as TIF-1beta and clinical features of patients who have autoantibodies to this antigen was characterized.

Methods: ~120kD protein recognized by a prototype DM serum was purified and identified by mass spectrometry. Sera from ~2200 patients with various diagnosis including 434 SLE, 119 scleroderma, and 263 PM/DM from 4 countries were tested by immunoprecipitation of ^{35}S-methionine labeled K562 cell extract. Sera that immunoprecipitated the similar protein was searched and identity of specificity was verified by immunoprecipitation, western blot, and ELISA. Clinical information was from database and charts.

Results: ~120kD protein was identified as TIF-1beta by mass spectrometry and its identity was verified by western blot using monoclonal antibodies. By immunofluorescence, anti-TIF-1beta showed fine speckled nuclear staining. Although the characteristic of the 120kD TIF-1beta band in autoradiogram was clearly distinct, it exactly comigrated with another MSA PL-12. Four cases of anti-TIF-1beta were identified; all are female, one each in Japanese, African American, Caucasian, and Mexican. Three had diagnosis of DM and one case was followed as undifferentiated connective tissue disease (UCTD) with elevated CPK but without significant muscle symptoms. This specificity was not found in SLE, scleroderma, or other conditions. A UCTD case had a history of colon cancer and cervical squamous metaplasia. The Japanese DM patient had elevated CPK (654IU/L), muscle weakness, positive biopsy and EMG, however, her myopathy was resolved without treatment. Two American patients had ~300IU/L CPK and controlled with moderate-low dose of steroid. The Mexican case also had anti-Mi-2 but coexistence of anti-TIF-1gamma (p155/140) was not seen.

Conclusion: Anti-TIF-1beta is a new dermatomyositis autoantibodies appear to be associated with mild form of myopathy. Whether it has association with malignancy as in the case of anti-TIF-1gamma or other unique features will need to be evaluated in future studies.

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Clinical Features and Survival in Anti-PL-7 Autoantibody Positive Myositis Patients From a Single Tertiary Care Center. Arcadio Agudelo-Hernandez[1], Chester V. Oddis[2], Noreen Fertig[2], Diane Koontz[2] and Rohit Aggarwal[1]. [1]University of Pittsburgh Medical Center, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: To describe the demographic, clinical features and survival in a cohort of anti-PL-7 autoantibody positive myositis patients from a single tertiary care center

Methods: All PL-7 (+) patients with their first evaluation between 1985–2009 were included regardless of connective tissue disease (CTD) diagnosis. Anti-PL-7 was detected using RNA and protein immunoprecipitation techniques. ANA and cytoplasmic pattern was determined by indirect immunoflourescence (IIF) using Hep2 cell. All data were collected from the registry database and medical record. Mortality data was determined using National Death Index or Social Security Death Index, and medical record review. Survival analysis was done using Kaplan Meier plots.

Results: We identified 25 PL-7 (+) patients in our cohort. Eighteen (72%) were female and 22 (88%) Caucasian with a mean (± SD) age of 55.1 (15.4) years at diagnosis. The initial CTD symptom occurred at a mean age of 49.1 (18.2), and their first evaluation at our center was at age 57.0 (13.3) with a diagnosis delay of 6.0 (10.2) years [median (IQR) = 1.08 (0.5–6.8) years]. Only 13 (52%) patients were ANA positive, whereas 23 (92%) had cytoplasmic pattern on IIF (7 speckled; 6 diffuse; 10 both diffuse and speckled). The initial diagnoses

included dermatomyositis (DM) (n=7), polymyositis (n=5), systemic sclerosis (n=1), overlap (n=7), UCTD/unknown (n=5). The most common initial CTD symptoms were Raynauds (n=9), arthralgia/arthritis (n=5), followed by muscle weakness (n=2), rash (n=2) and dyspnea (n=2). ILD was detected in 92% (23/25) of patients and 20% (5/25) had pulmonary hypertension (PHT) (3 primary/2 secondary). Most patients (19/23) developed pulmonary involvement before an established CTD diagnosis with nearly 50% having pulmonary symptoms > 6 months before the CTD diagnosis. The mean time of follow up was 4.9 (4.1) years with the cohort developing the following clinical features at some time during their course: fatigue 100%, Raynauds 84%, dyspnea 72% (n=18; 12 moderate to severe, 6 on home O_2), myalgia 48%, fever 44%, arthritis 44%, DM rash 36%, dysphagia 32%,telangectasia 32%, puffy fingers 32%,, pleurisy 16%, and mechanics hands in 5 of 8 evaluated specifically for it. Proximal muscle weakness was seen in 76% (19/25) of the cohort but nearly 50% (n=12) had mild/subtle weakness. Nineteen (76%) patients had CK elevations with a median peak CK 7 times the upper limit of normal [IQR 3.7–16.5]. The median (IQR) survival time in years for the entire cohort was poor at 6.42 (4.2–21.6) years. The 5 and 10 year unadjusted cumulative survival rates were: 66.5% (95% CI 41.8–82.6) and 30.8% (95% CI 11.7–52.4), respectively. Overall, 14 (56%) patients died during the study period with an average age at death of 59.2 (13.9) years. The most common cause of death was pulmonary in 11/14 (78.6%) patients (8 with fibrosis and 3 with PHT).

Conclusion: We describe detailed clinical features and survival of a large anti-PL-7 (+) cohort. We emphasize the importance of considering this autoantibody in patients presenting with both pulmonary symptoms and other CTD features even in the absence of clinically overt myositis. This subset of myositis is also associated with a high mortality rate.

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The Clinical Spectrum but Not the Evolution of Antisynthetase Syndrome Is Related to the Antisynthetase Antibody Specificity: A Retrospective Analysis of 142 Patients. Baptiste Hervier[1], Hervé Devilliers[2], Raluca Stanciu[1], Eric Hachulla[3], Yurdagul Uzunhan[4], Bruno Wallaert[5], Bruno Fautrel[6], Bernard Fournie[7], Lucile Musset[8], Aude Rigolet[1], Hilario Nunes[4], Patrice Cacoub[8], Daniel F. P. Adoue[9], Zahir Amoura[8], Mohamed Hamidou[10] and Olivier Benveniste[11]. [1]Pitie-Salpetriere Hospital, APHP, UPMC Paris VI, Paris, France, [2]CHU Dijon, Dijon, France, [3]Internal Medicine, Lille CEDEX, France, [4]Hopital Avicenne, APHP, Bobigny, France, [5]CHRU, Lille CEDEX, France, [6]Université Pierre et Marie Curie - Paris 6 - Pitie Salpetriere University Hospital, Paris, France, [7]CHU, Toulouse, France, [8]CHU Pitié-Salpêtrière, Paris, France, [9]CHU Toulouse Purpan, Toulouse, France, [10]Service de médecine interne, Hôpital Universitaire de Nantes, Nantes, France, Nantes, France, [11]Pitie-Salpetriere Hospital, Paris, France

Background/Purpose: Antisynthetase syndrome (ASS) is characterized by the association of an inflammatory myositis with interstitial lung disease (ILD) and different antisynthetase antibodies (AS-Ab). The clinical spectrum and the evolution of ASS are heterogeneous. This study was conducted to examine whether this heterogeneity would be related to the AS-Ab specificity.

Methods: Patients (n=142, 47.8+/− 15.3 years at diagnosis) from 7 French tertiary hospitals from 1985–2011 were included. The association of ≥ 1 symptom with the positivity of 1 AS-Ab (anti-Jo1: n=85, anti-PL12: n=40 and anti-PL7: n=17) defined ASS. At the end of the follow-up (median = 3,4 years, 0–25), a worsening disease was defined either by an uncontrolled myositis or a pulmonary aggravation. The ASS patterns were examined by multiple correspondence & cluster analyses. Differences between worsening & stable/improving patients were tested by the Mann-Whitney (countinuous data) and the Khi-2 (categorical data) tests and defined the prognosis factors. A p value <.05 was significant.

Results: Patients presented with myositis (n=100, 70%), ILD (n=125, 88%) and other symptoms, including arthralgia (n=79, 56%), Raynaud's phenomenon (n=57, 40%) and mechanic's hands (n=24, 17%). ASS overlapping with Systemic Sclerosis (SSc) and Sjögren Syndrome (SS) occurred in 41, 29% & 51, 36% cases respectively.

At diagnosis, myositis occurred more frequently in patients with anti-Jo1-Ab (85%) rather than anti-PL12/7-Ab (43%/41%, p<0,001). The myositis was more severe as attested by a higher frequency of muscular deficit (66% vs 20%/18%, p<.001) & myogenic electromyography pattern (n=40, p=0,002) and also a higher creatin-kinase (CK) level (5058 ± 5607 IU/L vs 452±576/1129±1529, p<.001). Patients with anti-PL12/7-Ab disclosed more frequently an ILD without myositis (50%/53 vs 11%, p<.001). The other ASS parameters were not correlated with the AS-Ab subtype.

Multiple correspondence analysis showed two different ASS patterns related to the AS-Ab specificity: patients with anti-Jo1-Ab presented a more diffuse disease with myositis, ILD, arthralgia and SS or SSc overlap, whereas patients with anti-PL12/7-Ab were quite similar to each other, disclosing a disease more restricted to the lungs. Moreover, the clustering analysis isolated a pattern of patients defined by the presence of anti-Jo1-Ab, severe myositis, ILD and arthralgia.

During the follow-up period, 36 patients (29%) developed a pulmonary hypertension (defined by a systolic PAP > 37 mmHg by echocardiography) and a total of 42 (30%) patients worsened. The evolution of the disease was not correlated to the AS-Ab specificity (p=.14). However, we identified different factors predictive of a worsening disease, including lung involvement (p<.02), co-occurrence of myositis & ILD at diagnosis (p<.04), severe rhabdomyolysis (p<.002) and development of pulmonary hypertension (p<.05).

Conclusion: Based on the AS-Ab specificity, two different ASS patterns can be described: anti-Jo1-Ab pattern with severe myositis, ILD and arthralgia vs anti-PL12/7-Ab pattern with ILD but inconstant myositis. Prognosis factors, independent of AS-Ab specificity, were lung involvement, severe myositis and pulmonary hypertension

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Anti-MJ/NXP-2 Antibodies Are the Most Common Specificity in a Cohort of Adult Caucasian Patients with Dermatomyositis. Angela Ceribelli[1], Micaela Fredi[2], Mara Taraborelli[2], Ilaria Cavazzana[3], Franco Franceschini[4], Angela Tincani[5], Steven J. Ross[1], Brad A. Pauley[1], Edward K.L. Chan[1] and Minoru Satoh[1]. [1]University of Florida, Gainesville, FL, [2]University of Brescia and Spedali Civili, Brescia, Italy, [3]Rheumatology Unit, University of Brescia, Brescia, Italy, Brescia, Italy, [4]University of Brescia, Brescia, Italy, [5]Rheumathology Unit, University of Brescia, Brescia, Italy, Brescia, Italy

Background/Purpose: Specific autoantibodies in patients with polymyositis/dermatomyositis (PM/DM) are associated with unique subsets, and they are useful in monitoring clinical course and predicting outcome. Anti-MJ antibodies, which recognize the nuclear protein NXP-2 in the PML (promyelocytic leukemia) nuclear bodies, are a new specificity reported in 23–25% of juvenile DM, usually associated with severe muscle atrophy, functional impairment, and calcinosis. The aim of our study is to analyze the prevalence and clinical significance of anti-MJ antibodies in a cohort of adult Caucasian PM/DM patients.

Methods: Autoantibodies in sera from 58 consecutive adult PM/DM patients (74% female, mean age 43±17, mean follow up 55 months) were analyzed by immunoprecipitation of ^{35}S-labeled K562 cell extracts, ELISA (anti-MJ, Ro52, La, Jo-1), Western Blot and Indirect Immunofluorescence (IIF). Clinical association of anti-MJ was analyzed using information from charts and database.

Results: Anti-MJ antibodies are the most prevalent specificity (10/58; 17%) in our PM/DM cohort, followed by anti-Jo-1 (10%), -p155/140 (5%), -SRP (5%), -EJ (4%), and anti-Mi-2, -SMN complex, -OJ with one case each. Anti-MJ was found in 30% of DM and 8% of PM (P = 0.02). Among 10 cases of anti-MJ, 8 were DM and 2 were PM. When clinical features of 10 cases of anti-MJ (+) vs 48 cases anti-MJ (−) were compared, DM is more common (P = 0.03) and no overlap syndrome patients were found in anti-MJ group (0% vs 13%). Age of onset (25.5 vs 46.1 years) and age at initial visit (37.6 vs 54.6 years) were younger in anti-MJ group (P = 0.002), and 2 anti-MJ (+) were pediatric onset DM. In anti-MJ (+) patients, heliotrope rash (P = 0.01) and calcinosis (P = 0.057) were common, however, none of them had heart involvement (0% vs 27%, P = 0.03), interstitial lung disease (0% vs 33%, P = 0.048), or cancer (0% vs 8%). Myopathy in anti-MJ (+) patients was well responsive to steroid therapy and elevated CPK in the last visit was not seen (0% vs 25%). Only 6/10 anti-MJ (+) showed PML body nuclear dots staining in IIF, suggesting that IIF cannot be used for screening of anti-MJ antibodies.

	Anti-MJ (+) n = 10	Anti-MJ (−) n = 48	p
Male	40%	23%	
Mean age, ys (±SD)	37.6 (±12)	54.6 (±14.8)	
DM/PM/overlap	80/20/0%	40/48/13 %	DM 0.03
Heliotrope rash	60%	19%	0.01
Calcinosis	30%	6%	0.06
Heart involvement	0%	27%	
Interstitial lung disease	0%	33%	0.05
Elevated CPK at last visit	0%	25%	

Conclusion: Anti-MJ antibodies are detected also in adult PM/DM, and they are the most frequent specificity in our cohort, found in 17% of PM/DM (30% in DM and 8% in PM). Anti-MJ (+) patients have DM of young onset, severe calcinosis, no internal organ involvement and good response of myopathy to steroid. Anti-MJ will be a useful new addition of myositis-associated autoantibodies to help clinical monitoring of patients with adult PM/DM.

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Distinctive Pattern of Myositis-Specific Autoantibody Production Between American Caucasian and Italian Patients with Polymyositis/ Dermatomyositis. Angela Ceribelli[1], Yi Li[1], Ilaria Cavazzana[2], Franco Franceschini[2], Steven J. Ross[1], Jason Y.F. Chan[1], Brad A. Pauley[1], Eric S. Sobel[1], Westley H. Reeves[1], Edward K.L. Chan[1] and Minoru Satoh[1]. [1]University of Florida, Gainesville, FL, [2]University of Brescia, Brescia, Italy

Background/Purpose: Myositis specific autoantibodies (MSA) in patients with polymyositis/dermatomyositis (PM/DM) are associated with unique clinical subsets and clinically useful biomarkers. Difference in prevalence of MSA between different races and a role of environmental factors within the same ethnicity have been suggested. However, differences of MSA production within Caucasians have not been well characterized. The aim of our study is to analyze the prevalence of MSA in adult Caucasian patients of American vs Italian origin.

Methods: Autoantibodies in sera from consecutive adult PM/DM patients from Italy (n = 58, 74% female) and American Caucasian patients (n = 68, 77% female) were analyzed by immunoprecipitation of ^{35}S-labeled K562 cell extracts. ELISA (anti-MJ, Ro52, Jo-1), Western Blot and Indirect Immunofluorescence (IIF) were also performed to verify specificity of autoantibodies.

Results: DM was more common in Italians than Americans (47% vs. 25%, P = 0.01). In all PM/DM patients, anti-MJ was the most common specificity in Italian (10/58, 17%) and significantly more prevalent than American Caucasian (2/68, 3%, P = 0.01). In contrast, anti-Jo-1 was the most common specificity in American Caucasian and more frequent (22% vs 10%; P = 0.09) than Italian. In comparison of DM in Italian vs American Caucasian, the distinctive pattern of MSA production became more apparent: anti-MJ was 30% vs 6% and anti-Jo-1, 0% vs 18% in Italian vs American Caucasian. Prevalence of other anti-synthetase antibodies and p155/140, Mi-2, and SRP were not different in total PM/DM or DM patients. Prevalence of MSA in PM between Italian and American Caucasian also was not significantly different.

Autoantibody	PM/DM Italian (58)	PM/DM American (68)	DM Italian (27)	DM American (17)
MJ	17%[1]	3%[1]	30%	6%
p155/140	5%	3%	8%	12%
Mi-2	1.7%	3%	4%	6%
SRP	5%	3%	0	0
Jo-1	10%[2]	22%[2]	0%[3]	18%[3]
Other synthetases	5% (2 EJ, 1 OJ)	3% (1 OJ, 1 PL-12)	4% (1 EJ)	0%
SMN complex	1.7%	3%	0	0

1, P = 0.01; 2, P = 0.09; 3, P = 0.05

Conclusion: Among PM/DM patients, DM was more common in Italian and difference in MSA specificity was mainly in DM population; Italian DM has very high prevalence of anti-MJ but no anti-Jo-1 whereas anti-Jo-1 was the most common in American Caucasian. Distinctive pattern of MSA in Italian vs American DM suggests roles of genetic differences within Caucasian and/or environmental factors and that testing for anti-MJ is more relevant for certain population such as Italian. More careful studies within same race may be necessary to understand the factors affecting MSA production.

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Persisting CD28^{null} T Cells, but Not Regulatory T Cells, in Muscle Tissue of Myositis Patients After Immunosuppressive Therapy. Ingela M. Loell, Jayesh Pandya, Sukanya Raghavan, Mei Zong, Vivianne Malmström and Ingrid E. Lundberg. Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) are characterized by infiltration of macrophages and T cells in skeletal muscle tissue. Immunosuppressive treatment has limited effects on the number of infiltrating cells providing a basis for persistent immune reaction targeting muscle fibers. Regulatory T cells are key players in the maintenance of peripheral tolerance by controlling T cell reactivity to self-antigen. CD28^{null} T cells are a highly enriched subset of proinflammatory T cells in patients with autoimmune diseases and are suggested to be resistant to apoptosis. Our aim was to establish whether the persisting T cells in myositis tissue belong to the regulatory T cell subset or to the apoptosis resistant, proinflammatory CD28^{null} T cell subset.

Methods: Muscle tissue biopsies were obtained from 14 patients with PM/DM before and after 8(4–16) month of treatment with glucocorticoids and additional immuno-suppressive drugs. Immunohistochemistry for CD3, FOXP3 and CD28^{null} surrogate marker CD244 was performed on muscle tissue. For clinical evaluation serum creatine kinase (s-CK) and functional index (FI) of myositis was used.

Results: Patients significantly improved in Functional Index following treatment ($p=0.002$) but only one patient regained 100% muscle function. Serum CK-levels went back to normal in all patients after treatment ($p=0.004$). The CD28^{null} T cell frequencies were increased or unaffected for majority of the patients, 11 out of 14, which was statistically significant ($p<0.05$). The proportion of T_{regs} did not differ before and after treatment at group level, but for the majority of the patients the frequency was lower or unaffected (10 out of 14).

Conclusion: Despite normalized CK-levels, patients only show partial functional improvement and many displayed persistent T cells in muscle tissue post treatment. The relative number of regulatory T cells was unchanged or decreased, while the CD28^{null} T cell proportion was mainly increased post treatment suggesting that high doses of glucocorticoid treatment might impair the regulation of autoreactive/pathogenic T cells including the CD28^{null} T cell populations in affected muscle.

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Proposal for the Development of An International Minimal Data Collection for Juvenile Dermatomyositis. Liza J. McCann[1], Clarissa A. Pilkington[2], L. Beard[3], Angelo Ravelli[4], Adam Huber[5] and Lucy R. Wedderburn[6]. [1]Alder Hey Children's NHS Foundation Hospital, Liverpool, United Kingdom, [2]Department of Rheumatology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [3]UCL Institute of Child Health, London, United Kingdom, [4]G. Gaslini Institute, Genova, Italy, [5]IWK Health Centre, Halifax, NS, [6]University College London (UCL), United Kingdom

Background/Purpose: Several groups collect prospective data on patients with juvenile idiopathic inflammatory myopathies (IIM), including the UK JDM Cohort Biomarker Study &Repository, CARRA, and Euromyositis. Datasets are partially overlapping. A consensus minimal data collection would facilitate comparison and communication between groups. We propose a new international minimal data collection, potentially valuable in trials and clinical contexts, to be collected by clinicians for all JDM patients, respecting data protection and ownership.

Methods: Variables collected within the UK JDM Cohort/Biomarker Study, CARRA, Euromyositis and a multi-national study of 27 centres in Europe/Latin America[1] were compared. Those common to at least 2 datasets were considered for inclusion, based on agreement between collaborators.

Results: To date, the group have identified 19 variables common to all data collections (UK JDM cohort, CARRA, Euromyositis and the inception cohort by Ravelli et al[1]), 16 variables common to 3 datasets and 24 variables common to 2 datasets. Collaborators have discussed each variable to determine which ones are most relevant to clinical practice and useful in research. Thereby, a minimal data collection has been proposed that includes demographic data, diagnostic data, clinical features, major organ involvement, measures of disease activity / damage (as defined by IMACS / PRINTO), health assessment questionnaires, investigations and treatment. The data collection is thought to be achievable by clinicians within their normal practice. Work is in progress to define each variable, including optional detailed collection of activity / damage indices within specialist / research environments.

Conclusion: An international minimal data collection for use in trials would allow greater understanding of disease course / prognosis, enhance international collaboration between groups, and facilitate linking to biobanks. The dataset requires testing through existing collaborations (IMACS, PRINTO etc). Collaboration with adult groups (eg. via Euromyositis) may allow harmonised data collection from paediatric to adult services, providing valuable outcome data for this rare disease.

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Ethnic but not Gender Differences in Disease Manifestations in Dermatomyositis Patients. Anna Tjärnlund[1], Lisa G. Rider[2], Frederick W. Miller[2], Victoria P. Werth[3], Clarissa A. Pilkington[4], Marianne de Visser[5], Elin Forslund[1], Anthony A. Amato[6], Richard J. Barohn[7], Matteo Bottai[8], Richard Finkel[9], Harold E. Paulus[10], Gerald J. D. Hengstman[11], Matthew H. Liang[12], Jasvinder Singh[13] and Ingrid E. Lundberg[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, MD, [3]Perelman School of Medicine at the University of Pennsylvania and Philadelphia V.A. Medical Center, Philadelphia, PA, [4]Department of Rheumatology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [5]Department of Neurology, Academic Medical Centre, Amsterdam, Netherlands, [6]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [7]Department of Neurology, University of Kansas Medical Center, Kansas City, MO, [8]Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [9]Department of Neurology, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, [10]University of California, Los Angeles, Los Angeles, CA, [11]Department of Neurology, Catharina-ziekenhuis, Eindhoven, Netherlands, [12]Brigham & Womens Hospital, Boston, MA, [13]University of Alabama and VA Medical Center, Birmingham, AL

Background/Purpose: Dermatomyositis (DM) is a subset of idiopathic inflammatory myopathies (IIM), which are heterogeneous rheumatic disorders characterized by inflammation of skeletal muscle and progressive weakness. New and improved treatment is needed but a significant and fundamental problem for conducting clinical trials is the inadequate classification criteria for IIM. To address this, the International Myositis Classification Criteria Project (IMCCP) was established with the aim to develop and validate new classification criteria for IIM and major subgroups of IIM. Clinical and laboratory data from 1600 IIM and comparator cases have been collected. Dissimilarities in disease manifestations among different patient groups have to be considered as classification criteria must be uniformly valid. Little, however, is known about these differences in relation to clinical phenotype for IIM. The aim of this study was to investigate ethnic or gender differences in clinical manifestations in adult DM, juvenile DM (JDM) and amyopathic DM (ADM).

Methods: We extracted data on serology, 23 muscle variables (e.g., pattern of muscle weakness) and 14 skin manifestations from the IMCCP database and assessed their prevalence among 238 DM, 233 JDM and 45 ADM patients. Comparisons were made between genders and patients of Caucasian and Asian origin. Correction for multiple testing was performed yielding a $p<0.0009$ for statistical significance.

Results: Comparisons between the two ethnic groups revealed significant differences in clinical phenotypes. For adult DM cases, several muscle variables were more prevalent among Caucasians compared to Asians and two, neck flexor weakness and muscle tenderness, remained statistically significant after correction for multiple testing. Moreover, the pattern of skin manifestations differed greatly between adult DM patients, and photodistributed violaceous erythema was found to be significantly more prevalent among Caucasians ($p<0.0001$). Fewer ethnic differences for JDM cases were found and none remained statistically significant after correction for multiple testing. As expected, the ADM patients displayed virtually no muscle manifestations and no significant differences were found. Comparison between prevalence of skin manifestations for Caucasian and Asian ADM patients showed a higher prevalence for most skin variables in Caucasians, where periungual erythema remained statistically significant after correction for multiple testing ($p<0.00001$). Autoantibody analyses revealed a difference only among JDM cases where rheumatoid factor (RF) was more prevalent in Asians than in Caucasians, but only with a $p<0.05$.

Gender analyses for serology, muscle variables and skin manifestations revealed fewer differences compared to ethnic differences, and none remained statistically significant after correction for multiple testing.

Conclusion: We found significant ethnic differences in clinical phenotypes for DM patients. Comparable analyses showed no significant gender differences. Results from this study are of importance for the continued work in defining diagnostic and classification criteria as well as defining inclusion criteria in clinical trials.

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Initial Predictors of Poor Survival in Patients with Dermatomyositis and Interstitial Lung Disease. Masataka Kuwana[1], Shinji Sato[2], Yuichiro Shirai[1], Tsutomu Takeuchi[1] and Takashi Fujita[3]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Tokai University School of Medicine, Isehara, Japan, [3]Institute for Virus Research and Graduate School of Biostudies, Kyoto University, Kyoto, Japan

Background/Purpose: Dermatomyositis (DM) is a heterogeneous disease with varying degrees of skin manifestations, myositis, and interstitial lung disease (ILD). A variety of serum autoantibodies are identified in patients with DM or clinically amyopathic DM (CADM), including antibodies to aminoacyl-tRNA synthetase (ARS), TIF1-γ, and CADM-140. Detection of these autoantibodies is useful in diagnosis as well as in classifying patients into distinct clinical subtypes. In this study, we examined if autoantibody profiles and clinical characteristics at diagnosis were useful in predicting prognosis in patients with DM and ILD.

Methods: Seventy patients diagnosed as having DM/CADM and ILD at Keio University Hospital between 1993–2007 were selected from our database. All clinical and laboratory findings were recorded at diagnosis. Autoantibodies were identified by immunoprecipitation assays, and anti-CADM-140 antibody was confirmed by ELISA using recombinant melanoma differentiation-associated gene 5 protein. Cumulative survival rates were calculated using the Kaplan-Meier method, and equality of survival curves was tested by the Wilcoxon test. Multivariate analysis was performed using the Cox proportional hazards regression model.

Results: Eighteen (26%) were positive for anti-CADM-140 and 38 (54%) were positive for anti-ARS (13 anti-Jo-1, 10 anti-EJ, 7 anti-PL-12, 5 anti-PL-7, 2 anti-OJ, and one anti-KS). The remaining 14 patients included 2 with anti-U1RNP, 2 with anti-Ku, and one with TIF1-g (reference group). When clinical characteristics at diagnosis were compared between anti-CADM-140 and anti-ARS groups, diagnosis of CADM and skin ulceration were more common, and muscle weakness and shortness of breath at presentation, mechanic hands, Raynaud's phenomenon, and elevation of KL-6 and CK were less common in anti-CADM-140 group ($P < 0.01$ in all comparisons). The onset of disease in all patients with anti-CADM-140 occurred between June and December, but anti-ARS-positive patients did not have any recognizable seasonal pattern. CT findings showed that NSIP pattern was predominant in anti-ARS group, but organizing pneumonia (OP) pattern was common in anti-CADM-140 group ($P < 0.0001$). Cumulative survival rates were significantly worse in anti-CADM-140 than in anti-ARS or reference group ($P = 0.004$ and 0.03, respectively). All deaths in anti-CADM-140 group were caused by progressive ILD and occurred within 7 months after onset, whereas survival rates in anti-ARS group were gradually reduced and were comparable with those in anti-CADM-140 group at 10 years. By univariate analysis, diagnosis of CADM, anti-CADM-140 antibody, skin ulceration, lack of muscle weakness, and OP pattern on CT were identified as initial parameters associated poor survival ($P < 0.05$ for all comparisons). However, multivariate analysis revealed that skin ulceration was the only parameter independently associated with poor survival: odds ratio was 4.1 (1.1–16.4) and 3.8 (1.2–12.2) at 1 and 10 years, respectively.

Conclusion: Autoantibody detection is useful in predicting outcomes in DM patients with ILD at presentation. Skin ulceration at lateral naifolds due to vasculopathy is the best predictor of poor survival in DM patients.

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Prevalence of Pulmonary Hypertension in Inflammatory Myopathies. Ashwini Mhatre, James Bena and Soumya Chatterjee. Cleveland Clinic, Cleveland, OH

Background/Purpose: In patients with polymyositis (PM) and dermatomyositis (DM), pulmonary complications can cause significant morbidity and mortality. These include interstitial lung disease (ILD), hypoventilation related to respiratory muscle weakness, and aspiration pneumonia associated with involvement of the striated muscles of the upper esophagus, cricopharyngeus, and hypopharynx. Pulmonary hypertension (PH) has been associated with other autoimmune rheumatic diseases. Though PH has been reported in a few case reports, it has been a hitherto under recognized cause of morbidity and mortality in patients with inflammatory myopathies (IM). We examined the prevalence of PH in patients with IM and compared that to the prevalence of idiopathic PH

in the general population and also to systemic sclerosis (SSc) associated PH.

Methods: Retrospective chart review of patients with a diagnosis of PM or DM based on ICD-9 codes was performed at a tertiary care center using electronic medical records (EPIC™). Prevalence of PH was suspected in this cohort based on echocardiography (TTE) or right heart catheterization (RHC) criteria.

Results: Diagnosis of IM was confirmed in 453 out of 683 charts reviewed. Seventy one patients had suspected PH based on TTE and 32 patients had diagnosis confirmed by RHC. This is significantly higher than population prevalence of PAH (15/ million, p <0.001) [Humbert et al., 2006]. The prevalence of RHC based PH was lower than that in systemic sclerosis controls (89/722, p = 0.004) [Mukerjee et al., 2003]. However, the prevalence of PH based on TTE and RHC was higher when compared to a similar study in SSc patients (62/599, p = 0.006) [Hachulla et al., 2005].

Conclusion: This is the first study to systematically investigate the prevalence of PH in IM. In our cohort of patients with IM, the prevalence of PH was significantly higher than expected. TTE was a sensitive non-invasive modality for detection of PH in these patients. In this retrospective study, all patients with IM were not routinely screened for PH, leading to its potential underestimation. Additionally, TTE diagnosis of PH was not always confirmed by RHC, leading to its potential overestimation. However, it seems apparent that PH is more common in IM than realized and should be added to the list of pulmonary complications in IM. Hence routine screening for PH in IM may be worthwhile, as its recognition might lead to better outcomes through earlier institution of vasoactive therapies.

Table. Comparison of observed prevalence compared to literature

Group	PH in IM (%)	Historical controls (%)	p-value
Confirmed PH (RHC)	32/453 (7.1%)	0.0015 [Humbert, 2006]	**<0.001**
	32/453 (7.1%)	12.3 [Mukerjee, 2003]*	**0.004**
Suspected PH (TTE)	73/453 (16.1%)	0.0015 [Humbert, 2006]	**<0.001**
	73/453 (16.1%)	10.4 [Hachulla, 2005]	**0.006**
Isolated PH #	10/453 (2.2%)	0.0015 [Humbert, 2006]	**<0.001**

* Higher prevalence of PH than the current study
\# PH without interstitial lung disease (ILD)

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Pulmonary Hypertension in Inflammatory Myopathies: Demographic and Clinical Characteristics. Ashwini Mhatre, James Bena and Soumya Chatterjee. Cleveland Clinic, Cleveland, OH

Background/Purpose: Patients with polymyositis (PM) and dermatomyositis (DM) can have significant morbidity and mortality from pulmonary complications. These include interstitial lung disease (ILD), hypoventilation related to respiratory muscle weakness, and aspiration pneumonia associated with involvement of the striated muscles of the upper esophagus, cricopharyngeus, and hypopharynx. Pulmonary hypertension (PH) has been associated with other autoimmune rheumatic diseases. Though PH has been reported in a few case reports, it has been a hitherto under recognized cause of morbidity and mortality in patients with inflammatory myopathies (IM). We describe demographic and clinical features in patients with IM and PH.

Methods: Retrospective chart review of patients with a diagnosis of PM or DM and PH (based on ICD-9 codes) was performed at a tertiary care center using electronic medical records (EPIC™).

Results: Out of 73 patients with IM and PH, 54 (74%) were female. The mean age at diagnosis of IM was 51 years, and ranged from 18 years to 82 years. Fifty three patients (72.6%) had ILD and 22 (30.1%) were positive for Jo1 antibody. All patients but one were on prednisone. At the time of the study 51 patients (70%) were alive. 54.5% of patients who were deceased had been on warfarin compared to 28% patients that were still alive (p = 0.031). Survival was independent of the presence of ILD. Use of immunosuppressive and vasodilator therapies had no impact on survival. Patients with ILD were more likely to be non-white (p = 0.014) and were significantly younger (p = 0.010). Patients with confirmed ILD (n = 63) were significantly more likely to be female (p = 0.036).

Table 1. Mortality data

Variable	Alive (n = 51)	Dead (n = 22)	p-value
Female	39 (76.5)	15 (68.2)	0.46
Caucasian	33 (73.3)	12 (54.5)	0.12
Anti Jo1 antibody	17 (43.6)	5 (41.7)	0.91
ILD	37 (72.5)	16 (72.7)	0.99
Immunosuppressive	48 (94.1)	19 (86.4)	0.091
Vasodilator	16 (31.4)	7 (31.8)	0.97
Warfarin	14 (28.0)	12 (54.5)	**0.031**
Age at diagnosis	50.5 [41.0, 60.5]	48.0 [34.0, 65.0]	0.74

Table 2. Comparison of patients with and without ILD

Variable	No ILD (n = 20)	ILD (n = 53)	p-value
Female	18 (90.0)	36 (67.9)	0.055
Caucasian	17 (89.5)	28 (58.3)	**0.014**
Anti Jo1 antibody	2 (20.0)	20 (48.8)	0.099
Immunosuppressive	17 (85.0)	50 (94.3)	0.43
Vasodilator	3 (15.0)	20 (37.7)	0.062
Warfarin	8 (40.0)	18 (34.6)	0.67
Age at diagnosis	60.0 [43.0, 74.0]	47.5 [37.0, 58.0]	**0.010**

Conclusion: This is the first study to systematically evaluate the association between PH and IM. It suggests that PH exists in patients with IM even without ILD (isolated PH). There was no difference in mortality in patients with or without ILD. Further prospective studies are needed to evaluate the effects of therapy on progression of PH in patients with IM.

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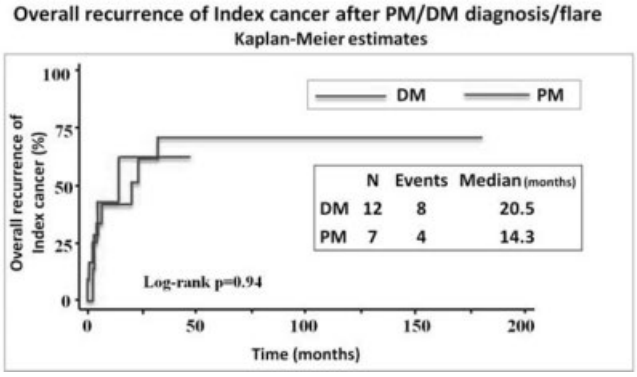
Cancer Associated Myositis: Temporal Relationship, Survival and Risk of Cancer Recurrence. Results From a Large Historical Cohort in United States of America. Christian A. Waimann, Kelechukwu A. Olejeme, Jean H. Tayar, Xiudong Lei and Maria E. Suarez-Almazor. University of Texas. M.D Anderson Cancer Center, Houston, TX

Background/Purpose: There is a well known association between cancer and myositis. However the temporal relationship between myositis and cancer development, and especially cancer recurrence, is still unclear. The aims of our study were to evaluate the temporal relationship between PM/DM and cancer diagnosis or recurrence.

Methods: Using electronic medical records, we identified a cohort of 93 patients with diagnosis of cancer and polymyositis/dermatomyositis (PM/DM) seen at a Comprehensive Cancer Center between 1998 and 2009. PM/DM diagnosis was confirmed using a stepwise procedure: 1st, definitive PM/PM according to Bohan and Peter criteria; 2nd, diagnosis made by a rheumatologist or neurologist; 3rd, full chart review by two rheumatologists. Data collected included: Age, gender, cancer and PM/DM clinical characteristics. Outcomes were: PM/DM flare (Worsening of muscle weakness and/or rash), cancer recurrence (appearance of a disease that was thought to be in remission), and death. The index cancer was defined as the cancer that was diagnosed closest to the DM/PM symptoms. Squamous and basal cells skin cancers in situ were not considered index cancer. The DM/PM diagnosis and the cancer were defined as concurrent if the time interval between the two incidences was within 6 months. Kaplan-Meier product limit method was used to estimate the overall survival (OS) and cancer recurrence outcomes. Groups were compared with the log-rank statistic (PM versus DM). Cox proportional hazards (PH) models were fit to determine the association of DM/PM disease with OS after adjustment for age and gender.

Results: 58 DM and 35 PM were included. Breast cancer was the most frequent cancer (DM 31%; PM 20%), followed by lung cancer (DM 17%; PM 12%). Adenocarcinoma was the predominant histological type (DM 60%, PM 39%). PM/DM diagnosis was concurrent with cancer diagnosis or recurrence in 40% of cases (DM 53%; PM 7%). Fifty seven percent of the PM cases versus 26% of the DM cases were diagnosed before cancer. At the moment of PM/DM diagnosis or flare, 19 patients had their cancer in remission. Sixty three percent of them developed a cancer recurrence within two years, being the first 6 months the higher risk period (Figure 1). There was no difference in OS after cancer diagnosis between PM and DM (mean survival was 5.5 and 3.9 years, respectively; log-rank p=0.96; Hazard ratio DM vs PM= 1.31, IC95:0.7=2.5).



Conclusion: In our knowledge this is the largest cancer associated myositis historical cohort in USA. Polymyositis and Dermatomyositis were concurrent with cancer diagnosis or recurrence in 40% of the cases. Almost half of the patients in remission developed a cancer recurrence within 6 months of PM/DM diagnosis or flare. There was no difference in survival between PM and DM.

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Defining Clinically Relevant Changes in Core Set Activity Measures for Adult and Juvenile Idiopathic Inflammatory Myopathies (IIM). Lisa G. Rider[1], Julia A. Lee[2], Anna V. Jansen[2], Nicola Ruperto[3], Adam M. Huber[4], Chester V. Oddis[5], Brian M. Feldman[6], Peter A. Lachenbruch[7], Rohit Aggarwal[8], Frederick W. Miller[2] and IMACS and PRINTO[9]. [1]NIEHS NIH, Bethesda, MD, [2]NIEHS, NIH, Bethesda, MD, [3]PRINTO-IRCCS, Genova, Italy, [4]Dalhousie University, Halifax, NS, [5]University of Pittsburgh, Pittsburgh, PA, [6]The Hospital for Sick Children, Toronto, ON, [7]Corvallis, OR, [8]University of Pittsburgh Medical Center, Pittsburgh, PA, [9]Bethesda

Background/Purpose: Both PRINTO and IMACS have established core set measures for assessment of patients with IIM in therapeutic trials, and developed preliminary definitions of improvement combining these. Our aim was to revisit the degree of clinically meaningful change and importance of each measure in defining clinically important change, as well as to define changes in these measures that represent moderate and major degrees of improvement.

Methods: Twenty-nine pediatric and 21 adult rheumatologists and neurologists experienced in the care of IIM patients and the myositis core set measures completed a Delphi questionnaire regarding the amount of change in each core set domain deemed to be clinically significant in a trial setting.

Results: Adult and pediatric specialists provided the percentage change in each core set domain in order to classify an IIM patient as minimally, moderately and majorly improved (see Table), with general agreement between the pediatric and adult specialists. Both groups required greater change in enzyme values, and pediatric specialists also suggested slightly greater degrees of change for patient global activity and physical function. Muscle strength was ranked as the most important core set measure, followed by MD Global Activity, and there was a suggestion that additional weight of 1.5–2 fold be given to both these measures in a definition of improvement or of moderate and major response. Both groups preferred a definition based on percentage change, or one that combined percentage with absolute change. Both adult and pediatric specialists suggested 2–4 measures be required to improve for the patient to be considered improved, except both groups preferred improvement in up to 5 measures for a major degree of change. More than 80% of participants felt that muscle strength and MD Global Activity must improve for the patient to be considered clinically improved, whereas for major improvement, physical function also has to improve in adults and extra-muscular activity in pediatric patients. Deterioration of a small degree (≤ 20%) would be allowable in 1or 2 measures, but for major change no more than 1 measure may worsen, which cannot be MD Global Activity for pediatric or muscle strength for adult myositis patients.

Conclusion: These data, along with these specialists' ratings of adult and juvenile IIM patient profiles, will be used to revise the definitions of improvement for adult and juvenile myositis, and to guide the development of new criteria for moderate and major degrees of improvement.

Core Set Domain (% Change, Median)	Minimum Percent Change (Median)		Moderate Percent Change (Median)		Major Percent Change (Median)	
	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric
Physician global activity assessment	20.0	20.0	30.0	40.0	50.0	60.0
Patient global activity assessment	20.0	25.0	30.0	40.0	50.0	60.0
Muscle strength (MMT or CMAS)	20.0	20.0	30.0	30.0	50.0	50.0
Physical function ([C]HAQ)	20.0	27.5	30.0	40.0	50.0	60.0
Extra-skeletal muscle disease activity	20.0	20.0	30.0	30.0	50.0	50.0
Laboratory Enzymes (CK, LDH, AST, ALT)	30.0	30.0	40.0	50.0	60.0	70.0
CHQ Physical Score (HR-QOL)	NA	22.5	NA	40.0	NA	55.0

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Fatigue In IDIOPATHIC Inflammatory Myopathy (IIM): Prevalence, IMPACT and ASSOCIATION with QUALITY of LIFE. Richard CJ Campbell[1], David L. Scott[1], Patrick D. Kiely[2] and Patrick Gordon[1]. [1]King's College London, London, United Kingdom, [2]St. Georges Hospital, London, United Kingdom

Background/Purpose: Fatigue is common and has a major impact on quality of life in RA and SLE. The prevalence, severity and association with quality of life have not previously been evaluated in IIM.

Methods: 95 patients with dermatomyositis and polymyositis were recruited from 3 South London teaching hospitals. To assess the importance of fatigue, patients were first asked to rate 7 typical IIM symptoms (pain, weakness, fatigue, daily functioning, sleep, memory, gastrointestinal upset) in the order of impact on their quality of life. Patients also rated each symptom on a severity scale out of 6. Fatigue was then measured using 3 generic tools (FACIT-F, fatigue severity scale (FSS) and the vitality component of SF-36). Assessments were repeated in one quarter of patients to evaluate test-retest reliability and for comparison with age, gender and ethnicity matched healthy controls (t tests, $p<0.05$). Quality of life was measured with the SF-36 questionnaire. Spearman's correlation ($r>0.6$, $p<0.05$) evaluated fatigue against domains of quality of life. Patients were compared with population normative data for healthy patients using t tests ($p<0.05$).

Results: 89% patients had fatigue (FSS score >3). Mean fatigue was consistently high for each measure: FACIT-F 25/52 (SD 13.3); FSS 5.42/7 (SD 4.2); SF-36 vitality 40.0/100 (SD 22.13) and more than the healthy controls (FACIT-F 47.68; FSS 1.67; SF36 vitality 83.23; $p<0.001$). There was good agreement between the scales in test-retest. FACIT-F correlated with FSS ($r=0.7$; $p<0.05$) and SF36 vitality scores ($r=0.8$; $p<0.05$). 28% of respondents reported fatigue as the symptom that most impacted on their quality of life; more than any other symptom (weakness 10%, pain 21%, physical function limitation 15%, sleep 16.3%, memory and concentration 2.5% and digestive 6.3%). Mean symptom severity (3.9/6) was greater for fatigue than any other symptom. SF-36 was lower across all domains when compared with normative UK population and the healthy controls. SF-36 showed association with FACIT-F in univariate regression across all SF-36 domains ($p=0.000$).

Conclusion: Fatigue is common in IIM and impacts on quality of life more than any other typical IIM symptom. It is also highly associated with poor quality of life. If there is a causal relationship between fatigue and quality of life, the symptom may contribute to the high morbidity associated with IIM and should be a focus for further evaluation.

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Fatigue In Idiopathic Inflammatory Myopathies (IIM) Is Not Caused by Peripheral Muscle Fatigability: Studies of Non-Volitional Quadriceps Muscle Endurance Using Repetitive Transcutaneous Stimulation. Richard CJ Campbell, Ged Rafferty, David L. Scott, Charles Rielly, Katie Ward and Patrick Gordon. King's College London, London, United Kingdom

Background/Purpose: Muscle endurance is the decline of capability of skeletal muscle to generate force with repeated activation. Fatigue is a major problem in patients with IIM. However, the relative contribution of peripheral and central factors is not known. Poor muscle endurance is likely to be a key peripheral factor. We used validated non-volitional techniques to repetitively stimulate quadriceps muscle trans-cutaneously to compare muscle endurance between IIM patients and controls. We also assessed whether there is a relationship between self-reported fatigue and muscle endurance.

Methods: Endurance Protocol: the quadriceps was stimulated repeatedly at a fixed voltage for 3 minutes (250ms on, 750ms off with a pulsed current, frequency of 30Hz). The force generated by each quadriceps contraction (Kg) was recorded throughout. Voltage was set to generate a starting contraction of 30% maximal voluntary contraction (MVC). This standardised participants for weight and strength. Self-reported fatigue was measured using the FACIT-F questionnaire. We compared mean time for initial starting force to decline to 70% between patients and controls (unpaired t tests). We also investigated whether this correlated with fatigue (FACIT-F) using Spearman's correlation.

Results: We compared 20 IIM patients (16 dermatomyositis and 4 polymositis; 10 females, 10 males) with age and sex matched controls. Fatigue measured by FACIT F and FSS was significantly reduced in the patients (table). Quadriceps power was also significantly reduced in the patients. In contrast, the endurance protocol showed no difference in the time taken to reach 70% of starting force between the patients and controls. Using Spearman's correlation, we found no relationship between measures of

fatigue (FACIT-F and FSS) and quadriceps endurance or quadriceps MVC in IIM patients.

	Patients	Controls	p
Number	20	20	
Gender/Ethnicity	10F, 10M 15 White, 5 Black	10F, 10M 17 White, 3 Black	
Mean Age (SD)	53.9 (9.78)	51.3 (8.43)	0.37
Mean FACIT-F (SD)	31 (10.26)	46 (11.90)	<0.05
Mean FSS (SD)	4.1 (1.75)	1.2 (1.28)	<0.05
MVC (Kg) (SD)	26.7 (8.82)	36.2 (7.04)	<0.05
Time to decline to 70% initial force (SD)	64.6 (17.76)	61.1 (18.25)	0.55

Conclusion: Patients with IIM have more fatigue and greater muscle weakness than matched controls. However, they show physiologically normal muscle endurance. Muscle endurance and muscle strength are also unrelated to fatigue which is almost certainly driven by central mechanisms in IIM. The impact of IIM on muscle strength over muscle endurance may influence types of rehabilitation programs offered for IIM.

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Predictors of Experienced Fatigue in Idiopathic Inflammatory Myopathy (IIM): Psychological Factors and Pain Are More Predictive Than Disease Activity, Damage or Strength. Richard CJ Campbell[1], David L. Scott[1], Patrick D. Kiely[2] and Patrick Gordon[1]. [1]King's College London, London, United Kingdom, [2]St. Georges Hospital, London, United Kingdom

Background/Purpose: To evaluate the relationship the between experienced fatigue and a range of potential associations. Clinical (including disease activity/damage), psychological and demographic factors were assessed prospectively in a large South London population of patients with IIM.

Methods: A total of 95 patients (64.3% female, 32.7% male) with IIM attending outpatients clinics at 3 South London teaching hospitals were recruited. Experienced fatigue was measured using Functional Assessment of Chronic Illness Therapy for Fatigue (FACIT-F) and the fatigue severity scale (FSS). Other concurrent measurements included: manual muscle testing (MMT/260), health assessment questionnaire (HAQ-DI), haemoglobin, erythrocyte sedimentation ratio (ESR), creatinine kinase (CK), current prednisolone dose, the hospital anxiety and depression scale (HADS), visual analogue scales (VAS) for global health and pain, and the IMACS core data set for disease activity and damage. Outcomes were assessed for degree of association with fatigue in uni-variate regression ($p<0.05$). Backward stepwise multivariate regression models were developed with fatigue as the dependent variable. Co-linearity between variables was taken into account before modelling.

Results: Pain, disease duration, CK or prednisolone dose were not predictive of fatigue in uni-variate regression. Factors moderately predictive of fatigue ($r^2>0.3$; $p<0.05$) included: HADS anxiety, HADS depression and HAQ. Factors with small predictive value ($r^2>0.1$; $p<0.05$) for fatigue included: Haemoglobin, VAS-pain, VAS-global health, MMT/260 and summary measures of disease damage (MDI severity %, MDI extent %, MDI severity muscle) and activity (MYOACT%). In multivariate modelling, 68% of the variance in fatigue was explained by HADS depression, VAS pain, haemoglobin and severity of muscle damage index. The strongest contributions came from depression and pain. MMT/260, MYOACT% and the other measures of disease damage were no longer statistically significantly predictive of fatigue in multiple regression modelling. HAQ was co-linear ($r>0.5$) with HADS, so was not included in multivariate models.

Conclusion: In IIM, psychological factors and pain are predictive of fatigue. However, disease activity, damage and strength show much weaker relationships. It is not known whether there is a causal relationship between depression, pain and fatigue in IIM. An interventional study treating pain and depression while measuring changes in fatigue is needed.

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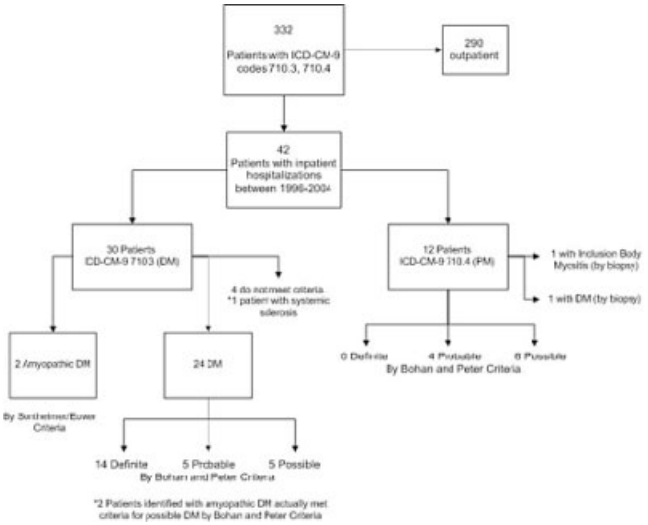
International Classification of Diseases-Clinical Modification-9 Codes for the Diagnosis of Dermatomyositis and Polymyositis in Discharge Summaries: Evidence of Acceptable Validity. Neera Narang[1], David Fiorentino[2], Eswar Krishnan[3] and Lorinda Chung[4]. [1]Stanford Univ Medical Center, Stanford, CA, [2]Stanford, Stanford, CA, [3]Stanford University, Stanford, CA, [4]Stanford Univ Medical Center, Palo Alto, CA

Background/Purpose: Dermatomyositis (DM) and polymyositis (PM) are rare autoimmune diseases classically characterized by muscle inflammation. Epidemiologic studies using large administrative and hospitalization databases rely on the accuracy of the International Classification of Diseases-Clinical Modification-9 (ICD-CM-9) codes for case definitions. The purpose of this study is to evaluate the accuracy of ICD-CM-9 codes for DM and PM in hospital discharge summaries.

Methods: We identified all patients in the Stanford Hospital and Clinics database who had the ICD-CM-9 codes for DM (710.3) and PM (710.4) associated with any clinical encounters during the years 1996–2004. Of those, only patients who had hospital discharge summaries with any mention of these ICD-CM-9 codes were included in our study. We then performed a comprehensive medical record review of both inpatient and outpatient medical records to determine the proportion of patients who fulfilled accepted classification criteria for the diagnosis of DM and PM. Bohan and Peter criteria was used to classify patients as definite, probable, and possible DM or PM. Patients with clinically amyopathic DM were evaluated using the Sontheimer/Euwer criteria.

Results: A total of 332 patients with the ICD-CM-9 codes 710.3 and 710.4 were identified in the Stanford Hospital and Clinics database. 42 of these patients had inpatient hospitalizations between 1996–2004. 30 patients had ICD-CM-9 code 710.3 (DM) and 12 had ICD-CM-9 code 710.4 (PM). Of the 30 patients with ICD-CM-9 code 710.3, 24 (80%) fulfilled Bohan and Peter criteria for DM (14 definite, 5 probable, 5 possible). Of these, 8 had muscle biopsies consistent with DM. 2 additional patients met Sontheimer/Euwer criteria for amyopathic DM. 1 of the 4 patients who did not fulfill criteria for DM actually met ACR criteria for systemic sclerosis. 10 of 12 (83%) patients with ICD-CM-9 code 710.4 met Bohan and Peter criteria for PM (0 definite, 4 probable, 6 possible), however, only 2 patients had muscle biopsies consistent with PM, and 1 of the "probable" patients had a biopsy more consistent with rhabdomyolysis. The 2 other patients with 710.4 coding actually had DM and inclusion body myositis as verified by muscle biopsy.



Conclusion: Our study suggests that ICD-CM-9 codes of 710.3 and 710.4 used for coding discharge summaries are ≥ 80% accurate in identifying cases of DM and PM, respectively, who fulfill currently accepted classification criteria for at least possible disease.

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Body Mass Index At Diagnosis Affects Disease Course In Juvenile Dermatomyositis. Anjali Patwardhan[1], Gloria Higgins[2], Charles H. Spencer[1] and Robert M. Rennebohm[3]. [1]Nationwide Childrens Hospital, Columbus, OH, [2]PRCSG, Columbus, OH, [3]Columbus Childrens Hospital, Columbus, OH

Background/Purpose: Pediatric obesity is increasing at an alarming rate. It is well known that obesity predisposes joints and bones to mechanical stress and increases musculoskeletal problems. Adipose tissue is considered an endocrine organ. Adipocytes secrete cytokines including TNF-α and IL-6, causing systemic inflammation and immune dysregulation. Obesity alters drug pharmacokinetics and affects drug dosing, blood levels and volume of distribution, possibly affecting efficacy of treatment. Obese persons may have altered sensitivity and response of the hypothalamic-pituitary-adrenal axis. Obesity also leads to a change in ACTH-mediated response to steroids, a category of drug commonly used in rheumatic diseases. We investigated the hypothesis that obesity at

diagnosis alters the disease course, response to treatment, and complication rate in juvenile dermatomyositis (JDM).

Methods: Institutional Review Board approval was obtained to retrospectively review the charts of 73 patients with JDM seen in pediatric rheumatology clinic at Nationwide Children's Hospital over the past 23 years by pediatric rheumatologists. Data on treatment and outcomes were collected up through the last clinic visit, or July 30, 2010, whichever came first. Body mass index (BMI) was calculated using 'Centers for Disease Control and Prevention—BMI calculator for children and teenagers'. We used the Wilcoxon two-sample test to compare numerical variables between the group of patients who were obese (BMI >85th percentile) and the group who were non-obese (BMI ≤85th percentile) at their initial visit. We used logistic regression to compare categorical variables between obese and non-obese groups in SAS 9.2

Results: Patient age ranged from 0–18 years. 28 patients had age- and sex-specific BMI ≥ 85th percentile, and 45 had < 85th percentile at disease onset. Average BMI of obese patients was 93rd percentile and of non-obese patients was 46th percentile. Comparatively fewer patients in the obese group received corticosteroid pulses at diagnosis (p=0.04) and developed osteonecrosis (p=0.030). Comparatively more patients in the obese group had elevated muscle enzymes at 12 months (p=0.027), developed calcinosis (p=0.03), received methotrexate for a longer time (p=0.040), continued to take steroids at last follow up (p=0.028), and continued to have active disease at 3 years (p=0.039), 5 years (p=0.039), and 10 years (p=0.027) following diagnosis.

Conclusion: JDM patients who were obese at diagnosis (BMI > 85th percentile) were less likely to receive pulse corticosteroids and had a lower incidence of osteonecrosis. On the other hand, they were more likely to have a chronic continuous and prolonged disease course, and calcinosis. It is not clear if these differences were related to treatment choices, or to metabolic differences in the two groups such as secretion of pro-inflammatory cytokines by adipose tissue, alteration of pharmacokinetics of medications, or altered sensitivity and response of the hypothalamic-pituitary-adrenal axis including response to corticosteroids in obese patients.

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Juvenile Dermatomyositis Is a Different Disease In Children up to Three Years of Age At Onset Than In Children Above Three Years At Onset. Anjali Patwardhan[1], Charles H. Spencer[1], Gloria Higgins[2] and Robert M. Rennebohm[3]. [1]Nationwide Childrens Hospital, Columbus, OH, [2]Nationwide Childrens Hospital, Columbus, OH, [3]Columbus Childrens Hospital, Columbus, OH

Background/Purpose: Juvenile Dermatomyositis (JDM) is a different disease than dermatomyositis in adults in many ways including more vascular inflammation and vasculopathic thrombosis as previously described. We tested the hypothesis that juvenile dermatomyositis (JDM) disease course in children with disease onset at or below age three years may be different than that of children with disease onset at greater than three years of age.

Methods: Institutional Review Board approval was obtained to retrospectively review the charts of 78 patients from age 0–18 years with JDM seen in pediatric rheumatology clinic at Nationwide Children's Hospital over the past 23 years the diagnosis was made by the treating pediatric rheumatologist. Not all the patients met the Bohan and Peter criteria, as muscle biopsy and EMG were not always performed. The data regarding disease course and outcome were collected as of the last clinic follow-up. Wilcoxon 2-sample test and Chi-square test and Fisher's exact test were used to compare continuous variables and categorical variables respectively.

Results: The mean times between onset of symptoms to diagnosis in younger and older age groups were 5.6 months and 4.5 months, respectively. The younger onset group had more females (p=0.05) and their disease onset occurred less frequently during the typical winter-spring seasons (p = 0.031). The younger onset group was more likely to have a preceding fever (p=0.029) and family history of autoimmune diseases (p=0.012). The younger onset group was less likely to have heliotrope rash (p=0.04), Gottron's sign (p=0.049), capillary loop abnormalities (p=0.010), or creatinine kinase (CK, p=0.022), aspartate aminotransferase (AST, p=0.021) and aldolase (p=0.035) elevations. The younger children were more likely to have atypical histopathology (p=0.02) at presentation. The younger onset group was treated less often with pulse methylprednisolone at diagnosis (p=0.043) and less often with hydroxychloroquine (p=0.035). The mean (p=0.06) and maximum (p=0.002) duration of methotrexate therapy, and the mean (p=0.06) and maximum (p=0.016) duration of oral steroid therapy, was shorter in the younger group. Younger age group patients were more likely to experience a monocyclic course (p=0.027) and less likely to have active disease at 5 (p=0.017) and 10 years post diagnosis (p=0.019). The younger patients were less likely to have osteonecrosis (p=0.023) and more likely to die of their disease

Conclusion: There were significant differences between JDM patients with disease onset at or below age three years, compared to their older counterparts. Younger patients in our cohort had fewer typical findings at diagnosis. They were more likely to experience a monocyclic course, a shorter and milder total disease course, and a shorter maximum duration of oral steroid and methotrexate therapy. Younger patients had predominantly monocyclic disease, and a lower proportion had active disease at 5 and 10 years. In spite of having milder disease course, patients with younger onset had a higher mortality rate and a similar complication rate compared to the older onset patients, except for osteonecrosis which was higher in the older onset group

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Comparison of Untreated Adult and Juvenile Dermatomyositis Muscle Biopsies: Difference of Inflammatory Cells Phenotyping. Samuel K. Shinjo[1], Adriana M. Sallum[2], Clovis A. Silva[1] and Suely K. N. Marie[3]. [1]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo-SP, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo (FMUSP)., São Paulo, Brazil

Background/Purpose: Inflammatory cell phenotyping in muscle fibers have been described in adult (ADM) and juvenile (JDM) dermatomyositis. Nevertheless, this alteration has not been systematically and simultaneously assessed and compared in both ADM and JDM untreated groups in a large series. Therefore, the aim was to study the cell phenotyping and MHC I and II expressions in muscle samples of untreated ADM and JDM patients, and to correlate with laboratory and clinical features.

Methods: Twenty-eight untreated ADM and 28 JDM patients, fulfilling Bohan and Peter criteria, diagnosed from 1990 to 2010, were included in this study. Routine histochemistry and immunohistochemistry (CD20 and CD68 (LSB+ system); CD4 and CD8 (EnVision-AP technique); MHC I and II (StreptoABComplex/HRP, Dakopatts)) were performed on serial frozen muscle sections. Each biopsy specimen was coded and analyzed independently by two investigators (SKS and AMES). The pathology readers were blinded to diagnosis and clinical status when the biopsies were evaluated. Inflammatory cell phenotyping was analyzed quantitatively in endomysial, perimysial, perivascular (endomysial and perimysial) areas in 10 fields (200x). Expressions of MHC I and II were assessed as negative or positive stained fibers.

Results: The mean age at disease onset was 42.0±15.9 and 7.3±3.4 years in ADM and JDM, respectively, whereas the symptoms duration before muscle biopsy were similar in both groups (9.4±11.1 and 11.3±16.0 mo, p=0.616). No statistical differences were observed regarding gender, ethnicity, frequency of constitutional symptoms and organ involvements (cutaneous, articular, pulmonary, cardiac or gastrointestinal) (p>0.050), except for the higher CK levels observed in ADM (CK: 3820.0±5332.3U/L *vs*. 1150.7±1332.3, p=0.024). The CD4 and CD8 positive cells distributions were similar in both groups in all analyzed area. The CD20 positive cells was predominantly observed in endomyosial (p=0.012) and perivascular perimysial (p=0.034) of ADM, whilst the CD68 positivity was mainly in all muscle specimen areas of ADM (p<0.001). The frequency of MHC I expression in fibers membrane (50.0 *vs*. 96.4%, p<0.001) was significantly higher in JDM than ADM, whereas MHC II expression was lower (50.0 *vs*. 14.3%, p=0.020). Additionally, all immunohistoquemical analyses were not correlated with demographic data, as well as with clinical and laboratorial features, including CK levels before muscle biopsy (p>0.050).

Conclusion: Different cells phenotyping of muscle biopsies were observed in the onset of two relevant inflammatory myopathies. Macrophages and B lymphocytes expressions in muscle fibers were a premature marker of ADM, whereas the MHC I expression in muscle fibers were evidenced in JDM.

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Pulmonary Function Tests in Idiopathic Inflammatory Myopathy: Association with Clinical Parameters. Adrienne Prestridge[1], Gabrielle Morgan[1], Deli Wang[2] and Lauren M. Pachman[3]. [1]Children's Memorial Hospital, Chicago, IL, [2]Northwestern University's Feinberg School of Medicine, Chicago, IL, [3]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: In adult idiopathic inflammatory myopathy (IIM), pulmonary involvement is found in close to half of patients[1] and many clinicians recommend routine screening with pulmonary function tests (PFTs).[2] Pulmonary involvement in children with IIM ranges from 18–50%, depending on the definition utilized.[3] Loss of core strength is a major component of JDM weakness. PFTs in juvenile dermatomyositis (JDM), when abnormal, are restrictive with a decreased diffusing capacity (DLCO) and have been shown to be associated with abnormal high resolution computed tomography of the chest (HRCT).[4] Correla-

tion with clinical disease parameters has not been well studied. The purpose of this investigation was to determine the association of abnormal lung function in pediatric patients with IIM with selected clinical parameters.

Methods: This is a cross-sectional study of children with a diagnosis of IIM between the ages of 5 and 21 years, who were seen for clinical care at the Children's Memorial Hospital. Those children who performed a PFT, between the years 2008 and 2011 were selected for study. Clinical parameters evaluated included: age at time of PFT, age at diagnosis, gender, ethnicity, myositis specific and associated antibodies (MSA/MAA), child myositis assessment scale (CMAS), Nailfold End Row Loop (ERL), Disease Activity Score (DAS) for muscle weakness, duration of untreated disease (DUD), muscle enzymes--including CPK, aldolase, SGOT, LDH—neopterin, Von-Willebrand Factor Antigen and flow cytometry. Comparisons were made between groups using Wilcoxon Rank Sum test for continuous variables and Chi square or Fisher exact test for dichotomous variables. We received IRB approval for this retrospective study.

Results: PFTs were considered abnormal if their total lung capacity (TLC) or DLCO was <80% predicted. Eighty five patients were included in the study, 39 with JDM, 7 with juvenile polymyositis, 38 with overlap syndromes and one with nonspecific myositis. PFTs revealed 24% of patients had decreased TLC and 31% of patients had decreased DLCO. Clinical parameters that differed in patients with either an abnormal TLC or DLCO, included race, MSA/MAA (PMScl, SCl 70), DUD, DAS for muscle and aldolase. Significant differences in patients with an abnormal TLC also included age at time of PFT, age at diagnosis, MSA/MAA (Ro), CPK and CMAS items 6, 10 and 12. Significant differences in patients with an abnormal DLCO included gender, race, MAS (U1RNP, U2RNP), neopterin and CMAS items 1 and 3.

Conclusion: Assessment of PFTs in children with IIM should be considered, since up to a third of patients have abnormalities. Concern for pulmonary involvement should be increased in patients with worse DAS for muscle strength and longer DUD. The identification of particular MSA/MAAs should also increase the requirement for screening for pulmonary complications of IIM. Further research is needed to determine which pediatric patients should be screened with PFTs in order to limit the associated morbidity secondary to pulmonary complications in IIM.

Supported by NIH/NINR 1R01NR012692 & CureJM (LMP)

1. Marie *Arthritis Rheum* 2002
2. Connors *Chest* 2010
3. Morinishi *ModRheumatol.* 2007
4. Sanner *Ann Rheum Dis.* 2011

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Increased Depression and Anxiety Symptoms in a Group of Dermatomyositis Patients. Elizabeth Ghazi[1], Mitchel A. Kling[2], Kathleen Propert[3], Joyce Okawa[4] and Victoria P. Werth[4]. [1]UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ, [2]Philadelphia Veterans Affairs Medical Center and University of Pennsylvania, Philadelphia, PA, [3]University of Pennsylvania, Philadelphia, PA, [4]Perelman School of Medicine at the University of Pennsylvania and Philadelphia V.A. Medical Center, Philadelphia, PA

Background/Purpose: Mood has never been studied in dermatomyositis (DM), a condition that can impact the skin, muscles, and other organs. However, it has been shown that DM patients have significantly lower quality of life (QOL) compared to other illnesses. This study compared the levels of depression, anxiety, and stress symptoms in the DM population to that of the general population. It hypothesized that facial involvement, skin damage, and muscle pain would lead to poorer mood scores and that mood scores would be highly associated with QOL scores.

Methods: This cross-sectional study evaluated depression using the following validated, self-report measures: the Patient Health Questionnaire 9 (PHQ-9) and the Depression Anxiety and Stress Scales 21 (DASS-21)-depression sub-scale (DASS-D). The DASS-21 anxiety and stress sub-scales (DASS-A and DASS-S) were used to look at anxiety and stress levels. The PHQ-9 functions as a screen, diagnostic tool, and determinant of severity, while the DASS-21 measures dimensions of mood. Skin severity was determined by the validated Cutaneous Dermatomyositis Disease Severity Index (CDASI) activity and damage scores. QOL was assessed with the validated skin-specific QOL measure, the Skindex-29. Eligible subjects required a diagnosis of DM and were seen between March and June of 2011 in Penn's autoimmune skin disease clinic. The DM group's PHQ-9 scores were compared to historic controls using a chi square test, with cut- off scores for mild and moderate to severe depression being 5 and 10, respectively. The DM group's DASS-21 median sub-scores were compared to historic controls using a Wilcoxon signed-rank test. Spearman's correlations were conducted between the mood measures and skin severity, including facial and overall skin activity and damage, and Skindex-29 scores. A point bi-serial correlation was conducted between the mood measures and the absence or presence of muscle pain.

Results: Of the 34 eligible patients, 12 of the 34 DM patients (35%) had a PHQ-9 score of 5 or greater. Of these patients with depressive symptoms, 66% had mild symptoms (score of 5–9) and 34% had moderate to severe symptoms (≥10). The DM group had a significantly greater proportion of depression versus controls using the 5 point cut-off (X^2= 4.97, p=0.03), but not when using the 10 point cut-off (X^2=1.32, p=0.25). DASS-A and DASS-D medians were significantly different from controls (W=271, p=.002; W=214, p=0.02), while the DASS-S median was not. DASS-A, DASS-D, and PHQ-9 scores all correlated with muscle pain (rpb= 0.48, 0.53, and 0.47, p=0.004, 0.001, and 0.005, respectively). The PHQ-9 and all DASS sub-scales correlated significantly with all sub-scales of the Skindex-29.

Conclusion: DM patients have more mild depressive symptoms than the general population, but similar rates of moderate to severe depression. DM patients experience more anxiety symptoms than controls. The presence of muscle pain may contribute to poorer mood. Skin specific QOL measures and mood measures are highly associated, possibly because the impact of skin disease activity on QOL mediates mood.

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R577X Alpha-Actinin 3 *ACTN3)* polymorphism Is Associated with Inflammatory Myopathies in Mexican population. Flavio Sandoval-Garcia[1], Marcelo Petri[2], Miguel A. Saavedra[3], Claudia Cruz-Reyes[4], Luis Jara-Quezada[3], Ingrid Dávalos[5], Mario Salazar-Páramo[6], Ivan Gámez-Nava[7], Laura Gonzalez-Lopez[8], Trinidad García-Iglesias[9], Esther Corona-Sánchez[10], Soraya Zavaleta-Muñiz[11], Raúl Vargas-Ramírez[10], Jorge Aguilar Arreola[12], Monica Vázquez-Del Mercado[11] and Beatriz T. Martín-Márquez[13]. [1]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, Mexico, [2]Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, Mexico, [3]Centro Medico La Raza Instituto Mexicano del Seguro Social Mexico D.F., México D.F., Mexico, [4]Centro Medico La Raza Instituto Mexicano del Seguro Social Mexico D.F., Mexico D. F., Mexico, [5]Departamento de Biologia Molecular y Genomica, Instituto de Genetica Humana, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, Mexico, [6]Departamento de Fisiología, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, Mexico, [7]Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, México, Mexico, [8]Hospital Regional de Zona 110, Instituto Mexicano del Seguro Social (IMSS), Guadalajara, Jalisco, Mexico, Guadalajara, Jalisco, Mexico, Mexico, [9]Laboratorio de Inmunología, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, Mexico, [10]Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Universidad de Guadalajara, Guadalajara, Jalisco, México, Mexico, [11]Universidad de Guadalajara, Guadalajara, Jalisco, México, Mexico, [12]Hospital Civil JIM, [13]Universidad de Guadalajara, Gudalajara, Jalisco, México, Mexico

Background/Purpose: Inflammatory myopathies (IM) such as Polymyositis (PM) and Dermatomyositis (DM) are characterized by muscle damage and proximal muscle weakness. The muscle are enriched by alpha-actinins (ACTN) that are cytoskeletal proteins which encode a spectrin superfamily genes tissue–specific for myocardial diseases: *ACTN1* and muscle tissues (*ACTN2*, *ACTN3*). The function of ACTN heterodimers is to cross-link and bind actin, along with preserving spatial association among myofilaments. ACTN3 expression is restricted to type II fibers (100% of type IIb/x fibers and 50% of type IIa). The *ACTN3* gene is located in the region 11q13–14 and in normal conditions, translates a 901 aminoacid protein. The R577X *ACTN3* polymorphism is characterized by a non sense polymorphism resulting in the replacing of Arginine (R) by a premature stop codon (X) in the exon 16 (R577X). The homozygous XX are associated with incomplete translation resulting in lost of function of ACTN3. The R577X *ACTN3* R allele is related with strength and power muscle phenotype and the X allele is associated with endurance. Since muscle weakness is a common feature in IM, the aim of this study was to analyze the influence of the R577X *ACTN3* polymorphism in a group of Mexican patients with PM/DM.

Methods: 37 patients with Dermatomyositis (DM)/ Polymyositis (PM) and 85 healthy subjects were analyzed using PCR-RFLP for the R577X *ACTN3* polymorphism. Genotypes and alleles were analyzed. Enzymes such as CPK, LDH, AST and ALT were taken at diagnosis and recruitment to the study.

Results: We found that 36% XX of healthy subjects were polymorphic

for the R577X *ACTN3* polymorphism (18% RR and 46% RX) compared with 70% of R577X *ACTN3* polymorphic in IM (70% XX, 6% RR and 24% RX). The R allele was present in 41% and X in 59% in healthy subjects compared with 18% of the R and 82% X allele within the IM group ($p<0.001$). The polymorphic allele X, is associated with the group of IM. Although, within patients with IM, the cases carrying XX genotype had lower levels of enzymes such as CPK, AST and ALT ($p<0.01$, $p<0.01$ and $p<0.05$ respectively) compared with RX genotype.

Conclusion: In our study since 70% of IM patients were carriers of the R577X *ACTN3* polymorphic XX genotype, the lack of the protein could be a genetic factor that facilitates the muscle weakness and poor muscle resistance, besides the inflammatory damage mediated by the immune system itself.

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Incidence and Prevalence of Idiopathic Inflammatory Myopathies in South Australia: A 30-Year Epidemiologic Study of Biopsy-Proven Cases. Ju Ann Tan[1], Peter J. Roberts-Thomson[2], Peter Blumbergs[3], Paul Hakendorf[4], Sally R. Cox[1] and Vidya Limaye[5]. [1]SA Pathology/Flinders Medical Centre, Adelaide, Australia, [2]Flinders Medical Centre, Adelaide, Australia, [3]Institute of Medical and Veterinary Sciences, Adelaide, Australia, [4]Flinders University, Adelaide, Australia, [5]Royal Adelaide Hospital, Adelaide, Australia

Background/Purpose: Idiopathic Inflammatory Myopathies (IIM) is a heterogenous group of autoimmune muscular disorders characterised by progressive proximal muscle weakness and inflammatory changes on muscle histology. Epidemiological data on IIM have been variable due to its rarity and heterogeneity. We aim to describe the epidemiology of a homogenously-defined population of biopsy-proven IIM in South Australia (SA).

Methods: Cases of IIM (Dermatomyositis DM, Polymyositis PM, Inclusion Body Myositis IBM) were ascertained by review of all muscle biopsy reports from the Neuropathology Laboratory, Hanson Institute from 1980–2009. All adult muscle biopsies in SA are reported in the same laboratory under the purview of an expert neuromuscular histopathologist, therefore minimizing inter-laboratory or inter-pathologist variability. Clinical correlation using the Bohan and Peter criteria was determined by review of patient medical records. The data collected was analysed for descriptive epidemiology. Binary data was tested for differences using the Pearson's chi-square test whereas continuous data was tested with the t-test. SA population denominator numbers were obtained from the Australian Bureau of Statistics.

Results: 352 biopsy-proven cases of IIM were identified between 1980–2009. The overall annual incidence of IIM appeared to be rising with a mean incidence of 8.0×10^{-6} (95% CI 7.2–8.9). This corresponded with an increasing annual incidence of IBM (*Fig 1)*. The mean incidence of DM is 1.0×10^{-6} (95% CI 0.8–1.4), PM 4.1×10^{-6} (95% CI 3.6–4.8) and IBM 2.9×10^{-6} (95% CI 2.4–3.4). We observed an IBM prevalence of 50.5 cases per million population in 2009 (95%CI 40.2–62.7). A female preponderance was noted in both DM (F:M = 2.75:1) and PM (F:M = 1.55:1) but gender distribution was almost equal in IBM (F:M = 1.1:1). Mean age at diagnosis for IBM (67.5 years) was higher than for DM (55.1 years) and PM (59.0 years). A higher proportion of DM patients reported urban dwellings and DM patients tended to be predominantly professionals.

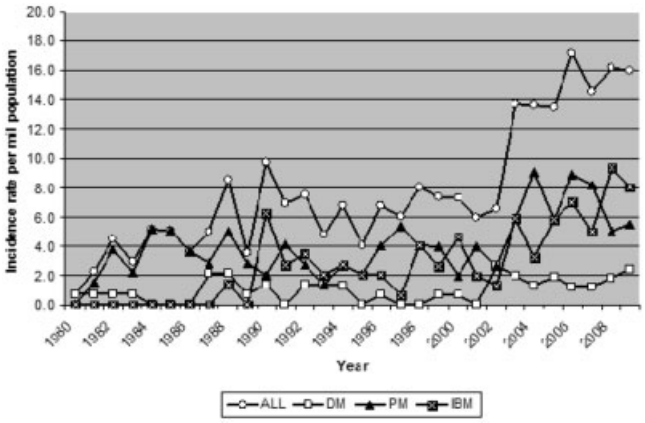

Figure 1. Annual incidence rates for all IIM cases and subsets from 1980–2009 in South Australia

Conclusion: The overall incidence of IIM is rising in SA, particularly for IBM and the prevalence of IBM is one of the highest reported to date. This may reflect an increase in the number of biopsies performed, improved histological techniques or a genuine increase in incidence.

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Epigenetic Control of Muscle Repair Identified in Inflamed Muscle Biopsies From Untreated Juvenile Dermatomyositis. Min Wang[1], Hehuang Xie[1], Peter Hendrickson[1], Sheela Shrestha[1], Simone Treiger Sredni[2], Gabrielle Morgan[1] and Lauren M. Pachman[2]. [1]Children's Memorial Hospital, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: A major barrier in characterizing disease severity in order to provide effective therapy for children with Juvenile Dermatomyositis (JDM) and other Idiopathic Inflammatory Myopathies (IIM) is the lack of accessible biomarkers and prognostic indicators of disease outcome, including the child's capacity to repair damaged muscle. In JDM, the duration of untreated disease, (DUD) alters both phenotype and genotype of the child. As an important gene regulatory mechanism, DNA methylation is an essential component of normal development, and participates in the tissue's response to inflammation and disease progression, but its role in JDM has not yet been explored.

Objectives: To profile the methylation patterns in a cohort of children with IIM in order to determine the impact of methylation alterations in JDM, Polymyositis (PM) and overlap syndromes and their association with disease status.

Methods: DNA from diagnostic muscle biopsies (MBx) from 20 white girls and boys (mean age = 6.4 ± 3.5 yrs) with definite/probable JDM were tested in Group 1: five with short DUD (duration ≤2 months) and 15 with long DUD (duration >2 months) at MBx were compared with four healthy age-, gender- and race-matched controls. The DNA was tested with Illumina Methylation27 BeadChip for genome-wide methylation profiling, and the results reviewed with GenomeStudio Analysis Software. Bisulfite pyrosequencing confirmed DNA methylation in 10 additional matched controls and 71 children with a spectrum of juvenile myositis. Group 2 patient population, (50/71 girls, mean age 7.6 ± 4.1 yrs), included children classified as 41 White, 14 Hispanic and 16 others.

Results: In Group 1, 20 JDM/4 matched healthy controls, the methylation arrays documented a significant methylation difference in a total of 27 genes. Among them, 6 were homeobox genes. In addition, the WT1 gene was significantly hypomethylated in JDM ($p< 0.01$). These results were confirmed by bisulfite pyrosequencing verification. Besides JDM, other types of juvenile IIM also displayed similar hypomethylation of the homeobox and WT1 genes. In addition, hypomethylation of WT1 was concordant with increased expression of the relevant protein, Wt1, in JDM muscles, compared with matched control. Of note, protein expression of Pax 7, a unique regulator of the stem cell generated muscle satellite cells, was increased in all JDM (both long and short DUD), indicating the capacity for repair and muscle fiber regeneration,

Conclusion: These results suggest that the affected muscles of children with JDM, irrespective of DUD, have the capacity to repair, and that the homeobox and WT1 genes are epigenetically marked to participate in this process.

Speculation: There may be potential for new therapeutic approaches in which the self-renewal ability of the damaged muscles in children with IIM can be enhanced, aiding muscle repair.

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Gene Expression In Affected Muscle of Patients with Polymyalgia Rheumatica and Matched Control Subjects Before and After Short-Term Prednisolone Treatment. Frederik Kreiner[1], Rehannah Borup[1], Peter Schjerling[2], Finn Cilius Nielsen[1] and Henrik Galbo[1]. [1]Rigshospitalet, Copenhagen, Denmark, [2]Bispebjerg Hospital, Copenhagen, Denmark

Background/Purpose: In polymyalgia rheumatica (PMR), the pathophysiology of symptomatic muscles is disputed. In the present study, we investigated baseline and post-treatment mRNA levels in symptomatic muscles.

Methods: Twelve glucocorticoid naïve patients (7 females and 5 men, age 73±10 years, BMI 23±4 kg/m2) with PMR just diagnosed according to the

Chuang criteria (Ann Intern Med 1982;97:672–80) and 12 controls (7 females and 5 men; 71±9 years; BMI 25±5 kg/m2) were studied.

In the fasting state, trapezius muscle biopsies were obtained before and after 14 days of prednisolone treatment (20 mg/day) from all subjects. mRNA was isolated using standard protocols and levels were determined using Affymetrix GeneChips (U133 Plus 2.0). Quantitative real-time PCR (qRT-PCR) was used for confirmation and also to more accurately measure expression levels of genes of special interest, e.g. IL6 that encodes interleukin (IL) 6, which in GeneChip runs did not differ between groups.

Results: Prednisolone treatment abolished symptoms in all patients within a few days; erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normalized by day 14. In controls, ESR and CRP were always normal.

Using GeneChips, 565 transcripts were identified ($p<0.05$ in 2-way ANOVA testing; filtering for fold change $> \pm 1.2$); of these, 59 transcripts fulfilled all 3 criteria of being of particular interest (subset shown in table): Differences in mRNA levels ($p<0.05$ in Welch t-testing) between 1) untreated patients and controls (97 genes), and 2) untreated and treated patients (172 genes), but not between 3) untreated and treated controls. Among these genes, 6 were selected for qRT-PCR analysis; most exhibited identical or similar expression patterns compared to the GeneChip runs (table). In addition, in contrast to the GeneChip measurements, qRT-PCR analysis showed that expression of IL6 was higher in patients than in controls before treatment (1.41±0.57 vs 0.39±0.21 arbitrary units; $p=0.006$) and decreased ($p=0.029$) to levels similar to those found in controls (after treatment, patients: 0.42±0.17; controls: 0.31±0.16; $p>0.05$).

	Untreated		Treated	
Genes (identified with Affymetrix GeneChips)	Patients	Controls	Patients	Controls
EIF4B: eukaryotic translation initiation factor 4B (*)	**3867**	**3088**	**3052**	**3202**
MAP2K3: mitogen-activated protein kinase kinase 3 (*)	261	**402**	**331**	**322**
NPM1: nucleophosmin (numatrin) 1	1763	**1442**	**1442**	**1432**
MTP18: mitochondrial protein 18 kDa (*)	102	**156**	**137**	**136**
PRSS23: protease, serine, 23 (*)	**291**	**141**	**429**	**160**
TUBD1: tubulin, delta 1	**167**	**129**	**124**	**133**
AKR7A2: aflatoxin aldehyde reductase	608	502	493	535
BCKDHA: branched chain keto acid dehydrogenase E1	970	798	715	753
BMPR1A: bone morphogenetic protein receptor, type IA	457	592	515	554
BPGM: 2,3-bisphosphoglycerate mutase	134	199	166	183
C6orf145: chromosome 6 open reading frame 145	274	224	397	222
CDNA clone IMAGE:6615994	276	225	229	233
CDNA FLJ36478 fis, clone THYMU2017362	168	119	125	129
CG018: hypothetical gene CG018	242	161	171	180
DFFA: DNA fragmentation factor, 45kDa, alpha polypeptide	354	279	285	272
DKFZp313A2432: hypothetical protein	115	68	69	71
EIF3G: eukaryotic translation initiation factor 3, subunit G	4367	3506	3461	3607
FAM69A: family with sequence similarity 69, member A	127	226	210	267
FBXO9: F-box protein 9	1611	2181	2055	2202
FMO2: flavin containing monooxygenase 2 (non-functional)	351	235	252	271
ITGB1BP2: integrin beta 1 binding protein (melusin) 2	439	702	646	663
JARID2: jumonji, AT rich interactive domain 2	367	509	472	508
MEMO1: Methylation modifier for class I HLA	1066	1438	1335	1221
MEST: mesoderm specific transcript homolog (mouse)	81	138	218	175
MGAT4B: mannosyl (alpha-1,3-)-glycoprotein transferase	337	412	391	403
MRPS2: mitochondrial ribosomal protein S2	510	422	404	417
NINJ2: ninjurin 2	182	309	410	361
OLFML2B: olfactomedin-like 2B	77	113	133	100
PAQR9: progestin and adipoQ receptor family member IX	78	160	112	129
PCID2: PCI domain containing 2	253	206	220	210
PSIP1: PC4 and SFRS1 interacting protein 1	1013	812	801	837
RBBP6: retinoblastoma binding protein 6	347	275	290	297
RERE: arginine-glutamic acid dipeptide (RE) repeats	1856	1427	1427	1442
RNF10: ring finger protein 10	2458	3187	2681	2809
RPL36AL: ribosomal protein L36a-like	5799	4878	4869	4775
RPL37: Ribosomal protein L37	568	391	386	396
RSBN1: round spermatid basic protein 1	436	349	356	359
SH3KBP1: SH3-domain kinase binding protein 1	349	625	453	567
TM4SF18: Transmembrane 4 L six family member 18	131	86	97	109
TMEM18: transmembrane protein 18	705	468	505	490
TMPO: thymopoietin	292	224	247	241
TMTC1: transmembrane and tetratricopeptide repeat containing	1217	840	845	776
TP53INP2: tumor protein p53 inducible nuclear protein 2	838	1525	1112	1336
ZNF195: zinc finger protein 195	146	114	111	120
ZNF313: zinc finger protein 313	1849	1434	1487	1424
ZNF331: zinc finger protein 331	292	211	215	217

Data are mRNA levels (arbitrary units). n = 12 in all groups.
Genes in **bold face** indicates that expression levels were measured using both GeneChips and qRT-PCR.
(*) qRT-PCR measurements confirmed GeneChip findings.

Conclusion: We show that in PMR, altered expression of a number of genes, including IL6, may contribute to the pathophysiology of affected muscles. Further studies are needed to clarify the exact role of these genes in the disease.

ACR Poster Session A
Pediatric Rheumatology - Clinical and Therapeutic Aspects I: Juvenile Idiopathic Arthritis (JIA)
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Ultrasound and Plasma Osteopontin Improve the Assessment of Remission in Oligoarticular Juvenile Idiopathic Arthritis. Miriam F. Parsa[1], Ornella J. Rullo[1], Jennifer M.P. Woo[1], David Elashoff[2], Tina Cunningham[2], Veena K. Ranganath[2], Kambiz Motamedi[2], Deborah K. McCurdy[1] and Harold E. Paulus[2]. [1]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [2]University of California, Los Angeles, Los Angeles, CA

Background/Purpose: Sustained remission is the treatment goal for children with Juvenile Idiopathic Arthritis (JIA). However, 50–75% of JIA patients meeting clinical remission (CR) criteria who discontinue medications have recurrence of disease activity within 5 years. Current CR criteria define disease states without the use of imaging or biomarkers. In patients categorized in clinical remission, musculoskeletal ultrasound may enable detection of the persistence of subclinical joint inflammation. Vascularization of inflamed JIA synovial tissue has been correlated with plasma osteopontin (pOPN) levels, a soluble cytokine that we have observed to be higher in oligoarticular JIA than healthy pediatric controls ($p=0.0002$). We hypothesize active synovitis, measured by an aggregate ultrasound inflammatory score (UIS) and pOPN, will decrease with longer durations of remission.

Methods: UIS of the knee and pOPN (by ELISA) were compared with the Juvenile Arthritis Disease Activity Score (JADAS) in four oligoarticular JIA disease states: active disease (AD), inactive disease (ID), CR on medications (CRM), and CR off medications (CR). AD patients requiring intra-articular steroid (IAS) injection had a pre-IAS and 1-month post IAS injection evaluation (UIS, pOPN, JADAS). US images were independently scored by two ultrasonographers, who were blinded to disease state. Baseline data was analyzed using the Kruskal-Wallis test to compare between states and a pairwise Wilcoxon rank sum test for post hoc pairwise comparisons.

Results: In this interim analysis of 35 study participants, median UIS strongly discriminates between disease states ($p=0.0001$). In states that are clinically indistinguishable, UIS is able to differentiate between ID and CR groups ($p<0.005$) (Figure 1). Moreover, US detects subclinical inflammation in 35% of the clinically inactive groups (ID, CRM, CR) ($p=0.0001$). In the IAS injection cohort, UIS and JADAS are significantly decreased when comparing pre-IAS and 1-month post IAS scores ($p=0.003$ for both). A strong correlation between UIS and JADAS ($r = 0.6$, $p = 0.008$) is observed, further confirming the applicability of UIS in JIA outcomes measurements. Overall p-value across disease states for pOPN is 0.0001, with the AD group exhibiting increased pOPN levels compared to both CRM and CR groups ($p=0.009$, $p=0.005$).

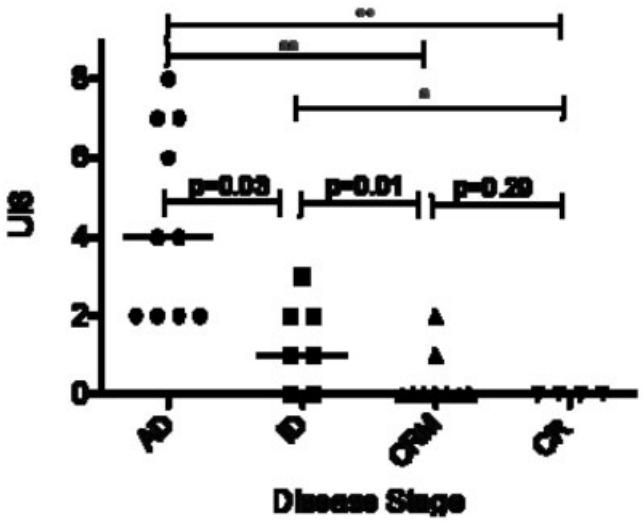

Figure 1. UIS in JIA disease stages (AD: n=12; ID: n=9; CRM: n=9; CR: n=5). Lines and p-values represent post hoc pairwise comparisons (**$p<0.0009$, *$p<0.005$).

Conclusion: The UIS may be more sensitive in the assessment of joint inflammation compared to clinical exam. UIS and pOPN levels may

differentiate patients who are in remission versus a subclinical disease state, a group that is at risk for disease flares. Confirming these associations in an expanded longitudinal cohort will allow us to construct risk assessment profiles for disease flare and will help determine the optimal duration of medical therapy in JIA.

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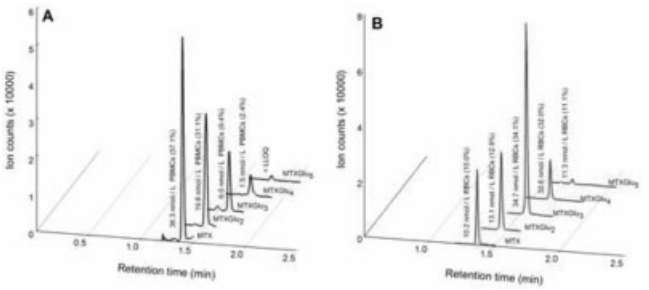
Measurement of Methotrexate Metabolites in Peripheral Blood Mononuclear Cells in Juvenile Idiopathic Arthritis: A More Relevant Cellular Biomarker for Drug Response? Leon van Haandel, J. Steven Leeder and ML Becker. Children's Mercy Hospital, Kansas City, MO

Background/Purpose: Regardless of age or disease subtype, considerable inter-individual variability in dose, optimal route of administration, clinical response and adverse reactions exist with methotrexate (MTX), and thus far, there are no quantitative biomarkers that can be utilized to maximize drug efficacy and minimize side effects at the level of the individual patient. Intracellular metabolism of MTX involves the formation of MTX polyglutamates ($MTXGlu_n$), which are responsible for its therapeutic effect, and long chain erythrocyte $MTXGlu_{3-5}$ have been reported to be associated with improvement in disease response in Rheumatoid Arthritis (RA). However, attempts to correlate erythrocyte $MTXGlu_n$ status with disease response to MTX in Juvenile Idiopathic Arthritis (JIA) have been less successful. Here we describe state of the art analytical methodology for the direct measurement of $MTXGlu_n$ in cells more directly associated with disease pathogenesis, the peripheral blood mononuclear cells (PBMCs).

Methods: After obtaining informed consent, 5 mL of blood was collected in EDTA vacutainer tubes. Erythrocytes, plasma and the buffy coat were separated and PBMCS were purified from the buffy coat using a Ficoll extraction per manufacturer protocol. $MTXGlu_n$ were extracted from PBMCs and RBCs by placing the sample tube in boiling water for 5 minutes, resulting in protein denaturation and liberation of the $MTXGlu_n$. Sample analysis occurred by a Waters UPLC system coupled to Xevo TQ-S tandem mass spectrometer (UPLC-MS/MS).

Results: Sample analysis by UPLC-MS/MS revealed that $MTXGlu_{total}$ concentrations between PBMCs and RBCs were within the same order of magnitude. However, the $MTXGlu_n$ distribution in PBMCs was shifted towards short chain metabolites ($MTXGlu_1$: 57.1%, $MTXGlu_2$: 31.1% and $MTXGlu_{1-2}$: 88.2%). Long chain metabolites represented only 11.8% of the intracellular drug concentration ($MTXGlu_3$: 9.4% and $MTXGlu_4$: 2.4% and $MTXGlu_5$: <LLOQ). The $MTXGlu_n$ metabolism fingerprint was therefore different when comparing PBMCs to RBCs (figure 1A, B respectively). Relative $MTXGlu_n$ distribution within the RBCs revealed a shift towards long chain $MTXGlu_{3-5}$, representing the vast majority (76.7%) of the intracellular drug concentration.



Conclusion: To our knowledge, this is the first reported method for detection of the active $MTXGlu_n$ metabolites in target PBMCs. Although RBCs represent an easily accessible source for measuring intracellular $MTXGlu_n$, from a drug effect perspective, the lack of association between increased concentrations on RBC $MTXGlu_n$ and clinical response to MTX in JIA suggests that PBMCs as effectors of disease pathogenesis may be a more relevant cell type. Additional investigation of the correlation of PBMC $MTXGlu_n$ and disease response is underway. Therapeutic drug monitoring in the PBMCs may provide clinicians a new quantitative biomarker for objective guidance of therapy in RA and JIA.

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Malignancy and JIA: Updated Results. Sasha Bernatsky[1], Kiem Oen[2], Ciaran M. Duffy[3], Alan M. Rosenberg[4], Emily von Scheven[5], Kathleen M. O'Neil[6], Laura E. Schanberg[7], Rosalind Ramsey-Goldman[8], Jeremy Labrecque[1], Elizabeth M. Turnbull[9], Jennifer LF Lee[1] and Ann E. Clarke[1]. [1]McGill UHC/RVH, Montreal, QC, [2]University of Manitoba, Winnipeg, MB, [3]Children's Hospital of Eastern Ontario, Ottawa, ON, [4]Royal University Hospital, Saskatoon, SK, [5]UC San Francisco, San Francisco, CA, [6]Okla Univ Health Science Ctr, Oklahoma City, OK, [7]Duke University Medical Center, Durham, NC, [8]Northwestern University, Chicago, IL, [9]McGill UHC/RVH, QC

Background/Purpose: To assess cancer incidence in a very large JIA sample.

Methods: We ascertained cancer incidence within JIA clinic registries maintained at four North American pediatric rheumatology centers (University of Manitoba N=816; Montreal Children's Hospital N=650; Royal University Hospital N=364; University of Oklahoma N=192). We also assessed JIA subjects assembled from administrative data at the University of California-San Francisco pediatric centre (N=1,009). Subjects were linked to cancer registries to determine cancer risk over the observational interval, spanning 1974–2009. In-situ cancers were excluded. Person-years were calculated from the date first seen at the rheumatology clinic, and the first of: death, cancer, or end of study interval (Dec. 31, 2009). Pooling the data, we determined the number of cancers occurring over the total person-years of observation. The number of cancers expected was calculated by multiplying the person-years in the cohort by the geographically matched age, sex, and calendar year-specific cancer rates, and summing over all person-years. Given differences in cohort assembly, data from the UCSF cohort are presented separately.

Results: The cohort was 65% female; average age at JIA diagnosis was 9.2 years (SD=5.1). There was a trend for fewer females and older average age in the UCSF cohort (59%, 11.0 years) versus the other cohorts (68%, 8.0 years). The majority of cohort members were Caucasian. Subjects were observed for a total of 18,250 patient-years, with an average follow-up of 6.0 years (SD=3.4). Within this observation interval, based on regional age- and sex-appropriate cancer rates, 7.4 invasive cancers were expected, however, only 6 occurred (SIR 0.8, 95 % confidence interval, CI 0.3, 1.8). All of these were hematologic cancers, five of these being leukemia and the other being poorly specified. These cancers arose an average of 2.7 years after JIA diagnosis (the most distant event occurring 8.8 years after JIA diagnosis).

Pooling data from the clinical cohorts, the SIR for hematological cancer was 1.4 (95% CI 0.2, 5.0). One of the hematologic cancers was diagnosed very shortly after JIA diagnosis in the UCSF cohort, and in this event the JIA may have been a paraneoplastic manifestation of the hematologic cancer. Excluding this case, the point estimate for the SIR for hematologic cancers in the UCSF cohort was high (37.5) but with a very imprecise 95% CI (7.56, 109.6).

Conclusion: These data represent the most up-to-date efforts to clarify baseline JIA cancer risk. Data from the clinically confirmed cohorts do not confirm an increased cancer risk in JIA, although there is a signal for a potentially increased risk of hematological cancer. The dramatic but imprecisely defined increased risk suggested by the UCSF cohort may reflect a somewhat biased (potentially sicker) sample, compared to the other cohorts. A limitation of available data is the relatively short follow-up time. Further work is in progress.

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Predictors of Disability in Children with Inflammatory Arthritis, Two and Three Years After First Presentation to Paediatric Rheumatology. Results From the Childhood Arthritis Prospective Study (CAPS). Roberto Carrasco[1], Joanna Cobb[1], Eileen M. Baildam[2], Helen Foster[3], Janet Gardner-Medwin[4], Alice Chieng[5], Lucy R. Wedderburn[6], Joyce Davidson[7], Kimme L. Hyrich[1], CAPS Study[8] and Wendy Thomson[1]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [3]Newcastle Hospitals NHS Trust, Newcastle, United Kingdom, [4]Royal Hospital for Sick Children, Yorkhill Hospital, University of Glasgow, Glasgow, United Kingdom, [5]Manchester Children's Hospital, Manchester, United Kingdom, [6]University College London (UCL), United Kingdom, [7]Greater Glasgow and Clyde Health Board and Royal Hospital for Sick Children, Glasgow, United Kingdom, [8]Manchester

Background/Purpose: Inflammatory arthritis (IA) in children is a chronic and often disabling disease with variable outcome. Up to one third of children are reported to have active disease progressing into adulthood although, data concerning disease course in children presenting with inflammatory arthritis in this modern treatment era are limited. The Childhood Arthritis Prospective Study (CAPS) is an ongoing prospective longitudinal inception cohort study the overall aim of which is to identify genetic and environmental predictors of short- and long-term outcome of childhood IA.

Within CAPS we have previously reported that the strongest predictor of persistent disability at one-year (as measured by the CHAQ) was moderate to severe disability at first presentation. The objective of this study was to extend the one year analysis to look at both two and three year outcomes.

Methods: CAPS recruits children <16 years with new inflammatory arthritis persisting for ≥ 2 weeks from five UK tertiary referral centres. Demographics, disease features, active and limited joint counts, CHAQ, physician's global assessment (PGA), parent's general evaluation of well-being (PGE), erythrocyte sedimentation rate (ESR) and treatment, are collected at first presentation to a paediatric rheumatologist, 6 months, then yearly. Independent predictors of moderate to severe CHAQ (CHAQ≥0.75) at two and three years in children with JIA were identified using multivariable logistic regression models. Imputation was performed in order to account for missing data.

Results: To date, 1059 children have been recruited; 901 had reached one year, 852 had reached two years and 618 three years of follow-up. Median age at presentation was 7.7 years, 63% girls. ESR, active and limited Joint counts, PGE and PGA score decreased every year for the majority of patients. Median CHAQ score was 0.75 (IQR: 0.125–1.375) at presentation and decreased to 0.25 (IQR: 0.0–1.0) at 1 year, 0.125 (IQR: 0.0–0.875) at 2 years and 0.125 (IQR: 0.0–0.75) at 3 years. Fifty percent of the children had CHAQ score ≥0.75 at presentation, 33% at 1 year, 32% at 2 years and 28% at 3 years. Amongst all the variables included in the study, moderate to severe CHAQ at presentation was the strongest predictor of moderate to severe CHAQ at one (OR 2.83 95% CI: 1.48, 5.37), two (OR 3.49 95% CI: 1.73, 7.08) and three years (OR 6.47 95% CI: 2.35, 17.8). After missing data imputation an additional predictor of a CHAQ score ≥0.75 at one, two and three years of follow up, PGE, was found.

Conclusion: Whilst the majority of children presenting with IA show continued improvement in the three years following first presentation, with many having no active or limited joints, our data show that there are still a significant proportion with moderate to severe disability. CHAQ score ≥0.75 at presentation, which was previously shown to predict disability at one year is still the strongest predictor of outcome at two and three years although an additional predictor, PGE may also be important. Future analysis will look at predictors of outcome, taking into account treatment.

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Etanercept in Juvenile Idiopathic Arthritis: Who Will Benefit? Results From the Dutch ABC Register. Marieke H. Otten[1], Femke H.M. Prince[1], Wineke Armbrust[2], Rebecca Ten Cate[3], Esther P.A.H. Hoppenreijs[4], Marinka Twilt[1], Yvonne Koopman-Keemink[5], Simone L. Gorter[6], Koert M. Dolman[7], Joost F. Swart[8], J. Merlijn Van den Berg[9], Nico M. Wulffraat[8], Marion A.J. Van Rossum[10] and Lisette W.A. Van Suijlekom-Smit[1]. [1]ErasmusMC Sophia Children's Hospital, Rotterdam, Netherlands, [2]Beatrix Children's Hospital, University Medical Centre Groningen, Groningen, Netherlands, [3]Leiden University Medical Centre, Leiden, Netherlands, [4]St Maartenskliniek and Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [5]Hagaziekenhuis Juliana Children's Hospital, Den Haag, Netherlands, [6]University Hospital Maastricht, Maastricht, Netherlands, [7]St. Lucas Andreas Hospital and Reade Institute, Amsterdam, Netherlands, [8]University Medical Center Utrecht, Utrecht, Netherlands, [9]Emma Children's Hospital/ Academic Medical Centre and Reade Institute, Amsterdam, Netherlands, [10]Emma Children's Hospital / Academic Medical Center (AMC), Amsterdam, Netherlands

Background/Purpose: The pharmacological treatment approach for juvenile idiopathic arthritis (JIA) has changed substantially since the introduction of biologics with nowadays inactive disease as realistic goal. However, inactive disease is still not achieved by all patients. Identifying baseline factors which predict etanercept response could improve treatment strategies.

Methods: The Arthritis and Biologicals in Children (ABC) register (observational study, ongoing since 1999), includes all Dutch JIA patients who use or previously used biologics. Disease activity variables were retrieved prospectively at start of treatment, after 3 months, and yearly thereafter. Analyzed were all biologic-naive patients who started etanercept before October 2009 (n=262). Drug survival (i.e. median duration from start until first discontinuation due to ineffectiveness or adverse events (AEs)) was estimated with Kaplan-Meier analysis. Excellent response (inactive disease or earlier discontinuation due to disease remission) and poor response (less than 50% improvement from baseline, or earlier discontinuation due to ineffectiveness or intolerance) was evaluated 15 months after initiation of etanercept. A univariate and multivariate logistic regression analysis was performed to identify pre-defined potential baseline predictors for excellent and poor response and for occurrence of AEs.

Results: Baseline characteristics: 71% female, 18% systemic-onset subtype, median age at onset 6.9 years. In the long-term (median follow-up duration, 35.6 months), the overall majority responded to etanercept and up to 40% reached inactive disease. The median drug survival was lower for the systemic-onset subtype (29.0 months, 95% CI 11.0–47.0) than for the non-systemic subtypes (76.8 months, 95% CI 45.7–108.0). Reasons for discontinuation were: ineffectiveness in 78, AEs in 25, and remission in 39 patients. Excellent response after 15 months (85 patients, 32%) was associated with low baseline disability (OR 0.49/point increase, 95%CI 0.33–0.74), fewer disease-modifying anti-rheumatic drugs (DMARDs) used before etanercept (OR 0.64/DMARD used, 95%CI 0.43–0.95) and younger age at onset (OR 0.92/year, 95%CI 0.84–0.99). Poor response (88 patients, 34%) was associated with female gender (OR 2.12, 95%CI 1.11–4.08) and systemic-onset JIA (OR 3.24, 95%CI 1.39–7.56). However, 24% of systemic-onset JIA patients reached excellent response. Etanercept was well tolerated (0.05 serious AEs, 0.14 infectious AEs and 0.26 non-infectious AEs per patient-year of exposure). Patients developing AEs could not be identified at baseline.

Conclusion: In daily practice, etanercept is very effective and well tolerated by patients with JIA. Inactive disease was reached in up to 40% of the patients and was sustained years after initiation of etanercept. Excellent response was associated with baseline low disability and less DMARD use before etanercept. Therefore, the focus should be on strategies with early introduction of etanercept to further improve outcomes for JIA. The role of etanercept for systemic-onset JIA remains debatable. However, etanercept should not be rejected as a therapeutic option for this subtype.

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Impact of Juvenile Idiopathic Arthritis on Parents' Work Absences. Rafia Rasu[1], Stephanie E. Kirbach[2], Oscar Hayes[2], Walter A. Bawa[1] and Mary A. Cifaldi[2]. [1]University of Missouri-Kansas City, Kansas City, [2]Abbott Laboratories, Abbott Park, IL

Background/Purpose: Children with juvenile idiopathic arthritis (JIA) have long-term morbidity with reduced quality of life and, therefore, require extensive parental assistance. This study aimed to evaluate the impact of children's JIA on parents' work absences compared with parents of children without JIA.

Methods: The Medstat MarketScan® claims database was assessed from 2000 to 2009 in order to identify adult parents with children who were newly diagnosed with JIA. A cohort of parents who had children without diagnoses of JIA was also identified, based on the matching of children with and without JIA. Data on parents' work absences (number of recorded absences, in hours) were analyzed using descriptive, multivariate regression, and logistic regression analyses. National estimates were calculated using parent and patient weights provided within the database.

Results: A total of 108 unweighted parents (mean age, 42.5 years) of children with newly diagnosed JIA represented a total of 3335 weighted nationally. The majority of these parents were from the south (46%), men (92%), and involved in the transportation and utilities industry (57%). Other industries represented were manufacturing (35%), oil and gas (3%), and services (3%). Demographic characteristics of control parents were similar. Children with JIA (mean age, 10.6 years) totaled 108 and represented 3528 weighted nationally. The mean (±standard error) number of reported work absences over the study period was 281.81 (±40.50) hours for parents of children who were newly diagnosed with JIA compared with 183.36 (±28.55) hours for parents of control children. Parents of children who were newly diagnosed with JIA reported 36.75 (±7.25) hours of work absences in the year prior to their children's JIA diagnosis compared with 69.01 (±18.44) hours for the year following diagnosis with JIA. Productivity loss was determined by noting parents' work absence difference 1 year before and after the diagnosis of JIA. An increase in the number of reported absences was considered to be productivity loss. After controlling for covariates, productivity loss was significantly related to the child's JIA status (with or without), parent's sex (men were more likely to have reported absences), and region (parents in the south and north-central regions were least likely to report absences compared with those in the northeast). Parents with children who had JIA were 2.78 times more likely to report productivity loss (OR=2.78; 95% CI=1.47–5.26) than parents whose children did not have JIA.

Conclusion: In this largely male population of employees, having a child with JIA resulted in significant work productivity losses, particularly in the year following diagnosis. This burden is likely experienced by both parents and represents the high level of care required by children with JIA.

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Long-Term Safety of Etanercept Compared to Methotrexate and Combinations in Children with Juvenile Idiopathic Arthritis – Data of the German BIKER-Registry. Gerd Horneff[1], Stephanie Bischof[1] and German BIKER Registry collaborative group[2]. [1]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [2]Sankt Augustin

Background/Purpose: Using the data base of the German BIKER registry the long-term safety of etanercept (ETA) alone or as combination therapy compared to methotrexate (MTX) was evaluated.

Methods: Cohorts of JIA patients receiving MTX alone, ETA alone, ETA & MTX, ETA & other DMARDs without MTX or ETA & MTX & other DMARDs were identified in the database. Safety was assessed by measuring rates of adverse events including grading for seriousness. For all AEs the current medical treatment was recorded for comparison of the rate of the total number of AEs and of AEs of interest. 20% of patients were current users of nonsteroidal antirheumatic drugs and 9% received steroids when AEs were documented. Exposure years of each category of treatment were calculated from the data base. The possible influence of JIA categories, disease duration and severity, concomitant morbidity or drug history was neglected for this analysis.

Results: In total 1249 AEs (139 SAEs) were documented during > 4700 patient years. AEs of interest were cytopenias, malignancies, flares of uveitis, chronic inflammatory bowel disease (IBD) and those graded as serious. Elevated liver function tests were listed as a *control* AE since their predominance upon MTX was expected. For each AE the actual treatment was assigned.

201 AEs (30 SAEs) occurred in 737 pts on ETA alone, 260 AEs (62 SAEs) on 1059 pts on ETA & MTX, 34 AEs (8 SAEs) on 192 pts on ETA & other DMARDs without MTX, 14 AEs (5 SAEs) on 34 pts on ETA & MTX & other DMARDs, 568 AEs (19 SAEs) on 1534 pts on MTX alone. 127 AEs were reported in pts who already completely discontinued treatment with DMARDs and biologics. 46 AEs were reported on biologics other than ETA or on combination regimen of MTX with cyclosporine, leflunomide or azathioprine without ETA. Categories of treatment in relation to rates of AEs and Aes of interest per patient and per year of exposure are outlined in table 1.

Table. Adverse events and SAE (rate per 100 patient years)

	MTX	ETA	ETA+MTX	ETA+MTX+DMARD	ETA+DMARD
Total no. of patients	1534	737	1059	34	192
Total patient-years of exposure	1976	1028	1471	115	147
Total adverse events	568 (29)	201 (20)***	260 (18)***	14 (12)	34 (23)***
Total SAE	19 (1.0)	30 (2.9)**	62 (4.2)***	5 (4.4)***	8 (5.4)**
Infection	65 (3.3)	52 (5)*	87 (5.9)***	2 (1.7)	10 (6.8)
SAE-Infection	5 (0.3)	8 (0.8)*	22 (1.5)***	0	2 (1.4)
Cytopenia	10 (0.5)	7 (0.7)	2 (0.1)	0	2 (1.4)
Malignancy#	3 (0.2)	0	3 (0.2)	0	1 (0.7)
Chronic inflammatory bowel disease	0	6 (0.6)***	1 (0.1)	0	0
Uveitis	13 (0.7)	16 (1.6)**	17 (1.2)	0	2 (1.4)
Abnormal liver function	70 (3.5)	4 (0.4)***	12 (0.8)***	1 (0.9)	1 (0.7)

One additional malignancy occurred in a patient who already had discontinued treatment with ETA and MTX. Difference of numbers per patient (chi-square-test) significant at p<0.0001 ***; p<0.01 **; p<0.05 * compared to MTX alone, respectively.

Significantly more AEs occurred on MTX alone compared to ETA alone while this rate was similar if abnormal liver functions tests were substrated. SAEs were more frequent on treatment groups including ETA than on MTX alone. Infections and serious infections were more frequent on ETA alone or in combination with MTX than on MTX alone. Furthermore uveitis and IBD occurred more frequently on etanercept alone.

Conclusion: These data indicate that adverse events in all treatment groups were rare and in the majority they were minor. Some adverse events of interest seem to be associated to etanercept treatment. The possible influence of disease duration and severity, concomitant morbidity or drug history limits the conclusions that can be drawn from these observations.

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Physician Versus Parent/Patient Assessment of Disease Activity in a Large Cohort of Patients with Juvenile Idiopathic Arthritis. Caitlin M. Sgarlat, Christina F. Pelajo, Jorge M. Lopez-Benitez and Laurie C. Miller. Tufts Medical Center, Boston, MA

Background/Purpose: Few previous large studies have examined the correlation between parent/patient versus physician assessment of disease activity though discordance between parent/patient and physician assessment has been reported in previous studies of JIA patients. Understanding the differences between parent/patient and physician assessment of disease is important for several reasons, including parent understanding of the patient's disease status, expectations about therapeutic interventions, and observations of disease progression or remission. The aims of our study were to examine the correlation between parent/patient and physician assessment of disease activity in JIA and to explore the association between parent/patient assessment of pain and parent/patient as well as physician assessment of disease activity.

Methods: The CARRAnet Registry database, a nationwide database containing information of >2,000 patients with JIA collected from May 2010 to June 2011, was used for analysis. This database contains demographics, a parent/patient pain report (0 to 10 scale with 0 = no pain and 10 = very severe pain), as well as parent/patient and physician disease activity reports (both on a 0 to 10 scale with 0 =no disease activity and 10 = very active disease), as well as other disease and medication information. Descriptive statistics were used to compare demographics of the sample population. Correlations between patient/parent and physician reports were measured with Pearson correlation coefficients.

Results: Of 2618 patients with a diagnosis of JIA, 1909 were female (73%) with a mean age of 11.5 years (±4.8). The overall parent/patient pain score was 2.5 (±2.6). The overall assessment of disease activity score was 2.5 (±2.7) while the mean physician global disease assessment score was 1.6 (±1.9). There was a positive correlation between physician and parent/patient assessment of disease activity ($c=0.50$, $p<0.001$). Parent report of pain was highly correlated with parent/patient report of disease activity ($c=0.75$, $p<0.001$), however, the correlation of parent/patient assessment of pain with physician assessment of disease activity was a much less robust association ($c=0.43$, $p<0.001$). When adjusted for pain, physician and parent/patient assessment of disease activity only had a weak correlation ($c=0.30$, $p<0.001$), indicating perceptions of pain by physicians and parents contributed strongly to assessments of disease activity.

Conclusion: We found that global assessment of disease activity between physician and parent/patient in a large cohort of patients with JIA was only modestly correlated. However, parent/patient report of pain correlated strongly with parent/patient report of disease activity but not with the physician report of disease activity. This suggests that parents or patients may take pain from JIA into more account when assessing overall disease activity, compared to physicians. These discrepancies suggest there are areas where communication between physicians and parents/patients could be improved. Poor communication may lead to difficulties regarding assessment of disease status and therapeutic efficacy and could possibly affect medication adherence and medical decision-making.

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Psoriasis in a First-Degree Relative As An Exclusion Criterion Contributes to Classification of Children As Having Undifferentiated Juvenile Idiopathic Arthritis. Mercedes O. Chan[1], Jaime Guzman[2] and Ross E. Petty[3]. [1]BC Children's Hospita/University of British Columbia, Vancouver, BC, [2]BC Children's Hospital, Vancouver, BC, [3]BCs Children Hosptial, Vancouver, BC

Background/Purpose: According to the International League of Associations for Rheumatology (ILAR) criteria, undifferentiated juvenile idiopathic arthritis (U-JIA) includes children who meet criteria in more than 1 category or fail to meet criteria for 1 of the other 6 categories. Classification requires application of 5 exclusion criteria: 1. psoriasis in the patient or a first-degree relative; 2. arthritis beginning after the 6th birthday in an HLA-B27 positive male; 3. HLA-B27 associated disease in a first-degree relative; 4. rheumatoid factor (RF) positivity; and 5. the presence of systemic JIA (SoJIA). The most frequent reasons for categorization of a patient as U-JIA are not clear.

Methods: Two independent reviewers extracted information from available charts of children with U-JIA at our center including inclusion and exclusion criteria. Discrepancies were resolved by consensus. Charts of children classified as juvenile psoriatic arthritis (JPsA) were also reviewed to determine the necessity for the history of psoriasis in a first-degree relative to classify children in this category.

Results: Of the 21 patients classified as U-JIA, in 11 it was due to having a first-degree relative with psoriasis; in 6 it was due to having a first-degree relative with psoriasis and arthritis beginning after the 6th birthday in an HLA-B27 positive male; in 3 it was due to arthritis beginning after the 6th birthday in an HLA-B27 positive male alone; and in 1 neither HLA-B27 status nor a history of psoriasis in a first-degree relative contributed to classification.

Chart reviews of 25 children with JPsA revealed that none were classified as JPsA on the basis of a history of psoriasis in a first-degree relative alone.

The table shows the JIA categories that children would be assigned to if the exclusion criterion "history of psoriasis in a first-degree relative" and/or "arthritis beginning after the 6th birthday in an HLA-B27 positive male" were disregarded for patients currently classified as U-JIA or JPsA.

Table. Diagnostic categories children with U-JIA and JPsA would belong to if the criterion "history of psoriasis in first-degree relative" and/or "arthritis after the 6th birthday in an HLA-B27 positive male" were disregarded.

	Children with U-JIA (n=21)	Children with JPsA (n=25)			
Criterion Disregarded	1st degree relative with psoriasis (n=11)	1st degree relative with psoriasis and arthritis in a B27+ male >6 years (n=6)	Arthritis in a B27+ male >6 years (n=3)	Neither B27+ male with arthritis >6 years nor 1st degree relative with psoriasis (n=1)	1st degree relative with psoriasis
Revised Category					
Oligo	6	0	1	0	0
Systemic	1	0	0	0	0
Poly RF+	1	0	0	0	0
Poly RF-	1	0	1	0	0
ERA	1	2	0	0	0
JPsA	0	0	0	0	25
U-JIA	1	4	1	1	0

Conclusion: At our center, the exclusion criterion of history of psoriasis in a first-degree relative was the most common reason determining classification of patients in the U-JIA category; and disregarding this criterion had no impact on the classification of children as JPsA. The conclusions of this small retrospective study require confirmation in a larger patient cohort before considering revision of the ILAR criteria.

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PD-L1 in Systemic Juvenile Idiopathic Arthritis. Susan Shenoi[1], Jing-Ni Ou[1], Claudia Macaubas[2], Elizabeth D. Mellins[2], Carol Wallace[1] and Anne M. Stevens[1]. [1]Seattle Children's Hospital, University of Washington, Seattle, WA, [2]Stanford University Med Ctr, Stanford, CA

Background/Purpose: *Systemic Onset Juvenile Idiopathic Arthritis (SJIA)* is a diagnosis of exclusion. There are no diagnostic tests for SJIA, thus identifying a diagnostic biomarker is crucial to facilitate accurate diagnosis and early treatment. *Programmed death ligand-1 (PD-L1*) is expressed on hematopoeitic and parenchymal cells and regulates self-tolerance by controlling activation of T lymphocytes. PD-L1 plays an important immunoregulatory role in the chronicity of inflammatory responses. PD-L1 expression is decreased in active systemic lupus erythematosus (SLE), an autoimmune disease with loss of lymphocyte tolerance, with normal/high PD-L1 expression in SLE remission. In contrast, elevated PD-L1 expression is associated with malignancies and acute and chronic infections.

Methods: We studied PD-L1 expression on 26 SJIA subjects and compared this to 11 subjects with polyarticular JIA and 5 healthy pediatric controls. Four SJIA subjects were recruited at Seattle Children's Hospital (SCH; new onset disease, characterized as SJIA flare). Stanford Medical Center (SMC) provided 22 samples of SJIA in different stages of diseaseactivity (SJIA subjects characterized clinically as remission (n=8), mild flare (n=11) and flare (n=3). Cells were cultured overnight without stimulation. Percentage of monocytes (Mo;CD14highCD11c+) and myeloid dendritic cells (mDC; CD14lowCD11c+) with PD-L1 expression (mean %) and MFI were quantified in peripheral blood mononuclear cells (PBMCs) by flow cytometry. For controls & SJIA subjects we also assayed activated Mo (aMo;CD14+CD11c+CD16+), natural killer (NK: CD3-CD56+CD16+) & NKT cells (CD3+CD56+).

Results: A trend toward lower % of cells expressing PD-L1 and lower MFI PD-L1 was seen in SJIA compared to controls and PolyJIA subjects:

	% PD-L1 expression (mean (SD))				
	Control (n= 5)	*Poly JIA (n= 11)*	*SJIA remission (n=8)*	*SJIA mild disease (n=11)*	*SJIA flare (n=7)*
Mo	91 (9)	97 (3)	49 (25)	46 (22)	74 (18)
mDC	53 (33)	32 (12)	33 (19)	34 (22)	36 (18)
aMo	96 (4)	–	62 (27)	62 (25)	77 (15)
NK Cells	44 (30)	–	5 (3)	2 (2)	27 (36)
NKT Cells	61 (46)	–	19 (19)	20 (20)	39 (39)
	MFI PD-L1				
Mo	8349 (5431)	29913 (10325)	5286 (8244)	2806 (3211)	3476 (29966)
mDC	2087 (1786)	1829 (927)	1715 (1845)	973 (639)	1494 (1656)

Conclusion: PD-L1 expression tends to be decreased on SJIA monocytes and NK cells compared to healthy control children. PD-L1 expression was upregulated in polyarticular JIA patients, as reported in adult rheumatoid arthritis patients. Thus, decreased PD-L1 expression in SJIA is a potential a diagnostic biomarker. Abnormal PD-L1 expression could be secondary to a defect in the PD-L1 gene or a regulatory dysfunction secondary to cytokine production.

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Application and Examination of the Key Clinical Parameters From the 2011 ACR Recommendations for the Treatment of JIA Using Electronic Medical Record-Derived Data From a Clinical Cohort. Michael L. Miller[1], Timothy Beukelman[2], George Lales[1], Sean McKenna[1], Jason Ruprecht[1], Megan L. Curran[1] and Marisa S. Klein-Gitelman[1]. [1]Children's Memorial Hospital, Chicago, IL, [2]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: Treatment decisions in the 2011 ACR Recommendations for the Treatment of JIA are based upon 4 key clinical parameters: treatment group (phenotype), prognostic features, disease activity, and current therapy. However, these key clinical parameters were based largely on expert consensus and have not been extensively studied. We used cross-sectional data from the electronic medical record (EMR) of a single academic pediatric rheumatology center to classify children with JIA according to the key clinical parameters and examine the characteristics of these patients.

Methods: We used Extract/Transform/Load methodology to extract EMR data for the most recent visit of all JIA patients seen from January – April 2011. Radiology reports were searched for text identifying erosions or joint space narrowing. Treatment group, prognostic features, disease activity, and current therapy were determined for all patients. Patients with MD (MDGA) and parent/patient global (PTGA) assessment scores of zero, joint count of zero, normal inflammatory markers (when available), and no active systemic features were determined to have no disease activity.

Results: Data from 299 patients were analyzed, median 11.7 yrs (8.0, 15.1 IQR); MDGA 2 (0,3 IQR); PTGA 1 (0,3 IQR). Distribution of MDGA scores resulted in few patients meeting criteria for high disease activity. Of 173 patients in the "History of ≤ 4 joints" group, 120 had oligoarticular JIA, 35 had enthesitis related arthritis (ERA), and 18 had undifferentiated arthritis, by ILAR criteria. Of the 105 patients in the "History of ≥ 5 joints" group, 14 had extended oligoarticular JIA, 5 ERA, 66 had polyarticular RF- JIA, 18 had polyarticular RF+ JIA, and 3 had undifferentiated arthritis. 20 patients had systemic arthritis and only 1 patient fit the active sacroiliac arthritis treatment group. Methotrexand and TNFi were used more frequently in patients with a history of ≥5 joints.

	N	Age (median, IQR)	RF+	Joint Count (median, IQR)	MDGA (median, IQR)	PTGA (median, IQR)	Current MTX use	Current TNFi use
History ≤ 4 joints	**173**	**11.2 (7.0, 14.6)**	**10 (6%)**	**0 (0, 1)**	**1 (0, 3)**	**1 (0, 3)**		
Poor Prognosis?								
No	163 (94%)	11.2 (6.5, 14.8)	10 (6%)	0 (0, 1)	1 (0, 3)	1 (0, 3)		
Yes	10 (6%)	10.9 (10.2, 14.8)	0 (0%)	0 (0, 1.25)	2 (1, 3.25)	0.5 (0, 4)		
Disease Activity								
None	26 (15%)	6.4 (4.0, 9.1)	0 (0%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0%)	0 (0%)
Low	51 (30%)	13.2 (9.2, 16.2)	2 (3%)	0 (0, 0)	1 (0, 2)	1 (0, 2)	20 (39%)	8 (16%)
Moderate	92 (53%)	11.7 (7.4, 14.8f)	8 (9%)	0 (0, 1)	3 (1, 4)	2 (1, 4)	20 (22%)	14 (15%)
High	4 (2%)	11.5 (3.7, 14.1)	0 (0%)	2.5 (2, 3.8)	7.5 (6.3, 8)	4 (1, 6.3)	0 (0%)	1 (25%)
History ≥ 5 joints	**105**	**12.8 (9.2, 16.0)**	**18 (17%)**	**0 (0, 3)**	**1 (2, 3.9)**	**1 (1, 2)**		
Poor Prognosis?								
No	71 (68%)	12.7 (8.4, 15.7)	0 (0%)	0 (0, 4)	2 (1, 4)	1 (0, 2.4)		
Yes	34* (32%)	13.3 (9.9, 16.7)	18 (53%)	0 (0, 2)	2 (1, 3)	1 (0, 2)		
Disease Activity								
None	11 (11%)	9.7 (5.8, 14.6)	1 (1%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	4 (36%)	11 (1%)
Low	37 (35%)	12.7 (9.6, 15.4)	9 (24%)	0 (0, 0.5)	1 (0, 2)	1 (0, 1.5)	22 (59%)	23 (62%)
Moderate	54 (51%)	14.0 (9.1, 16.4)	7 (13%)	2 (0, 5.3)	3.3 (2, 4.5)	2 (0.9, 3.5)	38 (70%)	26 (48%)
High	3 (3%)	13.6 (9.2 min, 21.9 max)	1 (33%)	10 (min, 4, 12 max)	7 (7 min, 8 max)	5 (0 min, 6 max)	2 (67%)	1 (33%)
Systemic Arthritis	**20**	**10.5 (2.8, 16.9)**	**0 (0%)**	**0 (0, 2)**	**2 (0.3, 5)**	**2 (0, 2.9)**		
Systemic features	1 (5%)	10.5	0 (0%)	0	5	2.5	0	0
Synovitis	9 (45%)	11.6 (10.0, 12.2)	0 (0%)	2 (1, 3.5)	5 (2.5, 5.5)	2.3 (0, 5.5)	8 (89%)	6 (67%)
No disease activity	10 (50%)	10.1 (6.8, 12.5)	0 (0%)	0 (0, 0)	0.5 (0, 1.3)	2 (0, 2.3)	6 (60%)	3 (30%)

* Patients in the "History of ≥5 joints" category were more likely to have a poor prognosis than those in the "History of ≤ 4 joints" category ($p<0.0001$, X^2 test).

Conclusion: In this cross sectional study, we found that patients with a history of ≥5 joints, all RF positive, were more likely to have indicators of poor prognosis, compared to patients with a history of ≤4 joints. In contrast, disease activity distributions were similar for the two groups. The key clinical parameters from the 2011 ACR Treatment Recommendations for JIA can be

applied to EMR-derived data in an automated fashion. Future longitudinal studies will address real-time physician guidance for treatment decisions and evaluate clinical outcomes resulting from adherence to the Recommendations.

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Long-Term Efficacy and Safety of Adalimumab for up to 6 Years in Patients with Juvenile Idiopathic Arthritis. Daniel J. Lovell[1], Nicolino Ruperto[2], Andreas Reiff[3], Lawrence K. Jung[3], Gloria Higgins[3], Isabelle Koné-Paut[2], Olcay Y. Jones[3], Melissa J. McIlraith[4], Nupun Andhivarothai[5], Hartmut Kupper[6], Edward H. Giannini[3], Theresa Peterson[5] and Alberto Martini[2]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]PRINTO-IRCCS, Genova, Italy, [3]PRCSG-Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Abbott, Rungis, France, [5]Abbott, Abbott Park, IL, [6]Abbott, Ludwigshafen, Germany

Background/Purpose: Adalimumab (ADA) has been shown safe and effective in a study of juvenile idiopathic arthritis (JIA) patients (pts) aged 4–17 years when dosed every other week for up to 3 years.[1] The purpose of this report is to evaluate the long-term efficacy and safety of ADA treatment for up to 6 years in JIA pts.

Methods: Pts with polyarticular course JIA were enrolled in a phase 3, randomized-withdrawal, double-blind (DB), stratified, parallel-group study, which consisted of a 16-wk open-label (OL) lead-in, a 32-wk DB phase, and an up to 5 year OL extension (OLE) phase that included BSA dosing (24 mg/m^2, max 40 mg) prior to a switch to a fixed dose (FD) of 20 mg for patients weighing ≤30 kg, and 40 mg for those >30 kg. Pts were required to achieve an American College of Rheumatology Pediatric 30% (ACR Pedi 30) during the OL lead-in to qualify for entry into the DB phase. Responses to ADA were evaluated based on ACR Pedi 30/50/70/90 and changes in JIA core set variables relative to baseline. Pts were monitored for adverse events (AEs).

Results: Approximately 79% of patients entering the study were female, with a mean age of 11 years and a mean disease duration of 3.8 years. The mean baseline Physician's Global Assessment of disease activity (PhyGA) was 58.9, Parent's Global Assessment of overall well-being (PaGA) was 48.3,active joint count (AJC) was 17.2, and Disability Index measured by the Childhood Health Assessment Questionnaire (CHAQ) was 1.1. Among the 171 pts who enrolled in this study, 144 (84%) met ACR Pedi 30 response criteria at week 16, but 133 (78%) entered the DB phase. A total of 128 (75%) continued to the OLE (initial BSA dosing), and 106 (62%) of these pts moved on to the FD phase. Sixty-two pts completed at least 5 years in the OLE. Most pts who discontinued in the OLE were lost to follow-up or withdrew consent. The most frequent concomitant anti-rheumatic medications used during the OLE were methotrexate, non-steroidal anti-inflammatory drugs, and steroids. ACR Pedi 30/50/70/90 responses and improvements in JIA core set variables were sustained in pts who completed the study and reached ~240 weeks in the OLE phase (**Table**). Of the 171 pts who received any ADA, 16 (9.4%) discontinued due to AEs. Eleven (6.4%) pts experienced serious infectious events (SIEs), and 1 (0.6%) had an opportunistic infection (cytomegalovirus). No deaths, malignancies, TB, demyelinating disease, or lupus-like reactions were reported.

Table. Observed ACR Pedi Responses and JIA Core Variables at the Last Study Visit for all ADA-treated Pts who Completed at Least 240 Weeks in the OLE (n=62)

ACR Pedi 30/50/70/90,%	95/90/82/69
PhyGA, mean	8.9
PaGA, mean	7.5
AJC, mean	1.6
Disability Index (CHAQ), mean	0.2

ACR indicates American College of Rheumatology; AJC, active joint count; CHAQ, Childhood Health Assessment Questionnaire (range: 0–3); PaGA, Parent's Global Assessment of overall well-being (range: 0–100 mm); PhyGA, Physician's Global Assessment of disease activity (range: 0–100 mm).

Conclusion: ADA was efficacious and well tolerated in JIA patients aged 4–17 years. Clinical responses and improvements in disease activity were maintained for up to 6 years with ADA. When compared with the 3 year study results, no new safety signals were observed through 6 years of ADA treatment.[1] No malignancies or deaths were reported.

1. Lovell DJ, et al. *NEJM* 2008;359:810–820.

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Effectiveness of Nonsteroidal Antiinflammatory Drug Monotherapy in Children with Systemic Juvenile Idiopathic Arthritis. Meredith P. Riebschleger, Jasmine Stannard, Matthew M. Davis, Sarah J. Clark and Barbara S. Adams. University of Michigan Health System, Ann Arbor, MI

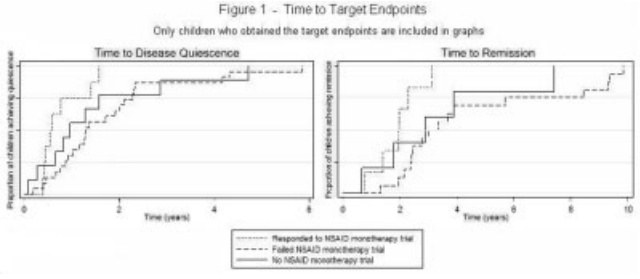
Background/Purpose: Traditionally, many pediatric rheumatologists have treated systemic juvenile idiopathic arthritis (sJIA) with a pyramid approach, starting with NSAID monotherapy prior to initiating DMARDs or biologic agents. Despite widespread use, the likelihood of response to NSAID monotherapy has not been well characterized. In addition, some clinicians have begun to advocate for the use of biologic agents as first-line therapy for all patients with sJIA, despite potential risks of pain, infection, and malignancy. The goals of this study are (1) to determine the frequency of clinical response to NSAID monotherapy in sJIA, and (2) to identify factors associated with that response.

Methods: We conducted a single-center cohort study of children aged 0–18 years who were diagnosed with sJIA between 1/1/2000 and 12/31/2009. Children who met ILAR criteria for sJIA and had at least 6 months of follow-up from the time of initial presentation were included. Outcomes included disease quiescence, defined as symptom-free with no active arthritis on exam and normal labs, if done; and remission, defined as disease quiescence off medications. Independent variables included patient demographics, disease characteristics, and medication regimens. Statistical analyses included chi square and Kruskal-Wallis tests for bivariate comparisons and time to event analyses for time to disease quiescence and remission. Continuous variables are presented as medians with interquartile ranges. Categorical variables are presented as frequencies.

Results: Of the 48 children in the cohort, 35 (73%) underwent an initial trial of NSAID monotherapy. Eight children (23%) experienced disease quiescence on NSAIDs alone and 6 achieved remission. Table 1 compares patient characteristics and clinical outcomes for the 3 groups of children in the cohort. Most children who responded to NSAID monotherapy had improvement within the first 2 months. The median delay to escalation of therapy for children who failed NSAID monotherapy was 1.2 months (IQR 0.7–1.8 months). The clinical outcomes of children who failed NSAID monotherapy were not significantly different than those of children who did not undergo a trial.

Table 1.

	Responded to NSAID monotherapy trial (N=8)	Failed NSAID monotherapy trial (N=27)	No NSAID monotherapy trial (N=13)	p value
Patient Characteristics				
Male	38%	52%	31%	42
Age at presentation (years)	2.8 (2.2–4.1)	5.4 (2.0–11.7)	5.5 (2.1–13.4)	.24
Time from onset of symptoms until presentation (years)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.2 (0.1–0.3)	.26
Hospitalized at presentation	13%	44%	31%	.23
CRP at presentation (mg/dl)	7.3 (6.0–8.8)	7.4 (5.3–14.1)	12.2 (10.3–13.0)	.09
Suspected macrophage activation syndrome at presentation	0%	11%	31%	.11
Number of joints involved at presentation	2 (1–3)	1 (0–5)	4 (1–12)	.50
Maximum number of joints involved in the first year after presentation	2 (2–3)	8 (4–18)	10 (6–15)	<.01
Clinical Outcomes				
Achieved disease quiescence	100%	85%	69%	.17
Time to disease quiescence (years)	0.6 (0.4–1.1)	1.3 (0.9–2.3)	1.0 (0.6–1.6)	<.04
Achieved remission	75%	59%	38%	.23
Time to remission (years)	2.1 (1.5–2.4)	3.5 (2.6–7.2)	3.1 (1.9–4)	<.01



Conclusion: NSAID monotherapy is able to achieve disease quiescence in a subset of children with sJIA. A short trial of NSAID monotherapy does not appear to result in worse outcomes, even for children who fail that trial. These findings indicate that a trial of NSAID monotherapy should be considered for some children with sJIA, prior to starting more aggressive treatment with DMARDs and biologic agents.

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Can Long-Term Use of Tocilizumab Induce Drug-Free Remission in Systemic Juvenile Idiopathic Arhtritis Refractory to Steroid Therapy?
Tomohiro Kubota[1], Yuichi Yamasaki[1], Junko Yasumura[2], Naomi Kuwada[3], Yukiko Nonaka[1], Tomoko Takezaki[1], Harumi Akaike[1], Yasuhito Nerome[1], Hiroyuki Imanaka[1] and Syuji Takei[1]. [1]Kagoshima University, Kagoshima City, Japan, [2]Hiroshima University, Hiroshima City, Japan, [3]Kumamoto University, Kumamoto City, Japan

Background/Purpose: Tocilizumab (TCZ), a humanized anti-human interleukin-6 receptor monoclonal antibody developed in Japan, is firstly approved in Japan as a biologic agent for systemic juvenile idiopathic arthritis (sJIA) in the world[1)]. Therefore, the purpose of this study is to investigate whether long-term TCZ therapy can induce drug-free remission in the sJIA patients refractory to conventional therapy.

Methods: Cumulative incidence of patients who attained our serial treatment goal of 1st) decreased dose of steroid less than 0.2mg/kg/day of prednisolone (PSL), 2nd) prolongation of TCZ interval from every 2w to 3w, 3rd) discontinuation of PSL, and 4th) discontinuation of TCZ was evaluated by Kaplan-Meier method. 20 patients who were resistant to 3 times of consecutive weekly intravenous methyl-prednisolone pulse therapy (3 consecutive days) in active phase and/or were refractory to long-term oral steroid therapy for more than 6 months were recruited, and treated by 8 mg/kg of TCZ for more than 6 months (max 7 years).

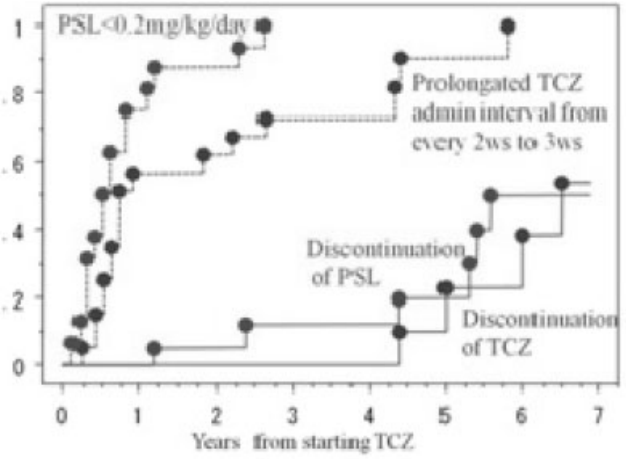

Fig: Cumulative incidence of patients attained each end-point

Results: Patient characteristics at starting TCZ were as follows: mean age was 8.5 years (2.2–20.2); mean disease duration of sJIA was 4.2 years (0.1–16.2 years); mean PSL dose was 0.5mg/kg/day (0.1–1.5).

Of 16 patients treated with more than 0.2mg/kg/day of PSL at the baseline, incidence of patient attained 1st endpoint of reduced PSL dose to <0.2mg/kg/day was 50% at 6 months and 75% at 1 year after initiating TCZ. The 2nd endpoint of prolongation of interval of TCZ administration from every 2 weeks to 3 weeks was attained in 57% of patients at 1year, in 73% at 3years, and in 91% at 5 years after starting TCZ.

Discontinuation of PSL, 3rd endpoint of this study, was attained in 12% of patients at 3years, in 20% at 5years, and in 50% at 6 years of TCZ therapy. Discontinuation of TCZ, the primary endpoint of this study, was attained in 23% of patients at 5yeras, and in 38% of patients at 6 years after TCZ induction. There were no patients who ceased TCZ therapy due to side effect during the study period (mean 4.5 years).

Conclusion: TCZ was effective and well-tolerated in Japanese sJIA patients in the long-term clinical setting. TCZ can induce drug-free remission in sJIA patients refractory to conventional steroid therapy.

Reference

1. Yokota S, *et al*. Lancet. 2008; 371: 998–1006

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Radiological Cervical Spine Involvement In Polyarticular Idiopathic Juvenile Arthritis.
Muriel Elhai[1], Ramin Bazeli[2], Veronique Freire[2], Antoine Feydy[2], Andre Kahan[1], Chantal Job-Deslandre[1] and Julien Wipff[1]. [1]Rheumatology A, Paris Descartes University, Cochin Hospital, APHP, Paris, France, Paris, France, [2]Radiology B, Paris Descartes University, Cochin Hospital, APHP, Paris, France, Paris, France

Background/Purpose: Several studies have assessed radiological involvement of the cervical spine in juvenile idiopathic arthritis (JIA) with a large range of prevalences (5–80%), but most studies have been performed in 50's, in symptomatic JIA and without differentiating subsets of JIA. In patients with a polyarticular JIA (pJIA), apophyseal joint ankylosis and atlanto-axial impaction are the most frequently described. To describe structural inflammatory cervical spine involvement in pJIA regardless of cervical symptoms and to compare observed lesions to those seen in rheumatoid arthritis (RA) using a cross-sectional observational study.

Methods: All consecutive pJIA followed in a transition program have been included in this study. Age, sex, disease duration, history of cervical manifestations (pain or limitation of motion) and medical or surgical treatments were collected. Laboratory tests (ESR, CRP, rheumatoid factors, anti-CCP and antinuclear antibodies) were performed. Standard radiographies of the cervical spine (antero-posterior, lateral view with flexion and extension and open mouth view), hands, feet and hip were analysed by two independent radiologists blinded to the diagnosis. A third reader established a consensus when required. A RA control group (<55years), matched for sex and disease duration, was recruited. Data were statistically analyzed using chi-square tests and the Student's t-test. A multivariate stepwise logistic regression analysis was also performed for all variables identified with $p \leq 0.10$. $P < 0.05$ was considered statistically significant.

Results: 58 pJIA (48 females/10 males) and 59 RA (52/7) were included. Mean age was 23.6±10.0 years and 43.2±9.6 years, respectively and mean disease duration 13.1±11.1 and 12.2±7.1 years, respectively. 60% and 80% (p=0.02) were RF positive and 57% and 79% (p=0.02) anti-CCP positive. Clinical involvement of the cervical spine was found in 42% and 44% of pJIA- and RA-patients, respectively. Radiographies showed inflammatory lesions in 38/58 pJIA (66%) and 40/59 (68%) RA-patients and respectively 3/58 and 2/59 patients underwent cervical surgery. In pJIA, the most frequent lesions were anterior atlantoaxial subluxation (53%), erosion of the odontoid process (34%), C1-C2 arthritis (26%) and apophyseal joint arthritis (26%). Cervical lesions observed in pJIA were similar to those in RA in adults except for ankylosis (8/38 vs 0/40, p<0.01). Presence of radiographic cervical lesions correlated with a more severe disease phenotype: higher number of DMARDs or biological agents per patient, more erosive disease (hands and feet) and higher frequency of surgery. In multivariate analysis, only a higher number of biological agents was associated with radiographic cervical lesions (p=0.04, OR=2.84 [1.01–7.96]). 50% of pJIA with radiographic abnormalities had no clinical symptoms.

Conclusion: Structural cervical spine involvement is a frequent manifestation in pJIA followed at adulthood, is asymptomatic in half of the cases and correlated with a more severe disease. Radiologic assessment of cervical spine should be done systematically at onset and regularly during the course of the disease regardless of clinical symptoms.

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Use of Intra–Articular Steroid Injection in a Large Cohort of Children with Oligoarticular Juvenile Idiopathic Arthritis—the ReACCh Out Study.
Julie Barsalou[1], Ronald M. Laxer[2], Lori B. Tucker[3], Rae SM Yeung[4], Kiem Oen[5], Ciaran M. Duffy[6] and ReACCh Out Study Group[7]. [1]Montreal Children's Hospital, McGill University, Montreal, QC, [2]The Hospital for Sick Children, Toronto, ON, [3]BC Childrens Hospital, Vancouver, BC, [4]Hospital for Sick Children, Toronto, ON, [5]University of Manitoba, Winnipeg, MB, [6]Children's Hospital of Eastern Ontario, Ottawa, ON, [7]Ottawa

Background/Purpose: Oligoarticular juvenile idiopathic arthritis (oJIA) is the most common subtype of JIA. Common treatment strategies, including the use of intra-articular steroid injection (IAS), have not been studied in large patient groups over time. The aim of this study is to describe patients with oJIA enrolled in a longitudinal cohort of Canadian children with JIA who have received IAS, and to explore factors associated with its use.

Methods: Research on Arthritis in Canadian Children emphasizing Outcomes (ReACCh Out) is a longitudinal cohort of JIA patients enrolled within 1 year of diagnosis from 16 centres across Canada. All oJIA patients who completed 24 months of follow up were included in this study. Demographic and clinical information were collected at each study visit. Functional status and quality of life were measured using the Childhood Health Assessment Questionnaire (CHAQ) and the Juvenile Arthritis Quality of Life Questionnaire (JAQQ), respectively. Early IAS was defined as an IAS injection given within 3 months of JIA diagnosis. A multivariate logistic regression model was used to identify predictors of early IAS.

Results: Data for 324 oJIA patients (71% female) enrolled in the ReACCh Out study were available. The median age at symptom onset and the median age at diagnosis were 4,0 (interquartile range (IQR) 2,0–9,0) and 5,0 (IQR 2,0–9,5) years old, respectively. The median time from symptom onset to diagnosis was 4,0 (IQR 2,0–6,0) months. The oJIA subtype was further divided into an oligo-persistent (67%) and oligo-extended (14%) course (subtype unavailable in 19%). At baseline, the median number of joints considered active was 1 (IQR 1–2) and 9% of patients had a leg length discrepancy (LLD) of more than 1cm. The median baseline CHAQ score was 0,25 (IQR 0-0,75) and JAQQ score was 2,3 (IQR 1,7-3,2). One hundred and seventeen (36%) oJIA patients received at least one IAS injection during the 24 months follow-up period: 54 (46%) had an early IAS injection as compared to 63 (54%) who received a late IAS. During the 24 months follow up period, 404 IAS procedures were performed on 117 patients. In 116 cases (29%), the IAS was used as the sole therapeutic agent. In the univariate logistic regression analysis, the following baseline variables were associated with an early IAS ($p<0,1$): recruiting centre, being on medication at enrollment, antinuclear antibody positivity and a higher erythrocyte sedimentation rate. Age at diagnosis, time from symptom onset to diagnosis, subtype of oJIA, number of active joints at baseline, presence of LLD at baseline and baseline CHAQ and JAQQ scores were not significantly associated with early IAS. The multivariate logistic regression model yield no independent predictors of early IAS.

Conclusion: More than one third of children with oJIA in this large cohort received an IAS injection, with nearly half of these performed within 3 months of diagnosis. Less than one third of IAS were done without concomitant pharmacotherapy. Practice differences between pediatric rheumatology centres in this multicentre study contributed to differences in use of IAS injections. No independent predictors for receiving an early IAS were found in this cohort of patients.

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Perception of Health Status in Young Adult Patients with Juvenile Idiopatic Arthritis: it's Good to Be Better but it's Better to Be Good. Elisa Gremese, Graziella D'Antona, Laura Messuti, Luca Petricca, Maria Rita Gigante and Gianfranco Ferraccioli. Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: The outcome of juvenile idiopatic arthritis (JIA) is generally regarded as "good", even though many patients have marked functional disability and active disease at 10 years of follow-up. Introduction of anti-TNF modified the course of JIA. The aim of the study was to evaluate quality of life (QOL) in young adults with JIA, using validated measures of functional disability and generic health status.

Methods: 29 JIA patients (>18 years old) switched from a pediatric to an adult rheumatologic setting and 29 healthy controls matched for age and sex were evaluated. Functional disability and generic health status/QOL were assessed by the Health Assessment Questionnaire (HAQ) and the Short Form 36-item health profile (SF-36), respectively. SF-36 physical summation score (PSS) and mental summation score (MSS) were considered to reduce the number of comparisons from 8 scales to 2 summary measures. A p value of < 0.05 was regarded as statistically significant.

Results: The 29 JIA patients had a mean age of 20.5 ± 2.8 years, a mean disease duration of 11.6 ± 6.3 years, an HAQ of 0.33 ± 0.47, a DAS of 1.4 ± 1.1. 82.4% were female, 8/29 (27.6%) had active joint disease, 16/29 (55.2%) were under treatment with anti-TNF agents and/or DMARDs, 13 only with DMARDs and/or NSAIDs. JIA patients showed a worse PSS ($p=0.02$) and in particular physical functioning ($p<0.001$) than healthy subjects. Taking into account only the 15 JIA patients with disease in remission and no physical disability (DAS<1.6 and HAQ=0), this group of patients presented a better MSS ($p=0.04$) and in particular of social functioning ($p=0.01$) with respect to control subjects, with no differences in physical function scores. Moreover, JIA patients taking anti-TNF drugs showed higher bodily pain score ($p=0.05$) but higher vitality score ($p=0.05$) that patients not taking them.

Conclusion: Despite the presence of a disease and the long disease duration, patients with JIA in remission and without disability had a better mental health index than control subjects, suggesting that QOL from a patient's perspective is dependent on a variety of factors, not just physical impairment and functional disability. Patients taking biologic drugs, indicative of a more aggressive disease, despite an higher component of bodily pain, had a better perception of their vital capacity.

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Race and Other Risk Markers in Juvenile Idiopathic Arthritis-Associated Uveitis. Sheila Angeles-Han[1], Christina Pelajo[2], Larry B. Vogler[1], Christine W. Kennedy[3], Lori Ponder[3], Traci Leong[4], Jorge M. Lopez-Benitez[2], Carolyn Drews-Botsch[4], Sampath Prahalad[1] and for the CARRAnet investigators[5]. [1]Emory Univ School of Medicine, Atlanta, GA, [2]Tufts Medical Center, Boston, MA, [3]Emory Children's Center, Atlanta, GA, [4]Emory University School of Public Health, Atlanta, GA, [5]Stanford

Background/Purpose: Juvenile idiopathic arthritis-associated uveitis (JIA-U) is an inflammatory eye disease that occurs in 20% of children with JIA and can cause visual impairment and blindness. Risk factors associated with JIA-U include early age at arthritis onset, JIA subtype, young age, and ANA and HLA-B27 positivity. Few studies on JIA-U focus on African American (AA) children. In this population, the role of ANA is unclear, predisposition to JIA subtype differs, and there appears to be a lower risk of JIA-U compared to White (W) children. Hence, the risk for JIA-U may differ by race and should be explored. Our objective is to characterize the epidemiology and clinical course of children with JIA-U in a cohort of children with JIA in the CARRAnet Registry.

Methods: Children with JIA from pediatric rheumatology clinics in the US were enrolled in the CARRAnet Registry from May 2010 to June 2011. Demographic and disease-related data were collected from time of diagnosis to enrollment visit. Only children whose uveitis status was known were included. Children with JIA alone were compared to those with JIA and uveitis. Children with JIA-U were then compared based on race, specifically AA and W. N may vary in some characteristics since we excluded data that was missing or unknown.

Table 1. Characteristics of Children with JIA-associated uveitis compared to children without uveitis

	All JIA N = 2675	JIA-U N = 302	JIA alone N = 2373	P-value
Demographic Characteristics				
Age, mean years ± SD[&]	11.5 ± 4.8	10.8 ± 4.5	11.5 ± 4.5	0.003**
Gender, female, N (%)	1951 (72.9)	243 (80.5)	1708 (72)	0.002**
Hispanic ethnicity, N (%)[&]	268 (10)	26 (8.6)	248 (10.4)	NS
Race, N (%)				
White	2416 (90.3)	282 (93.4)	2134 (89.9)	NS
Black or African American	165 (6.2)	9 (3)	156 (6.6)	0.014**
American Indian or Alaska Native	37 (1.4)	3 (1)	34 (1.4)	NS
Asian	68 (2.5)	9 (3)	59 (2.5)	NS
Native Hawaiian or Pacific Islander	16 (0.6)	0	16 (0.7)	NS
Other	78 (2.9)	5 (1.6)	73 (3.1)	NS
Disease characteristics				
Age at arthritis onset, mean years ± SD[&]	6.39 ± 4.4	4 ± 3.4	6.7 ± 4.4	<0.001**
Medications used[&]				
Glucocorticoids ever	1798 (67.2)	223 (74.8)	1575 (66.8)	0.005**
Biologics ever	1226 (45.8)	172 (57)	1054 (44.5)	<0.001**
Non-biologics, DMARDs	2049 (76.6)	277 (91.7)	1772 (75)	<0.001**
Extent/distribution joint involvement*				
Ever, <5 joints	1105 (41.3)	160 (53.2)	945 (40)	<0.001**
Uveitis[&]	302 (11.3)			
JIA subtype, %[&]				<0.001**
Oligo persistent	715 (26.7)	133 (44)	582 (24.5)	
Oligo extended	220 (8.2)	46 (15.2)	174 (7.3)	
Poly RF (+)	190 (7.1)	2 (0.7)	188 (8)	
Poly RF (−)	783 (29.3)	74 (24.5)	709 (30)	
Psoriatic	165 (6.2)	18 (6)	147 (6.2)	
Systemic	241 (9)	4 (1.3)	257 (10.8)	
ERA	274 (10.2)	17 (5.6)	262 (11)	
Undifferentiated	61 (2.3)	7 (2.3)	54 (2.3)	
Labs[&]				
ANA	1163 (48.8)	196 (69.2)	967 (46.1)	<0.001**
RF	122 (12.7)	2 (2)	120 (14)	0.001**
Anti-CCP	110 (11.5)	3 (3.5)	107 (12.3)	0.015**
HLA-B27	202 (14.1)	19 (11.9)	185 (14.5)	NS

[&] N varies since data that was "missing"or "unknown"was excluded
** $p<0.05$, NS = not significant
Values are N (%) unless indicated
Chi square and Mann Whitney test as appropriate.
Cases with missing and unknown data were excluded.

Table 2. Characteristics of African American Children with JIA-U

	Black N = 9	White N = 282	p-value
Demographic Characteristics			
Age, mean years ± SD	14.5 ± 4	10.65 ± 4.4	0.027**
Gender, female, %	4 (44.4)	230 (81.6)	0.019**
Hispanic ethnicity, %	2 (22.2)	19 (6.7)	NS
Disease characteristics			
Uveitis, N (% of all JIA-U)	9 (3)	282 (97)	0.014**
Current, N (%)	1 (11.1)	107 (37.9)	
Past, N (%)	8 (88.9)	175 (62.1)	
Age at arthritis onset, mean years ± SD&	7.8 ± 5.6	3.89 ± 3.3	NS
Medications used			
Glucocorticoids ever&	7 (77.8)	210 (75.2)	NS
Biologics ever	7 (77.8)	159 (56.4)	NS
Non-biologics, DMARDs	8 (88.9)	260 (92.2)	NS
Extent/distribution joint involvement			
Ever, <5&	5 (62.5)	149 (52.8)	NS
JIA subtype, %			0.009**
Oligo persistent	3 (33.3)	125 (44.3)	
Oligo extended	2 (22.2)	41 (14.5)	
Poly RF (+)	0	2 (0.7)	
Poly RF (−)	0	73 (26)	
Psoriatic	0	17 (6)	
Systemic	0	3 (1.1)	
Enthesitis related arthritis (ERA)	4 (44.4)	13 (4.6)	
Undifferentiated	0	7 (2.5)	
Lab&			
ANA	3 (37.5)	186 (70)	NS
RF	0	2 (2.2)	NS
Anti-CCP	1 (25)	2 (2.5)	NS
HLA-B27	2 (28.6)	14 (9.5)	NS

& N varies since data that was "missing"or "unknown"was excluded
** p<0.05, NS = not significant
Values are N (%) unless indicated
Chi square and Mann Whitney test as appropriate.
Cases with missing and unknown data were excluded.

Results: The mean age of children with JIA-U was 10.8 years (±4.5), 80% were female and 3% were AA (Table 1). Compared to children without uveitis, they were more likely to be younger, female, require more medications, have less joint involvement, have oligoarticular disease, be ANA (+), and RF, anti-CCP and HLA-B27 (−). AA children with JIA-U were significantly different from W children and had decreased frequency of uveitis, were more likely to be male, and have oligoarticular or enthesitis related JIA (Table 2).

Conclusion: With current therapy, the prevalence estimate of JIA-U in the CARRAnet registry is 11% which consists of the largest database of children with JIA to date. Consistent with the AAP guidelines for uveitis screening, known risk markers such as the ANA, age at arthritis onset, and oligo persistent subtype were more frequent in our JIA-U cohort. However, gender and race may also be important. In concurrence with the literature, this cohort of JIA-U consisted of 3% AA who had a lower frequency of JIA-U compared to W children. There were significant differences in gender, and JIA subtype, although the status of ANA, RF and HLA-B27 were similar. This suggests that risk factors associated with uveitis may differ depending on race and implies that a change in the screening schedule may be appropriate, but needs further investigation.

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A Meta-Analysis to Estimate the "Real" Placebo Effect in Juvenile Idiopathic Arthritis (Jia) Trials. Erkan Demirkaya[1], Roberta Galasso[1], Angelo Ravelli[2], Elena Palmisani[1], Alberto Martini[2], Angela Pistorio[3] and Nicolino Ruperto[1]. [1]IRCCS G Gaslini, Pediatria II, Reumatologia, PRINTO, Genova, Italy, [2]IRCCS G. Gaslini, Pediatria II, Reumatologia and Dipartimento di Pediatria, Università degli Studi, Genova, Italy, [3]IRCCS G Gaslini, Servizio di Epidemiologia e Biostatistica, Genova, Italy

Background/Purpose: To quantify placebo effect through a systemic review of juvenile idiopathic arthritis (JIA) trials using placebo as comparator.

Methods: This study was developed according to the PRISMA statement and pre-specified study selection, eligibility criteria, data extraction, quality assessment, and statistical analysis. Studies with parallel, cross-over or withdrawal design (open label followed by a double-blind placebo withdrawal period) were included in the analysis. Publications were retrieved from MEDLINE, Web of Science, EMBASE, and the Cochrane Controlled Trials Register from 1960 to May 2010, with literature search carried out from February to December 2010. Estimates of the placebo response rate and estimates of the placebo flare rate for the withdrawal trials with 95% Confidence Intervals (CI) were calculated.

Results: A total of 10 out of 18 trials were included in the final meta-analysis synthesis. In the 5 trials with parallel design the number of responders among the patients randomized to the placebo arms were 76/246 (30.7%) for recent studies with composite scores such as the ACR pediatric 30 criteria with a pooled placebo effect estimate (fixed effect method) equal to 30% (95% CI 24–36%).

In the withdrawal design trials the number of flared patients randomized to the placebo arms was 89/123 (72.4%) with a pooled effect estimates (percentages of placebo patients who have a flare during the double blind phase in the placebo group) equal to 74% (95% CI 67–82%).

Conclusion: This systematic review provides reference data for the mean placebo effect for parallel trials and mean placebo flare rate for trials with withdrawal design.

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Long-Term Follow-up of Systemic Onset Juvenile Idiopathic Arthritis Patients Treated with Anakinra. Aldo Naselli[1], Andrea Accogli[1], Sabrina Chiesa[1], Jessica Tebaldi[1], Martina Finetti[2], Antonella Buoncompagni[1], Stefania Viola[1], Paolo Picco[1], Angelo Ravelli[3], Alberto Martini[2] and Marco Gattorno[1]. [1]G. Gaslini Institute, Genova, Italy, [2]IRCCS G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [3]Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genova, Italy

Background/Purpose: Recombinant IL-1 receptor antagonist (anakinra) is an effective treatment in a subgroup of systemic onset JIA (SoJIA). So far no information is available on the long term follow-up of SoJIA patients treated with anakinra.

Methods: Since 2005, 34 SoJIA patients (19 M, 15 F) were treated with anakinra at the staring dose of 1 mg/kg/die. Complete response was defined as the absence of systemic and articular manifestations and normal acute phase reactants at follow-up, with anakinra as a monotherapy. Other patients were considered as partial responders (still in anakinra with evidence of disease activity) or non-responders (withdrawn of Anakinra due to inefficacy or severe side effects).

Results: At baseline, the mean age was 8.4 year (range 1–17 years) with mean disease duration of 3.05 years (3 months–10.2 years). All patients had active arthritis (mean number of active joints 12.3, range 1–80), 28/34 had fever, 20/34 had skin rash. Failure of anti-TNF treatment or DMARD was observed in 11/34 and 23/34 patients respectively. Ongoing steroid treatment 33/34 patients (mean prednisone mg 0.87/kg/day, range 0.1– 3). The mean follow-up was 4.02 year (range 1.05 – 6.16). At the last follow-up 13 patients (38%) were complete responders, 5 (14%) partial responders and 16 (48%) non responder.Among complete responders, 4 patients withdrawn anakinra without relapses after a mean of 3 years of treatment, 7 are in remission using anakinra as mono-therapy, 2 patients were switched to anti IL-1 monoclonal antibody with a full response. Despite the good control of their disease 11/13 displayed at least one relapse of their disease during the follow-up with a total of 22 relapses (range 1–4 for patient). In 16 non responders patients subsequent treatments were canakinumab (1 patient), tocilizumab (5 patients), or combined immunosuppressive treatment and/or anti-TNF (10 patients), with variable response. Adverse events and complications: 13 Anakinra-treated patients had skin reactions of variable intensity and duration, in 7 patients hitching was also present without an evident skin rash. Six patients (3 responder and 3 non responders) developed a MAS during follow-up. Two non-responders patients died for acute bacterial meningitis and multi-organ failure after an episode of MAS. As previously observed, responders patients confirmed to have an higher number of active and limited joints at baseline ($p = 0.006$) and higher WBC and neutrhophils count ($p = 0.002$). These results were confirmed in the newly enrolled patients. In this latter group responder patients displayed a significantly shorter disease duration in respect to non responder patients ($p = 0.03$).

Conclusion: In responder SoJIA patients Anakinra confirm to be an effective and safe drug in the long term. The use of Anakinra is still able to dissect two distinct populations of SoJIA patients on the basis of the presence or not of a severe joint involvement with a chronic polyarticular course

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Effects of Switching From Etanercept to Adalimumab in Juvenile Idiopathic Arthritis. Gerd Horneff[1], Ivan Foeldvari[2], Gerd Ganser[3], Johannes Peter Haas[4], Kirsten Minden[5] and Hans-Iko Huppertz[6]. [1]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [2]Hamburger Zentrum Kinder-und Jugendrheumatologie, Hamburg, Germany, [3]Sankt Josef Stift, Sendenhorst, Germany, [4]Childrens Hospital, Erlangen, Germany, [5]Charite, Berlin, Germany, [6]Krinikum Bremen-Mitte, Bremen, Germany

Background/Purpose: Etanercept has proved to be effective in the majority of JIA patients (pts.). Pts. who do not tolerate or do not benefit from treatment might benefit from switching to a second TNF-inhibitor.

To analyze reasons of switching and effects of switching from Etanercept to Adalimumab.

Methods: Data of the German Etanercept in JIA Registry covering a total of >1400 pts. recruited over a ten year period and followed in a multicentre, prospective observational study were used for analysis.

Results: Of a total of 115 pts. (8% of all pts.) switched from Etanercept to a second biologic, 80 patients (70%) switched to Adalimumab. This patient cohort resembles the total registry population with regard to JIA category distribution, gender, age at onset, disease duration and positivity for ANA or HLA-B27. A history of uveitis however was more frequent than in the total registry population. (13% vs. 7%, p=0.07). Reasons for switching were inefficacy or loss of efficacy of Etanercept in 60, uveitis in 12, occurrence of Crohn's disease in 1, patient's request in 2, decision of adult rheumalogist in 1 and other adverse events in 4 cases.

Upon Etanercept, all single core set response criteria showed response to treatment but also indicated residual disease activity which slightly decreased after switching to Adalimumab. When etanercept was discontinued due to inefficacy or loss of efficacy, this patient cohort still showed a PedACR30/50/70 response in 52%/34%/24% of pts., which was markedly lower than the maximum documented response rate on Etanercept in this cohort of 89%/85%/73%. After switching to Adalimumab PedACR30/50/70 response rates reincreased to 79%/74%/54%.

Active uveitis was the reason for switching in 12 pts. All but 1 of them showed a marked clinical response of their arthritis on Etanercept. In this patient sub-cohort, the PedACR30/50/70 increased slightly from 91%/67%/50% to 100%/90%/80% after switching to adalimumab.

There were only few patients who switched due to intolerance of Etanercept. In one patient Crohn's disease occurred while on Etanercept. In this patient the arthritis had responded dramatically to Etanercept and continued to be silent on Adalimumab.

During 216 treatment years on Etanercept in the pts-cohort there were 61 AEs (0.29/y) including 12 cases with uveitis flares and 11 SAE (uveitis, Crohn's, septic arthritis, flare). During 76 treatment years on ADA there were 19 AEs (0.35/y) including 2 uveitis flares and 2 SAE (both neuropsychatric).

Conclusion: Inefficacy or loss of efficacy is an uncommon reason for discontinuation of Etanercept. If this happened nevertheless Adalimumab was chosen in many patients. Switching from Etanercept to Adalimumab resulted into a decrease of disease activity parameters while the number of patients fulfilling the PedACR-criteria increased. Tolerability of both TNF-inhibitors was comparable. After failure of the first anti-TNF-fusion protein, switching to a TNF-Antibody seems reasonable in JIA.

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Clinical and Ultrasound Outcomes of Ultrasound-Guided Ankle Injection In Juvenile Idiopathic Arthritis; An Analysis of Current Clinical Practice.
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Background/Purpose: As part of our routine practice, musculoskeletal ultrasound is performed to identify the involved structures in the ankle region in children with Juvenile Idiopathic Arthritis (JIA). Our objective was to examine clinical and ultrasound outcomes in those who have had ultrasound directed injections of the ankle joint and/or surrounding tendon sheaths.

Methods: Twenty patients with first-episodes of swollen ankles were included: (Female 15, male 5, median age 7 years, range 1–16 years, 7 oligoarticular JIA, 9 polyarticular JIA, 2 Extended Oligoarticular JIA, 2 Psoriatic JIA). They underwent ultrasound examination of the ankle region, enabling the identification of structures involved, namely ankle joint, tibialis posterior or peroneal tendon sheaths. Ankle region was injected under US guidance, using Triamcinolone or Depomedrone depending on the structure involved. Details regarding the presence of clinical ankle swelling, ultrasound findings, ankle region injected (ankle vs. tendon sheaths) and outcomes at three, six months were noted.

Results: 38 injections to the ankle region (first episode) were recorded. Thirty-seven percent had only ankle involvement, 41% with ankle and tendon sheath involvement and 22% of episodes with involvement of the tendon sheath alone (tibialis posterior and/or peroneal tendons). At six months two had required repeat injections of the region.

Follow up of all injection episodes, showed that at 3 months 31 ankles were clinically normal, 7 ankles had remained swollen, five of which had resolved at six months. Three months post injection ultrasound findings indicated 3 ankles with effusions, 2 of which persisted at 6 months requiring repeat injections. Of the 31 ankles quiescent at 3 months,8 episodes of new synovitis/tenosynovitis involving the same or a de novo ankle structure were noted at six months. One child had an ankle effusion, the remaining 7 included either tibialis posterior or peroneus longus tenosynovitis.

Conclusion: Few studies have reported the outcome of ankle injections in JIA. We report a marked improvement in clinical ankle swelling and US findings following both injection of ankle joints and tendon sheaths using US guidance. Our results appear to be significantly better than non US guided injections. In our patients, those with Polyarticular JIA more commonly required repeated injection. Those with involvement of medial and lateral ankle tendons, in particular tibialis posterior, appear to be more likely to require repeated injections to achieve full resolution of tenosynovitis. A prospective study of targeted ankle injection under ultrasound would be beneficial to confirm these findings.

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Parent and Patient Treatment Preferences in Juvenile Idiopathic Arthritis.
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Background/Purpose: Parents of patients with Juvenile Idiopathic Arthritis (JIA) are confronted with increasingly complex treatment choices. Previous studies in adults with rheumatoid arthritis (RA) have demonstrated that demographics, disease-related factors, social support, real and perceived side effects, and trust in their physician play an important role in the process of medication decision-making. JIA is the most common chronic rheumatic disease in children; yet, there are no studies evaluating patient treatment preferences in pediatric rheumatology.

Objectives: To understand the factors that influence parents' decision-making regarding treatment for their children with JIA.

Methods: Using a multicenter cross sectional prospective study design, parents with children between the ages of 1 to 17 with a definite diagnosis of JIA were invited to participate. Questionnaires were completed by one of the parents, patient if older than 13 years of age and the physician or nurse practitioner evaluating the patient.

Results: To date, 131 eligible patients have been invited to participate. Of these, 124 subjects (95%) completed the questionnaire. In a descriptive analysis, 92% of the parents were Caucasian, 82% married, 54% reported having at least a college degree and 70% were considered to have good health literacy. Most of the children were white (88%) and female (75%), with a mean age of 10 years. Parents reported a mean disease activity of 7.13 at the time of diagnosis and associated uveitis in 20% of their children. All patients had medical insurance, 75% private insurance and 24% Medicaid. When families were asked to rank their considerations prior to initiating medical treatment for JIA, medication safety ranked as the most important, followed by efficacy, associated side effects, and physician's experience with the treatment. Pediatric rheumatologists and nurse practitioners were considered by parents and patients to be the most reliable and important source for information about arthritis (90% vs. 86%) and options for medical treatment (90% vs. 88%); results correlated with a physician trust score of 85 (range 0–100). Fifty five percent of patients older than 13 years of age reported being involved in the medication decision-making process. In our cohort, 96% of parents have used nonsteroidal antiinflammatory drugs (NSAIDs) as part of the treatment for their JIA children, 81% have used disease modifying anti-rheumatic drugs (DMARDs), 59% intra-articular joint injection (IAJI), 58% biologics, 51% systemic steroids and 22% herbal medicines. Time of initiation varied; NSAIDs, DMARDs, IAJI, biologics and systemic steroids were initiated in 95%, 51%, 63%, 34% and 14% of patients within 3 months of diagnosis. Use of DMARDs and biologics increased over time, with up to 76% and 26% respectively within 6 months of diagnosis.

Conclusion: As reported in adult patients with RA medication safety, efficacy, side effects and physician's experience were considered to be the most important factors when initiating medical treatment for JIA. Pediatric rheumatologists and nurse practitioners are the most preferred source of information about JIA and options for medical treatment.

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Intra-Articular Infliximab Treatment of Refractory TMJ Arthritis in Children with JIA.
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Background/Purpose: Temporomandibular joint (TMJ) arthritis occurs in up to 80% of children with juvenile idiopathic arthritis (JIA). Untreated, TMJ arthritis leads to micrognathia, poor mouth opening, facial dysmor-

phism, and life-time disability. Unlike other joints in children with JIA, TMJ arthritis responds poorly to systemic therapy, including anti-tumor necrosis factor (TNF) agents. Nevertheless, like other joints, TMJ arthritis responds to intra-articular (IA) long-acting corticosteroids, such as triamcinalone hexacetonide (TH). However, post-IA TH TMJ injections are effective in increasing inter-incisor openings and demonstrating improvement in inflammation by MRI in only about 50% of JIA patients treated. Moreover, repeated IA TH TMJ injections yield only minimal benefits. Recently, repeated IA infliximab TMJ injections, in an adult with psoriatic arthritis and severe TMJ arthritis refractory to systemic infliximab and IA corticosteroids, notably improved TMJ symptoms and halted progression of disease as noted by CT [Scand J Rheumatol 2008;37:155]. Interestingly, considerable benefit was noted after the first infliximab injection.

Methods: Five children (3 boys & 2 girls, ranging 11–21 years) with JIA and TMJ arthritis, refractory to at least 2 rounds of IA TH TMJ injections, received IA infliximab injections for their progressive TMJ arthritis. Five mg of infliximab was injected into each TMJ under deep sedation by an experienced oromaxillofacial surgeon (PDW). Approval for the procedures was attained from the UAB University Hospital Pharmacy and Therapeutics Committee. Demographic and clinical data were abstracted from the electronic medical records, and the extent and acuity of TMJ arthritis was documented by TMJ MRI with contrast before and after IA TMJ injections. Side effects from the IA infliximab were noted if present.

Results: TMJ arthritis was progressive in 5 children with spondyloarthopathies (1 HLA-B27+ psoriatic JIA, 4 with enthesitis-related arthritis JIA, 2 of whom had inflammatory bowel disease) despite multiple prior IA TH TMJ injections. TMJ arthritis was active clinically and by MRI despite systemic anti-TNF therapy [2 on etanercept, 2 on infliximab, 1 on adalimumab, +/− methotrexate (n=3)]. At the time of the IA infliximab TMJ injections, no other joints were active by history and clinical exam. All 5 JIA patients tolerated the IA infliximab TMJ injections without any reported side effects (follow-up range, 2 to 17 months). Two of the 5 patients had follow-up TMJ MRI exams post-IA infliximab injections of the TMJs. For one patient with bilateral erosive TMJ arthritis, there was no evidence of active left arthritis and minimal synovial enhancement on the right. This was the first of 5 TMJ MRI exams that did not reveal progression of arthritis. For the other child with bilateral erosive TMJ arthritis, there was no active disease on the left but active synovial enhancement and fluid on the right. However, this was the first of 6 TMJ MRI exams without evidence of progressive arthritis.

Conclusion: IA infliximab TMJ injections in children with JIA and severe refractory TMJ arthritis appear to be safe and potentially effective means of slowing TMJ arthritis.

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Utilization of Biologic and Non-Biologic Disease Modifying Anti-Rheumatic Drugs in the Treatment of Juvenile Idiopathic Arthritis: A Cross-Sectional Analysis of the Childhood Arthritis and Rheumatology Research Alliance Registry. Timothy Beukelman[1], Sarah Ringold[2], Trevor Davis[3], Esi M. Morgan DeWitt[4], Christina F. Pelajo[5], Pamela Weiss[6], Yukiko Kimura[7] and for the CARRAnet investigators. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]Children's Hosp Regional Med, Seattle, WA, [3]Floating Hospital for Children at Tufts Medical Center, Boston, MA, [4]Cincinnati Children's Hospital, Cincinnati, OH, [5]Tufts Medical Center, Boston, MA, [6]The Children's Hosp of Philade, Philadelphia, PA, [7]Hackensack Univ Medical Ctr, Hackensack, NJ

Background/Purpose: We characterized DMARD utilization in the treatment of JIA in clinical practice on a national level and determined patient factors associated with medication use.

Methods: We analyzed cross-sectional CARRA registry baseline enrollment data from 51 U.S. clinical sites for all children with JIA from May 2010 through May 2011. Patients were categorized into 3 discrete treatment groups comprising all categories of JIA: history of arthritis of ≤4 joints, history of arthritis of ≥5 joints, and systemic arthritis. Current and past medication use were combined. We calculated risk ratios (RR) to estimate univariate associations between patient factors and medication use. Owing to multiple comparison testing, only associations with p value <0.005 are reported.

Results: Among 1,045 children with history of ≤4 joints, 52% received methotrexate (MTX), 10% sulfasalazine (SSZ) and 1% leflunomide (LEF). MTX use was associated with psoriatic arthritis (PsA) (RR 1.5 (1.3–1.8)), uveitis (RR 1.8 (1.6–2.0)), and negatively associated with enthesitis related arthritis (ERA) (RR 0.7 (0.6–0.8)). SSZ use was associated with ERA (RR 4.0 (2.8–5.8)) and sacroiliac (SI) tenderness (RR 4.5 (3.2–6.6)). Among children with history of ≤4 joints, the only biologic class received was TNF inhibitor (TNFi) by 26% (14% of these had not received MTX, LEF, or SSZ). TNFi use was associated with PsA (RR 1.8 (1.4–2.5)), ERA (RR 1.6 (1.3–2.0)), uveitis (RR 2.0 (1.7–2.5)), inflammatory bowel disease (RR 2.5 (1.7–3.5)), SI tenderness (RR 2.0 (1.6–2.6)), and enthesitis (RR 1.8 (1.4–2.3)). TNFi use without MTX, LEF, or SSZ was associated with ERA (RR 2.9 (1.6–5.1)) and enthesitis (RR 3.3 (1.9–5.8)).

Among 1,443 children with history of ≥5 joints, 83% received MTX, 8% SSZ, and 5% LEF (only 1 of these had not received MTX). MTX use was associated with RF+ polyarthritis (RR 1.1 (1.1–1.2)), CCP antibody (RR 1.2 (1.2-1.2)), and negatively associated with ERA (RR 0.7 (0.6–0.8)). SSZ use was associated with ERA (RR 3.9 (2.8–5.6)) and SI tenderness (3.2 (2.3–4.7)). Among children with history of ≥5 joints, 56% received any biologic: 56% received any TNFi (6% of these had not received MTX, LEF, or SSZ), 4% abatacept (2 of these had not received TNFi), 1% rituximab, and 1% anakinra. TNFi use was associated with RF+ polyarthritis (RR 1.3 (1.2–1.5)), CCP antibody (RR 1.4 (1.2–1.6)), uveitis (RR 1.3 (1.1–1.4)), and psoriasis rash (RR 1.3 (1.1–1.5)). TNFi use without MTX, SSZ, or LEF was associated with ERA (RR 2.9 (1.5–5.7)) and SI tenderness (RR 2.8 (1.5–5.2)). Among TNFi users, 30% received more than 1 TNFi and 6% received 3 or more TNFi.

Among 246 children with SJIA, 81% received MTX and 13% cyclosporine (19% of these had not received MTX). MTX use was associated with polyarthritis (RR 1.4 (1.2–1.7)). Among children with SJIA, 65% received any biologic: 46% received any TNFi, 39% any IL-1 inhibitor, 5% tocilizumab, 5% abatacept, and 1% rituximab. TNFi use was associated with polyarthritis (RR 1.9 (1.3–2.8)).

Conclusion: Significant proportions of children with JIA are treated with biologic agents, particularly those with RF+ polyarthritis, uveitis, or systemic arthritis. Children with ERA are less likely to receive non-biologic DMARDs prior to TNFi use.

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Health Related Quality of Life and Psychosocial Developmental Trajectory in Young Female Beneficiaries with Juvenile Idiopathic Arthritis. Lotte Haverman[1], Eefje J.A. Verhoof[1], Heleen Maurice-Stam[1], Hugo S.A. Heymans[1], D. Gerlag[2], Marion A. J. Van Rossum[1] and Martha A. Grootenhuis[1]. [1]Emma Children's Hospital/Academic Medical Center (AMC), Amsterdam, Netherlands, [2]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: It is generally recognized that for all children the fulfilling of age-specific psychosocial developmental tasks in childhood is of great importance to adjustment in adult life, including participation in society. For young adults with Juvenile Idiopathic Arthritis (JIA) this is more difficult. We assume that the achievement of psychosocial milestones while growing up (psychosocial developmental trajectory) is also related to labour participation. A part of all young adults with JIA have to apply for disability benefits. This study assessed the health related quality of life (HRQOL) and the psychosocial developmental trajectory of young female beneficiaries with JIA compared to peers from the Dutch general population.

Methods: Data from the database of the Dutch EMWAjong-study, a Dutch cross-sectional study examining psychosocial factors affecting the employment of young adults with disability benefits (Wajong) because of chronic somatic diseases or childhood derived physical limitations, were used. From the EMWAjong database, 46 young adults (11.1%) reported to have JIA; including 43 females (16.1% of all females in the EMWAjong database). The data of these 43 young females with JIA were used for analyses (age: 25.8, SD = 2.3). The participants completed the RAND-36 (HRQoL) and the Course of Life Questionnaire (CoLQ; psychosocial developmental trajectory). Differences between respondents and the peer group were tested using analysis of variance and logistic regression analysis, both by group and age. Effect sizes (d) and odds ratios (OR) were calculated.

Results: The HRQOL of the beneficiaries (N = 43) was significant lower compared to the peer group on 6 out of the 8 domains: physical ($p<0.001$, $d=2.6$), social ($p<0.001$, $d=0.8$) role limitations physical ($p<0.001$, $d=1.3$), vitality ($p<0.001$, $d=0.7$), bodily pain ($p<0.001$, $d=1.4$), health perceptions ($p<0.001$, $d=1.8$). In addition, the beneficiaries achieved fewer milestones ($p<0.01$) in the autonomy (OR 0.26), social (OR 0.23–0.39) and psychosexual domains (OR 0.38–0.47) than the peer group.

Conclusion: Young females with JIA who have to apply for disability benefits are at risk for impaired HRQOL and a delay in their psychosocial developmental trajectory. We recommend parents, health care providers, occupational therapists and schools to pay systematic attention to the development of social and independent functioning of children with JIA in order to optimise their adaptation to society at the time of transition to adulthood.

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Enthesitis Is a Significant Predictor of Decreased Quality of Life, Function, and Arthritis-Specific Pain Across Juvenile Idiopathic Arthritis (JIA) Categories: Preliminary Analyses From the CARRAnet Registry. Pamela Weiss[1], Timothy Beukelman[2], Laura E. Schanberg[3], Yukiko Kimura[4], Robert A. Colbert[5] and CARRANet Investigators[6]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]Duke University Medical Center, Durham, NC, [4]Hackensack Univ Medical Ctr, Hackensack, NJ, [5]NIAMS NIH, Bethesda, MD, [6]Stanford

Background/Purpose: Descriptions of quality of life, function, and level of pain of JIA and differences in these outcomes between JIA categories are sparse. Additionally, the relative impact of clinical factors such as enthesitis, active joint count, and medications on quality of life, function, and pain in JIA have not been well described.

Methods: We conducted a retrospective cross-sectional study of baseline data for children with JIA who were enrolled in the CARRAnet registry between May 2010 and June 2011. The CARRAnet registry is a multicenter registry of U.S. children with rheumatic diseases organized by the Childhood Arthritis Rheumatology and Research Alliance (CARRA). Differences in clinical characteristics between JIA categories were compared using the Kruskal-Wallis or chi-square test, as appropriate. We tested whether certain clinical characteristics of JIA were associated with scores on the Childhood Health Assessment Questionnaire (CHAQ), Health Related Quality of Life (HRQOL), and parent/child arthritis-specific pain visual analogue scale (VAS) using multivariable linear and ordinal logistic regression, as appropriate.

Results: During the study period there were 2,571 patients evaluated for JIA. Patient characteristics by JIA category are presented in Table 1. Scores on the CHAQ, HRQOL, and parent/child pain VAS differed significantly between JIA categories (Table 1). Significant clinical predictors of a worse CHAQ score were a having RF+ polyarticular disease ($p=0.02$), oligoarticular extended disease ($p=0.03$), Enthesitis-related arthritis (ERA) ($p<0.01$), higher active joint count ($p<0.01$), enthesitis ($p=0.01$), and current non-steroidal anti-inflammatory (NSAID), biologic, or steroid use (all $p<0.01$). Significant clinical predictors of a worse HRQOL score were older age ($p<0.01$), systemic JIA ($p=0.01$), ERA ($p=0.02$), higher active joint count ($p<0.01$), and current NSAID, biologic, or steroid use (all $p<0.01$). Significant clinical predictors of a higher pain VAS score were older age ($p<0.01$), ERA ($p<0.01$), higher active joint count ($p<0.01$), enthesitis ($p<0.01$), and current NSAID, biologic, or steroid use (all $p<0.01$). The pair-wise correlation between standardized z-scores of physician global assessment of disease activity and parent/patient-reported CHAQ, HRQOL, and arthritis-specific pain VAS scores were low (0.37, 0.30, and 0.43, respectively).

Table. Patient characteristics by JIA subtype

	Systemic	Poly RF-	Poly RF+	Oligo persistent	Oligo extended	PsA	ERA	Undifferentiated	p-value
N (%)	232 (9)	761 (30)	190 (7)	697 (27)	210 (8)	161 (6)	268 (10)	52 (2)	
Active joint count, median (IQR)	0 (0, 2)	0 (0, 2)	1 (0, 4)	0 (0, 1)	1 (0, 2)	0 (0, 2)	1 (0, 2)	0 (0, 1)	<0.01
Enthesitis N (%)	2 (1)	10 (1)	2 (1)	2 (0.5)	6 (3)	11 (7)	62 (24)	3 (6)	<0.01
CHAQ, median (IQR)	0.1 (0, 0.6)	0.1 (0, 0.6)	0.3 (0, 0.7)	0 (0, 0.3)	0.1 (0, 0.6)	0.1 (0, 0.5)	0.3 (0, 0.6)	0.3 (0, 0.6)	<0.01
Parent/child pain VAS	1 (0, 4)	2 (0, 5)	2 (1, 5)	1 (0, 3)	1 (0, 4)	2 (0, 4)	3 (1, 6)	2 (0, 4)	<0.01
HRQOL N(%)	51 (22)	157 (21)	29 (15)	221 (32)	54 (26)	38 (24)	41 (16)	13 (25)	<0.01
Excellent	85 (37)	323 (43)	74 (39)	305 (44)	100 (48)	65 (40)	110 (41)	23 (44)	
Very good	81 (35)	246 (32)	75 (40)	154 (23)	53 (25)	56 (35)	99 (37)	15 (29)	
Good	11 (5)	29 (4)	11 (6)	9 (1)	2 (1)	2 (1)	16 (6)	1 (2)	
Poor	2 (1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Very Poor									
Physician global VAS, median (IQR)	1 (0, 3)	1 (0, 2)	2 (0, 3)	1 (0, 2)	1 (0.3)	1 (0.2)	1 (0, 2)	1 (0, 2)	<0.01

Conclusion: Significant differences on the CHAQ, HRQOL, and parent/child pain VAS exist across JIA categories. The ERA category consistently predicted worse scores on all 3 measures. Enthesitis is a previously unrecognized significant predictor of decreased function and increased pain. Future studies should investigate how to better quantify enthesitis and its response to therapy.

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A Cross Sectional Study of Juvenile Idiopathic Arthritis in African American Children Compared with Non-Hispanic White Children in the Childhood Arthritis and Rheumatology Research Alliance Registry. Sampath Prahalad[1], Sheila Angeles-Han[1], Christina F. Pelajo[2], Christine W. Kennedy[1], Lori Ponder[1], Jorge M. Lopez-Benitez[2], Larry B. Vogler[1] and CARRANet Investigators[3]. [1]Emory University School of Medicine, Atlanta, GA, [2]Tufts Medical Center, Boston, MA, [3]Stanford

Background/Purpose: JIA is the most common chronic childhood arthropathy with an estimated prevalence of ~1/1000 children under 16 years of age. Although JIA affects male and female children of all races, there are only few epidemiologic investigations in small cohorts that describe the characteristics of JIA in African American (AA) children. Our objective is to compare disease characteristics between AA and Non-Hispanic White (NHW) children with JIA enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, the largest multicenter observational Registry.

Methods: Children with JIA from pediatric rheumatology clinics in the US were enrolled in the CARRAnet Registry from May 2010 until June 2011. Demographic and disease-related data were collected from time of diagnosis to enrollment visit. Children reporting Hispanic ethnicity and those who categorized themselves as more than one race were excluded. Non-Hispanic African American children with JIA were compared with Non-Hispanic White children with JIA. Nominal variables were compared using Chi square or Fisher's exact tests. Continuous variables were compared using Student's T test.

Results: In all, 2167 NHW children and 125 AA children were analyzed. Table 1 shows demographic and disease characteristics of NHW and AA children. AA children with JIA were significantly older at disease onset, presentation and enrollment less likely to be female and have a family history of autoimmunity. There were significant differences in the frequencies of different JIA subtypes between AA and NHW children. AA children were more likely to have RF+ polyarticular JIA and less likely to have psoriatic JIA or uveitis. Laboratory variables demonstrated that AA children with JIA were less likely to have positive ANA and HLA B27, and more likely to have confirmed RF and CCP compared to NHW children. The differences in age of onset between AA and NHW children persisted after excluding polyarticular RF+ JIA (6.0 vs 8.4 years; $p < 2.5\times10^{-6}$).

Table 1. Characteristics of NHW and AA children with JIA*

	NHW	AA	p
Total Number	2167	125	
Age at baseline visit (mean ±SD)	11.4 ± 4.7	12.8 ± 4.4	**$<7\times10^{-9}$**
Age at symptom onset (mean ± SD)	6.2 ± 4.3	8.8 ± 4.3	**$<4\times10^{-9}$**
Age first seen by pediatric rheumatologist (mean ±SD)	7.1 ± 4.5	9.5 ± 4.5	**0.0009**
Gender: females	1594 (73)	78 (62)	**0.006**
Income	.	.	**$<1\times10^{-7}$**
<U$49,999	475 (26)	60 (63)	
U$50,000- 99,999	670 (36)	29 (30)	
>U$100,000	710 (38)	6 (6)	
Health insurance	2116 (99)	117 (99)	0.66
Family history of autoimmunity	577 (27)	22 (18)	**0.03**
JIA subtype	.	.	
ERA	223 (10)	7 (10)	0.14
Oligoarticular extended	193 (9)	5 (4)	**0.02med**
Oligoarticular persistent	593 (27)	22 (18)	0.06
Polyarticular RF-	660 (31)	27 (22)	**0.03**
Polyarticular RF+	108 (5)	24 (19)	**1×10^{-7}**
Psoriatic	150 (7)	2 (2)	**0.02**
Systemic-onset	168 (8)	20 (16)	**0.001**
Undifferentiated	62 (3)	6 (5)	ns
Uveitis	258 (12)	5 (4)	**0.008**
Measures of disease	.	.	
CHAQ (mean)	0.34	0.58	**0.0004**
MD Global (mean)	1.52	2.55	**$<8\times10^{-5}$**
Laboratory tests	.	.	
Positive ANA	970 (50)	36(34)	**0.001**
Positive HLA-B27	168 (14)	5 (6)	**0.05**
Confirmed RF positive	64 (9)	17(33)	**1×10^{-7}**
Anti-CCP positive	61 (8)	17(27)	**1×10^{-7}**
Treatment	.	.	.
Use of systemic steroids	1456 (68)	83 (70)	0.64
Use of DMARD ever	1675 (78)	91 (76)	0.66
Use of biologic ever	967 (45)	67 (55)	**0.03**

* All values are N(%) of those tested/reporting data for particular variables, except as indicated.

Conclusion: This is the largest described cohort of AA children with JIA, and we confirm reports of differences in disease characteristics reported in smaller earlier studies. Compared to non-Hispanic White children with JIA, African American children with JIA demonstrate significant differences in disease characteristics. Specifically they are older at disease onset, are more likely to have RF/CCP positive polyarthritis and are less likely to have uveitis, psoriatic arthritis, ANA or HLA B27. These observations support that the phenotype of JIA is different in African American children with JIA.

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Development of Consensus Treatment Plans for New-Onset Systemic Juvenile Idiopathic Arthritis. Esi Morgan DeWitt[1], Timothy Beukelman[2], Peter A. Nigrovic[3], Karen Onel[4], Sampath Prahalad[5], Rayfel Schneider[6], Matthew Stoll[7], Norman T. Ilowite[8], Carol A. Wallace[9] and Yukiko Kimura[10]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]Brigham and Women's Hospital, Boston, MA, [4]University of Chicago, Chicago, IL, [5]Emory Children's Center, Atlanta, GA, [6]Hospital for Sick Children, University of Toronto, Toronto, ON, [7]UT Southwestern Medical Center, Dallas, TX, [8]Children's Hospital Montefiore, Bronx, NY, [9]Childrens Hosp & Regional Med, Seattle, WA, [10]Hackensack Univ Medical Ctr, Hackensack, NJ

Background/Purpose: Currently, there is significant variability in the therapeutic approaches to new onset systemic Juvenile Idiopathic Arthritis (sJIA), as evidenced by surveys using case presentations administered to Childhood Arthritis and Rheumatology Research Alliance (CARRA) members. Understanding the comparative effectiveness of these diverse therapeutic approaches would likely result in better health outcomes. We therefore aimed to derive consensus based treatment plans, standardized assessment intervals and data collection plans for clinical use to facilitate comparative effectiveness studies for new-onset sJIA.

Methods: Case-based surveys were administered to CARRA members to identify prevailing treatments for new-onset sJIA. A 2-day consensus conference in April 2010 employed modified nominal group technique to formulate preliminary treatment plans and determine important data elements for collection. Follow-up surveys were employed to refine the plans and assess clinical acceptability.

Results: The CARRA sJIA Core Workgroup developed standardized treatment approaches, and a recommended schedule of visits and monitoring parameters. Four treatment plans were developed: 1) a corticosteroid based plan, 2) a methotrexate based plan with corticosteroids, 3) an anti-IL1 (anakinra) based plan, and 4) an anti-IL6 (tocilizumab) based plan. The biologic DMARD-based plans are to be used with or without corticosteroids. A survey of the CARRA membership was conducted in December 2010 to assess the acceptability and feasibility of these strategies. There was a 63% response rate (133 of 211 surveyed), of which 92.6% expressed willingness to follow 1 of the initial 3 treatment plans listed above. 82% concurred that an anti-IL6 based treatment arm should also be offered, which became the basis for development of the fourth treatment plan. Consensus was reached at the 78–85% level for all topics posed (specific details of treatment plans, ability to use plans). A feasibility study estimated that over 250 patients could be enrolled in these plans per year, and that physicians would likely enroll one-third to one-quarter of the patients in each of the original 3 plans.

Conclusion: The use of consensus derived standardized treatment plans for new onset SJIA is feasible and acceptable to most North American rheumatologists who are members of CARRA. Four treatment approaches to the first 9 months of treatment will be published as frameworks for use. Coupled with standardized data collection at routine intervals, use of these treatment plans will serve as the basis for rigorous study of comparative effectiveness of the regimens as used in clinical practice.

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Juvenile Idiopathic Arthritis (Jia) Affected Sibling Pairs Present High Correlation for ANA and ILAR Category. Giovanni Filocamo, Clara Malattia, Ivan Foeldvari, Valda Stanevicha, Susan Nielsen, Troels Herlin, Chris Pruunsild, Francesco Zulian, Zsolt Balogh, Frank Dressler, Ingrida Rumba, Maria Giannina Alpigiani, Elisabetta Cortis, Fernanda Falcini, Ralf Trauzeddel, Giuseppina Calcagno, Loredana Lepore, Maria Alessio, David Glass, Susan Thompson, Alberto Martini and Nicolino Ruperto. IRCCS G Gaslini, Pediatria II, PRINTO, Genova, Italy

Background/Purpose: 1) To investigate the clinical phenotypes and demographic characteristics of affected sibling pairs (ASPs) with juvenile idiopathic arthritis (JIA). 2) To provide an international resource of JIA DNA samples and a base of knowledge from which all genes contributing to the pathogenesis of JIA can be identified.

Methods: This is a cross-sectional multicentric study in which all paediatric rheumatology centres belonging to the PRINTO network were asked to participate. PRINTO asked to provide demographic and clinical characteristics of the ASPs through electronic format and to collect DNA samples of JIA familiar cases, including all first degree relatives, deriving from the different centres.

Results:

Table 1. Demographic, clinical features and concordance between the sibs (2 or more within the same family) of the 106 individual affected sibpairs with JIA

	N (%)	Mean (SD)	Median	Min	Max	Conc.
Male	25 (24)					0.24
Female	81 (76)					0.79
Onset age &endash;years		6.6 (4.4)	6.2	0.5	16.3	
JIA category	0 (0)					0.79
Systemic arthritis	61 (57.6)					/
Oligoarthritis persistent	18 (17)					0.85
Oligoarthritis extended	21 (19.8)					0.5
Polyarthritis RF negative	2 (1.9)					0.9
Polyarthritis RF positive	3 (2.8)					1
Psoriatic arthritis	0 (0)					0.67
Enthesitis related arthritis	1 (0.9)					/
Other						0
Presence of ANA	56 (56)					0.78
Absence of ANA	44 (44)					0.68
Presence of iritis	11 (10)					0.36
Absence of iritis	86 (81)					0.9

Conclusion: Preliminary results confirm the findings of earlier studies showing familial aggregation of clinical features among ASPs. In our study we observed high concordance of the presence of antinuclear antibodies (ANA), providing evidence for a genetic background in this disease. The DNA samples collected will allow to develop future studies on JIA.

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How Important Is Early Magnetic Resonance Imaging of the Temporomandibular Joint for the Treatment of Children with Juvenile Idiopathic Arthritis? Rotraud K. Saurenmann[1], Raphael Hauser[1], Silke Schroeder[1], Elvira Cannizzaro[1], Lukas Muller[2] and C.J. Kellenberger[1]. [1]University Children's Hospital, Zurich, Switzerland, [2]Center for dental, oral and maxillofacial diseases, Zurich, Switzerland

Background/Purpose: Temporomandibular joint (TMJ) arthritis is very common in children with juvenile idiopathic arthritis (JIA) but often clinically asymptomatic. Magnetic resonance imaging (MRI) is the most reliable examination method for early TMJ arthritis but in young children sedation is often required.

Study Aims: To evaluate how many patients with newly diagnosed JIA will profit from an early MRI of the TMJ for the management of their arthritis.

Methods: The database of our clinic was searched for all patients with a date of diagnosis of JIA between January 2007 and December 2010. The charts of all patients from this inception cohort were reviewed for MRI of the TMJ, diagnosis of TMJ involvement and JIA treatment.

Results: We found 147 patients with newly diagnosed JIA during this period. In 111 (76%) at least 1 MRI of the TMJ was available. Reasons why no TMJ MRI was done were parents' refusal (10), MRI of other locations (7) and fixed orthodontic appliances (16). A diagnosis of TMJ arthritis based on synovial enhancement on MRI was made in 91/111 (81%) patients. The first MRI was done at a median interval of 5 months from the diagnosis of JIA, and 61/111 patients (55%) required sedation for their first MRI. TMJ arthritis was diagnosed in 53/61 (87%) requiring sedation and in 35/50 (70%) patients without sedation ($p = 0.03$). Following the first TMJ MRI, intra-articular steroid injections were performed into 107 TMJs of 60 patients. 48/147 (33%) patients received at least one DMARD to control their disease, and in 12/48 (25%) the first DMARD was started following the first TMJ MRI. Factors associated with TMJ involvement as demonstrated by MRI were JIA subtype ($p= 0.007$) and a younger age at diagnosis of JIA ($p= 0.04$).

Conclusion: In our cohort of newly diagnosed JIA patients TMJ arthritis was very common. Early TMJ MRI led to changes in treatment in 65% of patients with additional joint injections in 60 patients and start of systemic medication in 12 patients. We especially recommend performing TMJ MRI in young children even if they require sedation, as they have an increased rate of TMJ involvement.

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Clinical and Immunological Effects of Etanercept on Juvenile Idiopathic Arthritis in China. Caifeng Li, Xiaohua Tan, Xiaohu He, Weiying Kuang, Yifang Zhou, Jiang Wang, Tongxin Han, Junmei Zhang, Jing Gao and Chao Li. Beijing Children's Hospital affiliated to Capital Medical University, Beijing, China

Background/Purpose: To study clinical effects and immunological mechanism of Etanercept in the treatment of Juvenile Idiopathic Arthritis (JIA).

Methods: (1) Clinical Observation:During October 2006 to February 2011, 241cases of refractory JIA patients were enrolled. All of them were given Etanercept(production of CPGJ, 0.4mg/kg/dose, given twice weekly, subcutaneous injection) with typical JIA treatment regimen. The course of Etanercept treatment was at least 3 months. We collected and recorded the clinical data before Etanercept treatment and at 2 weeks, 1, 3, 6, 12, 24 and 48 months after its use, respectively. We analyzed ACR Pedi 30/50/70 response rate according to the clinical data, and also analyzed inflammation indexes (ESR, CRP, HGB, WBC and serum ferritin), as well as observed the radiology image changing. Meanwhile, we recorded the side effect of Etanercept. (2) Immunology Study: During October 2006 to September 2009, 103cases of refractory JIA patients were enrolled. We collected peripheral serum from JIA patients before Etanercept treatment and at 2 weeks, 1, 3, 6, 12 and 24 months after treatment. We tested the level of TNF-α, IL-1β, IFN-γ and IL-6 by ELISA method. All data analyses were performed with the SPSS 11.5 software.

Results: 241 cases of JIA patients were enrolled, 120 boys and 121 girls. The age was between 2–18 years, mean age was 10 years. There were 67 cases of ERA, 93 cases of Poly JIA, 40 cases of SoJIA (11 cases of MAS among SoJIA patients) and 2 cases of JPsA. (1) Clinical effect: The ACR Pedi 30/50/70 response rates were 48%, 26% and 13% at 2 weeks after Etanercept treatment. The ESR and CRP level of all JIA patients were decreased significantly compared with baseline ($P<0.01$). The ACR Pedi 30/50/70 response rates were 74%, 58% and 23% after 6 months. 1.8% children with severe bone destruction had improved significantly by imaging after one year treatment. (2) Immunological effects: Compared with baseline, the serum TNF-α, IL-1β, IFN-γ level of all JIA patients were decreased after treatment ($P<0.05$). The serum IL-6 level of ERA and Poly JIA patients improved significantly ($P<0.05$), but SoJIA patients didn't improve significantly ($P>0.05$).Among the SoJIA patients who mainly suffered from joint symptoms at the later disease stage, inflammation indexes and clinical symptoms improved after using Etanercept. The safety of the drug: there were only 4 cases of JIA patients had temporary skin rashes within 2 weeks of the drug administration. The rashes disappeared automatically in several days, there was no influence on drug administration. 1 case of patient discontinue of the medication due to tuberculosis infection after one year of treatment, but without clinical symptom.

Conclusion: Etanercept could relief clinical symptoms, controll inflammation reaction and decrease the dosage of steroid in all types of JIA. But the effects of Etanercept on SoJIA patients with systemic symptoms or MAS was limited. The effect of Etanercept on Poly JIA and ERA was significant. Etanercept could control the clinical symptoms might be due to reducing serum inflammatory cytokines level.

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Effectiveness and Safety of Switching Between Biologics in Juvenile Idiopathic Arthritis; Results From the Dutch ABC Register. Marieke H. Otten[1], Femke H.M. Prince[2], Janneke Anink[1], Marion A. J. Van Rossum[3], Esther P.A.H. Hoppenreijs[4], Simone L. Gorter[5], Wineke Armbrust[6], Koert M. Dolman[7], Yvonne Koopman-Keemink[8], Joost F. Swart[9], J. Merlijn Van den Berg[10], Nico M. Wulffraat[9], Rebecca Ten Cate[11] and Lisette W.A. Van Suijlekom-Smit[12]. [1]ErasmusMC Sophia Children's Hospital, Rotterdam, Netherlands, [2]Brigham and Women's Hospital, Boston, MA, [3]Emma Children's Hospital/Academic Medical Center (AMC), Amsterdam, Netherlands, [4]St Maartenskliniek and Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [5]University Hospital Maastricht, Maastricht, Netherlands, [6]Beatrix Children's Hospital, University Medical Centre Groningen, Groningen, Netherlands, [7]St. Lucas Andreas Hospital and Reade Institute, Amsterdam, Netherlands, [8]Hagaziekenhuis Juliana Children's Hospital, Den Haag, Netherlands, [9]University Medical Center Utrecht, Utrecht, Netherlands, [10]Emma Children's Hospital/ Academic Medical Centre and Reade Institute, Amsterdam, Netherlands, [11]Leiden University Medical Center, Leiden, Netherlands, [12]ErasmusMC Sophia Childrens Hospital, Rotterdam, Netherlands

Background/Purpose: The introduction of biologics has led to dramatic improvements in juvenile idiopathic arthritis (JIA). However, despite this treatment success, some patients need to discontinue these agents because of a lack of effectiveness or intolerance. Little is known about the effectiveness and safety of switching to a second or third biologic for JIA patients who failed their first.

Methods: The Arthritis and Biologicals in Children (ABC) register (observational study, ongoing since 1999), includes all Dutch JIA patients who use or previously used biologics. Data on the course of the disease are prospectively retrieved, including when biologics were discontinued or type of biologic switched, until transfer to the adult care. Drug survival (i.e. median duration from start until discontinuation due to ineffectiveness or adverse events (AEs)) for the first, second, and third course biologics was estimated with Kaplan-Meier. AE-rates within 1 year after start of the first, second and third course biologic were calculated.

Results: Of the 411 JIA patients who started their first biologic, 88 patients (21%) switched to a second, and 28 (7%) patients to a third course biologic. Of the 88 patients who switched, 81 started etanercept as first biologic, and switched from etanercept to adalimumab (n=46), to infliximab (n=21) or to anakinra (n=14). Patients who also started a third course biologic most often switched between the anti-TNF-alpha agents only (n=19). The median follow-up duration since start of the second course biologic was 14.2 (4.2–29.4) months, and since start of the third course biologic 21.1 (IQR 3.4–33.6) months. Patients who switched to a second biologic had more often the systemic subtype ($p<0.000$), and at start of the first biologic higher disability scores ($p=0.001$) and more joints with arthritis ($p<0.000$) than patients who did not switch. Ineffectiveness of treatment (primary non-response or loss of response) was the most frequently reported reason for switching. At 12 months of treatment, drug survival of the first course biologics (83% (95% CI 79–87%)) was higher than for the second course (48% (95% CI 36–61%)), and third course 64% (95% CI 44–84%). The drug survival of the second course biologics was not different for subtype (systemic vs. non-systemic subtypes), type of second biologic started, and reason for switch. The AE-rates within 1 year after start were 0.21 AEs/patient-year for the first course, 0.20 AEs/patient-year for the second course, and 0.17 AEs/patient-year for the third course.

Conclusion: In daily practice, switching between biological agents occurred frequently. The observed switching patterns seem to be influenced by the availability of biologics within the study period. Risk factors for switching were the systemic-onset subtype and at start of the first biologic high disability scores and many joints with arthritis. While the drug survival of the first course was higher, still 48% of the switchers continued their second biologic after 12 months of treatment. Switching to a second (and third) course biologic seems to be safe and a reasonable option.

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Evaluation of Rheumatoid Factor Isotype Levels and Anti-Cyclic Citrullinated Peptide Antibody Isotype Levels in Juvenile Idiopathic Arthritis Patients At Baseline and Post-Treatment. Brooke E. Gilliam[1], Reema H. Syed[1] and Terry L. Moore[2]. [1]Saint Louis University, St. Louis, MO, [2]Saint Louis University, Saint Louis, MO

Background/Purpose: To investigate the effect of treatment on serum levels of rheumatoid factor (RF) isotypes and anti-cyclic citrullinated peptide (CCP) antibody isotypes in a cohort of juvenile idiopathic arthritis (JIA) patients.

Methods: Sera from 22 JIA patients, including 12 with IgM RF-positive polyarthritis and 10 with IgM RF-negative polyarthritis, were collected at baseline and one year following treatment. IgM and IgA RF were measured by enzyme-linked immunosorbent assay (ELISA) using cut-offs established by the manufacturer. Anti-CCP antibody isotypes (IgA, IgG, and IgM) were measured by ELISA.

Results: At baseline 55% and 36% were positive for IgM and IgA RF, while 36%, 36%, 27% were positive for anti-CCP antibody isotypes (IgA, IgG, and IgM, respectively). IgM RF, IgG and IgM anti-CCP antibody positivity was limited to IgM RF-positive polyarticular JIA patients. At one-year follow-up, IgM and IgA RF were positive in 55% and 32%, respectively. Anti-CCP antibody isotypes were positive in 27% (IgA), 18% (IgG), and 18% (IgM) of JIA patients. The serum levels of IgA RF were reduced by 35%, while IgM RF was only reduced by 8.3%. IgM anti-CCP antibodies were reduced by 49% following treatment, followed by IgG anti-CCP antibodies at 45%, and IgA anti-CCP antibodies at 20%. While all patients were not considered asymptomatic at follow-up, their disease had been well-controlled. The decreased in serum autoantibody levels was associated with this decreased disease activity.

Conclusion: All autoantibody levels markedly decreased in the JIA patients at follow-up, with the exception of IgM RF in the IgM RF-positive polyarthritis patients. Overall, fewer patients were positive for autoantibodies after one year. This lowering in autoantibody levels indicates good clinical response. Measurement of IgA RF and all 3 anti-CCP antibody isotypes may provide indication of how well JIA patients respond to treatment and indicate changes in disease activity.

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Current Evidence of Methotrexate Efficacy in Childhood Chronic Uveitis: A Systematic Review and Meta-Analysis. Gabriele Simonini[1], Priyamvada Paudyal[2], Gareth T. Jones[2], Rolando Cimaz[1] and Gary J. Macfarlane[2]. [1]Anna Meyer Children's Hospital, Florence, Italy, [2]University of Aberdeen, Aberdeen, United Kingdom

Background/Purpose: To summarize evidence regarding the effectiveness of Methotrexate (MTX) in the treatment of childhood autoimmune chronic uveitis.

Methods: A systematic search of articles published between January 1990 and February 2011 was conducted using following electronic databases: EMBASE, Ovid MEDLINE, EBM Reviewers–ACP Journal Club, all Cochrane library, and EBM Reviews–Database of Abstracts of Reviews of effects. Reference list and citations of those identified were also screened to find out relevant papers. Studies investigating the efficacy of MTX, as a single immunosuppressant medication in the treatment of chronic autoimmune uveitis, refractory to therapy with topic treatment and/or systemic treatment, in children (≤16 yrs) were eligible for inclusion. Primary outcome measure was the improvement of intraocular inflammation as Tyndall, as defined by the SUN working group criteria. When reported and available, tapering and/or stopping systemic steroid administration, improvement in visual acuity post MTX treatment, discontinuation of MTX, time for remission, time on remission, and safety of treatment were also considered as additional secondary additional outcomes. We determined a combined estimate of the proportion of children in the eligible studies responding to MTX. The effect measure for each study was therefore the proportion of people classified as responders.

Results: The initial search identified 246 articles, of which 52 were potentially eligible. A total of 9 articles that satisfied the eligibility criteria remained in the analysis All of the included studies were retrospective chart reviews. Number of children in these studies ranged from 3 to 25 and the dose of MTX varied from 7.5 mg/mq^2 to 30 mg/mq^2. Altogether, 95 children out 135 included responded to the treatment. The pooled analysis suggested that MTX has favourable effect in the improvement of intraocular inflammation: 0.73 (95% CI: 0.66–0.81), with a likelihood of improvement of 2.7.

Conclusion: The available evidence supports the use of MTX in the treatment of childhood chronic uveitis: patients on MTX can expect a 73% probability of improvement in intraocular inflammation; however randomised controlled trials on MTX are necessary before a firm conclusion can be drawn on efficacy.

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Characteristics of Anti-Cyclic Citrullinated Peptide Antibody and/or Rheumatoid Factor Positive Juvenile Idiopathic Arthritis in the Childhood Arthritis and Rheumatology Alliance Registry. Sampath Prahalad[1], Sheila Angeles-Han[1], Lori Ponder[1], Christine W. Kennedy[1], Larry B. Vogler[1] and CARRANet Investigators[2]. [1]Emory Children's Center, Atlanta, GA, [2]Stanford

Background/Purpose: JIA is a common chronic arthropathy with a prevalence of ~1/1000 in children under 16 years of age. The ILAR classification criteria categorize JIA into seven subtypes. Of these, rheumatoid factor (RF) positive polyarthritis resembles adults with seropositive RA. It is now recognized that anti-cyclic citrullinated protein antibodies (CCP) are highly specific for RA. Prior reports of CCP in children with JIA have been in modest sized cohorts from single institutions. Our objective is to characterize children with RF/CCP positive-JIA enrolled in the CARRANet Registry.

Methods: Children with JIA from pediatric rheumatology clinics in the US were enrolled in the CARRAnet Registry from May 2010 until June 2011. Demographic and disease-related data were collected from time of diagnosis to enrollment. Children who were positive only for CCP (RF negative) were compared with children who were positive for two out of three tests for biomarkers of RA: RF initial (RFI), RF confirmatory (RFC), and CCP. Nominal variables were compared using Chi-square or Fisher's exact tests. Continuous variables were compared using Student's T test.

Results: In all, of 2725 children with JIA in the database, 535 were reported as not having been tested for either RF/CCP. Children who were not tested for RF/CCP had an earlier onset age than children who were tested (5.2 vs. 6.7 years, p <0.0001). In those tested for RF and/or CCP, the prevalence of CCP was 11.4% (number positive/number tested = 112/978), RFI was 10.9% (234/2141), and RFC was 12.7 % (124/971). Of 937 children tested **for both** RFI and CCP, 82 % were negative for both, 10.4% positive for both, 1.8% positive for CCP only and 6.4% positive for RF only. Characteristics of children positive for CCP only compared to those who had at least two out of three positive tests are shown in **Table 1**. Except for subtype distribution, there were no differences. By contrast, the 35 children who were positive only for RFI were significantly younger compared to those who had at least 2 out of 3 positive tests, 6.5 vs. 10.9 years, p <0.0001. 32 individuals were positive for RFI, but were negative for RFC. 18 of these also had a negative CCP when tested. There were 12 children who had 2 positive RFs, but had a physician assigned diagnosis of a JIA subtype other than RF positive polyarticular or undifferentiated JIA (Systemic 2, RF negative poly 1, persistent oligoarthritis 6, psoriatic 2, ERA 1).

Table 1. Characteristics of CCP and RF positive children with JIA*

	CCP only	2 out of RFI, RFC and CCP	p
Total Number	16	153	
Age at symptom onset (mean ±SD)	9.3 (5.2)	10.9 (3.8)	ns
Demographic features	.	.	.
Female gender	13	133	ns
Hispanic ethnicity	4	42	ns
African ancestry	4	24	ns
Family history of autoimmunity	2	33	ns
Family history of RA	0	12	ns
Physician assigned JIA subtype	.	.	.
ERA	0	2	ns
Oligoarticular extended	2	1	<0.001
Oligoarticular persistent	3	8	ns
Polyarticular RF-	6	1	<0.0001
Polyaticular RF+	3	131	<0.0001
Psoriatic	1	2	ns
Systemic-onset	1	2	ns
Undifferentiated	0	5	ns
Measures of disease	.	.	.
CHAQ (mean)	0.43	0.46	ns
MD Global (mean)	2.6	2.4	ns
Imaging evidence of damage	4	62	ns
Current joint count (mean)	5.7	3.4	ns
Treatment	.	.	.
Use of systemic steroids	13	119	ns
Use of DMARD ever	15	144	ns
Use of biologic ever	10	109	ns

* All values are N, except as indicated. CCP: anti cyclic citrullinated protein antibody. RFI: Rheumatoid factor, initial. RFC: rheumatoid factor, confirmatory. ns: not significant.

Conclusion: This is the largest described cohort of RF/CCP positive children with JIA. Although ILAR criteria require testing of all children for RF, 21% of children with JIA in the CARRANet registry did not have reports of being tested for RF, possibly underestimating the number of children with RF positive JIA. The prevalence of RFI and CCP are comparable. A number of children with RFI were negative when retested for RF. Inclusion of CCP positivity in future revisions of the JIA criteria will improve the specificity of diagnosing childhood onset RA.

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Investigating children's beliefs about Juvenile Arthritis: A Study Using Cognitive Interviewing. Daniela Ghio[1], Wendy Thomson[2], Eileen M. Baildam[3], Kimme Hyrich[2], Michael W. Beresford[3], Carol Lydon[4], Olivia Lloyd[3], Gavin Cleary[3], Liza J. McCann[5], Childhood Arthritis Prospective Study (CAPS)[6], Fiona Ulph[1] and Lis Cordingley[7]. [1]School of Psychological Sciences, University of Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [3]Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [4]Alder Hey, Liverpool, United Kingdom, [5]Alder Hey Children's NHS Foundation Hospital, Liverpool, United Kingdom, [6]Manchester, United Kingdom, [7]School of Community Based Medicine, University of Manchester, Manchester, United Kingdom

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic illness in childhood. An understanding of how children make sense of their JIA symptoms is important for long-term management and treatment. There is increasing recognition that outcomes such as pain and disability are associated with an individual's beliefs about illness. In adults, beliefs about inflammatory arthritis were found to predict disability and quality of life

independently of disease activity (Graves et al, 2009). Beliefs have been assessed in adults using the Illness Perception Questionnaire (IPQ: Weinman et al, 1996). The aim of this study was to investigate the extent to which IPQ items can be understood by young people with JIA and the extent to which responses were associated with verbal ability and parent's beliefs.

Methods: Data were collected from 18 young people aged 11–16 diagnosed with JIA using cognitive interviewing (Willis et al, 1991). This involved two techniques, "think aloud" where participants describe their thoughts as they complete IPQ items and verbal probing where the interviewer elicits specific information about responses. All interviews were audio-recorded, transcribed and analysed using content analysis and thematic analysis. Participants also completed the British Picture Vocabulary Scale (Dunn, & Dunn, 1997) a measure of children's vocabulary to investigate whether verbal ability influences their responses to the IPQ items. Parents of participants completed written13 open-ended questions on their beliefs about their child's JIA which were analysed thematically.

Results: The analysis indicated that IPQ domains mapped onto illness concepts that were relevant to the young people with JIA, however, some individual items and response options may need adapting to take account of less abstract ways of thinking about illness and symptoms. Of particular interest were items assessing controllability of JIA and understanding of cause. Most participants believed they had a good understanding of their symptoms, but felt that their views were less well represented by IPQ items assessing beliefs about the causes of JIA. Difficulties were also found in relation to items asking about emotions with participants apparently disagreeing with IPQ items despite revealing that they felt emotional. Ability to complete the IPQ did not seem to depend upon verbal fluency. As anticipated, children's beliefs about JIA were largely reflected in the accounts of their parents.

Conclusion: There is a recognised need to capture patient reported outcome and process measures using valid, reliable and acceptable tools. For younger patients this presents particular challenges. The findings from this study indicate that children and young people with JIA find the domains assessed by the IPQ relevant but it did have specific limitations. We also gained some additional insights into the ways in which children's beliefs are influenced by those of their parents. Findings from this study will be used to adapt the IPQ for children with JIA in order to understand the long-term influences of children's beliefs upon outcomes including pain and disability.

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The Impact of ANA Titer Levels on Risk of Uveitis Development in Juvenile Idiopathic Arthritis. Meghan J. Ho[1], Rotraud K. Saurenmann[2], Pascal N. Tyrrell[3] and Susanne M. Benseler[3]. [1]University of Toronto, Toronto, ON, [2]University Children's Hospital, Zurich, Switzerland, [3]The Hospital for Sick Children, Toronto, ON

Background/Purpose: Uveitis is the most severe extra-articular involvement of juvenile idiopathic arthritis (JIA). Evidence of positive anti-nuclear antibody (ANA) is a known risk factor for development of uveitis in JIA, but thresholds for considering an ANA titer positive remain undefined. The impact of ANA titer on uveitis risk for children presenting with different clinical phenotypes of JIA is also unknown. The aims of the study were to describe the characteristic presenting features of JIA patients, to determine the overall association of ANA titer and development of uveitis, and to define the utility of ANA titers for individual uveitis risk prediction in clinical practice.

Methods: A single center cohort of children with JIA diagnosed between July 1984-June 2002, first seen at the Hospital for Sick Children before June 30, 2003 and followed for a minimum of 1 month was studied. Children not meeting the ILAR criteria for JIA diagnosis or with missing ANA titers were excluded from the database. Descriptive statistics and comparative analysis were performed on demographic, clinical and ANA laboratory data to characterize the study population. Logistic regression analysis was used to determine the association between ANA titer and uveitis development and the contribution of ANA titer to uveitis risk in the context of age and gender.

Results: A total of 715 children were identified and entered into the study (495 female, mean age 6.1 years; 220 male, mean age 7.6 years), in which 329 were ANA+ and 386 were ANA-. Girls diagnosed with JIA at a younger age were most at risk of developing uveitis (for every decreasing year: OR=1.3, 95% CI: 1.2–1.4). Children that were ANA+ at diagnosis were more likely to develop uveitis when accounting for age and gender (ANA titer <1/160: OR=3.4, 95% CI: 1.8–6.3; ANA titer >=1/160: OR=4.0, 95% CI: 2.3–6.9). A high ANA titer (>= 1/160) was found most often in the oligoarticular subtype (41%), followed by the polyarticular subtype (26%). Diagnosis subtype was not found to better explain the risk of uveitis development than ANA titer at diagnosis in the age and gender-adjusted model.

Conclusion: Age, gender, and ANA status (positive or negative) are important factors to consider when estimating the risk of uveitis development. ANA titer levels were also found to affect the risk of developing uveitis in JIA. These results can be used to inform the uveitis screening practices of pediatric rheumatologists and ophthalmologists in patients with JIA. The relationship between ANA titer levels and the different JIA subtypes needs to be further examined.

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Safety and Efficacy of Tocilizumab Treatment In Children with Systemic Juvenile Idiopathic Arthritis. Ekaterina Alexeeva, Rina Denisova, Saniya Valieva, Tatyana Bzarova, Kseniya Isayeva, Tatyana Sleptsova and Elena Mitenko. Scientific Center of Children's Health, Moscow, Russia

Background/Purpose: To evaluate safety and efficacy of tocilizumab treatment in children with systemic onset of juvenile idiopathic arthritis (JIA).

Methods: A retrospective observational study on JIA patients taking tocilizumab (n=39). Tocilizumab was administered intravenously at a dose of 8 mg/kg every 2 weeks during 2 months then every 4 weeks. All patients received DMARDs. Efficacy end points included the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), Pedi 50, Pedi 70, and Pedi 90 criteria for improvement.

Results: A total of 39 patients (21 boys and 18 girls) were included in this Median age was 7,5 years (range; 3 to 15 years) and median disease duration was 4,2 years (range; 0.5 to 8,3 years). A total of 16 of the 39 patients (25%) entered 52 weeks of continuous tocilizumab treatment. The frequently observed non-severe adverse events were nasopharyngitis, upper respiratory tract infection and gastroenteritis. No cases of opportunistic infections, malignancies, autoimmune diseases, or death were reported. One case of pneumonia. 21 patients had incidences of neutropenia.The ACR Pedi 30, 50, 70 and 90 were achieved by 82%,50%, 27% and 12% of patients at Week 4 (N=36), and by 100%, 81%, 69%, and 50% of patients at Week 24 (N=18), and by 100%, 85%, 78%, and 57% of patients at Week 52 (N=16), respectively.

Conclusion: Clinical improvements in the signs and symptoms of systemic JIA were also achieved in favorable levels in tocilizumab in the treatment of children with JIA.

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Evaluation of the Association Between Ethnicity and Disease Activity and Severity in a Large Cohort of Patients with Juvenile Idiopathic Arthritis. Christina F. Pelajo[1], Sheila Angeles-Han[2], Sampath Prahalad[3], Caitlin M. Sgarlat[1], Trevor Davis[1], Laurie C. Miller[1] and Jorge M. Lopez-Benitez[1]. [1]Floating Hospital for Children at Tufts Medical Center, Boston, MA, [2]Emory University, Atlanta, GA, [3]Emory Children's Center, Atlanta, GA

Background/Purpose: The impact of ethnicity on disease activity and severity in patients with juvenile idiopathic arthritis (JIA) is not well understood. Studies in large samples are needed to explore this association, since this could affect the future care of minorities with JIA. The aims of this study were to examine the association between ethnicity and disease activity in patients with JIA, and to determine the association of ethnicity with disease severity and disability in this population.

Methods: CARRAnet, a US database containing information (collected between May 10 and Jun 11) on almost 3,000 subjects with JIA, was used. Demographic variables were compared between Hispanic (or Latino) patients and non-Hispanic patients. Mann-Whitney and Chi-square tests were used to compare indicators of disease activity (number of active joints, physician assessment of disease activity, parent/subject assessment of disease activity, and parent/subject pain score), as well as imaging evidence of joint damage, and Childhood Health Assessment Questionnaire (CHAQ) scores between ethnicities. A linear regression model was used to determine the association of ethnicity with number of active joints in JIA.

Results: The sample analyzed included 2,704 patients with JIA (277 Hispanic and 2,427 non-Hispanic). Table 1 shows the demographic variables by ethnicity. Income and health insurance status were higher in non-Hispanics. RF-positive polyarticular JIA, positive RF and anti-CCP, as well as use of systemic steroids were more frequent in Hispanics.

Table 1. Demographic variables

Variable	Hispanic	Non-Hispanic	p-value
Age at baseline visit (mean ± SD)	11.3 ± 5.2	11.5 ± 4.7	0.59
Age at onset of symptoms (mean ± SD)	6.7 ± 4.5	6.4 ± 4.4	0.28
Age first seen by pediatric rheumatologist (mean ± SD)	7.7 ± 4.8	7.3 ± 4.6	0.23
Gender (females) % (N)	74 (206)	73 (1765)	0.56
Income (US$) % (N)			**<0.0001**
<25,000	20 (56)	10 (234)	
25,000–49,999	23 (64)	14 (348)	
50,000–74,999	13 (36)	16 (386)	
75,000–99,999	11 (31)	14 (343)	
100,000–150,000	11 (30)	19 (468)	
Above 150,000	5 (13)	12 (286)	
Unknown	17 (46)	15 (361)	
Health insurance % (N)	95 (264)	98 (2364)	**0.01**
JIA subtype % (N)			**<0.0001**
Enthesitis-related arthritis	8 (21)	11 (255)	
Oligoarticular extended	6 (17)	9 (206)	
Oligoarticular persistent	26 (73)	27 (647)	
Polyarticular RF−	23 (63)	30 (728)	
Polyarticular RF+	18 (50)	6 (144)	
Psoriatic arthritis	4 (10)	6 (157)	
Systemic-onset	11 (31)	9 (208)	
Undifferentiated	3 (8)	2 (53)	
Laboratory tests % (N)			
Positive ANA	44 (120)	44 (1052)	0.06
Positive HLA-B27	6 (16)	8 (185)	0.48
Confirmed RF positive	13 (32)	4 (92)	**<0.0001**
Anti-CCP positive	11 (28)	4 (83)	<0.0001
Treatment % (N)	44 (80)	43 (706)	**0.02**
Use of systemic steroids	18 (32)	12 (195)	
-Prior	76 (210)	77 (1859)	
-Current	48 (132)	46 (1100)	0.59
Use of DMARD ever			0.75
Use of biologic ever			

In the univariate analysis the number of active joints, the physician assessment of disease activity, and the parent subject/assessment of disease activity did not differ between ethnicities. However, the parent/subject pain score was significantly higher (worse) in Hispanics (3.0±2.9) than in non-Hispanics (2.5±2.6) (p=0.02). In the analysis of disability and disease severity, CHAQ was significantly higher (worse) in Hispanic patients (0.5±0.6) than in non-Hispanic (0.3±0.5) (p=0.0005), as well as imaging evidence of joint damage (32% vs. 24%) (p=0.008). In the multivariate linear regression analysis, the number of active joints was significantly higher in Hispanics than in non-Hispanics (p=0.03), after adjusting for confounders (income, health insurance, JIA subtype, positive RF, positive anti-CCP, use of intra-articular steroids, oral steroids, IV steroids, DMARDs, and biologics).

Conclusion: Hispanic patients with JIA had higher disease activity (determined by number of active joints and parent/subject pain score) than non-Hispanic patients, as well as higher disease severity (by imaging evidence of joint damage) and disability (by CHAQ). Since ethnicity influences disease activity, severity, and disability, different management and treatment plans should be planned accordingly.

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Pediatric Rheumatology - Pathogenesis and Genetics
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Gene Expression Profiling Reveals Dysregulation of Innate Immune Genes in Synovial Fluid Mononuclear Cells of Patients with Enthesitis Related Arthritis. Amita Aggarwal[1], Arpita Myles[2] and Amit Tuteja[3]. [1]Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Lucknow, India, [2]Sanjay Gandhi Postgraduate Institute of Medical Science, Lucknow, India, [3]The center for Genomic applications, New Delhi, India

Background/Purpose: Enthesitis related arthritis (ERA) category of juvenile idiopathic arthritis (JIA) is said to arise in genetically predisposed individuals in response to environmental triggers. Gene expression profiling has helped identify new pathogenic pathways in other JIA categories and have opened new avenues for therapy like IL-1Ra in Systemic JIA. Data on ERA is limited thus we studied expression profile of ERA patients' peripheral blood and synovial fluid mononuclear cells (PBMCs and SFMCs). PBMCs from polyarticular JIA (polyJIA) patients and healthy subjects were used as controls.

Methods: RNA from PBMCs of ERA, polyJIA patients and healthy controls (n=17, 8, 8) and 7 ERA SFMCs were converted to labelled cRNA and hybridised to Illumina Human WG-6_v3_BeadChip chips. Expression profiles were analysed using Genespring software. Genes differentially expressed at a fold-change cut-off of ≥ 2.0 and detection p values of < 0.05 were subjected to hierarchical clustering and pathway analysis. Selected genes of interest were validated at RNA and protein level.

Results: Although ERA PB could be distinguished from ERA SF, control PB and polyJIA PB using supervised clustering, yet, there was no statistically significant difference in PBMC gene expression of ERA, polyJIA and control groups. However, there was significant difference between gene expression profile of SFMCs and PBMCs of patients with ERA, with 131 genes being overexpressed and 216 being under-expressed in SFMCs. 182 genes were involved in 13 pathways, none of which was significantly dysregulated as per gene ontology analysis. Amongst these, highest number of genes (36) had an immunological function. Out of these CD1b, CD1d, MHC class II alpha and beta chain, soluble CD163, chemokines CXCR3 and CXCL16 were over expressed whereas genes related to NK cell function, namely, Granzyme H, KLRF1, KIR3DL3, NKG7 and other genes like CD244, CD248, FAIM3 were under-expressed.

Conclusion: ERA SFMC has a distinct gene expression profile from PBMCs and had higher expression of genes associated with antigen presentation, scavenger function, chemotaxis and proteases whereas genes involved in NK cell function, cell adhesion and inhibitors of apoptosis were under-expressed. All these genes have been associated with pathology of several inflammatory diseases, including rheumatoid arthritis and other JIA categories. Therefore, we hypothesise that they may contribute to disease exacerbation in ERA.

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KIR-HLA Gene Combinations in JIA-Associated Uveitis. Miriam F. Parsa[1], Deborah K. McCurdy[1], Ornella J. Rullo[1], Jennifer M.P. Woo[1], Tina Cunningham[2], Jennifer Thorne[3], Ralph D. Levinson[4], Raja Rajalingam[2] and Gary N. Holland[4]. [1]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [2]University of California, Los Angeles, Los Angeles, CA, [3]Johns Hopkins University, Baltimore, MD, [4]Jules Stein Eye Institute, University of California, Los Angeles, Los Angeles, CA

Background/Purpose: HLA class I-specific killer cell immunoglobulin-like receptors (*KIR*) gene and *HLA* gene combinations have been associated with autoimmune uveitis (e.g. birdshot chorioretinopathy (BCR) and Vogt-Koyanagi-Harada syndrome (VKH)). KIR-HLA genotypes that provide weak inhibition and strong activation may stimulate NK cells and NK-like T cells, thereby increasing susceptibility to autoimmune disease. In oligoarticular juvenile idiopathic arthritis (JIA), uveitis is one of the most serious complications and affects approximately 20% of patients. Given the importance of *HLA* Class I and *KIR* gene combinations in other forms of autoimmune uveitis, we hypothesize that an interplay between these genes contributes to the pathogenesis of uveitis in JIA. This study identified KIR gene combinations in Caucasian children with JIA with and without uveitis and compared them with healthy Caucasian controls.

Methods: The study population consisted of pediatric patients with oligoarticular JIA, with and without uveitis. DNA samples were typed for 16 *KIR* genes using a gene-specific PCR typing system. We analyzed the presence or absence of 16 KIR genes in patients with uveitis, patients without uveitis, and published healthy controls (n = 195). Data was analyzed using Fisher's exact tests and Spearman correlation.

Results: A total of 41 (58% with uveitis) DNA samples were collected and isolated from whole blood then genotyped for the 16 KIR genes. The B Haplotype T4 cluster (2DL5-3DS1–2DS5-2DS1) was present more frequently in controls (p<0.05) compared with JIA patients. In previous studies, KIR3DP1, -2DL4, -3DL2, -3DL3 were considered framework genes and present in all adults with autoimmune uveitis. These findings were replicated in our pediatric sample (p = 0.0001). There was no association of KIR genotype in JIA patients with or without uveitis as compared with controls.

Conclusion: In this small sample size, B Haplotype genes (T4 cluster), known to be activating in nature, were found more frequently in healthy controls, suggesting a protective effect against JIA. We did not find an association between KIR gene frequencies and JIA-associated uveitis. We are expanding our sample size to confirm this association, as well as identifying cognate HLA ligands. Uveitis remains a significant risk for disability in JIA; therefore, developing a risk prediction model will allow for aggressive screening and disability prevention.

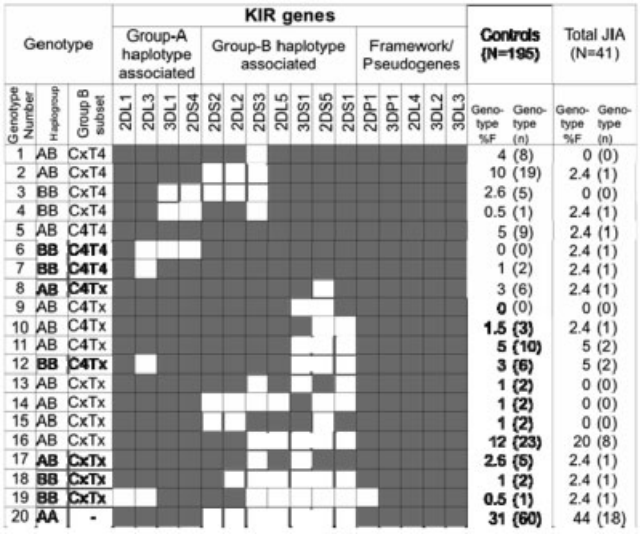

Figure 1. The presence and absence of 16 KIR genes are indicated as shaded and white boxes respectively. 15 distinct genotypes were found in the JIA group, each genotype represented by a row. Genotype frequency is presented as percentage frequency (%F) and defined as the number of individuals (N) divided by the number of individuals (n) in the given study group.

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Antigenic Targets and Pathogenicity of Anti-Endothelial Cell Antibodies in Kawasaki Disease. Rie Karasawa, Mayumi Tamaki and Kazuo Yudoh. Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan

Background/Purpose: Anti-endothelial cell antibodies (AECA) are autoantibodies detected frequently in patients with vasculitis and are thought to be involved in pathophysiology of vasculitis, including Kawasaki disease (KD). The pathophysiological role of AECA, however, is still uncertain. We tried to detect and identify target proteins of AECA comprehensively by proteomics. Furthermore, we investigated clinical importance of them in patients with KD.

Methods: We separated proteins extracted from HUVEC and HeLa cells respectively by 2-dimensional electrophoresis and then transferred them onto membranes. By WB using serum samples from patients with vasculitis, we detected antigens that were positive only in the HUVEC samples but not in the HeLa cell samples. We next identified the detected proteins by peptide mass finger-printing. After that, we characterized antigenecity by preparing recombinant antigens and antibodies to them.

Results: One of the identified 63 proteins was found peroxiredoxin2 (Prx2), an anti-oxidative enzyme. IgG antibodies to Prx2 were detected in 60% of the patients with KD, but not in healthy controls. On the other hand, IgM and IgA antibodies to Prx2 were not significant in patients with KD. Interestingly, IgG antibodies to Prx2 were detected in all tested KD patients with coronary artery lesions. In contrast, IgM and IgA antibodies to Prx2 weren't detected in them. In addition, IgG antibodies to Prx2 were detected in 9% of the patients with polyarteritis nodosa, small and medium vessel vasculitis. WB using cell lysate proved expression of Prx2 not only in HUVEC but also in other endothelial cells (ECs), including human coronary artery endothelial cells (HCAEC). The anti-Prx2 antibodies also increased various inflammatory cytokine secretion significantly, in particular, G-CSF in HCAEC. The addition of anti-Prx2 antibodies to ECs resulted in increased concentration of H2O2 in cell lysate from the ECs. Anti-Prx2 antibodies induced increased expression of adhesion molecule, such as E-selectin. Furthermore, apoptosis was detected in the ECs treated with anti-Prx2 antibodies. We measured anti- Prx2 IgG titers / serum IgG on the pre- and posttreatment (within a month after therapy) in 7 KD patients treated by IVIG. As a result, the titers on the posttreatment significantly decreased in all the tested KD patients. The duration of fever (>37.5°C) was significantly longer in the anti-Prx2 positive group than the anti-Prx2 negative group in KD patients. However, there was no significant difference in two inflammatory markers, white blood cell counts and C-reactive protein, between the both groups.

Conclusion: IgG antibodies to Prx2 would be a useful marker for KD. The anti-Prx2 antibodies may cause vascular dysfunction by inducing expression of endothelial adhesion molecules, inflammatory cytokine production, apoptosis and inhibition of anti-oxidative activity of Prx2 by binding Prx2 on ECs.

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Measuring S100A12 and Vascular Endothelial Growth Factor Can Differentiate Familial Mediterranean Fever and Early Onset Sarcoidosis From Systemic Juvenile Idiopathic Arthritis. Yuichi Yamasaki, Yasuhito Nerome, Tomohiro Kubota, Yukiko Nonaka, Harumi Akaike, Tomoko Takezaki, Hiroyuki Imanaka, Yoshifumi Kawano and Syuji Takei. Kagoshima University, Kagoshima City, Japan

Background/Purpose: A new consensus is now emerging that systemic juvenile idiopathic arthritis (sJIA) may be one of the autoinflammatory disease based on clinical and pathological mimicry. In fact, many children with autoinflammatory diseases such as familial Mediterranean fever (FMF) and early onset sarcoidosis (EOS) were initially diagnosed as sJIA[1)], a much more common febrile disease in children. Therefore, we examined serum levels of IL-6, S100 protein, and vascular endothelial growth factor (VEGF) so that measuring these biomarkers could be a screening test to differentiate these febrile conditions before undergoing a genetic testing.

Methods: Serum samples were obtained from 19 patients, 3 patients with FMF, 4 with EOS, and 12 with sJIA. Diagnosis of FMF and EOS were confirmed by gene examination. In these 19 patients, serum levels of IL-6, S100A12 and VEGF were examined by ELISA in both active (CRP>1.0 mg/dl) and inactive phase.

Results: In active phase of patients, serum IL-6 level did differ in all disease groups. However, serum S100A12 levels were significantly high in both s-JIA ($p<0.001$) and FMF ($p<0.001$) patients compared with EOS patients (Figure 1). On the other hand, high levels of serum VEGF was observed only in s-JIA patients but not in FMF or EOS patients even though they were in active phase ($p<0.001$) (Figure 2).

In inactive phase of patients, no significant difference was observed in serum VEGF levels among the three disease groups. On the other hand, high levels of S100A12 were observed only in FMF patients who were non-treated or colchicine resistant.

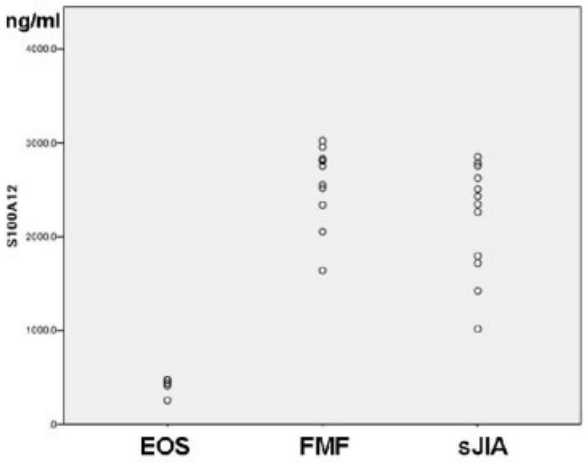

Fig1 : serum S100A12 level of EOS, FMF and sJIA in active phase

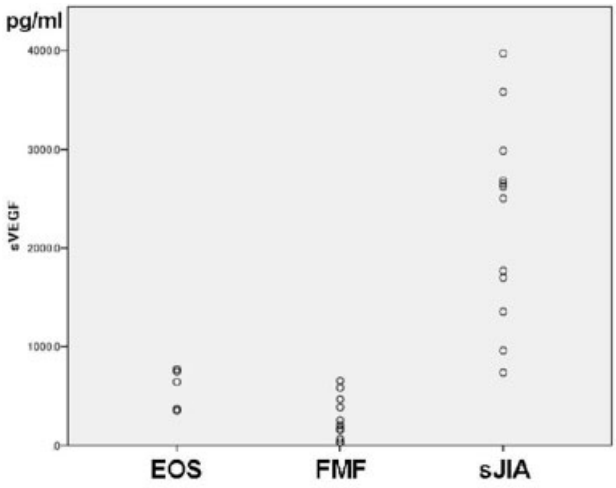

Fig2 : serum VEGF level of EOS, FMF and sJIA in active phase

Conclusion: Measuring serum S100A12 and VEGF levels at a time may be useful in differentiating FMF or EOS patients from patients clinically diagnosed as sJIA.

Reference

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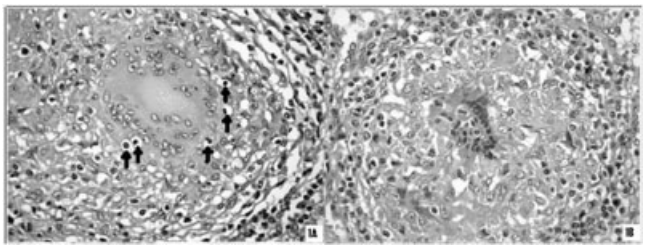
Emperipolesis and Cell Death in NOD2-Related Blau Syndrome and Crohn's Disease. Carl EI Janssen[1], Carlos D. Rose[2], A. Naranjo[3], Brigitte Bader-Meunier[4], Rolando Cimaz[5], Miroslav Harjacek[6], Pierre Quartier[7], Rebecca Ten Cate[8], Caroline Thomée[9], Isabelle Cleynen[1], Tammy M. Martin[10], Gert De Hertogh[1], Tania Roskams[1], Valeer J. Desmet[1] and Carine H. Wouters[11]. [1]University Hospital Leuven, Leuven, Belgium, [2]duPont Hospital for Children, Wilmington, DE, [3]Hospital de G C Dr Negrin, Las Palmas GC, Spain, [4]Hôpital Necker, Paris, France, [5]Anna Meyer Children's Hospital, Florence, Italy, [6]Zagreb, [7]IRCCS G. Gaslini, Pediatria II, PRINTO, Paediatric Rheumatology, Genova, Italy, [8]PO Box 9600, Leiden, Netherlands, [9]Centre Hospitalier, Luxembourg, Luxembourg, [10]Oregon Health & Science Univ, Portland, OR, [11]University Hosp Gasthuisberg, Leuven, Belgium

Background/Purpose: Blau Syndrome (BS), a rare autoinflammatory disease characterized by non-caseating granulomas, is caused by gain-of-function mutations in NOD2. Crohn's disease (CD) is associated with intestinal granulomas, and SNPs in NOD2. Emperipolesis, the 'inside round about wandering' of lymphocytes within other cells is a typical feature of Rosai-Dorfman disease, and seen occasionally in malignancies. Cell survival and cell death are possible outcomes for both the engulfed and engulfing cells. In the present study we investigate emperipolesis and cell death in BS and CD granulomas.

Methods: Morphological and immunohistochemical study of granulomas was undertaken in 8 BS and 7 pediatric CD biopsies, using H&E and immunohistochemistry for leukocyte markers (CD68, CD4, CD8, CD20), cytokines (IFNγ, IL6, IL10, IL17, TGFβ, TNFα) and death-proteins (Bcl2, Fas, FasL, activated caspase 3).

Results: All BS biopsies showed polycyclic granulomas with large lymphocytic coronas and extensive emperipolesis of lymphocytes within multinucleated giant cells (MGCs). This was associated with macrovesicular/microvesicular degeneration of lymphocytes inside MGCs (Fig1a), and MGC death (Fig1b). Emperipolesis selectively involved CD4+ T cells. In addition, vesicles and degenerative remnants inside MGCs stained strongly for IL-6 and IL-17. A moderate expression of Bcl2 was present, Fas and FasL expression were seen in emperipoletic lymphocytes and MGCs but caspase 3 was virtually absent. In contrast, CD biopsies demonstrated simple isolated granulomas with subtle lymphocytic coronas; emperipolesis was sporadically found in a few biopsies, and was associated with crystalline inclusions, but not with MGC death.



Conclusion: Emperipolesis of CD4+lymphocytes is an important feature of BS and is associated with MGC death. NOD2 mutations causing NF-*k*B hyperactivation and influencing autophagy pathways may be involved. In CD with NOD2-SNPs, emperipolesis is exceptional and crystalline inclusions are present.

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Novel Mutation of the *LPIN2* Gene in Majeed Syndrome. Response to IL-1 Inhibition. Troels Herlin[1], Mette Bjerre[2], Bente Fiirgaard[1], Gitte Kerndrup[3], Henrik Hasle[1] and Polly J. Ferguson[4]. [1]Aarhus University Hospital, Aarhus N, Denmark, [2]Aarhus University Hospital, Aarhus C, Denmark, [3]Vejle Hospital, Denmark, [4]University of Iowa Carver College of Medicine, Iowa City, IA

Background/Purpose: Majeed syndrome is a rare, syndromic form of chronic recurrent multifocal osteomyelitis (CRMO) first described in 1989. The syndrome starts during infancy with recurrent relapses of osteomyelitis typically associated with fever, congenital dyserythropoietic anemia (CDA) and often neutrophilic dermatosis (Sweet syndrome). Homozygous mutations in the *LPIN2* gene located on the short arm of chromosome 18 have been identified as being responsible for the Majeed syndrome. Aim of study was to report a novel mutation in the *LPIN2* gene detected in two brothers with Majeed syndrome and to describe the clinical characteristics and response to treatment.

Methods: Two Turkish brothers (13 months (Y) and 29 months old (M) with consanguinity of the parents were admitted with relapsing episodes of pain and 'pseudoparalysis' of upper and lower extremities since the age of 3 and 6 months, respectively. No concomitant fever has occurred during the attacks. *LPIN2* gene re-sequencing was performed on each of the affected child.

Results: Whole body MRI of the elder brother (M) revealed osteomyelitic changes of the metaphyses of tibiae, left fibula and left radius. Biopsy from lesions showed no malignancy and negative bacterial cultures. Both showed significant hypersedimentation (ESR 92 mm/hr (Y) and 96 mm/hr (M)), slight thrombocytosis, and moderate anemia (Hb 9.0 (Y) and 9.7 (M) g/dl). Bone marrow aspiration was consistent with congenital dyserythropoietic anemia (CDA) with 6%–9% bi- or multinucleated erythrocytes. *LPIN2* gene re-sequencing of each affected child revealed a homozygous 2 bp deletion (c.1312_1313delCT) resulting in an early truncation of the protein (L438fs+16X), which confirmed the diagnosis in both patients. Clinically, both were refractory to the treatment with corticosteroids and TNFα inhibition (etanercept). Elevated plasma levels of proinflammatory cytokines (IL-1β, IL-6, IL-8, TNFα) did not change significantly during the treatment. In M, rapid clinical and laboratory improvement was observed after introduction with anakinra (1.7 mg/kg/d), which has not yet been introduced to Y.

Conclusion: We describe a novel mutation of the *LPIN2* gene in two Turkish brothers with Majeed syndrome. Although our patients also presented with CDA none of them had fever during the attacks nor dermatological changes unlike previously described patients with Majeed. IL-1 inhibition showed promising clinical and laboratory results.

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Incidence and Identification of Citrullinated Proteins in Synovial Fluid of Juvenile Idiopathic Arthritis Patients. Brooke E. Gilliam[1], Melinda R. Reed[2], Anil K. Chauhan[1], Amanda Dehlendorf[1] and Terry L. Moore[3]. [1]Saint Louis University, St. Louis, MO, [2]Ozarks Medical Center, West Plains, MO, [3]Saint Louis University, Saint Louis, MO

Background/Purpose: To identify citrullinated autoantibodies, α-enolase and fibrinogen specifically, in juvenile idiopathic arthritis (JIA) synovial fluid (SF) and determine their role in the pathogenesis of JIA.

Methods: SF samples were obtained from 7 JIA patients, including 1 with IgM rheumatoid factor (RF)-positive polyarthritis, 2 with IgM RF-negative polyarthritis, and 4 with oligoarthritis. Two osteoarthritis (OA) SF samples were analyzed as non-inflammatory controls. SF were transferred to PVDF membrane and probed with antibodies to peptidyl arginine deiminase (PAD)-4, PAD-2, native α-enolase, and native fibrinogen. Citrullinated proteins were also identified. SF samples were immunoprecipitated with antibodies to fibrinogen and α-enolase. Citrullinated fibrinogen and α-enolase were then detected using the anti-modified citrulline (AMC) kit.

Results: PAD-2 and PAD-4 were observed in all JIA and OA SF samples. Intensity for PAD-2 was greater in the group of JIA patients who also demonstrated reactivity with anti-citrulline. Native α-enolase was present in all JIA samples, with 5 samples showing considerable activity. Trace amounts of α-enolase were evident in OA SF. Native fibrinogen was detected in all JIA SF samples, while neither OA sample demonstrated reactivity. Western blot analysis showed that 3/7 JIA patient samples, 2 polyarthritis and 1 oligoarthritis, contained multiple citrullinated proteins. No citrullinated proteins were detected in OA SF. Western blot analysis of SF immunoprecipitated for fibrinogen using AMC detection showed citrullination of the same 3 JIA SF samples. Immunoprecipitation with α-enolase, followed by AMC detection, yielded no detection of citrullinated α-enolase in JIA or OA SF.

Conclusion: The abundance of citrullinated proteins in JIA SF may be characteristic of inflammation, as seen in rheumatoid arthritis (RA) and spondyloarthritis. The presence of PAD-2 and citrullinated proteins in JIA SF suggests a role for PAD-2 in deimination of SF proteins, as seen in inflammatory arthritis. Presence of anti-PAD-4 antibodies has shown significant association with destructive disease in RA. Few studies have evaluated citrullination of proteins in JIA. Here we have shown the detection of citrullinated proteins at the site of inflammation, specifically identifying citrullinated fibrinogen and citrullinated α-enolase.

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Familial Periodic Fever Syndrome with Congenital Dyserythropoetic Anemia and Non-Bacterial Osteomyelitis. Sarah Keidel and Nick Wilkinson. Nuffield Orthopaedic Centre, Oxford, United Kingdom

Background/Purpose: The periodic fevers are a group of heritable disorders characterized by episodic fever and raised inflammatory markers, and are due to monogenic mutations of the innate immune system. We present a family of 3 patients with periodic fever, congenital dyserythropoetic anemia, synovitis, non-bacterial osteomyelitis and probable resolution by the 2nd decade. We compared with existing literature and undertook genetic analysis to provide prognostic information to the family.

Methods: Three females from a Pakistani family of four had a history of congenital dyserythropoetic anemia and infantile episodic fevers associated with non-bacterial osteomyelitis of the tibiae and failure to thrive. There was a history of parental and maternal grandparental consanguinity. The mother was asymptomatic after the age of six, the elder daughter was well by age eight with only occasional knee pain, and the youngest daughter (2.5yo at latest review) was improving with reduced frequency of fevers, increasing weight, and normal development. We compared the features of these patients with other periodic fevers and requested genetic analysis.

Results: This family's profile fits with conditions that include chronic recurrent multifocal osteomyelitis (CRMO), including Majeed syndrome (caused by LPIN2 gene mutations) and DIRA (deficiency of interleukin1–receptor antagonist syndrome caused by IL1RN mutations). However, atypical for Majeed syndrome was the isolated involvement of the tibiae, attenuation with age, and probable resolution in childhood[1]. The presence of fever and lack of skin abnormalities was against the diagnosis of DIRA[2]. Genetic sequence analysis on each of the family members was performed; no mutations of the PSTPIP2 or IL1RN genes were present. However, a homozygous mutation in exon 17 of the LPIN2 gene (c.2207A>G) was found in both parents and siblings, including the asymptomatic father. This mutation has not been reported to cause Majeed syndrome[3].

Conclusion: We present a unique family with an uncharacterized periodic fever syndrome of good prognosis, possibly representing a forme fruste of Majeed syndrome. At this point, the relevance of the genetic findings within this family's LPIN2 gene is unclear. We welcome collaboration in identifying patients with similar clinical features and conducting further genetic studies.

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3. Ferguson P et al. Med Genet. 2005;42:551–7.

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Evaluation of An Autoantibody Profile in Pediatric- and Adolescent-Onset Systemic Lupus Erythematosus and Their Association with Disease-Associated Manifestations. Brooke E. Gilliam[1], Amanda K. Ombrello[2], Rufus W. Burlingame[3], Peri H. Pepmueller[1] and Terry L. Moore[4]. [1]Saint Louis University, St. Louis, MO, [2]National Institutes of Health, Bethesda, MD, [3]INOVA Diagnostics, Inc., San Diego, CA, [4]Saint Louis University, Saint Louis, MO

Background/Purpose: To evaluate an autoantibody profile in pediatric- and adolescent-onset systemic lupus erythematosus (SLE) patients to determine the clinical and statistical associations with disease-related manifestations.

Methods: Sera from 53 SLE patients and 22 healthy individuals were collected. Antibodies to C1q, histone, chromatin, ribosomal P, double-stranded (ds) DNA, and high avidity (HA) dsDNA were measured by enzyme-linked immunosorbent assays. Patient records were evaluated for clinical and laboratory associations.

Results: Significantly elevated levels of all measured autoantibodies were found in SLE patients when compared to healthy individuals ($p<0.05$). The most prevalent autoantibody measured in the SLE cohort was anti-C1q antibodies, found in 60% of SLE patients. Anti-C1q antibodies correlated significantly with proteinuria, fever, urinary casts, and decreased complement levels ($p<0.05$). Antibodies to C1q, dsDNA, histone, and chromatin were significantly elevated in patients with active disease compared to those who were asymptomatic. Anti-C1q and anti-histone antibodies were significantly elevated in patients with class III/IV nephritis compared to class I/II/V nephritis. SLE patients with active nephritis demonstrated significantly elevated levels of anti-C1q antibodies compared to those without active nephritis (191U v. 80U, $p<0.05$), also exhibiting 100% sensitivity for active nephritis, proteinuria, and urinary casts. Chart-documented anti-dsDNA antibodies were positive in 28 SLE patients, INOVA anti-dsDNA antibodies in 25 patients, and HA anti-dsDNA antibodies in 8 patients. Anti-histone antibodies correlated significantly with leukopenia, hemolytic anemia, anti-dsDNA and HA anti-dsDNA antibodies.

Conclusion: Our findings indicate the importance of measuring anti-C1q antibodies in pediatric/adolescent-onset SLE patients because elevated anti-C1q antibody levels indicate renal disease activity, demonstrating significant correlation with proteinuria, urinary casts, and active nephritis. The HA anti-dsDNA antibody ELISA may eliminate potential false-positive results and provide a more accurate assessment by eliminating low avidity, weakly bound antibodies detected by traditional assays. Overall, antibodies to C1q, histone, dsDNA, and HA dsDNA exhibited the strongest association with clinical features, indicating the relevance of measuring all of these antibodies in the pediatric and adolescent SLE population.

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Juvenile Systemic Lupus Erythematosus and Juvenile Dermatomyositis Are Marked by Distinct Profiles of Soluble Apoptosis Molecules. Bernadete Liphaus[1], Maria H. B. Kiss[2], Solange Carrasco[3], Clovis A. A. Silva[1] and Claudia Goldenstein-Schainberg[4]. [1]Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [3]Disciplina de Reumatologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [4]University of São Paulo, São Paulo, Brazil

Background/Purpose: Conflicting results concerning the role of soluble apoptosis related molecules and their relationship to childhood rheumatic diseases still remains. Therefore, the aim of this study was to quantify sFas, sFasL, sTRAIL and sBcl-2 levels in sera from patients with Juvenile Systemic Lupus Erythematosus (JSLE) and evaluate their association with nephritis and disease activity biomarkers.

Methods: Soluble apoptosis molecules were measured in sera from 43 patients with JSLE (36F:7M, mean age=14.3, range 8.2–20.8 yrs according to revised ACR criteria) and 74 gender and age-matched controls (39 disease controls—26 Juvenile Idiophatic Arthritis (JIA), 13 Juvenile Dermatomyosistis (JDM); 35 healthy individuals). Commercial solid phase ELISA kits were used to quantify sFas, sFasL, sTRAIL and sBcl-2, in duplicate for each sample, following the manufacturer's instructions. Lupus activity biomarkers including SLEDAI score, ESR, serum anti-dsDNA (by quantitative ELISA), C3 and C4 (by standard methods) levels were evaluated at the moment of blood withdraw. Thirty JSLE patients presented active disease (SLEDAI ≥4) and 32 had nephritis. For statistical analysis, nonparametric Kruskal-Wallis test and Spearman's rank were performed, with P value < 0.05 considered significant.

Results: JSLE patients presented increased levels of sFas and sTRAIL, decreased concentrations of sFasL and similar sBcl-2 levels compared to healthy

controls, which were all related to active but not inactive disease (Table). SLEDAI score correlated positively with sFas (r=0.52; p=0.001), while anti-dsDNA, C3, C4, ESR and renal involvement had no association with soluble proteins. Of note, JIA patients had sFas, sFasL, sBcl-2 and sTRAIL levels similar to controls, but remarkably JDM patients presented a 2-fold higher sBcl-2 level compared with all control groups.

Table. Serum concentrations of soluble apoptosis molecules (sFas, sFasL, sTRAIL and sBcl-2) in patients with JSLE, disease controls (JDM and JIA) and healthy individuals.

Diagnosis (N° patients)	sFas (pg/ml)	sFasL (ng/ml)	sTRAIL (pg/ml)	sBcl-2 (mg/ml)
JSLE (43)	188.1 ± 69.2*	0.08 ± 0.1[#]	691.3 ± 631.8[#]	7.4 ± 8.6
Active JSLE (30)	199.1 ± 74.0**	0.06 ± 0.06**	731.7 ± 639.3**	6.1 ± 3.9
Inactive JSLE (13)	162.8 ± 50.0	0.14 ± 0.2	604.2 ± 631.7	10.9 ± 16.5
JDM (13)	126.2 ± 78.1	–	612.5 ± 486.3	16.6 ± 9.1[§]
JIA (26)	166.7 ± 84.3	0.31 ± 0.4	473.4 ± 437.8	6.7 ± 10.4
Healthy controls (35)	133.2 ± 80.6	0.36 ± 0.4	346.6 ± 251.1	9.3 ± 9.6

The results are presented as mean ± SD. *p<0.01, JSLE vs healthy controls and JDM; [#]p<0.01, JSLE vs controls; [§]p<0.01, JDM vs healthy controls, JSLE and JIA; **p<0.01, active JSLE vs controls; — only one JDM patient had detectable sFasL.

Conclusion: Increased levels of sFas and sTRAIL, decreased concentrations of sFasL and similar sBcl-2 levels in JSLE indicates a distinct profile of increased induction of apoptosis compared to JIA and JDM. This particular proapoptotic profile may contribute to perpetuation of JSLE, since it is typically present during active disease. Furthermore, increased sBcl-2 may indicate a different role of apoptosis in JDM, which deserves further investigation.

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Hereditary Autoinflammatory Syndromes: A Brazilian Multicenter Study. Adriana A. Jesus[1], Erika Fujihira[2], Mariana G. Watase[2], Maria Teresa Terreri[3], Maria Odete Hilario[4], Magda Carneiro-Sampaio[1], Claudio Len[3], Sheila K. Oliveira[5], Marta C. Rodrigues[5], Rosa M.R. Pereira[6], Blanca E. Bica[7], Nilzio A. Silva[8], Andre Cavalcanti[9], Roberto Marini[10], Flavio Sztajnbok[11], Maria V. Quintero[12], Virginia P. Ferriani[13], Dewton Moraes-Vasconcelos[2], Joao B. Oliveira[14] and Clovis A. Silva[15]. [1]Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil, [2]Laboratório de Investigação Médica em Dermatologia e Imunodeficiências (LIM 56) da FMUSP, Brazil, [3]Universidade Federal de São Paulo / UNIFESP, Sao Paulo, Brazil, [4]Universidade Federal de Sao Paulo / UNIFESP, Sao Paulo, Brazil, [5]Instituto de Pediatria e Puericultura Martagão Gesteira (IPPMG) da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil, [6]Disciplina de Reumatologia da FMUSP, Sao Paulo, Brazil, [7]Disciplina de Reumatologia da UFRJ, Rio de Janeiro, Brazil, [8]Faculdade de Medicina, Universidade Federal de Goias, Goiania, Brazil, [9]Universidade Federal de Pernambuco, Brazil, [10]Universidade Estadual de Campinas, Sao Paulo, Brazil, [11]Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [12]Santa Casa de Misericórdia de Belo Horizonte, Brazil, [13]FMUSP-Ribeirao Preto, Ribeirao Preto, Brazil, [14]Clinical Center, National Institutes of Health (NIH), Bethesda, MD, [15]Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: The most prevalent autoinflammatory syndromes (AIS) with an identified genetic defect are: Familial Mediterranean Fever (FMF); Tumoral necrosis fator (TNF) Receptor Associated Periodic Syndrome (TRAPS); Pediatric Granulomatous Arthritis (PGA); Cryopyrin Associated Periodic Syndromes (CAPS), which includes Neonatal Onset Multisystem Inflammatory Disease (NOMID) or Chronic Infantile Neurological Cutaneous and Articular (CINCA) syndrome, Muckle-Wells Syndrome (MWS) and Familial Cold Autoinflammatory Syndrome (FCAS); and Mevalonate Kinase Deficiency (MKD) or Hyper—IgD and periodic fever Syndrome (HIDS). The objectives of this Brazilian multicenter study were to assess the clinical and laboratory characteristics of patients with a clinical suspicion of AIS from the five regions of the country, and to determine the prevalence of identifiable genetic defects.

Methods: A cross-sectional multicenter study was performed and included 102 patients from 22 Pediatric Rheumatology centers distributed in the 5 Brazilian regions. All patients had a clinical diagnosis of one of the following disorders: CAPS, TRAPS, FMF, MKD and PGA. Demographic, clinical and laboratory findings and treatment related variables were collected for each patient. One of the five AIS-related genes (*CIAS1*, *TNFRSF1A*, *MEFV*, *MVK* and *NOD2*) was evaluated in each patient by direct DNA sequencing based on the most probable clinical suspect. The exonic regions and flanking intronic sites of these genes were amplified by polymerase chain reaction (PCR) using specific primers for each gene. The DNA fragments were directly sequenced in both directions and all mutations detected were confirmed in a second PCR product amplification followed by sequencing.

Results: The clinical diagnoses of the 102 patients were: CAPS in 28 patients, TRAPS in 31, FMF in 17, MKD in 17 and PGA in 9. The most frequent clinical findings present in the 102 patients were: fever (85%), arthralgia (61%), abdominal pain (56%) and skin rash (49%), while the most prevalent laboratory findings included: increased erythrocyte sedimentation rate (ESR) (81%), increased C reactive protein (CRP) (78%), anemia (48%) and leukocytosis (46%). The therapies received by all the 102 patients were: corticosteroids (52%), methotrexate (29%), colchicine (25%), cyclosporine (11%), anti-TNF treatment (9%), thalidomide (8%) and anti-IL1 (2%). Of the 102 patients, 32 (31%) had a confirmed genetic diagnosis by evaluation of only one gene per patient: 6/28 (21%) CAPS patients, 7/31 (23%) TRAPS, (41%) 7/17 FMF (41%), 4/17 (24%) MKD and 8/9 (89%) PGA. Within the 28 CAPS patients, 4 of the 13 (31%) NOMID patients had a mutation detected, while 2 of the 8 (25%) FCAS and none of the 7 MWS subjects had a confirmed genetic diagnosis. Seven (27%) of the different 26 mutations identified were novel, such as T433I and K173E in *CIAS1*, G87S and D122H in *TNFRSF1A*, A21V in *MVK*, and D512H and Y563H in *NOD2*. One TRAPS patient was homozygous for the G87S mutation.

Conclusion: This was the first Latin-American study evaluating the prevalence of AIS in a large country and demonstrated one third of genetically confirmed patients at first genetic evaluation.

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Pathway-Based Analysis Identifies Significant Enrichment of Apoptosis, Immune and Fibrosis Genes Associated with Cardiac Manifestations of Neonatal Lupus. Paula S. Ramos[1], Miranda C. Marion[1], Carl D. Langefeld[1], Jill P. Buyon[2] and Robert M. Clancy[2]. [1]Wake Forest School of Medicine, Winston-Salem, NC, [2]New York University School of Medicine, New York, NY

Background/Purpose: Cardiac manifestations of neonatal lupus, comprising atrioventricular conduction defects and cardiomyopathy, occur in fetuses exposed to anti-Ro/SSA antibodies, and carry substantial mortality. Several lines of evidence support a fetal genetic risk, including increased recurrence rates, concordance of monozygotic twins, and discovery associations in a recent published genome-wide association study (GWAS). Regarding the latter, while the non-HLA autoimmune disease loci did not correlate with cardiac neonatal lupus, we did observe a significant increase in inflation factor for the autoimmune-associated SNPs (i.e., 1.22 vs 1.01; $P < 0.03$, autoimmune vs. whole genome SNPs), suggesting collectively an enrichment of association with these loci. Thus, we evaluated enrichment of associations in specific pathway-related genes such as those that are based on the proposed pathogenesis which invokes an injury cascade initiated by antibody binding to apoptotic cardiocytes and subsequent inflammation and tissue fibrosis.

Methods: We used Ingenuity Pathway Analysis to compile a list of all genes with immune (n=1,993 genes) and fibrotic (n=327 genes) functions. To narrow down the specific immune-related pathways, we tested for enrichment in specific candidate immune pathways: apoptosis (2,283 genes), T cell function (980 genes), cell infiltration (311 genes), innate immune cell function (1,381 genes), interferon (102 genes), TLRs (10 genes) and calcium channels (13 genes). We then tested for an enrichment of admixture and genomic control adjusted significant P-values (at alpha=0.001) in SNPs that met quality control criteria. We performed linkage disequilibrium based SNP pruning so that only independent SNPs were used when calculating the enrichment of significant P-values.

Results: We observed a strong enrichment (P<E-09) of significant SNPs in both immune (n=8,262 SNPs) and fibrosis-related pathways (n=1,577 SNPs); the enrichment persisted after excluding the extended HLA region (n=8,100 immune SNPs, P=5.01E-04; n=1,556 fibrotic SNPs, P=2.27E-09). As a control, genes with bone functions (n=568 genes) did not exhibit enrichment (P=0.21; 2,891 SNPs outside of the HLA). When we analyzed the specific candidate immune pathways, the apoptosis- (P=7.67E-07; 10,211 SNPs), T cell- (P=2.23E-04; 3,804 SNPs), innate immune cell- (P=2.53E-06; 5,736 SNPs), and interferon- (P=1.64E-03; 294 SNPs) related pathways continued to show an enrichment of significance (results reported after exclusion of the extended HLA region).

Conclusion: These data exhibit highly significant enrichment of associations in apoptosis-, innate- immune-, and fibrosis-related genes, and suggest that these genes are likely involved in predisposing to cardiac manifestations of neonatal lupus.

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A Novel Mutation in the *PSTPIP1* Gene is Associated with An Autoinflammatory Disease Distinct From Classical Pyogenic Arthritis, Pyoderma Gangrenosum and Acne Syndrome. Dirk Holzinger[1], Judith Austermann[1], Peter Lohse[2], Ivona Aksentijevich[3], Steven Holland[4], Marco Gattorno[5], Carlos Rodríguez-Gallego[6], S. Fessatou[7], Bertrand Isidor[8], S. Tokio[9], Jon Bernstein[10], Barry Sampson[11], Cord Sunderkoetter[12], Dirk Foell[13] and Johannes Roth[13]. [1]University Muenster, Muenster, Germany, [2]University Munich, Munich, Germany, [3]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [4]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [5]G. Gaslini Institute, Genova, Italy, [6]Dr. Negrín University Hospital, Las Palmas de Gran Canaria, Spain, [7]Attikon Hospital, Athens, Greece, [8]Centre Hospitalo-Universitaire, Nantes, France, [9]Nagoya City University, Tokyo, Japan, [10]Stanford University Medical Center, CA, [11]Charing Cross Hospital, London, United Kingdom, [12]Muenster, Germany, [13]University of Muenster, Muenster, Germany

Background/Purpose: Hyperzincaemia and hypercalprotectinaemia, a rare condition within the spectrum of autoinflammatory diseases, is associated with recurrent infections, hepatosplenomegaly, arthritis, anemia, cutaneous inflammation, and failure to thrive. So far, no genetic cause has been identified in these patients. While the clinical appearance is heterogeneous, all affected individuals present with extremely elevated S100A8/S100A9 (calprotectin) serum concentrations (0.9–12.0 g/l (normal range $<$ 0.001 g/l)). The clinical phenotype of 8 patients was characterized. Screening of candidate genes *PSTPIP1* and *MEFV* was performed in 8 hyperzincaemia and hypercalprotectinaemia patients to identify disease-causing mutations.

Methods: Serum concentrations of S100A8/S100A9 were analyzed by an ELISA assay in 8 patients with hyperzincaemia and hypercalprotectinaemia and compared to PAPA patients with and without treatment. Candidate exons were amplified by PCR and sequenced on an ABI 3130 Genetic Analyzer.

Results: Seven of the eight patients were heterozygous carriers of a glutamic acid 250 (GAG)→lysine (AAG)/p.Glu250Lys/E250K substitution in exon 11 of the *PSTPIP1* gene. S100A8/S100A9 concentrations were extremely elevated in these patients (0.9–12 g/l) compared to seven patients presenting with classical PAPA symptoms (0.02–0.35 g/l), whose levels again were significantly higher compared to normal controls.

Conclusion: The PSTPIP1 E250K mutation causes an autoinflammatory disorder known as hyperzincaemia and hypercalprotectinaemia. The disease causes a heterogeneous spectrum of symptoms that only partially overlaps with the presentation of the classical PAPA syndrome. Elevated S100A8/A9 levels are a common hallmark and biomarker of disorders caused by mutations in the *PSTPIP1* gene.

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Cytokine Expression Array Analysis Segregates Oligoarticular Juvenile Idiopathic Arthritis Patients At Risk of Disease Extension. Sorcha Finnegan, Madeleine Rooney and David S. Gibson. Arthritis Research Group, Queen's University, Belfast, United Kingdom

Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common form of childhood arthritis with a prevalence of approximately one in 1000. It consists of a heterogeneous group of inflammatory disorders, within which there are a number of clinical subgroups. Diagnosis and assignment to a particular subgroup can be problematic and at present it is very difficult to predict disease progression from ≤ 4 joints (persistent oligo) to the more severe form which involves > 4 joints (extended oligo) within six months of disease onset. We investigated cytokines commonly involved in JIA to understand how their expression within the synovial joint levels relate to disease extension.

Methods: We used Biochip Array Technology (Randox Laboratories Ltd., UK) to simultaneously measure the levels of 12 different cytokines in 18 treatment-naïve JIA patients (mean disease duration 6 months, mean patient age 6.5 years). 120 ul of each patient's synovial fluid were added to a single 9×9 mm biochip and samples were run overnight on the Evidence Investigator ™ (Randox Laboratories Ltd., UK). Each sample was probed for EGF, IL 1α, IL 1β, IL 2, IL 4, IL-6, IL-8, IL-10, IFN-γ, MCP 1, TNF α and VEGF.

Results: Of the 12 analytes measured 3 were found at significantly elevated levels in the extended compared to the persistent oligoarticular group. TNF α was significantly higher ($p = 0.02$) in the extended (47.6 pg/ml) compared to the persistent patients (17.3 pg/ml). IL8 was raised ($P<0.05$) in the extended group as was IL1B ($p=0.05$) (extended= 30.4 pg/ml, persistent= 3.6 pg/ml for IL1B). EGF, IL 1α, IL 2, IL 4, IL-6, IL-10, IFN-γ, MCP 1 and VEGF levels were not significantly altered between the two groups.

Conclusion: Presently it is difficult to predict whether disease will spread to > 4 joints in a child who initially presents with oligoarticular JIA. If disease extension can be reliably predicted, more effective treatment could be initiated in a timely fashion. A prior histological study revealed differences in the synovial tissue of the two subgroups. However, synovial fluid is more accessible and the identification of increased levels of TNFA, IL8 and IL1B represents an initial step in the process of understanding the pathological differences between subgroups. An expanded cohort will be used in the future to test the predictive strength of a multi-analyte cytokine panel.

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Circulating IP-10 and MCP-1 Levels in Active Localized Scleroderma. Katherine Kurzinski[1], Christina Kelsey[1], Thaschawee Arkachaisri[2], Carol A. Feghali-Bostwick[3] and Kathryn S. Torok[1]. [1]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]KK Women's and Children's Hosp, Singapore, Singapore, [3]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Localized scleroderma (LS) is a fibrotic autoimmune disease of the skin and underlying tissues that primarily affects children. T-helper (Th) cell subsets and their associated cytokines are thought to contribute to the pathogenesis of LS and systemic sclerosis (SSc). Traditionally, a Th2 predominant response has been supported, but more recent data also implicate Th1, Th17, and various chemokine involvement. This study was designed to further evaluate the serum cytokine and chemokine profiles of patients with active pediatric LS.

Methods: Serum samples were obtained from pediatric LS, adult LS, pediatric SSc patients and healthy pediatric controls. All LS patients had active disease at the time of sample collection, defined clinically by the presence of new, expanding, and/or erythematous lesions, and were naïve to systemic therapy. Using Luminex technology, 27 cytokines and chemokines from Th1, Th2, and Th17 subsets were evaluated. Nonparametric analyses were performed to compare cytokine/chemokine levels between groups and to determine relationships between individual analyte levels and clinical parameters $p < 0.05$.

Results: Circulating levels of IP-10 and MCP-1 were significantly elevated in pediatric LS, adult LS, and pediatric SSc when compared with healthy controls (see Table). IP-10 levels correlated with mLOSDI, a validated skin damage measure for LS patients ($r_s=0.644$, $p=0.001$), and with the number of anatomical sites affected ($r_s=0.515$, $p=0.012$). IP-10 levels were also significantly higher in LS patients with positive single stranded DNA (ssDNA) antibodies.

		IP-10 (pg/ml)		MCP-1 (pg/ml)	
Group	n	Median	IQR	Median	IQR
Pediatric LS	23	407.59	201.99–1278.93	371.17	341.55–577.01
Adult LS	32	358.72	233.68–1435.05	652.5	415.97–938.58
Pediatric SSc	11	435.47	262.04–779.76	843.65	472.14–2101.77
Healthy Control	10	208.08	124.81–259.08	132.89	74.33–214.34

Conclusion: Elevated levels of IP-10, an IFN-γ-associated chemokine, and MCP-1, a profibrotic chemokine, were seen in pediatric and adult LS and SSc, suggestive of a shared pathogenesis between the diseases. Moderate to strong correlations were observed between IP-10 levels and the number of sites affected and ssDNA antibodies, indicating that IP-10 may be a predictor of disease severity in LS patients. Future investigation into the roles of IP-10 and MCP-1 and their association with Th cell lineages in LS will help lead to a greater understanding of the disease pathogenesis and to the development of more efficacious therapies.

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Presence and Significance of Anti-Citrullinated Type II Collagen and Anti-Citrullinated Vimentin Antibodies in Juvenile Idiopathic Arthritis Patients. Brooke E. Gilliam[1], Anil K. Chauhan[1] and Terry L. Moore[2]. [1]Saint Louis University, St. Louis, MO, [2]Saint Louis University, Saint Louis, MO

Background/Purpose: Anti-cyclic citrullinated peptide (CCP) antibodies in juvenile idiopathic arthritis (JIA) have been identified as an important indicator for destructive disease, as is the case in rheumatoid arthritis (RA).

While the role of anti-CCP antibodies in RA and JIA has become better understood, the identity of the target proteins of this modification has remained elusive. In this study, we evaluated serum from patients with various subtypes of JIA to investigate the presence of anti-citrullinated type II collagen (CII) and anti-citrullinated vimentin antibodies, and their association with rheumatoid factor (RF) and anti-CCP antibody isotypes. Additionally, our previous published data on anti-citrullinated fibrinogen and α-enolase antibodies will also be considered.

Methods: Sera were obtained from 25 JIA patients, 19 sytemic lupus erythematosus patients (SLE) patients, and 10 healthy children. All sera were measured for antibodies against citrullinated and native CII and vimentin by enzyme linked immunosorbent assays. Results were compared to anti-CCP antibody isotypes and RF isotypes, anti-citrullinated fibrinogen antibodies and anti-citrullinated α-enolase antibodies. The relationship between anti-citrullinated antibodies and joint damage and disease activity were also investigated. All results were correlated with clinical parameters.

Results: Eleven of 25 (44%) JIA patients were positive for anti-citrullinated CII, while 5/25 (20%) were positive for citrullinated vimentin. Six patients showed no reactivity to any of the measured anti-citrullinated antibodies, while 3 were only reactive to anti-citrullinated fibrinogen antibodies. The most common combination of positivity was anti-citrullinated CII antibodies with anti-citrullinated fibrinogen or anti-citrullinated α-enolase antibodies with 3 JIA patients each. None of the JIA patients showed reactivity to more than 2 citrullinated antibodies. JIA patients' positive for erythrocyte sedimentation rate and IgA anti-CCP antibodies demonstrated elevated levels of anti-citrullinated vimentin antibodies. Anti-citrullinated vimentin antibodies correlated significantly with anti-citrullinated α-enolase antibodies and anti-citrullinated fibrinogen antibodies ($p<0.05$). Anti-CII antibodies correlated significantly with anti-citrullinated vimentin antibodies, anti-citrullinated fibrinogen antibodies, citrullinated α-enolase antibodies, and IgA and IgG anti-CCP antibodies ($p<0.05$).

Conclusion: In addition to our previous study showing the presence of anti-citrullinated fibrinogen and α-enolase antibodies in JIA, we have also shown that anti-citrullinated and anti-citrullinated vimentin antibodies can also be detected in JIA sera. JIA patients exhibited a diverse citrullinated autoantibody repertoire, indicating the significance of measuring these specific citrullinated autoantibodies in JIA patients.

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Pathogenesis Study of Infantile-Onset, Severe Pustular Psoriasis Reveals a *De Novo* Mutation in *CARD14* Causing Psoriasis Which Responds Clinically to IL-12/23 Blocking Treatment with Ustekinumab. Nadia Habal[1], Yongqing Chen[2], Catherine Jordan[3], Yin Liu[2], Dawn C. Chapelle Neal[4], Deborah Stone[5], Damaris Garcia[5], Nicole Plass[6], Edward Cowen[4], Chyi-chia Lee[4], Michelle Lowes[7] and Raphaela T. Goldbach-Mansky[8]. [1]NIH/NIAMS, Bethesda, MD, [2]NIAMS, Bethesda, MD, [3]Washington University Division of Human Genetics, Saint Louis, MO, [4]NIAMS/NIH, Bethesda, MD, [5]Translational Autoinflammatory Disease Section, Office of the Clinical Director NIAMS, Bethesda, MD, [6]National Institutes of Health Clinical Center, Bethesda, MD, [7]Laboratory for Investigative Dermatology, The Rockefeller University, New York, NY, [8]NIH Building 10 Room 6D47B, Bethesda, MD

Background/Purpose: Monogenic autoinflammatory disorders in young children have provided us with insights into key inflammatory pathways that have helped to elucidate the pathogenesis of genetically complex and more common diseases. A pediatric patient with non familial, early onset and treatment resistant pustular psoriasis may provide new insights into the pathogenesis of psoriasis and was investigated genetically and immunologically.

Methods: A 4-year old female patient had pustular psoriasis involving 100% of her skin and nails and was unresponsive to treatments with methotrexate, cyclosporine, the TNF inhibitor infliximab, and the recombinant human IL-1 receptor antagonist, anakinra. Clinical and genetic assessment for skin infections, cutaneaous malignancies and the autoinflammatory syndrome, DIRA, were negative, patient was also negative for HLA Cw6 and B27. Genetic analysis of *CARD14,* a recently identified gene causing familial psoriasis was tested, and skin biopsies were stained for CARD 14, IL-12, IL-23 and IL-17. Treatment with ustekinumab (Stellara) was initiated.

Results: The patient harbored a *de-novo CARD14* mutation (p.Glu138Ala) that was not detected in both parents. The mutations enhanced NF-kB activation in mutant and wildtype CARD14 transfected HEK293 cells. Further upregulation by TNF-α stimulation that was seen with wildtype constructs was not observed in the constructs with the mutant allele. The patient had a dramatic clinical response to ustekinumab therapy with complete resolution of skin and nail findings. Delay in therapy led to recurrence of rashes on her leg but responded to retreatment. Immunohistochemistry of the skin showed presence of CARD 14 staining mainly in the keratinocytes in the epidermis and increased staining of IL-23 and IL-17 in mononuclear infiltrating cells in the inter-phase and epidermis before treatment, which was reduced after treatment with ustekinumab. IL-12 was present in the papillary dermis in a psoriasis case, but to a much lesser degree in our patient before treatment and was negative after treatment.

Conclusion: This is a first case with a *de novo* mutation causing pustular psoriasis and confirms the notion that sporadic mutations can cause common diseases. Our data suggest that upregulation of the IL-12/IL-23/p40 effector pathway is mediated by CARD14 signaling. Although the role of CARD14 protein in immune cells in the development of psoriasis remains elusive our observations raise the possibility of an important role of keratinocytes in the pathogenesis of psoriasis and possibly other inflammatory skin disorders.

ACR Poster Session A
Rheumatoid Arthritis Clinical Aspects I: Rheumatoid Arthritis Classification, Disease Activity and Remission; Biomarkers and Predictors of Response
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Defining Rheumatoid Arthritis From Radiographic Erosive Abnormalities in the Light of the ACR/EULAR 2010 Criteria. Cédric Lukas[1], R. Knevel[2], Annette H.M. van der Helm-van Mil[3], Nathalie Rincheval[4], Désirée van der Heijde[5] and Bernard G. Combe[6]. [1]Montpellier 1 University, Lapeyronie Hospital, 371, Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France, Montpellier, France, [2]LUMC, Department of Rheumatology, Leiden, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Institut Universitaire de Recherche Clinique, Montpellier, France, [5]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [6]Hopital Lapeyronie, Montpellier, France

Background/Purpose: Definition of rheumatoid arthritis (RA) with regard to the new 2010 ACR/EULAR criteria can be made based on the presence of radiographic abnormalities ("*erosions typical of RA*"). This work reports results from a EULAR taskforce aiming at defining these RA-specific erosive lesions.

Methods: Patients from the French observational ESPOIR cohort had arthritis ($\geq$1 swollen joint) lasting for between 6 weeks and 6 months, and had not been treated before inclusion. The relationship between baseline radiography (eroded joints on hands and feet) and the start of methotrexate (MTX) during the first 12 months of the disease was evaluated. The test characteristics/performance of radiography (sensitivity, specificity, negative and positive- predictive values and likelihood ratios) were tested against the start of a treatment (regarded as the gold standard to define RA, similarly as in the development of the new diagnostic criteria). Different number and sites of eroded joints were considered to define "abnormal radiography", and the respective characteristic tests were derived.

	N (%)	Se	Sp	PPV	NPV	LR+	LR−	AUC
no erosions	325 (45)				reference			
≥1 joint	398 (55)	0.60	0.57	0.84	0.27	1.38	0.71	0.58
≥2 joints	264 (45)	0.51	0.69	0.86	0.27	1.64	0.71	0.60
≥3 joints	179 (35)	0.42	0.81	0.89	0.27	2.16	0.72	0.61
≥4 joints	134 (29)	0.35	0.85	0.89	0.27	2.29	0.77	0.60
> 4 joints	97 (23)	0.28	0.92	0.92	0.27	3.46	0.78	0.60

Results: 723 patients (77% women) had both clinical follow-up and baseline radiographic assessment suitable for the scheduled analyses: 46% were rheumatoid factor-, 39% anti-CCP2 positive. 325 patients (45%) had no detectable erosion, 398 (55%) had at least 1, and 134 (19%) at least 4 eroded joints. Expectedly, definition of "*radiographic abnormality*" by an increasing number of eroded joint was related to increased specificity and decreased sensitivity. Presence of more than 4 eroded joints resulted in the highest specificity (92%) and positive predictive value (92%). Influence of the eroded site (*MCP*, *MTP*, *IP* or *wrist joints*) or their combinations had no clear influence, except for the wrist involvement which showed low sensitivity (12%) but high specificity (91%) of being treated by MTX. Se = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative

predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio

Conclusion: These results show that the presence of erosions in the wrist or in more than 4 joints is very specific for RA. Further discussion should aim at choosing an optimal cutoff to define "*typical abnormalities*" of RA.

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Comparison of the 1987 ACR and 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis in Clinical Practice. Ewa H. Berglin[1] and Solbritt M. Rantapaa-Dahlqvist[2]. [1]Umeå university, Umea, Sweden, [2]Umeå University, Umea, Sweden

Background/Purpose: To compare the application of 1987 ACR and 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) in clinical practice**.**

Methods: The medical records of patients (pts) attending the Rheumatology department of Umeå university hospital with diagnosis of arthritis except for crystal diseases were studied. Pts fulfilling the following criteria were included: (1) presence of synovitis in at least one joint at first presentation (2) no other diagnosis than RA better explaining the synovitis (3) duration of symptoms < 1 year at first presentation (4) ≥ 1 year of follow-up from first visit. IgM-rheumatoid factor (RF; Waaler-Rose test), ACPA (Eurodiagnostica or Phadia), and erosions on hand and wrist radiographs at inclusion and initiation of DMARDs during the first year were recorded. Fulfilment of the 1987 ACR and the 2010 ACR/EULAR criteria was evaluated at the first visit and the sensitivity and specificity for each criteria set estimated with initiation of methotrexate (mtx) during the first year and clinical diagnosis of RA at follow-up as outcome measures.

Results: 1026 medical records were screened from which 313 patients (65% women, 60 % RF positive, 64% ACPA positive, 17% erosions) with the mean age (±SD) of 56 (± 16.4) years and median (range) duration of symptoms of 4 (0.25–11.5) months were included. A total of 233 patients (74%) fulfilled the 2010 ACR/EULAR, 164 (52 %) the 1987 ACR criteria and 157 (50 %) both sets of criteria at first visit. The agreement between the two sets of criteria was 73%. The frequency of fulfilment of 2010 ACR/EULAR criteria was significantly higher in pts ≥ 56 years compared with pts < 56 years (79 % vs. 68 % $X^2 = 5.01$, $p = 0.025$). No difference was found for the 1987 ACR criteria between pts ≥ and < 56 years. The frequency of fulfilment of neither 1987 ACR nor 2010 ACR/EULAR criteria did differ between pts with duration of symptoms < or ≥ 4 months. The 2010 ACR/EULAR was tested with cut-off point 7 points which increased the sensitivity for mtx first year to 76 % and decreased the specificity to 63 %.

	Outcome: Mtx first year		Outcome: RA (rheumatologist opinion at one year follow-up	
	RA (1987 criteria)	RA (2010 criteria)	RA (1987 criteria)	RA (2010 criteria)
All pts; n = 313				
Sensitivity, %	64	84	68	91
Specificity, %	82	52	86	65
AUC	0.774	0.743	0.837	0.842
Pts < 56 years; n = 131				
Sensitivity, %	61	78	69	91
Specificity, %	82	61	90	79
AUC	0.770	0.715	0.899	0.896
Pts ≥ 56 years; n = 182				
Sensitivity, %	67	89	72	91
Specificity, %	82	53	82	52
AUC	0.780	0.773	0.786	0.795
Pts with duration of symptoms < 4 months at baseline; n = 128				
Sesitivity, %	64	82	66	89
Specificity, %	80	48	84	66
AUC	0.756	0.707	0.818	0.837
Pts with duration of symptoms 4–12 months at baseline; n = 185				
Sensitivity, %	65	85	70	92
Specificity, %	88	56	87	65
AUC	0.783	0.771	0.854	0.845

Conclusion: 2010 ACR/EULAR criteria had higher sensitivity but lower specificity than 1987 ACR criteria in this cohort of early arthritis patients. The 2010 ACR/EULAR criteria were significantly more often fulfilled in pts ≥ 56 years. Raising the cut-off point of 2010 ACR/EULAR criteria to 7 points would decrease the sensitivity but increase the specificity of that criteria set.

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The 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis: Earlier Diagnosis At the Expense of Increased Heterogeneity. Maria J. H. de Hair[1], K. A. Lehmann[1], Marleen G. H. van de Sande[1], Karen Maijer[1], Danielle M. Gerlag[1] and Paul P. Tak[2]. [1]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [2]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam The Netherlands, Amsterdam, Netherlands

Background/Purpose: Recently, new classification criteria for rheumatoid arthritis (RA) have been developed. We examined the implication of the use of the new criteria in clinical practice in a very early arthritis cohort.

Methods: 301 early arthritis patients (arthritis duration < 1 year; DMARD naive) included between 2002 and 2010 in the early arthritis cohort of the Academic Medical Center Amsterdam were studied. Baseline diagnosis was assessed applying 1987 ACR and 2010 ACR/EULAR criteria for RA as well as established diagnostic criteria for other rheumatic diseases. Diagnostic and prognostic (self limiting, persistent non-erosive and persistent erosive disease) data after 2 year follow up were available of 239 and 186 patients, respectively. We evaluated in the subset of patients classified as UA when applying 1987 ACR criteria the fulfillment of 2010 ACR/EULAR criteria and tested the sensitivity, specificity and positive and negative predictive value of the 2010 ACR/EULAR criteria at baseline using RA diagnosis according to 1987 ACR criteria after 2 years follow up as gold standard. In addition, we compared the clinical picture using the two criteria sets at baseline.

Results: Median disease duration at baseline in the whole cohort was 3.0 months (range 0–12). At baseline 28% fulfilled the 1987 ACR criteria compared to 45% for the 2010 ACR/EULAR criteria for RA. This percentage increased to 36% and 55%, respectively, after 2 years follow up. Fifty- three per cent of all patients included had UA at baseline when applying 1987 ACR criteria compared to 36% when applying 2010 ACR/EULAR criteria, which decreased to 44% and 22%, respectively, after 2 years follow up. Of the patients classified as UA at baseline when 1987 ACR criteria were applied, 36% fulfilled 2010 ACR/EULAR criteria already at baseline. Of the patients initially classified as UA at baseline when 1987 ACR criteria were applied, but who fulfilled 1987 ACR criteria after 2 years follow up, 85% already fulfilled 2010 ACR/EULAR criteria at baseline, confirming the increased sensitivity of the new criteria. Eighty-eight per cent of the patients fulfilling 1987 ACR criteria for RA after 2 years follow up fulfilled 2010 ACR/EULAR criteria at baseline, with a specificity of 0.76. The positive and negative predictive values were 0.77 and 0.91, respectively. Of the patients fulfilling 1987 ACR criteria at baseline 67% was IgM-RF and/or ACPA positive compared to 62% for patients fulfilling 2010 ACR/EULAR criteria at baseline. Four per cent of the RA patients fulfilling 1987 ACR criteria at baseline presented with monoarthritis compared to 9% of the patients fulfilling 2010 ACR/EULAR criteria at baseline. Of the patients fulfilling 1987 ACR criteria for RA at baseline 2% had self-limiting disease, compared to 12% of the patients fulfilling the 2010 ACR/EULAR criteria at baseline.

Conclusion: Use of the 2010 ACR/EULAR criteria clearly allows earlier diagnosis of RA, although some patients with self-limiting disease may be falsely diagnosed with RA. Patients fulfilling 2010 ACR/EULAR criteria during early disease are less likely to be autoantibody positive and more likely to have monoarthritis than those fulfilling 1987 ACR criteria.

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2010 American College of Rheumatology/European League Against Rheumatism Rheumatoid Arthritis Criteria Classifies 67% of Systemic Lupus Erythematosus and 38% of Psoriatic Arthritis As Rheumatoid Arthritis: Implications for Real World Use. Lauren M. Kennish[1], Monalyn Labitigan[2], Sam Budoff[3], Maria T. Filopoulos[1] and Yusuf Yazici[4]. [1]Hospital for Joint Diseases, New York, NY, [2]New York University, New York, NY, [3]Vanderbilt University, Nashville, TN, [4]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: The new 2010 ACR/EULAR criteria for rheumatoid arthritis (RA) have been designed to classify early onset RA and target patients who would benefit from rapid initiation of methotrexate therapy. It is not known how these criteria perform to identify RA in patients with arthritis seen in routine clinical care. The criteria have been studied in RA cohorts but not in patients with other conditions that may mimic RA. The purpose of this study is to test the validity of the 2010 RA criteria in a general rheumatology practice to determine how well it can distinguish RA from other types of inflammatory arthritides.

Methods: 126 consecutive new and established patients from a general rheumatology practice were recruited consecutively after screening by their primary rheumatologist and included if they had joint symptoms between 8/1/2010-4/30/2010. The ACR/EULAR RA criteria were applied, as laid out by the task force, by a single rheumatologist with questions followed by a targeted musculoskeletal and extra-articular exam. The patients were followed retrospectively and prospectively for additional exam findings, laboratory and radiographic tests, and physician diagnosis not present at time of screening. The gold standard for the diagnosis of RA was the primary rheumatologist's diagnosis. Sensitivity and specificity were calculated.

Results: 126 patients were recruited for the study, and 112 were analyzed. They had a mean age of 48.2 years, with 77.7% women, an average duration of disease of 5.3 years, and 25% were new patients diagnosed within the last six months. 30 (26.8%) patients had a primary diagnosis made by their physician of RA, the rest had psoriatic arthritis (PsA) n=24 (21.4%), systemic lupus erythematosus (SLE) n=24 (21.4%), osteoarthritis (OA) n=12 (10.7%), and other rheumatic conditions n=22 (19.6%). The sensitivity and specificity of the 2010 criteria in classifying RA were 97% and 55%, respectively, compared with the 1987 RA criteria which were 93% and 76%, respectively. The 2010 criteria as applied to this group of patients had a poorer positive predictive (44% vs 61%) and a similar negative predictive value (98% vs 97%) compared with the 1987 criteria. In patients with a known diagnosis of RA, 96.7% met the 2010 criteria. In the combined population of those without a rheumatologist diagnosis of RA, 45.1% fulfilled the 2010 criteria. More specifically, 66.7% of SLE patients, 50% of OA, 37.5% of PsA, and 27.2% of others (2 Sjogren's syndrome, 2 spondyloarthritis, 1 gout and 1 mixed connective tissue disease) fulfilled the new criteria and could have been classified as RA.

Conclusion: We believe this is the first study to examine the new 2010 ACR/EULAR RA criteria in a broad spectrum of rheumatologic diseases seen in routine care. These criteria are more sensitive in classifying RA patients compared with the 1987 criteria. However, the criteria have low specificity, and will therefore incorrectly label those as having RA when in fact they may have another type of inflammatory arthritis, as seen among these patients. Physicians need to be aware of this when applying the new criteria for classifying their patients for any purpose.

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Performances of the 2010 ACR/EULAR Classification Criteria of Rheumatoid Arthritis: Comparison with 1987 ACR Criteria in the Community-Based Vera Cohort. Julia Nicolau Jr.[1], Patrick Boumier[2], Alain Daragon[1], Othman Mejjad[1], Jean-François Ménard[1], Sophie Pouplin[1], Olivier Vittecoq[3], Patrice Fardellone[2] and Xavier Le Loët Sr.[3]. [1]Rouen University Hospital, Rouen, France, [2]Amiens University Hospital, Amiens, France, [3]Rouen University Hospital and Inserm U 905, Rouen, France

Background/Purpose: To compare performances of 1987 American College of Rheumatology (ACR) and 2010 ACR/EULAR (EUropean League Against Rheumatism) classification criteria of rheumatoid arthritis (RA) in the VErA (Very Early Arthritis) cohort.

Methods: VErA cohort had a community-based recruitment and was conservatively treated during the 2 first years. It comprised 310 patients included between 10–1988 and 01–2002: ≥18 year old, ≥ 2 swollen joints for ≥ 6 weeks and ≤ 6 months, naïve of DMARD and steroids. This cohort was not used to develop 2010 criteria. 1987 ACR and 2010 ACR/EULAR criteria were applied at baseline in the whole population and using tree algorithm; the sensitivity and specificity were determined using as outcome measure the 3 experts consensual diagnosis at 6 years.

Results: Characteristics of the overall population were: female 68%; median age 52 years [19–84]; swollen joint count 7 [2–37]; tender joint count 6 [0–58]; DAS 28 2.95 [0.45–7.53]; mean HAQ 0.75 [0–2.9] ESR 18mm/1st h [1–110]; CRP 7mg/l [5–206]; IgM RF+ 22.6% and anti-CCP+ 23.2%; ≥1 erosion 16.8%. 41 patients had alternative diagnoses (algorithm step 1). Among the 269 other patients at baseline, 67.7% and 59.5% fulfilled the 2010 ACR/EULAR and 1987 ACR criteria respectively. The ACR/EULAR 2010 criteria sensitivity was significantly higher: 85.9% *vs* 77.9% (Mc Nemar's test 0.023); the specificity was similar (59.0% *vs* 64.1%). The discriminative ability of 2010 ACR/EULAR and 1987 ACR criteria was comparable (p<0.09) with areas under the curve 0.81–0.76 respectively. Moreover the ROC curves showed that the score ≥6, proposed by the 2010 criteria for classification as definite RA, was relevant.

Conclusion: Using a very early community-based cohort the 2010 ACR/EULAR criteria classified slightly more patients with RA than the 1987 ACR criteria but otherwise they performed similarly than the older ones. Moreover the ≥6 score seems relevant.

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The New EULAR/ACR Classification ACPA Cutoff Levels Are Markers of Poor Radiological Outcome in Early Rheumatoid Arthritis. Jose Alfredo Gomez Puerta[1], Virginia Ruiz Esquide[1], M. V. Hernandez[1], Eduard Graell[2], Sonia Cabrera[3], M. J. Gómara[4], Juan D. Cañete[5], Isabel Haro[4] and R. Sanmarti[1]. [1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]Hospital Parc Tauli, Sabadell, Spain, [3]Hospital Clinic of Barcelona., Barcelona, Spain, [4]IQAC-CSIC, Barcelona, Spain, [5]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain

Background/Purpose: The recent proposed EULAR/ACR criteria for rheumatoid arthritis (RA) were established in part as a useful tool for identify and classified patients with early RA. The cutoff level of 3 times upper limit of normal (ULN) for ACPA antibodies have been pondered as an additional criteria item. Its value as prognostic marker in terms of radiological progression has not been established yet.

Aims: To analyzed the relation of high titers levels of ACPA according to EULAR/ACR criteria with radiological progression in a cohort of patients with early RA.

Methods: We conducted a prospective open-label study that included early RA patients from 2 referral centers. All patients were treated with a similar therapeutic protocol with DMARD. ACPA antibodies were determined by a second-generation anti-CCP2 ELISA test (Eurodiagnostica). We classified 3 populations according to ACPA titers: negative (<29 IU, using own cutoff), positive at low titers (< 3 times ULN) and positive at high titers (> 3 ULN). Additionally, positive ACPA patients were divided as low positive or high positive using median values (293 IU). The minimal clinically-important difference (MCID) was used as a measure of Larsen radiographic progression, with a change of two or more units in the Larsen score considered as indicative of progression after one year in early RA.

Results: One hundred and fifty-five patients were included, 83% of female gender. The mean age was 54.7 ± 14.9 years, with a mean disease duration of 9.7 ± 6.6 months. Rheumatoid factor was positive in 76.3% and ACPA in 75.7%. At baseline Larsen score was 1.9 ± 6.9 and erosion joint count was 0.4 ± 1.3. Thirty percent of patients had Larsen score ≥1 and the18.6% had erosion joint count ≥1.

At baseline, 23% of patients were negative for ACPA, 11% of patients were positive at low titers (<3 ULN) while 65% of patients had high titers of ACPA (>3 ULN).

After two years of follow-up those patients classified as ACPA positive at high titers had a higher radiological progression than those patients with ACPA negative or ACPA positive at low titers (See Table). When radiological progression was analyzed according to median levels, there were no differences among ACPA positive at low titers and ACPA positive at high titers.

Table. Radiological progression (Δ Larsen score ≥ 4) after 2 years of follow-up according to ACPA titers (categorized by cutoff and median)

		No progression		Progression		p value
		No.	%	No.	%	0,033
ACPA (> 3 ULN)	Negative	30	83	6	16	
	Low titers	13	76	4	23	
	High titers	65	65	35	35	
	Total	108		45		0,204
ACPA (Median)	Negative	30	83	6	16	
	(<median)	38	64	21	35	
	(>median)	40	68	18	31	
	Total	108		45		

Conclusion: After two years of follow-up, patients with early RA with high titers of ACPA according new EULAR/ACR criteria had greater radiographic progression than those patients ACPA negative or positive at low titers. ACPA titers could have not only classification utility but also prognosis implications.

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Very High Specificity of Anti-Citrullinated Peptide Antiboldies (ACPA) in a Tertiary Medical Center. Meriem Ridene[1], Jeremie Dion[2], Makoto Miyara[3] and Bruno Fautrel[4]. [1]Tunis Medecine University, Tunis, Tunisia, [2]Faculté paris 7 Dénis-Diderot, Paris, France, [3]Université Pierre et Marie Curie—Paris 6, Pitié-Salpêtrière University Hospital, Paris, France, [4]Université Pierre et Marie Curie—Paris 6—Pitie Salpetriere University Hospital, Paris, France

Background/Purpose: Anti-cyclic citrullinated peptide (ACPA) antibodies have been shown to be a specific marker for the diagnosis of rheumatoid arthritis (RA)./To assess the ACPA specificity and positive predictive value through the long term experience of a tertiary university medical center.

Methods: We collected information about all the patients detected positive for anti-CCP antibodies between 2003 and 2010 (October). Detection was based on an enzyme linked immunosorbent assay (ELISA) using the anti-CCP2 kit (Diasorin. Anthony France). We focused on patients with titres of anti-CCP; i. e., superior to 90 IU. All medical charts were reviewed by 2 investigators (RM, DJ) to assess patient main clinical and biological characteristics.

Results: Between 2003 and 2010, 12 476 ACPA testing were performed: 808 were positive (≥ 30IU), 623 highly positive (≥ 90IU). Clinical features were available for all 623 cases (443 female) near aged 54.4 (DS= 14.7).The diagnosis made by the physician in charge of the patients are presented in the table. 23 patients have non auto-immune disease specially, infections (n=2): HIV, coetaneous candida; neurological (n=4): mitochondrial myopathy, peripheral motor neuron disease, autoimmune encephalopathy, cerebral accident; chronic widespread pain (n=6), other Rheumatologic (n=6): SPID, microcrystalline arthropathies, knee arthrosis, monoarthritis, non determined rheumatism and other (n=5). None of the patients was diagnosed with neoplasm. PPV was 88, 7%.

	N° (%)	Anti-CCP (IU) (Average/Median)
Definitive or probable RA	553 (88.7%)*	1739/605
Probable RA associated with another Connectivite Tissue disease (CTD)	10 (1.6%)**	5835/2080
Other auto-immune disease		
Sjogren Syndrome	10 (1.6%)	1057/543
Systemic Lupus Erythematous	2 (0.3%)	1295/1295
Spondylarthritis	10 (1.6%)	1138/764
Mixed Connective	3 (0.5)	162/872
Connective and vasculitis	2 (0.3%)	829/829
Other	4 (0.6%)	203,4/79
Non auto-immune disease		
Non auto-immune disease	23 (3.7%)	558/295

* (88, 8% positif for RF)
** (87, 4 %positif for RF)

Conclusion: In a tertiary university center in which patients with complex, misleading or confusing diseases are referred, ACPA test remains highly specific and is associated with high PPV.

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Evaluation of the Patients with Early Arthritis by 2010 RA Criteria in Conjunction with MRI of Wrists and Finger Joints. Mami Tamai[1], Kazuhiko Arima[1], Masataka Uetani[1], Naoki Iwamoto[1], Junko Kita[1], Akitomo Okada[1], Tomohiro Koga[2], Shin-ya Kawashiri[1], Kunihiro Ichinose[1], Satoshi Yamasaki[1], Hideki Nakamura[1], Hiroaki Ida[3], Tomoki Origuchi[1], Kiyoshi Aoyagi[1], Katsumi Eguchi[4] and Atsushi Kawakami[1]. [1]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Nagasaki University School of Medicine, Nagasaki, Japan, [3]Kurume University School of Medicine, Kurume, Japan, [4]Sasebo City General Hospital, Sasebo, Nagasaki, Japan

Background/Purpose: 2010 rheumatoid arthritis (RA) criteria was published last year and are going to be applied in the clinical field of rheumatology. We have also been investigating a prediction rule for RA using magnetic resonance imaging (MRI) of wrists and finger joints at Nagasaki University. We have tried to examine the utility of MRI of wrists and finger joints in conjunction with 2010 RA criteria toward patients with early undifferentiated arthritis at our cohort.

Methods: Two hundred patients with early arthritis, who are not better explained by other diagnosis than RA at entry whose mean duration of symptoms is 3 months, were consecutively enrolled into this study. Japan College of Rheumatology-certified rheumatologists have examined the patients for at least 1 year. At entry, all of the patients were examined by gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI of both wrists and finger joints. Patients were evaluated by 2010 RA criteria at the initial visit. Diagnosis of RA was defined by the initiation of disease-modifying antirheumatic drugs (DMARDs) therapy during the first year. Diagnostic performance of 2010 RA criteria in conjunction with MRI of wrists and finger joints were investigated.

Results: At least one swollen joints were found in 138 patients at entry, being examined for further analysis. 2010 RA criteria classified RA at sensitivity 76.3 %, specificity 70.7 %, positive predictive value (PPV) 86.0 %, negative predictive value (NPV) 55.8 % and accuracy 76.4 %. However, twenty-three out of 52 patients, who had not been classified as RA at entry by 2010 RA criteria, developed RA at 1 year. Bone edema was defined as most RA-specific MRI finding. If we considered the patients to have RA in case bone edema is found, the diagnosis of RA was made at sensitivity 87.6% and specificity 65.9% in whom 2010 RA criteria at entry was less than 6.

Conclusion: MRI findings, especially bone edema, are quite useful to assist the diagnostic performance of 2010 RA criteria.

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Comparison of the 1987 and 2010 Classificatioh Criteria for Rheumatoid Arthritis in a Population of Patients with Early Arthritis. Ana M. Ortiz Garcia, Ana M. Fernández-Ortiz, Silvia Pérez-Esteban, Rosario Garcia-Vicuña and Isidoro González-Alvaro. Hospital Universitario de La Princesa. IIS Princesa, Madrid, Spain

Background/Purpose: The 1987 classification criteria for rheumatoid arthritis (RA) were developed after studying a population with long-standing disease. However, the current paradigm in the management of RA is to initiate DMARD treatment as soon as possible. Since, it was considered that 1987 classification criteria are less effective to identify RA when applied in patients with early arthritis (EA), a new set of criteria for the classification of RA has been developed and recently published. These new criteria need to be tested in different populations and settings. The objective was to compare the two sets of criteria for the classification of RA (1987 and 2010) in a population of patients with EA.

Methods: We analyzed data from 260 patients (81% women) of our EA register, which includes patients with at least one swollen joint for at least four weeks and with symptoms for less than one year. The age at onset was 50 [38–62] years (median [p25-p75]) and the duration of the disease in the first visit 5.3 [3.1–8.1] months. Rheumatoid factor (RF) was positive in 34.4% of patients (nephelometry; positive > 20 IU / ml [min: 0–max: > 3.000]) and anti-CCP antibody in 28.6% (ELISA, RA Inmunoscan Euro-Diagnostica, positive > 50 IU / ml [min: 0–max: 3125]). For the purposes of applying the 2010 criteria, the upper limit of C-reactive protein was considered 0.8 mg/dl and of ESR 10 or 15 mm/h (men and women, respectively). We performed a descriptive analysis of patients who met the criteria for RA 1987 and 2010 in the first visit. The gold standard was considered the diagnosis of the patient's attending rheumatologist after two years of follow up. In these conditions the prevalence of AR in our population was 40% of cases. This gold standard was considered for estimating sensitivity, specificity, positive and negative predictive value (PPV and NPV respectively) and likelihood ratio (LR) + and − of each of the sets of classification criteria.

Results: At the first visit, 134 patients (51.5%) were classified as RA with the 2010 classification criteria and 116 patients (44.6%) when the 1987 criteria were applied. Results from the statistical analysis carried out for both sets of criteria are shown in the following table:

	Sensitivity	Specificity	PPV	NPV	LR+	LR−
2010	88.2%	72.2%	67.2%	90.5%	3.17	0.163
1987	85.3%	81.6%	75%	89.6%	4.65	0.18

PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio

Conclusion: In our EA population there are no relevant differences in RA disease identification when the 1987 or the 2010 classification criteria are implemented except for a higher specificity for the 1987 set. This finding could be related to the relatively long duration of the disease when our patients enter in the register.

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New Index to Assess the Improvement From the Worst Rheumatoid Arthritis Activity without Formal Joint Count. Naoto Yokogawa, Kota Shimada, Yoshiki Nagai, Takahiro Nunokawa, Shinichi Inada and Shoji Sugii. Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

Background/Purpose: Rheumatoid arthritis (RA) is a life-long disabling disease. No composite indices can measure the disease activity without formal joint count and estimate the worst disease activity. Routine Assessment of Patient Index Data 3 (RAPID3) is a validated index which does not require formal joint count. Because most patients remember the worst level of disability and pain, the worst disease activity can be estimated using the method of RAPID3 (worst RAPID3). We proposed a new index to assess the improvement of the disease activity from the worst ever (%RAPID3).

Methods: The proportion of the improvement from the worst in RAPID3 was defined as %RAPID3. [%RAPID3=(Worst RAPID3−Current RAPID3)/Worst RAPID3)×100].

We measured RAPID3, worst RAPID3, and %RAPID3 along with the traditional indices which require joint count such as Disease Activity Score (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI). We set the remission criteria of %RAPID3 using the the American College of Rheumatology/European League Against Rheumatism provisional definition of remission. We compared the sensitivity and specificity of each remission criteria.

Results: Sixty-nine RA patients were included in this study. Seventeen patients (24.6%) were categorized in remission. By %RAPID3 cut-off of 75, we can screen the patients in remission with the highest sensitivity (100%). The sensitivity and specificity of each remission criteria were summarized in Table 1.

Table 1.

	Sensitivity (%)	Specificity (%)
SDAI remission	82.4	88.5
CDAI remission	82.4	88.5
DAS28 remission	82.4	69.2
RAPID3<3	82.4	82.7
RAPID3<2	76.5	88.5
%RAPID3≥a80	88.2	78.9
%RAPID3≥a75	100	65.4
%RAPID3≥a70	100	61.5

Conclusion: % RAPID3 is the only disease activity index which can reflect the total improvement in the disease course. Complementary use of RAPID3 and %RAPID3 may provide the most practical and patient-oriented strategy in all RA patients.

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Benefits of the Implementation of Specialized Clinics in Rheumatoid Arthritis for Rule Out False Positives of Disease and Osteoarthritis As a Frequent Cause of Misdiagnosis. Pedro Santos-Moreno[1], Felipe Gonzalez-Malaver[2], Luisa Fernanda Amador[1], Claudia Guzman-Saltis[2], Maria F. Cubides[1], Ana Milena Arbelaez[1] and Rafael Valle-Onate[2]. [1]Biomab IPS, Bogota, Colombia, [2]Universidad Militar, Bogota, Colombia

Background/Purpose: The lack of expertise in the diagnosis of rheumatoid arthritis (RA) has led to misdiagnosis of patients with the disease, which has had clinical, pharmaco-economic and social consequences. The objective of this study was to describe the clinical and demographic characteristics of a cohort of patients with misdiagnosis of RA, emphasizing in Osteoarthritis (OA) as one of the most frequent causes of erroneous diagnosis of RA and the beneficial role of a specialized in RA clinic for rule out false positive patients.

Methods: In a specialized center in RA for the past 6 months were followed 2204 patients with presumptive diagnosis of this disease (patients were seen and remitted to the center by general practitioners, internists, physiatrists and other related specialties).

Included in the study patients were evaluated by a rheumatologist; it was made a complete medical history; it was measured rheumatoid factor and anti-citrullinated antibodies, and other laboratories depending on each case-.Also was performed x-rays of hands, and in some cases of persistent doubt about the diagnosis was requested comparative MRI of hands.

Afterwards, patients with false positive diagnosis of RA were analyzed for obtain information about those diseases which can misdiagnosis RA.

Statistical analysis was performed using STATA10. It was applied Shapiro-Wilk test to assess the kind of distribution of data. Afterwards, it was used Wilcoxon's test (for these not normally distributed data) obtaining medians for each variable.

The analysis of continuous variables was performed descriptively by presenting summary statistics and P values. For categorical data, absolute and relative frequency was calculated. The difference of medians showed a statistically significant in each of the variables analyzed, given by a P value < 0.05 for all of them.

Results: Of all the 2204 patients evaluated, in 1186 patients (53.8%) had confirmed the diagnosis of RA. It was found that 1018 patients (46.2%) were misdiagnosed with RA. Of these "false positives" diagnoses were found the following entities: 729 osteoarthritis patients (71.6%), systemic lupus erythematosus 72 patients (7%), Sjogren syndrome 30 patients (2.9%), spondyloarthropathies 23 patients (2.3%) and other diagnoses 16.2% of the population remaining.

As was seen, OA still with 729 patients (71.6%) the disease most often led to misdiagnosis. 230 patients (37%) were men, and 499 patients (63%) women. The average age was 54.3 years. Many of these patients had diagnosis of RA and were receiving disease-modifying drugs (DMARDs) continuously on average during the last 4.5 years.

Conclusion: This study shows that OA is the main distraction in the misdiagnosis of AR with serious clinical, social and pharmaco-economic implications associated.

Also demonstrate the urgent need for the implementation of specialized clinics in RA avoiding internists and the development of effective education strategies for primary care physicians and related specialties to conduct a proper diagnosis of RA.

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Rheumatoid Arthritis Case Validation Strategies in Large Research Databases: The Women's Health Initiative Experience. Brian T. Walitt[1], Rachel Mackey[2], Lewis Kuller[2], Kevin D. Deane[3], William Robinson[4], V. Michael Holers[5], Russell Tracey[6], Yuefang Chang[2] and Larry W. Moreland[2]. [1]Washington Hospital Center, Washington, DC, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Colorado School of Medicine, Aurora, CO, [4]Stanford Univ School of Med, Stanford, CA, [5]Univ of Colorado School of Med, Aurora, CO, [6]Colchester, VT

Background/Purpose: Research of rheumatoid arthritis (RA) epidemiology and outcomes using large databases is often limited by insufficient case validity. Employing serologic measurements of anti-cyclic citrullinated peptide (anti-CCP) antibody and rheumatoid factor (RF) is a potential method to improve diagnostic validity of the RA case definition in large research databases. We report on our RA validation experiences in the Women's Health Initiative (WHI).

Methods: A previous validation study (J Rheumatol 2008; 356:811–8) collected and reviewed medical records at two WHI sites to determine RA case validity with definitions based on self-reported RA status, Disease Modifying Anti-Rheumatic Drug (DMARD) use, and responses of subjects to the Connective Tissue Screening Questionnaire (CSQ). In this current study, baseline blood samples of this validation cohort of women self-reporting RA (n=345) were additionally tested for anti-CCP2 (Axis-Shield, Dundee, Scotland) and RF by nephelometry. Positive and Negative Predictive Values were then calculated considering these additional factors.

Results: The addition of autoantibody studies increased the Positive Predictive Value (PPV) of the RA case definition (Table 1). When only two variables are considered, self-report RA and anti-CCP2 provide the highest PPV (76.9%). When anti-CCP2 results are combined with either DMARD use or CSQ results, the PPV is 100% but excludes all seronegative cases. The most valid definition that includes seronegative RA cases is 'self-report RA + DMARD or Self-report RA + anti-CCP2 + RF (PPV 63.6%). False negatives are minimized in these case, definitions as evidenced by Negative Predictive Values >90%.

Table 1. Positive and Negative Predictive Values of Rheumatoid Arthritis Case Definitions

Definition Used:	Positive Predictive Value	Negative Predictive Value
Self-Report RA	14.8%	–
Self-Report RA + CCP2	76.9%	93.9%
Self-Report RA + RF	44.6%	94.1%
Self-Report RA + DMARD*	62.2%	93.9%
Self-Report RA + DMARD + CCP2	100%	91.8%
Self-Report RA + DMARD + RF	78.9%	88.7%
Self-Report RA + DMARD OR Self-Report RA + CCP2	58.3%	95.3%
Self-Report RA + DMARD OR Self-Report RA + CCP2 + RF	63.6%	95.3%
Self-Report RA + CSQ	39.1%	94.9%
Self-Report RA + CSQ + CCP2	100%	91.8%
Self-Report RA + CSQ + RF	77.3%	92.4%
Self-Report RA + CSQ OR Self-Report RA + CCP2	40.3%	95.9%
Self-Report RA + DMARD + CSQ	82.4%	91.4%
Self-Report RA + DMARD + CSQ + CCP2	100%	90.4%
Self-Report RA + DMARD + CSQ OR Self-Report RA + CCP2	83.3%	93.6%

* Current standard RA case definition in the WHI

Conclusion: Serologic measurements improve the test characteristics of RA case definitions in the WHI. Diagnostic validity approaches 100% if only seropositive RA cases are considered.

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Evaluation of Definitions of Rheumatoid Arthritis Remission by Assessing Radiographic Progression in the Leiden Early Arthritis Cohort. Annette H.M. van der Helm-van Mil[1], Rachel Knevel[1], Ferhan Qureshi[2], William C. Manning[2], Guy Cavet[2], T.W.J. Huizinga[3] and Douglas J. Haney[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Crescendo Bioscience, Inc., South San Francisco, CA, [3]Leiden University Medical Centre, Leiden, Netherlands

Background/Purpose: Clinical remission is increasingly seen as a desirable and realistic objective in the management of Rheumatoid Arthritis (RA). Useful definitions of clinical remission should identify patients at reduced risk of progressive joint damage. A novel multi-biomarker test for disease activity (MBDA) in rheumatoid arthritis has recently been developed and validated. We set out to evaluate whether the MBDA test can augment existing classifications of remission.

Methods: Subjects were members of the Leiden Early Arthritis Cohort. Those included in the current study met the 1987 ACR criteria for RA. Patients and visits were selected non-randomly to have greater rates of radiographic progression than the overall RA cohort, to increase our ability to evaluate predictors of progression. The pre-specified MBDA algorithm combined the concentrations of 12 biomarkers to produce scores from 1–100. MBDA score and other variables were assessed at 271 study visits and evaluated for prediction of progression over the following 12 months. Subjects with change in Sharp-van der Heijde Score (ΔSHS) ≤3 were classified as non-progressors. The pre-test and post-test odds of non-progression were calculated for definitions of remission based upon DAS28CRP (<2.32), EULAR/ACR Boolean criteria[1] (SJC28≤1, TJC28≤1, GH≤1, CRP≤1mg/dL), or MBDA score (≤25). Definitions of remission were evaluated using the positive likelihood ratio[1]. In addition, we evaluated whether a high MBDA score (>44) provides information about the risk of progression of a patient in remission based on DAS28CRP.

Results: The positive likelihood ratio (PLR) for non-progression over 12 months of an MBDA score ≤25 vs >25 was 4.73 (95% CI = [1.67, 15.0]). PLRs were greater than 1 but not statistically significant for DAS28CRP <2.32 (PLR = 1.38; 95% CI = [0.90, 2.38]) and the EULAR/ACR Boolean criteria (PLR = 1.78; 95% CI = [0.72, 5.17]). Similar relative performance was observed with other ΔSHS thresholds for non-progression. For patients in DAS28CRP remission, those with a high MBDA score were 2.3 times as likely (95% CI = [1.1, 3.7]) to have progressive joint destruction during the next year.

Conclusion: In a cohort of early arthritis patients, MBDA score ≤25 is an indicator of limited radiographic progression over 12 months. Among patients in DAS28CRP remission, high MBDA scores identify those at elevated risk of progression. MBDA results may provide a useful adjunct to clinical assessment in estimating risk of radiographic progression.

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TNF-Like Ligand 1A Is a Promising Biomarker of Disease Activity In Rheumatoid Arthritis. Yoo Jin Hong, Yun Jong Lee, Kichul Shin, Byoung Youg Choi, Hye Won Kim, Sung Hae Chang, In Ah Choi, Eun Young Lee, Eun Bong Lee and Yeong Wook Song. Seoul National University Hospital, Seoul, South Korea

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of multiple joints. TNF-like ligand 1A (TL1A), a ligand belonging to the TNF superfamily, is expressed by endothelial cells, lymphocytes, monocytes and plasma cells. These are also the key cell lineages participating in the pathogenesis of RA. Moreover, TL1A is up-regulated by proinflammatory cytokines TNF-a and IL-1. We thereby examined the serum and synovial fluid levels of TL1A in patients with RA. In addition, we investigated the relationship between serum TL1A concentration and clinical parameters in RA patients.

Methods: Serum samples were obtained from 232 patients with RA and 29 with osteoarthritis (OA). Thirty-eight and 27 synovial fluid (SF) samples were collected from respective group of patients. Additional 45 serum samples before and after (14 weeks) anti-TNF-a treatment were collected from RA patients. TL1A concentrations were measured by ELISA. Clinical parameters were acquired at the time of sampling.

Results: Serum concentrations of TL1A in RA patients were significantly higher than those in OA patients (mean ± SD, 1327.4 ± 3858.8 pg/ml vs. 150.3 ± 269.6 pg/ml, p< 0.0001). The SF levels of TL1A were elevated in patients with RA compared with those in OA (965.7 ± 1617.2 vs. 271.4 ± 238.9, p= 0.013). Levels of TL1A were significantly increased in SF than serum in matched samples (RA; p= 0.006, OA; p< 0.0001). Serum levels of TL1A decreased substantially with anti-TNF-a treatment (p= 0.002). Serum levels of TL1A correlated well with DAS28-ESR (r= 0.170, p= 0.021), DAS28-CRP (r= 0.166, p= 0.037), SDAI (r= 0.201, p= 0.016), CDAI (r= 0.195, p= 0.011) and rheumatoid factor positivity (r= 0.876, p= 0.044).

Conclusion: Serum and SF levels of TL1A were significantly increased in RA patients compared with OA patients, and correlated well with clinical parameters representing disease activity. Our results support that TL1A could be a potential biomarker in assessing disease activity and treatment response in RA patients.

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Prevalence of Remission in Early RA—A Comparison of New Remission Criteria to Established Criteria. Bindee Kuriya[1], Ye Sun[2], Gilles Boire[3], Boulos Haraoui[4], Carol A. Hitchon[5], Janet E. Pope[6], J. Carter Thorne[7], Edward Keystone[2], Diane S. Ferland[8] and Vivian Bykerk[9]. [1]University of Toronto, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]CHUS - Sherbrooke University, Sherbrooke, QC, [4]Institut de Rhumatologie, Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]St. Joseph's Health Care, University of Western Ontario, London, ON, [7]Newmarket, ON, [8]LaSalle, QC, [9]Brigham & Women's Hospital, Boston, MA

Background/Purpose: New RA remission (REM) criteria have been proposed by ACR/EULAR.We evaluated the prevalence and agreement between REM definitions in the Canadian Early ArThritis CoHort (CATCH).

Methods: The % of patients (pts) in REM at 12 months based on 5 definitions were considered: DAS28 <2.6, DAS28 <2.0, CDAI </=2.8, SDAI </=3.3 and ACR/EULAR which requires TJC </=1 plus, SJC </=1, plus CRP </=1 mg/dL and patient global assessment (Pt-VAS) </=1 on a 0–10 cm VAS scale. Patients with complete data were included. Differences in core components for each REM definition were qualitatively described. Kappa-statistics of agreement between criteria were performed.

Results: Of 331 pts, 74% met 1987 and 91% met 2010 ACR criteria for RA; 76% were female, mean (SD) age was 52 (14.4) years and mean (SD) symptom duration was 6.3 (3.0) months. At baseline, the cohort had moderate-to-high disease activity according to all scores. Most were RF+ (63%) or anti-CCP+ (83%). Triple DMARD was the most common therapy. By 1 year, the % of pts who achieved REM by >/= 1 definition ranged from 22%–453% (Table). Higher TJC, SJC, Pt-VAS and MD-VAS were seen for DAS28-based definitions. Biologic use was similar for all definitions (range 6–10%). The ACR/EULAR criteria had substantial agreement with SDAI (k= 0.75) and CDAI (k=0.73). Agreement was fair with DAS28<2.6 (k=0.32) and DAS28<2.0 (k=0.35).

Table. Comparison of core components of remission definitions at 12 months.

	DAS28 <2.6	DAS28 <2.0	SDAI </=3.3	CDAI </=2.8	ACR/EULAR
Number in REM, (%)	176 (53)	118 (36)	88 (27)	83 (25)	73 (22)
Core Components					
TJC (%)					
0–2	129 (73)	94 (80)	79 (90)	76 (92)	73 (100)
>2–5	29 (16)	18 (15)	8 (9)	5 (6)	0
>5	18 (11)	6 (6)	1 (1)	2 (2)	0
SJC (%)					
0–2	129 (73)	97 (82)	83 (94)	79 (95)	73 (100)
>2–5	36 (20)	20 (17)	4 (5)	4 (5)	0
>5	11 (7)	1 (1)	1 (1)	0	0
CRP, mean ± SD mg/L	0.3 ± 0.4	0.3 ± 0.4	0.3 ± 0.3	0.4 ± 0.5	0.3 ± 0.2
Pt-VAS, mean ± SD mm	1.8 ± 2.2	1.8 ± 2.2	0.6 ± 0.8	0.5 ± 0.7	0.3 ± 0.4
MD-VAS, mean ± SD mm	0.8 ± 1.1	0.7 ± 1.0	0.2 ± 0.5	0.2 ± 0.3	0.3 ± 0.6

Conclusion: The prevalence of clinical REM ranged between 22 and 53% among this early RA cohort. Achievement of REM was lowest using the strict ACR/EULAR criteria and there was poor agreement between these criteria and frequently used DAS-based definitions. Thus, the choice of definition influences the proportion able to achieve REM and this has implications for long-term outcomes, choice of therapy and quality of care standards.

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Factors Associated with Relapse of Remission in Rheumatoid Arthritis. Leslie R. Harrold[1], George Reed[1], David H. Collier[2], Grace S. Park[2], Hong Chang[3], Andrew S. Koenig[4], Katherine C. Saunders[5], Debra J. Zack[6], Joel M. Kremer[7] and Jeffrey D. Greenberg[8]. [1]UMass Medical School, Worcester, MA, [2]Amgen Inc., Thousand Oaks, CA, [3]Tufts Medical Center, Boston, MA, [4]Pfizer Inc., Collegeville, PA, [5]CORRONA, Inc., Southborough, MA, [6]Amgen Inc, Thousand Oaks, CA, [7]Albany Medical College and The Center for Rheumatology, Albany, NY, [8]New York University School of Medicine, New York, NY

Background/Purpose: The goal of treatment in patients with rheumatoid arthritis (RA) is achievement of remission. However, little is known regarding persistency of remission. Therefore we proposed to assess factors associated with relapse of remission in a multi-centered observational registry within the United States (the Consortium of Rheumatology Researchers of North America: CORRONA).

Methods: From among 5,525 biologic naïve RA patients within CORRONA initiating a new nonbiologic disease modifying antirheumatic drug (nbDMARD) or TNF blockade (TNFi), we identified those who were not in remission at the time of drug initiation, achieved remission (Clinical Disease Activity Index [CDAI ≤ 2.8]) while on the drug at a follow-up visit within 12 months, and had at least one follow-up visit. Disease relapse (e.g., loss of remission) was defined as a CDAI>2.8 or adding an additional nbDMARD or biologic. Survival analyses and Cox proportional hazards models were used in both nbDMARD and TNFi initiators separately to assess the likelihood of relapse after adjusting for covariates assessed at the first visit in remission, including age, sex, race, education, insurance, comorbidities, disease duration, and concomitant medication use as well as clustering by physician.

Results: There were 377 nbDMARD initiators who met inclusion criteria of whom 74% women, with a mean age was 58.3 years, mean disease duration of 7.6 years and 42% used methotrexate. The median time until flare was 166 days (interquartile range=177 days) with an estimated 56%, 28%, 16% and 14% still in remission at 6, 12, 24 and 36 months respectively. No socio-demographic or clinical factors were predictive of a flare in those using nbDMARDs. There were 401 TNFi initiators who met inclusion criteria of whom 76% were women, with a mean age of 54.4, mean disease duration of 6.1 years and 81% were receiving concomitant methotrexate. The median time until flare was 182 days (interquartile range=251days) with an estimated 61%, 39%, 25% and 20% still in remission at 6, 12, 24 and 36 months respectively. Increasing age (HR 1.02; 95% CI 1.00–1.03), being disabled (HR 1.78; 95%CI 1.04–3.01), Medicaid insurance (HR 2.38, 95% 1.40–4.03) and having gastroesophageal reflux disease (GERD) (HR 3.89; 2.48–6.09) were all associated with an increased likelihood of relapse in TNFi initiators.

Conclusion: Relapses in remission occurred in the majority of patients newly initiated on nbDMARDs or TNFi in the first three years of therapy. Factors associated with relapse in TNFi initiators were older age, disability, insurance status and GERD.

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Current Smoking and Hypertension Are Associated with Synovitis As Measured by Ultrasonography in Therapy-Naive Patients with Recent Onset Arthritis: Results from an Early Arthritis Cohort. Gisela Westhoff[1], Georg Schett[2], Edmund Edelmann[3], Matthias Schneider[4], Angela Zink[5] and Marina Backhaus[6]. [1]German Rheumatism Research Center Berlin, Berlin, Germany, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Rheumatologische Gemeinschaftspraxis, Berufsverband Deutscher Rheumatologen e.V, Bad Aibling, Germany, [4]Heinrich-Heine-University, Duesseldorf, Germany, [5]Deutsches Rheumaforschungszentrum and Charité University Medicine, Berlin, Germany, [6]Charite University Hospital, Berlin, Germany

Background/Purpose: Smoking is a well known risk factor for the development of cardiovascular disease and rheumatoid arthritis (RA). Smoking also compromises response to therapy in established RA. Data on the effects of smoking on very early, untreated arthritis are rare. We therefore investigated the association between smoking and synovitis as measured by a semi-quantitative ultra-sonography score in therapy-naïve patients with recent onset arthritis.

Methods: Baseline data of 163 therapy-naive patients with either RA or undifferentiated arthritis (disease duration <6 months) of an ongoing early arthritis inception cohort were used. Demographic and disease specific data as well as smoking habits and cardiovascular risk factors (CV) were recorded. Synovitis was determined by B-mode ultrasonography, using a semi-quantitative score (no =0 to severe synovitis =3) of 5 synovial sites in 3 hand joints. Correlates of an above-average synovitis score (SynSc ≥5 of 0–15, μ 4.2±3.3; 44% of all patients) were determined using multivariate analyses, adjusting for age and sex.

Results: At first visit, patients had a symptom duration of 13±7 weeks. All were preliminarily diagnosed with either RA (56%) or uA; 71% were classified as having RA according to the new ACR/EULAR classification criteria. CV risk factors were common at first visit, with 38% of the patients having at least one. Prevalent hypertension (29%) and hypercholesterolemia (10%) were the most frequent. 34% of the patients smoked at inclusion and 28% had stopped smoking before the onset of arthritis. Patients with hypertension were significantly older than patients without (65 vs. 49 years, P <0.001) and those currently smoking were significantly younger than non-smokers (47 vs. 56 years, P <0.001). Multivariate regression analyses revealed older age (upper vs. lower tertile: OR 6.0, 95% CI 2.1–17.2, P = 0.001), hypertension (OR 2.5, 95% CI 1.04–5.8, P = 0.040) and current smoking (OR 3.4, 95% CI 1.4–7.3, P = 0.007) as significant risks for above-average synovitis scores (SynSc ≥5). Hypertension gained high significance when age was removed from the analysis (OR 4.11, 95% CI 1.9– 8:8, P <0.001).

Conclusion: Our data show that current smoking, hypertension as well as age are associated with synovitis as measured by ultrasonography in untreated patients with recent onset arthritis. It may be suggested that age, smoking and hypertension cause endothelial damage and thus increase the vulnerability of tissues for synovitis.

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Near Misses of ACR/EULAR Criteria for Remission: Effects of Patient Global Scores on the Boolean and Index Based Definitions. Paul Studenic[1], Josef Smolen[2] and Daniel Aletaha[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: The ACR/EULAR criteria allow definition of remission by two means: the Boolean approach requires swollen and tender joint counts (SJC, TJC), as well as C-reactive protein (CRP in mg/dL) and patient global assessment (PGA in cm) to be ≤1; the index based definition requires the Simplified Disease Activity Index (SDAI, linear sum of SJC, TJC, CRP, PGA, and physician global (MDGA)) to be ≤3.3. It has been argued that high PGA, if unrelated to RA disease activity, may prevent patients from fulfilling these criteria. We aimed to quantify the relevance of PGA in the definition of remission by the new ACR/EULAR criteria in a patient cohort from clinical practice.

Methods: We identified all visits of RA patients from an observational, prospective RA outpatient database. We investigated the proportion of patients who fulfilled only 3 of the 4 required Boolean criteria. Among those, we identified the proportion of patients who did not reach the criteria because of PGA, SJC, TJC or CRP.

We also looked at the proportion of patients fulfilling the index based definition (which allows scores of some variables to be >1 through compensation by other variables with lower scores), but who did not achieve Boolean criteria because of PGA.

In a next step we estimated the impact of PGA that is potentially unrelated to

RA disease activity (e.g. related to secondary fibromyalgia) as a reason for failure to classify as remission. To this end, we investigated the disconnect of PGA and MDGA, by identifying those who were rated by the MD as ≤1cm or not.

Results: We identified 8242 visits of 794 RA patients (81% female, 68% rheumatoid-factor (RF) positive, mean disease duration: 7.6 years). Four of five (82%) of these patients had at least one visit, where they fulfilled just 3 of the 4 required Boolean criteria: among those, PGA was the major reason for not achieving the criteria (53%; n=344; mean PGA=3.3cm), followed by SJC (21%), CRP (16%), and TJC (10%). Almost 1 in 4 of the patients (23.5%) who failed the Boolean criteria because of PGA fulfilled the index based definition of remission.

238 patients (69.2%) with Boolean criteria failure due to PGA had a disconnect of PGA and MDGA (i.e. PGA >1 & MDGA ≤1cm; mean disconnect: 2.8 cm). One third (31.9%) of those patients did fulfill the index based remission criteria. These patients showed significantly lower pain, PGA (mean PGA=1.7cm) and less disconnect of PGA and MDGA, than those not fulfilling index based criteria (mean PGA=3.7cm). Similar results were obtained when using the Boolean- and index-based definitions for clinical practice which exclude CRP from the respective formulae.

Conclusion: The majority of patients who fail to reach the Boolean definition of remission due to PGA are assessed as <1cm on the physician global. By means of the index based criteria, one third of these patients were classifiable as being in remission, because a slight elevation of the PGA above 1 was compensated by other variables in the index being <1. Thus PGA elevations unrelated to RA disease activity may need to be considered in clinical practice in patients who fail to classify as remission by both, the Boolean and, to a somewhat smaller extent, the index based criteria.

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Combinations of Anti-Citrullinated Peptide Antibodies with Rheumatoid Factor Isotypes Reveal An Attribute Associated with Disease Activity in Rheumatoid Arthritis Patients Treated with Methotrexate. Thierry Dervieux[1], Cole Harris[2] and Joel M. Kremer[3]. [1]Exagen Diagnostics, Albuquerque, NM, [2]Exagen Diagnostics, [3]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: Previous reports have established that anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) isotypes may predict disease severity in rheumatoid arthritis (RA). We sought to determine whether specific combinations/multi-biomarker panel of ACPA and RF isotypes (IgM, IgG and IgA) were associated with disease activity in RA patients treated with methotrexate (MTX).

Methods: The study was multicentered, cross sectional, and enrolled 232 patients with established RA (74% females, median age 63yrs, median duration of disease 10 yrs) under MTX therapy (median dose 15mg/week) for at least three months (median 35 months). Disease activity score (DAS) was calculated and used to differentiate patients with low disease activity (DAS≤3.2; 82 patients, 35%) from those with medium to high disease activity (DAS>3.2; 150 patients, 65%). ACPA measured consisted of second generation anti-cyclic citrullinated peptide antibodies (anti-CCP2) (Euroimmune, Lübeck, Germany; Eurodiagnostica, Malmö, Sweden), third generation anti-CCP3.1 (Inova Diagnostics, San Diego, CA) and anti-mutated citrullinated vimentin antibodies (anti-MCV, Orgentech, Germany). IgM, IgG and IgA RF isotypes were from Inova Diagnostics. All serological markers were measured using validated enzyme linked immunosorbent assays. Data analysis consisted of Receiver operating characteristic (ROC) curves and data mining algorithms (COPERNA platform) to determine the optimal combination of cutoffs differentiating low from high disease activity. Models were developed using a training set of 155 patients and validated independently in a test set of 77 patients.

Results: Univariate ROC analyses in the training set revealed that anti-CCP2 (Euroimmune, AUC=0.577, p=0.078), anti-MCV (AUC=0.584, p=0.056) and IgA RF isotype (AUC=.587, p=0.023) differentiated low from high disease activity. IgG and IgM RF levels were not associated with disease activity in this population of RA patients. Data mining algorithms established that an attribute consisting of anti-MCV (cutoff> 20 units, 63% positive), antiCCP2 (cutoff >7 units, 62% positive) and IgA RF (cutoff> 11 units, 31% positive) was associated with higher disease activity (Table). The findings were significant in the training and tests set. Overall, carriers of the attribute (positivity for at least 2 of three markers, 59% of patients) were 3.8 fold more likely (OR=3.6 CI95%: 2.1–6.8; p<0.01) to present with high disease activity than none carriers. These findings remained significant after adjusting for covariate such as age, disease duration, MTX dose and duration of treatment.

	Training set (n=155)	Test set (n=77)	Overall (n=232)
Sensitivity	68.0%	73.6%	70.0%
Specificity	60.0%	62.5%	61.0%
Accuracy	65.2%	70.1%	66.8%.

Conclusion: Selective combinations of ACPAs and IgA RF isotype contribute to disease activity in RA.

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Disease Duration As a Determinate Factor of Disease Activity and Radiographic Progression in Rheumatoid Arthritis. Tahmina Ferdousi, Andrew S. Koenig and Thomas V. Jones. Pfizer Inc., Collegeville, PA

Background/Purpose: Clinical evidence has established the importance of early, aggressive treatment of RA to decrease disease activity and prevent joint damage.[1] The relationship between disease duration and disease activity is not well understood. The objective of this analysis is to examine the relationships between disease duration, disease activity, and inhibition of radiographic progression in patients treated with etanercept (ETN) + MTX or MTX monotherapy.

Methods: Subjects from 2 clinical trials (TEMPO and COMET) were pooled and stratified by short (≤2 years) and long (>2 years) disease duration. Subjects randomized to receive ETN 50 mg weekly + MTX or MTX alone for 52 weeks were included. Disease activity as measured by DAS28 and SDAI was assessed at week 24 and compared to the mean rates of change in mTSS and with radiographic non-progression (mTSS ≤0.5) for each disease duration category and by treatment group. Stratified and multivariate regression analyses (observed data) were performed to determine the relationships between variables.

Results: Among subjects in the ETN+MTX group who achieved DAS28 remission (<2.6) at week 24, the mean (SD) change in mTSS was significantly (P<0.05) lower in those with long duration [–1.38 (2.94)] compared to those of short duration [–0.12 (2.86)]. In the MTX group, mean (SD) change in mTSS was similar in those with long and short duration (Table). Among ETN+MTX subjects who achieved DAS 28 remission, the majority achieved radiographic non-progression regardless of disease duration (long 82.4% vs short 77.1%, p=0.4473), although the trend was towards a higher proportion of subjects with long duration achieving non-progression. Similar findings for radiographic non-progression were observed for MTX subjects who achieved DAS 28 remission (long 68.4% vs short 61.3%, p=0.5742). Among ETN+MTX subjects who achieved SDAI remission (≤3.3) at week 24, the mean (SD) change in mTSS was similar (p=0.3375) in those with long [–1.14 (1.93)] and short [–0.37 (4.14)] duration. Similar findings were observed for the MTX group who achieve SDAI remission [–0.67 (0.76) vs 0.44 (1.78), p=0.1162]. A trend towards a lower rate of radiographic progression was observed in subjects with long duration regardless of treatment. Disease duration was significantly associated with radiographic progression (P<0.05) independent of treatment, DAS 28, or SDAI score at week 24.

Table. Subjects with short and long disease duration by disease duration and radiographic progression at week 24

		ETN + MTX		MTX	
DAS28	**Disease Duration**	**n**	**mTSS Mean Change (SD)**	**n**	**mTSS Mean Change (SD)**
Remission (≤2.6)	≤2 years	109	−0.12 (2.85)	62	0.45 (5.38)
	>2 years	51	−1.38* (2.94)	19	0.55 (2.61)
Low (2.6<3.2)	≤2 years	49	0.11 (1.70)	30	2.03 (5.23)
	>2 years	20	−1.35* (2.37)	15	−0.13 (2.64)
Moderate (3.2≤5.1)	≤2 years	79	0.16 (3.61)	88	2.72 (6.42)
	>2 years	63	−0.63 (3.19)	73	1.49 (7.66)
High (>5.1)	≤2 years	17	0.91 (3.52)	36	8.78 (22.14)
	>2 years	16	−0.59 (3.23)	33	1.07* (4.42)

* P<0.05 versus short disease duration (≤2 years) within each disease duration category per treatment group.

Conclusion: Inhibition of radiographic progression and achievement of non-progression was robust, regardless of disease duration; although the trend was towards greater inhibition patients with longer duration. Caution should be used when interpreting these findings due to the limited number of subjects in the sub-groups. Further analyses will assess the impact of baseline estimated radiographic change and other factors on the relationship between disease duration and treatment response.

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Routine Assessment of Patient Index Data-3 (RAPID3), a Patient-Reported Index to Guide a Treat-to-Target Strategy for Rheumatoid Arthritis in Usual Care. Martin J. Bergman[1], Theodore Pincus[2] and Isabel Castrejón[2]. [1]Taylor Hospital, Ridley Park, PA, [2]NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Treat-to-target according to the disease activity score (DAS28) in patients with rheumatoid arthritis (RA) has resulted in better outcomes in 7 clinical trials. However, DAS28 is not available at most patient visits, because laboratory test results are pending and formal quantitative joint counts are not recorded. The clinical disease activity index (CDAI) does not require complex calculations or laboratory tests, but does require formal joint counts. RAPID3 (routine assessment of patient index data 3) includes only the 3 patient self-report questionnaire measures in the RA Core Data Set—physical function, pain and patient estimate of global status—and can be calculated in 5 seconds on a multidimensional health assessment questionnaire (MDHAQ), versus about 120 seconds for DAS28 or CDAI. We analyzed a treat-to-target strategy in the care of patients with RA at one rheumatology practice setting according to 3 indices: DAS28, CDAI and RAPID3.

Methods: All patients in this setting complete a multidimensional health assessment questionnaire (MDHAQ) at each visit. RAPID3 scores are the sum of physical function, pain and patient global estimate, each scored 0–10 (total 0–30), with levels of severity: high=>12, moderate=6.1–12, low=3.1–6 and remission=0–3. All RA patients have a physician/assessor 28 joint count, physician global estimate of status, and erythrocyte sedimentation rate (ESR) at each visit, so that DAS28, CDAI and RAPID3 are scored. The treatment target is low disease activity/severity, i.e., a score of ≤10 for CDAI, ≤3.2 for DAS28 and ≤6 for RAPID3. The 3 indices were compared for low activity/severity or remission versus high or moderate activity/severity at baseline and 3-month follow-up, according to percent agreement and kappa statistics.

Results: At baseline, low activity/severity or remission was seen in 10 of 34 patients (29%) according to DAS28, 6 (18%) according to CDAI, and 5 (15%) according to RAPID3. Three months later, low activity/severity or remission was seen in 11 (32%) by DAS28, 13 (38%) by CDAI, and 16 (47%) by RAPID3. Kappas of DAS28 vs RAPID3 were 0.09 at baseline and 0.45 at 3 months, of CDAI vs RAPID3 0.46 at baseline and 0.22 at 3 months, and of DAS28 vs CDAI 0.52 at baseline and 0.40 at 3 months, indicating fair-to-moderate agreement, other than baseline DAS28 vs RAPID3, for which 68% of patients were nonetheless classified similarly by the two indices. Agreement for low activity/severity or remission versus high or moderate activity/severity was seen for 62%–85% of comparisons of RAPID3 with DAS28 or CDAI.

DAS28	High/Moderate (>3.2)	Low/Remission (≤3.2)	Agreement vs RAPID3	Kappa vs RAPID3	Agreement vs CDAI	Kappa vs CDAI
Baseline	24 (71%)	10 (29%)	68%	0.09	82%	0.52
3 mo	23 (68%)	11 (32%)	73%	0.46	71%	0.36
CDAI	**High/Moderate (>10)**	**Low/Remission (≤10)**				
Baseline	28 (82%)	6 (18%)	85%	0.46	NA	NA
3 mo	21 (62%)	13 (38%)	62%	0.22	NA	NA
RAPID3	**High/Moderate (>6)**	**Low/Remission (≤6)**				
Baseline	29 (85%)	5 (15%)	NA	NA	85%	0.46
3 mo	18 (53%)	16 (47%)	NA	NA	62%	0.22

Conclusion: RAPID3 appears similar to DAS28 and CDAI to recognize low activity/severity or remission versus high or moderate activity/severity to guide a treat-to-target strategy for RA in usual care settings.

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Successful Maintenance of Remission Defined by the New ACR/EULAR Criteria Leads to Better Functional Outcomes in Rheumatoid Arthritis in Daily Practice, Especially in Patients with Early RA, Based on the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) Cohort. Kumi Shidara, Eiichi Tanaka, Eisuke Inoue, Yohei Seto, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Remission has become a therapeutic target in the management of patients with rheumatoid arthritis (RA). New remission criteria were proposed by ACR/EULAR to achieve better patient outcomes in 2010. However, the clinical outcomes of RA patients in daily practice who satisfy the new criteria have not been well elucidated. To evaluate long-term functional outcomes in RA patients who satisfied the new ACR/EULAR or DAS28 remission criteria in daily practice based on a cohort of RA patients.

Methods: We established a large observational cohort of RA patients, IORRA (Institute Of Rheumatology, Rheumatoid Arthritis) cohort, in our institute beginning in October 2000. Clinical parameters including physician's assessment, patient's assessment, and laboratory data are collected twice yearly (in April and October). Those RA patients who were in DAS28 remission in April 2008 (baseline) and who completed all IORRA assessments every 6 months from April 2008 to October 2010 (six data collections) were selected for this study. All patients were evaluated whether or not they achieved the ACR/EULAR or DAS28 remission criteria at every data collection. Functional disability was assessed by J-HAQ, the validated Japanese version of HAQ. Boolean trial, Boolean practice, SDAI remission, and CDAI remission were used as ACR/EULAR remission criteria. Among those patients, the percentages whose J-HAQ score progressed during the observation period were calculated.

Results: A total of 915 RA patients in DAS28 remission at baseline who completed all IORRA data collections in the succeeding 3 years were selected (females, 76.3%; mean age, 57.6 years; mean RA disease duration, 11.7 years; mean DAS28, 2.0; mean J-HAQ, 0.32). Percentages of patients whose J-HAQ progressed during the observation period among patients who had continuously achieved remission defined by Boolean trial, SDAI, Boolean practice, CDAI, and DAS28 in all six data collections were 6.2% (10/161), 8.5% (21/247), 5.7% (10/175), 7.1% (16/227), and 14.2% (45/318), respectively. In contrast, the percentages of patients whose J-HAQ progressed was higher among patients who did not fulfill the remission criteria continuously during the 3 years of observation. When patients satisfied the Boolean trial, SDAI, Boolean practice, CDAI, and DAS28 remission criteria in only one of the six data collections during the succeeding 3 years, percentages of patients whose J-HAQ score progressed were 30.8%, 47.4%, 31.7%, 47.1%, and 57.1%, respectively. This was more apparent in patients with a shorter duration of RA than in those with long-term disease.

Conclusion: Remission defined by the new ACR/EULAR resulted in better functional outcomes in RA patients compared to that of DAS28 remission in daily practice. However, maintenance of remission for a longer period of time is important for preventing patients from progression of disability as assessed by J-HAQ using any criteria of remission. This is more important in patients in earlier disease stages than patients with established disease. Thus, introduction and maintenance of remission in early-stage disease is recommended to achieve better functional outcomes in RA patients.

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The Relationship Between Time in Remission and Functional Status in Rheumatoid Arthritis. Femke H.M. Prince[1], Siri Lillegraven[2], Vivian P. Bykerk[1], Nancy A. Shadick[3], Bing Lu[1], Michelle A. Frits[1], Christine K. Iannaccone[1], Michael E. Weinblatt[1] and Daniel H. Solomon[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital / Diakonhjemmet Hospital, Boston, MA, [3]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

Background/Purpose: It is presumed that patients with rheumatoid arthritis (RA) in sustained remission have a more favorable outcome. Our objective was to describe change in functional outcome in relation to the number of annual examination in remission in RA patients.

Methods: We analyzed annually collected disease activity variables and outcomes from a prospective, observational, single-center RA cohort, including participants with at least two years follow-up (n=871). Remission was determined by the DAS28-CRP4<2.6, SDAI<=3.3 and 2010 ACR/EULAR criteria. The outcome of functional status was measured using the multidimensional HAQ (mdHAQ) and data were analyzed using linear mixed models. For a secondary analysis we examined the relationship between remission and the minimal clinical important improvement (MCII) in mdHAQ (set at −0.3). In the secondary analysis, subjects with mdHAQ<0.5 at baseline were excluded since improvement is unlikely.

Results: Subjects in remission at one or more annual examinations, regardless of the remission criteria, had a more favorable outcome of mdHAQ compared to subjects who never reached remission ($p<0.001$). In addition, more time points in remission produced more favorable outcomes (see **Figure**). After 4 years of follow-up, more subjects (72%) with >60% of time in DAS28 remission reached the MCII compared to subjects with <60% ($p=0.03$) or no examinations in remission ($p<0.001$). When stratifying according to baseline mdHAQ, subjects with

a low mdHAQ (0–0.5) at baseline remained at approximately the same level when in DAS28 remission (mean change mdHAQ= −0.004), while subjects with a high mdHAQ (1.0–3.0) at baseline showed improvement in functional status during DAS28 remission (mean change mdHAQ= −0.504, p<0.001) after 4 years.

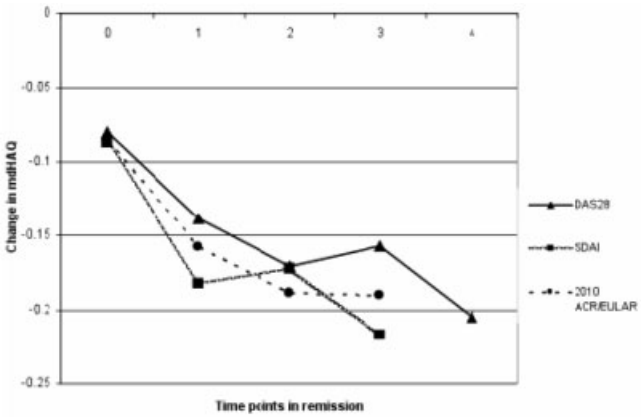

Figure. Change in mdHAQ score in relation to the number of time points in remission. For instance, for patients in DAS28 remission at 4 time points mdHAQ improved with 0.21 per year compared with the improvement of 0.14 per year of patients with only 1 time point in DAS28 remission.

Conclusion: In our study, subjects with more annual examinations in remission experienced greater improvement in mdHAQ. During sustained remission, subjects with high baseline mdHAQ scores improved more than those with lower baseline mdHAQ.

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Using the Patient Activity Score (PAS-2) to Assess Rheumatoid Arthritis Disease Activity: Bias From the Presence of Comorbid Musculoskeletal Conditions. John T. Schousboe[1], Peter D. Kent[2], Tawatchai Paisansinsup[1], Scott L. Glickstein[1] and Eric S. Schned[1]. [1]Park Nicollet Health Services, Minneapolis, MN, [2]Park Nicollet Clinic, Minneapolis, MN

Background/Purpose: Self-report measures of pain and functional status have been proposed as outcome measures that can be followed to assess rheumatoid disease activity and quality of care for RA patients. The Patient Activity Score (PAS-2) (highly similar to the RAPID-3), is a measure combining self-reported pain, patient global assessment, and Health Assessment Questionnaire-II into a global score. Other musculoskeletal conditions also affect these outcomes. We hypothesized that RA accompanied by fibromyalgia, degenerative spondylosis, or knee, hip, or generalized osteoarthritis is associated with higher pain, impaired function, and higher PAS-2 scores than RA unaccompanied by any of these comorbid musculoskeletal conditions.

Methods: All patients seen in the rheumatology department of a large urban integrated health care delivery organization are asked to fill out the PAS-2 at each clinic visit. The study population was all patients with a primary or secondary diagnosis of RA (ICD-9 code 714.0) seen in rheumatology between July 1, 2010 and December 31, 2010. The presence of comorbid fibromyalgia (729.1), degenerative spondylosis (721.90 or 721.91), knee osteoarthritis (OA) (715.96), hip OA (715.95), or generalized OA (715.89), was identified by two or more encounters with a primary or secondary diagnosis of the comorbid condition within the three years prior to the RA visit date. The three components of the PAS-2 and overall PAS-2 scores were modeled as four-level ordinal variables due to skewed distributions. The associations between PAS-2 and each of its three component scores and RA with one of the five comorbid conditions compared to RA with no musculoskeletal comorbidity were estimated with ordinal logistic regression models.

Results: The mean PAS-2 score (standard deviation) and the odds ratios (95% C.I.) for one level increase of PAS-2 with each comorbid musculoskeletal condition compared to its absence (adjusted for age, sex, race, use of DMARD or biologic therapies, use of neuropathic pain agents, the other four comorbid conditions, and provider) were as follows:

Diagnosis	PAS-2 Score (SD)	Association with one level change of PAS-2 compared to RA alone (OR, 95% C.I.)
RA alone (n = 758, 56.6%)	7.7 (6.4)	–
RA +Fibromyalgia (n = 82, 6.1%)	14.8 (6.2)	**3.8 (2.5–5.8)**
RA + Degenerative Spondylosis (n = 32, 2.4%)	16.4 (6.4)	**6.2 (1.9–20.1)**
RA + Knee OA (n = 192, 14.3%)	10.3 (6.4)	1.1 (0.7–1.6)
RA + Hip OA (n = 15, 1.1%)	13.5 (6.3)	2.7 (0.7–9.8)
RA + Generalized OA (n = 430, 32.1%)	10.7 (6.6)	**1.7 (1.3–2.4)**

The multivariable-adjusted associations of RA plus comorbid musculoskeletal conditions compared to RA alone with pain, patient global assessment, and HAQ-II score were similar to the associations with PAS-2 score.

Conclusion: Co-morbid generalized OA is common among patients with RA and is associated with a moderate increase in PAS-2 scores compared to RA alone. Co-morbid fibromyalgia or degenerative spondylosis substantially increase PAS-2 scores among those with RA. Use of the PAS-2 as an outcome measure in observational studies of RA therapies or RA quality of care in clinical practice may lead to underestimation of the effects of RA therapies, quality of RA care and potential overtreatment with RA medications if the presence of musculoskeletal comorbid conditions is not taken into account.

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Application of the New American College of Rheumatology/European League Against Rheumatism Rheumatoid Arthritis Remission Criteria in a United States Cohort. Iris Navarro-Millan[1], Lang Chen[1], Jeffrey D. Greenberg[2] and Jeffery R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]New York University School of Medicine, New York, NY

Background/Purpose: The ACR and the EULAR proposed an RA remission definition for clinical trials that uses very stringent levels of disease activity for RA. The applicability and usefulness of this definition in a real-world setting where comorbidities and other factors could impact measurement of RA disease activity is not clear.

Objectives: Using data from participants enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) cohort:

1) To determine the distribution of pain, fatigue, disability, and ESR in patients that meet the ACR/EULAR RA remission criteria
2) To determine the prevalence of RA remission by different RA therapies and comorbidities

Methods: RA patients in CORRONA who met the provisional ACR/EULAR remission criteria (TJC ≤ 1, SJC ≤ 1, CRP ≤ 1 mg/dL and patient global ≤ 1) at any CORRONA visit were identified. If remission was observed at more than 1 CORRONA visit, the last visit was used. Descriptive statistics were used to describe pain (0–10 Visual Analog Scale [VAS], fatigue (0–10 VAS), disability (mHAQ), and ESR (<10, 10–20, >20mm/hr). The prevalence of remission was then evaluated in subgroups of patients using various RA therapies and with comorbidities of interest.

Results: A total of 2,105 individuals met the ACR/EULAR remission criteria in the CORRONA registry. A majority of patients in remission had low pain scores (85% with pain ≤ 1) and low fatigue scores (73% with fatigue ≤ 1). A total of 78% of patients had mHAQ = 0. Approximately one-half of patients in remission had ESR < 10, and an additional one-quarter had an ESR between 10 and 20mm/hr. The overall prevalence of remission in CORRONA was 8%. The likelihood of remission varied by RA treatment between 4 and 10% (Table). Remission was less common among RA patients treated with prednisone (1%- 6%, depending on dose) compared to those on no prednisone (13%). There were also significant differences in the prevalence of remission by different comorbidities (Table).

Table. Proportion of RA in remission by RA Treatment and Comorbidities

	Frequency n (%)	p-value
DMARD/Biologic treatment		0.0003
MTX monotherapy	582 (8)	
MTX + DMARD	200 (9)	
DMARDs w/o MTX	208 (8)	
TNF monotherapy	273 (10)	
TNF + DMARD	638 (10)	
Non-TNF Biologic monotherapy	27 (4)	
Non-TNF Biologic + DMARD	52 (4)	
Prednisone (mg/day)		<0.0001
None	873 (13%)	
< 5	128 (6%)	
5–10	99 (2%)	
> 10	39 (1%)	
COPD		0.0003
Yes	14 (4)	
No	1880 (10)	
Diabetes		<0.0001
Yes	116 (5)	
No	1989 (8)	
Fibromyalgia		0.0025
Yes	0 (0)	
No	549 (9)	
Smoking		<0.0001
Current	211 (5)	
Not current	1493 (8)	

Conclusion: Among patients in remission according to the new ACR/EULAR definition, the domains of pain, fatigue and disability were generally concordant with the factors in the remission criteria. The overall prevalence for RA remission was low (8%) and varied modestly by RA treatments and common comorbidities. These new remission criteria appear feasible to apply in real-world settings.

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Discrepancy Between Boolean Remission and DAS28 Remission Is Dependent on the Differences in Number of Swollen Joints and Patient Global Assessment in Daily Practice, Based on the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) Cohort. Eiichi Tanaka, Kumi Shidara, Eisuke Inoue, Yohei Seto, Ayako Nakajima, Atsuo Taniguchi, Shigeki Momohara and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: The new remission criteria for rheumatoid arthritis (RA) by ACR/EULAR are expected to predict better patient outcome, however, there are substantial discrepancies between various remission criteria. We need to analyze which variables have a strong influence on achievement of the new ACR/EULAR remission criteria among RA patients with DAS28 remission based on a cohort before applying the new remission criteria in daily practice.

Methods: The Institute of Rheumatology, Rheumatoid Arthritis (IORRA) is a hospital-based observational cohort of RA patients. Complete medical information including physician's and patient's global assessment and laboratory data have been collected biannually. The subjects in this study were RA patients who participated in IORRA in October 2010, and were in DAS28 remission (DAS28 < 2.6). Boolean-based remission for clinical trials (Boolean trials) /clinical practice (Boolean practice), the Simplified Disease Activity Index (SDAI) remission and the Clinical Disease Activity Index (CDAI) remission were used as ACR/EULAR remission. Factors that affected the discrepancy between DAS28 remission and ACR/EULAR remission were analyzed. Univariate analysis was used to evaluate the differences in clinical features between patients with and without ACR/EULAR remission by each ACR/EULAR remission criteria. Multivariate logistic regression and analysis of deviance were conducted to determine the significance of effects on achieving each ACR/EULAR remission.

Results: We studied 2162 RA patients (39.0%) with DAS28 remission (female, 79.0%; mean age, 57.1 years; mean RA duration, 11.6 years; and mean DAS28, 1.98) among 5545 RA patients who participated in IORRA in October 2010. Among these patients, the numbers achieving Boolean trials, SDAI remission, Boolean practice and CDAI remission were 1169 (54.1%), 1602 (74.1%), 1205 (55.7%) and 1536 (71.0%), respectively. The patients with each ACR/EULAR remission were significantly older age, shorter RA disease duration, fewer tender and swollen joints, better patient's and physician's global assessment, and higher ESR compared to those without the respective ACR/EULAR remission. Having a better patient's global assessment and a smaller number of tender and swollen joints were the factors most significantly contributing to achievement of each ACR/EULAR remission criteria by multivariate logistic regression. The patient's global assessment and the number of swollen joints had a significant impact on achievement of each ACR/EULAR remission criteria by analysis of deviance. The combination of the patient's global assessment and the number of swollen joints accounted for 74.1%, 68.0%, 86.9% and 68.5% of the contribution to achieving Boolean trials, SDAI remission, Boolean practice and CDAI remission, respectively.

Conclusion: Of the remission criteria applicable to daily practice, Boolean remission is a more stringent than DAS28 remission, and the difference is mainly dependent on the patient's global assessment and number of swollen joints. Thus, patient management aimed at improving the patient's global assessment and number of swollen joints is critical for tight control of disease activity targeting to Boolean remission.

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Comparison of Disease Activity Score Using Erythrocyte Sedimentation Rate and C-Reactive Protein In African-Americans with Rheumatoid Arthritis. Ashutosh Tamhane[1], David Redden[1], Gerald McGwin[1], Elizabeth Brown[1], Andrew Westfall[1], Richard J. Reynolds[1], Laura B. Hughes[1], Doyt L. Conn[2], Leigh F. Callahan[3], Beth L. Jonas[3], Edwin A. Smith[4], Richard Brasington[5], Larry W. Moreland[6] and S. Louis Bridges Jr.[7]. [1]Univ of Alabama at Birmingham, Birmingham, AL, [2]Emory Univ School of Medicine, Atlanta, GA, [3]Univ of North Carolina, Chapel Hill, NC, [4]Med Univ of South Carolina, Charleston, SC, [5]Washington Univ School of Med, St. Louis, MO, [6]University of Pittsburgh, Pittsburgh, PA, [7]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Racial/ethnic differences in genetic polymorphisms that influence CRP levels exist. However, data on differences between erythrocyte sedimentation rate (ESR) versus C-reactive protein (CRP) based Disease Activity Scores (DAS28) is lacking in African-Americans with Rheumatoid Arthritis (RA).

Methods: Analysis included participants (N=120) from the cross-sectional arm of the CLEAR Registry (African-Americans with RA) for whom both standard ESR and CRP-based DAS28 were available. Additionally, based on the study-data novel DAS28-CRP values (with and without age-sex adjustment) were calculated using regression. Agreement measures between standard ESR-based and (standard and novel) CRP-based DAS28 were examined.

Results: Mean age at enrollment was 54.5 years, median disease duration was 9 years and 85% were women. Standard DAS28-ESR was significantly higher than the standard DAS28-CRP (means: 4.7 vs. 3.9; $p<0.001$). When disease activity was categorized (high, moderate, low, remission) using conventional cut-offs (5.1, 3.2, and 2.6) overall agreement between the standard DAS28-ESR and DAS28-CRP was 59% and the standard DAS28-CRP underestimated disease activity in 40% of participants. With the novel DAS28-CRP agreement with the standard DAS28-ESR improved to 79% and underestimation decreased to 8%; adjustment for age-sex did not greatly increase agreement (82%) or decreased underestimation (6%).

Conclusion: These findings have implications for assessment or treatment response in clinical trials as well as in treatment decisions in individual patients. Significant improvement in agreement was achieved using simple modification of the standard DAS28-CRP measure. However, whether population-specific measures are needed or a universal DAS28-CRP measure could be derived using variety of databases remains to be examined.

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Trajectory of Anti-Cyclic Citrullinated Peptide Antibodies and Rheumatoid Factor Over Time Does Not Predict Disease Activity in the Canadian Early Arthritis Cohort. Lillian J. Barra[1], V. Bykerk[2], Janet Pope[3], Ye Sun[4], Boulos Haraoui[5], Carol A. Hitchon[6], Diane S. Ferland[7], J. Carter Thorne[8], Edward Keystone[4] and Gilles Boire[9]. [1]University of Western Ontario, London, ON, [2]Brigham & Women's Hospital, Boston, MA, [3]Univ of Western Ontario, London, ON, [4]Mount Sinai Hospital, Toronto, ON, [5]Institut de Rhumatologie, Montreal, QC, [6]University of Manitoba, Winnipeg, MB, [7]LaSalle, QC, [8]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [9]CHUS - Sherbrooke University, Sherbrooke, QC

Background/Purpose: Autoantibodies associated with Rheumatoid Arthritis (RA) consist of Rheumatoid Factor (RF) and anti-citrullinated protein

antibodies, including anti-Cyclic Citrullinated Peptide (anti-CCP). It has been reported that the presence of these antibodies is associated with worse outcomes.[1] Our objective is to determine whether anti-CCP and RF remain stable over time and whether changes in these autoantibodies predict outcomes in Early Inflammatory Arthritis (EIA).

Methods: Data was collected from the Canadian Early Arthritis Cohort (CATCH), a prospective multicentre observational cohort of patients ≥ 16 years of age with symptom duration of 6 weeks up to 12 months and ≥ 2 swollen joints or ≥ 1 swollen small joint of the hand and ≥ 1 of positive rheumatoid factor, positive anti-CCP, morning stiffness ≥ 45 minutes, good response to non-steroidal anti-inflammatories or positive metatarsal-phalangeal squeeze test. Subjects were included in the analyses if anti-CCP and RF values were available at baseline and at least one follow-up visit.

Results: Baseline and follow-up anti-CCP and RF values were available in 361 and 340 patients respectively of the 1330 subjects enrolled in CATCH. Mean follow-up time was 21 months (range 3–72 months). At baseline, 198 (54.8%) were anti-CCP positive. Of these, 18 (9.1%) became anti-CCP negative during the follow-up period. Interestingly, 39 (23.9%) of anti-CCP negative patients became positive. RF positivity at baseline was 197 (57.9%) and 40 (20.4%) of these patients became negative at follow-up. 18 (12.5%) RF-negative patients seroconverted after a mean of 15.6 months. Patients who were RF and/or anti-CCP positive at baseline did not have worse outcomes at follow-up and changes in anti-CCP or RF over time did not predict erosive disease, DAS28 score or DAS28 remission.

Conclusion: Anti-CCP positivity appears relatively stable in EIA patients with positive anti-CCP at baseline. However, a large proportion of initially anti-CCP negative patients seroconverted later in disease. RF is more variable throughout disease course and shows a potential to convert and revert. Trajectories of anti-CCP and RF over time do not appear to predict clinical outcomes. These results are consistent with those from another large, recently published North American EIA cohort[2].

References:

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Patients with Early Rheumatoid Arthritis Determined to Be Inadequate Responders After 12 Weeks May Still Have Substantial Improvement in Core Set Measures. Results from an Early Arthritis Cohort. Pooneh S.Akhavan[1], Vivian Bykerk[2], Ye Sun[3], Gilles Boire[4], J. Carter Thorne[5], Janet Pope[6], Carol A. Hitchon[7], Boulos Haraoui[8], Diane S. Ferland[9], Edward Keystone[1] and CATCH Investigators[10]. [1]University of Toronto, Toronto, ON, [2]Brigham & Women's Hospital, Boston, MA, [3]Mount Sinai Hospital, Toronto, ON, [4]CHUS - Sherbrooke University, Sherbrooke, QC, [5]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [6]Univ of Western Ontario, London, ON, [7]University of Manitoba, Winnipeg, MB, [8]Institut de Rhumatologie, Montreal, QC, [9]LaSalle, QC, [10]Toronto, ON

Background/Purpose: ACR or EULAR response criteria have been used in trials and also in routine clinical practice to guide treatment decisions in RA. Patients who fail to achieve DDAS28 ≥1.2 or ACR20 are generally considered inadequate responders.To evaluate clinical improvement in individual core set measures in patients considered inadequate responders using DAS28 and ACR composite measures of disease activity.

Methods: Patients with early RA who were enrolled and prospectively followed in the Canadian Early Arthritis Cohort (CATCH) were studied. Patients receiving DMARD therapy for 3 months who failed to achieve DDAS28 ≥ 0.6, DDAS28 ≥ 1.2 or ACR20 were examined for 20% and 30% improvement in their disease activity core set measures.

Results: 416 patients with mean age 52.5 yr (14.3)(SD), disease duration 6.1 mo (3.0), Tender Joint Count (TJC) 9.2 (7.1), Swollen Joint Count (SJC) 8.2 (6.2) and DAS28 5.1(1.6) at baseline were included in this analysis. At 3 months 197(47%) patients had not achieved ACR20, 304 (73%) had not achieved ACR50 and 348 (84%) had not achieved ACR70. Half of included patients had DAS28 improvement < 1.2 and in 142 (34%) patients DAS28 improvement was < 0.6 at 3 months. About a third of patients with DDAS28 < 0.6 had 30% improvement in TJC, SJC, patient and physician global. This proportion varied from 30% to 44% in patients with DDAS28 < 1.2 and from 20–41% in patients who did not achieve ACR20. Mean core set measure improvement in patients with DAS28<0.6 was found to vary from 18% (patients global) to 26% (SJC). Thirty seven percent of patients with DDAS28< 0.6 achieved HAQ Minimal Clinically Improvement (MCID)[0.22]. This proportion was 42% for patients with DDAS28<1.2 or 35% in patients who failed to achieve ACR20.

Conclusion: A substantial proportion of patients who fail to achieve a significant improvement in composite measures of disease activity frequently used in clinical studies may still exhibit substantial improvement in their individual core set measures. These findings should be considered when making treatment decisions in real world clinical settings and identifying patients with an inadequate clinical response.

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Performance of the American College of Rheumatology/European League Against Rheumatism (2011) Remission Definition Versus Disease Activity Score, 28-Joint Disease Activity Score and American College of Rheumatology Criteria. Karla Chiapas-Gasca, Luis M. Amezcua-Guerra and Angélica Vargas. Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico

Background/Purpose: Remission has become the treatment goal in rheumatoid arthritis (RA). Current remission criteria have several limitations, the more frequently used are the ACR, DAS and DAS28; so recently, ACR/EULAR proposed a new remission definition. Objective: to compare the performance of the ACR/EULAR remission definition versus DAS, DAS-28 and ACR criteria.

Methods: Between February 21st and June 10th, 2011, we analyzed the medical records of 198 consecutive outpatients attending our Rheumatology Department. Inclusion criteria were: diagnosis of RA according the ACR 1987 criteria. The database include demographic data, comorbidity, disease duration, extraarticular manifestations, rheumatoid factor (RF), anti-cyclic citrullinated protein antibodies (anti-CCP), erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and drug therapy. Remission was calculated with DAS, DAS28, ACR remission criteria and the ACR/EULAR provisional remission definition. Data are expressed as percentages or mean with standard deviation (SD). Associations were calculated by the unweighted Cohen's kappa (k) index with 95% confidence intervals (95%CI) Differences were estimated by chi-square or unpaired t tests as appropriate.

Results: 47 of the 198 patients fulfilled the ACR/EULAR provisional remission definition; since this is the method we are assessing, in table 1 we report patients characteristics according this evaluation. There was no significant difference according therapy. The distribution of patients in remission and not remission according to each criterion is shown in table 2. The κ index between ACR/EULAR vs ACR was 0.61 (0.50–0.72), ACR/EULAR vs DAS was 0.37 (0.27–0.47), ACR/EULAR vs DAS28 was 0.42 (0.32–0.52), ACR vs DAS was 0.57 (0.47–0.68), ACR vs DAS28 0.57 (0.46–0.67), and DAS vs DAS28 0.75 (0.66–0.84). DAS criteria were met by 111 patients, DAS 28 by 103 and ACR by 74. Only 43 of the 198 patients fulfilled remission criteria for all methods.

Table 1. Characteristics of patients according ACR/EULAR results

	Remission (n=47)	Not remission (n=151)	*p*
Women (%)	41 (87.2)	135 (89.4)	NS
Age	52.7 ± 14.8	53.5 ± 15	NS
Duration of the disease	10.8 ± 10.2	12.7 ± 8.6	NS
Extra-articular manifestations (%)	10 (21.2)	61 (40.3)	0.009
Positive RF (%)	45 (95.7)	143 (94.7)	NS
Positive anti-CCP (%)	41 (91.1)	134 (88.7)	NS
ESR in mm/h	21.02 ± 9.9	29.07 ± 11.3	<0.0001
CRP in mg/L	3.48 ± 1.85	12.8 ± 25.7	0.01
DAS	0.93 ± 0.17	1.8 ± 0.75	<0.0001
DAS28	1.82 ± 0.33	3.27 ± 1.29	<0.0001
Morning stiffness, +	1 (2.1)	47 (31.1)	<0.0001
Fatigue, +	0 (0)	50 (33.1)	<0.0001
Joint tenderness, +	5 (10.6)	106 (70.1)	<0.0001
Tenderness on examination, +	3 (6.3)	104 (68.8)	<0.0001
Joint/tendon sheath swelling, +	6 (12.7)	126 (83.4)	<0.0001
Patients with swollen/tender areas out of DAS28	0 (0)	57 (37.7)	<0.001

Data are expressed in mean ± SD unless otherwise specified. NS, no significance; +, positive

Table 2. Patients on remission according the different criteria

Criteria	Remission	Not remission
ACR	74	124
DAS	111	87
DAS28	103	95
ACR/EULAR	47	151

Conclusion: The recently proposed ACR/EULAR remission definition seems to be more stringent to discriminate patients on remission, whereas remission is easier to achieve with DAS and DAS-28.

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What Is A Realistic Treatment Target in Rheumatoid Arthritis: Remission or Minimal Disease Activity? Yvonne M.R. de Punder[1], Jaap Fransen[1], Wietske Kievit[1], Pieternella Houtman[2], Henk Visser[3], Mart A.F.J. van de Laar[4] and Piet LC van Riel[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Medical Centre Leeuwarden, Leeuwarden, Netherlands, [3]Alysis Care Group, Arnhem, Netherlands, [4]Arthritis Centre Twente, Medisch Spectrum Twente and University Twente, Enschede, Netherlands

Background/Purpose: Treatment targets for RA do shift towards remission of disease activity. However, remission does not occur regularly in practice and the question may be raised what currently is the appropriate treatment target: remission or low disease activity? This is especially relevant in patients treated with anti-TNF. The objective in this study was to analyze the prevalence of remission and minimal disease activity (MDA) and the residual disease activity according to the new ACR/EULAR remission criteria, MDA, and DAS28<2.6, in RA patients treated with anti-TNF.

Methods: In the DREAM biological registry the prevalence of DAS28<2.6, MDA and ACR/EULAR remission criteria was measured in patients six months after starting a TNF blocker. The variable Patient Global Assessment of disease activity (PtGA) was only available in a subsample and was replaced by VAS Pain, as no systematic difference appeared between PtGA and VAS Pain in this subsample. Residual disease activity during MDA or remission was calculated, measured by the percentage of patients with swollen and tender joints, elevated acute phase reactants, and pain.

Results: Six months after initiation of anti-TNF, the prevalence of DAS28<2.6 was 26% and prevalence of MDA was 32%, while ACR/EULAR remission was reached by 6,7% of patients. The low prevalence of ACR/EULAR remission was due to the cut point of the patient's global assessment/pain item. Exclusion of the variable VAS Pain increased the prevalence of ACR/EULAR remission to 21%. Residual disease activity was highest in the most lenient criteria and occurred most on the level of SJC and PtGA: At least one swollen joint in DAS28<2.6, MDA and ACR/EULAR remission was present in resp. 51%, 54% and 34% of patients. VAS Pain > 1 cm was present resp. 64%, 67% and 0%. When the patient reported variable was left out of the definition of ACR/EULAR remission, 68% of patients scored VAS Pain >1. Accordingly, absence of tender and swollen joints and CRP<1 mg/dl was reached by 190/1679 patients (11%). However, 125 (66)% of these patients would not be in remission according to the complete ACR/EULAR remission criteria because VAS Pain was >1.

Conclusion: In daily clinical practice, MDA and DAS28<2.6 are realistic treatment targets with sufficient prevalence, while in turn residual disease activity still is present. ACR/EULAR remission criteria leave little residual disease activity, but might be too stringent due to the strict cut point on Patient Global Assessment of Disease Activity.

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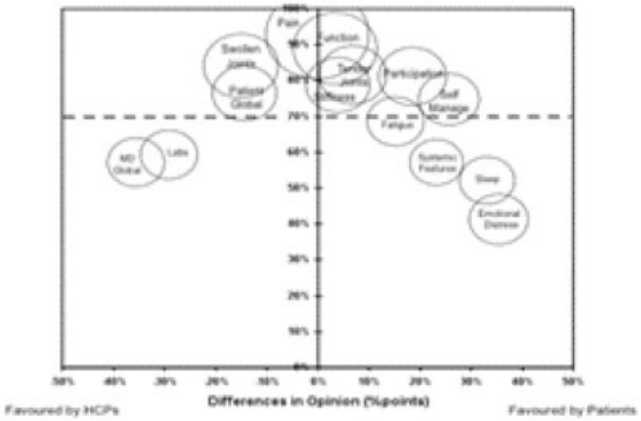
Consensus Among Patients and Health Care Professionals for Essential Domains to Assess Disease Flares in Rheumatoid Arthritis: Results of Final OMERACT Delphi. Susan J. Bartlett[1], Thasia G. Woodworth[2], Clifton O. Bingham III[3], Rieke Alten[4], Christoph Pohl[5], Ernest Choy[6], Sarah Hewlett[7], Tessa Sanderson[7], Annelies Boonen[8], Vivian Bykerk[9], Amye L. Leong[10], Vibeke Strand[11], Daniel E. Furst[12], Robin Christensen[13] and OMERACT Flare Working Group. [1]McGill University, Montreal, QC, [2]Leading Edge Clinical Research, Stuart, FL, [3]Johns Hopkins University, Baltimore, MD, [4]Rheumatology Schlosspark-klinik, Berlin, Germany, [5]Schlosspark Klinik, Berlin, Germany, [6]Cardiff University, Cardiff, ENGLAND, United Kingdom, [7]University of the West of England, Bristol, United Kingdom, [8]University Hospital Maastricht, Maastricht, Netherlands, [9]Brigham & Women's Hospital, Boston, MA, [10]Bone & Joint Decade, Santa Barbara, CA, [11]Stanford University, Palo Alto, CA, [12]UCLA Medical School, Los Angeles, CA, [13]Copenhagen, Denmark

Background/Purpose: Although the term "flare" is often used to describe episodes of disease worsening, no established definition currently exists for rheumatoid arthritis (RA). As a result, little is known about the impact of RA flares on treatment outcomes such as function, disability, health-related quality of life and work productivity. The goal of the OMERACT RA Flare Group is to establish a framework to assess RA flares from both patient and health care professional (HCP) perspectives and develop a measurement tool for use in research and clinical settings.

Methods: Flare was defined as a worsening of disease activity of sufficient intensity and duration to result in consideration of a change of therapy. Formative research to identify relevant domains included focus groups/surveys with patients, stakeholder interviews and a literature search. An international group of patients and HCPs participated in subsequent rounds of Delphi exercises to rate candidate domains as "essential" or "not essential." Core domains were defined *a priori* as those with ≥70% support from all participants.

Results: Results are from the final Delphi round conducted through December 2010. Participants included 125 patients from 10 countries and 108 HCPs from 23 countries. Patients had a mean (± SD) age of 56 ±12 yrs and disease duration of 18 ± 12 yrs. HCPs included physicians from clinical practice/research (79%) and industry (6%), allied health providers (8%), researchers (6%) and undisclosed (1%), with 17 ± 11 yrs clinical rheumatology experience. Most (>82%) had participated in earlier surveys.

Core domains identified include: *Pain* (93%), *Function* (89%), *Swollen Joints* (84%), *Tender Joints* (81%), *Participation* (81%), *Stiffness* (79%), *Patient Global Assessment* (76%) and *Self-Management* (75%); *Fatigue* (68%) will receive further consideration. Domains which did not reach the level of consensus will continue to be explored separately. The figure below shows the pooled proportions and relative strength of agreement between groups; bubble size reflects estimate precision.



Conclusion: As part of the process to develop a measure, core domains of RA flare were identified by patients and HCPs: *Pain, Function, Swollen Joints, Tender Joints, Stiffness, Participation, Patient Global Assessment* and *Self Management*, with *Fatigue* receiving additional consideration. Next steps include identifying potential items for each domain and conducting studies to validate and refine the measurement tool.

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Development and Validation of a New Disease Activity Index As a Numerical Sum of 4 Variables, Including Erythrocyte Sedimentation Rate and/or C-Reactive Protein, to Assess Rheumatoid Arthritis. Isabel Castrejón[1], Loreto Carmona[2], Ana M. Ortiz[3], Miguel A. Belmonte Serrano[4], Juan A. martínez-López[5] and Isidoro González-Alvaro[3]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Universidad Camilo José Cela, Villanueva de la Cañada, Spain, [3]Hospital Universitario de La Princesa. IIS Princesa, Madrid, Spain, [4]Hospital General de Castellon, Castellon, Spain, [5]Fundación Jimenez Díaz, Madrid, Spain

Background/Purpose: To describe the development and validation of an activity index in early arthritis that can be used in daily practice and clinical research without special computing.

Methods: The HUPI (Hospital Universitario la Princesa Index) was driven from patient data analysis of an early arthritis cohort. It is the sum of four variables graded from 0 to 3: tender and swollen 28-joint counts, patient global assessment, and acute phase reactants, erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). The 0–3 score of each variable was based on its quartile distribution in our cohort. To develop HUPI we assayed different combinations of

these four variables considering differences by gender and age. For its validation the following were tested: feasibility, internal consistency (Cronbach's alpha), convergent validity (Pearson's *r* coefficients with other activity measures), accuracy by the area under the ROC curve (AUC) with minimum disease activity (MDA) as external criteria and sensitivity to change by the AUC using a change higher than 10 between baseline and the 6 month evaluation on physician assessment and on DAS28-ESR as external criteria of change.

Results: The analysis comprised 202 patients (756 visits) of whom 77% were women, mean age at onset of the disease was 53±16, 70% diagnosed of RA and 30% of undifferentiated arthritis. The best version of HUPI was defined as the sum of the scores reached by each variable in accordance to the following table:

Score	0	1	2	3
TJC28				
Female	0	1–2	3–6	>6
Male	0	1	2–3	>3
SJC28	0	1–2	3–4	>4
GDA Patient	0–15	16–30	31–50	>50
ESR				
Female	0–15	16–20	21–30	>30
Male	0–10	11–15	16–20	>20
CRP (mg/dl)	<0.10	0.11–0.8	0.81–1.50	>1.50

TJC: tender joint count; SJC: swollen joint count; GDA: global disease assessment; ESR and/or CRP can be used depending on which one is available. When both were available the mean score of them was used.
HUPI shows a reasonable internal consistency (Cronbach's α 0.63) and it correlates well with activity measures like DAS28 (r=0.89), and SDAI (r=0.70), but slightly worse with functional index HAQ (r=0.69). HUPI has a high accuracy, it discriminates MDA state (AUC=0.956) better than DAS28-ESR (0.929; p=0.001) and DAS28-CRP (0.945; p=0.07) and similar to SDAI (0.956; p=ns), and its sensitivity to change (AUC= 0.902) is slightly superior than those of DAS28-ESR (0.864; p=ns), DAS28-CRP (0.889; p=ns) and SDAI (0.791; p=0.01).

Conclusion: HUPI is an index easy to calculate, valid, and a sensitive tool for the assessment of disease activity in patients with early arthritis, both on clinical research and on routine practice.

This work has been partially supported by a grant of MEICA Project (Genoma España).

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Investigation of the Relationship Between Patient-Centered Factors and Baseline Disease Activity (DAS28) in Rheumatoid Arthritis (RA). Rita Prajapati[1], Darren Plant[2], Deborah Maskell[2], Ann W. Morgan[3], Anthony G. Wilson[4], John Isaacs[5], Lis Cordingley[1] and Anne Barton[1]. [1]University of Manchester, Manchester, United Kingdom, [2]The University of Manchester, Manchester, United Kingdom, [3]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [4]Sheffield Uni /Medical School, Sheffield, United Kingdom, [5]University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom

Background/Purpose: The disease activity score (DAS28) is a composite score made up of clinical, biological and a patient self-report measure. As an indicator of current disease activity it, it is an important part of the eligibility criteria for starting anti-tumour necrosis factor (TNF) therapy in rheumatoid arthritis (RA). Clinical, demographic and genetic factors may play a role in influencing baseline disease activity, but the contribution of patient-centred factors such as patients' views of their illness have not yet been thoroughly explored. The aim of this study was to identify which illness beliefs were associated with baseline disease activity in RA.

Methods: An observational study of patients about to commence anti-TNF therapy was undertaken. Patients completed measures of mood (Hospital Anxiety and Depression Scale[HAD] Zigmond & Snaith, 1983), of beliefs about RA (Brief Illness Perception Questionnaire [BIPQ]; Broadbent et al, 2006), beliefs about RA treatment (Beliefs about Medicines Questionnaire [BMQ] Horne et al 1999), of self-efficacy (General Self Efficacy Scale; Schwarzer & Jerusalem, 1995). Using baseline DAS28 as the outcome variable, statistical analyses in the form of regression modelling were performed in STATA.

Results: Complete data were available on 322 patients. A significant association with baseline DAS28 was associated with item 5 of the brief IPQ (coef 0.16, p<0.001), the identity domain, which asks how much patients experience symptoms from their rheumatoid arthritis. Upon breakdown of the DAS28, item 5 of the brief IPQ correlated with tender joint counts (coef 0.66, p=0.019), erythrocyte sedimentation rate (ESR) (coef 2.0, p=0.03), and the visual analogue scale (VAS) (coef 3.71, p<0.0001). To explore whether these associations were mediated by other pathways, we found anxiety and depression correlated strongly with illness perception (p<0.0001). No significant associations were detected between baseline DAS28 and anxiety, depression or self-efficacy.

Conclusion: Illness cognitions, particularly patients' perception of symptoms, play a key role in influencing baseline disease activity in RA. Future work investigating the pathways by which illness representations in influencing treatment response may provide key insights into why some patients respond to biologic agents, whilst others fail.

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To Screen Remission without Formal Joint Count: Analysis of Routine Assessment of Patient Index Data 3 in Japanese National Database. Naoto Yokogawa[1], Kota Shimada[1], Shoji Sugii[1] and Shigeto Tohma[2]. [1]Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, [2]Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, National Hospital Organization, Sagamihara, Japan

Background/Purpose: American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) set a provisional definition of remission in rheumatoid arthritis (RA) as a stringent but achievable goal: scores on the tender joint count, swollen joint count, CRP (in mg/dl), and patient global assessment (0–10 scale) are all ≤1. Precise formal joint count is crucial to classify remission however formal joint count is not easy even to expert rheumatologists. Routine Assessment of Patient Index Data 3 (RAPID3) is an index which does not require formal joint count. RAPID3 less than 3 was proposed as a remission criteria in the past however not validated in the new remission criteria.

Methods: Modified Health Assessment Questionnaire (mHAQ) is still widely used in Japan to assess patient function capacity. To utilize the existing data of mHAQ, modified RAPID3 (mRAPID3) was defined as follows: mRAPID3 (scale:0–30) =[mHAQ (scale:0–3)x10/3] + [Patient pain VAS (scale:0–10)]+[Patient global VAS (scale:0–10)]. After validation of mRAPID3, a method to convert from RAPID3 to RAPID3 was developed. In the National Database of Rheumatic Diseases by iR-net in Japan (NinJa), we compared RAPID3 with the indices that include a formal joint count, such as the traditional Disease Activity Score (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI). A cut-off RAPID3 of 90% sensitivity for the ACR/EULAR provisional definition of remission was calculated.

Results: By regression analysis using 147 patients' data at our hospital, a conversion method was formulated: RAPID3=0.288+1.034xm RAPID3(p<0.0001) (Figure 1).

In NinJa 2009, 4479 patients were analyzed. RAPID3 showed good correlation with DAS28, CDAI, and SDAI (Spearman rank correlation coefficient: rho 0.65, 0.73, 0.73).

By the ACR/EULAR provisional definition of remission, 675 patients (15.1%) were categorized as remission. The sensitivity and specificity for the remission criteria of DAS28, CDAI, and SDAI were shown in Table 1. RAPID3 less than 2 revealed sensitivity of 90.5% and specificity of 79.4%.

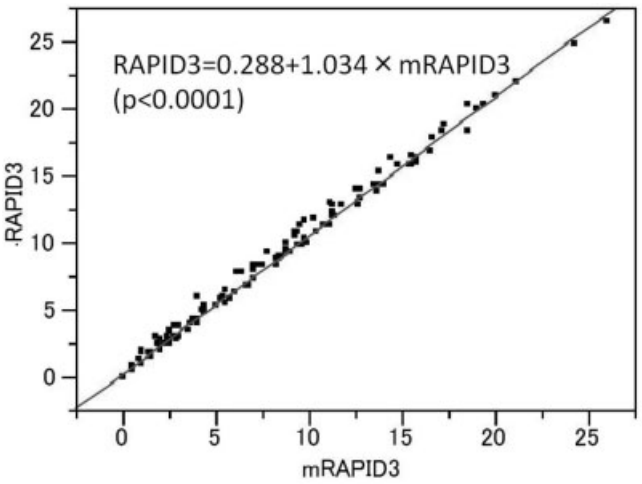

Figure 1. Regression analysis of RAPID3 and mRAPID3 in 147 patients

Table 1. Sensitivity and specificity for the ACR/EULAR provisional definition of remission

NÅÅ4479	Sensitivity (%)	Specificity (%)
SDAI remission	91	93
CDAI remission	89.3	93.8
DAS28 remission	76.9	84.7
RAPID3<2	90.5	79.4
RAPID3<3	95.4	31.6

Conclusion: RAPID3 less than 2 can successfully screen the RA remission without formal joint count.

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The Clinical Characteristics of Rheumatoid Arthritis Patients in Clinical Remission: Many Faces of DAS-28 Remission. Kyeong Min Son[1], Inje Kim[2] and Hyun Ah Kim[1]. [1]Hallym university sacred heart hospital, Kyunggi, South Korea, [2]Hallym University Kangdong Sacred Heart hospital, Seoul, South Korea

Background/Purpose: DAS-28 is widely used to define remission of rheumatoid arthritis (RA) in clinical settings, including clinical trial. The aim of this study was to observe the clinical characteristics of RA patients in DAS-28 remission. In addition, the extent of foot and ankle involvement in RA patients with DAS-28 remission was explored.

Methods: RA patients who visited rheumatology clinic of Hallym University Sacred Hospital were evaluated with DAS-28 including ankle and foot MTP joint evaluation since August, 2010. Patients who were treated with disease-modifying anti-rheumatic drugs for at least 3 months and who were in DAS-28 remission (DAS<2.6) were included in this study.

Results: A total of 119 patients were included. Mean age was 51 years and 72.3% were female. Mean disease duration was 46.6±43.0 months. Rheumatoid factor and anti-CCP positivity at the start of treatment was 59.4% and 46.6% respectively. At the time of remission, patients were treated with methotrexate (54.6%), hydroxychloroquine (43.7%), leflunomide (13.4%) and biologic agent (etanercept n=4, adalimumab n=1, tocillizumab n=4, Golimumab n=1, Abatacept n=1) (9.2%). Corticosteroid was used in 75.6% of patients with mean daily dose of 3.4mg prednisolone. Mean DAS-28 was 1.83(range 0.14–2.59) at the time of remission. Mean swollen and tender joint count within 28 joints at the time of remission was 0.5(range 0–6) and 1.3(range 0–13), respectively. Mean erythrocyte sedimentation rate and C-reactive protein were 6.0 mm/hr and 1.0 mg/L. Twelve percent and 39.5% of patients in clinical remission had swollen and tender joint in either foot MTP or ankle joinst, respectively (mean swollen and tender joint count 0.3{range 0–8} and 1.0{range 0–9}). 5.9% and 9.2% of patients in clinical remission had swollen and tender joint in either foot MTP or ankle joint without involvement of 28 joints included in DAS-28.

Conclusion: Our result shows that RA patients with DAS-28 remission sometimes have residual disease activity including ankle and foot joint involvement. DAS28 remission may have insufficient construct validity and should be used with caution in clinical practice.

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Clinical Outcome in Early Undifferentiated Arthritis Is Best Predicted by a Combination of Baseline Clinical Features and Serum Biomarkers. Carol A. Hitchon[1], Gilles Boire[2], Michael Centola[3], Andrew Lloyd[4], Richard Kay[4] and Hani S. El-Gabalawy[1]. [1]University of Manitoba, Winnipeg, MB, [2]CHUS - Sherbrooke University, Sherbrooke, QC, [3]Oklahoma Medical Research Fdn, Oklahoma City, OK, [4]Astra-Zeneca, Cheshire, United Kingdom

Background/Purpose: Clinical outcome of patients with early undifferentiated arthritis (EUA) is variable and only partially predicted by clinical features at presentation. Biologically relevant markers reflecting pathogenic mechanisms may aid in identifying UA at risk of persistent disease. We sought to determine if biologically relevant markers reflecting pathogenic mechanisms aid in identifying UA patients who respond to standard treatment or enter remission after one year.

Methods: Patients with early undifferentiated arthritis not meeting ACR 1987 criteria for another arthropathy and with symptoms of less than one year received standard DMARD therapy aimed at disease remission. EULAR treatment response and clinical remission (DAS28CRP<2.6) were assessed at one year. Baseline pre-treatment serum was tested for ACPA, MMP3, MMP9, TIMP1, TIMP2, (by ELISA) and a panel of 23 cytokines (by Luminex multiplex assay). Random Forest/gradient boost methods with K class loss of function were used to determine the contribution of clinical variables, cytokines and MMPs to predicting clinical outcomes. Multiple iterations (2000–5000) were done for each analysis and the best cross validation iteration chosen to reflect best accuracy without over fitting the data. The following models were generated: baseline clinical variables alone, baseline biomarkers alone and baseline clinical and biomarkers.

Results: UA patients (n=123; 72% female, mean age 48 (15), baseline DAS28CRP3 3.67(1.22), mHAQ 0.48(0.48) were treated with DMARDs at the discretion of their physician. At one year, 66% has a good or moderate EULAR response and 52% were in remission. Baseline tender joint count and crp were the best clinical predictors of remission in UA (predictive accuracy 79%). The predictive accuracy was increased with the inclusion of baseline treatment naïve MMP and cytokine biomarkers (model accuracy 92%, PPV 97%, NPV 89%). Baseline MMP3, CRP, TJC, IL6, IL8 and mHAQ were the most important predictors in this model. Biomarkers added modestly to prediction accuracy for EULAR treatment response in UA (80% clinical alone, 83% clinical and biomarkers). The sample size was too small to evaluate predictors of UA evolving to RA. Baseline and one year paired biomarker assays were available on 49 Manitoba patients. Change in biomarker level in combination with baseline clinical features had accuracy 96%, DAS tjc28, sjc28, ip10, vegf, il8, mip1, il12, eotaxin, mmp).

Conclusion: Clinical variables are important in predicting clinical outcomes in EUA however, biomarkers provide increased predictive value over clinical factors alone. The best combination of biomarkers needs further evaluation.

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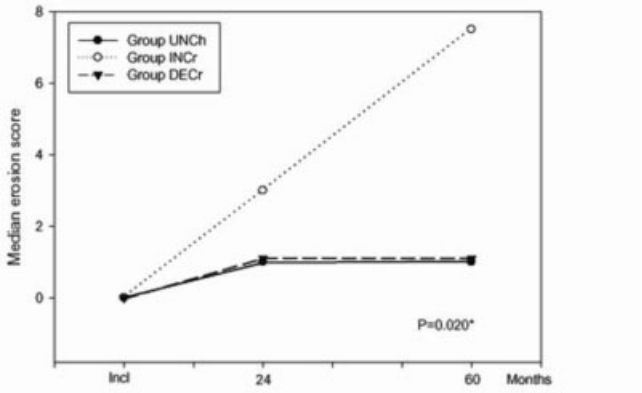
Early Increase In Serum-COMP Is Associated with Joint Damage Progression Over the First Five Years In Patients with Rheumatoid Arthritis. Maria LE Andersson[1], Bjorn Svensson[2], Ingemar F. Petersson[3], Ingiald Hafstrom[4], Kristina Albertsson[4], Kristina Forslind[5], Dick Heinegard[6] and Tore Saxne[7]. [1]R&D centre, Spenshult Hospital for Rheumatic Diseases, Oskarstrom, Sweden, Oskartrom, Sweden, [2]Paulinsvag 7D, Bastad, Sweden, [3]Lund University Hosp, Lund, Sweden, [4]Karoliska Institute, Stockholm, Sweden, [5]Lund, Sweden, [6]University of Lund, Lund, Sweden, [7]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden

Background/Purpose: Serum-COMP has shown promise as a prognostic indicator in rheumatoid arthritis (RA). However, serum concentrations may to some extent be genetically determined and thus reflect levels of cartilage matrix turnover not related to disease (Williams et al, 2006). We have examined if changes in serum-COMP early in the disease course of RA correlate with joint damage progression in hands and feet after 5 years.

Methods: In all 348 patients (64% women) included in the BARFOT study in Sweden from 1997 to March 1999 were examined. Their median age (range) was 58 years (16–84), and median disease duration 6.0 months. Serum-COMP was analysed at inclusion and after 3 months by ELISA (AnaMar, Lund). Based on changes in serum-COMP over the first 3 months, three subgroups of patients were defined: unchanged serum-COMP levels (change ≤ 20%) (group UNCh), increasing levels (increase > 20%) (group INCr) and decreasing levels (decrease > 20 %) (group DECr).Radiographs of hands and feet were obtained at inclusion and after 5 years and scored by the van der Heijde modification of the Sharp (SHS) method. The smallest detectable change in SHS was 5.8. Radiographic progression was defined as a change of total score of 5.8 or more.

Results: For all patients the median (range) serum COMP level at inclusion was 12.7 U/L (4.5–32.0). Group UNCh, with no change in serum-COMP consisted of 142 (41%) patients, group INCr, with increasing levels consisted of 34 (10%) patients and group DECr with decreasing COMP-levels of 172 (49%) patients. Group INCr had an increased risk of radiographic joint damage progression (total SHS) compared with group UNCh, OR 2.8 (95% CI 1.26–6.38), p=0.011. Group DECr did not differ in this respect from group UNCh. After 5 years the patients in group INCr had higher erosion score compared to the other groups, figure 1. There were no significant differences between the groups regarding JSN score (p=0.19) or total Sharp score (p=0.07). Group INCr had the lowest levels of serum-COMP at baseline compared with the other groups, p<0.01 and higher ESR than group DECr, 42 (2–140) vs. 27 (2–115), p=0.02. There were no differences between the groups at inclusion regarding age, gender, disease duration, DAS28, HAQ or CRP.

Figure 1 Median erosion score in the groups from inclusion to 60 months follow-up



Group UNCh, patients with unchanged serum-COMP levels from inclusion to 3 months follow-up (change ≤ 20%).
Group INCr, increasing serum- COMP levels from inclusion to 3 months follow-up (increase > 20%)
Group DECr, decreasing serum-COMP levels from inclusion to 3 months follow-up (decrease > 20 %)

Kruskall-Wallis between groups at 60 months

Conclusion: Early increase in serum-COMP in RA patients suggesting altered activity in the process of pathological cartilage turnover was in this study associated with joint damage progression over a 5 year period. These findings merit further studies to clarify whether early changes in serum-COMP may contribute to the clinician's assessment of prognosis.

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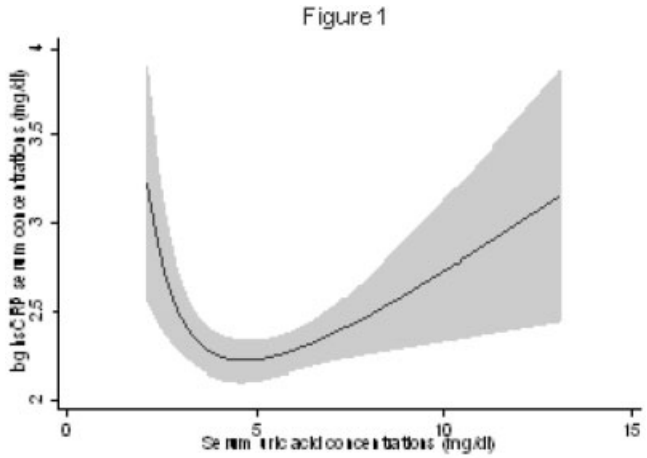
Is There An Association Between Uric Acid and Inflammation in Patients with Rheumatoid Arthritis? Paola de Pablo[1], Vasileios F. Panoulas[2], Karen MJ Douglas[2], Christopher D. Buckley[1] and George Kitas[2]. [1]University of Birmingham, College of Medical & Dental Sciences, School of Immunity & Infection, Rheumatology, Birmingham, United Kingdom, [2]Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Dudley, West Midlands, UK, Dudley, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA), a chronic inflammatory disease, is associated with cardiovascular morbidity and mortality. High-sensitivity C-reactive protein (hsCRP), a biomarker of inflammation, is an independent predictor of future vascular events in the general population. Previous studies have suggested that serum uric acid (SUA) may have a direct role in atherogenesis and large epidemiologic studies have observed an independent association between SUA and CRP in the general population. However, it is unclear whether this association holds in the context of a "high-grade" chronic inflammatory disease, such as RA. The purpose was to evaluate the association between SUA and hsCRP levels in a cohort of patients with RA.

Methods: We used data from a cohort of 400 consecutive patients with RA meeting ACR criteria for RA classification. Participants were recruited from routine outpatient clinics at the Department of Rheumatology, Dudley Group of Hospitals, United Kingdom, between 1 August 2004 and 31 July 2006 1. A priori we excluded participants with concomitant gout. We performed linear regression analyses of log transformed hsCRP on SUA concentrations, adjusting for potential confounders. We used fractional polynomial regression to evaluate the association between SUA and hsCRP, adjusting for age, gender, smoking, seropositivity, hypertension, diabetes, creatinine levels, glomerular filtration rate (GFR<60), body mass index (BMI), and use of medications such as diuretics, antihypertensives, aspirin, and statins. Sensitivity analyses included further adjustment for presence of the metabolic syndrome, disease activity score (DAS28), and medications used for RA management (i.e. DMARDS, biologics and steroids).

Results: After excluding participants with concomitant gout, the study sample included 385 participants with RA. Of those, 74% were female, 76% were seropositive, 67% were ACPA positive, 70% were hypertensive and 10% had diabetes. Mean age was 61 years (SD±12) and mean disease duration was 12.6 years (SD±10.6). Men had higher SUA and hsCRP concentrations than women [SUA mean (±SD): 6.04 (±1.35) vs. 4.88 (±1.46) mg/dl; hsCRP median (IQR): 10 (6–22) vs. 8 (5–19) mg/dl, respectively]. ACPA positive participants had higher SUA and hsCRP levels than those who were ACPA negative. There was a non-linear association between SUA and hsCRP concentrations (overall p-value=0.01) independent of BMI age, gender, smoking, seropositivity, hypertension, diabetes, creatinine levels, GFR<60, BMI, and medications (Figure 1). Sensitivity analyses showed similar results (overall p-value=0.02).

Figure 1



Conclusion: Serum uric acid concentrations are independently associated with hsCRP among individuals with RA. The physiologic basis of this association, as well as its significance in terms of the articular and vascular phenotype of RA require further exploration.

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Baseline Serum Levels of CXCL13 Are Associated with Ultrasonographic Synovitis and Predict Power Doppler Persistency in Early Rheumatoid Arthritis. Antonio Manzo, Serena Bugatti, Francesca Benaglio, Barbara Vitolo, Monica Todoerti, Garifallia Sakellariou, Roberto Caporali and Carlomaurizio Montecucco. Division of Rheumatology, University of Pavia School of Medicine, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Background/Purpose: The course of rheumatoid arthritis (RA) is highly variable among different patients. To optimise management, individual's outcomes need to be recognised as early as possible. Novel biological markers specifically reflecting the severity of synovial inflammation at presentation could be more predictive than routine clinical and laboratory assessments. Here we aimed at investigating the associations of baseline serum levels of CXCL13 (sCXCL13), a chemokine critically involved in B and T cell recruitment and cooperation within lymphoid and extra-lymphoid sites, with changes in clinical and ultrasonographic (US) disease activity in patients with recent-onset RA over a 12 months follow-up.

Methods: Study subjects were 161 early RA patients (disease duration < 1 year) treated according to a disease activity score (DAS)-driven step-up protocol aimed at low disease activity (LDA, DAS28<3.2). US examination of hands was performed at baseline and 12 months. Power Doppler (PD) synovitis was scored (0–3), with overall scores as the sum of each joint score. sCXCL13 was assessed by ELISA at baseline and, in 87 patients, after 2 months of therapy. sCXCL13 levels were analysed in relation to the following outcomes at 12 months: clinical LDA and remission according to conventional DAS28 and SDAI cut-off values, total PD score and US remission (total PD score = 0).

Results: At baseline, sCXCL13 levels were associated with objective and semi-objective measures of disease activity, such as the swollen joint count (rho 0.22, p=0.009), the evaluator global assessment of disease activity (rho 0.26, p=0.002), the erythrocyte sedimentation rate (ESR) (rho 0.41, p<0.0001) and C-reactive protein (CRP) levels (rho 0.41, p<0.0001). Confirming the specific relationship with measures of synovitis, sCXCL13 significantly correlated with baseline PD scores (rho 0.26, p=0.006). When compared to CRP, only sCXCL13 retained independent predictive value for the PD score. Furthermore, differently from CRP, sCXCL13 levels were significantly higher in ACPA-positive patients [96.82 (95%CI 72.61–117.19) vs 68.53 (95%CI 54.37–75.03), p=0.001]. sCXCL13 levels appeared mostly unchanged after 2 months of therapy (mean difference 4.62, 95% CI −3.37 11.4, p=0.27), as opposite to the other clinical and laboratory parameters which all significantly decreased. Baseline sCXCL13 did not predict clinical outcomes at 12 months. Rather, sCXCL13 levels were the only independent predictor of the 12 months PD score (p=0.02) and PD remission (p=0.04), irrespective of initial PD scores, disease activity status, acute phase reactants and autoantibodies. Using the Receiver Operating Characteristic curve, the relative risk of US remission was averaged 60% higher in patients with baseline sCXCL13 <106.75 pg/ml (OR 3.56, 95%CI 1.44–8.79).

Conclusion: CXCL13 emerges as a new biological marker in early RA,

accurate in assessing the severity of sinovitis and its persistency over time in response to conventional treatments.

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A Novel Multi-Biomarker Disease Activity Score (Vectra™DA algorithm score) Reflects Clinical Disease Activity Score and Health Assessment Questionnaire for Rheumatoid Arthritis in the BeSt Study. Shintaro Hirata[1], Linda Dirven[2], Guy Cavet[3], Yijing Shen[4], Michael Centola[5], Willem F. Lems[6], Tom W.J. Huizinga[2], Cornelia F. Allaart[2] and Yoshiya Tanaka[1]. [1]University of Occupational & Environmental Health, Kitakyushu, Fukuoka, Japan, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Crescendo Bioscience, South San Francisco, CA, [4]Geron Corporation, Menlo Park, CA, [5]Oklahoma Medical Research Foun, Oklahoma City, OK, [6]VU University Medical Center, Amsterdam, Netherlands

Background/Purpose: Disease activity measurement is the cornerstone of tight control and treat to target strategies, and is recommended by ACR and EULAR guidelines. A novel multi-biomarker based disease activity (MBDA) score has been validated in a broad RA population. However, the utility of the MBDA for evaluating disease activity and for predicting functional disability specifically in very early RA patients has not been investigated.The purpose of the study is to confirm the utility of the MBDA score as a novel disease activity index and as a predictor of Health Assessment Questionnaire (HAQ), in the BeSt study, a cohort of very early RA patients.

Methods: We analyzed 124 RA patients in the BeSt study. Clinical data and serum samples were available from 180 visits, 91 at baseline (BL) and 89 at year 1. The MBDA score combines 12 serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA) in a pre-specified algorithm, resulting in a score between 1 and 100. Associations between continuous variables were evaluated by Pearson's correlation. MBDA scores for groups stratified by DAS28 were compared by one-way factorial ANOVA. The association of categorical variables was assessed by Fisher's exact test.

Results: The MBDA score was correlated to DAS28 (cor = 0.66, $p < 0.0001$). Similar results were obtained for DAS28CRP, and the original DAS. ΔMBDA score was also correlated to ΔDAS28 (cor = 0.54, $p < 0.0001$). MBDA scores in groups stratified by EULAR disease activity (DAS28 < 3.2, 3.2 to 5.1, and > 5.1) were significantly different ($p < 0.0001$). MBDA score could discriminate low disease activity (DAS28 < 3.2) with area under ROC curve of 0.83 ($P < 0.0001$). Correlation between MBDA score and HAQ-DI (cor = 0.51, $p < 0.0001$), and also ΔMBDA and ΔHAQ-DI (cor = 0.47, p = 0.0003) were significant. Furthermore, the group with MBDA low disease activity (MBDA ≤ 28) at year 1 showed significantly higher ratio of HAQ remission (HAQ-DI ≤ 0.5) (68.6%) than that of the other group (36.8%; p=0.041).

Conclusion: The MBDA score reflects current clinical disease activity and can track changes in disease activity over time. In addition to DAS, the MBDA score is associated with HAQ in early RA patients. Furthermore, the MBDA score indicates HAQ remission.

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Polymorfisms In IL15 Associate with Progression of Joint Destruction In Rheumatoid Arthritis; A Multi Cohort Study. R. Knevel[1], A. Krabben[1], Elisabeth Brouwer[2], M.D. Posthumus[3], T. Saxne[4], E. Lindqvist[5], A. G. Wilson[6], Diederik P.C. de Rooy[1], N. Daha[1], M.P.M. van der Linden[1], René E.M. Toes[1], Tom W.J. Huizinga[1] and Annette H.M. van der Helm-van Mil[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands, [3]Berenkoog 28, Alkmar, Netherlands, [4]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [5]Lund University Hospital, Lund, Sweden, [6]Sheffield Uni /Medical School, Sheffield, United Kingdom

Background/Purpose: IL15 affects T-cell activation and proliferation. In RA IL15 levels are increased in serum and synovial fluid and are correlated to disease activity. Data are emerging that IL15 affects osteoclastogenesis as well. We therefore investigated *IL15* as a candidate gene for rate of joint destruction in RA.

Methods: Caucasian RA-patients included in four independent cohorts were studied; the total number of patients was 1,418 and the total number of hand and feet X-rays 4,885. X-rays were scored using the Sharp-van der Heijde or Larsen scores. For each patient the radiological progression rate was estimated. Three of the four cohorts had repeated radiographs of their patients, providing a sensitive estimation of the progression rate. First, explorative analyses were performed on 600 early RA-patients enrolled in the Leiden Early Arthritis Clinic. 25 SNPs, that together completely tagged IL15, were genotyped. Subsequently, SNPs with significant associations were typed in three other cohorts (from Lund, Groningen and Sheffield). Analyses were adjusted for age, gender or treatment if appropriate. For each cohort, the effect sizes indicated a relative increase of the progression rate per year in the presence of a genotype, and as such are comparable. An inverse weighting meta-analysis was done on the data of all cohorts.

Results: Five SNPs were significantly associated with rate of joint destruction in the first cohort and were typed in the other cohorts. Four of these SNPs were significant in the meta-analysis (Figure 1). Patients homozygous for the minor allele of rs6821171 had a 0.96 (95%CI 0.92–0.99) fold rate of joint destruction per year compared to other patients (P=0.01). Patients homozygous for the minor allele of rs7667746, rs7665842 and rs4371699 all had a 1.07 fold progression rate per year compared to the patients with only one or no minor allele (respectively 95%CI 1.03–1.10 P<0.001, 1.03–1.12 P<0.001, 1.02–1.12 P=0.01). These three SNPs were in close LD (r2 0.5–0.8, D'=0.97–1). Haplotype analyses of these SNPs resulted in two haplotypes; one consisting of all minor and the other of all major alleles. The estimated effects of the haplotypes on joint destruction were comparable to the results of the individual SNP analysis.

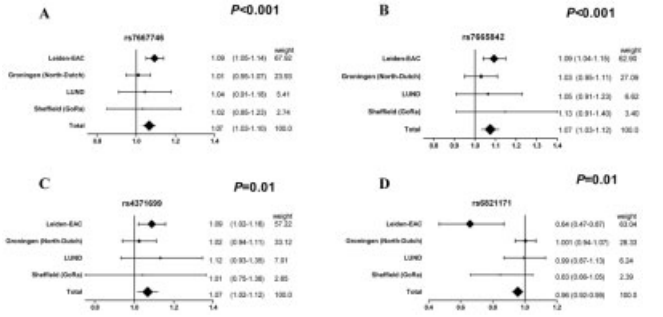

Figure 1. Depicted are the results of the meta-analyses of the four significant SNPs. The effect sizes indicate a relative increase in rate of joint destruction of patients homozygous for the minor allele compared to patients with only one or no minor allele.

Conclusion: Genetic variants in IL-15 are associated with the progression rate of joint destruction in RA.

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Identification of Patients Who Could Require Early Biologic Therapy by Developping a Matrix Predicting Rapid Radiographic Progression in Early Rheumatoid Arthritis Patients Treated by Methotrexate. A Study Based on the ESPOIR Cohort Data. Bruno Fautrel[1], Benjamin Granger[2], Bernard G. Combe[3], Xavier X. Le Loet[4] and ESPOIR Scientific Committee[5]. [1]Université Pierre et Marie Curie - Paris 6 - Pitie Salpetriere University Hospital, Paris, France, [2]Université Pierre et Marie Curie - Paris 6; AP-HP, Paris, France, [3]Hopital Lapeyronie, Montpellier, France, [4]CHU de ROUEN, Rouen CEDEX, France, [5]Paris

Background/Purpose: Although international guidelines recommend to start very rapidly synthetic DMARDs in early rheumatoid arthritis (ERA), some patients will fail to respond adequately and thus display rapid radiographic progression(RRP) as soon as the first year of the disease. To identify, by developing a prediction matrix, ERA patients at risk of RRP despite early synthetic DMARD initiation, who thus could justify biologics as first line agents.

Methods: The ESPOIR cohort included between 2002 and 2005 813 patients with early arthritis of less than 6 months disease duration. Among them, 398 received a synthetic DMARD – either MTX or LEF – for ≥ 3 months within the 1st year of follow-up. The structural damage progression on X-rays was measured by the Sharp/van der Heijde score (vSHS) and RRP was defined as an increase of the vSHS ≥ 5 points during the 1st yr. RRP determinants were estimated bivariately with the Student or Mann-Whitney U tests for continuous and the exact Fisher test for categorical variables ($p < 0.1$), and multivariately with a stepwise logistic regression. A matrix was then developed to predict at the patient level the probability of RRP.

Results: Main patient characteristics were: mean age 49.3 yrs, female 73.6%, FR+ or ACPA+ 62%, typical RA erosion 18.1% (central reading), ACR/EULAR 2010+ 86.4%, mean DAS28 5.35, mean swollen joint count (SJC) 8.1, mean tender joint count (TJC) 8.9, mean CRP 25.R mg/L. During

the 1st year, the mean vSHS progression was 1.7 ±5.0 and 46 patients (11.6%) were classified as rapid radiographic progressors.

In the bivariate analysis, variables associated with RRP were SJC, CRP, ACPA and RF status, typical RA erosion. In the logistic regression, all but RF remain significantly associated with RRP. The fit of the model was good with an area under the curve (AUC) of 0.765. A prediction matrix was then built after determination of the most discriminating threshold for each variable (Table).

Table. Prediction matrix for rapid radiographic progression (ΔvSHS ≥ 5 points) based on baseline characteristics

		Absence of typical RA erosion on X-ray			Presence of typical RA erosion on X-ray			
		SJC < 14	14 ≤ SJC < 20	SJC ≥ 20	SJC < 14	14 ≤ SJC < 20	SJC ≥ 20	RRP Risk
ACPA+	CRP ≥ 33	0.13	0.15	0.35	0.38	0.41	0.69	
	4 ≤ CRP < 33	0.12	0.13	0.33	0.36	0.39	0.67	>40%
	CRP < 4	0.05	0.06	0.18	0.19	0.22	0.47	>20%
ACPA−	CRP ≥ 33	0.04	0.05	0.14	0.16	0.18	0.41	>10%
	4 ≤ CRP < 33	0.04	0.05	0.13	0.14	0.16	0.39	<10%
	CRP < 4	0.02	0.02	0.06	0.07	0.08	0.21	

Conclusion: The ESPOIR matrix enables the identification of patients at high risk of RRP. Compared to previously reported matrices, the ESPOIR matrix requires higher thresholds for SJC.

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Local Swelling and Prolonged Local Pain in a Large Joint Are Independent Predictors of Damage in That Joint in Recent Onset Rheumatoid Arthritis Patients. M. van den Broek[1], L. Dirven[1], H.M. Kroon[1], M. van Oosterhout[2], K.H. Han[3], P.J.S.M. Kerstens[4], Tom W.J. Huizinga[1], W. F. Lems[5] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Groene Hart Hospital, Gouda, Netherlands, [3]Maasstad Hospital, Rotterdam, Netherlands, [4]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands, [5]VU University medical center, Amsterdam, Netherlands

Background/Purpose: To assess the association between local swelling and pain in the large joints in the first 2 years after diagnosis of RA with radiological damage in these joints after 8 years.

Methods: Two-year clinical data and 8-year radiological data from the BeSt study, a randomized controlled trial designed to assess 4 different treatment strategies, were used. Two-year clinical data were chosen because disease activity was highest in these years and clinical symptoms were unlikely to be caused by large joint damage. Patients were treated according to a disease activity steered protocol. Radiographs were scored by an experienced radiologist (HK) using the Larsen score (ranging from 0–5 in each joint). Swelling and pain in these joints were assessed 3-monthly, with exception of swelling in the hips. The association between swelling and pain in each large joint (at least once, or prolonged, i.e. at least 2 consecutive visits) and joint damage in this joint was assessed using generalized estimating equations. Swelling (model 1), pain (model 2) and swelling and pain (model 3) were entered as predictors, adjusted for baseline age, ESR, and body mass index (BMI), gender and time-averaged DAS, treatment strategy, rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), or a combination of these variables. Large joint damage (yes/no) was the outcome measure.

Results: Clinical and radiological data were available in 290 patients. Joint damage was observed in 64/532 (12%) shoulders, 51/538 (9.5%) elbows, 141/541 (26%) wrists, 67/521 (13%) hips, 95/528 (18%) knees and 39/544 (7%) ankles. Damage in at least 1 large joint was found in 64% of patients. Local pain and swelling in the first 2 years after diagnosis were most often observed in the wrists and ankles. Local swelling at least once in the first 2 years was independently associated with joint damage of the large joints, with an odds ratio (OR) of 1.8 (95% C.I. 1.3–2.3) (Table 1). Prolonged swelling and prolonged pain were both independent predictors of local joint damage, with an OR of 2.5 (95% C.I. 1.8–3.4) for prolonged swelling and of 1.4 (95% C.I. 1.05–1.9) for prolonged pain. Other independent predictors were baseline ESR (OR 1.01, 95%C.I. 1.001–1.02) and the presence of RF or ACPA (OR 2.2, 95% C.I. 1.3–3.8), or a combination of these two (OR 2.4, 95% C.I. 1.5–4.0).

Table 1. The association between local swelling, pain or swelling and pain with joint damage.

		At least once	At least 2 consecutive
Model 1	Swelling	2.0 (1.5–2.6)	2.9 (2.1–3.9)
Model 2	Pain	1.7 (1.2–2.2)	1.9 (1.4–2.5)
Model 3	Swelling	1.8 (1.3–2.3)	2.5 (1.8–3.4)
	Pain	1.4 (0.99–1.9)	1.4 (1.05–1.9)

Conclusion: Local swelling and prolonged local pain in a large joint in the first 2 years after diagnosis of RA are independent predictors of later joint damage in that joint. These results suggest that local control of inflammation might be beneficial to prevent damage.

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Calprotectin in Rheumatoid Arthritis: Relation with Disease Activity in a Transversal and Longitudinal Study. Miriam García-Arias[1], Alejandro Balsa[2], Dora Pascual-Salcedo[3], Susana Ramiro[4], Patricia Alcocer[1], Sara García Carazo[1] and Emilio Martín Mola[2]. [1]Rheumatology. La Paz Hospital, Madrid, Spain, [2]Rheumatology. La Paz Hospital. IdiPaz, Madrid, Spain, [3]Immunology. La Paz Hospital. IdiPaz, Madrid, Spain, [4]Immunology. La Paz Hospital, Madrid, Spain

Background/Purpose: Biomarkers are useful in the management of rheumatoid arthritis (RA) by enabling assessment of disease severity and monitoring of response to therapy. Calprotectin, a major leucocyte protein, has shown to correlate with clinical and laboratory markers of activity in several inflammatory diseases. The objective of this study is to analyze the relation between calprotectin and disease activity in RA patients and to evaluate changes in calprotectin levels during treatment. Also, this study investigates whether baseline calprotectin levels can predict response to treatment.

Methods: Two different cohorts of patients were studied. One transversal study included 60 patients with different disease activity according to DAS28: 15 (25%) were in clinical remission, 15 (25%) had low disease activity, 15 (25%) had moderate activity and 15 (25%) had high disease activity. In the second cohort, 20 patients who started biological treatment, 10 responders and 10 non responders, were longitudinally evaluated at three different time points. Disease activity was measured by DAS28 and SDAI. Serum calprotectin levels were determined by ELISA. Non parametric test and Pearson correlation analysis were using to perform the univariate analysis. A linear mixed model for longitudinal data was adjusted to analyzed changes in calprotectin.

Results: In the transversal study serum concentrations of calprotectin correlated significantly with swollen joint counts ($r=0.41$; $p<0.01$), erythrocyte sedimentation rate ($r=0.28$; $p<0.05$), C reactive protein ($r=0.37$; $p<0.01$) and disease activity (DAS28 $r=0.27$; $p<0.05$ and SDAI $r=0.40$; $p<0.01$). Patients with higher disease activity had higher calprotectin levels as compared with patients with mild, low disease activity and remission, according to both DAS28 (6.80 ± 4.19 vs 3.93 ± 2.41 vs 3.51 ± 1.80 vs 4.34 ± 3.10, $p<0.05$) and SDAI (7.73 ± 4.87 vs 4.97 ± 2.27 vs 3.99 ± 3.83 vs 3.29 ± 1.60, $p<0.01$). In the longitudinal study, serum calprotectin levels decreased during treatment in responders (6.23 ± 0.47 vs 3.47 ± 0.47 vs $3,03 \pm 0.47$, $p<0.0001$), but no differences in calprotectin were found in non responders (6.72 ± 1.65 vs 6.03 ± 1.65 vs 6.72 ± 1.65, $p=0.94$). There were no differences between basal calprotectin levels in responders as compared with non responders (6.23 ± 3.52 vs 6.72 ± 3.50, $p=0.85$). No correlation between changes in calprotectin levels and changes in disease activity was found in the mixed model ($p=0.85$).

Conclusion: Calprotectin correlates with clinical and laboratory markers of disease activity in RA patients. Thus, calprotectin may be a promising marker in the assessment and monitoring of disease activity. However, baseline calprotectin levels were not predictive for response to treatment.

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Moderate and Heavy Alcohol Use Is Associated with Less Patient-Derived Inflammation and Better Health-Related Quality of Life in Female Swedish Rheumatoid Arthritis Patients. Data From BARFOT, a Multicenter Study on Early RA. Maria K. Söderlin, Sofia Symeonidou, Maria Andersson and Stefan Bergman. R&D Center, Oskarström, Sweden

Background/Purpose: Earlier studies report a positive effect of alcohol use on disease activity rheumatoid arthritis (RA). The aim of this study was to study alcohol use and its effects on disease activity in Swedish RA patients.

Methods: Between 1992 and 2005, 2800 patients were included in the BARFOT early RA study in Sweden. Disease Activity Score 28 joints (DAS28), C-reactive protein (CRP), Health Assessment Questionnaire (HAQ), rheumatoid factor (RF), general health and pain visual analog scales (VAS), and drug treatment were registered at inclusion and at

follow-up at 3, 6 and 12 months and 2, 5, 8 and 15 years. EULAR response and remission criteria were applied at the same follow-up points. In 2010, a self-completed postal questionnaire was sent to 2102 patients (all prevalent patients) in the BARFOT study enquiring about life style factors. Alcohol use was assessed using the self-completed validated questionnaire AUDIT-C.

Results: In 2010 1238/1460 (85%) of the patients had data on alcohol use: 11% were non-drinkers, 67% moderate drinkers and 21% heavy drinkers. Women who drank moderately or heavily had lower patient-reported disease activity and higher health-related quality of life (HRQL) in a cross-sectional analysis in 2010, but no effect of alcohol use on disease activity was seen in men. For current smokers alcohol use was only associated with fewer patient-derived swollen joints. Female moderate and heavy drinkers had lower physician-reported DAS28 levels up to 5 years of follow-up, which were driven by lower ESR levels. Alcohol use did not emerge as an independent predictive factor for higher EuroQol, HAQ or VAS scores in multivariate regression models adjusted for sex, age, disease duration, smoking status and socioeconomic status.

Conclusion: A total of 21% of patients were heavy drinkers. Women who drank moderately or heavily had best patient-derived disease activity and HRQL, but no effect of alcohol on patient-derived disease activity was seen in men. Women drinking heavily or moderately had lower physician-reported DAS28 up to 5 years of follow-up due to lower ESR.

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Plasma Talin Is a New Diagnostic and Monitoring Marker for Rheumatoid Arthritis. Kensei Tsuzaka[1], Yuka Itami[1], Naoshi Shinozaki[2] and Morishita Tetsuo[1]. [1]Dept of Internal Medicine, Ichikawa General Hospital,TDC, Ichikawa, Chiba, Japan, [2]Cornea Center, Ichikawa General Hospital, TDC, Ichikawa

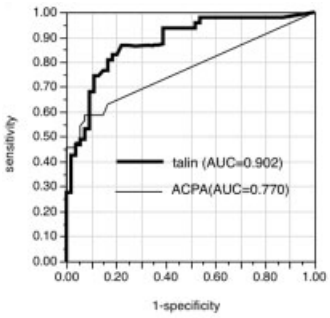
Background/Purpose: Anti-CCP antibody (ACPA) has been reported to as a useful and highly specificity marker for the diagnosis of rheumatoid arthritis (RA). However, more sensitive diagnostic biomarker might be expected because the sensitivity of ACPA in early RA has been shown to be lower than expected. Talin is a protein that completes the link between integrins and the actin cytoskeleton, and plays an important role in the establishment of focal adhesions. In this paper, we focused on plasma talin as a diagnostic marker for RA.

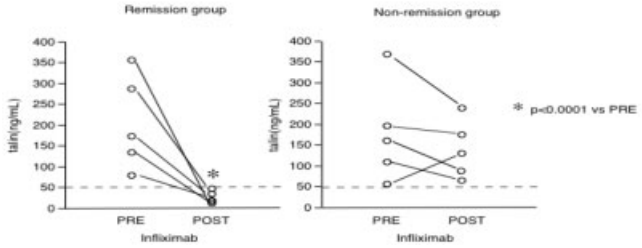
Methods: RA was diagnosed as the 2010 Rheumatoid Arthritis Classification Criteria. Plasma and sera were obtained simultaneously from 50 RA patients (Age, 60.9±14.4 y/o; DAS28, 5.23 ± 1.11) and 70 controls (Ctrl) (30 osteoarthritis (OA) patients, 20 SLE patients, and 20 normal healthy controls (NC)). Twenty-two (44.0 %) of these 50 RA patients were early-onset (≤ 6 months) RA and 39 (78.0 %) of these patients were untreated at the time of collecting blood. Plasma talin was quantified using a sandwich ELISA with anti-talin capture and detecting antibodies. Serum ACPA was measured using a commercial ELISA kit. Plasma was obtained at baseline and 14 weeks after treatment with IFX from 5 RA patients who entered remission (SDAI<3.3) (Remission group) and 5 RA patients who did not enter remission (Non-remission group) at 14 weeks after IFX treatment.

Results: Plasma level of talin was significantly ($p<0.0001$) higher in RA patients (177.3 ± 167.3 ng/mL) than in OA (28.8 ± 29.7 ng/mL), SLE (38.1 ± 38.0 ng/mL), and NC (41.9 ± 51.3 ng/mL), respectively. The area under ROC curve (AUC) of talin (0.902) was larger than AUC of ACPA (0.770) in differentiation between RA and Ctrl (Fig.1). Moreover, the sensitivity of talin (82.3%) for the diagnosis of RA was higher than that of ACPA (58.0%), rheumatoid factor (Rf) (76.1%), and MMP-3 (74.0%) while its specificity (85.1%) was higher than that of Rf (57.0%) and MMP-3 (55.3%) (Table.1). Interestingly, the plasma level of talin before treatment (PRE) was significantly ($p<0.001$) down-regulated to the normal range (<50 ng/mL) after IFX treatment (POST) in Remission group whereas it did not reduce to the normal range in Non-remission group (Fig. 2).

Table 1.

	Sensitivity (%)	Specificity (%)
talin	82.3	85.1
ACPA	58.0	90.8
Rf	76.1	57.0
MMP-3	74.0	55.3





Conclusion: Our findings suggest clinical usefulness of plasma talin as a new diagnostic and monitoring biomarker for RA.

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Serum 14-3-3η: A Rheumatoid Arthritis Biomarker. Walter P. Maksymowych[1], Robert Landewe[2], Désirée van der Heijde[3], Paul-Peter Tak[4] and Anthony Marotta[5]. [1]University of Alberta, Edmonton, AB, [2]Academic Medical Center, Amsterdam, Netherlands, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [4]Professor of Medicine/ Director, Division of Clinical Immunology and Rheumatology, Amsterdam, Netherlands, [5]Augurex Life Sciences Corp, North Vancouver, BC

Background/Purpose: Intracellular 14-3-3 proteins represent a family of ubiquitously expressed chaperonins consisting of seven highly conserved isoforms. Only one isoform, 14-3-3η, is significantly detected in arthritis and is differentially expressed extracellularly in rheumatoid arthritis (RA) compared to healthy controls and may have independent diagnostic utility from other RA serological markers. This study compared 14-3-3η serum expression in patients with RA versus ankylosing spondylitis (AS) and in autoimmune (AI) disease controls.

Methods: Levels of serum 14-3-3η were measured in 267 patients, 135 RA, 67 AS and 65 AI controls, using an investigational-grade 14-3-3η ELISA to evaluate the biomarker's differential expression in RA. Mean (SD) age for RA patients (72% female) was 59.4 (12.7) and 41.9 (13.2) for AS patients (25% female). Diagnosis was according to ARA 1987 and modified New York criteria, respectively. RA patients were on standard DMARDs but naïve of biological therapy. AI controls included 10 each of psoriasis, ulcerative colitis, type 1 diabetes, SLE, Crohn's, and 5 each of primary Sjogren's, scleroderma, and multiple sclerosis. Two-tailed t-tests and Mann-Whitney u-tests were used to compare group differences in serum concentrations. ROC curves were generated and diagnostic utility estimated by area under the curve and likelihood ratios (LR) for various 14-3-3η serum concentration cut-offs.

Results: 14-3-3η mean and medium serum concentrations were significantly higher in RA subjects at 4.58 and 1.12ng/ml, respectively compared to AS (0.14 and 0.02ng/ml; $p<0.0001$) and AI (0.21 and 0.03ng/ml; $p<0.0001$). The area under the ROC curve for RA versus AS was 0.86 (95%CI 0.81 to 0.91; $p<0.0001$) and RA versus AI was 0.85 (95%CI 0.79 to 0.90; $p<0.0001$). There were no differences in mean or median 14-3-3η serum concentrations between the AS and AI groups. A best cut-off level of 0.23ng/ml provides a positive likelihood ratio (LR+) of 5 and a negative likelihood ratio (LR-) of 0.30 for RA versus AS. For 14-3-3η levels above 0.72 and 0.88ng/ml, LR+ was 10 and 36, and LR- was 0.40 and 0.47, respectively.

Conclusion: Differential expression of 14-3-3η in RA versus AS and its absence in a wide range of other autoimmune disorders supports its utility as a diagnostic marker in RA.

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Can Anti-Cyclic Citrullinated Peptide Antibody Negative Rheumatoid Arthritis Be Subdivided in Clinical Subphenotypes?. Diederik P.C. de Rooy[1], Annemiek Willemze[1], Bart Mertens[2], Tom W.J. Huizinga[1] and Annette H.M. van der Helm-van Mil[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Netherlands

Background/Purpose: Studies investigating genetic risk factors for susceptibility to Rheumatoid Arthritis (RA) studied anti-citrullinated peptide antibody (CCP)-positive-RA more frequently than anti-CCP-negative RA. One of the reasons for this is the perception that anti-CCP negative RA may include patients that fulfilled criteria for RA but belong to a wide range of diagnoses. We aimed to evaluate the validity of this notion and explored whether clinical subphenotypes can be discerned within anti-CCP-negative RA.

Methods: 318 patients with anti-CCP-negative RA (1987 ACR-criteria), included in the Leiden Early Arthritis Clinic between 1993 and 2006, were studied for baseline characteristics and radiological progression data during a mean follow-up of 5 years. Grouping was studied both at variable and patient level. Principal Components Analysis and Partial Least Squares regression were applied to study for clustering of variables. A Cluster Analysis was performed in order to look for clustering of patients.

Results: The simultaneous presence of patient characteristics at disease presentation was observed for several groups; however the 3 largest groups of patients' characteristics explained only 26.5% of the total variance. Plotting the contribution of each patient to these 3 groups did not reveal clustering of patients. Comparable observations were done when data on progression of joint destruction were studied in relation to baseline clinical data. A Cluster Analysis, evaluating whether patients resemble each other, revealed no grouping of patients. Altogether, no clinically distinguishable subphenotypes were observed.

Conclusion: This study suggests that in studies assessing risk factors in anti-CCP negative RA, all patients can be studied as one group.

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Elevated Plasma Soluble TREM-1 Levels Is Correlated with Disease Activity in Rheumatoid Arthritis. Sang Tae Choi[1], Eun-Jin Kang[2] and Jung-Soo Song[1]. [1]Chung-Ang University College of Medicine, Seoul, South Korea, [2]Busan Medical Center, Busan, South Korea

Background/Purpose: Triggering receptor expressed on myeloid cells 1 (TREM-1) is an immunoglobulin-like cell surface receptor mainly expressed on neurtophils, monocytes and macrophages. TREM-1 serves as a critical amplifier of inflammatory signaling, and its expression is increased in the synovium of rheumatoid arthritis (RA) patients. It can exist as a soluble form. In this study, we investigated whether plasma soluble TREM-1 (sTREM-1) levels are elevated in patients with RA and whether its levels are correlated with disease activity and other parameters.

Methods: This cross-sectional study included 71 patients with RA and 50 age- and sex- matched healthy controls. Plasma samples were obtained from patients with RA during active and inactive disease status and from controls. We assessed clinical characteristics and laboratory parameters including the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and disease activity score 28 (DAS28). Their plasma levels of sTREM-1 and tumor necrosis factor (TNF)-α were quantitatively measured by enzyme-linked immunosorbent assay (ELISA).

Results: Patients with RA had significantly higher plasma sTREM-1 levels than healthy controls (170.10 $\pm$ 84.71 pg/mL vs 97.41 $\pm$ 40.64 pg/mL, $p < 0.001$). In RA patients, the plasma sTREM-1 levels were correlated with DAS28, ESR, and CRP ($r = 0.329$, $p = 0.005$; $r = 0.241$, $p = 0.043$; $r = 0.314$, $p < 0.001$, respectively), but not with plasma TNF-α levels. Plasma sTREM-1 levels in the patients with active disease status (DAS28 $\geq$ 3.2) were significantly higher than those without it (208.89 $\pm$ 100.14 pg/mL vs 150.29 $\pm$ 68.70 pg/mL, $p = 0.005$).

Conclusion: Patients with RA had higher levels of plasma sTREM-1 compared to healthy controls. The plasma sTREM-1 levels were correlated to DAS28, ESR, and CRP. The soluble form of TERM-1 may be useful as a disease activity marker in RA.

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Investigation of a Multi-Biomarker Disease Activity (Vectra DA) Signature and Algorithm Score in Rheumatoid Arthritis Patients with Low Disease Activity: The REMIRA Study. Margaret H. Ma[1], Saroja Ramanujan[2], Guy Cavet[2], Douglas J. Haney[2], Xiaoyan Zhao[2], P. Scott Eastman[2], Gabrielle H. Kingsley[1], David L. Scott[3] and Andrew P. Cope[1]. [1]King's College Hospital, London, United Kingdom, [2]Crescendo Bioscience, Inc., South San Francisco, CA, [3]King's College Hospital, Dulwich, United Kingdom

Background/Purpose: With intensive therapy, low disease activity (LDA) states and remission are becoming increasingly common in patients with RA. Yet, discriminating true remission from persistent sub-clinical disease remains a challenge. Thus, there is an urgent need to improve the definition of LDA using a wider range of clinical and laboratory variables. A multi-biomarker signature that combines levels of 12 serum biomarkers to produce a score between 1 and 100 was recently validated as a test for RA disease activity. We examined the use of this multi-biomarker disease activity (MBDA) test in assessing the heterogeneity of LDA states and differentiating remission vs. non-remission.

Methods: RA patients on stable therapy with $<$10 yrs disease duration and DAS28ESR$\leq$3.2 were recruited to the REMIRA study. Concentrations of 12 protein biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, YKL-40, MMP-1, MMP-3, leptin, resistin, SAA, CRP) were determined by immunoassay in baseline serum samples and used to generate MBDA scores according to a pre-specified algorithm. Association between the MBDA score and clinical remission was assessed by calculating the area under the ROC curves (AUROCs) for various definitions of remission, including the ACR/EULAR 2011 Boolean definition. Comparison of biomarker concentrations between remission and non-remission LDA patients was performed using the Wilcoxon test and a fixed-sequence procedure to control for the effects of multiple testing.

Results: 70 RA patients with mean(SD) age of 58(14) and disease duration of 50(31) months were recruited. 61% were female, 82% were Caucasian, 14% were Afro-Caribbean, 4% were Asian, and 68% were seropositive. Mean DAS28ESR was 1.84(0.83); mean DAS28CRP was 1.98(0.69). Wide variation in biomarker levels and profiles was seen across the cohort. SAA was most suppressed and EGF most elevated relative to historical data. The MBDA score was significantly associated with remission vs. non-remission (AUROC=0.74, 95% CI=(0.60,0.85), p$<$0.001 for Boolean remission; similar for other criteria). Individually, IL-6, CRP, and SAA were significantly lower in remission than in non-remission patients. Although proinflammatory biomarkers were generally lower in remission, a small subgroup of patients had elevated biomarkers and MBDA scores despite being in clinical remission.

Table 1. Concentrations of biomarkers differing between remission and non-remission LDA patients, as classified by the ACR/EULAR Boolean definition. IQR=Inter-Quartile Range

Biomarker	Median (IQR) LDA/remission	Median (IQR) LDA/non-remission	p-value
IL-6 [pg/ml]	6.0 (4.4–8.0)	10 (6.6–17)	0.001
CRP [mg/L]	1.4 (0.52–2.3)	2.4 (1.1–7.2)	0.009
SAA [mg/L]	0.93 (0.57–1.5)	1.6 (0.90–3.1)	0.01

Conclusion: The REMIRA LDA cohort is heterogeneous as reflected by wide biomarker variation. The MBDA score can differentiate between LDA/remission and LDA/non-remission and has a potential role for disease activity assessment in LDA patients. Longitudinal follow-up may improve our understanding of the relationship between elevated biomarkers and disease progression in patients in clinically-judged remission.

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Serum 25 OH Vitamin D Levels Are Low in North American Native Populations with Early Inflammatory Arthritis but Do Not Correlate with Clinical Activity or Outcome. Carol A. Hitchon, Neeloffer Mookherjee, Keng Wong, Christine A. Peschken, Peter Nickerson and Hani S. El-Gabalawy. University of Manitoba, Winnipeg, MB

Background/Purpose: Low 25 OH vitamin D (VitD) levels have been associated with inflammatory arthritis and with disease activity. North American Native (NAN) populations have a high prevalence of shared epitope, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), and worse clinical

outcomes than Caucasians from the same geographical area. We sought to determine the prevalence of vitD deficiency and the contribution of VitD to disease severity and outcomes in a cohort of NAN and Caucasians with early inflammatory arthritis.

Methods: NAN and Caucasians with early inflammatory arthritis (<12 months symptoms, 1+ active joint), were followed for one year and clinical outcomes (remission, EULAR treatment response) determined. Disease activity was measured using the DAS28(3variable) CRP composite score. Treatment was at the discretion of the attending rheumatologist. Shared epitope was determined by DNA sequencing. VitD levels were measured in baseline serum by ELISA and categorized as deficient (<25 nmol/L), insufficient (25- <75 nmol/L), optimal (75–250 nmol/L) or toxic (>250 nmol/L). Statistical significance was considered as $p<0.05$ using non-parametric Mann Whitney U and Chi2 tests and multivariate regression models.

Results: At baseline, 77% of EIA had insufficient (61%) or deficient (16%) levels of VitD. Baseline VitD levels were lower in NAN compared to Caucasian even after correcting for season of first visit 49 (32) vs 59 (30) nmol/L $p=0.008$) and NAN were more likely to be deficient (25% vs 11% $p=0.006$). No associations with gender, serology (RF and/or ACPA), shared epitope, baseline disease activity DAS28 (3variable)CRP, individual components, or ESR) or smoking status were seen. Baseline VitD levels were not associated with clinical outcomes of remission or treatment response in univariate or multivariate models. Repeated VitD levels were available at 6 months (n= 50) and 12 months (n=164) on selected subjects without adjustment of vitD supplementation. At one year, the majority had vitD levels similar to their baseline vitD category, 33 (20%) improved and 28 (12%) worsened. No significant seasonal variability was seen. Change in VitD correlated with DAS28(3variable)CRP at one year ($r= -0.215$ $p=0.01$) but not with change in DAS28(3variable) CRP p=NS).

Conclusion: The prevalence of VitD deficiency is high in this Canadian cohort of early inflammatory arthritis especially for NAN. However, serum levels do not correlate with disease activity or outcome. In this high risk NAN population, low VitD may be more important in predisposing individuals to future inflammatory arthritis.

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A New Definition of Treatment Response in Rheumatoid Arthritis: Identification of the Critical Difference in Disease Activity. Frank Behrens[1], Michaela Koehm[1], Eva C. Scharbatke[2], Stefan Kleinert[2], Geerd Weyer[3], Rieke Alten[4], Hans Peter Tony[2] and Harald Burkhardt[1]. [1]CIRI/Rheumatology, J.W. Goethe-University, Frankfurt/Main, Germany, [2]Rheumatology, University of Würzburg, Würzburg, Germany, [3]Biostatistics, ICRC, Berlin, Germany, [4]Rheumatology Schlossparkklinik, Berlin, Germany

Background/Purpose: Situational effects and measurement errors inducing fluctuations in disease activity measurements complicate the evaluation of a clinically meaningful therapeutic response in rheumatoid arthritis (RA). To itemize this complexity, a statistical approach was used to determine a critical difference (dcrit) defining valid criterion for clinical response as assessed by the Disease Activity Score-28 joints (DAS28).

Methods: The population comprised a total number of 728 RA patients with stable response to DMARD, steroid or biological therapy (including TNF-inhibitors and Rituximab) derived from three different clinics in Germany (University Würzburg (n=50), University Frankfurt (n=51), Berlin (n=50)) and from a prospective observational study with Adalimumab. Patients were included with stable therapy and disease course from months 12 to 24 after therapy initiation. To evaluate changes in DAS28 score, DAS28 scores at 12, 18 and 24 months were subjected to an ANOVA model to determine the error of measurement which was used to establish a 95% one sided confidence interval (95% CI) for decrease occurring by chance within the range of normal fluctuations. The limit of the confidence region defined the critical difference (dcrit) in disease activity for a reliable change in a single patient.

Results: The overall dcrit value in the 728 patient populations was detected at 1.75. Values for dcrit were comparable in all evaluated subgroups, regardless of treatment centre, class of therapy (DMARDs or biologics including TNF-inhibitors and Rituximab), or baseline disease activity (Table).

	All patients	DAS28 M12		Class of therapy		Age		Gender	
		≤3.2	>3.2	DMARDs	Biologics	≤60 years	>60 years	male	female
n	728	393	335	57	671	460	268	167	561
dcrit	1.75	1.57	1.79	1.90	1.73	1.74	1.77	1.65	1.78

Conclusion: Based on our data, a dcrit value of 1.8 (DAS28 improvement of 1.8 points) signifies an individual therapeutic response that exceeds the threshold of random fluctuation. The dcrit value determined by statistical analysis of expected variation in DAS28 scores higher than the DAS28 change required to achieve a good EULAR response (1.2 points) and is independent of baseline activity, which may make it more convenient for clinical use. Further studies in larger populations will be required to confirm the utility of the dcrit value in determining therapeutic response. However, our data suggest that a dcrit value of 1.8 has the potential to guide treatment decisions in daily clinical practice and to facilitate research on treatment responders.

ACR Poster Session A

Rheumatoid Arthritis - Human Etiology and Pathogenesis I

Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Characterization of TLR7 and TLR8 in Rheumatoid Arthritis. Nathan D. Chamberlain[1], Michael Volin[2], Richard M. Pope[3], Arthur M. Mandelin II[3] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL, [3]Northwestern Univ Med School, Chicago, IL

Background/Purpose: The aim of the study was to characterize the expression of TLR7 and TLR8 in rheumatoid arthritis (RA) synovial tissue and to examine their regulation and pathogenic role in RA monocytes and macrophages.

Methods: Expression of TLR7 and TLR8 was determined in RA, osteoarthritis (OA) and normal (NL) synovial tissues employing immunohistochemistry. Expression and regulation of TLR7 and TLR8 was determined in RA peripheral blood (PB) monocytes and *in vitro* differentiated macrophages by real-time RT-PCR and ELISA. Next, the mechanism by which TLR7/8 ligation mediates the proinflammatory response in RA PB macrophages was examined using Western blot analysis and ELISA.

Results: We found that in RA, TLR7 immunostaining was markedly higher in synovial tissue lining and sublining macrophages compared to NL synovial tissue. TLR8 immunostaining was greatly increased in RA synovial tissue lining compared to OA and NL synovial tissue. Additionally, sublining macrophages had greater TLR8 expression in RA compared to NL synovial tissue. Further expression of TLR7 and TLR8 was significantly elevated in RA synovial fluid macrophages and RA PB monocytes compared to RA and NL PB macrophages by real-time RT-PCR. Expression of TLR7 is reduced when RA PB monocytes differentiate to macrophages, however in PB macrophages TLR7 expression levels can be induced by IL-17 and IL-8 while PB monocytes are unresponsive to stimulation. In contrast, TLR8 expression is modulated by LPS and IL-1b in both RA PB monocytes and macrophages. To determine whether RA PB monocytes and macrophages respond to TLR7/8 ligation, cells were exposed to different doses of a potent synthetic agonist of TLR7/TLR8, R848 (100 ng/ml and 1mg/ml), and screened for transcription (6h) and production (24h) of proinflammatory factors, TNF-a, IL-6 and CCL2. Secretion of TNF-a and IL-6 were dose dependently increased by R848 stimulated RA PB monocytes and macrophages. However, production of CCL2 did not follow a dose responsive increase in RA PB monocytes or macrophages. Although TLR7/8 expression was greatly elevated in RA PB monocytes compared to RA PB macrophages, ligation of these receptors with the highest dose of R848 tested (1mg/ml) resulted in production of comparable levels of TNF-a, IL-6 and CCL2 in both cell types. With this highest dose of R848 similar levels of TNF-a and CCL2 were produced from RA PB macrophages which were greater than IL-6 production in these cells. We next inhibited pathways in R848 activated RA PB macrophages to determine signaling intermediates contributing to TLR7/8-mediated proinflammatory factor production. R848 mediated activation of the p38 pathway (15 min) occurs prior to that of ERK, AKT or NF-kB (35 min). We chose to examine the regulation of R848-induced CCL2 since this chemokine was comparably produced from RA PB monocytes and macrophages following lower and higher doses of R848. While inhibitors to NF-kB and PI3K suppressed R848-induced CCL2 secretion 3 fold in RA PB macrophages, inhibition of p38 or ERK pathways was ineffective in this process.

Conclusion: We identify for the first time, regulators of TLR7 and TLR8 expression in their target cells, macrophages, and document the role of TLR7/8 ligation in the pathogenesis of RA.

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TLR5; A Novel and Unidentified Inflammatory Mediator in Rheumatoid Arthritis. Nathan D. Chamberlain[1], Michael Volin[2], Richard M. Pope[3], Arthur M. Mandelin II[4] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL, [3]Northwestern Univ Med School, Chicago, IL, [4]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: Previous studies strongly support the role of TLR2 and 4 in the pathogenesis of rheumatoid arthritis (RA) and experimental arthritis models however the regulation and pathogenic effect of TLR5 is undefined in RA.

Methods: Expression of TLR5 in RA, osteoarthritis (OA) and normal (NL) synovial tissue (ST) was determined by immunohistochemistry. Employing real-time RT-PCR regulating factors of TLR5 expression were determined in RA monocytes and macrophages. In the same cells, production of proinflammatory factors and/or the mechanism by which these factors were induced was examined following TLR5 ligation.

Results: In this study we demonstrate that in both RA and OA, TLR5 staining was markedly higher on synovial lining and sublining macrophages compared to NL tissue. Therefore we asked whether expression of these factors was increased in RA *in vitro* differentiated peripheral blood (PB) and synovial fluid macrophages compared to normal PB monocytes and *in vitro* differentiated macrophages. Expression of TLR5 was elevated 9- and 35-fold in RA synovial fluid macrophages compared to RA and NL PB macrophages respectively by real-time RT-PCR. Levels of TLR5 were 7- and 3-fold greater in RA PB monocytes compared to RA PB macrophages and normal monocytes. We further demonstrate that TLR5 expression was modulated by TNF-a in RA monocytes and by IL-17 and IL-8 in RA macrophages however expression levels of TLR5 was suppressed by TLR4 ligation in both cell types. Next, we asked whether RA monocytes and macrophages respond to the ligation of flagellin to TLR5. For this purpose RA PB monocytes and macrophages were activated with different doses of flagellin (10–100 ng/ml) and cells were screened for transcription (6h) and production (24h) of proinflammatory factors such as TNF-a, IL-6 and CCL2. Generally, transcription but not the secretion of TNF-a, IL-6 and CCL2 was dose dependently increased with flagellin stimulation in RA PB monocytes and macrophages. Although TLR5 expression was greatly elevated in RA PB monocytes compared to RA PB macrophages, TLR5 ligation resulted in higher (TNF-a) or comparable levels of proinflammatory factors (IL- 6 and CCL2) in RA PB macrophages compared with RA PB monocytes. Similar levels of TNF-a and IL-6 were produced from RA PB monocytes and macrophages following TLR5 ligation which were lower than CCL2 production in these cells. We next inhibited pathways in flagellin activated RA PB macrophages in order to determine signaling intermediates contributing to flagellin-mediated proinflammatory factor production in these cells. We found that flagellin-mediated activation of the p38 and AKT pathways (5 min) occurs prior to that of ERK (35 min) or NF-kB (15 min). We chose to examine the regulation of flagellin-induced CCL2 since this chemokine had the highest production level in RA macrophages. While inhibitors to NF-kB and PI3K suppressed flagellin-induced CCL2 secretion by 3- to 6-fold ($p < 0.05$), inhibition of p38 or ERK pathway did not reduce the levels of CCL2 in RA macrophages.

Conclusion: These results suggest that macrophages in RA synovial tissue and fluid are an important source of TLR5. These observations also suggest that TLR5 may be a potential therapeutic target in RA.

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Methyl Supplementation of Rheumatoid Arthritis Synovial Fibroblasts Attenuates Their Aggressive Behaviour. Emmanuel Karouzakis[1], Maria Berdasco[2], Astrid Jungel[1], Caroline Ospelt[1], Andrew Filer[3], Karim Raza[3], Renate E. Gay[1], Beat A. Michel[1], Christopher D. Buckley[3], Manel Esteller[2], Steffen Gay[1] and Michel Neidhart[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Bellvitge Institute for Biomedical Research, Barcelona, Spain, [3]School of Immunity and Infection, MRC Center for Immune Regulation, Birmingham, United Kingdom

Background/Purpose: Previously, we reported that global genomic hypomethylation in rheumatoid arthritis synovial fibroblasts (RASF) contributes to the intrinsically activated phenotype. Therefore, the reversal of hypomethylation in RASF might reduce their state of activation. Since, methyl supplementation with Folate, L-methionine and Vitamin B12 has been shown to increase DNA methylation, we treated RASF with this combination and measured the adhesion, migration and invasion.

Methods: Global hypomethylation was measured in genomic DNA of osteoarthritis SF (OASF, n=5), early RASF (n=4) and RASF (n=8) by High Performance Liquid Chromatography (HPLC). Hypomethylated RASF (n=2 patients) were cultured in DMEM/ F12 medium (control) supplemented with 10 (HS) fold excess amount of folate, vitamin B12 and L-methionine for 1 month. After the last day of treatment, DNA methylation was assessed by staining of nuclei with 5-methylcytosine antibodies. Mean fluorescence intensity (MFI) was calculated from the histograms. In addition, the ability of the RASF to adhere to a variety of extracellular matrixes (ECM) such as fibronectin, collagen types I and II were tested with a cell adhesion assay. The effect of methyl supplementation on the migratory properties of RASF was analysed by scratch assay. The untreated or treated RASF were implanted together with normal human cartilage into the SCID mouse model of RA.

Results: RASF and early RASF revealed a lower percentage of total 5-methylcytosine (5-MeC) than the OASF (RASF: 3.8±0.22 % 5-MeC, $p<0.0001$, n=8; early RASF: 4.4±0.15% 5-MeC, $p<0.0028$, n=4; OASF: 5.5±0.12 % 5-MeC, n=5). The supplementation with methylation compounds increased the percentage of 5-MeC in comparison to normal treated RASF in patient 1 (Patient 1: control 7.31; HS 18.92 MFI, Patient 2: control 9.18; HS 9.18 MFI). The steady treatments of RASF with HS methylation supplementation inhibited the migration of cells as shown by scratch assays in both patients. However, HS treatment of RASF did not change the cell adhesion to fibronectin and collagen types. Most interestingly, the steady HS treatment of RASF from patient 1 that responded to the treatment *in vitro* showed reduced invasion and perichondrocytic degradation in the *in vivo* SCID mouse invasion model (invasion score: control 2.25±0.27; HS 1.26±0.26, $p<0.03$, n=5; perichondrocytic score: control 1.91±0.18; HS 1.17±0.23, $p<0.01$, n=5).

Conclusion: Reversal of DNA hypomethylation in RASF inhibits the migratory and invasive properties of the RASF and might be used as a novel therapeutic approach to inhibit cartilage destruction in rheumatoid arthritis.

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Endogenous gp96 in Rheumatoid Arthritis Synovial Fluid Promotes Macrophage Activation Through TLR2 Signaling. Qi Quan Huang[1], Robert Birkett[1], Andrea Dorfleutner[1], Renee E. Koessler[1], Christopher V. Nicchitta[2] and Richard M. Pope[1]. [1]Northwestern University Medical School, Chicago, IL, [2]Duke university Medical Center, Durham, NC

Background/Purpose: We have recently demonstrated that endoplasmic reticulum stress response protein gp96 is highly expressed in joints of patients with rheumatoid arthritis (RA) and that recombinant gp96, purified from *E.coli* activates macrophages primarily via TLR2 signaling. However, no studies have ever documented that the potential TLR ligand expressed in the RA joint is capable of activating through TLR signaling.

Methods: Supernatants from HeLa cells infected with a recombinant adenoviral (Ad) vector expressing gp96 NTD (gp96HeLa) or Ad control supernatants (CMV-HeLa) were harvested. The ability of the gp96-HeLa and gp96 in RA synovial fluids (SFs) to activate HEK-TLR2 (HEK2) and HEK-TLR4 (HEK4) cell lines and human and murine macrophages was determined by the activation of NF-kB and the expression of TNFa, IL-6 or IL-8. Cell surface gp96 was identified by flow cytometry.

Results: RA SFs induced the expression of TNFa and IL-8 ($p < 0.01$) by control macrophages, and this activation was suppressed by neutralizing antibodies to TLR2 ($p<0.05$) and TLR4 ($p=0.06$). To determine if endogenous gp96 in RASF mediates macrophage activation, SFs were stratified on the basis of gp96 concentration, quantified by ELISA, and macrophage activation examined. RA SFs with gp96 concentrations >800 ng/ml (n=4), but not those with lower concentrations of endogenous gp96, demonstrated significant suppression by a neutralizing anti-gp96 antiserum for both TNFa ($p<0.03$) and IL-8 ($p<0.03$) mRNA. RA SF was also capable of activating HEK2 and HEK4 cells. However, only HEK2 activation by the RA SFs with gp96 >800 ng/ml were suppressed by pre-incubation of the SFs with the neutralizing anti-gp96 antiserum ($p<0.02$). Further, macrophages isolated from SFs of RA patients expressed increased cell surface gp96, compared with monocytes from RA or healthy donor peripheral blood. Neutralizing gp96 antibody suppressed the spontaneous expression of TNFa by RA SF macrophages compared with control rabbit serum ($p<0.05$), suggesting that cell surface gp96 contributed to the constitutive activation observed with RA SF macrophages. To confirm the ability of mammalian expressed gp96 to activate through TLR2, gp96-HeLa activated HEK2, but not HEK4 cells, while CMV-HeLa activated neither cell line. The HEK2 activation was suppressed by a neutralizing anti-gp96 antibody. Additionally gp-96-HeLa,

but not CMV-HeLa, activated human macrophages, that was inhibited by neutralizing antibody to TLR2, but not TLR4. Lastly, gp96-HeLa activated murine bone marrow derived microphages from WT and TLR4-/- mice, but not TLR2-/- mice. Together these observations document that gp96 in RA SF and mammalian cell-expressed gp96, in the absence of endotoxin, is an agonist of TLR2 signaling.

Conclusion: These data for the first time document the presence of a functional, endogenous TLR2 ligand in inflamed RA joints, employing RA SFs and RA SF macrophages. Data also demonstrates inhibition of gp96 in RA SF or RA SF macrophages resulted in reduced macrophage activation. These observations document the potential role of endogenous TLR ligands in the pathogenesis of RA and support targeting the TLR2 signaling pathway as a therapeutic option in RA.

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Functional Changes of Bone Marrow Derived Mesenchymal Stem Cell Through Adipogenesis. A Possible *in Vitro* Model of Bone Edema in Rheumatoid Arthritis. Satoshi Yamasaki[1], Akitomo Okada[2], Tomohiro Koga[1], Shin-ya Kawashiri[1], Mami Tamai[1], Hideki Nakamura[1], Tomoki Origuchi[1] and Atsushi Kawakami[2]. [1]Nagasaki University School of Medicine, Nagasaki, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Background/Purpose: Bone oedema is a pathological change in rheumatoid arthritis (RA) that is detectable by magnetic resonance imaging. A histological examination of the lesion revealed that adipose tissue, which normally occupies the bone cavity, is replaced by inflammatory cells such as monocytes, fibroblasts, and osteoclasts. Mesenchymal stem cell (MSC), which is abundant in bone marrow, is a multi-potent stem cell that can differentiate into adipocytes. In the present study, we tested the roles of MSC in the formation of bone oedema, and in the onset and progression of RA.

Methods: Adipogenesis of bone marrow-derived human MSC was induced by standard adipogenic induction medium (hMSC Differentiation BulletKit", Adipogenic, Lonza Walkersville Inc.) in the presence or absence of cytokines including tumor necrosis factor α (TNFα), interleukin (IL)-1β, IL-6, and Transforming growth factor β (TGFβ). The transcript makers for adipogenesis such as *ppar*, *ap2* and *lpl* were determined by polymerase chain reaction. The cytokine productions from MSC were comprehensively analyzed by Human Inflammation Antibody Array 3 (RayBiotech, Inc.), and further confirmed by ELISA. The wound-healing assay was performed to determine the locomotive abilities. The expression of F-actin were evaluated by fluorescent Phalloidin to examine the expression and structures of stress fibers.

Results: TNFα, IL-1β, IL-6 and TGFβ strongly inhibited the adipogenesis of MSC, however, the mRNA expression levels of adipogenesis gene markers in the MSC treated with these cytokines were comparable with the non-treated cell. IL-6 production from MSC was significantly reduced after the adipogenesis induction. The wound-healing assay demonstrated that the mobility of MSC after adipogenesis was clearly reduced compared to that of undifferentiated MSC. Consistent with these findings, the structure of stress fibers visualized by F-actin staining was disrupted in MSC after adipogenesis.

Conclusion: The facts that the inflammatory cytokines blocked the adipogenesis of MSC imply that inflammation contributes to the formation of bone oedema through the replacement of adipose tissue with undifferentiated MSC. Secondly, adipogenesis attenuates the abilities of MSC to produce IL-6 and to migrate, which suggest that bone oedema containing undifferentiated MSC can produce IL-6 and invade into surrounding tissues just like a pannus in RA joint. Therefore, bone oedema should be regarded as a hallmark of active RA and an important therapeutic target for the disease.

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Dopamine D2-Like Receptor Signaling Inhibits Human Osteoclast Differentiation From Monocytes. Kentaro Hanami[1], Kazuhisa Nakano[2], Kunihiro Yamaoka[1], Kazuyoshi Saito[1] and Yoshiya Tanaka[1]. [1]University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, [2]UCSD School of Medicine, La Jolla, CA

Background/Purpose: Osteoclasts in the synovium of rheumatoid arthritis (RA) play an important role for bone destruction of the affected joints. It is known that increased sympathetic nervous activity increases both osteoclast differentiation and osteoclast activity, leads to bone loss. A major neurostransmitters dopamine transmits signals via five different seven-transmembrane G protein-coupled receptors termed D1-D5, modifying cAMP levels in the cell. However, the involvement of sympathetic nervous system in bone metabolism remains unknown. Therefore, we have assessed the relevance of dopaminergic signaling to differentiation and function of human osteoclasts using chemical compounds that modify the dopamine signaling.

Methods: Human $CD14^+$ cells isolated from peripheral blood mononuclear cells (PBMCs) from healthy donor were cultured with M-CSF (50ng/ml) and RANKL (50ng/ml) for 14 days to obtain osteoclast-like cells. Multinuclear cells positive for TRAP-staining were counted under microscope as osteoclast-like cells and absorptive function was evaluated by pit formation assay. Dopamine-receptor subtypes on $CD14^+$ cells were analyzed by flow cytometer. Intracellular cAMP concentrations of $CD14^+$ cells cultured for 4 days with M-CSF were measured using a cAMP enzyme-immunoassay kit.

Results: All dopamine receptor subtypes were similarly expressed on human $CD14^+$ cells. When $CD14^+$ cells were cultured with M-CSF for 4 days, further enhanced expression of all subtypes was observed. By the addition of dopamine (0.1–100nM) to the culture from day 4 onwards, the number of TRAP-positive cells decreased in a dose-dependent manner and maximum reduction from 122 ± 12 /cm^2 (mean $\pm$ SEM) in controls to 29 ± 8 /cm^2 ($p<0.01$) was observed at 10 nM of dopamine. When D2-like receptor agonists, such as pramipexole (5–500pg/ml) or quinpirole (0.1–10nM), were added, the number of osteoclast-like cells also decreased in a dose-dependent manner. This dopamine-mediated decrease of osteoclast-like cells was inhibited by pretreatment with pertussis toxin, a Gai inhibitor or haloperidol, a D2-like receptor antagonist, but not with a D1-like receptor antagonist SCH-23390. Intracellular cAMP concentration was also decreased with addition of pramipexole at day 4 in a dose-dependent manner, while a D1-like receptor agonist SKF38393 had no effect on both intracellular cAMP and osteoclast differentiation. Furthermore, the total pit areas per dentin slice also markedly decreased with the addition of dopamine, pramipexole, or quinpirole from day 4 onwards.

Conclusion: We here demonstrate that dopaminergic D2-like receptor signaling directly inhibits osteoclast differentiation and function with decrease cAMP levels in the pre-osteoclast. From these results, we first document the pivotal mechanism of regulation of osteoclasts through sympathetic nervous system and a novel therapeutic target for bone destruction in RA as well as osteoporosis.

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Downregulation of Mcl-1 by Ursolic Acid, a Pentacyclic Triterpenoid, Sensitizes Rheumatoid Arthritis Synovial Fibroblasts for TRAIL-Induced Apoptosis. Carolyn Zielinski, Maria Beamer and Salahuddin Ahmed. Department of Pharmacology, University of Toledo College of Pharmacy & Pharmaceutical Sciences, Toledo, OH

Background/Purpose: In rheumatoid arthritis (RA), enhanced expression of Mcl-1 contributes significantly to the resistance of synovial fibroblasts to apoptosis. In the present study, we evaluated the effect of ursolic acid (UA), a potent anti-inflammatory pentacyclic triterpenoid, on TRAIL-induced apoptosis in RA synovial fibroblasts.

Methods: Effects of UA (2.5–20 μM) and TRAIL (100 ng/ml), alone or in combination, on the cultured RA synovial fibroblast morphology and cell viability were determined through 72 hours of observation by microscopy and a colorimetric MTT cell viability assay. Caspase-3 activity was determined by a colorimetric assay. Apoptosis was measured by the cleavage of poly-ADP-ribose polymerase (PARP). Western blotting was used to evaluate the apoptosis mediators, Bcl-2, Mcl-1, Noxa, and Bax; the cell survival protein Akt; and nuclear translocation of nuclear factor-κB (NF-κB).

Results: UA (2.5–20 μM) decreased the cell viability of RA synovial fibroblasts in a dose-dependent manner and synergistically enhanced TRAIL-induced cell death by ~15% as compared to the UA alone treated group. Importantly, UA (5–20 μM) selectively induced RA synovial fibroblast Mcl-1 degradation within 24 hours of treatment, with no marked effect on the expression levels of Bcl-2 or Bax ($p<0.05$; $n=3$–5). In addition, UA treatment dose-dependently induced the expression of BH3-only Noxa, which may partly contribute to the inhibition of Mcl-1 expression by UA ($p<0.05$; $n=3$). Inhibition of Mcl-1 by UA resulted in the sensitization of RA synovial fibroblasts to TRAIL-induced PARP cleavage and apoptotic cell death. The addition of MG132 (a proteasome inhibitor; 10 μM) blocked the inhibitory effect of UA on Mcl-1 expression and downstream apoptotic events, implicating the proteasomal degradation of Mcl-1 as a fundamental mechanism of RA synovial fibroblast sensitization to apoptosis by UA. Furthermore, evaluation of the signaling events showed that UA specifically blocked the constitutive and TRAIL-activated phospho-Akt expression and the nuclear translocation of NF-κB to induce apoptosis in RA synovial fibroblasts.

Conclusion: Our novel findings indicate that UA itself induces apoptosis and further sensitizes RA synovial fibroblasts to TRAIL-induced apoptosis by specifically blocking Mcl-1 expression partly through Noxa expression. Thus, UA may be a promising adjunct therapeutic option in regulating the invasive growth of synovial fibroblasts in RA.

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Expression Levels of the Nicotinic Acetylcholine alpha7 Receptor on Monocytes and Synovial Tissue of Rheumatoid Arthritis Patients. Frieda. A. Koopman, Maria J. H. de Hair, Danielle M. Gerlag, Paul P. Tak and Margriet Vervoordeldonk. Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: The cholinergic anti-inflammatory pathway is a potential new therapeutic target for the treatment of rheumatoid arthritis (RA). Preclinical studies have confirmed the therapeutic potential of targeting the alpha 7 subunit of the nicotinic acetylcholine receptor family (α7nAChR). Agonists of the nAChR are known to inhibit the production of pro-inflammatory cytokines from human monocytes and macrophages through the stimulation of alpha7 subunit in vitro. In view of the possible new treatment options, we investigated the expression of the α7nAChR on monocytes of RA patients. In addition, we evaluated the effect of methotrexate (MTX) treatment on the expression levels.

Methods: Monocytes from healthy subjects (n=9) and RA patients (n=9) were isolated from fresh blood using density gradient fractionation. These patients used methotrexate (MTX) monotherapy. Monocytes were analysed by flow cytometry using CD14-APC (1:12.5) and α-bungarotoxin-FITC-labeled (α-bgt-FITC, 1:10) antibodies. In addition, synovial tissue was collected from early RA patients (n=18). Synovial tissue was also available from 6 of these 18 patients after 6 months, when patients were using MTX monotherapy. Frozen sections were stained for α7nAChR using the polyclonal rabbit anti-α7nAChR antibody (Abcam, 2 ng/ml) and evaluated by digital image analysis.

Results: The α7nAChR could be detected on monocytes from both RA patients and healthy subjects (mean CD14+/α-bgt+ cells: 49.7% [range 1.44–94.1] versus 44.05% [range 10.26–95.52], respectively; P=0.75). Of interest, significantly lower α7nAChR expression ($r = -0.831$, $p = 0.034$) was observed after MTX treatment with a dose-dependent effect, independent of DAS28 values. The α7nAChR expression in the RA synovium was also significantly reduced after 6 months of MTX treatment (mean α7nAChR positive cells: 2334 [range 714–3840] versus 1639 [range 188–3363], p=0.03).

Conclusion: The α7nAChR is expressed by peripheral blood monocytes in health and disease, consistent with the view that the cholinergic anti-inflammatory pathway plays an important regulatory role in the immune system. MTX treatment reduces the expression levels of α7nAChR both in the peripheral blood and in the synovium, suggesting an unfavorable effect of MTX on this pathway.

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***RasGRP1* and *RasGRP3* Expressed in Lymphocytes From Rheumatoid Arthritis Patients Have An Anti-Inflammatory Role.** Marie-Laure Potier[1], Thibault Vandhuick[2], Céline Derambure[1], Martine Hiron[1], Olivier Boyer[1], Xavier Le Loët[2], Olivier Vittecoq[2] and Thierry Lequerré[2].[1] Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [2]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France

Background/Purpose: RasGRP is a member of the CDC25 family of Ras guanyl nucleotide exchange factors. RasGRP1 is expressed in T and B cells whereas RasGRP3 is only expressed in B cells. These proteins are involved in T cell receptor and B cell receptor signalling. Indeed, Ras activation stimulates various effector systems, leading to changes in genes expression which are critical for T or B cell development and activation during the cellular immune response. In previous studies, it has been shown that *RasGRP1* and *RasGRP3* were dysregulated in peripheral blood mononuclear cells (PBMC) and synovium from rheumatoid arthritis (RA) patients leading to the question of *RasGRP1* and *RasGRP3* involvement in RA pathophysiology. To measure *RasGRP1* and *RasGRP3* gene expression level in B and T cells from both RA and spondylarthropathy (SpA) patients compared to healthy controls (HC) in order to confirm their dysregulation in RA.

Methods: PBMC were isolated from whole venous blood of 24 RA patients [53 ± 15 years old (yo)] with active disease (DAS28 = 4.98 ± 1.32), 18 patients with active SpA (45 ± 12 yo; BASDAI = 55.2 ± 16.1 / 100) and 19 HC (32 ± 9 yo). After negative cell selection, total RNA from B ant T cells were extracted. Immunofluorescence staining was performed to check the cell purity by flow cytometry. *RasGRP1* and *RasGRP3* expression levels were measured by qRT-PCR and their transcripts were compared by PCR.

Results: *RasGRP1* was more expressed in T cells than in B cells (x 3.5; $p<0.0001$) while *RasGRP3* was more expressed in B cells than in T cells (x 8; $p<0.0001$). Moreover, *RasGRP1* was significantly overexpressed in T cells from RA ($p<0.05$) and SpA ($p<0.005$) patients in comparison with those from HC. Surprisingly, *RasGRP1* was also significantly overexpressed in B cells from RA patients ($p<0.05$) in comparison with those from HC. *RasGRP3* expression level was similar in RA or SpA patients and HC whatever the cellular lineage (B and T cells). Moreover, *RasGRP1* expression level in T cells was inversely correlated with the disease activity measured by DAS28 in RA patients ($p<0.05$). Otherwise, two *RasGRP1* variants are expressed in T cells from RA patients compared to HC. Moreover, a minority of RA patients have *RasGRP3* full length transcript in B cells. Indeed, we found the major form of 1.6 Kb expressed both in controls and RA patients. Nevertheless, this shorted variants remains to identify.

Conclusion: This study has shown for the first time the *RasGRP1* and *RasGRP3* overexpression respectively in human T cells and B cells. Moreover, *RasGRP1* is overexpressed in T and B cells from RA patients and only in T cells from SPA patients. Furthermore, we identified different *RasGRP1* and *RasGRP3* variants in B and T cells from RA patients compared to HC; these variants correspond to deletions of exons that remain to be confirmed. Otherwise, the inverse correlation between *RasGRP1* expression in T cells from RA patients and disease activity score confirms the hypothesis of the anti-inflammatory role of RasGRP1. In addition, *RasGRP1* expression in B cells induces apoptosis of these one. Therefore, specific *RasGRP1* overexpression in B and T cells opens broad perspectives for research and therapy.

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Circadian Rhythms of Cellular Immunity In Rheumatoid Arthritis. Cornelia M. Spies[1], Timo Gaber[1], Paula Hoff[1], Jeannine Mazuch[1], Bert Maier[1], Martin Hahne[1], Cindy Strehl[1], Cam Loan Tran[1], Natascha Soboleva[1], Alexander Stoehr[2], Ferenz L. Lohanatha[1], Markus Wagegg[1], Monique Fangradt[1], Manuela Jakstadt[1], Doerte Huscher[2], Gerd R. Burmester[1], Jacqueline Detert[1], Achim Kramer[1] and Frank Buttgereit[1]. [1]Charité – Universitätsmedizin Berlin, Berlin, Germany, [2]German Rheumatism Research Center (DRFZ), Berlin, Germany

Background/Purpose: The knowledge about circadian rhythms of clinical findings and humoral immunity in rheumatoid arthritis (RA) has already led to the development of glucocorticoid chronotherapy (Buttgereit et al., Lancet, 2008). In contrast, there is little information on circadian rhythms of cellular immunity. For this reason, in this pilot study we investigated cellular, humoral and molecular circadian parameters in postmenopausal female patients with RA in comparison to healthy controls.

Methods: Peripheral blood samples from postmenopausal female patients with active RA (DAS 28 ≥ 4.2) (n=5) and postmenopausal female healthy controls (n=5) were taken every 2 hours over 24 hours for flow cytometric analysis, multiplex suspension array of 28 cytokines and quantitative RT-PCR of clock gene expression in isolated CD14+ monocytes. Furthermore, macrophages were lentivirally transduced with a *Bmal1*-promotor driven luciferase reporter construct to analyze endogenous circadian rhythm dynamics. Statistical analysis was performed by Cosinor analysis of the groups.

Results: The clock gene *RevErbα* displayed a significant circadian expression pattern in both RA patients and healthy subjects, whereas *Per2* and *Per3* were rhythmically expressed in the control group only. The endogenous circadian rhythm of macrophages of RA patients was unchanged to healthy controls regarding period length, whereas the amplitude tended to be lower. The frequency of *CD3-CD56+ natural killer (NK) cells, Interleukin-8 Receptor (IL-8R) expressing CD4+ T helper and CD8+ cytotoxic T cells*, respectively, and *CXCR4 expressing CD4+ T helper and CD8+ cytotoxic cells*, respectively, showed a significant circadian rhythm in both RA-patients and healthy subjects. In contrast, a significant circadian rhythm was detectable for *CD3+CD56+ NK T cells* only in healthy controls and for *IL-8R+ monocytes* only in RA patients. Of note, *CCR7* did not show a circadian expression. Using multiplex suspension array of different cytokines and chemokines, a significant circadian variation was detectable only for the expression of *MCP-1* in healthy controls.

Conclusion: Our findings show for the first time that clock gene expression and endogenous circadian rhythms in immune cells of RA patients are disturbed. In particular, NK cells and chemokine receptor expressing cells display circadian rhythms of expression with characteristic peak phases.

Exclusive detection of significant rhythms in healthy subjects may indicate a loss of "normal" rhythm in RA, whereas exclusive detection in RA patients may suggest an establishment of "inflammatory" rhythms. These findings provide new insights into the chronobiology of RA and may have therapeutic implication.

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Aberrant Basal and TLR-Stimulated Expression of TSLP in Rheumatoid Synovial Fibroblasts. Michele Bombardieri[1], Yvonne NW Kam[1], Andrew Filer[2], Christopher D. Buckley[2] and Costantino Pitzalis[1]. [1]Centre for Experimental Medicine and Rheumatology, QMUL, London, United Kingdom, [2]School of Immunity and Infection, MRC Center for Immune Regulation, Birmingham, United Kingdom

Background/Purpose: Thymic stromal lymphopoietin (TSLP) is an interleukin-7-like cytokine which is a strong activator of dendritic cells mainly leading to a Th2 polarization. Recent studies in the collagen-induced arthritis (CIA) model demonstrated that TLSP is an important pro-inflammatory cytokine capable of exacerbating disease severity via a T-cell dependent mechanism. Here we investigated the expression of TSLP and its receptor (TSLPR) in the synovium of rheumatoid arthritis (RA) patients and in rheumatoid synovial fibroblasts (RASF), in basal conditions and upon stimulation with Toll-like receptors (TLR) ligands.

Methods: mRNA expression of TSLP in RASF, osteoarthritis (OASF) and RA dermal fibroblasts (RADF) in basal conditions or upon stimulation with TLR2, TLR3 and TLR4 ligands was assessed by Taqman PCR (QT-PCR). Intracellular and soluble TSLP protein expression was assessed by immunocytochemistry and ELISA, respectively. The expression of TSLP and TSLPR in the rheumatoid synovium of 40 RA patients was investigated by QT-PCR and immunohistochemistry.

Results: RASF and, to a lesser extent OASF, displayed significantly higher constitutive mRNA expression compared to RADF (between 8–16 fold basal increase in RASF vs RADF). In vitro stimulation of TLR3 and TLR4, but not TLR2 on RASF led to strong induction of TSLP (~20-fold increase with TLR3) mRNA expression which peaked at 8h and return to baseline values at 48h. In response to TLR3, cytoplasmic staining of TSLP was strongly increased in RASF but not RADF, while soluble TSLP was time-dependently released in the supernatant of TLR3-stimulated RASF (~100pg/ml) but was undetectable in RADF. Finally, expression of TSLP mRNA was observed in all the RA samples examined while TSLPR was significantly increased in patients with follicular synovitis.

Conclusion: Here we demonstrated that the pro-arthritogenic and pro-inflammatory IL-7-like cytokine TSLP and its receptor TSLPR are abundantly expressed in the rheumatoid synovium. In addition, we showed that RASF but not RADF display an aberrant expression of TSLP in basal conditions which is further stimulated upon TLR3 and TLR4 ligations. Overall, these data strongly support a pivotal role for RASF in the dysregulated production of TSLP in the rheumatoid synovium, suggesting that the TSLP/TSLPR pathway contributes to chronic inflammation in RA.

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EBV Infection In the Rheumatoid Synovium: Relationship with Ectopic Lymphoid Structures, In Situ Autoantobody Production and CD8 T Cell Activation. Cristina Croia[1], Michele Bombardieri[1], Barbara Serafini[2], Eliana M. Coccia[2], Martina Severa[2], Stephen Kelly[1], Francesca Aloisi[1] and Costantino Pitzalis[1]. [1]Centre for Experimental Medicine and Rheumatology, QMUL, London, United Kingdom, [2]Istituto Superiore di Sanita', Rome, Italy

Background/Purpose: The ubiquitous ψ-herpesvirus Epstein-Barr virus (EBV) infects B cells and modifies their differentiation programme leading to B cell activation and immortalization. Increasing evidence supports a link between EBV and common B cell-related autoimmune diseases, i.e. multiple sclerosis (MS), myasthenia gravis (MG) and Sjogren's syndrome. Recent data demonstrated that ectopic B cell follicles in the brain of MS and the thymus of MG patients are preferential sites of EBV persistence and reactivation. Here we aimed to investigate the role of EBV in B cell dysregulation and autoimmunity in the RA synovium by analysing its relationship with ectopic lymphoid structures (ELS), B cell infiltration, in situ autoantibody production and cytotoxic immune response.

Methods: Forty RA synovial biopsies were characterized for the degree of B cell infiltration, the presence of ELS with germinal center-like structures (GC-LS) and the status of EBV latent and productive infection using immunohistochemistry (IHC), double immunofluorescence (IF), in situ hybridization (ISH) and real-time RT-PCR.

Results: Using IHC and IF all 10 RA samples with GC-LS and 17 with high/medium B cell infiltration displayed evidence of EBV infection. Conversely, EBV+ cells were not detected in 13 RA samples with low/absent B cells. Latent EBV infection (LMP2A and EBER) was detected in a significant proportion of B cells, particularly within ELS. Using standard real-time RT-PCR, 40% of RA cases with high B cell infiltration were found LMP2A+, while after selective pre-amplification we observed that 100% of the RA cases were positive for LMP2A and LMP1 and 60% for EBER. In addition, numerous CD138+ plasma cells expressed the EBV early lytic antigen BFRF1 and were in close contact with CD8+ and/or granzyme B+ cells. Interestingly, a significant proportion of BFRF1+ plasma cells displayed reactivity against citrullinated fibrinogen. Finally, markers of productive viral infection (gp350/220, p160) were seldom found in RA samples with ELS.

Conclusion: Overall, these findings suggest that a dysregulated EBV infection likely exert an important role in the activation and differentiation of auto-reactive B cells within the RA synovium and might be partly responsible for the activation of a cytotoxic T cell response.

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Chemerin Activates Fibroblast-Like Synoviocytes In Patients with Rheumatoid Arthritis. Kayoko Kaneko[1], Yoshishige Miyabe[1], Aiko Takayasu[1], Shin Fukuda[1], Chie Miyabe[1], Masashi Ebisawa[1], Waka Yokoyama[1], Kaori Watanabe[2], Toshio Imai[3], Kenzo Muramoto[4], Yuya Terashima[5], Takahiko Sugihara[6], Kouji Matsushima[5], Nobuyuki Miyasaka[2] and Toshihiro Nanki[1]. [1]Graduate School of Medicine and Dentistry, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan, [2]Tokyo Medical and Dental University, Tokyo, Japan, [3]KAN Research Institute, Inc., Chuo-ku, Kobe, Japan, [4]Eisai Co., Ltd,, Tsukuba-shi, Ibaraki, Japan, [5]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [6]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

Background/Purpose: Chemerin is a chemotactic agonist identified as a ligand for ChemR23, expressed on macrophages and dendritic cells (DC). Chemerin is produced as a precursor protein, prochemerin, and is converted into active chemerin through the C-terminal six or seven amino acids processing by protease, produced by neutrophils and mast cells in inflammatory sites. In this study, we analyzed the expression of chemerin and ChemR23 in the synovium of rheumatoid arthritis (RA), and the stimulatory effects of chemerin on fibroblast-like synoviocytes (FLS) from RA

Methods: Expression of chemerin and ChemR23 in the RA and osteoarthritis (OA) synovium was examined by immunohistochemistry. ChemR23-expressing cells in the RA synovium were identified by double staining analysis. ChemR23 expression by FLS was evaluated by western blotting. Expression of chemerin, interleukin-6 (IL-6), CCL2 and matrix metalloproteinase-3 (MMP-3) from FLS was analyzed by enzyme-linked immunosorbent assay. FLS cell motility was evaluated by scrape motility assay. Phosphorylation of p44/42 mitogen-activated protein kinase (ERK1/2), p38 mitogen-activated protein kinase (MAPK) and Akt in FLS was analyzed by western blotting.

Results: Strong immunohistochemical staining for chemerin was noted on endothelial cells and synovial lining and sublining cells in the RA synovium. Widespread immunostaining for ChemR23 was noted in RA samples, with dense staining on the sublining cells. In contrast, the expression of chemerin and ChemR23 in the synovium of OA was minimal. Double staining analysis showed the expression of ChemR23 on most of $CD68^+$ macrophages, $CD1a^+$ immature DC, and on a few of DC-$LAMP^+$ mature DC. Interestingly, ChemR23 was also expressed on vimentin$^+$ FLS. *In vitro*, chemerin and ChemR23 were expressed on unstimulated FLS. Tumor necrosis factor-a and interferon-g upregulated chemerin production from FLS in dose-dependent manner. Chemerin enhanced the production of IL-6, CCL2 and MMP-3 by FLS, and the cell motility of FLS. The effects of chemerin on FLS were mediated by activation of ERK1/2, p38 MAPK and Akt. Inhibition of the ERK1/2, p38 MAPK, and Akt signaling pathways significantly suppressed chemerin-induced IL-6 production. Moreover, blockade of p38 MAPK and Akt pathways, but not that of ERK1/2, inhibited the chemerin-enhanced cell motility.

Conclusion: Chemerin and ChemR23 interaction may play an important role in the pathogenesis of RA, through the activation of FLS.

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α-Defensin-1 Is Increased in the Synovial Fluid of Rheumatoid Arthritis Patients and Induces IL-6 and IL-8 Expression in Fibroblast-Like Synoviocytes. Joong Kyong Ahn[1], Jiwon Hwang[2], Jaejoon Lee[2], You Sun Lee[3], Chan Hong Jeon[4], Eun-Mi Koh[2] and Hoon-Suk Cha[2]. [1]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul, South Korea, [3]Samsung Changwon Hospital, Changwon, South Korea, [4]Soonchunhyang University College of Medicine, Bucheon, South Korea

Background/Purpose: Fibroblast-like synoviocytes (FLS) play an essential role in the pathophysiology of rheumatoid arthritis (RA). Neutrophils are the most abundant cell type in the acute synovial effusion of RA patients. α-defensin-1 is released into the extracellular milieu from neutrophils during inflammation. Little is known about the role of α-defensin-1 for the development of joint inflammation in RA. Thus, we assessed the concentration of α-defensin-1 in synovial fluid (SF) of RA patients and osteoarthritis (OA) patients and evaluated the association between its concentration and clinical characteristics. We also investigated the effect of α-defensin-1 on the expression of IL-6 and IL-8 in rheumatoid FLS.

Methods: The concentrations of SF α-defensin-1 from 51 RA patients and 21 OA patients were measured using ELISA. Real-time PCR was performed to measure the expression of IL-6 and IL-8 mRNA at 8 hours after stimulation with α-defensin-1(15 ug/ml) in rheumatoid FLS (n=5).

Results: Patients with RA were composed of 47 female (92.1%) and 4 male patients, with a mean age of 54.3 ± 1.8 years, and mean disease duration of 81.1 ± 9.9 months. Forty-one patients (80.4%) were rheumatoid factor positive. Thirty-three patients (64.7%) had erosion on radiographic imaging. The SF α-defensin-1 concentration was significantly increased in RA patients compared to OA patients (39.3 ± 3.5 vs. 18.0 ± 5.6 ng/ml, p=0.002). Seropositive RA patients had significantly higher concentration of SF α-defensin-1 compared to seronegative patients (43.1 ± 3.8 vs. 20.8 ± 5.0 ng/ml, p=0.006). RA patients with ESR>50mm/hr or CRP>2mg/dl had significantly higher concentration of SF α-defensin-1 compared to patients with lower level of ESR or CRP, respectively (46.0 ± 3.9 vs. 21.7 ± 5.0 ng/ml, p=0.001; 48.2 ± 4.4 vs. 29.2 ± 4.7 ng/ml, p=0.005). SF α-defensin-1 concentration was more increased in RA patients with erosive change than non-erosive patients (43.1 ± 4.2 vs. 32.2 ± 5.8 ng/ml), although this difference did not reach statistical significance. There was no significant difference in SF α-defensin-1 level according to disease duration and age at disease onset. Both IL-6 and IL-8 mRNA expressions were significantly increased (13.34 ± 22.89-fold increase and 2.89 ± 1.49-fold increase, respectively, $p < 0.05$) at 8 hrs after α-defensin-1 stimulation in rheumatoid FLS.

Conclusion: SF α-defensin-1 concentration is increased in RA patients, especially in patients with positive RF and higher level of ESR and CRP. α-defensin-1 induced proinflammatory cytokine expression in RA FLS. These findings suggest that α-defensin-1 may play an important role as a potential inflammatory mediator for the development of joint inflammation in RA.

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Extracellular 14-3-3η: An Early Rheumatoid Arthritis Pathogenic Factor. Anthony Marotta[1], Vivian Bykerk[2], Katherine A. Siminovitch[3], Maarten Boers[4], Robert Landewe[5], Désirée van der Heijde[6], Paul-Peter Tak[7], M. C. Genovese[8], Michael E. Weinblatt[9] and Walter P. Maksymowych[10]. [1]Augurex Life Sciences Corp, North Vancouver, BC, [2]Brigham & Women's Hospital, Boston, MA, [3]Mount Sinai Hospital, Toronto, ON, [4]VU University Medical Center, Amsterdam, Netherlands, [5]Academic Medical Center, Amsterdam, Netherlands, [6]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [7]Professor of Medicine/ Director, Division of Clinical Immunology and Rheumatology, Amsterdam, Netherlands, [8]Stanford University Medical Center, Palo Alto, CA, [9]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [10]University of Alberta, Edmonton, AB

Background/Purpose: 14-3-3 proteins are ubiquitously expressed intracellular chaperonins. We previously showed that the η isoform is 1) uniquely expressed in the synovial fluid and serum of patients with inflammatory arthritis 2) differentially expressed in established rheumatoid arthritis (RA) and 3) a novel extracellular mediator that may contribute to the disease process. This study examines 14-3-3η serum levels and its pathophysiological role in early disease.

Methods: Serum 14-3-3η was measured in 37 DMARD-naïve early RA patients, 25 from the Toronto Early Arthritis Cohort (TEACH) and 12 from the intensified-COBRA cohort, and 50 osteoarthritis (OA) controls using an investigational-grade 14-3-3η ELISA. 2-tailed t-tests and Mann-Whitney u-tests were run to compare group differences in serum concentrations. An ROC curve was generated and sero-positivity rates of 14-3-3η, rheumatoid factor (RF) and anti-citrullinated cyclic peptide (anti-CCP) were evaluated. To examine the effects of 14-3-3η on intracellular signalling in monocytes, THP-1 monocytic cells were stimulated with 12.5ng/ml of recombinant human 14-3-3η (0–30min) and activation of the MAPK signalling cascades (ERK, JNK/SAPK and p38) were assessed by immunoblot analysis using phosphospecific antibodies. The mRNA levels of IL-1β, IL-8, CCL2/MCP-1 and CCL4/MIP1- β following 18h incubation with a dose range of 0.10 to 100ng/ml of recombinant human 14-3-3η or vehicle were assessed by RT-PCR. Densitometry was used to measure % change with stimulation above control.

Results: Mean and median 14-3-3η serum concentrations in RA patients [TEACH (3.13 & 0.63ng/ml) and i-COBRA (5.90 & 1.43ng/ml)] were significantly higher than in OA controls (0.32 & < 0.20ng/ml), p-values <0.0006 and <0.0001, respectively. The corresponding areas under the ROC curve were 0.72 (95%CI 0.58–0.86) and 0.87 (95%CI 0.72–1.00) for TEACH and i-COBRA RA patients versus OA. 14-3-3η, RF and anti-CCP positivity were 60%, 32% and 44% in TEACH and 82%, 82% and 82% in i-COBRA. 72% of TEACH and 100% of i-COBRA RA patients were positive for any one of the three markers. Stimulation of THP-1 cells with 14-3-3η activated ERK and JNK/SAPK by 227% and 87% above control at 5 and 2 min, respectively. No activation of p38MAPK was observed at any of the time points. 14-3-3η was associated with potent induction of transcripts of early pro-inflammatory factors, with IL-8 (47% increase at 0.1ng/ml) and MIP-1β (53% increase at 0.25ng/ml) being the most sensitive followed by MCP-1 (44% increase at 0.5ng/ml) and IL-1β (49% increase at 5ng/ml).

Conclusion: 14-3-3η is differentially expressed in the serum of patients with early RA compared to OA controls and is a novel factor that may contribute to pathological processes involved in early disease. 14-3-3η serum expression when combined with standard serological RA tests may mark early RA.

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TNFα Modulates the Expression of Circadian Clock Genes in Rheumatoid Synovial Cells. Kohsuke Yoshida[1], Akira Hashiramoto[2], Nao Shibanuma[3], Kazuko Shiozawa[4] and Shunichi Shiozawa[5]. [1]Kobe University Graduate School of Health Sciences, Kobe, Japan, [2]Kobe University Graduate School of Medicine/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, [3]The Center for Rheumatic Diseases, Kobe University Hospital/Kobe Kaisei Hospital, Kobe, Japan, [4]Rheumatic Diseases Center, Konan Kakogawa Hospital, Kakogawa, Japan, [5]Kobe University Graduate School of Health Sciences and Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Background/Purpose: Circadian rhythm in mammals is organized by transcriptional and/or posttranscriptional machineries regulating the core clock genes including *Clock* (circadian locomotor output cycles kaput), *Bmal1* (brain and muscle Arnt-like protein 1), *Per* (Period), and *Cry* (Cryptochrome). The transcription factor BMAL1/CLOCK complex activates *Per* and *Cry* gene transcription by binding to E-box motif in the promoter region. Thereafter, PER and CRY proteins inhibit the binding of BMAL1/CLOCK complex to E-box in a feedback fashion, resulting in generation of oscillating circadian expression of *Per* and *Cry* genes. We previously showed the regulation between biological clocks and arthritis in that the expression of *Bmal1*, *Per1/2* and *Dbp* (D site of albumin promoter binding protein), also known as a clock controlled gene, was disturbed in the synovium of experimental arthritis in mice, and *Cry* regulated TNFα in mouse embryonic fibroblast (J Immunol. 2010;184:1560–5). Here we examine, by using primary cultured human rheumatoid synovial cell, the effect of TNFα on the expression of circadian clock genes and found that TNFα was the key modulator for the expression of clock genes.

Methods: Primary cultured rheumatoid synovial cells were synchronized upon incubation with 50% horse serum for 2 hours, and then stimulated with TNFα. Total RNA was extracted from synovial cells every 8 hrs until 32 hrs' culture period, and mRNA expression of clock genes (*Bmal1*,*Clock*, *Per1/2*, *Cry1/2*, *Dbp*) were analyzed by real-time PCR. Synovial cells were transfected with the luciferase reporter vector containing the human *Per2* promoter to measure the transcriptional activity of *Per2* gene.

Results: The expression of *Per2* mRNA in unstimulated synovial cells was highest at 24 hrs after serum incubation. However, the expression of *Per2*

mRNA was inhibited between 24 and 32 hrs by the stimulation with TNFα. Further, transcriptional activity of *Per2* gene was significantly inhibited by TNFα by luciferase reporter assay. Since the promoter region of *Per2* gene contains three E-box and another DBP binding motif D-box, we next examined the effect of TNFα on the expression of *Bmal1*, *Clock* and *Dbp* mRNA. As results, the expression of *Dbp* mRNA was significantly inhibited upon incubation with TNFα while those of *Bmal1* and *Clock* were increased, suggesting that inhibition of DBP expression, induced by TNFα, was involved in the inhibition of *Per2* expression in synovial cells as well.

Conclusion: TNFα significantly modulates the expression of circadian clock genes in rheumatoid synovial cells, and thereby may contribute to the pathogenesis of RA.

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TL1A Induces the Production of Follicular Helper T Cells in Rheumatoid Arthritis. Xia Li[1], Rui Liu[1], Qian Wu[1], Jing Zhao[2], Xiaolin Sun[2], Zhanguo Li[3] and Lingyun Sun[1]. [1]The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, China, Nanjing, China, [2]Peking University People's Hospital, Beijing, China, [3]Peking University People's Hospital, 11 Xizhimen South Street, Beijing, 100044, PR China, Beijing, China

Background/Purpose: Tumor necrosis factor (TNF)-like protein 1A (TL1A) is a member of the TNF superfamily which is a T-cell costimulator. It can increase IFN-γ production of $CD4^+$ T cells by acting in synergy with IL-12 and IL-18. Furthermore, TL1A also promotes type 17 T-helper (TH17) cell functions and responses. Follicular helper T (TFH) cells can provide a helper function to B cells, so they play a key role in the pathogenesis of rheumatoid arthritis (RA). The purpose of this study is to examine the hypothesis that TL1A might induce the production of TFH cells in RA.

Methods: Concentrations of TL1A in sera were measured by ELISA. TL1A relative mRNA expression was assessed by RT-PCR and the percentages of $CD4^+CXCR5^+PD\text{-}1^+$ T cells were analyzed by flow cytometry in peripheral blood mononuclear cells (PBMC) from RA patients and healthy controls. PBMC from RA patients were stimulated with different concentrations of TL1A (10ng/ml, 20ng/ml and 50ng/ml) after TCR engagement and then $CD4^+CXCR5^+PD\text{-}1^+$ T cells were evaluated.

Results: The results showed that concentrations of TL1A in sera of RA patients (789.29±622.42ng/ml, n=97) were significantly higher than that of healthy controls (518.12±134.52ng/ml, n=50, $p<0.05$). The relative mRNA level of TL1A from RA patients (5.702±4.342, n=17) was enhanced compared to healthy controls (2.168±3.024, n=11, $p<0.05$). In addition, the percentages of circulating TFH cells from RA patients (9.197%±0.686%, n=23) were increased in comparison with healthy controls (7.029%±0.465%, n=14, $p<0.05$). After TCR engagement the different concentrations of TL1A (10, 20 and 50ng/ml raised circulating TFH cells production compared with no TL1A stimulation(22.92%±6.567%), and 50ng/ml of TL1A(29.17%±7.253%) was more effective than 10ng/ml (26.21%±7.055%) and 20ng/ml (27.84%±7.123%) in inducing TFH cells production(n=6).

Conclusion: These results suggest that increased TL1A expression from RA patients might upregulate circulating TFH cells that support B cell survival and antibody secretion.

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CD15s Expression Pattern in the Synovial Tissue of Patients with Rheumatoid Arthritis and Its Role in RASF Migration. Birgit Zimmermann[1], Sebastian Ullrich[2], Nina Kesel[2], Markus Rickert[3], Jürgen Steinmeyer[3], Stefan Rehart[4], Angela Lehr[4], Udo Schumacher[2], Ulf Müller-Ladner[5] and Elena Neumann[5]. [1]University of Gieβen, Bad Nauheim, Germany, [2]University Medical Center Hamburg, Hamburg, Germany, [3]University Hospital Gieβen and Marburg, Gieβen, Germany, [4]Markus-Hospital, Frankfurt, Germany, [5]Justus-Liebig-University of Gieβen, Bad Nauheim, Germany

Background/Purpose: It is well known that the tetrasaccharide CD15s is a ligand for E-selectin. In the extravasation of leukocytes, this interaction mediates the primary adhesion to the endothelial cells of the vessel wall. Recently, we could show that rheumatoid arthritis (RA) synovial fibroblasts (SF) are able to migrate over a long distance in the SCID-mouse model of RA. This was facilitated by leaving the synovial tissue and migration through the vascular system to distant cartilage matrix followed by cartilage invasion. To elucidate the underlying mechanisms, we analyzed the role of CD15s and E-selectin in the interaction of SF with endothelial cells to characterise the extravasation process of RASF.

Methods: Cultured RASF and synovial tissue of different RA patients were stained for CD15s by immunohistochemistry. To link CD15s expression with general inflammation, the presence of CD15s positive cells was correlated with serum CRP. To show the adherence of RASF to E- and P-selectin, a flow chamber assay was used. RA- and OASF were perfused with different flow rates through a capillary of μ-Slides coated with 30 μl E-, P-selectin solution or 100 % FCS as negative control. Using an inverse microscope and a video camera system, the rolling, tethering and adherent cells were recorded and quantified. Using the SCID mouse model of RA, E-and P-selectin deficient SCID mice as well as normal SCID mice were compared for RASF migration. For this approach, at the ipsilateral site (I) human cartilage was implanted together with RASF and at the contralateral site (C) cartilage without RASF. After 45 days, the implants were removed and evaluated histologically.

Results: Cultured RASF expressed CD15s. Interestingly, CD15s expression on RASF was higher when cultured in RPMI in contrast to culture in DMEM. CD15s was detectable in most RA synovial tissues. The presence of CD15s positive cells in the synovial tissue of RA patients correlated with an increased systemic CRP level. RASF rolling, tethering and adhesion was increased in E-selectin coated slides in comparison to OASF in the flow chamber assay (RASF: 0.55 dyn/cm: 16 cells, 0.89 dyn/cm: 5.5 cells and 1.77 dyn/cm: 3.5 cells per visual field; OASF: 0.55 dyn/cm: 12.5 cells, 0.89 dyn/cm: 1 cell and 1.77 dyn/cm: 1 cell per visual field). No SF bound to P-selectin or FCS coated capillaries were detectable. A reduced RASF invasion was observed in E-/P-Selectin deficient mice at the contralateral, RASF-free implantation side when compared to normal SCID mice after 45 days ($E\text{-/P-selectin}^+$ (I): 1.56±0.64; (C): 2.23±0,60 vs. $E\text{-/P-selectin}^-$: (I) 1.81±0.72; (C):1.69±0.74).

Conclusion: CD15s, a selectin-ligand, was detectable on cultured RASF, and CD15s expressing cells were detectable in the synovium and correlated with increased CRP levels. With respect to RASF migration, the attachment of RASFs to the vessel wall appears to be dependent on E-selectin expression in contrast to P-selectin expression. Therefore, the CD15s/E-selectin interaction seems to be a key step in RASF extravasation.

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Leptin Stimulates Interleukin-6 Production *Via* phosphorylation of Signal Transducer and Activator of Transcription-3 in Rheumatoid Synovial Fibroblasts. Sei Muraoka, Natsuko Kusunoki, Hirahito Endo, Toru Suguro and Shinichi Kawai. Toho University School of Medicine, Tokyo, Japan

Background/Purpose: Leptin is one of the adipose tissue-secreted cytokines (adipocytokines) which regulate central metabolic conditions, however, it has a number of other functions including immune system and inflammation. Serum leptin concentration was elevated and associated with serum C-reactive protein concentration in patients with rheumatoid arthritis (RA) (Yoshino T, et al. *Intern Med* 2011; 50: 269). The aim of this study is to determine the effects of leptin on production of proinflammatory cytokines in rheumatoid synovial fibroblasts (RSF).

Methods: Synovial tissues were obtained at total knee replacement operation from patients with RA who gave written consent to use their tissue for research. RSF were harvested from the synovial tissues of these patients. After 24h incubation with various concentrations of leptin, the productions of interleukin (IL)-1β, tumor necrosis factor (TNF) -α, and IL-6 in the culture medium were detected by respective ELISA kit. An RNAi was introduced into RSF to down-regulate the expression of Ob-Rb. We next examined effect of JAK (Janus tyrosine kinase) -2 inhibitor, AG490 on production of IL-6. Leptin receptor mRNAs were detected by RT-PCR. STAT-3 (Signal transducer and activator of transcription-3) and phosphorylated STAT-3 (p-STAT-3) in RSF were determined by Western blot analysis.

Results: The concentrations of TNF-α and IL-6 were enhanced in concentration-dependent manners by addition of leptin (up to 300nM), however, the concentration of IL-1β was not changed. We detected leptin receptor Ob-Rb and Ob-Re mRNAs by RT-PCR in RSF. Leptin-induced IL-6 production was decreased by Ob-Rb mRNA knockdown in RSF. AG490 also decreased leptin-induced IL-6 production. Since Ob-Rb is a member of IL-6 receptor family, we measured STAT-3 and p-STAT-3 by Western blot analysis. Enhancement of p-STAT-3 by addition of leptin was observed in RSF. This effect was not affected by neutralization of IL-6 by anti-IL-6 antibody.

Conclusion: STAT-3 regulates cell proliferation and migration, and mediates vascular function. In this study, we demonstrated that leptin possibly

is one of the proinflammatory cytokines to up-regulate IL-6 production *via* phosphorylation of STAT-3 in RSF. Leptin and JAK-STAT pathway may represent a new alternative therapeutic target in the treatment of RA.

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Mechanisms Underlying the Generation of Soluble IL-6 Soluble Receptor (sIL-6R) in Rheumatoid Arthritis: mRNA Alternative Splicing and Proteolytic Cleavage As Independent Contributors. Jose Ramon Lamas[1], Luis Rodriguez-Rodriguez[2], Pilar Tornero-Esteban[2], Lydia Abasolo[2], Jezabel Varade[1], Roberto Alvarez-Lafuente[1], Esther Villafuertes[2], Jose Hoyas[2], Elena Urcelay[1] and Benjamin Fernandez-Gutierrez[2]. [1]Hospital clinico San Carlos, Madrid, Spain, [2]Department of Rheumatology, Hospital Clinico San Carlos, Madrid, Spain

Background/Purpose: Given that IL-6 bioactivity is greatly modulated through trans-signalling by sIL-6R/IL-6 complexes, the aim of this study was to describe the contribution of proteolytic cleavage and alternative splicing mechanisms in the generation of soluble forms of IL-6 receptor (sIL-6R) and their pathological relevance in rheumatoid arthritis (RA).

Methods: RA patients were randomly selected from a cohort of subjects previously genotyped for the non-synonymous polymorphism rs8192284 (A>C) of the IL-6R gene resulting in an amino acid change located at the proteolytic cleavage site (D358A). Expression of the membrane-bound IL-6 receptors (IL-6R and gp130) was evaluated in different peripheral blood populations by flow cytometry. Plasma concentrations of sIL-6R, soluble gp130, the sIL-6R/IL-6 complexes and the proteolytic enzyme responsible for the cleavage (TACE/ADAMTS17) were measured by ELISA. The contribution of alternative splicing in the generation of sIL-6R was assessed by qRT-PCR.

Results: No differences were found in IL-6R membrane expression according to the rs8192284 variation. sIL-6R plasma levels were positively associated with the presence of the C allele, AA: 79.36±5.8 ng/ml, AC: 100.50±4.05 ng/ml, CC: 128.9±6.8 ng/ml, $p < 0.0001$. Only 32% of the IL-6 present in plasma was not bound to sIL-6R. The contributions of alternative splicing and TACE concentrations were independent of the genotype studied.

Conclusion: Both mechanisms of sIL-6R generation coexist in RA. The rs8192284 polymorphism determines differences in sIL-6R plasma levels through differential proteolytic cleavage efficiency mediated by TACE. In addition, most IL-6 molecules form IL-6/sIL-6R complexes, suggesting the important contribution of trans-signalling in modulating the biological effects of IL-6 in RA.

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IL-21 and IL-21 Receptor Expression in the Inflamed Synovium From Patients with Rheumatoid Arthritis. Ditte Tornehave[1], Berit O. Krogh[1], Henning Bliddal[2], Niels H. Søe[3] and Dorthe Lundsgaard[1]. [1]Novo Nordisk A/S, Måløv, Denmark, [2]Copenhagen University Hospital at Frederiksberg Hospital, Frederiksberg, Denmark, [3]Gentofte Hospital, Hellerup, Denmark

Background/Purpose: The aim of the present study was to investigate expression of IL-21 and IL-21 receptor (IL-21R) and to characterize receptor-positive cells in the synovium from patients with rheumatoid arthritis (RA).

Methods: In-situ hybridization studies investigating IL-21 and IL-21R mRNA expression were performed on synovial tissues from patients with RA (n=6) and normal synovial samples (n=2). Immunohistochemical studies investigating IL-21R protein expression were performed on synovial tissues, including synovectomy samples, from patients with RA (n=26) and normal synovial samples (n=4). Characterization of the IL-21R-positive cells was performed by double immunofluorescence staining on arthroscopic and synovectomy samples from RA patients (n=9) and normal synovial samples (n=5) with markers for T cells (CD3), B cells (CD20), plasma cells (CD138), and macrophages (CD68).

Results: IL-21 mRNA expressing cells were present in the synovium from 5/6 patients with RA but not in normal synovial samples (0/2). IL-21 mRNA positive cells were present only in lymphoid aggregates in the sublining layer. IL-21R mRNA expressing cells were present in the synovium from 6/6 patients with RA and 2/2 normal samples. IL-21R mRNA expressing cells were present in lymphoid aggregates and stroma in the sublining layer and in the lining layer. IL-21R immunopositive ($IL\text{-}21R^+$) cells were present in the synovium from 26/26 patients with RA and in 4/4 normal samples. The $IL\text{-}21R^+$ cells in the sublining layer were present in lymphoid aggregates and stroma in 22/24 and 18/26 RA patients, respectively. Few $IL\text{-}21R^+$ cells were present in the stroma of the sublining layer from normal synovium. In the synovial lining $IL\text{-}21R^+$ cells were present in 22/22 patients with RA and in 4/4 normal samples. There was an overlap in distribution of IL-21R mRNA and protein in RA and normal synovium. Double immunostainings for IL-21R and T cells, B cells, plasma cells and macrophages revealed presence of $IL\text{-}21R^+CD3^+$ T cells in the synovium from 9/9 RA patients with 25–50% double-positive T cells. $IL\text{-}21R^+CD20^+$ B cells were present in 7/9 RA patients with close to 50% double-positive B cells. $IL\text{-}21R^+CD138^+$ plasma cells were present in 6/9 RA patients with close to 50% double-positive plasma cells. The $IL\text{-}21R^+CD20^+$ B cells and $IL\text{-}21R^+CD138^+$ plasma cells were found in lymphoid aggregates in close proximity to $CD3^+$ T cells. $IL\text{-}21R^+CD68^+$ macrophages were present in the sublining layer in 9/9 RA patients and 1/5 normal samples with 25–50% double-positive macrophages. The $IL\text{-}21R^+CD68^+$ macrophages were present in lymphoid aggregates and stroma. In 8/9 RA patients and 5/5 normal samples all $IL\text{-}21R^+$ cells in the synovial lining were $CD68^+$ macrophage-like synoviocytes.

Conclusion: We found that both IL-21 and IL-21R expressing cells are present in the inflamed synovium from RA patients. The $IL\text{-}21R^+$ cells have been identified as T cells, B cells, plasma cells and macrophages. These data suggest that in the synovium, locally produced IL-21 can activate $IL\text{-}21R^+$ T cells, B cells, plasma cells and macrophages. IL-21 therefore represents a promising target for treatment of rheumatoid arthritis.

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Regulation of DNA Methylation by Pro-Inflammatory Cytokines in Rheumatoid Arthritis. Kazuhisa Nakano[1], David L. Boyle[2] and Gary S. Firestein[2]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]UCSD School of Medicine, La Jolla, CA

Background/Purpose: Rheumatoid arthritis fibroblast-like synoviocytes (RA FLS) exhibit a unique aggressive phenotype that contributes to the cytokine milieu and joint destruction. While the pathogenesis of partial transformation is not fully understood, epigenetic mechanisms are one possible explanation. DNA methylation is a major epigenetic determinant that modulates gene expression, and abnormal methylation is associated with dyregulated cell function. DNA methyltransferases (DNMTs) are critical enzymes involved in establishing proper control of DNA methylation. Global hypomethylation has been described in RA FLS, but the mechanisms have not been defined. We hypothesized that persistent exposure of pro-inflammatory cytokines can contribute to DNA hypomethylation through decreased of DNMT expression, thereby contributing to the aggressive phenotype of FLS.

Methods: FLS were obtained from RA and osteoarthritis (OA) synovium at total joint replacement and studied in the 4th through 7th passage. Gene expression was determined by qPCR and protein expression by Western blot analysis. Nuclear extracts and genomic DNA were purified from control or stimulated FLS. DNMT activity was measured with a functional assay and global methylation was determined by an immunoassay that detects methylcytosine.

Results: Unstimulated RA and OA FLS expressed similar amounts of DNMT1, -3a, and -3b mRNA (n=10 each; n.s.). Western blot showed abundant DNMT1 and DNMT3a protein, but only trace amounts of DNMT3b. DNMT1 and DNMT3a mRNA expression were decreased when FLS were stimulated with IL-1β (2 ng/ml) for 24 hr (49±8% and 58±6% respectively; $p<0.01$). Dose responses with IL-1 showed significant suppression of DNMT expression with concentrations as low as 1 pg/ml. DNMT mRNA levels decreased rapidly, with significant suppression after 2 to 8 hrs of IL-1 stimulation. DNMT functional activity was also decreased by IL-1 when FLS were cultured continuously for 14 days with IL-1β (74.0±6.5% of control, n=11, p=0.0012). 14-days exposure to the DNMT1 inhibitor 5-aza-dC decreased global DNA methylation in OA FLS (78.7±10% of control, n=6, $p<0.05$), but not in RA FLS (105±6.7% of control, n=6, p=0.22).

Conclusion: Exposure to pro-inflammatory cytokines in the synovium decreases DNMT expression and potentially suppresses DNA methylation. The inability of 5-aza-dC to alter RA FLS global methylation suggests that DNMT3a is primarily responsible for DNA methylation in RA, while DNMT1 contributes to methylation OA FLS. These data suggest that the rheumatoid synovium can imprint FLS by altering DNA methylation and potentially inducing a more aggressive phenotype.

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A Transcriptional Profile Present in CD4+ T-Cells of Patients with Undifferentiated Arthritis Predicts the Future Development of Seronegative Rheumatoid Arthritis and Implicates IL-6 in Disease Evolution. Arthur G. Pratt[1], Dan Swan[2], Sarah Richardson[1], Gillian Wilson[3], Catharien Hilkens[1], David Young[1] and John D. Isaacs[1]. [1]Newcastle University, Newcastle Upon Tyne, United Kingdom, [2]Newcastle University, Newcastle-upon-Tyne, United Kingdom, [3]Freeman Hospital, Newcastle-upon-Tyne, United Kingdom

Background/Purpose: The diagnosis of seronegative RA remains challenging in the early arthritis clinic. Recent GWAS data strongly implicate CD4+ T-cells in the pathogenesis of seropositive RA. Our objectives were to identify biomarker(s) present in CD4+ T-cells, or in serum, that identified patients with undifferentiated arthritis (UA) destined to develop seronegative RA.

Methods: Total RNA was isolated from highly purified peripheral blood CD4+ T-cells of early arthritis clinic patients. Paired serum samples were also stored. Microarray analysis of 111 RNA samples was performed using the Illumina® platform, and differential transcript expression confirmed using real-time quantitative PCR (discovery cohort). Machine learning approaches were used to test the utility of a classification model amongst an independent validation cohort of 62 patients presenting with UA. Cytokine measurements were performed using a highly sensitive electro chemo-luminescence detection system (Mesoscale Discovery®).

Results: A 12-gene expression "signature" predicted the subsequent development of RA amongst ACPA-negative UA patients in the validation cohort (sensitivity 85%, specificity 75%). The signature had a predictive value equivalent to the Leiden score in these patients and provided enhanced predictive power in combination with the Leiden score. The 12-gene signature contained an over-representation of STAT3-target genes, and pathway analysis confirmed that genes functionally involved with CD4+ T-cell survival, including STAT pathway components, were deregulated in early RA. Baseline levels of serum IL-6 (which signals primarily via STAT3) distinguished anti-CCP negative RA from non-RA inflammatory arthritis patients matched for CRP (corrected $p<0.05$). Furthermore the expression of STAT3-inducible genes correlated with circulating serum IL-6 levels, and incubation of purified CD4+ T-cells with IL-6 replicated the in vivo 'signature'.

Conclusion: We have identified a 12-gene transcriptional signature with similar predictive utility to the Leiden score for the evolution of UA to ACPA-negative RA. Part of the signature appears to be IL-6 driven, and circulating IL-6 may also provide a useful biomarker for UA patients destined to develop ACPA-negative RA.

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Interleukin-22 Serum Levels Are Associated with Radiographic Progression in Rheumatoid Arthritis. Jan Leipe[1], Markus A. Schramm[1], Mathias Grunke[1], Michael Baeuerle[2], Matthias Witt[2], Axel P. Nigg[1], Christiane Reindl[1], Claudia Dechant[1], Alla Skapenko[1] and Hendrik Schulze-Koops[1]. [1]Division of Rheumatology and Clinical Immunology, Med. Poliklinik, University of Munich, Munich, Germany, [2]Medizinische Poliklinik, Munich, Germany

Background/Purpose: To study the role of interleukin (IL)-22 in rheumatoid arthritis (RA).

Methods: IL-22 serum levels were measured in patients with early, treatment-naive RA (n=49) and for control in 45 age- and sex-matched healthy individuals. Patients were assessed clinically and radiographically at baseline and followed-up for two years. IL-22 serum levels were correlated with parameters of disease activity, serological markers, demographic factors, and the incidence of erosions.

Results: 24 of 49 RA patients demonstrated elevated IL-22 levels compared to the range of healthy controls. At baseline, 33% (8/24) of the patients with elevated IL-22 serum levels demonstrated bone erosions, whereas only one patient (4%) from the group with normal IL-22 had erosions. During the two years of follow-up, six additional patients with increased IL-22 at baseline developed erosions. In contrast, none of the patients in whom IL-22 levels were normal developed erosions despite similar treatment regimens. Multivariate regression analysis accounting for other parameters predictive for erosions, such as the presence of rheumatoid factor or anti-cyclic citrullinated peptide antibodies and disease activity, revealed that elevated IL-22 baseline levels were independently and significantly associated with erosive RA.

Conclusion: IL-22 is elevated in the serum of half of the RA patients. Elevated serum IL-22 allows discriminating patients with different radiographic progression and indicates a possible involvement of IL-22 in the pathophysiology of RA.

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Serum Cytokine Levels Predict Mortality Among Postmenopausal Women Reporting Rheumatoid Arthritis. Jeremy Sokolove[1], William H. Robinson[2], Brian T. Walitt[3], Kevin D. Deane[4], Yuefang Chang[5], Russell Tracy[6], V. Michael Holers[7], Lewis Kuller[5], Larry W. Moreland[5] and Rachel Mackey[5]. [1]Stanford University, Palo Alto, CA, [2]Stanford University, Stanford, CA, [3]Washington Hospital Center, Washington, DC, [4]University of Colorado School of Medicine, Aurora, CO, [5]University of Pittsburgh, Pittsburgh, PA, [6]University of Vermont, Colchester, VT, [7]Univ of Colorado School of Med, Aurora, CO

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased risk of total mortality, which is in part explained by increased cardiovascular (CV) mortality. We sought to determine whether levels of plasma cytokines could further inform risk of mortality among the anti-CCP2+ and anti-CCP2 negative RA population.

Methods: We performed multiplex profiling of 17 cytokines in stored baseline plasma from postmenopausal women sampled from the Women's Health Initiative (WHI) study cohort who self-reported RA. We additionally assessed for the presence of anti-CCP2 antibodies and rheumatoid factor (RF) using commercial ELISA kits and the HLA shared epitope (SE) by PCR. Cox proportional hazards regression was used to model the relationship of plasma cytokine levels (in quartiles) to total mortality using follow-up data through April 2009 (mean (SD) follow-up time= 10.2 (3.0) years). Analyses were weighted to reflect the sampling from the WHI cohort. Women with a baseline report of CVD or cancer were excluded. To maximize true clinical RA diagnoses, we limited our analysis to women who were either 1) anti-CCP2+ (n=512; 71 deaths), or 2) anti-CCP2 negative (n=272; 36 deaths) with self-reported use of disease modifying anti-rheumatic drugs.

Results: The women in this study had a mean age of 62.8 years at baseline and 64.5% were white. Among anti-CCP2+ subjects, higher levels of IL-1b, IL-2, IL-6, IL-13, and MCP-1 predicted higher total mortality in age-adjusted models. After additional adjustment for RF, SE and additional risk factors including hypertension, ever smoking, and ethnicity, only higher IL-6 remained a significant predictor of total mortality (HR (95%CI) for highest quartile (Q4) vs. lowest quartile (Q1)=3.03, 1.14–8.03; $P=0.02$).

Among anti-CCP2 negative subjects, higher plasma MCP-1 levels strongly predicted total mortality and this relationship persisted even after adjustment for RF, SE, and additional risk factors (HR Q4 vs. Q1: 3.20, 1.13–9.02). Interestingly, elevated plasma IL-2, was associated with reduced age-adjusted mortality (HR Q4 vs. Q1: 0.40, 0.16–0.99; p=0.02). However, this association was attenuated after adjustment for RF, SE, hypertension, ever smoking, and ethnicity (HR Q4 vs. Q1=0.49, 0.18–1.33, p=0.06).

Conclusion: In addition to the increased mortality rates we have previously reported among anti-CCP2+ subjects, elevated levels of serum cytokines, especially IL-6, predict a further increased risk of total mortality. Among anti-CCP2 negative subjects, higher levels of MCP-1 and lower levels of IL-2 were associated with increased risk of total mortality. The mortality risk associated with lower levels of plasma IL-2 perhaps suggests spontaneous activation of autoreactive T cells as has been associated with RA as well as CVD.

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Treatment-Related Changes in Weight and Adipokine Levels and Associations with Radiographic Progression in Rheumatoid Arthritis. Joshua Baker[1], Gary Toedter[2], Daniel G. Baker[3] and Joan Marie Von Feldt[4]. [1]University of Pennsylvania, Philadelphia, PA, [2]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Malvern, PA, [3]Centocor R & D, a division of Johnson & Johnson Pharmaceutical Research and Development, LLC, Malvern, PA, [4]Univ of Pennsylvania/Philadelphia VAMC, Philadelphia, PA

Background/Purpose: Body mass and changes in weight may be predictors of radiographic outcomes in rheumatoid arthritis (RA). Adipocytokines have been

implicated in disease outcomes, however, associations with weight and disease-specific measures are unclear.

Methods: 100 randomly-selected subjects from the Go-BEFORE Trial of golimumab had adiponectin and leptin levels performed as part of a multi-analyte panel at baseline and 24 weeks of treatment. Radiographic data was available at baseline and 52 weeks. Using spearman correlations and logistic regression analysis, associations between baseline and treatment-related changes in weight, cytokines, and adipokines, and their independent association with disease activity and radiographic scores were assessed.

Results: Adiponectin and leptin were associated with BMI at baseline. On average, subjects gained weight during treatment (Mean increase in BMI 0.42 (1.12) kg/m^2 $p<0.001$). Both leptin and adiponectin tended to increase over the first 24 weeks of the trial. Changes in leptin were highly correlated with changes in weight ($p<0.0001$), whereas changes in adiponectin were negatively correlated with Il-6, TNF-a, and CRP levels (all $p<0.01$), but not BMI ($p>0.5$). No available baseline or longitudinal variables independently predicted changes in weight. Greater increase in weight was independently associated with a lower probability of radiographic progression at 52 weeks. Adiponectin and leptin were *not* independently associated with radiographic changes in multivariable models.

Table 1. Spearman correlations and of the association between changes in adiponectin and leptin (Δ) with continuous and dichotomous clinical treatment and response variables.

Continuous Variables	Δ Adiponectin	Δ Leptin
Δ BMI	−0.027	**0.37‡**
Δ CRP	**−0.36‡**	0.069
Δ TNF	**−0.25†**	0.047
Δ IL-6	**−0.29†**	0.066
Δ DAS28(CRP)	−0.16	−0.14

* $p<0.05$, †$P<0.01$, ‡$P<0.001$

Table 2. Multivariable logistic analysis of the associations between body mass, changes in body mass, and adiponectin with the risk of radiographic progression (defined as a vdHS change of >0.5). (N=86)

	Model 1*		Model 2*		Model 3*	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Baseline BMI (per 1 kg/m^2)	0.92 (0.80–1.06)	0.2	0.93 (0.81–1.08)	0.4	0.94 (0.81–1.10)	0.4
Δ BMI (per 1 kg/m^2 increase)	0.45 (0.24–0.85)	0.01	0.49 (0.25–0.94)	0.03	0.46 (0.24–0.90)	0.02
DAS28(CRP)	–	–	1.16 (0.68–1.99)	0.6	1.18 (0.68–2.04)	0.6
Δ DAS28(CRP)	–	–	1.43 (0.92–2.25)	0.1	1.35 (0.85–2.13)	0.2
Adiponectin (per 1 μg/mL)	–	–	–	–	1.26 (0.89–1.78)	0.2

* Also adjusted for age, race, sex, treatment group, CCP status, and a high vdHS at baseline.

Conclusion: Treatment-related increases in adiponectin correlate inversely with changes in inflammatory markers, whereas changes in leptin correlate positively with changes in body weight. Greater increases in weight at 24 weeks are associated with less radiographic change at 1 year, independent of adipokines and other disease severity measures.

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B Cell Activating Factor (BAFF) Binding Receptors (BBR) on B Cells: Characterization in Patients with Rheumatoid Arthritis (RA) Receiving Anti-TNF-a Agent Infliximab (IFX). Lara Valor[1], Diana Hernandez[2], Geraldine Cambridge[3], Maria J. Leandro[3], Lina Martinez-Estupiñan[1], Luis Carreño[1] and Inmaculada de la Torre[1]. [1]Gregorio Marañón Hospital, Madrid, Spain, [2]Gregorio Maranon Hospital, Madrid, Spain, [3]University College of London, London, United Kingdom

Background/Purpose: B-cells play a cardinal role in the pathogenesis of RA as demonstrated by the effectiveness of Rituximab (RTX). Expression of BBR on B-cells namely BAFF-R, TACI (transmembrane activator and calcium-modulating and cyclophilin ligand interactor) and BCMA (B-cell maturation molecule) are key controllers of B cell survival and maturation. Dysregulation of BBR may contribute to the pathogenesis of RA and to re-establishment of disease after Rtx (1). Anti-TNFa agents are also effective in treating RA. TNFa has been shown to reduce CD38+ germinal center (GC) B cells and peripheral blood memory B cells (2). It remains unclear whether these 2 therapeutic targets are mechanistically linked. We have therefore analysed BBR expression on B-cells in response to the anti-TNFa agent IFX in patients with RA.

Methods: We included 23 patients with RA on IFX: 12 not in remision (DAS28>2.6) and 11 in remision (DAS28<2.6) and healthy controls (HC; n=12). Using multiparametric flow cytometry we measured % of naïve and memory B cells expressing BBR in peripheral blood, using combinations of directly conjugated monoclonal antibodies to CD19, CD27, IgD, CD38, BAFF-R, TACI and BCMA.

Results: Despite similar expression of BAFF-R on naïve and memory B-cells of active and inactive RA patients compared to HC, we found significatively increased TACI expression on memory B-cells (CD19+CD27+) of active and inactive patients compared to HC ($p=0.01$ and $p=0.004$, respectively), with the postGC compartment (CD19+IgD-CD38+) most affected vs. HC ($p=0.03$ and $p=0.01$ respectively). No changes in TACI expression on naïve B-cells (CD19+CD27-) were found. A significantly lower % of B cells expressed BCMA on naïve population (active and inactive RA vs. HC; $p=0.01$ and $p=0.06$, respectively). This was found in both naïve mature (CD19+IgD++CD38+) in active and inactive RA vs. HC ($p=0.01$ and $p=0.001$, respectively) and naïve transitional B cells (CD19+IgD+CD38++) in active and inactive RA vs. HC ($p=0.0007$ and $p=0.01$, respectively). % memory B-cells expressing BCMA+ were also lower (active and inactive RA vs. HC, $p=0.01$); affecting more the plasmablast compartment(CD19+IgD-CD38+++) (active and inactive RA vs. HC; both $p=0.03$) with a tendency for even lower BCMA on Post-GC memory B-cells in inactive RA on infliximab when compared to active patients ($p=0.04$).

Conclusion: Our data supports the concept that major disruption of BBR receptor expression is present in patients with RA. Whilst, after BCDT, restablishment of disease has been related to impared BAFF-R expression on the repopulating naive B-cell subset (1), IFX may influence maintenance of BAFF-R expression on both naïve and memory B-cell pools, in, both active or inactive disease. Blocking TNF a could restore the defect on the maturation-survival process on naïve B cell in patients with RA, preventing short lived B cells from becoming antibody-producing plasmacells. However, as active RA patients on anti-TNF therapy show increased TACI and decreased BCMA expression only on memory B-cells, suggesting that, defects in the memory B-cell pool might persist due to contributions by other mediators. (1) De la Torre et al. ARD 2010. (2) Anolik et al. J Immunol. 2008

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Tumor Necrosis Factor Blocking Therapy Alters Oxidative Stress and Hypoxia-Induced Mitochondrial Mutagenesis in Inflammatory Arthritis. Monika Biniecka[1], Aisling Kennedy[1], Chin Teck Ng[1], Ting C. Chang[1], Emese Balogh[1], Edward Fox[2], Douglas J. Veale[1], Ursula Fearon[1] and Jacintha N. O'Sullivan[3]. [1]Translation Rheumatology Research Group, Dublin, Ireland, [2]Department of Pathology, University of Washington, Seattle, WA, [3]Department of Surgery, Trinity Centre for Health Sciences, St James's Hospital, Dublin, Ireland

Background/Purpose: To investigate if successful anti TNF-α treatment alters the levels of early mitochondrial genome alterations which can play a crucial role in governing clinical response or resistance. Furthermore, we determine if TNF-α blocking therapy changes the levels of synovial lipid peroxidation, further confirming the relationship between hypoxia, oxidative damage and mitochondrial mutagenesis.

Methods: Eighteen inflammatory arthritis patients underwent synovial tissue oxygen (tpO_2) measurements and clinical assessment of disease activity (DAS28-CRP) at baseline (T0) and three months (T3) after starting biologic therapy. Synovial tissue lipid peroxidation (4-HNE), T and B cell specific markers and synovial VEGF were quantified by immunohistochemistry. Synovial levels of random mitochondrial DNA (mtDNA) mutations were assessed using Random Mutation Capture (RMC) assay.

Results: 4-HNE levels pre/post anti TNF-α therapy were inversely correlated with *in vivo* tpO_2 ($p<0.008$; $r=-0.60$). Biologic therapy responders showed a significantly reduced 4-HNE expression ($p<0.05$). High 4-HNE expression correlated with high DAS28-CRP ($p=0.02$; $r=0.53$), TJC-28 ($p=0.03$; $r=0.49$), SJC-28 ($p=0.03$; $r=0.50$) and VAS ($p=0.04$; $r=0.48$). Strong positive association was found between the number of 4-HNE positive cells and CD4+ cells ($p=0.04$; $r=0.60$), CD8+ cells ($p=0.001$; $r=0.70$), CD20+ cells ($p=0.04$; $r=0.68$), CD68+ cells ($p=0.04$; $r=0.47$) and synovial VEGF expression ($p=0.01$; $r=063$).

In patients whose *in vivo* tpO_2 levels improved post treatment, significant reduction in mtDNA mutations and DAS28-CRP was observed ($p<0.05$). In contrast in those patients whose tpO_2 levels remained the same or reduced at T3, no significant changes for mtDNA mutations and DAS28-CRP were found.

Conclusion: There is a close association between oxidative stress, mitochondrial mutagenesis and clinical responses to TNF blocking therapy in inflammatory arthritis patients. The greater mitochondrial mutation burden in synovial tissue is associated with higher hypoxia levels *in vivo* and these significant mitochondrial genome alterations are rescued following successful anti-TNF treatment.

ACR Poster Session A
Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy I

Sunday, November 6, 2011, 9:00 AM–6:00 PM

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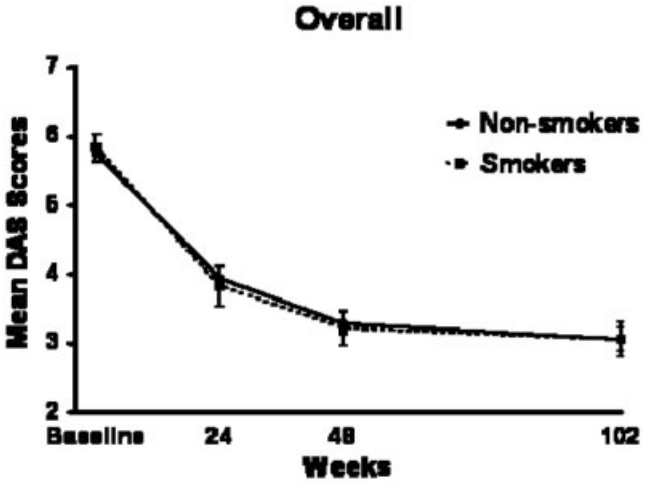
Active Smoking Is Not Associated with Treatment Response In Early Rheumatoid Arthritis In a Large Randomized Blinded Trial. Leann Maska[1], James R. O'Dell[2], Jeffrey R. Curtis[3], S. Louis Bridges Jr.[4], Larry W. Moreland[5], Stacey Cofield[6] and Ted R. Mikuls[7]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Univ of Nebraska Med Ctr, Omaha, NE, [3]Univ of Alabama-Birmingham, Birmingham, AL, [4]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [5]University of Pittsburgh, Pittsburgh, PA, [6]Univ of Alabama at Birmingham,, Birmingham, AL, [7]Omaha VA and University of Nebraska, Omaha, NE

Background/Purpose: Cigarette smoking has emerged as a major environmental risk factor for the development of rheumatoid arthritis (RA). Recent studies have suggested current smoking leads to lower treatment response rates with methotrexate (MTX) and biologics in RA. Knowledge of whether tobacco exposure reduces treatment efficacy is important as smoking could represent a modifiable factor in optimizing RA treatment strategies.

Methods: Study subjects included participants with early RA (< 2 years duration, autoantibody-positive or with radiographic erosions) enrolled in the Treatment of Early Aggressive RA (TEAR) trial. TEAR is a randomized, blinded, placebo-controlled clinical trial (RCT) comparing early intensive therapy versus step-up to one of two combinations of medications (MTX + etanercept vs. MTX + hydroxychloroquine + sulfasalazine (triple therapy)). The primary outcome of this analysis was mean DAS28 between 48 and 102 weeks by cotinine status, adjusting for baseline disease activity. Serum cotinine was measured using a commercially available ELISA at baseline and 48 weeks. Detectable concentrations at both visits served as an indicator of persistent tobacco exposure. In an independent RA cohort (n = 691) we found that any detectable serum cotinine yielded excellent concordance with self-reported current smoking (area under the ROC curve 0.90). Patients with inconsistent smoking status at weeks 0 and 48 were excluded.

Results: After excluding subjects for whom serum was not available (n = 192), and those with discordant cotinine category at the two time points (n = 34), a total of 412 subjects were analyzed with 293 (71%) categorized as non-smokers and 119 (29%) as current smokers. Mean age of those included was 50 years, disease duration 3.7 months, and baseline DAS28 score 5.8. No significant difference in dropout rate existed based on smoking status. There was no difference in the primary outcome based on smoking status ($p=0.881$) (See Figure), nor were there differences in outcomes of analyses stratified by TEAR treatment groups (data not shown). Using secondary outcomes of 'good' response or 'remission' as defined by EULAR response criteria, there was again no difference based on smoking status overall or by treatment group at any time point. LOCF imputation method was used for sensitivity analysis of all subjects with baseline serum available, with no significant difference of change in DAS observed. The frequency of SAEs including all infections, respiratory infections, and pneumonia was similar between smokers and nonsmokers both overall and based on treatment assignment.



Conclusion: Among 412 patients enrolled in an RCT of early aggressive RA, smoking status did not affect treatment response in early combination vs. step-up therapy, or biologic agent versus triple therapy. Smoking status also does not appear to be correlated with frequency of SAEs in this population.

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Effect of Disease Modifying Anti-Rheumatic Drugs (DMARDs) On Anti-CCP2 and Anti-Citrullinated Protein Antibody (ACPA) Levels During Longitudinal Assessments In Rheumatoid Arthritis Patients. Makoto Soejima[1], Aarat M. Patel[1], Danielle Goudeau[1], Donald M. Jones[1], Christine L. Amity[1], Lynne M. Frydrych[1], Dawn McBride[1], Derek Sippel[1], Heather Eng[2], David Kyle[2], Melissa Saul[2], Stephen R. Wisniewski[2], Larry W. Moreland[1] and Marc C. Levesque[1]. [1]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [2]Univ of Pittsburgh, Pittsburgh, PA

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are specific markers for rheumatoid arthritis (RA) and may have a pathogenic role in the development of rheumatoid synovitis. ACPA are produced by B cells and some studies suggest that TNF regulates B cell development. Therefore, the purpose of these studies was to determine the effect of TNF antagonists on ACPA levels and to correlate these changes with changes in B cell subsets in patients with RA.

Methods: 115 RA patients with 3 longitudinal samples in the University of Pittsburgh Medical Center Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry and 226 RA patients with 4 longitudinal samples in the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) study were clinically assessed at each visit. Quantitative serum levels of ACPA were measured using ELISAs. B cell subsets were analyzed using flow cytometry. The effect of treatment on ACPA levels and on B cell subset numbers were analyzed using a mixed effects regression model, ANOVA, and t-test. Disease activity was controlled for in the analyses.

Results: Age, sex, race, rheumatoid factor (RF), and disease activity scores at baseline were similar among the different treatment groups within each cohort. ACPA levels changed following therapy and changes in ACPA levels were similar in the TEAR and RACER cohorts. ACPA levels decreased during the first 6 months of oral DMARD and TNF antagonist therapy. After 6 months, ACPA levels declined further in patients treated with oral DMARDs but returned to baseline levels in patients treated with TNF antagonists. This resulted in significant differences in ACPA levels between these groups (for TEAR subjects, $p=0.0015$ for anti-CCP2 (cyclic citrullinated peptide), $p=0.0045$ for anti-P6c (citrullinated fibrinogen peptide) and $p=0.0058$ for anti-P20c (citrullinated fillagrin peptide)). The percentages of pre-switch IgD^+CD27^+ and post-switch IgD^-CD27^+ memory B cells in RA patients treated with TNF antagonists were significantly lower than in healthy control subjects and subjects treated with oral DMARDs only ($p=0.0018$ and $p=0.0018$, respectively). The percentage of naïve B cells was higher among RA subjects treated with TNF antagonists compared to subjects treated with oral DMARDs only ($p=0.0068$).

Conclusion: We found a differential effect of oral DMARD therapy versus anti-TNF therapy on ACPA levels in patients with RA. After 6–12 months of treatment, TNF therapy was associated with an increase in ACPA levels, a lower percentage of peripheral blood (PB) pre-switch IgD^+CD27^+ and post-switch IgD^-CD27^+ memory B cells and with an increase in naïve

B cells. Naïve B cells in RA patients as compared to healthy subjects have been reported to produce higher levels of autoreactive antibodies. Taken together, these studies suggest that TNF blockade in RA patients may initially lower ACPA levels via diminished inflammation within the synovium where ACPA are produced. However, TNF blockade later leads to increased numbers of naïve autoreactive B cells that subsequently lead to increased ACPA levels.

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Adalimumab Added to Methotrexate and Intra-Articular Glucocorticoid Increases Remission Rates At One Year In Early, DMARD-Naïve Patients with Rheumatoid Arthritis—An Investigator-Initiated Randomized, Controlled, Double-Blinded Study. Kim Hørslev-Petersen[1], Merete L. Hetland[2], Peter Junker[3], Jan Pødenphant[4], Torkell Ellingsen[5], Palle Ahlqvist[6], Hanne M. Lindegaard[3], Asta Linauskas[7], Annette Schlemmer[8], Mette Y. Dam[9], Ib Hansen[10], Hans Chr Horn[6], Anette Jørgensen[9], Sophie B. Krintel[2], Johnny Raun[1], Christian G. Ammitzbøll[9], Julia Johansen[2], Mikkel Østergaard[11] and Kristian Stengaard-Pedersen[9]. [1]University of Southern Denmark, Graasten, Denmark, [2]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [3]Odense University Hospital, Odense C, Denmark, [4]Copenhagen University at Gentofte,, Hellerup, Denmark, [5]University Hospital, Silkeborg, Denmark, [6]Vejle Hospital,, Vejle, Denmark, [7]Vendsyssel Hospital, Hjørring, Denmark, [8]Aalborg Hospital, Aalborg, Denmark, [9]Arhus University Hospital, Aarhus, Denmark, [10]Viborg Hospital, Viborg, Denmark, [11]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark

Background/Purpose: To assess efficacy and safety, including remission rates by adding adalimumab (ADA) to methotrexate (MTX) and intra-articular glucocorticoid (triamcinolone) in patients with early DMARD-naïve rheumatoid arthritis (RA) fulfilling the ACR 1987 criteria.

Methods: DMARD naive RA patients with disease duration < 6 months (n=180) were randomized 1:1 to MTX 7.5 mg weekly + ADA 40 mg (ADA) every other week or MTX + placebo (PLA). At week 0, 4, 8, and 12 followed by every 3rd month up to 12 months, patients had triamcinolone injections into swollen joints (max 4 joints or max 4ml/visit). In addition the patients were contacted fortnightly during the first 3 months and monthly thereafter. If disease activity was suspected, an extra visit was scheduled and swollen joints were injected. MTX was increased to 20 mg/week within two months. If persisting DAS28(CRP)>3.2 after three months, sulphasalazine 2g/day and hydroxychloroquine 200mg/day were added. Patients with persistent DAS28(CRP)>3.2 in spite of triple therapy were excluded and started rescue biologic medication. NSAID, muscle relaxants, or medium or strong analgesics were not allowed. Clinical response was assessed according to DAS28(CRP), SDAI and ACR/EULAR remission criteria. Primary analysis was by ITT with last observation carried forward. Completer analysis and ITT without imputations were also performed and gave similar results (not shown). Differences between groups were tested by Mann-Whitney or by Pearson's chi-square test.

Results: At baseline no significant differences were seen between MTX+PLA and MTX+ADA: 69%/63% were women, median age was 54.4/56.2 years, disease duration 83/84 days, anti-CCP positive 70%/60%, IgM-RF positive 74%/70%, DAS28(CRP) 5.4/5.3, tender joint count (40) 16/15, swollen joint count (40) 11/10, patient's VAS pain 58/63mm and fatigue 54/67mm, doctor's VAS global 51/57mm, HAQ 1.0/1.1. Data for MTX after 12 months and use of triamcinolone 0–12 months are presented in the table. Triple therapy was added in 25/17 patients (p=0.25). 80/81 patients completed the study. 2/4 patients started rescue biologic medication. Serious adverse advents were reported in 13 patients, including three with malignancies (urothelial, lung and non-melanoma skin cancer). The frequency of DAS28(CRP)<3.2 (primary outcome) did not differ significantly between the groups, but in the MTX+ADA group significantly more patients achieved clinical remission (DAS28, SDAI and ACR/EULAR remissions) at 12 months (secondary outcome) (table).

	MTX+PLA	MTX+ADA	p
Number of patients	91	89	–
Methotrexate (mg/week) 12 months	20 (7/25)	20 (7.5/20)	0.33
Triamcinolone (ml) 0 – 12 months	7 (2/17.8)	5.4 (1.8/16.6)	0.084
DAS28 (CRP) 12 months	2.2 (1.3/4.5)	1.7 (1.2/5.2)	0.0007
DDAS28 (CRP) 0–12 months	−3.0 (−0.2/−5.0)	−3.2 (−0.2/−5.7)	0.11
DAS28 (CRP)<3.2; 12 months	81%	84%	0.74
DAS28 (CRP)<2.6; 12 months	49%	74%	0.0011
SDAI ≤ 3.3; 12 months	40%	63%	0.0028
ACR/EULAR (28 joints) remission; 12 months	31%	48%	0.0241
ACR/EULAR (40 joints) remission; 12 months	27%	47%	0.0098

Values are medians(5%/95% percentiles) unless otherwise stated (%).

Conclusion: In DMARD naïve patients with early RA, excellent disease control was achieved by a targeted step-up strategy using methotrexate and intra-articular glucocorticoid injections. Addition of adalimumab to methotrexate and intra-articular glucocorticoid improved the remission rates considerably. The treatments were well tolerated.

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Tocilizumab Improves Arterial Stiffness Compared with Abatacept In Patients with TNF Blockers-Resistant Active Rheumatoid Arthritis.An Open Label Randomized Controlled Trial. Kensuke Kume[1], Kanzo Amano[1], Susumu Yamada[1] and Kazuhiko Hatta[2]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]Hatta Clinic, Kure, Japan

Background/Purpose: Rheumatologists need to develop primary prevention strategies for cardiovascular disease(CVD) in rheumatoid arthritis (RA) patients.To compare the effect of tocilizumab(TCZ) plus methotrexate (MTX), with the effect of abatacept(ABT) plus MTX on arterial stiffness in TNF blockers resistant active RA patients, in a open label randomized study design.

Methods: RA patients were eligible if they had active disease despite treatment with MTX plus TNF blockers. All patients have no steroids, and no previous history of CVD. 32 patients with moderate to severe active RA patients (DAS28 >3.2) were randomly assigned to receive TCZ plus MTX (n=16) or ABT plus MTX (n=16). All patients with worsening disease activity at week 12, the patients were allowed to escape to another group (by clinician's judgment).Arterial stiffness was assessed with cardio-ankle vascular index (CAVI) and augmentation index corrected for a heart rate of 75 beats per minute (AIx@75) at baseline and 24 weeks follow-up. Cardiovascular risk factors and clinical data was collected at regular visits.CAVI was calculated by the following formula:CAVI= $2\rho/dP \times \ln(Ps/Pd)PWV2$, where Ps is systolic blood pressure, Pd is diastolic blood pressure, PWV is pulse wave velocity, dP is Ps– Pd,ρ is blood density.CAVI measures arterial wall stiffness independent of blood pressure and it is superior to PWV as an index of arterial stiffness.

Results: The characteristics of each group at baseline were not significantly different. 15 each in the TCZ and ABT groups completed 24 weeks.CAVI and AIx@75 were attenuated significantly by TCZ (CAVI; week 0–week 24, 0.92±0.15 m/s, $p = 0.02$) (AIx@75; week 0–week 24, 3.59±0.33%, $p = 0.03$).On the other hand, CAVI and A,hx@75 were not attenuated significantly by ABT (CAVI; week 0–week 24, 0.22±0.11 m/s, $p = 0.52$) (AIx@75; week 0–week 24, 0.98±0.21%, $p = 0.66$). The change (week 0–week 24) CAVI and AIx@75 of the TCZ group were significantly improvement than those of the ABT group (TCZ vs. ABT, CAVI: $p = 0.024$; AIx@75: $p=0.032$). TCZ and ABT did not significantly change carotid intima-media thickness (week 0–week 24, TCZ: 0.00±0.11 mm, ABT: −0.00±0.13 mm), and did not produce significant changes in carotid artery plaque (week 0–week 24, numbers of combined grade 0/1/2/3/4, TCZ: −1/1/0/0, ABT: −1/0/−0/0). There were no significant changes either within ratio of serum total cholesterol (TC) to high-density lipoprotein cholesterol (week 0–week 24, TCZ: 0.02±0.04; ABT: 0.03±0.03) ($p>0.05$). In the TCZ, TC was significantly increased (week 0–week 24, −18.0±5.2 mg/dL, $p = 0.03$). There were no significant changes within the ABT group in TC (ABT: −2.0±0.6 mg/dL; $p=0.75$). The change TC levels of the TCZ group were significantly higher than those of the other groups (TCZ vs. ABT, $p = 0.034$). DAS28 and CRP improved significantly in both groups (week 0–week 24; DAS28, TCZ: −2.13±0.35, ABT: −2.20±0.42) (CRP, TCZ: 22.3±3.2 mg/l, ABT: 19.5±2.3 mg/l) ($p<0.05$). They were no significant difference between groups.

Conclusion: TCZ improves arterial stiffness compared with ABT and in TNF blockers resistant RA. If RA patients were resist TNF blocker, we might think the patients were treated by TCZ than ABT.

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Tocilizumab Monotherapy Improves BONE Mineral Density AS Well AS TNF Blockers PLUS Methotrexate with Methotrexate-RESISTANT Activerheumatoid Arthritis. AN OPEN-Label RANDOMIZED CLINICAL TRIAL. T-BONE TRIAL. Kensuke Kume[1], Kanzo Amano[1], Susumu Yamada[1] and Kazuhiko Hatta[2]. [1]Hiroshima Clinic, Hiroshima, Japan, [2]Hatta Clinic, Kure, Japan

Background/Purpose: To compare the effects of tocilizumab (TCZ) monotherapy, and infliximab (IFX) plus methotrexate(MTX), and adalimumab(ADA) plus MTX, respectively on bone mineral density (BMD) in patients

with rheumatoid arthritis (RA; without osteoporosis) patients despite MTX treatment, in a prospective open-label randomized controlled design.

Methods: 42 RA patients with moderate to severe active disease (DAS28 > 3.2) despite MTX treatment were randomly assigned to receive TCZ (8mg/kg per 4 weeks) alone (n=14), IFX (3–10mg/kg per 8 weeks) plus MTX (n=14), or ADA (40mg per 2 weeks) plus MTX (n=14). All patients have no previous history of lumbar and hip fractures. Patients receiving or having received bisphosphonates or hormone replacement therapy, steroids, or any biologics were excluded. The dosage of all disease modifying anti-rheumatic drugs had been stable for at least 8 weeks prior to enrollment. The primary outcomes were changes in lumbar and femoral BMD by dual-energy X-ray absorptiometry, secondary outcome were serum osteocalcin and serum crosslaps from baseline to12 months. Clinical data were collected at regular visit. All patients were taking calcium (1 g/day) and vitamin D (800 IU/day).

Results: The characteristics of each group at baseline were not significantly different. In all groups there was significant increase from baseline to 12 months in BMD in the spine (month12-baselineTCZ: BMD 0.04±0.002 g/cm^2, $p < 0.001$; T-score, $p < 0.001$; Z-score, $p < 0.01$; IFX: BMD 0.03±0.004 g/cm^2, $p < 0.001$; T-score, $p < 0.001$; Z-score, $p < 0.01$; ADA: BMD 0.03±0.003 g/cm^2, $p < 0.001$; T-score, P < 0.001; Z-score, $p < 0.01$) and the femoral neck (TCZ: BMD 0.03±0.002 g/cm^2, $p < 0.001$; T-score, $p < 0.001$; Z-score, $p < 0.01$; IFX: BMD 0.03±0.006 g/cm^2, $p < 0.001$; T-score, $p < 0.001$; Z-score, $p < 0.01$; ADA: BMD 0.02±0.008g/cm^2, $p < 0.001$; T-score, $p < 0.001$; Z-score, $p < 0.01$). The change (month12-baseline) BMD were no significant differences between each group in BMD in spine or in femoral neck. In all groups there was significant increase from baseline to 12 months in osteocalcin serum levels (month 12-baseline, TCZ:7.2±0.65 ng/ml, p<0.01; IFX: 6.2±0.85 ng/ml, p<0.01;ADA: 6.8±0.76 ng/ml p<0.01) and significant decrease in crosslaps serum levels (month 12-baseline, TCZ: −3.2±0.28 ng/ml, p<0.01;IFX: −2.9±0.45 ng/ml, p<0.01; ADA: −2.5±0.66 ng/ml p<0.01) but no change in serum calcium was observed. There were no significant differences between each group in osteocalcin serum levels or in crosslaps serum levels. However, the changes in markers of bone metabolism and BMD were not correlated in all groups. HAQ score, DAS28-ESR score, and CRP improved significantly in all groups from baseline to 12 months ($p<0.05$). They were no significant difference between groups.

Conclusion: The data support the hypothesis that TCZ monotherapy may exert beneficial effects on bone metabolism in active RA patients despite MTX to the same extent as IFX or ADA plus MTX. We need further studies to compare the effects of TCZ alone, and TCZ plus MTX on BMD in patients with RA patients despite MTX treatment.

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Efficacy, Safety and Pharmacokinetics of Vidofludimus, a Novel Oral Immunomodulator, in Patients with Active Rheumatoid Arthritis on Methotrexate Background Therapy: The COMPONENT Study. Stanislaw Sierakowski[1], Bruno Dietrich[2], Bernd Hentsch[2] and Aldo Ammendola[2]. [1]Medical University Bialystok, Bialystok, Poland, [2]4SC AG, Planegg-Martinsried, Germany

Background/Purpose: Vidofludimus is an oral immunomodulator inhibiting dihydroorotate dehydrogenase (DHODH) and the expression of pro-inflammatory cytokines including interleukin-17 (IL-17A and IL-17F) and INF-gamma. In the presented Phase II COMPONENT study efficacy, safety, and pharmacokinetics of vidofludimus in combination with methotrexate (MTX) has been evaluated in rheumatoid arthritis (RA) patients. Vidofludimus has previously successfully completed a Phase IIa study in inflammatory bowel disease (IBD).

Methods: Primary endpoint of this randomized, double-blind, placebo-controlled Phase II study was ACR20 response at week 13. Secondary endpoints included ACR50, ACR70, DAS28, safety and pharmacokinetics. 241 patients were enrolled in two study arms across 28 sites in Eastern Europe. The first arm received 35 mg vidofludimus QD plus MTX over 13 weeks, the second arm received placebo plus MTX. Eligible patients must have had active RA, have received weekly doses of MTX (10–25 mg/week) for a minimum of 3 months prior to Day 1 dosing, and a stable MTX dose for at least 6 weeks prior to Day 1 dosing.

Results: ACR20 response improvement of the vidofludimus group compared to placebo was statistically significant (p<0.05) at week 2 (16.7% vs. 6.9%) and week 8 (46.7% vs. 31.9%), but did not reach statistical significance at week 13 (50.0% vs. 44.8%). The vidofludimus group also reported higher ACR50 (25.8% vs. 17.2%) and ACR70 (12.5% vs. 6%) response rates compared to placebo at week 13. DAS28 (CRP) response rate of vidofludimus also was significantly higher compared to placebo at week 4 (55.8% vs. 42.3%). Mean change of CRP (ESR) at week 13 compared to baseline was −1.82 mg/l (−3.98 mm/h) for vidofludimus and 1.38 mg/l (3.18 mm/h) for placebo. Mean changes of RA-specific parameters (joint counts, disease activity, pain, HAQ) were similar in both groups at week 13. In contrast to preclinical interaction studies, a substantial decrease of vidofludimus plasma concentrations below levels detected in earlier clinical trials has been observed with increasing MTX doses.

Vidofludimus was safe and well tolerated. No obvious differences in the adverse event profile between the vidofludimus and placebo group were observed. In particular, there were no relevant increases of diarrhea, neutropenia, anemia, hypertension, cholesterol or liver enzyme levels. Only one serious adverse event was reported in the vidofludimus group which was judged as unlikely drug-related. No deaths occurred. These safety results were consistent with previous clinical trial results in RA and IBD.

Conclusion: Certain efficacy endpoints (ACR20/DAS28) have been statistically significant at specific time points during the treatment period, though vidofludimus missed the primary ACR20 efficacy endpoint of the COMPONENT study at week 13. Decreases in objective inflammatory parameters CRP and ESR strongly support a general anti-inflammatory effect of vidofludimus. These results and the very clean safety profile indicate that a vidofludimus dose of 35 mg QD might be not high enough to show statistically significant results in RA. In addition, the observed drug interaction of vidofludimus with MTX may have hampered the full anti-inflammatory activity of vidofludimus.

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Rituximab and Methotrexate but Not TNF-Blockers Are Associated with Impaired Antibody Response Following Pneumococcal Vaccination Using 7-Valent Conjugate Vaccine (Prevenar®) In Patients with Established Rheumatoid Arthritis. Meliha C. Kapetanovic[1], Carmen Roseman[1], Göran Jönsson[2], Lennart T. Truedsson[3], Tore V. Saxne[1] and Pierre Geborek[1]. [1]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [2]Dept of Clinical Sciences Lund, Section of Infectious Diseases, Lund, Sweden, [3]Dept of Clinical Sciences Lund, Section of Microbiology, Immunology and Glycobiology, Lund, Sweden

Background/Purpose: To investigate the impact of anti-rheumatic treatments including methotrexate (MTX), TNF blockers, rituximab (RTX), abatacept and tocilizumab on antibody response following pneumococcal vaccination using 7-valent conjugate vaccine (Prevenar®) in patients with established RA.

Methods: Altogether, 294 patients with established RA and 86 patients with spondylartropathy (SpA) including psoriatic arthritis received one dose of 0.5 ml Prevenar® intramuscularly. The RA treatment groups (number of participants, % female, mean age (years)) were studied: MTX (85; 79; 62); anti-TNF as monotherapy (79; 87; 60); anti-TNF+MTX (89; 78; 60); RTX as monotherapy (15; 80; 68); RTX+MTX (10; 70; 56); abatacept (10; 100; 57) and tocilizumab (5; 100; 62). SpA patients on NSAIDs/analgesics (86; 39; 52) served as controls. Levels of serotype specific IgG against 23F and 6B were measured at vaccination and 4–6 weeks after vaccination using standardised ELISA. Antibody response ratio (ARR) calculated on logarithmic values as ratio post/prevaccination antibody levels were compared between treatment groups. Positive antibody response (posAR) was defined as ≥2 ARR.

Results: ARR different significantly between the groups for both serotypes (univariate analysis of variance, ANCOVA; p<0.001). Compared to controls, all other RA treatments groups showed significantly lower ARR except for patients treated with anti-TNF as monotherapy for both serotypes (p-value between 0.023 and <0.001). Furthermore, patients receiving RTX as monotherapy or RTX+ MTX showed significantly decreased ARR compared to anti-TNF as monotherapy and MTX alone. None of RTX treated patients had posAR for serotype 6B which was the reason that predictors of positive immune response were studied only for serotype 23F. After adjustment for age and sex in logistic regression model, MTX treatment predicted impaired posAR (p= 0.038; OR 0.5; 95% CI 0.31–0.97) as well as RTX (p<0.001; OR 0.09; 95% CI 0.03–0.3).

Conclusion: MTX and RTX but not TNF-blockers are associated with impaired antibody response following vaccination with heptavalent pneumococcal conjugate vaccine (Prevenar®) in this cohort of patients with established RA. Insufficient statistical power precluded detailed studies of abatacept and tocilizumab on vaccination response.

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Genetic Variations within the CD6 and Syntaxin Binding Protein 6 Genes Associated with Response to Tumor Necrosis Factor Alpha Inhibitors in Danish Patients with Rheumatoid Arthritis Treated in Routine Care. Sophine B. Krintel[1], Giuseppe Palermo[2], Assaf Wool[3], Julia S. Johansen[4], Laurent Essioux[2], Ehud Schreiber[3], Tomer Zekharya[3], Pinchas Akiva[3], Mikkel Østergaard[1] and Merete L. Hetland[5]. [1]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [3]Compugen Ltd., Tel Aviv, Israel, [4]Copenhagen University Hospital at Herlev, Copenhagen, Denmark, [5]Copenhagen University Hospital at Glostrup, on behalf of DANBIO, Copenhagen, Denmark

Background/Purpose: Tumor necrosis factor alpha (TNFα) inhibitors have greatly improved treatment of patients with rheumatoid arthritis (RA). However, at least 30% of the patients do not respond and no validated predictive biomarker has been identified. Lack of response and risk of adverse drug reactions emphasize the need for predictive biomarkers. We aimed to investigate genetic variations associated with response to TNFα inhibitors in Danish patients with moderate to severe RA treated in routine care.

Methods: In the nationwide DANBIO registry we identified 237 TNFα inhibitor naive patients with RA (81% women, median age 56 years (interquartile range 44–64), disease duration 6 years (2–14.3)) who initiated treatment with infliximab (n=160), adalimumab (n=56), and etanercept (n=21) according to national guidelines between 1999 and 2008. The patients were registered in DANBIO at onset of treatment and followed prospectively. Clinical response was assessed at week 26 using EULAR response criteria. Over 200 genetic variations were tested for association with response. Genomic segments were amplified by polymerase chain reaction, and genotyped by either Sanger sequencing or fragment analysis. We tested the association between genotypes and EULAR good response versus no response, and EULAR good response versus moderate/no response using Fisher's exact test.

Results: Median disease activity score (DAS28) at baseline was 5.1 decreasing to 3.6 at week 26. Sixty-eight (29%) patients were EULAR good responders, while 81 (34%) patients were moderate responders and 88 (37%) patients were non responders. A 19 base pair insertion within the CD6 gene was associated with EULAR good response versus no response (OR=4.43, 95% CI: 1.99–10.09, p=7.211 × 10-5, minor allele frequency (MAF) =0.15) and with EULAR good response versus moderate/no response (OR=4.54, 95% CI 2.29–8.99, p= 3.336 × 10-6). A microsatellite within the syntaxin binding protein 6 (STXBP6) on chromosome 14 was associated with EULAR good response versus no response (OR=4.01, 95% CI 1.92–8.49, p=5.067 × 10-5, MAF=0.25). Patients with one of these variations were more likely to achieve a EULAR good response compared to patients without these variations (OR=5.8; 95% CI 2.50–14.24; p=3.623 × 10-6).

Conclusion: Genetic variations within the CD6 gene and the STXBP6 gene were significantly associated with EULAR good response in a cohort of Danish patients with RA treated with TNFα inhibitors in routine care. This suggests that genetic variations within these genes may influence response to TNFα inhibitors and therefore may be useful as predictive biomarkers in patients with moderate or severe RA treated with TNFα inhibitors.

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A Calcineurin Inhibitor FK506 Suppresses Joint Destruction in Patients with Early Rheumatoid Arthritis and Low Disease Activity. Yoshiya Tanaka[1], Shinichi Kawai[2], Tsutomu Takeuchi[3], Kazuhiko Yamamoto[4], Shinya Tani[5], Toshiyuki Okada[5] and Nobuyuki Miyasaka[6]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [2]Toho Uni Sch of Med, Tokyo, Japan, [3]Keio University School of Medicine, Tokyo, Japan, [4]Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan, [5]Astellas Pharma Inc., Tokyo, Japan, [6]Tokyo Medical and Dental University, Tokyo, Japan

Background/Purpose: A multicenter, randomized, double-blind, placebo-controlled study of the calcineurin inhibitor FK506 (tacrolimus) was performed in patients with early-stage RA and a poor response to DMARDs (*Modern Rheumatology*, in press). In this paper, background factors related to suppression of joint destruction by FK506 were clarified and subanalysis was performed in patients with those factors to assess a change in the total Sharp score (ΔTSS).

Methods: A 52-week, multicenter, randomized, double-blind, placebo-controlled study was performed in 123 patients with RA for no more than 3 years who showed a poor response to DMARDs and were randomized to additional FK506 (3 mg/day) or placebo while continuing their previous therapy. Univariate analysis was performed in patients with X-ray films obtained in week 12 or later to examine the factor contributing most to ΔTSS<0.5 in week 52. Subanalysis was done in the patients with this factor to examine the primary endpoint (ΔTSS in week 52) and the secondary endpoints (ACR improvement criteria, EULAR improvement criteria, and safety) of this study. Missing data on X-ray films were supplemented by extrapolation and other missing data were obtained by LOCF.

Results: A baseline CRP level<1.5 mg/dL was extracted by univariate analysis as the factor contributing most to ΔTSS<0.5 in the FK506 group by week 52. Then subanalysis was performed of the patients with a baseline CRP<1.5 mg/dL. Significant differences of patient background were not observed between the groups. The primary endpoint (ΔTSS in week 52) was 2.67±5.40 (n=29) in the FK506 group and 8.05±10.32 (n=31) in the placebo group, and was significantly smaller in the FK506 group (p=0.017: analysis of covariance with the baseline data and with or without concomitant MTX as covariates) (Table). The FK506 group also had a significantly higher percentage of patients with a moderate response or better by EULAR criteria in week 52 (Table). Both groups had a similar incidence of adverse drug reactions.

Radiographic progression in week 52 (baseline CRP<1.5 mg/dL)

	FK506 (n=29)	Placebo (n=31)	*p*-value
ΔTSS	2.67 ± 5.40	8.05 ± 10.32	0.017

Clinical outcome in week 52 (baseline CRP<1.5 mg/dL)

	FK506 (n=32)	Placebo (n=31)	*p*-value
EULAR good/moderate (%)	78.1	51.6	0.030

Conclusion: Addition of FK506 to DMARDs significantly suppressed disease activity and joint destruction in patients with early rheumatoid arthritis and low disease activity who had a disease duration≤3 years, a CRP<1.5 mg/dL, and a poor response to oral DMARDs.

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One Year Efficacy and Safety Results of a Phase II Trial of Secukinumab in Patients with Rheumatoid Arthritis. Mark C. Genovese[1], Patrick Durez[2], Hanno B. Richards[3], Jerzy Supronik[4], Eva Dokoupilova[5], Jacob A. Aelion[6], Sang-Heon Lee[7], Christine E. Codding[8], Herbert Kellner[9], Takashi Ikawa[10], Sophie Hugot[3], Gregory Ligozio[11] and Shephard Mpofu[3]. [1]Stanford University, Palo Alto, CA, [2]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, [3]Novartis Pharma AG, Basel, Switzerland, [4]NZOZ Centrum Medyczne Artur Racewicz, Bialystok, Poland, [5]Medical Plus s.r.o, Uherske Hradiste, Czech Republic, [6]Arthritis Clinic, Jackson, TN, [7]Konkuk University Medical Center, Seoul, South Korea, [8]Health Research of Oklahoma, Oklahoma City, OK, [9]Centre for Inflammatory Joint Diseases, Munich, Germany, [10]Kobe–Konan Yamate Clinic, Kobe, Japan, [11]Novartis Pharmaceuticals Corporation, East Hanover, NJ

Background/Purpose: To assess the efficacy and safety of secukinumab (AIN457) in patients with active rheumatoid arthritis (RA) despite stable methotrexate (MTX) up to Week 52.

Methods: Adult RA patients (n=237) on MTX were randomized equally to receive monthly s.c injections of secukinumab 25mg, 75mg, 150mg, 300mg or placebo. The primary endpoint was the proportion of patients achieving American College of Rheumatology (ACR) 20 at Week 16. After Week 16, responders on secukinumab remained on the same dose whereas doses were escalated in non-responders at Week 20 (except patients dosed initially on 300mg who remained on the same dose). All placebo patients were switched to secukinumab 150mg. Patients were followed through Week 52.

Results: Demographics and baseline characteristics were comparable across all groups. ACR20 responder rates at Week 16 were higher with secukinumab 75mg, 150mg and 300mg (47%, 47% and 54%, respectively) *vs* placebo (36%) but did not reach statistical significance.

Responders on secukinumab maintained their ACR20 response from Week 24 to 52. Improvement in ACR20 response rates at weeks 24 and 52 were seen in patients who remained on secukinumab 150mg for the entire study [15/20 (75%) and 18/20 (90%), respectively]. Through Week 52, responders who remained on secukinumab 150mg had further improvement in ACR50 and ACR70 with the highest increases seen in ACR70 [4/20 (20%)

and 8/20 (40%) at weeks 24 and 52, respectively] as did responders who switched from placebo to secukinumab 150mg [1/18 (6%) and 4/18 (22%) at weeks 24 and 52, respectively] (Figure 1).

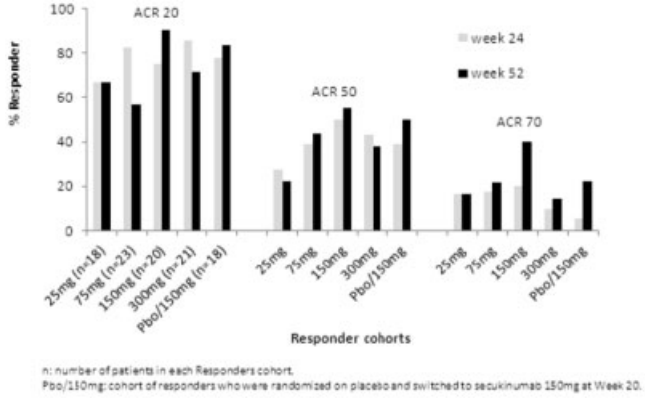

Figure 1. ACR20, ACR50 and ACR70 response rates in Week-16 responders at weeks 24 and 52.

DAS28-CRP reductions were sustained up to Week 52 in responders. Responders who remained on secukinumab 150mg had improvement in HAQ scores (−0.6 at Week 24 *vs* −0.8 at Week 52). Non-responders did not gain much additional efficacy benefit after dose escalation as assessed by ACR20/50/70 and DAS28-CRP. The overall rates of AEs at Week 52 remained comparable to data seen at Week 20 (60–70%) and most AEs were mild to moderate in severity and did not lead to study discontinuation (6.9%). The rate of infections was 31.9% overall. Twenty one (9.7%) SAEs were reported including 6 cases of serious infections without dose relationship. There were 3 malignancies and no deaths up to Week 52.

Conclusion: The primary efficacy endpoint was not achieved in this trial possibly due to an unexplained increase in ACR20 in the placebo group between weeks 12 (24%) and 16 (36%). However, ACR20-responders at Week 16 experienced maintenance or improvement of efficacy through Week 52 with highest efficacy in patients who remained on 150mg throughout the trial. Patients on secukinumab who were non-responders at Week 16 did not gain much additional efficacy benefit after dose escalation. Secukinumab was well tolerated and the rate and frequency of AEs remained stable over time without unexpected safety findings.

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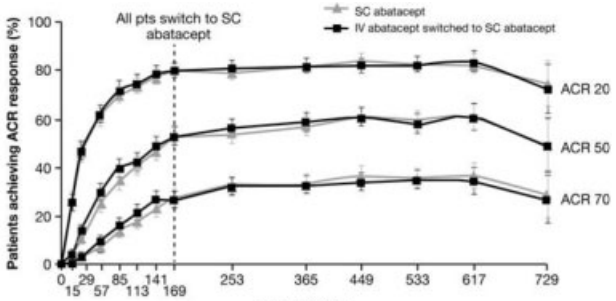
Subcutaneous (SC) Abatacept (ABA) Versus Intravenous (IV) ABA in Patients (pts) with Rheumatoid Arthritis: Long-Term Data From the ACQUIRE (Abatacept Comparison of Sub[QU]cutaneous versus Intravenous in Inadequate Responders to MethotrexatE) Trial. Mark C. Genovese[1], Arturo Covarrubias Cobos[2], Gustavo Leon[3], Eduardo F. Mysler[4], Mauro W. Keiserman[5], Robert M. Valente[6], Peter T. Nash[7], J. Abraham Simon Campos[8], Wieslawa Porawska[9], Jane H. Box[10], Clarence W. Legerton III[11], Evgeny L. Nasonov[12], Patrick Durez[13], Ramesh Pappu[14], Ingrid Delaet[14], Julie Teng[14] and Rieke Alten[15]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]Calle Maiz No 49, Mexico, Mexico, [3]Instituto De Ginecologia Y Reproduccion, Lima, Peru, [4]OMI, Buenos Aires, Argentina, [5]Pontiphycial Catholic Univ, Porto Alegre, Brazil, [6]Arthritis Center of Nebraska, Lincoln, NE, [7]University of Queensland, Brisbane, Australia, [8]Centro De Especialidades Médicas, Merida, Mexico, [9]Poznański Ośrodek Medyczny 'Novamed', Poznań, Poland, [10]Box Arthritis & Rheumatology of the Carolinas, Charlotte, NC, [11]LowCountry Rheumatology, Charleston, SC, [12]Institue of Rheumatology, Moscow, [13]Université Catholique de Louvain, Brussels, Belgium, [14]Bristol-Myers Squibb, Princeton, NJ, [15]Schlosspark-Klinik, Berlin, Germany

Background/Purpose: Efficacy and safety of IV ABA is well established in RA. The ACQUIRE trial showed comparable safety and efficacy in SC vs IV ABA over 6 mths[1]; here, we present 18-mth data from the long-term extension (LTE).

Methods: ACQUIRE was a Phase IIIb, 6-mth, double-blind (DB) double-dummy study of pts with active RA (≥10 swollen and ≥12 tender joint count [TJC and SJC], CRP ≥0.8 mg/dL) refractory to MTX. Pts were randomized to SC ABA (125 mg/week) with IV ABA loading (~10 mg/kg) on Day 1 or IV ABA (~10 mg/kg) on Days 1, 15, 29 and every 4 wks for 6 mths; all pts received MTX. After 6 mths pts could enter the open-label LTE to receive SC ABA 125 mg/week. Safety, immunogenicity (by electrochemiluminescence), and efficacy (ACR 20, 50 and 70 and HAQ-DI responses [improvement from baseline (BL) ≥0.3]) were assessed for pts treated with ≥1 dose of ABA in the LTE. Efficacy data are as-observed; not all pts reached later timepoints at time of analyses.

Results: Of 1372 pts entering the LTE, 1222 (89.1%) remained on therapy at time of reporting. Overall mean BL RA duration was 8 yrs, TJC and SJC were 30 and 20, and HAQ-DI was 1.7; characteristics were similar between groups. Median (SD) ABA exposure was 22 (3.8) mths. The IR (events/100 pt–yrs) of SAEs in the LTE was comparable with that seen with SC ABA in the DB period (9.00 [95% CI: 7.69–10.55] and 9.02 [6.31–12.90], respectively) and did not increase with increasing exposure (not shown). The IR of overall and serious infections in the LTE did not increase vs the DB period (47.64 [44.01–51.58] vs 84.62 [74.50–96.11] and 1.97 [1.41–2.74] vs 1.48 [0.62–3.56] respectively) and did not increase with increasing exposure (not shown). Opportunistic infections in the LTE included 3 TB cases and 2 candidiasis cases; no opportunistic infections were observed in the DB period. Injection site reactions occurred in 24 (1.7%) pts in the LTE (none serious). ABA-induced antibodies occurred in 39/1365 (2.9%) pts in the LTE; 4/11 pts with anti-CTLA4 antibodies eligible for testing were positive for neutralizing antibody. Immunogenicity did not affect efficacy, safety or ABA pharmacokinetics (data not shown). ACR responses up to Mth 24 were maintained from Mth 6 and comparable between original SC vs IV groups (Fig). DAS28 remission rates (95% CIs) were 24 (21–27) [n=685] vs 25% (22–28) [n=688] at Day 169 and 32 (22–42) [n=85] vs 31% (20–41) [n=72] at Day 729 in the original SC vs IV groups, respectively. HAQ responses (95% CIs) were 73 (69–76) [n=691] and 68% (65–72) [n=672] at Day 169 and 63 (53–73) [n=87] and 56% (45–67) [n=77] at Day 729 in the original SC and IV groups, respectively. At the time of analyses, most patients had not completed the later timepoints (Days 617, 729).



	Original treatment group	Patients with available data at each visit*												
		15	29	57	85	113	141	169	253	365	449	533	617	729
ACR 20	SC abatacept	685	687	684	685	687	685	686	685	661	648	587	325	86
	IV abatacept	665	668	668	669	670	671	670	667	652	635	572	312	76
ACR 50	SC abatacept	688	690	687	686	686	684	689	683	663	648	588	324	85
	IV abatacept	669	673	671	672	670	671	672	668	653	635	571	311	77
ACR 70	SC abatacept	689	689	688	686	689	690	690	685	666	650	586	326	87
	IV abatacept	669	673	670	672	669	671	671	666	655	637	571	312	78

*Not all patients reached later timepoints at time of data analysis; SC=subcutaneous; IV=intravenous

Conclusion: Over 24 mths, SC ABA showed acceptable safety, with high pt retention, similar to the IV experience. Efficacy was comparable between SC and IV groups; ACR and HAQ responses and DAS28 remission rates were maintained in the LTE.

[1]Genovese et al. *A&R* 2011;DOI:10.1002/art.30463

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Safety Profile of Subcutaneous Abatacept Focusing on Clinically Relevant Events in Patients with Rheumatoid Arthritis (RA) and up to 4.5 Years of Exposure. Rieke Alten[1], Jeffrey L. Kaine[2], Edward Keystone[3], Peter T. Nash[4], Ingrid Delaet[5], Keqin Qi[5] and Mark C. Genovese[6]. [1]Rheumatology Schlossparkklinik, Berlin, Germany, [2]Sarasota Arthritis Center, Sarasota, FL, [3]Mount Sinai Hospital, Toronto, ON, [4]University of Queensland, Brisbane, Australia, [5]Bristol-Myers Squibb, Princeton, NJ, [6]Stanford Univ Medical Center, Palo Alto, CA

Background/Purpose: Biologic therapies for RA can increase the risk of some safety events such as infections, autoimmune events and malignancies. Furthermore, with subcutaneous (SC) biologics, some patients (pts) may experience injection site reactions (ISRs), such as burning and stinging[1]. Integrated analyses of clinical trial data are important to monitor these events over the long term. Here, we investigate such events using integrated clinical

trial data of SC abatacept in a large group of pts with RA refractory to traditional DMARDs.

Methods: Data from the short- and long-term periods of five SC abatacept RA clinical trials were pooled; one Phase IIa and two Phase IIIb randomized controlled trials (ACQUIRE, ALLOW), and two Phase IIIb open-label studies (ATTUNE, ACCOMPANY). Safety events were assessed for pts who received ≥1 dose of SC abatacept (125 mg/week fixed dose). Overall and 6-mthly (up to Mth 24) incidence rates (IRs) were calculated as number of patients with events per 100 patient–years (p–y) of exposure, with 95% confidence intervals (CIs). IRs post Mth 24 not shown due to low pt numbers at time of data analysis.

Results: The analysis included 1879 pts with 3086 p–y of exposure. Mean (range) exposure was 20 (2–56) mths; 1191 pts had >18 mths of exposure. Serious infections occurred at an IR (95% CI) of 1.94 (1.50–2.50), in 59 (3.1%) pts; the most frequent (IR>0.10) were pneumonia (0.36 [0.20–0.65]), urinary tract infection (0.16 [0.07–0.39]) and gastroenteritis (0.13 [0.05–0.35]). TB, pulmonary TB and peritoneal TB were recorded in one pt each (0.03 [0.00–0.23] each). Malignancies excluding non-melanoma skin cancer occurred at an IR of 0.68 (0.45–1.05) in 21 (1.1%) pts. The most frequent (IR>0.10) malignancies were basal cell carcinoma (0.46 [0.27–0.77]), breast cancer and squamous cell carcinoma of skin (0.16 [0.07–0.39] each). Autoimmune events occurred with an IR of (1.28 [0.93–1.75]) in 39 (2.1%) pts. The most frequent (IR>0.10) autoimmune events were psoriasis (0.29 [0.15–0.56]) and Sjögren's syndrome (0.19 [0.09–0.43]). IRs of serious infections, malignancies and autoimmune events did not increase with increasing exposure (Table). ISRs occurred with an IR of (2.22 [1.74–2.82]) in 66 (3.5%) pts; the most frequent were erythema, hematoma, pain and pruritus (0.46 [0.27–0.77] each). Events were mostly (94%) mild in intensity; two pts discontinued due to ISRs. ISRs mainly occurred during the first 6 mths (Table).

Table 1. Incidence rates of events in pts receiving SC abatacept (N=1879)

Mths	0–6	6–12	12–18	18–24
Serious infections*	2.42 (1.60–3.68)	2.12 (1.33–3.36)	1.28 (0.66–2.46)	1.51 (0.68–3.36)
	n = 22	n = 18	n = 9	n = 6
Malignancies excl. NMSC	0.44 (0.16–1.17)	1.17 (0.63–2.17)	0.56 (0.21–1.49)	0.25 (0.03–1.75)
	n = 4	n = 10	n = 4	n = 1
Autoimmune events†	1.54 (0.91–2.60)	0.94 (0.47–1.87)	0.99 (0.47–2.08)	1.75 (0.84–3.68)
	n = 14	n = 8	n = 7	n = 7
Total ISRs†	5.59 (4.24–7.38)	0.72 (0.32–1.59)	1.30 (0.68–2.50)	0
	n = 50	n = 6	n = 9	

* Subset of serious adverse events; †Pre-specified based on a list of MedDRA preferred terms; Data are IR (95% CI); NMSC = non-melanoma skin cancer; ISR=injection site reaction; Mths 0–6 is Day 1–Day 180, Mths 6–12 is Day 181–Day 360, Mths 12–18 is Day 361–Day 540, Mths 18–24 is Day 541–Day 720.

Conclusion: These pooled safety data, from 1879 pts with up to 4.5 yrs of treatment and 3086 p–y of exposure, demonstrate that long-term treatment with SC abatacept is well tolerated, and does not lead to an increase in infections, malignancies or autoimmune events over time. ISRs were generally mild and infrequent. Data presented here are consistent with observations for IV abatacept[1].

[1]Curtis JR, et al. *Curr Med Res Opin* 2011;**27**:71–8
[2]Hochberg M, et al. *Arthritis Rheum* 2010;**62**:S164

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Efficacy, Safety and Pharmacokinetics of Subcutaneous Abatacept in Patients with Rheumatoid Arthritis, with or without An Intravenous (IV) Loading Dose. Peter T. Nash[1], Charles L. Ludivico[2], Ingrid Delaet[3], Keqin Qi[3], Bindu Murthy[3], Michael Corbo[4] and Jeffrey L. Kaine[5]. [1]University of Queensland, Brisbane, Australia, [2]East Penn Rheumatology Associates, East Stroudsburg, PA, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Bristol-Myers Squibb (at time of study), Princeton, NJ, [5]Sarasota Arthritis Center, Sarasota, FL

Background/Purpose: Use of IV abatacept is well established in pts with RA. Pivotal trials of SC abatacept ± MTX have shown efficacy. Some trials included an IV abatacept loading dose to rapidly achieve therapeutic steady-state drug concentrations (C_{minss} ≥10 μg/mL). We evaluated open-label data from two Phase III trials to examine the 3-mth efficacy and clinical pharmacokinetics (PK) of SC abatacept (125 mg/wk), with/without IV loading, in pts with established DMARD-refractory RA.

Methods: In the initial open-label (OL) period of the ALLOW trial, pts received SC abatacept + MTX, with IV loading on Day 1 (~10 mg/kg according to weight; SC + IV load). In the OL ACCOMPANY trial, pts were stratified to SC abatacept ± MTX, with no IV load (SC only). Pts in both trials had RA refractory to biologic or non-biologic DMARDs. Data up to Mth 3 for disease activity (DAS28-CRP) and physical function (HAQ-DI) were based on pts with data available (clinically meaningful responses [CMRs] defined as reductions of ≥1.2 in DAS28 and ≥0.3 in HAQ-DI). PK was assessed for both trials using a validated ELISA to determine abatacept serum trough concentrations (C_{min}).

Results: A total of 167 pts entered ALLOW and received SC abatacept+ IV load, 100 pts entered ACCOMPANY and received SC only (± MTX). Mean (SD) baseline demographics were generally similar between studies, although baseline disease was less severe in SC + IV versus SC only pts; tender and swollen joints were 14.3 (10.3) and 11.0 (5.7) vs 24.1 (16.2) and 17.2 (12.1), DAS28 was 4.7 (0.9) vs 5.4 (1.4) [n=98] and HAQ-DI was 1.3 (0.7) vs 1.4 (0.7) [n=99]. Mean (SD) disease duration was 7.5 (8.0) yrs vs 10.1 (11.1) yrs in SC + IV versus SC only pts, respectively. All SC + IV pts and 81% of SC only pts had previously failed MTX; 11 and 23% of pts had previously received biologics. Improvements in DAS28 and HAQ-DI were generally comparable with or without IV load (Table); CMRs were observed in both trials by ≤Mth 2. By Mth 3, mean (SD) DAS28 was 3.2 (1.3) vs 3.8 (1.4) for SC + IV vs SC only, respectively, and HAQ-DI was 0.7 (0.7) vs 1.1 (0.7). Mean (SE) changes in DAS28 from baseline to Mths 1, 2 and 3 were –1.00 (0.07), –1.35 (0.08) and –1.53 (0.10) for SC + IV and –0.85 (0.11), –1.35 (0.12) and –1.57 (0.14) for SC only. Occurrence of serious adverse events, including infections, was similar with or without IV load. PK assessments indicated target therapeutic C_{min} was achieved by Day 15 in 88% of pts in the SC only study. C_{minss} concentrations were achieved by Mth 2 in both trials and remained consistent to Mth 3 (Table).

Mean percentage change from baseline (95% CI)	ALLOW (SC + IV load)	ACCOMPANY (SC only)		
	DAS28 (CRP)	HAQ-DI	DAS28 (CRP)	HAQ-DI
Month 1	−21.7 (−24.8, −18.7)	−27.3 (−32.6, −22.0)	−14.2 (−19.1, −9.3)	−21.3 (−28.7, −13.9)
	n = 165	n = 166	n = 95	n = 94
Month 2	−28.0 (−31.5, −24.6)	−37.7 (−44.7, −30.8)	−24.0 (−28.4, −19.6)	−29.8 (−37.5, −22.1)
	n = 164	n = 163	n = 96	n = 93
Month 3	−31.6 (−35.5, −27.7)	−44.6 (−51.8, −37.5)	−27.8 (−32.8, −22.9)	−32.2 (−40.4, −24.0)
	n = 161	n = 163	n = 94	n = 92
Geometric mean (CV%) of C_{min} (μg/mL)	**ALLOW (SC + IV load)**		**ACCOMPANY (SC only [without MTX − with MTX])**	
Month 0.5 (Day 15)	Not collected		11.2 (44) − 13.7 (30)	
			n = 81	
Month 2	27.0 (37)		21.7 (47) − 24.4 (28)	
	n = 144		n = 86	
Month 3	27.6 (40) n = 132		20.4 (41) − 28.8 (37)	
			n = 86	

CI = confidence interval; ALLOW = Evaluation of **A**batacept Administered Subcutaneous**L**y in Adu**L**ts With Active Rheumat**O**id Arthritis: Impact of **W**ithdrawal and Reintroduction on Immunogenicity, Efficacy and Safety; ACCOMPANY = **A bataC**ept in Subje**C**ts with Rheumat**O**id Arthritis Ad**M**inistered **P**lus or Minus Background MTX Subcut**AN**eous**lY**; SC = subcutaneous; IV = intravenous; DAS28 = Disease Activity Score 28; CRP = C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; CV = co-efficient of variation; C_{min} = serum trough concentration.

Conclusion: Comparable improvements in clinical efficacy were observed over the first 3 mths, with or without IV loading. Target PK values required for efficacy were achieved in both regimens, and the majority of pts achieved therapeutic abatacept concentrations by Day 15 without IV loading. These data, although a non-comparative cross-study assessment, support the hypothesis that IV loading may not be needed to achieve desired efficacy with SC abatacept.

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Prevention of Cartilage Destruction by Etanercept (PRECEPT) Study: the Comparison of Joint Destruction Between Low-Dose and Standard-Dose Etanercept in Rheumatoid Arthritis. Masahiro Tada, Tadashi Okano, Yuko Sugioka, Kenji Mamoto, Shigeyuki Wakitani, Hiroaki Nakamura and Tatsuya Koike. Osaka City University Medical School, Osaka, Japan

Background/Purpose: The efficacy and safety of etanercept (ETN) in patients with rheumatoid arthritis (RA) have been demonstrated in clinical trials. The combination therapy of ETN and methotrexate could inhibit the progression of joint destruction and repair the bone erosion. However, it is a fact that biologics therapy forces patients to an economic burden. To reduce the treatment cost of biologic agents, low-dose ETN has been administered without evidence in real world practice. Although clinical symptom might be improved by low-dose ETN, it has not been reported whether low-dose ETN could inhibit joint destruction. To evaluate the prevention of joint destruction and clinical efficacy of low-dose ETN (25mg/W), we compared with standard-dose ETN (50mg/W) in RA patients.

Methods: This prospective, randomized, open-label study was registered

with the UMIN Clinical Trials Registry (UMIN000001798). This study was conducted at 7 sites in Japan between July 2008 and February 2010. 70 patients were randomly assigned to receive either ETN 50mg or 25mg at subcutaneous injection for 52 weeks. The primary end point of this study was the variation of modified total Sharp score (TSS), and the secondary end points were variation of disease activity score 28 (DAS28), modified Health Assessment Questionnaire (mHAQ), and adverse events. TSS was performed at baseline and after one year. No progression was estimated as *delta* TSS <= 0.5 and no progression rate was compared between groups. DAS28 and mHAQ were calculated at baseline and after 4, 8, 12, 24 and 52 weeks. No progression rate was analysed by Fisher's exact probably test. The characteristics between groups were tested using the Mann-Whitney and Fisher's exact probably test.

Results: Patients had mean disease duration of 9.2 years, DAS28 of 5.45, and annual progression of TSS of 26.1 at baseline. There were no significant differences in all parameters between groups at baseline (Table 1). At week 52, no progression rate of 25 mg/W group (36.7%) was significantly less than that of 50mg/W group (67.7%) (P = 0.041). *Delta* TSS of 25mg/W (1.03) was higher than that of 50mg/W group (−0.13) in Table 2. DAS 28 was significantly improved at week 4 and the effect of treatment lasted for one year in both groups, without significant differences between groups. There were no differences in mHAQ and adverse events between groups.

Table 1. Characteristics of patients at baseline

	Etanercept 25mg/W	Etanercept 50mg/W
Age, years (±SD)	61.7 ± 11.8	59.6 ± 10.0
Women, no. (%)	74.3	85.7
Weight, kg (±SD)	55.3 ± 9.0	51.9 ± 10.1
BMI, kg/m^2 (±SD)	22.8 ± 2.7	21.4 ± 3.0
Disease duration, years (±SD)	9.0 ± 8.0	9.3 ± 6.5
DAS28 - ESR (±SD)	5.36 ± 1.24	5.53 ± 1.25
SDAI (±SD)	23.9 ± 13.5	25.7 ± 12.9
mHAQ score (±SD)	0.9 ± 0.6	1.0 ± 0.6
modified total Sharp score (±SD)	136.5 ± 107.2	183.2 ± 102.6
Erosion score (±SD)	74.2 ± 65.4	99.3 ± 64.4
Joint space narrowing score (±SD)	62.3 ± 43.2	83.9 ± 39.3
Annual TSS progression (±SD)	24.6 ± 23.4	27.5 ± 21.0

Table 2. Change in radiographic scores at week 52

	Etanercept 25mg/W	Etanercept 50mg/W
modified total Sharp score	1.03 (−0.23 to 2.29)	−0.13 (−1.46 to 1.20)
Erosion score	0.47 (−0.22 to 1.16)	−0.26 (−1.00 to 0.48)
Joint space narrowing score	0.56 (−0.15 to 1.28)	0.13 (−0.65 to 0.91)

Conclusion: Low-dose ETN was not inferior to standard-dose ETN in the effect on clinical manifestations. However, from the viewpoint of joint destruction suppression, it was inferior to the effect of standard-dose ETN.

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No Change in the Levels of PPD Reaction During Treatment with TNF Inhibitors in Rheumatoid Arthritis Patients in Japan, a Country with High Morbidity of Tuberculosis. Shotaro Yamamoto, Shino Takatori, Masahiro Iwamoto, Katsuya Nagatani, Kohei Ikenoya and Seiji Minota. Jichi Medical University, Tochigi, Japan

Background/Purpose: TNF inhibitors (TNFi) may depress cell-mediated immunity resulting in a higher incidence of tuberculosis among RA patients. Post-marketing surveillance of infliximab in Japan revealed 14 cases of tuberculosis out of 5,000 (0.28%) that developed after starting infliximab. The morbidity is ~6 times higher than that in the general population in Japan. To estimate the level of cell-mediated immunity and the risk of tuberculosis reactivation, levels of PPD reaction were examined before and after treatment with TNFi.

Methods: Of 209 RA patients treated with TNFi (infliximab or etanercept) for more than 1 year, written informed consent was obtained from 91 (43.5%), who were included in this study. The study group included: 76 females, 15 males; age, 55.3 ± 14.3 years; infliximab 40, etanercept 51; prednisolone dose at the start, 3.7 ± 2.9 mg/day; and duration of TNFi treatment, 2.5 ± 1.0 years. DMARDs used simultaneously with TNFi included methotrexate in 69, sulfasalazine in 16, bucillamine in 6, actarit in 4, leflunomide in 1, tacrolimus in 1, and azathioprine in 1. The PPD reaction level was measured 48~72 hr after intra-dermal injection and categorized as: diameter < 10 mm, negative (N); ≥ 10 mm, weakly positive (WP); ≥ 10 mm with induration, intermediately positive (IP); and IP with double-circumscribed erythema, vesicles or necrosis, strongly positive (SP). PPD skin tests were performed before and after > 1 year of continuous TNFi. All patients with IP and SP received prophylaxis with isoniazid as recommended.

Results: Just before the introduction of TNFi, 49.4%, 20.9%, 22.0% and 7.7% of the patients showed PPD reactions of N, WP, IP and SP, respectively, and after >1 year of TNFi, 48.3%, 22.0%, 17.6% and 12.1% exhibited PPD reactions, respectively. There was no significant difference in the reactions before and after TNFi-treatment (Wilcoxon signed rank test [p = 0.652]). PPD reaction levels were in the same category in 54.9%, decreased by more than 1 category in 23.1% and increased by more than 1 category in 22.0%, and highly correlated with a Spearman's correlation coefficient of 0.491 (p < 0.001). Only one patient initially SP became WP, whereas, no patients initially SP became N. This patient had been in clinical remission of RA after TNFi-treatment and showed no sign of compromised immunity. Two patients initially N became SP at the second PPD test. Both were in clinical remission of RA, and showed no sign of tuberculosis.

Conclusion: Higher positivity rates for PPD reaction in this study compared to other studies may be due to BCG inoculation, which is routine in Japan. Overall, levels of PPD reaction stayed unchanged before and after > 1 year of continuous TNFi. Two patients initially N became SP without any sign of tuberculosis; this could be due to a booster effect of PPD or a dormant reactivation of tuberculosis that cured spontaneously. One patient who became WP after the initial SP needs to be followed carefully for possible immunosuppression. Since no RA patients developed overt tuberculosis until now, recommended prophylaxis against tuberculosis would be appropriate.

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Tofacitinib (CP-690,550), An Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Open-Label, Long-Term Extension Studies up to 36 Months. J. Wollenhaupt[1], J. C Silverfield[2], E. B. Lee[3], S. Wood[4], K. Soma[5], L. Wang[5], H. Nakamura[6], Y. Komuro[6], C. I. Nduaka[5], D. Gruben[5], S. H. Zwillich[5] and J. D. Bradley[5]. [1]Teaching Hospital of the University of Hamburg, Hamburg, Germany, [2]Tampa Medical Group, P.A., Tampa, FL, [3]Hanyang University Hospital, Seoul, [4]Pfizer Inc., Groton, NJ, [5]Pfizer Inc., Groton, CT, [6]Pfizer Inc., Tokyo, Japan

Background/Purpose: Tofacitinib (CP-690,550) has recently reported efficacy and safety data in pts with active rheumatoid arthritis (RA) in randomized Phase 3 studies of up to 12 months (mo) treatment duration. Here we report the safety and tolerability of tofacitinib and the durability of clinical response up to 36 mo in long-term extension (LTE) studies in pts with RA.

Methods: Data were pooled from two Phase 2/3, open label studies (NCT00413699, NCT00661661) involving pts who had participated in prior randomized studies of tofacitinib (PRST). Treatment was initiated with either 5 or 10 mg tofacitinib twice daily (BID). The baseline was that of the PRST for pts who enrolled within 14 days of PRST participation; if enrollment was >14 days after PRST participation, baseline was the start of the LTE study. The primary endpoints were laboratory safety and adverse event (AE) reports. Secondary endpoints included ACR20, ACR50, and ACR70 response rates, DAS28-4(ESR), and the HAQ-DI. Data are reported for all patients regardless of dose.

Results: A total of 3227 pts were treated for a total duration of 3118 patient-years (pt-y); mean (maximum) duration of treatment was 349 (1456) days (d). 441 pts (13.7%) discontinued from the LTE studies: 223 (6.9%) due to AEs and 42 (1.3%) due to insufficient clinical response. A total of 7747 treatment-emergent AEs (TEAEs) were reported in 2135 patients (66.2%). The most commonly reported class of TEAEs was infections and infestations (39.7%), followed by gastrointestinal disorders (18.8%), musculoskeletal and connective tissue disorders (15.9%), and investigations (11.7%). The most frequent investigator-reported TEAEs (n, %) by MedDRA preferred term were nasopharyngitis (322, 10.0%), upper respiratory tract infection (236, 7.3%) and urinary tract infection (150, 4.6%). Serious AEs were reported in 337 pts (10.9%) with an incidence rate per 100 pt-y of 11.34 (95% CI 10.20, 12.62). Serious infection events were reported in 93 pts (2.9%) with an incidence rate per 100 pt-y of 3.01 (95% CI 2.45, 3.68).

Decreased hemoglobin (≥2 g/dL from baseline, or hemoglobin <8) was observed in 81 pts (2.5%). Raised aminotransferases (>3 × upper limit of normal) were observed in 1.7% (alanine) and 1.1% (aspartate) of evaluable pts. Moderate to severe neutropenia (absolute neutrophil count [ANC] $<1.5 \times 10^3/mm^3$) was reported in 16 pts (0.5%); no serious neutropenia (ANC $<0.5 \times 10^3/mm^3$) was reported. Confirmed increase in creatinine (≥33% from baseline) was noted in 393 (12.2%) pts. Mean overall values for laboratory safety tests were stable over time.

ACR20, ACR50, and ACR70 response rates were consistent over time

between Mo 1 and 36. At Mo 1, ACR20, ACR50, and ACR70 response rates for patients initially treated with tofacitinib 5 or 10 mg BID were 71.0%, 47.3%, and 26.3%, respectively; corresponding rates at Mo 36 were 72.7%, 52.3%, and 35.2%, respectively.

Mean DAS28-4(ESR) was 6.25 at baseline, and was reduced to approximately 3.5 between Mo 1 and 36. Mean HAQ-DI score was 1.41 at baseline and improved to approximately 0.8 between Mo 1 and 36.

Conclusion: Treatment with tofacitinib at doses of 5 or 10 mg BID in pts with RA demonstrated a well-tolerated safety profile and sustained long-term efficacy over a 36-mo period.

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Tofacitinib (CP-690,550), An Oral Janus Kinase Inhibitor, or Adalimumab Versus Placebo in Patients with Rheumatoid Arthritis on Background Methotrexate: A Phase 3 Study. R.F. van Vollenhoven[1], R. M. Fleischmann[2], S. B. Cohen[3], E. B. Lee[4], G. Meijide[5], S. Wagner[6], S. Forejtova[7], S. H. Zwillich[8], D. Gruben[8], T. Koncz[9], G. Wallenstein[8], S. Krishnaswami[8], J. D. Bradley[8], B. Wilkinson[8] and the ORAL Standard investigators[10]. [1]Karolinska Institute, Stockholm, Sweden, [2]Metroplex Clinical Research Center, Dallas, TX, [3]Metroplex Clinical Research Centre, Dallas, TX, [4]Seoul National University, Seoul, South Korea, [5]Hospital Ntra. Sra. de la Esperanza, Santiago de Compostela, Spain, [6]Internistische Schwerpunktpraxis für Rheumatologie, Halle, Germany, [7]Revmatologicky ustav no 5, Prague, Czech Republic, [8]Pfizer Inc., Groton, CT, [9]Pfizer Inc., New York, NY, [10]Groton, CT

Background/Purpose: Tofacitinib (CP-690,550) is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator in rheumatoid arthritis (RA). This 12-month (Mo) study (NCT00853385) compared the efficacy and safety of tofacitinib and an active comparator, adalimumab (ADA), vs placebo (PBO) in pts with active RA with inadequate response to methotrexate (MTX).

Methods: Pts on background MTX were randomized in a 4:4:4:1:1 ratio to 1 of 5 sequences: tofacitinib 5 mg BID; 10 mg BID; ADA 40 mg subcutaneous injections (Q2W); PBO advanced to tofacitinib 5 mg BID; and PBO advanced to 10 mg BID. All pts self-administered injections Q2W (ADA or PBO). Pts on PBO advanced to tofacitinib at Mo 6, or at Mo 3 if non-responders (<20% reduction from baseline in swollen/tender joint counts).

Results: 717 pts were treated. Pts were comparable at baseline for age, disease duration, HAQ-DI, DAS28, and %RF positive. Tofacitinib 5 and 10 mg BID were statistically superior to PBO for all primary efficacy endpoints (Table). ADA was also superior to PBO for these endpoints. Significant ACR20, ACR50, and HAQ-DI responses were seen vs PBO by Mo 1. Efficacy results for tofacitinib and ADA were numerically similar for all outcomes. About half the pts in the tofacitinib 5 and 10 mg BID, ADA, and PBO groups experienced ≥1 adverse event (AE). Most AEs were mild; the % of pts who experienced a serious AE (SAE) was numerically higher in the tofacitinib groups. There were 2 deaths: sepsis syndrome (5 mg BID) and cardiac arrest (ADA), and 2 pts with pulmonary tuberculosis (both 10 mg BID). In Mo 0–3, serious infection events were reported for 3 (5 mg BID), 4 (10 mg BID), and 1 (PBO) pts; in Mo 3–6, for 2 (5 mg BID), 1 (10 mg BID), and 2 (ADA) pts. Decreases in mean neutrophil counts were seen with tofacitinib and ADA; increases in LDL and HDL, and small increases in serum creatinine were seen with tofacitinib. Safety results for Mo 6–12 for tofacitinib and ADA were consistent with safety for Mo 0–6 (Table).

Table. Primary and selected secondary efficacy endpoints and safety data

Efficacy		5 mg BID n=204	10 mg BID n=201	ADA 40 mg SC Q2W n=204	PBO n=108
ACR20[a]† (%)	Mo 6	51.5***	52.6***	47.2**	28.3
ACR50† (%)	Mo 6	36.7***	34.7***	27.6**	12.3
ACR70† (%)	Mo 6	19.9***	21.9***	9.1**	1.9
Mean change HAQ-DI[a]	Mo 3	−0.55***	−0.61***	−0.49***	−0.24
DAS28 <2.6[a]† (%)	Mo 6	7.3*	12.5***	6.2*	1.1
Mean change DAS28‡	Mo 3	−2.0***	−2.0***	−1.9***	−1

Safety n (%)		5 mg BID n=204	10 mg BID n=201	ADA 40 mg SC Q2W n=204	PBO n=108 (Mo 3) n=59 (Mo 3–6)	PBO to 5 mg BID n=28	PBO to 10 mg BID n=21
Mo 0–3	AEs	106 (52.0)	94 (46.8)	105 (51.5)	51 (47.2)	NA	NA
	SAEs	12 (5.9)	10 (5.0)	5 (2.5)	2 (1.9)	NA	NA
Mo 3–6	AEs	67 (32.8)	62 (30.8)	68 (33.3)	16 (27.1)	7 (25.0)	9 (42.9)
	SAEs	10 (4.9)	7 (3.5)	6 (2.9)	2 (3.4)	0	0

[a] Primary endpoints were tested by a step-down procedure. All p values are nominal and not corrected for multiple comparisons.
* p<0.05; **p<0.001; ***p<0.0001 vs PBO
† Non-responder imputation; ‡mixed-effect longitudinal linear model; NA, not applicable

Conclusion: Tofacitinib demonstrated rapid, significant, and clinically meaningful reductions in signs and symptoms of RA and physical function. No new tofacitinib safety signals were detected. Efficacy results with tofacitinib and ADA, when both were given on MTX background, were similar.

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Tofacitinib (CP-690,550), An Oral Janus Kinase Inhibitor: Analysis of Infections and All-Cause Mortality Across Phase 3 and Long-Term Extension Studies in Patients with Rheumatoid Arthritis. S. Cohen[1], S. C. Radominski[2], P. Asavatanabodee[3], S. P. Wood[4], K. Soma[4], C. I. Nduaka[4], L. Wang[4], D. Gruben[4], H. Valdez[5], S. H. Zwillich[4] and J. Bradley[4]. [1]Metroplex Clinical Research Centre, Dallas, TX, [2]Universidade Federal do Paraná, Curitiba, Brazil, [3]Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand, [4]Pfizer Inc., Groton, CT, [5]Pfizer Inc., New York, NY

Background/Purpose: Tofacitinib (CP-690,550) is a novel oral, selective Janus kinase inhibitor being investigated in Phase 3 (P3) as a targeted immunomodulator for the treatment of RA. Here we show pooled P3 and long-term extension (LTE) infection and mortality data for pts with RA.

Methods: Data were pooled from five randomized double-blind P3 RA studies. Most studies required stable background DMARDs to which tofacitinib was added (NCT IDs: 00960440, 00847613, 00856544, 00853385); one study evaluated tofacitinib monotherapy (NCT ID: 00814307). Pts from these studies had the option to join pts from P2 studies in one of two open-label, LTE studies (NCT IDs: 00413699, 00661661). LTE pts were treated with tofacitinib 5 or 10 mg twice daily (BID) and generally continued their background DMARD therapy as appropriate.

Deaths in the P3 programs and those that occurred after February 25, 2009 in the LTE studies were classified by an independent, blinded Cardiovascular Safety Endpoint Adjudication Committee (CV-SEAC).

Results: A total of 3030 pts with RA from P3 and 3227 from LTE studies were included in the analyses, resulting in approximately 2000 and 3000 pt-years (pt-y) of exposure to tofacitinib, respectively (Table). In the P3 studies, there were a total of 12 CV-SEAC-classified all-causality deaths (5 due to infections, 3 other [noncardiac], 2 cardiac, 1 trauma and 1 cause unknown) and 2 deaths with adjudication not available. In the LTE studies, there were a total of 8 CV-SEAC-classified all-causality deaths (3 due to infection, 2 other [noncardiac], 1 cancer, 1 cardiac, and 1 cause unknown) and 12 deaths were not adjudicated.

Concerning infections, the most common treatment-emergent infection adverse events (AEs) (>5% in any treatment group) in LTE studies were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, herpes zoster, and influenza. Infection AEs in P3 studies were all <5% in any treatment group. Most infection AEs were mild or moderate and discontinuation due to infection was infrequent (approximately 1–2%). There was no apparent increase in the rate of non-serious or serious infections over time. The rates of infection events were similar regardless of whether pts received tofacitinib as monotherapy or with background DMARDs. Although the rate of serious infections among tofacitinib 10 and 5 mg BID groups was similar in P3, in the LTE studies that rate for 10 mg BID was approximately twice that of 5 mg BID (4.9 vs 2.3 /100 pt-y). Events of opportunistic infections, including tuberculosis, were uncommon.

Table. Exposure estimates and incidence rates of all-cause mortality and serious infections in tofacitinib P3 and LTE studies

	P3 studies			LTE studies
	Tofacitinib All doses N = 3030	Placebo N = 681	Adalimumab N = 204	Tofactinib All doses N = 3227
All-cause mortality				
Deaths, n (%)	12 (0.40)	1 (0.15)	1 (0.49)	20 (0.62)
Exposure, pt-y	2098	203	179	3118
Incidence rate, events/100 pt-y (95% CI)	0.572 (0.325, 1.007)	0.494 (0.070, 3.505)	0.559 (0.079, 3.967)	0.641 (0.414, 0.994)
Serious infections				
Unique pts with events, n (%)	61 (2.0)	3 (0.44)	3 (1.5)	93 (2.9)
Exposure, pt-y	2094	202	179	3101
Incidence rate, events/100 pt-y (95% CI)	2.912 (2.266, 3.743)	1.482 (0.478, 4.594)	1.679 (0.542, 5.206)	2.999 (2.448, 3.675)

Conclusion: In P3 and LTE studies, mortality rates were consistent with the expected rate in pts with active RA, including those receiving therapy with other DMARDs. The safety profile of tofacitinib with regard to infection AEs was consistent with the previously reported P2 experience and no new safety signals were observed.

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Impact of Body Mass Index on Response to Etanercept Therapy in Subjects with Moderately Active Rheumatoid Arthritis in the PRESERVE Trial. Josef S. Smolen[1], Annette Szumski[2], Andrew S. Koenig[2] and Thomas V. Jones[3]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]Pfizer Inc., Collegeville, PA, [3]Pfizer, Inc, Collegeville, PA

Background/Purpose: The role of adipose tissue in immune-mediated inflammatory diseases such as rheumatoid arthritis (RA) has not been well studied. Patients with RA and a high body mass index (BMI) have demonstrated significantly less radiographic joint damage[1–2] than those with low BMI. Paradoxically, in a recent study, increasing BMI was negatively correlated with clinical response to biologic therapy in patients with active RA.[3] The relationship between BMI and responses to etanercept (ETN)-methotrexate (MTX) treatment was assessed in subjects with moderately active RA in the PRESERVE trial.

Methods: Subjects with DAS28 >3.2 and ≤5.1 despite stable doses of oral MTX received open-label ETN 50 mg once weekly (QW) plus MTX (titration to ≤25 mg/week through week 28) for 36 weeks (Period 1). Posthoc analyses of response by BMI category at baseline were conducted in subjects who received ≥1 treatment dose and had Week-36 assessments. For continuous outcomes, BMI trend was analyzed as an ordered category in ANCOVA models, adjusted for baseline response; for dichotomous outcomes, BMI trend was analyzed as ordered BMI categories from a CMH test of non-zero correlation. Analyses were also conducted in rheumatoid factor positive (RF+) and RF negative (RF-) subgroups.

Results: Of 761 subjects analyzed, 386 subjects (50.7%) had a baseline BMI of <25 kg/m^2, 248 (32.6%) had a BMI of 25–<30 kg/m^2, and127 (16.7%) had a BMI of ≥30 kg/m^2. Significant negative correlations ($P<0.05$) were observed between BMI categories of <25, 25–<30, and ≥30 kg/m^2 and Week-36 adjusted mean changes for DAS28 (−2.1, −2.1, and −1.8, respectively), CDAI (−12.3, −12.0, −10.4), and SDAI (−12.9, −12.7, −10.8), but not for HAQ (−0.6, −0.5, −0.5) or annualized change in mTSS (0.3, 0.5, 0.4). Similar correlations between BMI and Week-36 changes were seen in RF+ subjects (n=550); tests in RF− subjects (n=207) were not adequately powered due to the small BMI ≥30 subgroup (n=33). Increasing BMI was associated with a significant decreasing trend ($P<0.05$) in the proportion of subjects achieving Week-36 remission based on DAS28 (<2.6), CDAI (≤2.8), and SDAI (≤3.3) and normal HAQ (≤0.5) but not radiographic non-progression (annualized Δ mTSS ≤0).

Summary of Responses to ETN-MTX Therapy by BMI Category at Week 36 in Subjects With Moderate RA

		% of Subjects (n/N)			P
	Variable	BMI <25 kg/m^2	BMI 25–<30 kg/m^2	BMI ≥30 kg/m^2	value*
DAS28	Remission (<2.6)	70.8 (271/383)	68.1 (171/251)	56.7 (72/127)	0.01
	LDA (<3.2)	87.5 (335/383)	86.5 (217/251)	79.5 (101/127)	0.05
CDAI	Remission (≤2.8)	29.5 (113/383)	28.0 (70/250)	17.3 (22/127)	0.02
	LDA (<10)	85.4 (327/383)	81.2 (203/250)	78.7 (100/127)	0.06
SDAI	Remission (≤3.3)	27.7 (105/379)	26.7 (66/247)	16.0 (20/125)	0.02
	LDA (<11)	86.8 (329/379)	83.8 (207/247)	81.6 (102/125)	0.13
HAQ	Normal (≤0.5)	60.1 (230/383)	58.2 (145/249)	44.1 (56/127)	0.01
mTSS	Non-progression (Δ≤0)	82.1 (294/358)	83.2 (193/232)	81.5 (97/119)	0.99

* From a Cochran-Mantel-Haenszel (CMH) test of the non-zero correlation between ordered BMI categories and ordered Week-36 response categories. DAS28 = Disease Activity Score based on a 28-joint count; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; HAQ = Health Assessment Questionnaire; mTSS = modified Total Sharp Score

Conclusion: Subjects with moderate RA and higher BMIs demonstrated a diminished clinical response after 36 weeks of etanercept-MTX treatment compared with their counterparts with lower BMIs. Consistently high rates of radiographic non-progression were seen independent of BMI. Similar trends were found in RF+ subjects. Further research is needed to evaluate the relationship between adipose tissue, treatment outcomes, and RF in RA.

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Risk of Malignancy in Australian Rheumatoid Arthritis Patients Treated with Tumour Necrosis Factor Inhibitors. Sharon Van Doornum[1], Margaret P. Staples[2], Lynette March[3], Marissa N. Lassere[4] and Rachelle Buchbinder[5]. [1]The University of Melbourne, Melbourne, Australia, [2]Cabrini Institute and Monash University, Malvern, Australia, [3]University of Sydney, Insitute of Bone and Joint Research, Royal North Shore Hospital, St Leonards NSW, Australia, [4]St. George Hospital, Kogarah, Australia, [5]Cabrini Institute and Monash University, Malvern, Victoria, Australia

Background/Purpose: To investigate the risk of cancer in Australian rheumatoid arthritis (RA) patients treated with tumour necrosis factor inhibitors (TNFi).

Methods: The Australian Rheumatology Association Database (ARAD) is a national prospective database established to monitor the long term outcomes of biologic therapy in Australian patients with inflammatory arthritis. Data concerning drug therapy and morbidity are collected from patients at 6-monthly intervals using self-reported questionnaires. Ascertainment of cancers is achieved using histology confirmed cancer and/or linkage with national cancer statistics. We compared the incidence of cancer in "biologic-naïve" RA patients with the incidence of cancer in RA patients after commencement of TNFi therapy. Person-years of exposure for biologic-naïve patients were calculated from birth until cancer diagnosis, death, commencement of a TNFi or analysis cut-off date. For TNFi-treated patients, exposure began at the start date of TNFi therapy and continued until cancer diagnosis, death or analysis cut-off date. The relative risk (RR) of cancer after exposure to TNFi therapy was calculated by comparison with the biologic-naïve RA patients using the Mantel-Cox method with a logrank test of significance, with adjustment for age, gender and smoking status.

Results: We identified 2962 RA patients in ARAD, including 808 patients who never received TNFi treatment and 2154 patients who did receive treatment with TNFi therapies. Of the "never TNFi-treated" group, 70% were female, 80% had ever taken methotrexate and 56% had ever taken prednisolone. Of the "TNFi-treated" group, 73% were female, 97% had ever taken methotrexate and 88% had ever taken prednisolone. Follow-up was 19,158 person-years for the patients receiving TNFi therapies and 38,313 person-years for biologic-naïve patients. The table shows the number of cancers in both groups and the adjusted relative risk of cancer in the TNFi treated RA patients compared with the biologic-naïve RA patients.

Site	Biologic-naïve RA 38,313 patient years	TNFi-treated RA 19,158 patient years	RR*	95% CI
All cancers, n	152	63	**2.20**	**1.62–2.98**
Melanoma, n	30	14	**2.65**	**1.41–4.96**
Non-melanoma skin cancer, n	150	98	**3.36**	**2.56–4.35**
Lung, n	7	6	2.48	0.79–7.82
Breast, n	29	7	1.47	0.63–3.45
Bowel, n	21	1	0.28	0.05–1.69
Prostate, n	20	11	2.12	0.99–4.56
Thyroid, n	5	1	1.68	0.19–15.11
Kidney, n	4	2	2.21	0.29–17.05
Cervix, n	9	1	1.36	0.22–8.56
Lymphoid cancers, n	8	7	**6.52**	**2.11–20.18**

* adjusted for gender, age and smoking status

The adjusted relative risk of melanoma, non-melanoma skin cancer and lymphoma was significantly increased in the TNFi-treated RA patients. Restricting the analysis to those RA patients who ultimately received TNFi therapy (ie a before and after comparison) did not change the results significantly.

Conclusion: Using ARAD data we found a significantly increased risk of lymphoma and skin cancer in Australian RA patients who have received TNFi therapy compared to RA patients who are biologic-naïve. These observational registry data must be interpreted with caution, particularly in light of possible differences in disease severity between the compared groups, however this study provides an important signal which warrants further investigation.

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Clinical Response within 12 Weeks As a Predictor of Future Low Disease Activity in Early RA Patients: Results From the TEAR Trial. Jeffrey R. Curtis[1], Theresa McVie[2], Ted R. Mikuls[3], James R. O'Dell[4], S. Louis Bridges Jr.[5], Larry W. Moreland[6] and Stacey Cofield[7]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, [3]Omaha VA and University of Nebraska, Omaha, NE, [4]Univ of Nebraska Med Ctr, Omaha, NE, [5]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [6]University of Pittsburgh, Pittsburgh, PA, [7]Univ of Alabama at Birmingham,, Birmingham, AL

Background/Purpose: Predicting future clinical treatment outcomes based upon early clinical response would be useful to help optimize RA management. However, there is no validated method to allow one to predict response for patients with early RA. We derived and validated a clinical prediction rule to predict low disease activity (LDA) at 1 year among early RA patients participating in the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial.

Methods: We identified TEAR participants who were not in LDA (defined as DAS28 < 3.2) 24 weeks after beginning methotrexate (MTX) and who added either etanercept (E) or sulfasalazine / hydroxychloroquine (triple therapy, or TT). Among these individuals (derivation cohort), predictors within the next 12 weeks were evaluated to characterize LDA 1 year later. Multivariable logistic regression was used to derive a clinical prediction rule which was scaled to approximate the likelihood of response ranging from 0 – 100%. Variables were selected based upon change in the Akaike's Information Criteria (AIC). Validation of the prediction rule was performed using data from TEAR participants randomized to start MTX+E or TT at baseline ((validation cohort); the outcome for the validation cohort was LDA at 48 weeks.

Results: Among the 186 RA patients in the derivation cohort, mean ± SD age was 50 ± 13 years, median RA disease duration 3.3 +- 6.0 months, mean DAS28 4.9 ± 1.1, mean BMI 30.3 +- 7.6, and 90% RF+. Factors identified in the best-performing prediction model included age, body mass index (BMI), and DAS28 at time of treatment escalation and at 6 and 12 weeks later. A number of additional factors were not predictive of response

By 12 weeks after treatment escalation, 24% of patients were predicted to be responders with 91% accuracy; 39% of patients were predicted to be non-responders with 82% accuracy, and the remaining 37% of patients were classified as 'uncertain responders' at 12 weeks. There were minimal differences in the performance of the prediction rule between MTX+E vs. TT patients.

In the validation cohort (n=103) that tested the prediction rule, 14% of patients were predicted to be responders with 93% accuracy, and 50% of patients were predicted to be non-responders with 73% accuracy; the remaining 36 % of patients were classified as 'uncertain' responders at week 12. In both the derivation and validation cohorts, approximately 80% of patients could be predicted by 12 weeks to be responders or non-responders at 1 year if >= 80% overall accuracy was considered acceptable. Greater accuracy was possible at the expense of fewer patients being able to be classified at 12 weeks.

Conclusion: In a clinical trial of patients with early RA, clinical data collected early after starting or escalating DMARD/biologic treatment could predict LDA at 1 year with high accuracy. In the patients predicted to be non-responders, treatment could be changed earlier to optimize outcomes.

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Association of Tuberculosis with Anti-Tumor Necrosis Factor Therapy in Asia Using a Number Needed to Harm Approach. B. Tang[1], S. Navarra[2], L. Lu[3], H. Y. Lin[4] and M. U. Rahman[5]. [1]Pfizer Inc., New York, NY, [2]University of Santo Tomas Hospital, Manila, Philippines, [3]Jiaotong University School of Medicine, Manila, Philippines, [4]Veterans General Hospital, Taipei, [5]University of Pennsylvania/Pfizer, Collegeville, PA

Background/Purpose: The risk of tuberculosis (TB) is a major concern for anti-tumor necrosis factor (anti-TNF) therapies, and the association between TB and anti-TNFs are well studied. The risk of developing TB may be higher with the use of monoclonal antibodies (greater risk with adalimumab [ADA], and infliximab [IFX]) compared with the recombinant soluble TNF-receptor etanercept (ETA). The French Research Axed on Tolerance of Biotherapies (RATIO) registry showed that the standardized incidence ratios (SIR) of TB in patients receiving ADA and IFX were statistically different from control groups while SIR of ETA was not statistically different from the control group. No data are available on the relative risks in Asia where TB is endemic. The purpose of this study was to evaluate the risk of TB in patients who are candidates for anti-TNF therapy in Asia.

Methods: SIR of TB for 3 anti-TNF therapies (ADA, IFX and ETA) were based on a published study from the RATIO registry as Asia-specific relative risk data are not currently available. In order to evaluate the impact of anti-TNF therapy on TB in Asia, the 2009 World Bank report of country-specific TB incidences was used to determine the absolute risks. The relative risks and the number needed to harm (NNH; the number of individuals needed to be exposed to the risk factor for one individual to develop the disease) were calculated for each anti-TNF therapy. A sensitivity analysis was performed based on the 95% CI of SIR for each anti-TNF. The number needed to treat (NNT) to avoid one TB event by using ETA instead of ADA or IFX was also calculated.

Results: The RATIO registry reported the SIR of TB as 12.2 (95% CI 9.7, 15.5) for all anti-TNFs. The individual SIRs were 29.3 (95% CI 20.3, 42.4) for ADA, 18.6 (95% CI 13.4, 25.8) for IFX, and 1.8 (95% CI 0.7, 4.3) for ETA. Fifteen Asian countries were included in this analysis (Table). According to the World Bank report the baseline TB incidence among the 15 Asian countries ranged from 0.02 (Japan) to 0.44 (Cambodia). The NNH ranged from 8–163 for ADA, 12–256 for IFX, and 126–2646 for ETA. The sensitivity analysis by 95% CI of the SIRs indicated the results were consistent. The NNH ranged from 5–235 for ADA, 9–355 for IFX, and 53–6803 for ETA.

Table. The relative risks of TB, NNH, and NNT for each anti-TNF therapy in patients in Asia

Country	Baseline incidence (%)	Projected incidence of TB with anti-TNFs (%)			NNH for TB with anti-TNFs			NNT with ETA instead of ADA or IFX to avoid one TB event	
		ADA	IFX	ETA	ADA	IFX	ETA	ADA	IFX
Cambodia	0.44	13.0	8.2	0.8	8	12	126	8	13
Philippines	0.28	8.2	5.2	0.5	12	19	198	13	21
Pakistan	0.23	6.8	4.3	0.4	15	23	241	16	26
Bangladesh	0.23	6.6	4.2	0.4	15	24	247	16	26
Vietnam	0.20	5.9	3.7	0.4	17	27	278	18	30
Indonesia	0.19	5.5	3.5	0.3	18	28	294	19	31
India	0.17	4.9	3.1	0.3	20	32	331	22	35
Thailand	0.14	4.0	2.5	0.2	25	39	406	27	43
China	0.10	2.8	1.8	0.2	36	56	579	38	62
Korea	0.09	2.6	1.7	0.2	38	60	617	40	66
Taiwan	0.09	2.6	NA	0.2	39	NA	637	42	NA
Malaysia	0.08	2.4	1.5	0.1	41	65	669	44	72
Hong Kong	0.08	2.4	1.5	0.1	42	66	678	44	73
Singapore	0.04	1.1	0.7	0.1	95	149	1543	101	165
Japan	0.02	0.6	0.4	0.04	163	256	2646	173	283

NA, not available on market

Conclusion: While taking into account the limitations inherent in applying the RATIO registry data to Asian incidences of TB, the NNH for ADA and IFX appear to be several-fold lower than ETA in Asia. The NNT with ETA instead of ADA or IFX to avoid one TB event is also low. The lower risk of developing TB with ETA relative to ADA and IFX may be more pronounced and more clinically relevant in Asia given the higher endemicity of TB. Further studies using real-world practice data in Asia are suggested.

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Rheumatoid Arthritis Bone Fragility Is Associated with Increased Dickkopf-1 Expression and Disturbances in the Bone Turnover Regulating genes. Joana Caetano-Lopes[1], Ana M. Rodrigues[2], Ana Lopes[3], Ana Catarina Vale[4], Michael A. Pitts-Kiefer[5], Bruno Vidal[6], Inês P. Perpétuo[1], Jacinto Monteiro[7], Yrjo T. Konttinen[8], Maria Fátima Vaz[4], Ara Nazarian[5], Helena Canhão[9] and João E. Fonseca[10]. [1]Rheumatology Research Unit, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [2]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisbon, Portugal, [3]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [4]Department of Mechanical Engineering, Instituto Superior Técnico, ICEMS, Lisbon, Portugal, [5]Center for Advanced Orthopaedic Studies, Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [6]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal., Lisbon, Portugal, [7]Orthopaedics Department, Hospital de Santa Maria, Lisbon, Portugal, [8]Helsinki Univ Central Hospital, Helsinki, Finland, [9]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisboa, Portugal, [10]Lisbon Academic Medical Center, on behalf of Rheumatic Diseases Portuguese Register (Reuma.pt), Lisbon, Portugal

Background/Purpose: Rheumatoid arthritis (RA) and primary osteoporosis (OP) induce bone fragility. In this study we aimed at identifying differences in the mechanisms involved in bone fragility by comparing gene expression between RA and OP bone samples with similar fracture risk factors.

Methods: Patients with RA submitted to hip replacement surgery were recruited. Trabecular bone microarchitecture was assessed by micro-computed tomography and bone mechanical behavior by compression tests. Bone cell activity was analyzed by studying gene expression. RA patients compared with OP patients were matched for bone mineral density (BMD) and major clinical fracture risk factors (age, gender, BMI, FRAX).

Results: Twenty four patients were included, ten with RA, seven with primary established OP and seven with normal BMD. Bone microarchitecture did not differ between the groups, but mechanical bone properties were similarly decreased in RA and primary OP patients compared to the normal BMD group. RA bone microenvironment, compared to primary OP, had a gene expression profile characterized by upregulated pro-osteoclastogenic cytokines and Dkk-1, increased RANKL/OPG ratio, paralleled by raised expression of factors that promote osteoblastic activity, but with low COL1A1 expression.

Conclusion: Bone fragility in RA patients is induced by an unbalanced bone turnover that is qualitatively different from the pathobiologic phenomena that occur in primary OP. The type of bone gene disturbances is suggestive of a pivotal role for Dkk-1 in this process, suggesting that it could be used as a therapeutic target to prevent RA bone damage.

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Effect of Sirukumab on Hepcidin Levels and Markers of Anemia: Results of a Phase 2b Trial in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy. Gary Toedter[1], Sarah Sague[2], Xiaoying Wu[2], Mark Curran[3] and Benjamin Hsu[4]. [1]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Malvern, PA, [2]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, [3]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA, [4]Centocor R&D, a division of J&J Pharmaceutical R& D, LLC/Univ. of Pennsylvania, Malvern/Philadelphia, PA

Background/Purpose: Anemia of chronic inflammation is found in patients with rheumatoid arthritis (RA). Studies have found that RA patients with anemia are more likely to have more severe joint damage (Peeters HR, et al. Ann Rheum Dis. 1996; 55: 162–168). Hepcidin is a peptide hormone that regulates iron homeostasis, is elevated in anemic conditions, and is up-regulated by interleukin-6 (IL-6). IL-6 is also elevated in RA. Sirukumab (CNTO136), a human anti-IL-6 monoclonal antibody, was investigated for efficacy in a Phase 2b dose ranging study of patients with active RA despite concurrent methotrexate treatment. This analysis examines if sirukumab treatment had positive effects in RA patients anemic at baseline (week 0) by reducing hepcidin and increasing hemoglobin through week 12 of treatment.

Methods: Serum samples collected in the Ph2b study at week 0, day 5, week 2, and the pre-specified week 12 primary endpoint were analyzed for hepcidin, hemoglobin, and anemia-related markers (ferritin, iron, total iron biding capacity, unsaturated iron bind capacity). Patients were treated with SC placebo (PBO; n= 30) or SC sirukumab 100 mg 2QW, 100 mg 4QW, 50 mg 4QW (n=30 for each arm), or 25 mg 4QW (n=31).

Results: The overall ACR 50 response at week 12 to sirukumab was 24.0% (PBO 3.3%). At week 0, 5/30 (16.7%) of PBO and 37/121 (30.6%) of sirukumab-treated patients were anemic. In the anemic patients, the mean week 0 hepcidin concentrations were 25.1 ng/mL in the PBO group, and 87.4 ng/mL in the sirukumab-treated patients. At week 12, the sirukumab- treated patients mean hepcidin concentration was significantly reduced to 38.1 ng/mL ($p=0.0029$), while the PBO mean hepcidin concentration was unchanged (31.4 ng/mL; $p=0.6250$). No dose-response of sirukumab on serum hepcidin concentration was seen. Hemoglobin levels in the anemic patients increased in the sirukumab-treated patients (10.6 g/dL at week 0; 11.8 g/dL at week 12; $p<0.001$) but were unchanged in the PBO group (10.2 g/dL at week 0; 9.8 g/dL at week 12; $p=0.6250$). By week 12, no patients in the PBO group normalized hemoglobin levels, while 19 patients in the sirukumab-group normalized hemoglobin (51.4% of the week 0 anemic patients). All of the measured anemia-related markers correlated significantly with post-treatment hepcidin concentrations. There was no relationship between ACR20 or ACR50 response at week 12 and normalization of hemoglobin.

Conclusion: Sirukumab was effective in reducing serum concentrations of hepcidin through week 12 of treatment. Serum hemoglobin levels in anemic patients increased significantly following sirukumab treatment, with half of the patients normalizing hemoglobin levels. This indicates that in addition to demonstrating efficacy, treatment of RA patients with sirukumab may be effective in reversing inflammation-related anemia.

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Body Mass Index Is Associated with Decreased Response to Initial and Delayed Treatment with Dose Escalated Infliximab in Patients with Recent Onset Rheumatoid Arthritis. L. Heimans[1], M. van den Broek[1], L. Dirven[1], A.A. Schouffoer[1], I. Speyer[2], P.J.S.M. Kerstens[3], T.W.J. Huizinga[4], W.F. Lems[5] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Bronovo Hospital, Den Haag, Netherlands, [3]Jan van Breemen Research Institute|Reade, Amsterdam, Netherlands, [4]Leiden University Medical Centre, Leiden, Netherlands, [5]VU University medical center, Amsterdam, Netherlands

Background/Purpose: Patients with established RA with a high Body Mass Index (BMI) respond less well to delayed treatment with a fixed dose of TNF-blocker infliximab (IFX).[1] The aim of this study was to assess the relationship between BMI and the response to initial and delayed treatment with IFX with dose escalation to a maximum of 10 mg/kg in recent onset RA patients treated according to a disease activity score (DAS) steered treatment protocol.

Methods: In a post-hoc analysis of the BeSt study, outcome of treatment with IFX and methotrexate (MTX) was assessed and compared between BMI-categories. (table 1) Initial treatment with IFX (3mg/kg/8 weeks, after a loading dose) and MTX was started in 120 patients. In addition, in 109 patients, IFX and MTX were started after they had failed on 3 treatment steps with disease modifying antirheumatic drugs (DMARDs). In case of insufficient response (DAS >2.4), the IFX dose was increased to 6, then 7.5 and a maximum of 10 mg/kg. Adequate response to IFX was defined as having a DAS ≤2.4 for at least 6 months on the IFX initial dose of 3 mg/kg. Failure to respond was defined as being assigned to another treatment regimen because of insufficient response to the maximum IFX dose. Response could be defined as adequate or insufficient in 143 patients. The association between BMI and failing to respond to IFX was assessed with multivariate regression analyses, adjusted for baseline DAS, age, sex, smoking, and anti-citrullinated protein antibody (ACPA)-status.

Results: Outcome of treatment could be defined in 143 patients, of whom 96 received IFX as initial treatment. Patients were categorized as having a normal BMI (<25), being overweight (BMI >25 but <30) or being obese (BMI >=30), according to the WHO classification criteria. No statistically significant differences were found in other baseline characteristics between the three groups. The proportion of rapid responding patients was significantly lower in overweight patients (68%) and obese patients (64%), compared to patients in the normal BMI category (84%). BMI was an independent predictor of failure to respond, with odds ratios (OR) of 2.9 (95% CI 1.1;8.0) for the overweight group and 3.6 (95%

CI 1.0;12.6) in the obese group. (table 1) Other independent predictors of failure to respond were female gender (OR 3.4 (95% C.I. 1.05;11.3)) and high baseline DAS (OR 2.1 (1.3;3.6)).

Table 1. BMI and failure to respond to IFX

BMI category*	n	Crude Odds ratio 95%C.I.	Adjusted# Odds ratio 95% C.I.
<25	52	*ref*	*ref*
25–<30	66	2.6 (1.0; 6.4)	2.9 (1.1; 8.0)
>=30	25	3.1 (1.0; 9.4)	3.6 (1.0; 12.6)

*BMI according to WHO classification of adult normal weight, overweight and obesity. #Adjusted for age, sex, smoking, baseline DAS and anti-citrullinated protein antibody (ACPA)-status.

Conclusion: These results confirm that BMI is associated with response to IFX, with overweight and obese patients more often failing to treatment with IFX than patients with normal BMI, even when IFX is increased to the maximum dose (10mg/kg).

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Clinical and Radiographic Implications of Time to Treatment Response in Early Rheumatoid Arthritis Patients with Baseline Levels of Disease Activity Reflective of a Clinical Practice Setting. Edward Keystone[1], Michael E. Weinblatt[2], Boulos Haraoui[3], Benoit Guerette[4], Neelufar Mozaffarian[5], Shufang Liu[5], Benjamin Wolfe[5] and Arthur Kavanaugh[6]. [1]University of Toronto, Toronto, ON, [2]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [3]Institut de Rhumatologie, Montreal, QC, [4]Abbott, Rungis, France, [5]Abbott, Abbott Park, IL, [6]University of California San Diego, San Diego, CA

Background/Purpose: A retrospective analysis of the PREMIER trial demonstrated that in early RA patients (pts) on methotrexate (MTX) both the timing and magnitude of a clinical response determines long-term outcomes. Cohort data reveal that the baseline (BL) disease activity of pts in clinical trials is often more severe than that in clinical practice. This study aimed to evaluate the association of clinical responses occurring by 12 weeks (wks) or 24 wks with long-term outcomes in MTX-treated pts from PREMIER who had BL levels of disease activity more closely resembling those observed in "real world" practice.

Methods: In this post hoc analysis, observed data from MTX-pts in PREMIER who had BL DAS28(CRP) ≤6.0 were evaluated in the context of the total MTX population [mean DAS28(CRP) =6.3]. Pts were categorized as early- or delayed-responders (R) based on clinical measures [50%/70% improvement in ACR response criteria or improvement in DAS28(CRP) >1.2] at 12 and 24 wks: early-R achieved the clinical target by wk 12 and maintained it at wk 24; delayed-R did not achieve the target at wk 12 but met it by wk 24. Long-term outcomes for early- and delayed-R were the percentage in DAS28(CRP) remission (<2.6) or with rapid radiographic progression [RRP, ΔmTSS >3) at 52 wks; odds ratios (95% CI) were used to compare outcomes of early- and delayed-R.

Results: A total of 72 of the 199 evaluable MTX-pts had BL DAS28(CRP) ≤6.0 [mean (SD) DAS28(CRP) =5.5 (0.4)]. The percentages of pts who achieved early and delayed responses were 29.2% and 27.8% for ACR50, 13.9% and 18.1% for ACR70, and 58.8% and 22.1% for DAS28(CRP) improvement >1.2; all percentages were comparable with those in the total MTX population. Long-term outcomes were somewhat better for pts with lower DAS28(CRP) at BL, although the trends observed in the overall population remained: early-R, irrespective of the magnitude of the response, had better clinical and radiographic outcomes at wk 52 (**Table**). Delayed-R with an ACR50 or improvement in DAS28(CRP) >1.2 had significantly reduced odds of achieving remission at wk 52. In fact, pts with delayed responses needed to reach an ACR70 by wk 24 to have comparable odds of reaching remission at wk 52. Delayed-R, regardless of the magnitude of response, also had a high proportion of RRP at wk 52. Indeed, pts with delayed ACR70 responses had an RRP prevalence of >30%.

Table. Association of Baseline Disease Activity and Time to Clinical Response With Week 52 Outcomes

Population	Responder Type	Response by Week 12	Response by Week 24	DAS28 (CRP) <2.6 (%)	Odds Ratio[a] (95% CI)	mTSS >3, RRP (%)	Odds Ratio[a] (95% CI)
Total MTX Population	Early	ACR50R	ACR50R	64		23	
	Delayed	ACR50NR	ACR50R	31	4.13 (1.81, 9.42)*	47	0.35 (0.15, 0.81)*
	Early	ACR70R	ACR70R	94		18	
	Delayed	ACR70NR	ACR70R	51	15.15 (1.82, 126.31)*	40	0.32 (0.08, 1.30)
	Early	ΔDAS28[b]>1.2R	ΔDAS28>1.2R	39		41	
	Delayed	ΔDAS28>1.2NR	ΔDAS28>1.2R	12	4.73 (1.56, 14.29)*	53	0.61 (0.29, 1.29)
Baseline DAS28 (CRP) ≤6.0	Early	ACR50R	ACR50R	86		19	
	Delayed	ACR50NR	ACR50R	45	7.33 (1.63, 33.08)*	35	0.44 (0.11, 1.82)
	Early	ACR70R	ACR70R	100		10	
	Delayed	ACR70NR	ACR70R	69	>999 (<0.001, >999)	31	0.25 (0.02, 2.70)
	Early	ΔDAS28>1.2R	ΔDAS28>1.2R	64		33	
	Delayed	ΔDAS28>1.2NR	ΔDAS28>1.2R	20	7.14 (1.72, 29.68)*	47	0.55 (0.16, 1.85)

[a] Odds ratio for early (wk 12) versus delayed (wk 24) responders.
[b] ΔDAS28 is improvement in DAS28(CRP).
R = responder; NR = non-responder.
* Statistically significant.

Conclusion: MTX-pts with lower BL DAS28(CRP) achieved somewhat better clinical and radiographic outcomes at wk 52 than the overall MTX-population. Still, pts who did not achieve a strong clinical response by wk 12 had a lower likelihood of achieving remission and were at increased risk of developing RRP compared with early-R. Therefore, these data lend support to the applicability of the findings in PREMIER to pts with lower BL disease activity, a population that may be more reflective of RA pts typically seen in a rheumatology clinic.

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Rapid Radiological Progression in the First Year of Rheumatoid Arthritis Predicts Both Disability and Radiological Joint Damage Progression Over 8 Years of Targeted Treatment. M. van den Broek[1], L. Dirven[1], A.J. Dehpoor[1], J.K. de Vries-Bouwstra[1], Y.P. Goekoop-Ruiterman[2], A.J. Peeters[3], P.J.S.M. Kerstens[4], Tom W.J. Huizinga[1], W. F. Lems[5] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]HAGA hospital, The Hague, Netherlands, [3]Reinier de Graaf Gasthuis, Delft, Netherlands, [4]Jan van Breemen Research Institute|Reade, Amsterdam, Netherlands, [5]VU University medical center, Amsterdam, Netherlands

Background/Purpose: To assess whether rapid radiological progression in the first year of treatment of RA is associated with functional disability and progressive joint damage over 8 years of tight control targeted treatment.

Methods: All patients with radiological data at baseline and after 1 year from the BeSt study were used in this analysis. All patients were dynamically treated with medication adjustments aimed at achieving a disease activity score (DAS) =<2.4, measured three-monthly. Rapid radiological progression (RRP) was defined as an increase of >= 5 points Sharp v/d Heijde Score (SHS) as scored after the first year of treatment. Functional ability over 8 years, measured 3-monthly with the Health Assessment Questionnaire (HAQ), was compared in patients with and without RRP using linear mixed models, adjusted for treatment group, baseline ESR, SHS and rheumatoid factor (RF), anti-citrullinated protein antibody-status (ACPA) or a combination of RF and ACPA. Subsequently, disease activity score (DAS) over time was added to this model.

Results: RRP was observed in 102/463 (22%) patients. Patients with RRP were more often treated with initial monotherapy (74% vs. 41%) than patients without RRP and more often RF (82% vs. 60%) and ACPA (77% vs. 55%) positive, with a higher baseline ESR (53 mm/hr vs. 37 mm/hr). They also had a higher baseline HAQ (1.5 vs. 1.4, p=0.04).

Over 8 years, despite relatively equal suppression of DAS in both groups, patients with RRP had a statistically and clinically significantly higher HAQ (difference 0.22, 95% C.I. 0.09–0.34) (figure 1). After adjustment for DAS over time, this difference was 0.15 (0.05–0.26). Patients with RRP in the first year had more joint damage progression in year 1 to year 8 (figure 2).

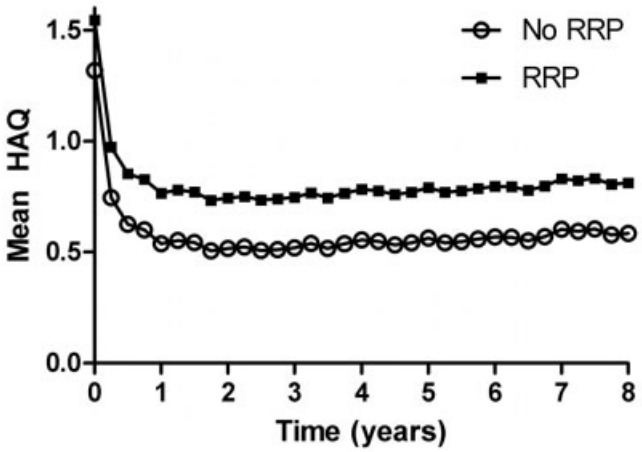

Figure 1. Mean HAQ over time, adjusted for treatment strategy, baseline ESR and SHS and RF and/or ACPA (using linear mixed models) for patients with and without RRP in year 1.

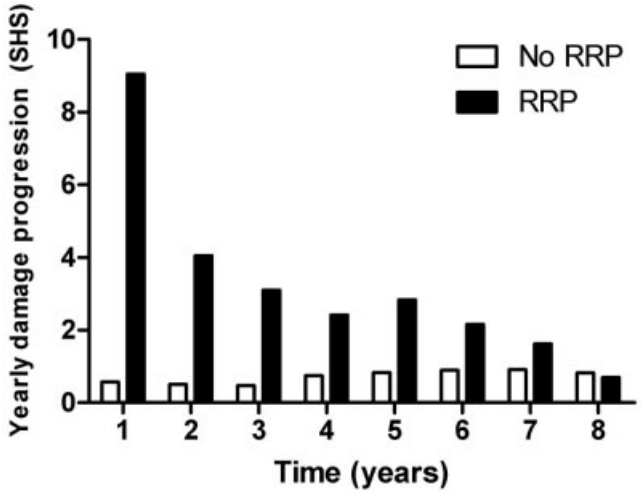

Figure 2. Mean yearly joint damage progression for patients with and without RRP in year 1.

Conclusion: In a tight control cohort of recent onset RA patients with treatment targeted at DAS =<2.4, rapid radiological progression in year 1 is an independent predictor of functional disability over 8 years. Approximately one third of the difference in functional ability between patients with and without RRP is explained by differences in disease activity. Patients with rapid radiological progression in the first year of treatment continue to have more joint damage progression in subsequent years than patients without RRP.

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No Deterioration of Glucose Levels During Oral Glucose Tolerance Tests Following High-Dose Prednisolone Treatment in Early Active Rheumatoid Arthritis. Debby den Uyl[1], Daniel H. van Raalte[2], Michael T. Nurmohamed[3], Willem F. Lems[1], Johannes W.J. Bijlsma[4], Jos N. Hoes[4], Ben A.C. Dijkmans[5] and Michaela Diamant[2]. [1]VU University medical center, Amsterdam, Netherlands, [2]VU University medical center, Diabetes Center, Amsterdam, Netherlands, [3]Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, Netherlands, [4]UMC Utrecht, Utrecht, Netherlands, [5]Reade, Centre for Rehabilitation and Rheumatology and VU University Medical Centre, Department of Rheumatology, Amsterdam, Netherlands

Background/Purpose: Glucocorticoids (GCs) are frequently used in the treatment of rheumatoid arthritis (RA) due to their strong anti-inflammatory properties. However, GCs may induce glucose intolerance and even clinically overt diabetes by reducing insulin sensitivity and, as recently shown, by impairing insulin secretion. Additionally, inflammation as such is also associated with impaired glucose metabolism. Here we studied the interaction of the anti-inflammatory and diabetogenic effects of GCs in patients with early, active RA. This study was set up to evaluate the effects of one-week treatment with prednisolon 30mg or 60mg QD on insulin secretion and insulin sensitivity in patients with active, early RA.

Methods: Drug-naive patients with early, active RA (n=41) were randomised to prednisolone 60mg QD or prednisolone 30mg QD. Before and after 1 week of treatment, a frequently-sampled 75-g oral glucose tolerance test (OGTT) was performed after an overnight fast. The area under the curve (AUC) for glucose, insulin and C-peptide concentration were calculated. Beta-cell function was estimated by the insulinogenic index (IGI): $(I_{30}-I_0)/(G_{30}-G_0)$ and the AUC_{CP}/AUC_G ratio. Glucose tolerance state was assessed according to ADA guidelines. Insulin sensitivity was estimated by oral glucose insulin sensitivity (OGIS) index.

Results: Patients (age: 55±13 years, BMI: 25.0±4.1 kg/m^2) had active disease: DAS44 score: 4.0±0.8 and C-reactive protein (CRP): 17 (5–37) mg/L. At baseline, 56% of the patients had impaired glucose tolerance and 7% unknown type 2 diabetes mellitus (T2DM). ESR and CRP levels were associated with AUC_G (β=2.484; 95% CI 0.097–4.872, P=0.04 and β=2.360; 95% CI 0.163–4.501, P=0.04 respectively). Treatment with both prednisolone dosages reduced CRP levels significantly. Mean AUC glucose, insulin and c-peptide did not change in both arms. At individual level the glucose tolerance state improved in 22%, while the T2DM incidence increased to 24% (P<0.001), evenly distributed across the groups. Beta-cell function (IGI*)* improved during PRED60 treatment (P=0.02), and PRED30 treatment (P=0.04). There were no significant differences between the two treatment groups. Disease duration was positively associated with changes in AUC_G (β=3.733; 95% CI 1.077–6.390, P=0.004) and with deterioration of glucose profile (OR=1.068; 95% CI 1.016–1.122, P=0.01).

Conclusion: Short-term exposure to 60 or 30 mg PRED q.d. improved disease activity without deterioration of glucose tolerance in patients with active RA. These data suggest that the diabetogenic effects of high-dose prednisolone treatment can be counteracted by the anti-inflammatory properties of GCs, at least during short-term treatment. Given the individual differences, monitoring is recommended.

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Effects of the Oral SYK Inhibitor, Fostamatinib (R788), on Health-Related Quality of Life in a Phase II Study of Active Rheumatoid Arthritis. Michael E. Weinblatt[1], Arthur Kavanaugh[2], Mark C. Genovese[3], David A. Jones[4], Theresa K. Musser[5], Elliott B. Grossbard[5] and Daniel B. Magilavy[5]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of California San Diego, San Diego, CA, [3]Stanford University, Palo Alto, CA, [4]AstraZeneca, Macclesfield, United Kingdom, [5]Rigel Pharmaceuticals, South San Francisco, CA

Background/Purpose: Fostamatinib (R788), an oral spleen tyrosine kinase inhibitor, met its primary signs and symptoms efficacy endpoint in a 6-mo, phase II, multicenter, randomized, double-blind, placebo (pbo)-controlled study in patients with rheumatoid arthritis (RA) who failed to respond to methotrexate (MTX) (NCT00665925).[1] This current analysis assessed the impact of fostamatinib on health-related quality of life (HRQL) measures in this phase II study.

Methods: RA patients with prior long-term MTX treatment (n=457) were randomized to receive fostamatinib (150 mg qd [n=152]/100 mg bid [n=152]) or pbo (n=153), and background MTX. Patients self-administered the American College of Rheumatology (ACR) patient-reported outcomes (PRO) core set: pain (visual analog scale [VAS]); patient's global assessment (PtGA) of disease activity [VAS]; and physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI]) at baseline, Week (Wk) 1, 2, 4, 6, 8, 12, and 24. HRQL (Short Form-36 [SF-36]) was assessed at baseline and Wk24, and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue]) was assessed at baseline, Wk12, and 24. The main analyses compared the mean changes from baseline between the treatment groups using a generalized linear model. A responder analysis of the proportion of patients achieving a minimum clinically important difference (MCID) in each treatment group used the Cochran Mantel-Haenszel test. All tests of statistical significance were 2-sided; α=0.05.

Results: The study population had a duration of RA in excess of 8 years.[1] ACR responder rates were significant with fostamatinib 100 mg bid vs pbo (ACR20: 67% vs 35%; ACR50: 43% vs 19%; p≤0.001).

Fostamatinib 100 mg bid significantly improved pain, PtGA, and physical function at Wk1 vs pbo ($p \leq 0.001$), and was sustained throughout the trial (24 wks) (Table). Also, by Wk24, a significantly greater proportion of patients receiving fostamatinib 100 mg bid achieved MCID for pain, PtGA, and physical function vs pbo (73.3% vs 62.0% [$p < 0.05$] for pain; 74.0% vs 55.4% [$p \leq 0.01$] for PtGA; 74.8% vs 55.8% [$p \leq 0.01$]) for physical function). A significant improvement in the SF-36 physical component summary (PCS) was seen with fostamatinib 100 mg bid vs pbo at Wk24 ($p \leq 0.001$, including for each SF-36 physical domain), as well as for fatigue ($p < 0.05$) but not for the SF-36 mental component summary (Table). Moreover, at Wk24, a significantly greater proportion of patients (achieved the SF-36 PCS MCID with fostamatinib 100 mg bid vs pbo (72.9% vs 57.6%; $p \leq 0.01$) and a numerically greater percentage for fatigue (59.8% vs 48.6%; $p \geq 0.05$).

Table 1. Results of the main PRO analyses

		Mean change from baseline		
		Pbo	Fostamatinib	
			150 mg qd	100 mg bid
Pain	Wk 1	4.5 (20.7)	10.3 (19.4)*	15.4 (22.0)**
	Wk 24	17.8 (27.0)	23.0 (24.1)	31.3 (28.1)**
PtGA	Wk 1	4.4 (20.2)	8.3 (19.4)	14.6 (23.3)**
	Wk 24	16.7 (26.6)	20.3 (25.3)	29.1 (25.9)**
Physical Function	Wk 1	0.06 (0.41)	0.24 (0.43)**	0.22 (0.39)**
	Wk 24	0.34 (0.67)	0.54 (0.66)*	0.65 (0.74)**
Other PROs				
SF-36 physical component summary	Wk 24	4.9 (8.5)	5.9 (9.0)	8.5 (8.7)**
SF-36 mental component summary	Wk 24	3.7 (10.7)	2.0 (10.7)	4.0 (10.5)
FACIT-Fatigue	Wk 24	4.5 (9.8)	5.7 (10.3)	7.4 (10.9)*

Data are mean (SD). Difference from pbo: *$p < 0.05$; **$p \leq 0.001$.
PRO, patient-reported outcome; ACR, American College of Rheumatology; PtGA, patient's global assessment; HAQ-DI, Health Assessment Questionnaire-Disability Index; SF-36, Short Form-36; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; SD, standard deviation; pbo, placebo.

Conclusion: In this phase II study, 100 mg bid fostamatinib significantly improved HRQL outcomes including physical function, pain, fatigue, and overall physical health status. Phase III clinical trials of fostamatinib in RA are in progress.

Reference:
Weinblatt ME, et al. *N Engl J Med.* 2010;363:1303–1312.

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Epistasis in Folate Mediated One Carbon Metabolism Contributes to High Disease Activity in Two Cohorts of Rheumatoid Arthritis Patients Receiving Long Term Methotrexate Therapy. Thierry Dervieux[1], J. M. Kremer[2], Rebecca Roberts[3] and Lisa K. Stamp[3]. [1]Exagen Diagnostics, Albuquerque, NM, [2]Albany Medical College and The Center for Rheumatology, Albany, NY, [3]University of Otago, Christchurch, Christchurch, New Zealand

Background/Purpose: Previous reports have established that single nucleotide polymorphisms (SNPs) in folate mediated one carbon metabolism contribute to Methotrexate (MTX) efficacy in patients with rheumatoid arthritis (RA). Our objective was to evaluate whether epistasis (gene-gene interactions) would contribute to disease control in two cohorts of RA patients treated with MTX.

Methods: The study was multicentered, cross sectional, and enrolled 424 patients from the United States (n=252) and the New Zealand (n=172). All patients presented with established RA (74% females, median age 63yrs) and were treated with MTX monotherapy (median dose 15mg/week) for at least three months (median 39 months). The majority of patients (>95%) in both cohorts were Caucasians. Disease activity score (DAS) was calculated and used to differentiate patients with high disease activity (DAS>5.1) from those with low to medium disease activity (DAS≤5.1). A total of 12 SNPs in folate (RFC-1, MTHFR, MTHFD1, MS, GGH, SHMT1), purine (ATIC, AMPD1) and pyrimidine (TYMS) pathways were measured using standard molecular methods. Data analysis consisted of univariate logistic regression and multifactor dimensionality technique (MDR). MDR detects non-linear gene-gene interactions by combining predisposing genotypes of high disease activity (predisposing genetic attribute) into two separate groups depending on whether they are more common in patients presenting with high disease activity or not. The robustness and significance of the model was tested through cross validation consistency (CVC, 10-fold) and 1000-fold permutation testing.

Results: High disease activity was observed in 11.8% of patients enrolled. Using univariate analysis, none of 12 SNPs measured were significantly associated with high disease activity when the two cohorts were combined ($p > 0.06$). However, MDR analysis revealed a nonlinear pattern of interactions between genes controlling 1-carbon derivatives synthesis of tetrahydrofolate (MTHFD1 G1958A), thymidylate (TYMS *2/*3), and purines (ATIC C347G). The stepwise addition of the three genetic variants increased the testing accuracy from 0.584 (ATIC C347G) to 0.635 (ATIC C347G + MTHFD1 G1958A + TYMS *2/*3) (Table). The constructed predisposing genetic attribute pooling higher and lower likelihood of poor disease control in two separate groups revealed a 7.2 fold (CI 95%: 3.4–15.3) greater likelihood of high disease activity in carriers (43%) versus non carriers ($p < 0.001$). Sensitivity was 81% and specificity was 62%. These findings were significant in both US (OR=6.6 CI95%: 2.8–15.8; $p < 0.01$) and NZ cohorts (OR=6.9 CI95%: 1.3–35.0; $p < 0.001$).

Conclusion: These hypothesis generating data suggest that epistasis in folate mediated one carbon metabolism may contribute to disease control in RA patients treated with MTX.

Table. Multifactor dimensionality reduction analysis

Model	Training accuracy	Testing accuracy	CVC	P value
ATIC C347G	0.601	0.584	10/10	0.178
ATIC C347G+ MTHFD1 G1958A	0.652	0.582	5/10	0.196
ATIC C347G+ MTHFD1 G1958A+ TYMS *2/*3	0.721	0.635	10/10	0.018

CVC: cross validation consistency. ATIC: 5-Aminoimidazole-4-carboxamide ribonucleotide formyltransferase; MTHFD1: methylenetetrahydrofolate dehydrogenase; TYMS: Thymidylate Synthetase.

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Patterns of Pain Medication Use Among Rheumatoid Arthritis Patients From 2000–2010. Yvonne C. Lee[1], Frederick Wolfe[2] and Kaleb D. Michaud[3]. [1]Brigham and Women's Hospital, Boston, MA, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Univ of Nebraska Med Ctr & National Data Bank for Rheumatic Diseases, Omaha, NE

Background/Purpose: Over the past decade, several new biologic disease modifying antirheumatic drugs (DMARDs) were approved for the treatment of rheumatoid arthritis (RA). Concurrently, many changes occurred in the treatment options for pain. Two cyclooxygenase-2 inhibitors were removed from the market, and central-acting pain modulating agents were approved for the treatment of fibromyalgia and chronic musculoskeletal pain. We examined patterns and predictors of pain medication use among RA patients in a large, prospective observational cohort.

Methods: The study population included 15,006 RA patients followed at semi-annual intervals between 2000 and 2010. Pain medication use was defined as any patient report of: 1) non-steroidal anti-inflammatory drugs (NSAIDs), 2) weak opioids, 3) strong opioids, or 4) central-acting pain-modulating drugs (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentin and pregabalin) during each calendar year. Pain and fatigue were assessed using visual analog scales (0–10). Disability was assessed using the Health Assessment Questionnaire (HAQ). General estimating equations (GEE) and predictive margins were used to adjust prevalence rates for demographic variables, pain, disability, mood and fatigue. GEE was also used to examine associations between clinical characteristics and pain medication usage.

Results: In this cohort of established RA patients, HAQ scores increased from 0.98 to 1.09 between 2000 and 2010, while overall pain levels remained steady (between 3.7 and 3.9). Biologic DMARD use increased from 18.9% to 38.3%, whereas prednisone use decreased from 35.1% to 28.2%. When examining specific types of pain medication use, different trends emerged. NSAID use declined from 67.3% to 41.4%, whereas strong opioid use increased from 2.6% to 6.0% (Figure). The use of central-acting agents also increased from 8.7% to 15.8%. Female sex was associated with increased use of NSAIDs, weak opioids and central-acting agents ($P < 0.005$), whereas male sex was associated with increased use of strong opioids ($P = 0.02$). Obesity was associated with increased use of NSAIDs, weak opioids and central-acting agents ($P <$

0.02), whereas low body mass index (BMI) was associated with increased use of strong steroids ($P = 0.004$). Both past and current smoking was associated with opioid use ($P < 0.003$). Pain severity, poor mood and fatigue were associated with increased use of all types of pain medications ($P < 0.05$).

Conclusion: Despite increases in biologic DMARD therapy, pain levels remained the same over the past 10 years. Although NSAID use declined, all other types of pain medication use increased. Clinical characteristics, including sex, BMI and smoking, were differentially associated with specific types of pain medication use.

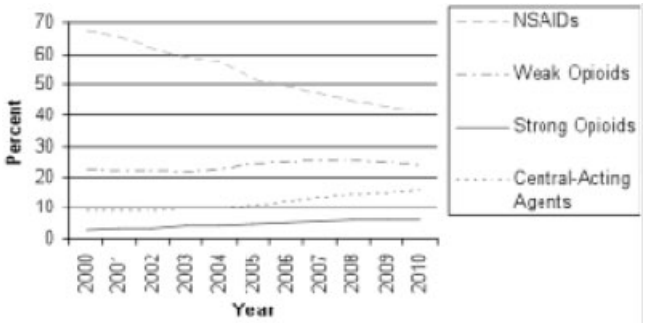

Figure. Patterns of pain medication use among RA patients from 2000-2010.

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The Effect of Anti-Tumor Necrosis Factor Therapy with Two Different Doses of Golimumab on Radiographic Progression in Definite Ankylosing Spondylitis: 4-Year Results. Jürgen Braun[1], Desirée van der Heijde[2], Kay-Geert Hermann[3], Xenofon Baraliakos[4], Atul Deodhar[5], Anna Beutler[6], Michael Mack[6], Weichun Xu[7], Benjamin Hsu[8], Robert D. Inman[9] and GO-RAISE Clinical Investigators. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Charite Medical School, Berlin, Germany, [4]Ruhr-University Bochum, Herne, Germany, [5]Oregon Health & Science University, Portland, OR, [6]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA, [7]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, [8]Centocor R&D, a division of J&J Pharmaceutical R& D, LLC/Univ. of Pennsylvania, Malvern/Philadelphia, PA, [9]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: Three clinical trials in which structural spinal changes in patients with ankylosing spondylitis (AS) treated with tumor necrosis factor (TNF) antagonists over 2 years (yrs) were assessed in comparison to a historical cohort have indicated that such therapy may not alter radiographic progression as quantified by the modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS). Longer-term data are scarce. The purpose of this analysis was to assess the effects of two different dosages of the anti-TNF agent golimumab (GLM) on radiographic progression in patients (pts) with AS through 2 and 4 yrs of treatment.

Methods: Pts (n=356) were randomly assigned (1:1.8:1.8) to subcutaneous injections of PBO, GLM 50mg, or GLM 100mg q4weeks (wks). At wk16, pts in the PBO or 50mg groups with <20% improvement in both total back pain and morning stiffness entered early escape (EE) to GLM 50 or 100mg, respectively. At wk24, pts still receiving PBO crossed over (CO) to GLM 50mg. Lateral view radiographs of the cervical and lumbar spine were performed at baseline, wk104 and wk208. Radiographs were read by 2 independent, central, trained readers using mSASSS methodology (range 0–72).

Results: Among all randomized pts, median time since first AS symptoms was 11.0 yrs. Treatment groups were comparable with regard to age, gender, BASDAI, BASFI, BASMI, CRP, mSASSS, and baseline syndesmophytes. Overall mean changes in mSASSS were 1.1 at wk104, with no obvious treatment group differences, and 3.6 at wk208, with numerically larger changes in the GLM 100mg group (Table). Due to wide distribution of change values, the numerical differences in mean change in mSASSS for the 100mg group or for the 19 radiographically evaluable pts who dose-escalated from 50 to 100mg via EE (data not shown) are not significant by ANOVA on the van der Waerden normal scores. At wk 104 and wk 208, 23.1% and 35.1% of pts had a definitive change (>2 points) in mSASSS.

Table. Baseline and change from baseline in mSASSS

	PBO→GLM 50mg[1] (n=66)	GLM 50mg[2] (n=111)	GLM 100mg[3] (n=122)	All GLM (n=299)
Baseline	16.1 (18.7)	11.7 (16.4)	13.5 (18.9)	13.4 (18.0)
Mean (SD)	7.9	3.1	3.5	4.0
Median				
Wk104	1.6 (4.6)	0.9 (2.7)	0.9 (3.9)	1.1 (3.7)
Mean (SD) change	0.0	0.0	0.0	0.0
Median change	17 (25.8%)	22 (19.8%)	30 (24.6%)	69 (23.1%)
% pts with change >2				
Wk208	3.2 (8.6)	2.4 (6.6)	4.9 (10.6)	3.6 (8.9)
Mean (SD) change	0.5	0.0	1.1	0.5
Median change	22 (33.3%)	34 (30.6%)	49 (40.2%)	105 (35.1%)
% pts with change >2				

[1] Pts in this group either met the early escape criteria at wk16 or crossed over to GLM 50mg at wk24.
[2] Includes pts who did (n=19) and did not (n=92) meet the early escape criteria at wk16.
[3] Includes pts who did (n=25) and did not (n=97) meet the early escape criteria at wk16.

Conclusion: Changes in mSASSS from baseline to wk104 and wk208 indicated that anti-TNF treatment with GLM does not prevent radiographic progression in the spine of pts with AS. There was a trend to more radiographic changes in the group with the higher GLM dosage.

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Increased Visceral Adiposity During Anti Tnfa Treatment for Inflammatory Rheumatic Disease Is Associated with Various Changes on Serum Adipokines: A 2 Year Prospective Study. Eric Toussirot[1], Laurent Mourot[2], Nhu Uyen Nguyen[3], Malika Bouhaddi[4], Daniel Wendling[5] and Gilles Dumoulin[6]. [1]Rheumatology and CIC Biotherapy 506, Besançon, France, [2]University of Franche Comté, Besançon, France, [3]department of Physiology, Besançon, France, [4]Physiology, France, [5]Minjoz University Hospital, Besancon, France, [6]Department of Physiology, France

Background/Purpose: TNFa blocking agents are very effective in rheumatoid arthritis (RA) or ankylosing spondylitis (AS) and has been associated with weight gain. Adipokines are proteins produced by the adipose tissue with many physiologic functions and can also influence the inflammatory response. Certain adipokines could represent a link between the immune response, the metabolic functions and the nutritional status. We evaluated the long term effects of anti TNFa treatment on body weight, body composition and distribution. The changes on the serum levels of adipokines (leptin, adiponectin and resistin) and ghrelin, a gastric peptide involved in appetite regulation were also studied.

Methods: 20 patients (6F) were evaluated (12 AS [modified NY criteria], age [mean ± SD]: 40.7 ± 16.1 yrs; and 8 RA [ACR criteria], age 60.5 ± 9.7 yrs; mean disease duration: 9.6 ± 9.8 yrs). They received infliximab (2), etanercept (6) or adalimumab (12). Body weight, body mass index (BMI), serum levels of adipokines and ghrelin were measured (IRMA) at baseline and then at months (M) 1, 3, 6, 12, 18 and 24. Body composition was evaluated at baseline and then at M6, 12 and 24. Total and regional body fat and lean masses were measured by total body DEXA (Lunar iDXA). Adiposity was calculated as the ratio between total fat tissue and total lean mass + total fat tissue. Fat distribution was evaluated as the relative proportion of fat tissue in the android (central) and the gynoid (hip and thigh) regions.

Results: There was a slight but significant increase in body weight (+ 1.35 kg) and BMI (+ 0.55 kg/cm^2) ($p<0.005$). All the patients responded to the treatment with clinical improvement and decline of erythrocyte sedimentation rate and CRP ($p<0.01$). Although fluctuating during the study, leptin and resistin levels did not significantly change. By contrast, adiponectin increased at M1, and then decreased slowly and reached lower values at M24 compared to baseline (baseline: 12.1 ± 4.8; M24: 11.4 ± 5.4 mg/ml; p= 0.01). We also observed a rapid decline in ghrelin which remained low until the end of the study (baseline: 1256 ± 387; M24: 1117 ± 429 pg/ml; p= 0.035). Lean mass and fat mass in the gynoid

region did not change while there was a significant increase at M24 in adiposity (+ 1.36%; NS), in total fat mass (+ 2.4 kg; p= 0.003) and in fat tissue located in the android region (+ 366 g; p= 0.025).

Conclusion: Long term administration of TNFa blocking agents was associated with gain of body weight and BMI. Leptin and resistin levels fluctuated while ghrelin decreased. However, TNFa blockade is associated with a modest but significant gain in total fat and especially fat in the android region. It is known that abdominal or visceral adipose tissue is associated with the development of atherosclerosis. These changes, together with the decrease in adiponectin serum levels, could negatively influence the cardiovascular risk of these patients.

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Glucosteroid Treatment in Early Arthritis Leads to Increased Fat Mass Despite Reduced Disease Activity. Karin Britsemmer[1], Dirkjan van Schaardenburg[1], W. F. Lems[2] and Michael T. Nurmohamed[1]. [1]Jan van Breemen Research Institute / Reade, Amsterdam, Netherlands, [2]VU University medical center, Amsterdam, Netherlands

Background/Purpose: Several studies provided evidence for excess cardiovascular (CV) morbidity and mortality in rheumatoid arthritis (RA). Rheumatoid cachexia, defined as an decreased lean body mass and an increased truncal fat distribution, is one of the possible predictors for CV morbidity. Rheumatoid cachexia may improve with anti-rheumatic treatment. Evidence on changes in body composition is scarce, therefore we studied the changes in body composition and the association with glucocorticoid (GC) use in patients with early arthritis during the first year.

Methods: Consecutive patients from our early arthritis cohort with a disease duration of <2 years, at least 2 swollen joints and no prior DMARD treatment were investigated. At baseline and 12 months, body composition was assessed by whole body dual-energy X-ray absorptiometry (Lunar DXA). Fat mass was reported as total body fat mass (BFM), truncal fat mass (TFM) and fat mass of arms and legs (FMAL). Lean mass was reported as total lean body mass (LBM) and lean mass of arms and legs (LMAL). Truncal fat distribution reflects the proportion of truncal fat, calculated as the FMT divided by the FMAL, and body fat percentage was calculated as the BFM divided by the total body mass. Clinical assessment included the 28 joint Disease Activity Score (DAS28) and body mass index (BMI)

Results: Of 100 patients (mean age 52 [13], 68% female, median symptom duration 2.3 [1.9] months, mean DAS28 4.9 [1.3]), 85% had RA according to the ACR/EULAR criteria, the others had undifferentiated arthritis. 74% used GCs in the first year (mean oral daily dose 7.6 (2.6) mg). DAS28 decreased and FMAL increased significantly in both the GC+ and GC– groups, however, these changes were more pronounced in the GC+ versus the GC– group (table 1). After one year BMI, total BFM, FMAL, LMAL and BF% had increased significantly in the GC+ group. These differences in body composition were not observed in patients without GC treatment. There were no significant correlations between changes in DAS28 and changes in body composition measurements.

Table 1. Changes in body composition after 1 year in early arthritis patients with and without glucocorticoid (GC) use

	GC+ baseline	GC+ after 1 year	GC–baseline	GC–after 1 year	p-value‡
DAS28	5.2 (1.4)	2.7 (1.2) *	4.1 (1.2)	2.8 (1.2) *	<0.001
BMI, kg/m2	25.9 (4.7)	26.6 (4.9) *	24.6 (4.7)	24.9 (5.2)	ns
Total BFM, kg	27.0 (9.9)	28.5 (10.7) *	25.7 (9.8)	25.9 (10.3)	ns
TFM, kg	14.9 (7.3)	15.5 (7.0)	13.8 (7.5)	14.0 (7.6)	ns
FMAL, kg	11.5 (4.1)	12.2 (4.4) *	11.1 (3.0)	11.1 (3.3)	0.027
Total LBM, kg	45.7 (8.9)	45.8 (8.6)	43.4 (9.6)	43.1 (8.4)	ns
LMAL, kg	20.0 (4.5)	20.2 (4.5) *	18.8 (4.4)	19.0 (4.4)	ns
BF%	0.35 (0.09)	0.37 (0.09) *	0.35 (0.08)	0.35 (0.08)	ns
TFD	1.31 (0.57)	1.30 (0.49)	1.22 (0.51)	1.21 (0.47)	ns

* significant change in GC+ group (p<0.05;
# significant change in GC– group (P<0.05);
‡ differences in change between GC+ and GC– groups

Conclusion: In this early arthritis cohort there were unfavorable changes in body fat composition after one year in GC users, that were not observed in GC nonusers. This effect occurred despite a greater decrease of disease activity in the group of GC users, which would be expected to favorably influence body fat distribution.

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Anti Tumour Necrosis Factor Therapy Is Associated with Reduced Mortality From Ruptured Abdominal Aortic Aneurysm: Results From the British Society for Rheumatology Biologics Register. Audrey SL Low[1], James B. Galloway[1], Louise K. Mercer[1], Rebecca Davies[1], Mark Lunt[1], Kath D. Watson[1], British Society for Rheumatology Biologics Register (BSRBR) control centre consortium[1], Kimme L. Hyrich[1], William G. Dixon[1], Deborah PM Symmons[1] and On behalf of the BSRBR[2]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]British Society for Rheumatology, London, United Kingdom

Background/Purpose: People with RA are at increased risk of mortality from atherosclerotic cardiovascular events such as myocardial infarction and cerebrovascular disease. Less is known about peripheral vascular disease in RA; in particular abdominal aortic aneurysm (AAA) rupture. The aim of this analysis was to explore the influence of anti-TNF therapy on the mortality from AAA rupture.

Methods: People with RA who had recently started anti-TNF therapy were recruited by the BSRBR from 2000–2008. Alongside this cohort, a biologic-naive comparator group treated with non-biologic disease modifying agents (nbDMARD) was also recruited. Patients were followed up by physician and patient questionnaires and flagged with the national death register. All patients were followed until 07/31/2010 or death, whichever came first. Mortality from AAA was identified from International Classification of Diseases 10 (ICD-10) codes I71.3 or I71.4 on the death certificate. The standardised mortality ratio (SMR) with 95% confidence intervals (CI) was calculated for AAA for both anti-TNF and nbDMARD cohorts with reference to the general population. Cox regression models were used to compare mortality rates of AAA between the anti-TNF and nbDMARD cohorts, with adjustment made using an inverse probability of treatment weighting (IPTW) model. Hazard ratios (HR) were calculated.

Results: 12051 patients treated with anti-TNF and 3767 patients treated with nbDMARD contributed to this analysis, with 63807 and 14892 person-years of follow-up respectively. 9 deaths from ruptured AAA were identified (3 in anti-TNF cohort; 6 in nbDMARD cohort), of which 2 were peri-operative (1 per cohort). There was a trend towards increased mortality from ruptured AAA in the nbDMARD cohort compared to the general population: SMR 2.7 (1.0–5.9) but this effect was not observed in the anti-TNF cohort: SMR 0.6 (0.1–1.7). After adjustment, patients ever exposed to anti-TNF were less likely to have died from a ruptured AAA compared to patients in the nbDMARD cohort: HR 0.08 (0.01–0.39).

Conclusion: This is further evidence supporting a biological link between TNF and atherosclerosis. Differences in the SMR could be explained by other factors e.g. hypertension and smoking. Strengths of this study include the size of the cohort and the completeness of death and cause of death ascertainment. Limitations include the low number of outcomes of interest which precluded examining for an influence of response to therapy or an effect of treatment duration.

	nbDMARD (n=3767)	Anti-TNF (n=12051)
Person-years of follow-up	14892	63807
Mean age (SD)	60.1 (12.4)	56.2 (12.3)
Females (%)	72.4	76.2
Median disease duration (IQR)	6 (1–15)	11 (6–19)
Mean DAS28 (SD)	5.1 (1.3)	6.6 (1.0)
Number of deaths from ruptured AAA	6	3
Mortality rate per 100,000 person-years	40	5
Standardised mortality ratio (95%CI)	2.7 (1.0–5.9)	0.6 (0.1–1.7)
Hazard ratio (unadjusted)	Referent	0.09 (0.02–0.38)
Hazard ratio (IPTW)*	Referent	0.08 (0.01–0.39)

* age, gender, smoking, hypertension, disease activity, disease duration, year of entry into study

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Tocilizumab Monotherapy and Tocilizumab Plus Disease-Modifying Antirheumatic Drugs in a US Rheumatoid Arthritis Population with Inadequate Response to Anti-Tumor Necrosis Factor Agents. Michael E. Weinblatt[1], Joel M. Kremer[2], John J. Cush[3], William Rigby[4], Lichen Teng[5], Natasha Singh[5], Raymond L. Malamet[6] and Mark C. Genovese[7]. [1]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Albany Medical College and The Center for Rheumatology, Albany, NY, [3]Baylor Research Institute, Dallas, TX, [4]Dartmouth Medical School, Lebanon, NH, [5]Roche, Nutley, NJ, [6]Genentech, South San Francisco, CA, [7]Stanford University, Palo Alto, CA

Background/Purpose: ACT-STAR, a 24-wk, prospective, open-label, US study, demonstrated similar safety/tolerability/efficacy with tocilizumab (TCZ) monotherapy (MONO) or TCZ+DMARD combination (COMBO) in adult patients (pts) with moderate-to-severe active RA who had an inadequate response (IR) to current biologic or nonbiologic DMARDs. Efficacy of TCZ MONO was also previously demonstrated in a randomized trial of methotrexate-IR or naïve patients (AMBITION), but it is important to understand the risk-benefit profile of TCZ MONO specifically in the difficult-to-treat population of anti-TNF-IR pts. Therefore, a subanalysis of ACT-STAR was conducted to compare the safety/efficacy of TCZ MONO or COMBO therapy in anti-TNF-IR pts.

Methods: In ACT-STAR, pts on nonbiologic DMARDs alone or combined with biologic DMARDs were randomized to 2 TCZ COMBO groups (4 mg/kg [TCZ 4]+DMARD or 8 mg/kg [TCZ 8]+DMARD); pts on biologic DMARD monotherapy before baseline were assigned to TCZ 8 MONO. Biologic DMARDs were discontinued before baseline. At wk 8, pts randomized to TCZ 4+DMARD who did not achieve ≥20% improvement in joint counts had TCZ dose increased to 8 mg/kg; from week 12 onward pts on TCZ 4+DMARD had dose increased at investigator's discretion. Pts on TCZ 8+DMARD could have TCZ dose decreased at any time for safety. We reviewed safety/efficacy results for pts who previously received anti-TNF agents. Primary outcome was number (%) of pts with serious adverse events (SAEs) and serious infection events (SIEs). Secondary variables included ACR20/50/70 and DAS28 scores.

Results: The anti-TNF-IR subset in the intent-to-treat population comprised 552 pts (TCZ 4+DMARD=202; TCZ 8+DMARD=221; TCZ 8=129). Baseline disease characteristics in each group are shown in the table. Incidence rates of SAEs and SIEs were similar between COMBO groups and higher than those in the MONO group (Table). Most common SIEs were cellulitis and pneumonia; 2 pts in TCZ 4+DMARD group experienced GI perforations. Week 24 ACR response rates and DAS28 remission are also shown in the table for each treatment group (comparable to results for the overall population). At wk 24, pts in each group achieved a statistically significant change from baseline in DAS28 score ($P<0.0001$) (Table).

Table. Baseline Characteristics, Efficacy and Safety in the Anti-TNF-IR Subset of ACT-STAR

	Treatment Group		
Parameter	**TCZ 4/8+DMARD**	**TCZ 8+DMARD**	**TCZ 8 Monotherapy**
Baseline Characteristics			
n (intent-to-treat population, anti-TNF-IR)	202	221	129
RA disease duration (yrs), mean (SD)	12.7 (9.81)	12.0 (8.57)	13.2 (9.93)
DAS28 score, mean (SD)	5.78 (1.024)	5.65 (0.997)	6.13 (0.942)
Swollen joint count, mean (SD)	19.0 (11.53)	19.1 (10.62)	22.0 (12.00)
Tender joint count, mean (SD)	29.4 (14.30)	29.4 (15.70)	34.3 (16.26)
CRP (mg/dL), mean (SD)	1.70 (2.450)	1.43 (2.080)	1.85 (3.123)
Patients using ≥2 previous anti-TNF agents,%	45.8%	54.6%	53.2%
Efficacy (intent-to-treat population, anti-TNF-IR)			
Week 24 ACR20 response,% of pts	43.1	48.9	47.3
Week 24 ACR50 response,% of pts	22.8	22.6	20.9
Week 24 ACR70 response,% of pts	6.9	8.1	5.4
Change from baseline in DAS28 score at week 24, mean (SD)	−1.76 (1.283) $P<0.0001$	−1.85 (1.373) $P<0.0001$	−1.95 (1.445) $P<0.0001$
DAS28 remission at week 24,% of pts	17.6	22.8	15.7
Safety			
n (safety population, anti-TNF-IR)	203	240	109
AEs, Total Patients With ≥1, n (%)	170 (83.7)	200 (83.3)	87 (79.8)
AEs causing discontinuation	21 (10.3)	10 (4.2)	4 (3.7)
Total Patients With ≥1, n (%)	6 (3.0)	1 (0.4)	1 (0.9)
Infections and infestations	4 (2.0)	1 (0.4)	–
Gastrointestinal disorders	4 (2.0)	1 (0.4)	–
Skin and subcutaneous tissue disorders			
SAEs, Total Patients With ≥1, n (%)	15 (7.4)	19 (7.9)	5 (4.6)
Most common	2 (1.0)	2 (0.8)	2 (1.8)
SAEs (≥1%), n (%)	3 (1.5)	3 (1.3)	–
Cellulitis	2 (1.0)	–	–
Pneumonia			
Coronary Artery Disease			
SIEs, Total Patients With ≥1, n (%)	9 (4.4)	9 (3.8)	2 (1.8)
Most common SIEs (≥1%), n (%)	2 (1.0)	2 (0.8)	2 (1.8)
Cellulitis	3 (1.5)	3 (1.3)	–
Pneumonia			
Deaths, n (%)	1 (0.5)	–	–

Conclusion: In this refractory, US population of pts failing at least 1 anti-TNF, SAE and SIE rates were comparable in COMBO groups, but higher than those in the MONO group. This subanalysis represents the first data assessing TCZ monotherapy specifically in anti-TNF-IR patients, demonstrating equivalent efficacy at the 8 mg/kg dose to TCZ+DMARD combination therapy and a positive risk-benefit profile. These results may have important implications for the use of TCZ monotherapy in the refractory population of patients who have failed therapy with an anti-TNF agent.

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14-3-3η, a Novel Mediator Upregulated by TNFα, Reflects Clinical Response to Anti-TNFα Therapy. Walter P. Maksymowych[1] and Anthony Marotta[2]. [1]University of Alberta, Edmonton, AB, [2]Augurex Life Sciences Corp, North Vancouver, BC

Background/Purpose: TNFα targeted therapies are routinely used in the treatment of RA and despite their efficacy, patient response remains heterogeneous. This underscores the unmet need for biomarkers to assist in the identification of likely responders. 14-3-3 proteins are intracellular proteins mediating several key signalling pathways but one isoform, 14-3-3η, has been detected extracellularly in the joints and serum of patients with arthritis. It has been described as a specific RA serum marker and as a novel drug target based on its induction of key factors, including TNFα, that are involved in the pathogenesis of RA. We investigated the direct effects of TNFα on 14-3-3η and whether its clinical expression reflects response to anti-TNFα therapy.

Methods: To examine the stimulatory effects of TNFα on 14-3-3η, monocytic THP-1 cells were stimulated with 50ng/ml, for 18h and % induction was determined through densitometry. Serum 14-3-3η was measured in a cohort of 74 RA patients who were refractory to standard DMARDs and candidates for anti-TNF therapy at pre-treatment and approximately 15 weeks post-treatment using an investigational-grade 14-3-3η ELISA. EULAR classification criteria were used to define good, moderate or non-response. Two-tailed paired and unpaired t-tests and Mann-Whitney U-tests were used to determine group differences in 14-3-3η levels pre-treatment and its modifiability post-treatment. Correlations were calculated between 14-3-3η and clinical variables using the Pearson chi-square.

Results: Stimulation of monocytes with TNFα resulted in a 30% increase in 14-3-3η transcripts. A good EULAR response was observed in 15 of the 74 patients (20%). The mean (SD) and median levels of 14-3-3η were higher in those who failed to achieve a good EULAR response [mean = 7.56 (8.28), median = 2.52ng/ml] compared to the good EULAR

responders [mean = 4.23 (6.86), median = 0.72ng/ml], with median differences being statistically significant (p=0.015). Post-treatment 14-3-3η serum levels were significantly lower than pre-treatment (mean difference of 0.93ng/ml (95% CI 0.089 to 1.78, t=2.21, p=0.031) indicating that serum 14-3-3η levels are modifiable with anti-TNFα therapy. There were no significant correlations between pre-treatment clinical variables and serum levels of 14-3-3η. For the whole cohort, Δ14-3-3η correlated moderately with ΔESR (r=0.35, p=0.002), ΔHAQ (r=0.28, p=0.016) and ΔCRP (r=0.25, p=0.036). A subset analysis of good EULAR responders (15 patients, 10 females) versus non-responders (17 patients, 11 females) revealed no correlation in the Δ14-3-3η with the change in clinical variables in non-responders but a high correlation with ΔESR (r=0.89, p<0.00001), ΔCRP (r=0.68, p=0.006) and importantly ΔDAS (r=0.56, p=0.009) in good responders.

Conclusion: 14-3-3η is up-regulated by TNFα in vitro and its serum levels are lower in patients who respond well to anti-TNFα therapy. Serum 14-3-3η expression is modifiable with anti-TNF therapy. In patients with good EULAR response, serum 14-3-3η levels correlate strongly with measures of clinical improvement. 14-3-3η should be further investigated as a promising candidate biomarker that predicts response to anti-TNF therapy.

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Evaluation of the Association Between Disease Activity and Risk of Serious Infections in Subjects with Rheumatoid Arthritis When Treated with Etanercept or Disease -modifying Anti-rheumatic Drugs. Paul Emery[1], G. Gallo[2], C. L. Morgan[3], C. J. Currie[4], C. D. Poole[3] and Henk Nab[5]. [1]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [2]Pfizer, Rome, Italy, [3]Pharmatelligence, Cardiff, United Kingdom, [4]Cardiff University, Cardiff, United Kingdom, [5]Pfizer Europe, Rome, Italy

Background/Purpose: It has been reported that there is increased risk of serious infections (SI) when subjects are switched from disease modifying anti-rheumatic drugs (DMARD) therapy to a biologic. This increased risk is not seen following longer-term use of biologics and its aetiology is unknown. The purpose of this study was to determine if the rates of SI in subjects switched to etanercept (ETN), compared with a DMARD reference cohort, correlated with the level of disease activity.

Methods: Anonymised data on ETN and DMARD treated subjects were provided by the British Society of Rheumatology Biologics Register (BSRBR), a prospective observational study monitoring the long-term safety of TNF inhibitors and standard DMARDs in rheumatoid arthritis (RA) patients. At baseline subjects underwent detailed clinical assessment by a rheumatologist. Consultants and subjects completed follow-up questionnaires every six months for three years, then annually by consultants only for two years. Disease activity was measured using the DAS28. Infections were considered serious if they led to hospitalisation or the use of intravenous antibiotics or death. The risk of SI was compared in two ways at six months and for the entire period of follow-up. Firstly, using a simple calculation of the rate per 1000 person years (py) for each aggregated level of the DAS28. Secondly, using a multivariate Cox model. Models were specified using a forward manual inclusion method for parameters where significance was P<0.05.

Results: ETN n=3,470, DMARD n= 1,365. There were differences in baseline characteristics: ETN subjects were significantly younger (55.4 vs. 59.5 yrs; P<0.001) but with a longer duration of RA (13.6 vs. 9.6 yrs; P<0.001) compared to DMARD subjects. ETN subjects had significantly greater disease activity (DAS28 6.5 vs. 5.7; P<0.001) and greater disability (HAQ 2.07 vs. 1.68; P<0.001). In a combined analysis for the whole observational period, there was an association between DAS28 and risk of SI. Where DAS28 ≤5, the infection rate was 27.1 per 1,000 py. This increased to 40.5 per 1,000 py at DAS28 >6 and ≤7, and 64.2 per 1,000 py at DAS28 >8. In Cox regression models, DAS28 was associated with a 16% increase in hazard ratio for each integer increase in the score (HR = 1.17, 95% CI 1.08–1.27; p<0.001). Other significant variables were age, gender, baseline HAQ score and comorbidity index. Treatment type was not significant in the model, ETN vs. DMARD (HR =1.07, 95% CI 0.86–1.32; p=0.561).

Conclusion: There was a linear association between DAS28, and the risk of SI. This infers that reducing disease activity would reduce the likelihood of SI. These data support the hypothesis that it is disease activity per se that is associated with SI. With long term follow up, treatment type was not associated with SI. It is important to note that these are observational data, and further corroboration is required.

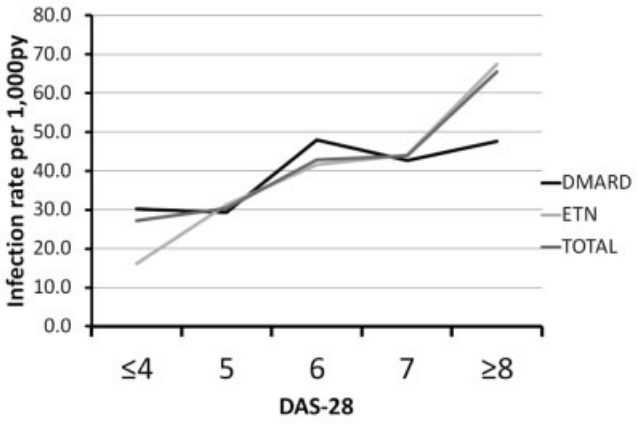

Figure 1. Crude rate of infection by DAS28

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A Nationwide Survey on Patient's Versus Physician's Evaluation of Biological Therapy in Rheumatoid Arthritis in Relation to Disease Activity and Route of Administration: The Be-Raise Study. Jan Lenaerts[1], Bert Vander Cruyssen[2], H. Mielants[3], Rene Westhovens[4], Patrick Durez[5] and Dirk Elewaut[6]. [1]Department of Rheumatology, Catholic University Leuven, Belgium, Reuma-instituut Hasselt Belgium., Hasselt, Belgium, [2]OLV Hospital Aalst and St-josephs hospital Bornem, Aalst, Belgium, [3]University Hospital, Gent, Belgium, [4]University Hospital KU Leuven, Leuven, Belgium, [5]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, [6]Gent University Hospital, Ghent, Belgium

Background/Purpose: The Belgian Be-raise survey aimed to explore how patients experience their current treatment with biologicals and correlate this with the treating physician's opinion.

Methods: This is a nationwide cross-sectional survey in which all Belgian rheumatologists were invited to participate. Each rheumatologist could include 10 RA patients treated with a biological for at least 6 months. Both patients and physicians completed a similar extensive questionnaire, but were blinded for each other's judgments. Questions covered various items on current treatment (including participation, compliance and practical issues); in this abstract we focus on patients satisfaction with disease control and compare this to the perception of the treating rheumatologist. Most questions were reported on a 0–10 likert scale. Good satisfaction was defined by a score of ≥9

Results: As of April 2011, 478 questionnaires were available from 255 intravenously (IV) treated and 223 subcutaneously (SC) treated patients coming from 37 centers and 63 rheumatologists, which represents about one third of all Belgian rheumatologists. Patients were treated with Etanercept (17.7%), Adalimumab (26.9%), Certolizumab (0.8%) Golimumab (2%), Rituximab(10.2%), Abatacept (7.7%), Infliximab (21%) orTocilizumab (13.6%). The mean DAS-28-CRP was 2.8. 46% of patients were in remission, 18% had low disease activity, 34% moderate disease activity and 3% high disease activity.

The patient satisfaction on the overall control of RA symptoms was higher (44% scored≥9)) than this of the treating physician (35%), regardless of the route of administration (p<0.005). In addition, no differences were seen for the patients treated with an IV compared to a SC administration. In striking contrast herewith, the physicians perception of satisfaction with disease control was markedly lower for IV treated patients (31% scoring ≥9)) as opposed to SC treated patients (47%) (p< 0.01). Further regression analyses, corrected by a propensity score for IV/SC allocation (including amongst others sex, age, professional status and disease duration) revealed that patients are significantly more satisfied of the way of administration when they are also comfortable about disease control (OR = 4.6, 95% CI 3.0–7.1) whereas IV or SC route (OR = 0.89,

95% CI 0.57 – 1.38) or the frequency of administration (OR = 0.74, 95% CI 0.48–1.13, p = NS) did not affect the appreciation of therapy. This is again contrasted with the physicians appreciation of the patient's score: IV use was consistently rated lower than SC use (OR = 0.54, 95% CI = 0.33 – 0.89, p = 0.017), irrespective of disease activity or the frequency of therapy administration.

Conclusion: There is a considerable mismatch between patients and rheumatologists appreciation on the route of administration of biological therapy in RA. Physicians consistently consider iv biological therapy to be less satisfactory, whereas the patients appreciation is independent of the route of administration. Overall, the data underscore the importance of patient reported feedback in overall assessment of biological treatment regimens.

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Combination of Disease-Modifying Antirheumatic Drugsprohibits the Need of Early Initiation of Biologicals, Independent of Glucocorticosteroids. A clinical trial to Investigate Different Induction Therapies in Early Rheumatoid Arthritis. P.H.P. de Jong[1], Johanna Hazes[2], P.J. Barendregt[3], A.M. Huisman[4], D. van Zeben[4], P.A. van der Lubbe[5], A.H. Gerards[5], M.H. de Jager[6], P.B. de Sonnaville[7], B.A. Grillet[8], Jolanda J. Luime[9] and A.E.A.M. Weel[3]. [1]University Medical Center, Rotterdam, Netherlands, [2]Erasmus Medical Centre Rotterdam, Rotterdam, Netherlands, [3]Maasstad Hospital, Rotterdam, Netherlands, [4]Sint Franciscus Gasthuis, Rotterdam, Netherlands, [5]Vlietland Hospital, Schiedam, Netherlands, [6]Albert Schweitzer Hospital, Dordrecht, Netherlands, [7]Admiraal de Ruyter hospital, Goes, [8]Zorgsaam hospital, Terneuzen, Netherlands, [9]Erasmus MC - University Medical Center, Rotterdam, Netherlands

Background/Purpose: The recently published EULAR treatment guideline recommend treatment targeted to achieve remission or at least low disease activity within 3 months and definitely within 6 months. Recommended treatment for DMARD naïve patients is Methotrexate (MTX) with or without glucocorticoids (GCs). Combination therapy however is not recommended, because well proven evidence of superior efficacy is suggested to be lacking. Furthermore possible drug toxicities might influence the choice of induction therapy. To compare the 3 month clinical efficacy of: (1) combination DMARD vs. MTX mono-therapy and (2) oral GCs bridging therapy vs. 1 dose of intramuscular (im) GCs in patients with early RA.

Methods: For this study data are used of a currently ongoing single-blinded randomized clinical trial in patients ≥18 years with recent-onset arthritis (tREACH). We included patients who had a high probability (> 70%) according to their likelihood of progressing to persistent arthritis based of the prediction model of Visser. The Visser algorithm and 2010 criteria for RA have similar discriminative abilities to identify patients at risk of persistent arthritis at 1 year. Patients were randomized into 3 induction therapy strategies: (A) Combination therapy (MTX 25 mg + Sulphasalazine (SASP) 2 gr. + Hydroxychloroquine (HCQ)) 400 mg with im GCs (Depomedrol 120mg), (B) Combination therapy with an oral GCs tapering scheme (starting 15 mg) and (C) MTX with oral GCs similar to B. In case of *'treatment failure'*, defined as DAS>2.4, medication is intensified to MTX with a biological.

We investigated following response parameters: treatment failure, EULAR response criteria and decrease in DAS and HAQ. Statistical comparison between the baseline characteristics and clinical response parameters of all treatment arms were made by the student's t-test, χ^2 test, or the Wilcoxon rank-sum test, when appropriate.

Results: We random allocated 279 patients (mean symptom duration: 166 days, 59% ACPA pos and 16% with erosive disease) over 3 treatment arms. Baseline characteristics per arm are given in table 1.

Table 1. Baseline characteristics of patients with a high probability to develop a persistent arthritis

	A. Combination therapy + intramuscular GCs (n = 91)	B. Combination therapy + oral GCs (n = 93)	C. MTX + oral GCs (n = 95)
Age (yrs), *mean (95% CI)*	52 (48–55)	53 (50–56)	54 (51–57)
Sex, female, *no (%)*	55 (60%)	67 (72%)	68 (72%)
Symptom duration (days), *mean (95% CI)**	164 (141–187)	185 (164–207)	151 (132–169)
RF pos., *no (%)*	55 (60%)	51 (55%)	50 (53%)
ACPA pos., *no (%)*	59 (65%)	50 (54%)	55 (58%)
Erosion, *no (%)***	23 (26%)	10 (11%)	10 (11%)
Fullfillment RA criteria, *no (%)*			
1987	65 (75%)	55 (61%)	57 (63%)
2010	79 (91%)	78 (87%)	77 (86%)
DAS, *mean (95% CI)*	3.26 (3.06–3.46)	3.41 (3.16–3.65)	3.40 (3.17–3.63)
DAS28, *mean (95% CI)*	4.76 (4.49–5.03)	4.85 (4.54–5.16)	4.77 (4.47–5.07)
HAQ, *mean (95% CI)*	0.96 (0.81–1.12)	0.92 (0.78–1.07)	1.08 (0.93–1.23)

Abbreviations: CI = Confidence Interval, RF = Rheumatoid Factor, ACPA = Anti-citrullinated protein/peptide antibodies,
DAS = Disease Activity Score, HAQ = Health Assessment Questionnaire.
* P<0.05 B vs C
** P<0.01 A vs. B/C

After 3 months the DAS declined more in patients with combination DMARD (A:−1.35 & B:−1.54 vs.C: −1.14) with 11% less biological initiations (table 2). There effect of GCs on these clinical outcome parameters was not different between group A and B (table 2).

Table 2. Clinical response after 3 months for each treatment arm.

	A. MTX + SASP + HCQ + im GCs (n = 74)	B. MTX + SASP + HCQ + oral GCs (n = 74)	C. MTX + oral GCs (n = 73)
DAS, *mean (95% CI)*	1.92 (1.64–2.19)[1]	1.91 (1.70–2.11)[1]	2.33 (2.09–2.59)
ΔDAS (T3–T0), *mean (95% CI)*	−1.35 (−1.07 to −1.62)	−1.54 (−1.29 to −1.78)[2]	−1.14 (−0.89 to −1.40)
Disease state according to DAS, *no (%)*			
*Starting biological**	17 (23%)[3]	17 (23%)[3]	32 (44%)
low disease activity	26 (35%)	31 (42%)	21 (29%)
remission	31 (42%)	26 (35%)	20 (27%)
EULAR response criteria, *no (%)*			
good	37 (50%)	33 (45%)	29 (40%)
moderate	21 (28%)	27 (36%)	19 (26%)
none	16 (22%)	14 (19%)[4]	25 (34%)
HAQ, *mean (95% CI)*	0.53 (0.39–0.67)	0.54 (0.40–0.67)	0.72 (0.56–0.87)
ΔHAQ (T3–T0), *mean (95% CI)*	−0.40 (−0.28 to −0.53)	−0.41 (−0.28 to −0.54)	−0.41 (−0.26 to −0.55)

Abbreviations: MTX = Methotrexate, SASP = Sulphasalazine, HCQ = Hydroxychloroquine, GC = glucocorticosteroids, CI = Confidence Interval
* moderate to high disease activity
1: P<0.05 B vs. C and P<0.01 A vs. C
2: P<0.05 B vs. C
3: P<0.01 A/B vs. C
4: P<0.05 B vs. C

Conclusion: In patients with early RA according to the new ACR/EULAR 2010 a combination of DMARDs (MTX + SSZ + HCQ) are superior to MTX monotherapy in achieving low disease activity. Furthermore both intramuscular and oral GCs can be used as bridging therapy.

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Sustained Remission in Anti-TNF Treated Rheumatoid Arthritis Patients. Observational Data From Southern Sweden. Jon T. Einarsson, Pierre Geborek, Tore Saxne and Meliha C. Kapetanovic. Dept of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Sweden, Lund, Sweden

Background/Purpose: Remission is increasingly becoming a treatment goal in rheumatoid arthritis (RA) patients and DAS28 remission criteria are widely used, despite their limitations. The purpose of this study was to study frequency, duration and predictors of sustained remission (SR), defined as DAS<2.6 for at least 6 months, in patients with established RA treated with anti-TNF drugs in the observational setting of Southern Sweden.

Methods: Patients with a clinical diagnosis of RA initiating any anti-TNF treatment between March 1999 and December 2009 were eligible for this study. Disease and treatment characteristics at baseline and at each follow up were retrieved from the South Swedish Arthritis Treatment Group register (SSATG). The registry was searched for patients fulfilling the DAS28 remission criteria on at least two occasions ≥3 months after treatment initiation. Remission time was defined as time between first visit with DAS28<2.6 and first visit with DAS28>2.6. To compensate for intercurrent diseases patients were allowed to have DAS28>2.6 at one occasion given that they fulfilled the remission criteria for at least 6 months before and afterwards. All data were assessed by one researcher (JTE) who identified patients fulfilling the SR definition. Possible baseline predictors of SR were studied using multivariate binary logistic regression models.

Results: Of 3446 initiated treatments, 481 (14 %) treatments fulfilled SR criteria. Of these, 222 (6 %) were still in remission at last follow up. 181

treatments escaped remission. Of these 159 remained on the original treatment, 2 stopped, and 23 switched to another biologic. Altogether 77 patients in the SR group stopped the original treatment, 15 (0.4 %) due to remission. Mean time before SR was achieved was 18 months, range 0–100. Number of treatments, time to- and duration of SR, stratified according to SR ever, ongoing, escape, and 1st,2nd or 3rd anti TNF course are given in the table. Predictors for reaching SR were (OR; 95%CI): male gender 1.83; 1.5–2.3, low age 0.83, 0.8–0.9, low HAQ 0.43 0.4–0.5, low DAS28 0.68; 0.6–0.8, methotrexate treatment 1.64; 1.3–2.1), and no previous biologic treatment OR 1.66; 1.3–2.1.

Conclusion: SR was not common in RA patients on TNF inhibitors in the observational setting and in general required long time to be reached. However, patients achieving SR remained in remission for a substantial period of time. Male gender, and lower age, low DAS or HAQ, concomitant methotrexate, and no previous biological treatment at treatment initiation were positive predictors of SR.

	All	Etanercept	Adalimumab	Infliximab
Treatments (N)	3446	1549	852	1045
Remission on 1st/2nd /3rd TNF inhibitor	379/93/8	169/53/6	78/37/2	132/3/0
Remission Ongoing N (%)	222 (6%)	113 (7%)	63 (7%)	46 (4%)
Mean time to/Mean duration (months)	15.2/41.5	12.5/39.5	14.0/37.5	24.0/52.5
Remission Escape (N;%)	181 (5%)	85 (6%)	40 (5%)	56 (5%)
Mean time to/Mean duration (months)	44.5/27.0	44.5/28.0	36.0/25.5	50.5/26.5

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Risk of Fatal Infection and Malignancy Related to Use of Anti-Tumor Necrosis Factor-Alpha Biologics by Rheumatoid Arthritis Patients. Veena Thyagarajan[1], Heather Norman[2], Kimberly Alexander[3], Pavel Napalkov[3] and Cheryl Enger[1] [1]OptumInsight, Ann Arbor, MI, [2]OptumInsight, Waltham, MA, [3]Genentech, Inc., South San Francisco, CA

Background/Purpose: Rheumatoid arthritis (RA) may be treated with biologics which inhibit the pro-inflammatory cytokine tumor necrosis factor alpha (aTNF). The pro-inflammatory and apoptotic properties of TNF play a role in controlling infection and reducing malignant cell formation. This study estimated the risks of fatal infection and fatal malignancy among RA patients treated with aTNF biologics.

Methods: A retrospective cohort study of RA patients who initiated treatment with adalimumab (ADA), etanercept (ETN), or infliximab (INF) (including aTNF naïve and aTNF switchers) from January 2000 to December 2008 was conducted using the Normative Health Information (NHI) database, an administrative database of a large US healthcare insurer. Patients were followed for the occurrence of fatal infection and fatal malignancy. aTNF therapy was identified in the NHI database by procedure claims for physician-administered drugs and by pharmacy dispensings for patient-administered drugs. Current exposure for physician-administered drugs was defined according to prescribing guidelines for RA plus 30 days and by recorded days supply in pharmacy records for patient-administered drugs plus 30 days. Study outcomes were identified by external linkage to the National Death Index database. Unadjusted incidence rates (IRs) per 1,000 person-years (PY) for study outcomes were calculated for each aTNF. Intent-to-treat analysis was the primary analysis for fatal malignancy where exposure status is based on the aTNF on which the person entered the cohort, regardless of whether the patient discontinued the drug or switched to another aTNF during follow-up. Time-on-drug analysis was the primary analysis for fatal infections where exposure status is based on current exposure with exposure censored upon treatment discontinuation or switch to a different aTNF. The association between baseline covariates and fatal infection were estimated with unadjusted ORs and 95% CIs for each covariate.

Results: 7,734 patients initiated ADA, ETN, or INF (13,296 PY for fatal malignancy; 10,710 PY current exposure for fatal infections). 21 fatal malignancies were identified. The IR for fatal malignancy was 1.24 (95% CI: 0.42–2.96) among ADA initiators, 1.57 (95% CI: 0.78–2.87) among ETN initiators, and 1.84 (95% CI: 0.87–3.48) among INF initiators. 12 fatal infections, including 2 fatal opportunistic infections, were identified. The IR for fatal infection was 0.78 (95% CI: 0.15–2.49) during current ADA exposure, 0.88 (95% CI: 0.30–2.10) during current ETN exposure, 0.83 (95% CI: 0.23–2.21) during current INF exposure, and 1.16 (95% CI: 0.32–3.09) during no current drug exposure. An increased unadjusted OR of fatal infection was observed with baseline chronic lung disease (OR: 13.62; 95% CI: 2.98–51.16), cardiovascular disease (OR: 10.12; 95% CI: 2.22–37.96), and steroidal estrogen use (OR: 4.79; 95% CI: 1.52–15.12).

Conclusion: The occurrence of fatal malignancy and fatal infection was rare. Risks for fatal malignancy and fatal infections were similar across aTNFs. The small number of outcomes limits inference of these risk estimates and prevented inclusion of baseline covariates into an adjusted model.

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Early Reductions in Tissue Inflammation with Tocilizumab As Either Monotherapy or in Combination with Methotrexate: 12-Week Unblinded Results From a Magnetic Resonance Imaging Substudy of a Randomized Controlled Trial. Philip G. Conaghan[1], Charles G. Peterfy[2], Julie DiCarlo[2], Ewa Olech[3], Alan R. Alberts[4], Jeffrey A. Alper[5], Jenny Devenport[6], Andrew M. Anisfeld[6] and Orrin M. Troum[7]. [1]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [2]Spire Sciences LLC, San Francisco, CA, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]West Broward Rheumatology Associates, Inc., Tamarac, FL, [5]Jeffrey Alper MD Research, Naples, FL, [6]Genentech, South San Francisco, CA, [7]USC Keck School of Medicine, Santa Monica, CA

Background/Purpose: Tocilizumab (TCZ) monotherapy (MONO) has been shown to be superior to methotrexate (MTX) in achieving clinical reduction of disease activity in rheumatoid arthritis (RA).[1] A 24-week (wk) interim analysis of the double-blind phase 3b ACT-RAY study[2] showed no additional clinical benefit from adding MTX to TCZ vs switching to TCZ+PBO in patients with an inadequate response to MTX. It is important to determine if tissue inflammation, an important predictor of radiographic damage, is reduced in an analogous pattern. While MRI results from the blinded TCZ±MTX population have been reported,[3] this analysis examined effects of MRI measures of synovitis (SYN), osteitis (OST), and erosion (ERO) through wk 12 after therapy initiation by treatment assignment in patients with erosive RA.

Methods: In the ACT-RAY study, RA patients with inadequate response to MTX were randomized to continue stable MTX or receive placebo (PBO), both in combination with TCZ 8 mg/kg IV every 4 wks. In a substudy of this trial (N=63), 0.2T extremity MRI of one hand (metacarpophalangeal joints 1–5) and wrist was acquired at baseline (BL) and wks 2, 12, and 52. MRIs were quality-controlled and scored by 2 blinded radiologists by a RAMRIS method. Change in scores from BL through wk 12 for the TCZ+MTX and TCZ+PBO groups in this substudy are compared to evaluate early effects on joint inflammation between the two treatment regimens.

Results: BL mean RAMRIS scores showed high disease severity and burden in both groups (Table). Decreases in SYN and OST were observed at wk 2 and became statistically significant in both groups by wk 12. No significant changes from BL in mean ERO score emerged (Table). BL osteitis scores were higher in the PBO group; the proportion of patients who experienced improvements ≥Smallest Detectable Change (SDC) for both SYN and OST was higher in the PBO group than in the MTX group. Similar numbers of patients experienced ERO progression vs regression in each group (Table). During this period, no patient in the TCZ+PBO group and only 1 (3.3%) patient in the TCZ+MTX group developed a newly eroded bone.

Table. Mean Values and SDC-Based Classification of RAMRIS Scores

	TCZ+MTX (N = 31)					TCZ+PBO (N = 32)				
Mean RAMRIS Score	BL (n = 31)	Wk 2 (n = 31)	BL to Wk 2 Δ (95% CI) (n = 31)	Wk 12 (n = 30)	BL to Wk 12 Δ (95% CI) (n = 30)	BL (n = 32)	Wk 2 (n = 32)	BL to Wk 2 Δ (95% CI) (n = 32)	Wk 12 (n = 29)	BL to Wk 12 Δ (95% CI) (n = 29)
SYN	7.2	7.1	−0.1 (−0.5, 0.3)	6.3	−0.9* (−1.6, −0.2)	7.4	6.5	−0.9† (−1.5, −0.4)	5.7	−1.9‡ (−2.8, −1.0)
OST	7.8	7.6	−0.2* (−1.3, 0.9)	4.4	−3.6† (−6.5, −0.7)	11.1	10.3	−0.7 (−1.8, 0.3)	5.5	−5.1* (−8.6, −1.6)
ERO	19.4	19.4	0.0 (−0.4, 0.5)	19.2	−0.3 (−1.2, 0.6)	16.0	16.2	0.2 (−0.0, 0.5)	16.6	0.0 (−0.6, 0.6)

* $P<0.01$, † $P<0.001$; ‡ $P<0.0001$.
Wilcoxon Signed Rank test for no change from BL within group; Percentile interval: 95% CI of mean change from BL within group.

	TCZ+MTX (N=30) n (%)		TCZ+PBO (N=29) n (%)	
Classification Derived from SDC[a] at Wk 12	Regressors (Change ≤ SDC)	Progressors (Change ≥ SDC)	Regressors (Change ≤ SDC)	Progressors (Change ≥ SDC)
SYN	7 (23.3)	1 (3.3)	11 (37.9)	0
OST	6 (20.0)	0	9 (31.0)	1 (3.4)
ERO	3 (10.0)	2 (6.7)	3 (10.3)	2 (6.9)

[a] SDC values at wk 12:
SYN: 1.71
OST: 4.27
ERO: 1.51

Conclusion: These MRI data (previously blinded for TCZ±MTX, but now unblinded to evaluate TCZ+MTX and TCZ+PBO groups separately) demonstrate that TCZ is associated with early suppression of SYN and OST, with no mean increase in ERO score observed through wk 12. The similarities

in MRI findings between TCZ+PBO and TCZ+MTX groups suggest that continuation of MTX in combination with TCZ or switching to TCZ MONO are equally beneficial for early suppression of joint inflammation. TCZ MONO may be an appropriate alternative to TCZ+MTX in patients who are intolerant or unwilling/unable to take MTX.

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Infliximab Versus Placebo in Adult Patients with ACPA Positive Undifferentiated Arthritis. Patrick Durez[1], Laurent Meric de Bellefon[1], Genevieve Depresseux[1], Adrien Nzeusseu Toukap[1], Bernard Lauwerys[1] and Frédéric. A. Houssiau[2]. [1]Cliniques Universitaires St Luc, Brussels, Belgium, [2]Université catholique de Louvain, Brussels, Belgium

Background/Purpose: Patients (pts) with Undifferentiated Arthritis (UA), positive for ACPA antibodies are at high risk of progressing to Rheumatoid Arthritis (RA). TNF plays a key role in the pathogenesis of RA. Very early treatment with the combination of Methotrexate and Infliximab (IFX) in a small cohort of UA showed a benefit in clinical symptoms and reduction of MRI evidence of synovitis and erosions[1].

Objectives: To assess whether IFX is more effective than placebo (Pbo) in preventing the development of RA in adult pts with UA at high risk of the development of RA. Other end points were clinical response and synovitis assessed by MRI and synovial biopsy.

Methods: This was a randomized, double-blind, Pbo-controlled, two-arm parallel design study of 12 months to the primary endpoint (proportion of pts who developed RA by ARA 2007 criteria). Pts with UA and symptomatic clinical synovitis of ≥1 joints and ACPA positivity were randomized 1:1 to IFX (3 mg/kg) or Pbo at week 0, 2, 6, 14 and 22, after which treatment was terminated. NSAIDs/stable low-dose oral corticosteroid (≤5 mg/day prednisone or equivalent) were permitted but no DMARDs. Pts who developed RA at any time were discontinued and could receive standard of care. Paired synovial biopsies were harvested by needle-arthroscopy at baseline and at week 12 from the knee of 8 Pbo and 8 IFX patients.

Results: 30 pts were randomized (mean age: 48 +/− 12 yrs; mean duration of arthritis: 0.34 +/− 0.53 yr; mean CRP level: 1.67 +/− 2.23 mg/dL); 7 had preexisting erosions. By 1 yr, 11/15 pts treated with IFX developed RA vs 10/15 Pbo-treated pts (Kaplan Meier, log rank p=0.868). At week 14, peak ACR 20, 50, 70 responses were observed respectively in 71.4%, 42.9%, 28.6% pts treated with IFX vs 21.4%, 0%, 0% treated with Pbo. Remission DAS28CRP rate was observed in 50% in the IFX group vs 21.4% in the Pbo group. Pbo and IFX did not display any differential effect on semi-quantitative evaluation of synovial CD3, CD15, CD20, CD68 and CD138 positive cells between baseline and week 12.

No severe safety issue was observed except one case of severe hepatotoxicity induced by Isoniazid.

Conclusion: IFX is effective in ACPA positive UA patients but did not prevent the progression to definite RA. In a majority of these patients, longterm DMARDs therapy is indicated.

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Predicted Versus Observed Radiographic Progression in a Randomized Trial. Ronald F. van Vollenhoven[1], Heléne Hanses[1], Kristina Forslind[2], Pierre Geborek[3], Ingemar F. Petersson[3], Sofia Ernestam[4] and Johan Bratt[4]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Helsingborgs Lasarett and Lund University, Lund, Sweden, [3]Lund University, Lund, Sweden, [4]Karolinska University Hospital, Stockholm, Sweden

Background/Purpose: Radiological progression is a key outcome in early RA. We previously developed a method of predicting radiological progression based on the patient's report of symptom duration and the radiological damage at first examination[1]. In the SWEFOT trial[2], 487 patients with early RA were given MTX, and those who had not responded after 3–4 months (DAS28>3.2) were randomized to MTX+SSZ+HCQ ("Triple therapy") vs. MTX+infliximab ("anti-TNF"). The others continued on MTX ("MTX-responders"). Here, we employed analysis of prediction radiological progression (prediction of progression in early RA, POPERA) to these 3 patient groups from the SWEFOT trial.

Methods: Hand and foot X-rays were obtained at baseline and after 1 and 2 years, and analyzed by the Sharp-van der Heijde (SvdH) method. Predicted progression over 1 and 2 years was calculated as the SvdH score at baseline divided by the duration of symptoms in months × 12 and × 24, respectively. The analyses were based on intention-to-treat without imputations. Additional analyses focused on patients in the randomized arms of the trial who had discontinued the trial (i.e. they had "failed" the randomized treatment) and on the patients who maintained the randomized treatment for the full two years ("completers"). Comparisons between predicted and observed progression were done by non-parametric testing.

Results: In patients who had failed both MTX monotherapy and subsequent randomized triple-therapy treatment, the observed radiological progression was numerically similar to predicted progression. In all three groups of patients, observed radiological progression was reduced from predicted by 67–101% (table). After 12 months, the reduction in progression was numerically greater for MTX-responders and for patients randomized to anti-TNF than for those randomized to triple therapy, but the difference was not statistically significant. After 24 months, anti-TNF therapy provided significantly greater reduction of progression compared to triple therapy in both ITT and responder analyses, and for anti-TNF completers the reduction of progression was also significantly greater than that seen in MTX responders (p=0.004).

	MTX responders	Triple therapy ITT	Anti-TNF ITT	Triple therapy completers	Anti-TNF completers
At 12 months	75.7%	67.1%	77.9%	75.5%	81.0%
At 24 months	80.6%	85.7%*	94.1%*	85.5%**	101.2%**

* Triple therapy vs. anti-TNF (ITT) p<0.02
** Triple therapy vs. anti-TNF (responders) p<0.05

Conclusion: The progression observed in patient who failed their first 2 antirheumatic therapies was close to predicted, indirectly supporting the validity of this method. The overall results demonstrated significant reductions of radiological progression in patient groups who were successfully treated with MTX and in those who were included in either group of the randomization. Over 24 months, the reduction of predicted radiological progression was significantly greater in anti-TNF treated patients than in the triple therapy group.

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A Novel SYK Specific Inhibitor for the Treatment of Rheumatoid Arthritis. Eun-Ho Lee[1], Sun-Hwa Chang[1], Hae Jun Hwang[1], Jang-Sik Choi[1], Dong Sik Jung[1], Sung Ho Park[1], Sun Ju Wang[1], Il Hwan Yang[1], Sang Yeop Lee[1], Jung-Ho Kim[1], Ho-Juhn Song[2], Jaekyoo Lee[2], Jong Sung Koh[2], Se Won Kim[1] and Jung Kun Kim[1]. [1]OSCOTEC Inc., Choongnam, South Korea, [2]GENOSCO, Cambridge, MA

Background/Purpose: Spleen tyrosine kinase (SYK) is known to a key mediator of immunoreceptor signalings in various cell-types. Those immunoreceptors are well known to have important roles in the pathological changes of immune disease, such as rheumatoid arthritis, allergy and asthma. Currently SYK is considered as the one of the promising targets for RA treatment. SKI-O-259, a novel oral SYK-specific inhibitor, is under development as an inflammation modulator for the treatment of rheumatoid arthritis. We have characterized its SYK-specific *in vitro* profiles and evaluated *in vivo* efficacy in mouse collagen-induced arthritis (CIA) model.

Methods: *In vitro* efficacy and selectivity of SKI-O-259 was evaluated in kinase assays. Effects on the immune and inflammatory cells were assessed from FcRg-, FcRe- and BCR-mediated cells based assays and western blot analysis. *In vivo* efficacy of SKI-O-259 was carried out in the mouse CIA model. *In vitro* and *in vivo* pharmacokinetic studies, CYP450 inhibition assay, hERG inhibition assay and mouse toxicity studies were also performed. R406 or its pro-drug, R788 was used as a reference to compare pharmaceutical profiles with SKI-O-259.

Results: SKI-O-259 showed potent inhibitory effect on SYK (IC_{50} of 19.5 nM). It was highly specific for SYK in a panel of 138 kinases at 100 nM. Its potency and specificity were also confirmed from isolated cell-free assays. SKI-O-259 effectively inhibited FcRg-, FcRe- and BCR-mediated signaling pathway with IC_{50} ranging from 56.7 to 410 nM. Interestingly *in vitro* SYK inhibition activities were maintained relatively constant in the presence of 10% serum. Also, SKI-O-259 showed sufficient potency in the physiologically relevent concentration of 1.5 mM ATP. Orally administered SKI-O-259 showed significant and dose-dependent inhibition of paw edema comparable to a reference in the mouse CIA models. SKI-O-259 showed a good *in vivo* pharmacoki-

netic profiles after single oral administration (Cmax: 402 ng/ml, AUC: 1627 ng*h/mL, and $T_{1/2}$: 3.1 hr). No significant inhibitions of CYP450 isozymes and hERG were observed. Oral maximum tolerated doses were higher than 2000 mg/kg in the single dose toxicity study and higher than 500 mg/kg in the 5-day repeated dose toxicity study in mice.

Conclusion: Our results suggest that SKI-O-259 is a potent SYK inhibitor with high target selectivity and feasibility under physiologically relevant condition of serum and ATP. SKI-O-259 showed a potent anti-arthritis effect after oral administration along with a good pharmacokinetic and safety profiles. Therefore, SKI-O-259 is a novel and potential candidate for orally available RA drug.

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Comparative Effectiveness of Rituximab and Abatacept in 1192 Patients with Rheumatoid Arthritis Included in the French Society of Rheumatology AIR and ORA Registries. Jacques-Eric Gottenberg[1], Philippe Ravaud[2], Thomas Bardin[3], Patrice Cacoub[4], Alain G. Cantagrel[5], Bernard G. Combe[6], Maxime Dougados[7], Rene-Marc Flipo[8], Bertrand Godeau[9], Loic Guillevin[10], Xavier X. Le Loet[11], Eric Hachulla[12], Thierry Schaeverbeke[13], Jean Sibilia[14], Isabelle Pane[15], Gabriel Baron[16] and Xavier Mariette[17]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Hotel Dieu University hospital, France, [3]Service de Rhumatologie. Centre Viggo Petersen. Hôpital Lariboisiere, Paris, France, [4]CHU Pitié-Salpêtrière, Paris, France, [5]Hopital Purpan, Toulouse CEDEX 9, France, [6]Hopital Lapeyronie, Montpellier, France, [7]Paris-Descartes University, Cochin Hospital, Paris, France, [8]Hopital R Salengro CHRU, Lille CEDEX, France, [9]Service de médecine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, Creteil, France, [10]Cochin University Hospital, Paris, France, [11]CHU de ROUEN, Rouen CEDEX, France, [12]Internal Medicine, Lille CEDEX, France, [13]Pellegrin Hospital, Bordeaux, France, [14]Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, Strasbourg, France, [15]France, [16]Epidemiology, Paris, France, [17]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: No randomized head-to-head trial compared rituximab (RTX) to abatacept (ABA) in rheumatoid arthritis (RA), and their effectiveness was only compared to placebo, synthetic DMARDs, and infliximab (for abatacept). We aimed to compare the efficacy of RTX with ABA in patients included in the French Society of Rheumatology registries.

Methods: The French Society of Rheumatology has set up "AutoImmunity and Rituximab" (AIR) and "Orencia and Rheumatoid Arthritis" (ORA) 5-year independent prospective registries using the same protocol. Patients have been included between 2006 and 2010 in 92 centers for AIR, 84 centers for ORA, including 72 centers common for both, by the same clinicians. Data have been collected by the same trained clinical nurses in both registries. The primary efficacy outcome was EULAR response. Secondary efficacy outcomes were low disease activity and remission. A propensity score weighted outcome model was used to adjust for group diffences.

Results: Among the 3028 RA patients included in AIR(n= 1995) and ORA (n= 1033), 2396 had already a follow-up longer than 4 months, including 2240 with no prior treatment with RTX or ABA. Thus, 2240 patients, including 1732 patients treated with RTX and 508 treated with ABA, were presently analyzed. DAS28 data were available at baseline and 6 months in 828 patients treated with RTX and 364 patients treated with ABA. The main baseline differences concerned the proportion of patients with a history of cancer (12.6% and 6.1%, respectively), number of prior synthetic DMARDs (3.1±1.4, and 2.8±1.4, respectively), DAS28 (5.6±1.2 and 5.3±1.3, respectively) and without any previous anti-TNF (21.2% and 10.7%, respectively). At 6 months, 511 (61.7%) patients treated with RTX were EULAR responders, including 173 (20.9%) good and 338 (40.8%) moderate response and 214 (58.8%) patients treated with ABA were EULAR responders, including 80 (22.0%) good and 134 (36.8%) moderate response. Median DAS28 decrease was −1.3±1.4 and −1.2±1.6, respectively. Before adjustment with propensity score, EULAR response (good and moderate), low disease activity and remission rate were not statistically different between patients treated with RTX or ABA (61.7% vs 58.8%, 23.6% vs 28.8% and 12.2% vs 15,9%, respectively). After multivariate regression analysis adjusted on the propensity score, no significant difference was observed between RTX and ABA, regarding EULAR response (OR=1.00, 95%IC=[0.84–1.20]), low disease activity (OR=0.86, 95%IC=[0.70–1.05]) and remission (OR=0.79, 95%IC=[0.61–1.02]).

Conclusion: The present study presents the first to date comparison of efficacy between RTX and ABA in RA, using the same protocol for data collection, in patients depending on the same healthcare system, with similar disease characteristics and included during the same period. No significant difference was observed between RTX and ABA on the evaluated efficacy endpoints. Further comparisons of tolerance and drug retention rate are currently ongoing. The similar response observed in RA in real life with RTX and ABA at the level of a population emphasizes the need for the identification of predicting factors of efficacy for each of these drugs in the perspective of personalized medicine.

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Interferon Type I Signature Predicts Non Response to Rituximab in Rheumatoid Arthritis. Hennie G. Raterman[1], Saskia Vosslamber[1], Michael T. Nurmohamed[2], Willem F. Lems[1], Maarten Boers[1], Ben A.C. Dijkmans[3], Cornelis L. Verweij[1] and Alexandre E. Voskuyl[1]. [1]VU University medical center, Amsterdam, Netherlands, [2]Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, Netherlands, [3]Reade, Centre for Rehabilitation and Rheumatology and VU University Medical Centre, Department of Rheumatology, Amsterdam, Netherlands

Background/Purpose: B Lymphocyte depletion therapy is effective in rheumatoid arthritis (RA). However, about 35% of RA patients do not respond to rituximab (RTX). Identification of nonresponders before initiation of RTX would prevent unnecessary costs, risk for adverse effects and delays in effective treatment. We investigated whether baseline gene expression levels can predict RTX nonresponse.

Methods: Genome–wide gene expression profiling in whole peripheral blood of 14 consecutive RA patients starting RTX (test cohort) was performed using Illumina® HumanHT beadchip microarrays. Nonresponse was defined in two ways: ΔDAS28 $<$ 1.2 and EULAR non response Supervised cluster analysis on gene expression profiles based on difference in disease activity score (DAS28) after 6 months RTX) was used to identify genes expressed differentially between responders and non-responders. The predictive capacity of the genes of interest was subsequently assessed in a validation cohort (n = 28) by quantitative real-time PCR. The clinical potential of the possible predictive genes was determined based on Receiver Operating Characteristics (ROC)-curve analysis.

Results: In the test cohort 6/14 patients were nonresponders defined as ΔDAS28 $<$ 1.2. Genome-wide gene expression analysis revealed that only interferon response genes (IRG) were significantly differentially expressed with ΔDAS nonresponse. High IRG expression levels of a cluster of 5 IRG strongly predicted nonresponse: Area Under Curve (AUC): 0.92 ($p = 0.01$) for ΔDAS28 $<$ 1.2 and 0.82 ($p = 0.05$) for EULAR nonresponse. In the validation cohort AUC was 0.74 ($p = 0.04$) and 0.70 ($p = 0.09$), respectively. Logistic regression demonstrated an inverse association between IRG expression levels and clinical response defined as ΔDAS28 $>$ 1.2 (OR: 0.33, 95% C.I.: 0.13–0.79, $p = 0.013$). Adjustment for positivity for IgM rheumatoid factor, ACPA or previous use of more than 1 TNF blocking agent did not influence these results.

Conclusion: High baseline IRG expression levels are a potential biomarker to predict RTX nonresponse.

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Remission Induction Therapy with Methotrexate and Prednisone in Patients with Early Rheumatoid and Undifferentiated Arthritis. K.V.C. Wevers-de Boer[1], L. Heimans[1], K. Visser[1], H.K. Ronday[2], T.H.E. Molenaar[3], P.E.H. Seys[4], C. Bijkerk[5], M.L. Westedt[6], W. De Beus[7], P.B. de Sonnaville[8], T. Huizinga[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Haga Hospital, The Hague, Netherlands, [3]Groene Hart Hospital, Gouda, Netherlands, [4]Franciscus Hospital, Roosendaal, Netherlands, [5]Reinier de Graaf Gasthuis, Delft, Netherlands, [6]Bronovo Hospital, The Hague, Netherlands, [7]MCH, The Hague, Netherlands, [8]Admiraal de Ruyter Hospital, Goes

Background/Purpose: To assess the proportion remission after 4 months of treatment with methotrexate (MTX) and a tapered high dose prednisone in patients with undifferentiated arthritis (UA) and early rheumatoid arthritis (RA). To identify independent predictors for remission.

Methods: IMPROVED is a multicenter clinical study in patients with recent onset RA ($<$ 2 years symptoms) and UA, with a baseline Disease Activity Score (DAS) $\geq$ 1.6. 610 patients were included, 479 (79%) patients could be classified as RA patients (according to the 2010 criteria), 121 (20%) patients could not (UA). All patients started MTX 25 mg/wk and prednisone 60 mg/day tapered to 7.5 mg/day in 7 weeks, aimed at achieving remission, defined as DAS $<$ 1.6. Percentages remission after four months were compared between RA and UA. Independent predictors for remission were identified using univariate followed by multivariate logistic regression.

Results: At baseline, RA patients had a higher mean DAS (SD) than UA patients (3.34 (0.92) vs 2.70 (0.66), P<0.001), were more often female (70% vs 60%, P=0.05) and ACPA positive (68% vs 3 %, P<0.001) and had more involvement of small joints (100% vs 93%, P<0.001). After 4 months, remission was achieved in 61% of the patients without a difference between RA and UA (61% vs 64%, P=0.51). ACPA positive RA patients achieved more remission (68% vs 51%, P=0.001) compared to ACPA negative RA patients, but had a lower mean baseline DAS (3.20 (0.89) vs 3.64 (0.94), P<0.001). Of the ACPA negative RA patients, those who achieved remission had a shorter median symptom duration than those who did not (13 (8–26) vs 20 weeks (10–31), P=0.02). Independent baseline predictors for remission in all patients were low joint counts, low HAQ, ACPA positivity, male sex, short symptom duration and low Body Mass Index (BMI) (Table).

Table. predictors of remission in the total study population identified with univariate and multivariate regression analysis.

Univariate regression	Odds	95% CI
Diagnosis RA	0.87	0.57–1.33
Baseline DAS	0.49	0.40–0.59
Baseline HAQ	0.43	0.32–0.56
Age (years)	1.00	0.99–1.02
Symptom duration (weeks)	0.99	0.99–1.00
Male sex	2.23	1.52–3.27
ACPA positivity	1.63	1.16–2.28
BMI (kg/m^2)	0.94	0.90–0.98
Small joints*	0.93	0.90–0.95
Large joints*	0.71	0.65–0.79
Multivariate regression		
Small joints*	0.96	0.93–0.99
Large joints*	0.80	0.72–0.90
Baseline HAQ	0.63	0.46–0.88
Symptom duration (weeks)	0.99	0.98–0.99
Male sex	2.06	1.35–3.14
ACPA positivity	1.49	1.01–2.19
BMI (kg/m^2)	0.94	0.90–0.98

* Number of swollen and/or tender joints

Conclusion: Remission induction with MTX and a tapered high dose of prednisone results in similarly high remission percentages in RA (61%) and non-RA (64%) patients after four months. Independent predictors for remission in the total study population indicate that early treatment while disease activity is relatively low, might be most effective, even if ACPA is positive and regardless of fulfilling the ACR 2010 criteria.

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Treatment Outcomes Based on Methotrexate Dose Range in Patients with Rheumatoid Arthritis Receiving Etanercept Plus Methotrexate Versus Methotrexate Alone. Roy Fleischmann[1], Andrew S. Koenig[2], Ronald Pedersen[2], Tahmina Ferdousi[2] and Eustratios Bananis[2]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Pfizer Inc., Collegeville, PA

Background/Purpose: Methotrexate (MTX) is often the first DMARD prescribed for the treatment of RA and has been shown to be more effective in reducing disease activity when combined with biologic therapies than when used alone.[1–3] The aim of this analysis is to assess the possibility of an optimal dose range of MTX in combination with etanercept (ETN) for the treatment of RA that results in optimal treatment response.

Methods: In the COMET study (NCT00195494), MTX-naïve subjects were randomized to receive either MTX+ETN 50 mg per week or MTX monotherapy for 52 weeks. Subjects started with a low MTX dose (7.5 mg/week) and were titrated up to a maximum of 20 mg/week by week 8, if needed. After week 8, MTX dose was stable unless an AE or intolerability. Subjects with a known, stable MTX dose after week 8 were included in this post-hoc analysis. Subjects in both treatment arms were divided into 3 MTX dose ranges (low 7.5–12.5 mg; medium 12.6–17.5 mg; high 17.6–20 mg). The percentage of subjects in each MTX dose group was assessed according to DAS28/DAS44 remission, EULAR, and ACR responses at week 52 utilizing T-tests and Fisher's exact test to compare between and within each treatment group.

Results: 414 subjects (220 ETN+MTX; 194 MTX) from the COMET trial were included in this analysis. Subjects who dropped out due to lack of efficacy were considered non-responders. The majority of subjects randomized to the ETN+MTX treatment group were categorized in the high MTX dose range (50.5%) followed by the medium (27.3%) and low (22.3%) dose ranges. Subjects in the MTX monotherapy treatment group had a similar distribution trend (high 68.0%; medium 21.6%; low 10.3%). Subjects receiving low dose MTX in either treatment arm had less severe disease at baseline (DAS28, DAS44, CRP, ESR, HAQ, mTSS, ESR, CCP+, RF+); especially in the ETN+MTX group which reached statistical significance for DAS28, DAS44, CRP and HAQ. Baseline disease characteristics were not significantly different between treatment arms across MTX dosage groups except for DAS44 in the low dosage group ($P<0.05$) and HAQ in the medium dosage group ($P<0.001$). Subjects in the medium MTX dose category for both treatment groups exhibited better responses for all outcomes except DAS44 <1.6 and HAQ ≤0.5 (Table). In comparison between treatment groups, ETN+MTX was superior in all outcome measures compared to MTX monotherapy across MTX dose ranges, especially in the high MTX dosage group.

Table. Treatment outcomes at week 52

	MTX N=194			ETN+MTX N=220		
MTX Dose Category	Low (≤12.5 mg)	Medium (12.6–17.5 mg)	High (≥17.6)	Low (≤12.5 mg)	Medium (12.6–17.5 mg)	High (≥17.6)
n	20	42	132	49	60	111
Median MTX Dose (mg)	10	15	20	7.5	15	20
% DAS28<2.6	20.0	40.5	32.6	46.9	58.3	55.0 ($P<0.001$)
% DAS44<1.6	35.0	38.1	31.1	49.0	55.0	55.0 ($P<0.001$)
% ACR70	14.3	43.2	32.8	41.7 ($P<0.05$)	57.6	52.3 ($P<0.01$)
% HAQ ≤ 0.5	35.0	52.4	41.5	66.7 ($P < 0.05$)	59.3	54.9 ($P<0.05$)
% Good EULAR Response	45.0	61.9	50.8	73.5 ($P < 0.05$)	83.3 ($P<0.05$)	72.1 ($P<0.001$)
% Mod/Good EULAR Response	80.0	88.1	83.3	95.9	100.0 ($P < 0.01$)	91.9
% mTSS Δ ≤ 0.5	61.1	64.3	51.6	80.9	90.0 ($P < 0.01$)	73.9 ($P<0.001$)

P-values represent significance between treatment groups of the same MTX dose range category (e.g. High MTX treatment group vs high MTX+ETN treatment group).

Conclusion: Patients achieve higher treatment responses with medium and high doses of MTX; however, the moderate MTX dose category consistently trended toward higher improved outcome measures in both treatment groups. Regardless of MTX dose, the ETN+MTX group was more efficacious than MTX monotherapy across dose categories, including the inhibition of radiographic progression. The ETN+MTX group was statistically superior in the highest dose category except moderate/good EULAR response.

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No Increased Malignancy Risk in Tumor Necrosis Factor-α Antagonists Treated Adult Rheumatoid Arthritis Patients: A Meta-Analysis of 29 Randomized Controlled Trials. Guillaume Moulis, Agnès Sommet, François Montastruc, Laurent Sailler, Jean-Louis Montastruc and Maryse Lapeyre-Mestre. Toulouse University Hospital, INSERM U1027, University of Toulouse, France, Toulouse, France

Background/Purpose: The risk of malignancies on anti-TNF-α therapies is controversial. We conducted a meta-analysis (MA) of randomized controlled trials (RCTs) restricted in a first analysis to arms treating adult rheumatoid arthritis patients in line with the New Drug Application (NDA) and including the five marketed anti-TNF-α.

Methods: We conducted a search strategy to identify published double-blind RCTs with an exposure to TNF-α antagonists in line with NDA for more than 12 weeks in MEDLINE, CENTRAL and ISI Web of Science by two evaluators. Unpublished trials were assessed through the ACR and EULAR abstracts, the scientific evaluation of the drugs leading to marketing approval and clinicaltrials.gov. Quality of RCTs was assessed with Delphi list and Oxford scale. Authors and laboratories were contacted to provide missing data particularly regarding the occurrence of malignancies. Random-effect MAs were conducted on pooled data to assess the risk of cancers overall, solid tumors, hematological malignancies, skin cancers, non-melanoma skin cancers (NMSC) and melanomas. Null values were treated with continuity corrections (three methods tested). In case of multiple anti-TNF-α arms in a

RCT, we first considered for the analysis the arm in line with NDA. Sensitivity analyses were performed pooling all anti-TNF-α arms regardless of the dose. We conducted intention to treat (ITT) and per protocol (PP) surveys. Publication bias was assessed by Egger test.

Results: Among 2037 published references and 22 unpublished trials, we selected 29 trials for MA. Whatever the model (ITT or PP), there was no significant excess cancer risk when TNF-α antagonists were administered in line with NDA or pooling all doses in treatment group. Odds ratio in PP analysis for anti-TNF-α in line with NDA was 0.80 95%CI [0.50–1.29]. Odds ratio in ITT analysis for anti-TNF-α used whatever the dose was 1.18 95%CI [0.78–1.79]. Similar results were found for the various types of malignancies and with the three continuity corrections tested. For each model, there was no heterogeneity (Cochran's Q>10%, I^2=0%) and no publication bias (Egger's test: p= 0.55). In univariate metaregression, there was no difference between the five TNF-α antagonists and the estimation of overall cancer risk (p>0.05 in PP and ITT analyses).The increased risk in ITT compared with PP analyses can be explain by i) a gain of power, ii) a dose-effect relation and iii) a bias of diagnosis. Indeed, more patients are lost to follow-up or withdraw the trials in placebo arms, which may lead to overestimate the cancer risk on anti-TNF therapies. PP analysis prevents this bias, but it increases odds in placebo groups whatever the continuity correction used. So it may be not appropriate for very sparse events (hematological neoplasm and melanoma).

Conclusion: The risk of cancer the first year of treatment is not increased in patients exposed to TNF-α antagonists whatever the method used for analysis, particularly when drugs are used at recommended doses.

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Risk of Herpes Viruses Infections (HSV, VZV) During Anti-TNF Therapy in Patients With Inflammatory Rheumatic Diseases Systematic Review and Meta-Analysis. Hélène Che, Jacques Morel, Bernard G. Combe and Cédric Lukas. Hopital Lapeyronie, Montpellier, France

Background/Purpose: TNFblockers have shown efficacy in inflammatory rheumatic diseases (IRD) and are now widely used. They are related with an increased risk of infections, especially bacterial ones but little is known about the reactivation of herpes zoster infections.To assess the risk of herpes zoster infections in patients with IRD treated with TNF blockers by performing a systematic review and meta-analysis based on available reported data in the literature.

Methods: A systematic literature search was performed to January 2011, in Medline, Embase, Cochrane library and abstracts from ACR and EULAR congresses from 2006 to 2010. Studies were included if they reported the respective incidences of herpes infections in anti-TNF and conventional DMARDs-treated patients, for meta-analysis. The Mantel-Haenszel method was used to provide a pooled odds-ratio (OR) estimate and a 95% confidence interval (CI) in anti-TNF versus conventional DMARDs. Statistical heterogeneity was assessed on the basis of the Q test (χ^2), using a significance level of 0.05. Incidence of severe herpetic infections (multidermatomal lesions or requiring hospitalization or intravenous treatment) was extracted and reported when available.

Results: The literature search identified 655 articles and 134 congress abstracts, of which 21 articles and 29 abstracts were included in the study. Among these, 2 articles [1, 2] and 2 abstracts [3, 4] allowed a meta-analysis to estimate the relative risk of herpes infections, with a total follow up of 112 001 patient-years (PA) (68 037 PA in biologics group and 43 964 PA in conventional DMARDs group). Based on these 4 registries, the pooled OR was 1.65 [95%CI 1.39–1.95] without significant heterogeneity (I^2=42%) (figure). Proportions of severe herpes infections, reported in the US and German populations were respectively 4.9% and 20.9% [1,2]. In the British registry, the respective rates were 6% and 0.02% with biologics and conventional DMARDs. Other articles reported incident herpetic infections in patients treated with TNF blockers, but could not be pooled in the meta-analysis due to the lack of a comparison group.

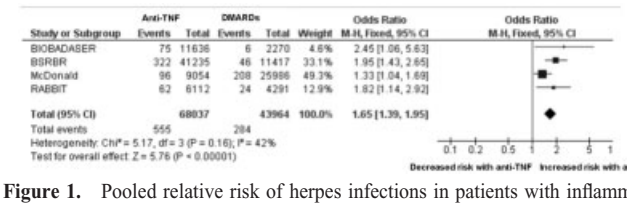

Figure 1. Pooled relative risk of herpes infections in patients with inflammatory rheumatic diseases: TNF blockers vs conventional DMARDs.

Conclusion: This meta-analysis of registries shows a significant increased risk of herpes zoster infections up to 65% in patients with IRD treated with TNF blockers. These data raise the issue of a systematic prophylactic treatment in patients with anterior herpetic infections, or vaccination in naive patients.

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Early Versus Delayed Retreatment with Rituximab (RTX) in Relation to Long Term Clinical Response—Data From the CERERRA Collaboration. Elisabeth Lie[1], Katerina Chatzidionysiou[2], Evgeny L. Nasonov[3], Galina Lukina[3], Karel Pavelka[4], Dan C. Nordström[5], Matija Tomsic[6], Cem Gabay[7], Ioan Ancuta[8], Piet LC van Riel[9], Juan J. Gomez-Reino[10], João E. Fonseca[11], Merete L. Hetland[12], Ulrik Tarp[13], Ronald F. van Vollenhoven[2] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Karolinska Institute, Stockholm, Sweden, [3]Institute of Rheumatology, Moscow, Russia, [4]1Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [5]ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, [6]University Medical Centre Ljubjana, Ljubljana, Slovenia, [7]Geneva University Hospitals, for the SCQM registry, Geneva, Switzerland, [8]Cantacuzino Hospital, Bucharest, Romania, [9]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [10]Hospital Clinico Universitario, Santiago, Spain, [11]Lisbon Academic Medical Center, on behalf of Rheumatic Diseases Portuguese Register (Reuma.pt), Lisbon, Portugal, [12]Copenhagen University Hospital at Glostrup, on behalf of DANBIO, Copenhagen, Denmark, [13]Aarhus University Hospital, Aarhus, Denmark

Background/Purpose: Open-label extensions of RCTs have shown sustained clinical response with repeated courses of RTX in rheumatoid arthritis (RA). However, there has been a lack of data on retreatment and long term effectiveness in patients (pts) treated with RTX in clinical practice. Our objective was to characterize pts receiving early vs. delayed retreatment with RTX during the 1st year and compare long-term responses.

Methods: 10 European biologics registries provided anonymized data sets of pts treated with RTX in clinical practice for analysis of pooled data. Pts were grouped as having received early (up to approx. 7 months after baseline) or delayed (after approx. 8–13 months) retreatment; pts not retreated the 1st year were excluded. Baseline (BL) characteristics, and year 1 and year 2 DAS28 states and changes were compared. Due to heterogeneity in timing of follow-up visits, overall mean DAS28 was calculated for the period 3–12 months and for year 2. Two-samples T, Mann-Whitney U and Chi^2 tests were applied as appropriate. The main effectiveness outcome was mean DAS28 during year 2. Associations between retreatment group and longitudinal DAS28 values and low disease activity (DAS28 ≤3.2; LDA) were examined by generalized estimating equations (GEE).

Results: 932 pts were retreated the 1st year (496 pts with 'early' and 436 pts with 'delayed' retreatment). 83.9%/83.5% were female, 79%/81% RF pos (p=0.39), and 83%/78% received concomitant DMARDs at baseline (BL) (p=0.07). Pts had used mean 2.7 vs. 2.6 (p=0.38) prior synthetic and 0.86 vs. 0.97 (p=0.50) prior biologic DMARDs, and 40% vs. 44% were biologics naïve (p=0.24). Pts in the early group were significantly younger (50.1 vs. 53.7 years, p<0.001). Mean DAS28 was similar for months 3–12 overall, but higher in the early group at 6 months and higher in the delayed group at 9 and 12 months (Table). 27% of pts in the early group also received a third course of RTX within month 13. 82% in the early vs. 90% in the delayed group had >18 months follow-up time, and mean(SD) total number of RTX courses from baseline through year 2 was 2.75(0.95) vs. 2.52(0.72) (p=0.001). Overall year 2 mean DAS28 and ΔDAS28 BL to year 2 were very similar (Table). Proportions of EULAR good response, LDA and remission were also similar between groups across year 2 visits. The GEE analyses showed no significant associations between timing of retreatment (early vs. delayed) and DAS28 value or LDA state neither during months 3–12 (p=0.38 for DAS28/

p=0.34 for LDA), year 2 (p=0.41/p=0.93), or the two periods combined (p=0.61/p=0.27).

	Early retreatment n=496	Delayed retreatment n=436	p-value
BL DAS28	6.22	6.08	0.08
DAS28 months 3/6/9/12	4.42/4.51/4.11/4.21	4.26/4.05/4.95/4.51	0.07/<0.001/<0.001/0.01
DAS28 month 3–12	4.36	4.42	0.44
ΔDAS28 BL to month 3–12	−1.86	−1.66	0.01
DAS28 year 2	4.16	4.10	0.58
ΔDAS28 BL to year 2	−2.06	−2.03	0.77
ΔDAS28 month 3–12 to year 2	−0.22	−0.32	0.30

Conclusion: Younger pts who with higher disease activity and greater functional impairment at BL were more likely to have earlier relapses leading to retreatment. Perhaps owing to more frequent retreatment, their results over 2 years were similar to pts retreated at longer intervals. These results suggest that certain subsets of pts for whom earlier retreatment should be considered, may be identified.

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RAPID3 (Routine Assessment of Patient Index Data 3) At Week 12 Predicts Progression of Joint Damage At Year 1 in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol Plus Methotrexate. Edward Keystone[1], Owen Davies[2] and Kristel Luijtens[2]. [1]University of Toronto, Toronto, ON, [2]UCB, Brussels, Belgium

Background/Purpose: The RAPID3 (Routine Assessment of Patient [Pt] Index Data 3) pt-derived assessment of disease activity has been demonstrated to correlate with DAS28 in pts treated with certolizumab pegol (CZP).[1] Previous post-hoc analyses have shown that a lack of improvement in DAS28 by Week (Wk) 12 predicts failure to achieve low disease activity at Wk 52.[2,3] The objective of this post-hoc analysis was to investigate if RAPID3 or EULAR response criteria predict structural joint damage (change from baseline [BL] in modified Total Sharp score [mTSS]) in RA pts treated with CZP + methotrexate (MTX) or placebo (PBO) + MTX.

Methods: Data from pts treated with CZP 200 mg + MTX or PBO + MTX in RAPID 1 (NCT00152386) were analyzed. At Wk 12, pts were categorized according to good, moderate or poor proposed RAPID3 or EULAR DAS28(ESR) response criteria. Data were pooled for pts in each group achieving a good or moderate RAPID3 or EULAR response, and progression of joint damage was evaluated in good/moderate vs poor RAPID3 or EULAR responders. Radiographic non-progression was defined as a change of ≤0.5 units from baseline in mTSS. For mTSS, linear extrapolation was used.

Results: At Wk 12, the majority of CZP + MTX pts had good/moderate RAPID3 or EULAR responses (CZP 200 mg + MTX vs PBO + MTX: RAPID3, 66.8% vs 23.5%; EULAR, 77.6% vs 29.1%). Mean RAPID3 scores at BL were similar between Wk 12 response groups for RAPID3 (range: 15.10–16.99) and EULAR (range: 15.62–16.93) criteria. At BL, mean and median mTSS were similar between Wk 12 response groups (RAPID 3: mean = 35.29–45.14, median = 19.75–24.50; EULAR: mean = 35.94–47.65, median = 20.00–21.50). At Wk 52, pts with a poor RAPID3 or EULAR response at Wk 12 had a greater increase in mTSS from BL than those pts with a good/moderate response; differences between categories were greatest in the PBO + MTX group (Table). Furthermore, fewer pts with a poor RAPID3 or EULAR response at Wk 12 were mTSS non-progressors vs pts with a good/moderate RAPID3 or EULAR response at Wk 12; differences between categories were greatest in the PBO + MTX group. There was greater inhibition of radiographic progression with CZP + MTX vs PBO + MTX irrespective of the level of response at Wk 12 (good/moderate or poor) and how response was determined (RAPID3 or DAS28).

Table. Percentage of patients with structural joint damage at Wk 52 according to RAPID3 or EULAR response at Wk 12

		Change in mTSS from BL at Wk 52, mean (SD)	mTSS non-progressors at Wk 52, %
RAPID3 response at Wk 12*			
CZP 200 mg + MTX	Good/moderate (n = 246)	0.22 (5.98)	79.7%
	Poor (n = 117)	0.87 (4.98)	70.1%
PBO + MTX	Good/moderate (n = 44)	1.67 (4.63)	63.6%
	Poor (n = 135)	3.25 (8.65)	51.1%
EULAR response at Wk 12**			
CZP 200 mg + MTX	Good/moderate (n = 284)	0.23 (5.11)	78.5%
	Poor (n = 79)	1.14 (7.36)	68.4%
PBO + MTX	Good/moderate (n = 52)	1.00 (4.55)	69.2%
	Poor (n = 127)	3.63 (8.79)	48.0%

* RAPID3 response criteria: good = improvement >3.6 units AND final score <6; moderate = improvement >3.6 AND final score ≥6 OR improvement 1.8–3.6 AND final score ≤12; poor = improvement <1.8 OR improvement 1.8–3.6 AND final score >12.
** EULAR response criteria: good = DAS28(ESR) <3.2 and an improvement from baseline >1.2; moderate = DAS28(ESR) <3.2 AND improvement 0.6–1.2, OR DAS28(ESR) 3.2–5.1 AND improvement >1.2 OR 0.6–1.2, OR DAS28(ESR) >5.1 AND improvement >1.2; poor = DAS28(ESR) <3.2 OR 3.2–5.1 OR >5.1 AND improvement <1.2, OR DAS28(ESR) >5.1 AND improvement 0.6–1.3.

Conclusion: In this post-hoc analysis, RAPID3 or EULAR responses at Wk 12 predicted progression of structural joint damage at Wk 52, particularly in pts who received PBO + MTX. These results suggest that both RAPID3 or EULAR response criteria can be used as predictors, offering the physician the choice of clinical- or pt-focused prediction tools. For RA pts receiving MTX, assessing RAPID3 response at Wk 12 could be used to aid treatment decision making.

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Pretreatment Synovial Transcriptional Profile Predicts Early and Late Clinical Response in Rheumatoid Arthritis Patients Treated with Rituximab. Vanessa E. Hogan[1], Cecile TJ Holweg[2], David F. Choy[2], Sarah Kummerfeld[2], Jason Hackney[2], Yko Teng[3], Michael J. Townsend[2] and Jacob M. Van Laar[4]. [1]Newcastle University, Newcastle, United Kingdom, [2]Genentech Research and Early Development, South San Francisco, CA, [3]Leiden University Medical Centre, Leiden, Netherlands, [4]Musculoskeletal Research Group, Newcastle, United Kingdom

Background/Purpose: The development of personalized medicine is contingent on the identification of biomarkers that represent disease relevant pathogenic pathways and predict response to therapy. We postulated that transcriptomics of synovial tissue from rheumatoid arthritis (RA) patients could be used to construct a response specific gene expression profile.

Methods: We conducted a proof-of-concept study in 20 RA patients treated with rituximab, who underwent arthroscopy of clinically inflamed joints to allow sampling of synovial tissue before and after treatment with rituximab. Clinical response was defined using DAS28 scores. Gene expression of 125 genes was assessed using high throughput semiquantitative mRNA analysis to identify genes associated with clinical response. Statistical analysis was performed using principle components analyses, Spearman correlation, and t-tests with correction for multiple testing.

Results: Based on principal components analysis and unsupervised hierarchical cluster analysis of baseline gene expression, patients in our study could be categorised in two groups with distinct gene expression profiles, an inflammatory and a remodelling profile. These two groups were associated with distinct clinical, laboratory and histological features of inflammation. In an attempt to predict response, a composite gene score (GS) was constructed based on genes that correlated strongly with change in disease activity score (dDAS) between baseline and month 3.

Besides an expected strong correlation with dDAS at month 3 (Rho=0.76, P=0.0001), the baseline GS also significantly correlated with dDAS at month 7 and with the conclusion of the study (month 21–24) after treatment (Rho=0.55, P=0.01 and Rho=0.50, P=0.02, respectively). In addition, the GS significantly correlated with the inflammatory component of the DAS28 score, ESR, at baseline (Rho=0.69, P=0.0008), but not with swollen or tender joint counts or visual analogue scale. Another strongly correlating baseline variable with baseline GS was with thickness of the lining layer (R=0.74, P=0.006), suggesting that some of the GS genes might be expressed by cells residing in the synovial lining. A number of positive predictor genes included in the gene score represented macrophage and T-cell rather than B-cell biology, while the negative predictor genes were involved in bone and cartilage biology and the interferon-a pathway. Patients with a high signature score, mostly clinical responders (9/11), showed higher expression of the positively correlated genes with dDAS and lower expression of the negatively correlated genes, whilst the opposite was true for patients with a low score who were mostly non-responders (6/9).

Conclusion: In our study, we created a baseline synovial gene expression score, representing mainly macrophage, T-cell biology and tissue remodeling processes, that significantly predicted both early and late response to rituximab in RA patients.

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Sulfasalazine and Its Metabolites Inhibit Platelet Function in Patients with Inflammatory Arthritis. Paul A. MacMullan[1], Anne M. Madigan[1], Nevin Paul[2], Aaron J. Peace[2], Paola M. Bagaglia[1], Ahmed Alagha[2], Kevin B. Nolan[2], Dermot Kenny[3] and G M. McCarthy[1]. [1]Mater Misericordiae University Hospital, Dublin 7, Ireland, [2]RCSI, Dublin 2, [3]RCSI, Dublin 2, Ireland

Background/Purpose: Patients with inflammarory arthritis (IA) are at increased risk of adverse cardiovascular events. Sulfasalazine therapy has been shown to decrease this risk, independent of disease severity. Previous evidence suggests that sulfasalazine inhibits platelet thromboxane synthetase, but its effecs on platelet function are unknown.Therefore, we decided to assess the effect of sulfasalazine and its metabolites on platelet function in patients with IA.

Methods: 135 consecutive patients with an established diagnosis of IA were screened. Those with a history of cardiovascular disease (CVD), taking anti-platelet agents or NSAIDs were excluded. A total of 32 patients were investigated, 15 taking sulfasalazine and 17 taking other DMARDs and no sulfasalazine. Platelet function in response to multiple agonists was tested, and these 2 cohorts were compared to 15 patients with stable CVD on long-term aspirin. The effect of sulfsalazine and its metabolites on arachidonic acid (AA) induced platelet aggregation was also tested *in vitro*, in samples from healthy donors (n=18).

Results: Demographics, CVD risk factors, and disease activity indices were similar in the Sulfasalazine and Other DMARDs groups. AA-induced platelet aggregation was significantly inhibited in the Sulfasalazine group (9±7%) and comparable to that in the Aspirin group (10±6%), (see Figure). In contrast, there was no effect on AA-induced platelet aggregation in the Other DMARDs group (77±12%), ($p<0.001$). Sulfasalazine therapy had no effect on platelet function in response to the other agonists. Sulfasalazine and its metabolites (5-aminosalicylic acid and sulfapyridine) exerted an additive and dose-dependent inhibitory effect on AA-induced aggregation *in vitro* ($p<0.001$).

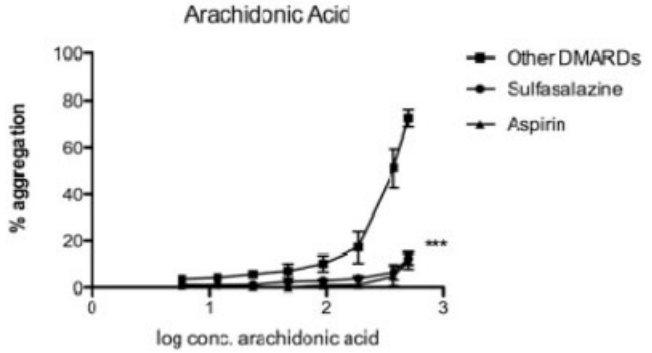

Figure. Platelet aggregation in response to arachidonic acid is significantly inhibited in both the Sulfasalazine and Aspirin group compared to those on Other DMARDs. *** $p<0.001$.

Conclusion: The inhibition of AA-induced platelet aggregation by sulfasalazine is comparable to that achieved by aspirin, and is dependent on both sulfasalazine and its metabolites. This is a potential mechanism that may contribute to the known cardioprotective effect of sulfasalazine in patients with IA.

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Impact of Tumor Necrosis Factor Inhibition on Healthcare Costs in Patients with Rheumatoid Arthritis. Walter P. Maksymowych[1], Nguen Xuan Thanh[2], Joanne Homik[1], Cheryl CM Barnabe[3], Liam Martin[3], Susan G. Barr[3] and Arto Ohinmaa[1]. [1]University of Alberta, Edmonton, AB, [2]Institute of Health Economics, Edmonton, AB, [3]University of Calgary, Calgary, AB

Background/Purpose: Linkage of patient registry data and administrative databases enables a powerful assessment of treatment efficacy and associated costs in real world practice. The objective of our study is to assess the impact of anti-tumor necrosis factor (anti-TNF) therapy for rheumatoid arthritis (RA) on total and RA-attributable healthcare costs in an inception cohort of biologic treated patients compared to patients on standard disease-modifying antirheumatic drug (DMARD) therapy, accounting for confounding by indication.

Methods: A pharmacovigilance registry captures clinical treatment and safety parameters for RA patients treated with either standard DMARDs or one of the three available anti-TNF agents. Provincial healthcare administrative databases for fiscal years 2004/2005 to 2008/2009, including physician billing claims, ambulatory care visits, and hospitalizations were linked to the clinical database to analyze the cost of physician visits, emergency room and other ambulatory care visits, and hospitalizations per treatment group. A propensity score matching technique was used to compare the costs in those patients receiving a first anti-TNF agent to patients receiving DMARDs only, patients initially on DMARDs but then switched to anti-TNF therapy, and those patients requiring a switch to another anti-TNF agent. Variables included in logistic regression to estimate propensity scores were socio-demographic characteristics, medical co-morbidities, disease duration and functional severity at baseline as measured by the HAQ score. We estimated the 95% confidence intervals for the differences between groups using a bootstrap method. All costs were standardized to 2008 Canadian dollars. We also specifically considered RA-attributable costs associated with diagnostic codes.

Results: We provide results on 1,086 patients from our cohort who had at least 3 months of administrative data available. The mean annual cost per patient associated with physician visits, emergency room visits, and hospitalizations was higher in patients who had to switch to another anti-TNF agent for inefficacy or adverse events relative to patients who responded well to their first anti-TNF agent without adverse events (Table 1). Patients remaining on DMARD therapy and those eventually moving to anti-TNF therapy had non-statistically higher costs. In each group about 30% of all costs were directly RA-attributable.

Table 1. Annual mean healthcare costs, and percentage of cost directly attributable to RA (in parentheses) per patient in the four treatment groups

Cost category	First Anti-TNF-only (n=731)	Anti-TNF, switch (n=212)	DMARD-only (n=75)	DMARD, switch (n=68)
Total cost	4,849 (29.1%)	7,374* (31.1%)	6,898 (29.1%)	5,832 (30.4%)
Hospital	2,008 (31.7%)	3,349* (38.4%)	2,909 (31%)	2,486 (28.8%)
Emergency room	238 (22.3%)	458* (22.3%)	434 (9.9%)	393 (15.3%)
Outpatient clinic	986 (11%)	1,631* (10.5%)	1,558 (16.9%)	1,231 (26.7%)
Physician	1,617 (39.3%)	1,936* (38.9%)	1,997* (40%)	1,722 (38.8%)

* Total costs statistically significantly (95% Confidence Intervals) differences from first anti-TNF-only group.

Conclusion: As expected, patients requiring a switch in anti-TNF therapy have higher healthcare costs. Patients responding well to their first anti-TNF agent have the lowest healthcare costs. Over two-third of healthcare costs in RA patients are not related to RA directly, indicating significant disease co-morbidity in our rheumatic disease patients.

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Trend of Tumor Necrosis Factor Inhibitors Use Among Patients with Rheumatoid Arthritis: Analysis From the Consortium of Rheumatology Researchers of North America Registry. Pim Jetanalin[1], Susan P. Messing[2], Kimberly Kaukeinen[2], Joel M. Kremer[3] and Susan J. Lee[1]. [1]University of California San Diego, La Jolla, CA, [2]University of Rochester School of Medicine and Dentistry, Rochester, NY, [3]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: Studies have suggested that early institution of biological therapies in rheumatoid arthritis (RA) can improve clinical outcomes, decrease disability, and retard radiographic progression. With the development of the new ACR/EULAR criteria for RA combined with efforts for early referral and aggressive therapy, we hypothesize that tumor necrosis factor inhibitors (TNF-I) are being used earlier in RA patients. Using the Consortium of Rheumatology Researchers of North America (CORRONA) registry, we sought to determine if the pattern of TNF-I use has changed over time.

Methods: Data on demographics (age, sex, race, education) and disease characteristics (seropositivity, disease duration) were obtained from 27,412 RA patients in the CORRONA registry. Patients starting on first TNF-I were divided into 3 equal groups of ~1,000 patients spanning 3 time periods (2000–05, 2006–08, 2009–11). Each interval was analyzed for pattern of TNF-I use, disease activity (DAS28, CDAI, MD VAS for global disease, patient VAS for pain and global function), and DMARDs use.

Results: Of the 15,270 RA patients who were TNF-I naïve at enrollment, 3,031 patients were started on TNF-I at one of the CORRONA visits. The racial composition was similar in TNF-I naïve and TNF-I initiated group with 83% Caucasians, 6% Hispanics, 8% African Americans, and 1% Asians. The majority were female (74–76%) with seropositive disease (RF and/or CCP, 72–75%). Compared to patients who remained TNF-I naïve, TNF-I initiators were younger (60.1 ± 13.9 years vs 56.7 ± 13.5 years) with longer disease duration (7.6 ± 9.5 years vs 8.5 ± 9.3 years) and more active disease (HAQ 0.33 vs 0.43, CDAI 12.8 vs 15.9) with $p<0.0001$ for all. TNF-I initiators were more likely to have college education with OR 1.15, $p<0.0001$. When assessed over 2000–05, 2006–08, 2009–11 time period, patients in 2009–11 were being started on TNF-I earlier (disease duration 9.9 vs 8.5 vs 6.9 years respectively, $p<0.0001$). Compared to 2000–05, TNF-I initiators in 2009–11 had less disease activity (CDAI 17.1 vs 15.5 $p=0.002$, MD VAS global disease 29.0 vs 26.1 $p=0.004$, SJC 6.1 vs 4.5 $p<0.0001$) at the start of TNF-I. The number of prior DMARDs failed before starting TNF-I also decreased over time from 1.7 to 1.3 ($p<0.0001$). In multivariate analysis, patients with college education, worse functional disability (HAQ), and higher number of prior failed DMARDs were more likely to start TNF-I. Interestingly, the number of *new* TNF-I initiators in the CORRONA registry decreased from 53% in 2002–05 to 12% in 2009–11. Despite this decrease in the number of new TNF-I initiators, the overall prevalence of TNF-I use among RA patients increased over the recent years (31% in 2000 to 41% in 2011) suggesting persistence of TNF-I use once patients are started on TNF-I for the treatment of RA.

Conclusion: With the proven efficacy of TNF-I coupled with earlier diagnosis and referral, there is a trend towards earlier initiation of TNF-I at shorter disease duration and lower disease activity. Instead of traditional slow step-up approach, physicians are starting TNF-I sooner and after failing a fewer number of DMARDs. Despite an overall lower % of patients starting TNF-I, it is still widely used with 41% of all RA patients on TNF-I.

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Dermatologicals Manifestations Induced by Tumor Necrosis Factor Antagonists Therapy in Rheumatic Diseases. Incidence Rate in BIOBADASER 2.0 Registry. Maria Victoria Hernández Miguel[1], Miguel A. Descalzo[2], Loreto Carmona[3], Melina Meineri[1], Sonia Cabrera[4], Maria Eugenia Gomez Caballero[4], Jose Alfredo Gomez Puerta[1], Virginia Ruiz Esquide[1], Julio Ramirez[1], Juan D. Cañete[5] and Raimon Sanmarti[1]. [1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]Spanish Society of Rheumatology, Madrid, Spain, [3]Universidad Camilo José Cela, Villanueva de la Cañada, Spain, [4]Hospital Clinic of Barcelona., Barcelona, Spain, [5]Hospital Clínic de Barcelona., Barcelona, Spain

Background/Purpose: Biologic therapy has proven efficacy in several rheumatic diseases in the last decade, but, recently, different cutaneous manifestations associated with these treatments have been described. Our purpose was to analyze the incidence rate and characteristics of cutaneous adverse events (CAE) in patients with inflammatory rheumatic diseases treated with TNF antagonists therapy.

Methods: We analyzed all patients diagnosed of inflammatory rheumatic diseases treated with TNF antagonists therapy and included in the spanish registry of safety in biological treatments (BIOBADASER), in which our hospital is a participant, that have developed a CAE (as a main symptom) since 2000 to November 2010. The sociodemographic and clinical characteristics collected were: age, gender, diagnosis of rheumatic disease, type of CAE (classified as: local or systemic cutaneous manifestation related to treatment administration (CTA); infection; malignancy; development of autoimmune disease (AD)) and CAE outcome. We calculated the incidence rate of CAE events per 1000 patients-years of exposure with 95% confidence intervals (CI). Risk factors for CAE in all patients exposed to TNF antagonists were investigated assuming a Poisson distribution of the data. Results were expressed as incidence rate ratio (IRR) with their 95% CI.

Results: During these 10 years, 5437 patients (61% female, mean age 55 (SD=14years) received TNF antagonists therapy. Main diagnoses were: 2957 patients with rheumatoid arthritis (RA) (54%); 968 ankylosing spondylitis (AS) (18%); 926 psoriatic arthritis (PsA) (17%); 463 chronic arthritis (CA) (9%) and 123 chronic immune mediated diseases (CID). Biological therapy received was: infliximab 2504 patients, etanercept 1605, adalimumab 1328. The global incidence rate of CAE was 54 [95%CI 51–57] per 1000 p-y. According to the type of CAE, the incidence rates were: infection (most were *herpes zoster* and cellulitis) 27 [25–29]; CTA 16 [14–17]; AD (psoriasis, vitiligo, alopecia areata, cutaneous lupus, polychondritis, morphea, dermatomyositis) 5 [4–6]; malignancy 3 [3–4]. We found a higher rate of CAE for infliximab (IRR in multivariate analysis: 1.26 (1.05–1.52) ($p<0.05$), concomitant use of leflunomide (1.46 (1.17–1.83) $p<0.001$), concomitant glucocorticoids (1.36 (1.16–1.61) $p<0.001$), and in women (1.5 (1.27–1.77) ($p<0.001$).

Conclusion:TNF antagonists therapy is frequently associated with the development of cutaneous manifestations that, sometimes, requires treatment withdrawal with a favourable outcome. Most frequents CAE were infections and those related to treatment administration, although different autoimmune diseases could also been developed.

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Tofacitinib Reduces Interleukin-6 and Matrix Metalloproteinase-3 Production and Inhibits Cartilage Destruction in Rheumatoid Arthritis. Kunihiro Yamaoka[1], Satoshi Kubo[1], Keisuke Maeshima[2], Koshiro Sonomoto[1], Kazuhisa Nakano[3], Norifumi Sawamukai[1], Masao Nawata[1], Kazuyoshi Saito[1] and Yoshiya Tanaka[1]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Oita University, Faculty of Medicine, Yufu, Japan, [3]University of California San Diego, La Jolla, CA

Background/Purpose: Tofacitinib, a tyrosine kinase inhibitor targeting Janus kinase (JAK), has recently gained attention due to its prompt clinical response and efficacy in treating rheumatoid arthritis (RA). It has been shown to inhibit JAK1 and JAK3 known to be crucial for multiple cytokine signaling pathways. However, its precise mechanism of action in RA patients remains unknown. We herein analyzed the effect of tofacitinib in RA patients and a chimera mouse model of RA.

Methods: [Investigation 1] Fifteen RA patients enrolled in the tofacitinib clinical trials were randomized to 1, 3, 5 or 10mg BID for 12 weeks. Blood was collected at 0 and 12 weeks and serum stored for further cytokine measurement by ELISA. [Investigation 2] Synovium from RA patients undergoing joint replacement was implanted in severe combined immunodeficiency (SCID) mice (SCID-huRAg mouse). Tofacitinib was administered via osmotic mini-pump and serological and histological examinations were performed.

Results: [Investigation 1] Patient background: mean age; 56.4 years, mean disease duration; 95.1 months, methotrexate (MTX) and tofacitinib were administered in all 15 patients, median doses were 9.4 mg/week and 4.1 mg BID respectively, glucocorticoids were administered in 6 patients, median dose was 5.4 mg/day. Baseline characteristics of the disease activity was as follows; SDAI 30.0, DAS28 (ESR) 6.3, HAQ 1.1, CRP 21.0mg/l, ESR 57.1mm/h, MMP-3 259.3ng/ml, RF 216.2U/ml. All these parameters decreased after 12 weeks treatment with statistical difference ($P<0.05$) as follows; SDAI13.8, DAS28(ESR) 4.0, HAQ 0.8, CRP 8.1mg/l, ESR 30.9mm/h, MMP-3 149.9ng/ml, RF 150.8U/ml. Among the multiple cytokines measured, IL-6 and IL-8 tended to decrease, from 52.2pg/ml to 28.2pg/ml ($p<0.05$) and from 41.7pg/ml to 29.5pg/ml (not significant), respectively. Among the clinical parameters measured, there was a statistically significant correlation between reduction of IL-6 and reduction of MMP-3.

[Investigation 2] In SCID-huRAg mouse, marked growth of RA-derived synovium and its apparent invasion into cartilage were observed. However, when

tofacitinib was administered, invasion of synovial tissue into cartilage was markedly suppressed. In order to investigate the relevance with our findings in investigation 1, cytokines were measured utilizing SCID-huRAg mouse serum after administration of tofacitinib for 7 days. Interestingly, tofacitinib significantly decreased production of human IL-6 and IL-8 as well as human MMP-3 from 29.79 pg/ml to 2.89pg/ml, 17.89 pg/ml to 4.22 pg/ml and 65.96 pg/ml to 33.13 pg/ml respectively.

Conclusion: Tofacitinib improved disease activity in patients with RA and high baseline disease activity within 12 weeks. Serum IL-6 and IL-8 concentration was decreased in both RA patients and SCID-huRAg mouse in connection with reduced MMP-3 in RA patients and suppressed cartilage destruction in mouse. These results indicate that tofacitinib possesses the ability to reduce inflammation by suppressing IL-6 production and consequently inhibiting cartilage destruction in the initial several months of administration.

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One Single Infusion of Rituximab 1g Might Be Sufficient in the Long-Term Management of Rheumatoid Arthritis Patients Responding to a First Cycle of Rituximab (2 × 1g): Results of a 2-Year Multi-Center Randomized Controlled Trial. Maxime Dougados[1], Stephanie Rouanet[2], Jean Sibilia[3], Bernard G. Combe[4], Xavier X. Le Loet[5], Jacques G. Tebib[6], Rosemary Jourdan[7] and Xavier Mariette[8]. [1]Paris-Descartes University, Cochin Hospital, Paris, France, [2]Roche, Neuilly sur Seine, France, [3]Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, Strasbourg, France, [4]Hopital Lapeyronie, Montpellier, France, [5]CHU de ROUEN, Rouen CEDEX, France, [6]Centre Hosp Lyon Sud, Pierre Benite, France, [7]Roche, Neuilly Sur Seine, France, [8]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: To assess the symptomatic efficacy and the safety profile of 2 dose regimens of rituximab (RTX) in patients (pts) who had a EULAR response (good or moderate) 6 months after a 1st cycle of 2 infusions of RTX 1g and who necessitated subsequent therapy

Methods: *Patients:* Definite rheumatoid arthritis (1987 ACR criteria); active disease (DAS >3.2 and either swollen joint count ≥6 and tender joint count ≥6 or CRP ≥10 mg/l or ESR ≥28 mm/1st hour; refractory or intolerant to at least one anti-TNF. *Study design and allocated treatments*: The 1st 24 week-period was a prospective, multi-center non-controlled trial followed (from week 24 to week 104) by a randomized, controlled trial. At week 0, the 1st cycle of RTX consisted of 2 × 1g RTX two weeks apart. At week 24, pts who experienced a EULAR response were randomized to receive RTX 1g in one single infusion (Arm A) or the licensed dose of RTX 2 × 1g (Arm B) as subsequent retreatment following assessment of disease activity every 6 months (*e.g.* DAS >3.2). *Outcome measures*: DAS28-CRP, number of required cycles of RTX, time to a second retreatment. *Analysis*: Non inferiority of Arm A versus (vs.) Arm B on the DAS28-CRP Area Under the Curve (AUC) during 104 weeks, with a non-inferiority margin defined by 20% of the mean DAS AUC of the reference group (δ=444). Main analysis was performed on the per-protocol (PP) and intention to treat (ITT) population using a covariance analysis that included baseline DAS value as covariate.

Results: Of the 234 screened pts, 224 received the 1st cycle of RTX. DAS28-CRP changed from 5.8±0.9 to 4.2±1.2 at week 24, resulting in a EULAR response in 152 patients (71%). Pts (n=152) were randomized in the 2nd part of the study (ITT: 70/Arm A and 73/Arm B) without any inter-group difference (females: 82%; age: 56±11 years; disease duration: 13±9 years; anti-CCP positivity: 84%; DAS28-CRP: 3.7±0.9). Following withdrawals and major protocol deviations, the final PP population was 51pts/Arm A and 49/Arm B. The DAS28-CRP AUC at week 104 (PP population) was 2761±508 in Arm A and 2666±490 in Arm A vs. Arm B, resulting in an adjusted inter-group difference of 51.4 with a 95% CI of [−131.2; 233.9] demonstrating the non-inferiority of retreatment in Arm A vs. Arm B. Similar results have been shown for the ITT population. The number of required cycles per year after the first retreatment was similar in both arms (1.0±0.3), as was the estimated median time to a second retreatment using the Kaplan-Meier method (263 and 255 days in Arm A vs. B, respectively). During the study the percentage of any and serious adverse events was similar (92% and 29% vs. 96% and 37% in Arm A vs. B, respectively). The percentage of pts with an IgG level below 6.82 g/L (LLN) at week 104 was 2% (1/48) and 11% (6/53) in Arm A vs. B (p=0.12). The percentage of serious infections was 12% (8/66) and 3% (2/68) in Arm A vs. B (p=0.05) corresponding to a serious infection rate of 7.2 and 1.5/100 pt-yrs.

Conclusion: This study suggests that in case of a EULAR response after a first cycle of 2 infusions of RTX 1g, retreatment with a RTX 1g single infusion provides similar clinical outcomes compared with 2 × 1g infusions. The structural (radiographic) effect of these 2 strategies was not assessed in this study.

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Patients' Preferences for the Treatment of Moderate to Severe Rheumatoid Arthritis. A. Brett Hauber[1], Christine Poulos[1], Juan Marcos Gonzalez[1], Sarika Ogale[2], Dalia Moawad[2] and Adam Turpcu[2]. [1]RTI Health Solutions, Research Triangle Park, NC, [2]Genentech, South San Francisco, CA

Background/Purpose: Biologic treatments for rheumatoid arthritis (RA) vary in terms of both the time required to administer treatment and the frequency of treatment. This study estimates patients' preferences for RA treatment attributes.

Methods: Patients with moderate to severe RA completed a web-enabled survey with a series of treatment-choice questions. The severity of self-reported RA symptoms was determined by the Routine Assessment of Patient Index Data 3 (RAPID3) score (ranging from 0 to 30). The treatment-choice questions required subjects to choose between two hypothetical RA treatments with differing levels of six treatment attributes including response rate (ranging from 40–75%), mode of administration (injection or infusion), treatment time (ranging from 10 minutes to 4 hours), treatment frequency (once per week, once every two weeks, once per month, and two times [two weeks apart] every six months), and the risks of immediate, mild and severe treatment reactions (which both ranged from 1% to 25%). An index of the importance of each treatment attribute, in terms of impact on treatment choice, was estimated using a mixed-logit choice model controlling for patient-specific characteristics. The index ranged from 0 to 10, with 10 being most important and 0 being not important at all.

Results: Among the 901 patients who completed the survey, 505 were in the RA Information, Services and Education group (www.risesupport.com) and 396 were members of an online web panel. Sixty percent of the sample was 55 years of age or older, 75% were female, and 29% of patients had at least a bachelor's degree. The majority of respondents had some difficulty dressing themselves (67%), getting out of bed (66%), walking outdoors (61%), washing themselves (59%), picking items off the floor (74%), getting out of a vehicle (74%), walking 2 miles (88%), and participating in recreational activities (95%). The average RAPID3 score was 14.3, and 94% of patients had a score greater than 6, indicating moderate or severe RA. Most patients (77%) used an oral medicine prescribed by a physician, 30% received regular injections of medicine, and 18% received regular infusions.

The chance of an immediate, serious treatment reaction was the most important treatment attribute (Figure 1). The second most important treatment attributes were the frequency of infusions and the treatment response rate, which were equally important. The frequency of injections was less important than treatment response rate, as was the amount of time needed to administer infusions. The least important attribute was the chance of an immediate, mild treatment reaction.

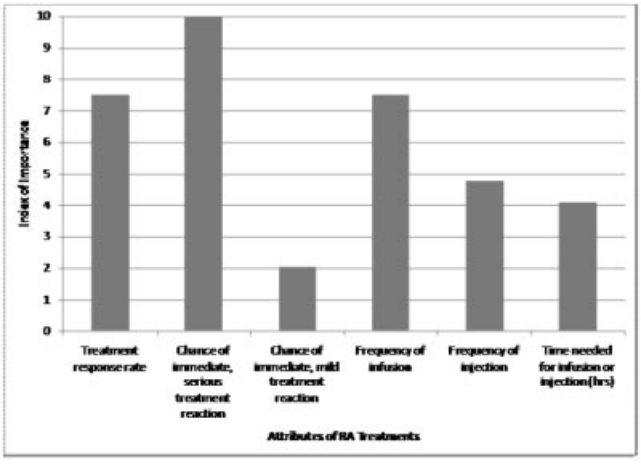

Figure 1. Relative importance of attributes of RA treatments

Conclusion: In addition to concerns over safety and efficacy, convenience attributes of RA treatment such as frequency of administration are important to patients and could play an important role in the choice of treatment.

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Simvastatin and Toll-Like Receptor-2 Mediated Signaling Augment Apoptosis and reactive Oxygen Species Associated Gene Expression in Rheumatoid Arthritis Synoviocytes. Mohammad Saeed Khan[1], Krishnaswamy Kannan[1] and Robert Ortmann[2]. [1]University of Arkansas for Medical Sciences, Little Rock, AR, [2]University of Arkansas, Little Rock, AR

Background/Purpose: Statins (HMG-CoA reductase inhibitors) exert beneficial effects on lipoprotein metabolism, but also possess anti-inflammatory properties. However, the molecular mechanisms subserving such immunomodulatory activities remain unclear. Signaling through Toll-like receptors (TLR) pathway has been implicated in the pathogenesis of rheumatoid arthritis (RA). TLRs 2, 3, 4 and 7 are expressed by cells within the RA joint and in particular, TLR2 was found to be highly expressed at the sites of bone erosion suggesting the importance of TLR2 in inflammatory arthritis. TLR2 activation is an essential step in RA animal models. The purpose of this study was to examine the anti-inflammatory effects of simvastatin, in the presence of an activated TLR2 signaling pathway, *in vitro* by using synoviocyte cell lines derived from control subjects and patients with RA.

Methods: Fibroblast-like synoviocyte (FLS) cell lines derived from normal healthy subjects and RA were obtained commercially and were maintained in complete synoviocyte medium supplemented with 2% FCS and growth factors. Cells (10^5 cells/well) were grown in 12 well plates and treated with Simvastatin in triplicates for 4 hours and subsequently washed and then treated with TLR2 ligand (Pam3CSK4, 100ug/ml) for 24-hours. Cytotoxicity was assessed by Alamar blue assay and apoptosis by flow cytometry based Annexin V staining method. Gene expression analysis of 84-Reactive oxygen species (ROS) associated genes was performed using a real time PCR array profiling kit from SABiosciences (catalog # PAHS-065).

Results: Simvastatin mediated cytotoxicity in RA derived FLS (RA-FLS) was lower than control synoviocytes. Increasing doses of simvastatin followed by TLR2 ligation led to increased cytotoxicity in both normal and RA-FLS. Flow cytometry analysis by annexin V staining showed that apoptosis was the cause of the cytotoxicity. Interestingly, the basal apoptosis was higher in normal synoviocytes compared to RA-FLS (14% vs 4.3%). TLR2 stimulation alone increased apoptosis in both normal and RA-FLS (16.4% / 9.7%). Upon treatment with 30 μM simvastatin followed by TLR2 ligation, significantly increased apoptosis was observed in both normal and RA-FLS (25% vs 24.8%) suggesting a synergistic effect. Gene expression analysis of ROS associated genes demonstrated that GSR, TXNRD1, and PRDX1 genes were significantly upregulated in RA-FLS upon treatment with simvastatin alone, or in combination with TLR2 ligation. SOD2, MT3, and PTGS2 were upregulated by simvastatin and TLR2 ligand in a synergistic fashion.

Conclusion: The basal apoptosis in RA-FLS was lower than normal synoviocytes. However, *in vitro* exposure of simvastatin followed by TLR2 ligation resulted in significant increase of apoptotic events as well as upregulation of gene expression of ROS metabolizing enzymes/proteins in RA-FLS. Thus simvastatin may exert its anti-inflammatory effect in RA by increasing apoptosis of RA-FLS and preventing ROS associated joint damage by upregulating protective genes.

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Symptomatic Subcutaneous Anti-Tumor Necrosis Factor-Treated Rheumatoid Arthritis Patients Improve Following An Active Switch to Golimumab: An Initial 14 Week Assessment. J. Eugene Huffstutter[1], Rebecca Bolce[2], Shelly P. Kafka[3], Lawrence H. Brent[4], Jim Wang[5], Raphael J. DeHoratius[2], Trev Sprabery[2] and Dennis Decktor[2]. [1]Arthritis Associates PLLC, Hixson, TN, [2]Janssen Services, LLC, Horsham, PA, [3]Mountain State Rheumatology, Clarksburg, WV, [4]Albert Einstein Med Ctr, Philadelphia, PA, [5]Johnson & Johnson Pharmaceutical Research and Development, LLC, Belle Mead

Background/Purpose: GO-SAVE is a Phase 3b, multicenter, switch assessment of the efficacy of subcutaneous (SC) and intravenous (IV) golimumab (GLM) in rheumatoid arthritis (RA) patients who have inadequate disease control despite treatment with etanercept (ETN) or adalimumab (ADA). The primary objective of GO-SAVE is to assess the efficacy of GLM at week 14 in patients with active RA and an inadequate response to therapy with ETN or ADA.

Methods: Patients with active RA (defined as DAS28 score $\geq$ 3.6 and $\geq$ 6 swollen and $\geq$ 6 tender joints) who were currently receiving methotrexate (MTX) and anti-TNFa therapy with ETN or ADA were switched to GLM. Patients entered the screening period 6 weeks prior to receiving GLM (week −6), remained on their original anti-TNFa therapy, and were re-screened again at week 0. All eligible patients were actively switched to open-label GLM 50 mg SC injections at weeks 0, 4, 8 and 12. The primary endpoint was ACR 20 response at week 14. Here, we report the results of our interim analysis.

Results: Of the first 200 patients enrolled, all were included in the interim modified intention-to-treat (mITT) population analysis, and 160 were eligible for the interim per protocol population analysis. 163 patients (81.5%) were female and 37 patients (18.5%) were male; mean age was 55.9 ±11.26 years and mean disease duration was 9.8 ±9.70 years. At baseline, the mean number of swollen and tender joints was 18.8 ±11.93 and 32.3 ± 16.61, respectively, and the mean DAS28 (ESR) score was 6.2± 0.87. 106 patients (53%) were switched from their ongoing treatment of ETN, and 94 patients (47%) were switched from ADA. 35 patients from this study population had been previously exposed to both ETN and ADA, but not concomitantly. At week 14, 67 of the 200 patients (33.5%; 95% CI: 27%, 40%) achieved the primary endpoint of ACR 20 response; 36 (18% CI:12.7%, 23.3%) and 43 (21.5%CI:15.8%, 27.2%) patients responded by week 1 and week 2, respectively. In the per protocol analysis, 62 of the 160 patients (38.8%; 95% CI: 31.2%, 46.3%) achieved an ACR20 response at week 14, while 37 patients (23.1%CI:16.6%, 29.7%) responded as early as week 2. A clinically meaningful EULAR response was achieved in 101patients (50.5%; 95% CI: 43.6%, 57.4%) with a mean DAS28 improvement of 1.50 ($p<0.001$) from baseline. In the per protocol analysis, 58.1% of patients achieved a EULAR response by week 14. HAQ improved with a mean of 0.19 (95%CI: 0.123, 0.265, $p<0.0001$) with 39% of the patients demonstrating a clinically meaningful improvement of $\geq$ 0.22 from baseline. Prior to week 14, 31 (15.5%) of the 200 patients discontinued the study agent; 5 patients (16.1%) withdrew due to an adverse event (AE). 122 (61%) of the 200 patients experienced AEs and 9 patients (4.5%) experienced serious AEs. Injection site reactions were reported in 5 (2.5%) patients.

Conclusion: GLM improves signs and symptoms in patients with moderate or severe RA who were responding inadequately to ETN or ADA, with responses observed as early as week 1. Over half of the treated patients also achieved a DAS28-defined EULAR response. GLM was safe and well-tolerated. Additional results obtained from the on-going GO-SAVE clinical trial will further the understanding of clinical response in this population.

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Baseline Serum Interferon Beta/Alpha Ratio Predicts Response to Tumor Necrosis Factor Alpha Inhibition in Rheumatoid Arthritis. Rachna Aggrawal[1], Beverly S. Franek[1], Marlena Kern[2], Peter K. Gregersen[2] and Timothy B. Niewold[1]. [1]University of Chicago, Chicago, IL, [2]Feinstein Institute for Medical Research, Manhasset, NY

Background/Purpose: Response to tumor necrosis factor alpha (TNF-α) inhibition is heterogenous in rheumatoid arthritis (RA). Previous studies have suggested that circulating type I interferon (IFN) levels may predict treatment response to TNF-α inhibitors and other biological agents in RA. Prediction of likely responders prior to initiating therapy would represent a major advance in biological treatment strategies for RA.

Methods: We studied sera from 32 RA patients from the ABCoN Consortium pre-treatment and 4–6 weeks after beginning treatment with TNF-α inhibitors, selecting patients who either had a good response or no response at 14 weeks by EULAR criteria. 27 of the 32 subjects were of European ancestry. Total serum type I IFN activity as well as IFN-α vs. IFN-β activity were measured using a functional reporter cell assay. Data were available regarding baseline and follow up disease activity score (DAS), EULAR response criteria at 14 weeks, anti-CCP antibody titer, and type of TNF-α inhibitor used.

Results: An increased ratio of IFN-β/IFN-α >1.3 in the pre-treatment serum sample was associated with lack of response by EULAR criteria at 14 weeks ($p=0.009$). Similarly, higher IFN-β/IFN-α ratio was positively correlated with higher DAS score at 14 weeks (Spearman's rho= 0.57, $p=0.0075$). Anti-CCP antibody titer and type of TNF-α inhibitor did not influence this relationship. In follow up sera at 4–6 weeks, the EULAR non-responders were more likely to have increased total type I IFN activity than good responders ($p=0.008$), and this increase was characterized by a shift toward increased IFN-α as compared to good responders ($p=0.039$).

Conclusion: Increased pre-treatment serum IFN-β/IFN-α ratio was strongly associated with non-response to TNF-α inhibition by EULAR criteria at 14 weeks. A previous study of IFN-β/IFN-α ratio and response to TNF-α inhibiton in Hispanic-American RA patients reported an association, although in a different direction than our predominantly European ancestry population. This may represent a population-specific difference, and both studies support the potential utility of serum type I IFN in predicting outcome of TNF-α inhibition in RA.

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Validation of Algorithms Using Genome-Wide SNP Analysis for Prediction of Remission Criteria for Infliximab or Etanercept-Treated Rheumatoid Arthritis Patients Using Multiple Medical Cohorts. Tsukasa Matsubara[1], Satoru Koyano[2], Keiko Funahashi[2], Takafumi Hagiwara[1], Takako Miura[1], Kosuke Okuda[1], Takeshi Nakamura[1], Akira Sagawa[3], Takeo Sakurai[4], Hiroaki Matsuno[5], Tomomaro Izumihara[6], Eisuke Shono[7], Kou Katayama[8], Toyomitsu Tsuchida[9], Mitsuyoshi Iwahashi[10], Tomomi Tsuru[11] and Motohiro Oribe[12]. [1]Matsubara Mayflower Hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [4]Inoue Hospital, Takasaki, Japan, [5]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [6]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [7]Shono Rheumatology Clinic, Fukuoka, Japan, [8]Katayama Orthopedic Rheumatology Clinic, Asahikawa, Japan, [9]Tsuchida Clinic, Chiba, Japan, [10]Higashi-Hiroshima Memorial Hospital, Higashi-hiroshima, Japan, [11]PS Clinic, Fukuoka, Japan, [12]Oribe Rheumatism and Internal Medicine Clinic, Oita, Japan

Background/Purpose: Achievement of remission in infliximab (IFX) and etanercept (ETN) treatment is currently one of the most important matters in RA treatment. However, there is no method for prediction of remission criteria. In our first and second cohorts, we established and validated SNP algorithms for prediction of remission or non-remission among IFX or ETN-treated RA patients (Matsubara T, et al., *The 72nd annual meeting of the ACR* San Francisco, CA, USA (2008) Matsubara T, et al., *The 73rd annual meeting of the ACR* Philadelphia, PA, USA (2009)). In this study, we then validated the third population sample by using the first and second population algorithms.

Patients and Methods: The first population sample included 187 RA patients, the second, 206 patients, and the third, 145 patients, for a total of 538 patients from eleven hospitals in different regions of Japan. Remission criteria was determined by DAS28(CRP) within 24–30 weeks after the initiation of treatment with the biologics. Case-control analyses between 285,548 SNPs and remission was examined by Fisher's exact test. We selected 5, 10 or 20 SNPs associated with IFX or ETN-remission which were common in both analyses of the first and second population ($p < 0.05$). We scored the relationship between each SNP and responsiveness, the estimated total score of 5, 10 or 20 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in remission: +1 point, hetero allele: 0 points, and homo allele in the majority of non-remission: −1 point), and then examined relationships between remission and non-remission, and the total score.

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)), and sensitivity (true positive/(true positive+false negative)) of the algorithms for remission with infliximab or etanercept ranged from 60–71% in the validation using third population sample. It is therefore suggested that these SNP algorithms can predict remission prior to the initiation of treatment with infliximab and etanercept.

Conclusion: These highly accurate algorithms using SNP analysis may be useful in the prediction of remission before treatment with infliximab or etanercept, and in this way can contribute to future tailor-made treatment with biologic agents.

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52-Week Results of Clinical, Radiographic and Pharmacokinetic Assessments: Golimumab, a Human Anti-TNF Monoclonal Antibody, Administered Subcutaneously Every Four Weeks in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy. Yoshiya Tanaka[1], Masayoshi Harigai[2], Tsutomu Takeuchi[3], Hisashi Yamanaka[4], Naoki Ishiguro[5], Kazuhiko Yamamoto[6], Minoru Kanazawa[7], Yoshinori Murakami[8], Toru Yoshinari[9], Daniel G. Baker[10], Nobuyuki Miyasaka[11] and Takao Koike[12]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [2]Tokyo Medical and Dental Univ, Tokyo, Japan, [3]Keio University School of Medicine, Tokyo, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [5]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan, [6]Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan, [7]Director of Respiratory Center Professor of Respiratory, Medicine Saitama Medical University, Moroyama, Iruma-Gun, Saimata, Japan, [8]Janssen Pharmaceutical KK, Tokyo, Japan, [9]Mitsubishi Tanabe Pharma Corporation, Osaka, Japan, [10]Centocor R & D, a division of Johnson & Johnson Pharmaceutical Research and Development, LLC, Malvern, PA, [11]Tokyo Medical and Dental University, Tokyo, Japan, [12]Hokkaido University Graduate School of Medicine, Sapporo, Japan

Background/Purpose: To assess the efficacy and safety of golimumab-(GLM) in Japanese patients (pts) with active RA despite MTX therapy.

Methods: GO-FORTH is a multicenter, randomized, double-blind, placebo(PBO)-controlled study in pts with active RA despite MTX. Pts were randomized to SC PBO, GLM50 mg, or GLM100 mg q4 wks. All pts received MTX 6–8 mg orally/wk. Pts with <20% improvement in SJC/TJC entered early escape(EE) at wk 16 in a blinded manner so that PBO→GLM50 mg and GLM50 mg→100 mg. Pts receiving GLM100 mg continued the same dose. Pts who did not enter EE continued initial therapy until wk 24. After wk 24, pts who entered EE maintained the wk 24 regimen. Pts randomized to PBO who did not enter EE crossed over (CO) to GLM50 mg at wk 24. Primary endpoint was the proportion of pts achieving ACR20 at wk 14. Secondary variables included ACR20, ACR50, ACR70, DAS28 and HAQ, and changes from BL to wks 24/52 in total vdH-modified Sharp (vdH-S) score. Data were analyzed using the all patients receiving ≥1 dose of study treatment. Missing clinical response data were not imputed. For vdH-S score, treatment grp comparisons at wks 24/52 were based on randomized grps regardless of EE/CO status. Missing data were imputed using median change from BL in total vdH-S scores (TSS) of all pts or by linear extrapolation. Wk 24 data have been reported; wk 52 results of nonparametric analyses using the van der Waerden method are now reported.

Results: 261 pts received treatment (88 PBO, 86 GLM50 mg, 87 GLM100 mg). Both GLM doses were significantly better than PBO in improving signs and symptoms/physical function through wk14 (PBO-controlled period). After wk 24, all pts received either GLM50 mg or 100 mg, and wk 14 efficacy was sustained thorough wk 52 in all grps. At wk 52, both of GLM50 mg and 100 mg yielded significantly less radiographic damage than PBO and pts who received 100 mg continued to exhibit less progression through wk 52 (Table). The proportions of pts with changes in TSS greater than the smallest detectable change (SDC) were significantly lower in GLM- vs. PBO-treated pts at wks 24 and 52. Significantly more pts treated with GLM 100 mg vs. PBO had no progression (change in TSS<0) at wk 52. Median serum GLM concentrations were approximately dose proportional and appeared to have reached steady-state by wk12.

The incidence of adverse events (AEs) through wk 52 was 89.1% in all GLM-treated pts. Among all AEs, the system organ class with the highest incidence by treatment grp (except for pts who CO GLM50 mg→100 mg) was "Infections and Infestations." Through wk 52, serious AEs occurred in 1.1%, 9.3% and 6.9% of PBO, GLM50 mg only and GLM100 mg only treated pts, respectively. There were no deaths and no tuberculosis. A colon cancer was reported in GLM50 mg grp.

	PBO	GLM	
		50 mg	100 mg
n	88	86	87
Change from BL in TSS mean ±SD	5.2±10.7	2.4±8.0 p=0.0101	0.9±5.2 p<0.0001
Pts with progression based on TSS >SDC=4.33 n(%)	30(34.1)	14(16.3) p=0.0069	10(11.5) p=0.0004
Pts with change ≤0 in TSS from BL n(%)	44(50.0)	51(59.3) p=0.2179	59(67.8) p=0.0166

Conclusion: Treatment with GLM50 mg and 100 mg+MTX significantly improved signs/symptoms and inhibited progression of structural damage vs. PBO+MTX. The GLM+MTX safety profile was similar to other anti-TNF agents.

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Sick Leave and Disability Pension in Patients with Early Rheumatoid Arthritis Randomized to Infliximab Plus Methotrexate or Triple Therapy: One-Year Results. Jonas Eriksson[1], Martin Neovius[2], Johan Bratt[3], Ingemar F. Petersson[4], R.F. van Vollenhoven[5], Pierre Geborek[6] and Sofia Ernestam[7]. [1]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Solna, Sweden, [3]Karolinska Univ Hosp Huddinge, Stockholm, Sweden, [4]Musculoskeletal Sciences, Dept of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [5]The Karolinska Institute, Clinical Trials Unit, Stockholm, Sweden, [6]Lund University, Lund, Sweden, [7]Karolinska University Hospital, Huddinge, Sweden

Background/Purpose: In early RA patients in whom methotrexate (MTX) has failed, adding infliximab to MTX was clinically superior to triple therapy (MTX+sulfasalazine+hydroxycloroquine) with 39% vs 25% achieving EULAR good response at 1y (Lancet 374:459; 2009). The aim of this study was to evaluate whether this clinical superiority translated into greater improvement in work ability.

Methods: RA patients with <1y symptom duration were recruited from 15 rheumatology clinics in Sweden. Patients who did not achieve low disease activity after 3–4 months MTX therapy were randomized to infliximab+MTX or triple therapy. The study population was restricted to patients <64y at baseline, and the outcome at 12 months after randomization was mean days/month of sick leave and disability pension. Complete outcome data for all patients and time points were retrieved from the Swedish Social Insurance Agency. Analysis of covariance (ANCOVA) was used on the intention to treat (ITT) population, including all randomized patients.

Results: Of 210 eligible patients, 109 were randomized to infliximab+MTX and 101 to triple therapy. Seven patients in the infliximab+MTX and four in the triple therapy group never received study drug. At baseline, mean days/month of sick leave and disability pension were 17 (SD 13; median 16) in the infliximab+MTX group and 17 (SD 13; median 16) in the triple therapy group (**Figure**). At 6 months, mean days/month had decreased by 2.7 and 3.2 in the respective treatment groups (ANCOVA difference −0.7, 95%CI −3.1 to 1.8). Corresponding means at 12 months were 4.2 and 4.0 (ANCOVA difference 0.0, −2.8 to 2.8). In a modified ITT analysis, including patients receiving at least one dose of assigned treatment, similar differences were seen at 12 months (0.3, −2.6 to 3.3). Analyses based on last/baseline observation carried forward or per-protocol gave similar results, and adjustment for various baseline characteristics did not change the overall results.

Conclusion: Work ability improved significantly from baseline in this early RA cohort on combination therapy after an insufficient response to MTX, with no difference between the treatment arms. However, the average did not return to the premorbid level (6 months before randomization), underscoring the need for more effective interventions in this regard.

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Golimumab, A Human Anti-TNF Monoclonal Antibody, Administered Subcutaneously Every Four Weeks As Monotherapy in Patients with Active Rheumatoid Arthritis Despite DMARD Therapy: 52-Week Results of Clinical, Radiographic and Pharmacokinetic Assessments. Tsutomu Takeuchi[1], Masayoshi Harigai[2], Yoshiya Tanaka[3], Hisashi Yamanaka[4], Naoki Ishiguro[5], Kazuhiko Yamamoto[6], Minoru Kanazawa[7], Yoshinori Murakami[8], Toru Yoshinari[9], Daniel G. Baker[10], Nobuyuki Miyasaka[11] and Takao Koike[12]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Tokyo Medical and Dental Univ, Tokyo, Japan, [3]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [5]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan, [6]Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan, [7]Director of Respiratory Center Professor of Respiratory, Medicine Saitama Medical University, Moroyama, Iruma-Gun, Saimata, Japan, [8]Janssen Pharmaceutical KK, Tokyo, Japan, [9]Mitsubishi Tanabe Pharma Corporation, Osaka, Japan, [10]Centocor R & D, a division of Johnson & Johnson Pharmaceutical Research and Development, LLC, Malvern, PA, [11]Tokyo Medical and Dental University, Tokyo, Japan, [12]Hokkaido University Graduate School of Medicine, Sapporo, Japan

Background/Purpose: To assess the efficacy and safety of golimumab (GLM) as monotherapy in Japanese patients (pts) with active rheumatoid arthritis (RA) despite DMARD therapy.

Methods: GO-MONO is a multicenter, randomized, double-blind, placebo (PBO)-controlled study in pts with active RA despite treatment with DMARDs. Pts were randomized to SC PBO, GLM50 mg, or GLM100 mg q4 wks as monotherapy. At wk16, pts in the PBO group (grp) crossed over (CO) GLM50 mg q4 wks. Primary endpoint was the proportion of pts achieving ACR20 at wk 14. Secondary endpoints included ACR50, ACR70, and ACR-N, changes from baseline (BL) to wks 14/24/52 in DAS28 and HAQ, and changes from BL to wks 24/52 in total modified vdH-Sharp (vdH-S) score. Data were analyzed using all patients receiving ≥1 dose of study treatment. Missing data imputation was not done for the data of signs and symptoms/physical function. Comparisons of vdH-S score at wks 24 and 52 were between GLM and PBO grps, based on the original randomized grps even for PBO pts who CO to 50 mg after wk16. Missing data were imputed using median change from BL in total vdH-S scores (TSS) of all pts or by linear extrapolation. The results of the non-parametric data analyzed using van der Waerden method is being reported. Wk 24 data were previously presented; data through wk 52 are now reported.

Results: 308 pts received treatment (105 PBO, 101 GLM50 mg, and 102 GLM100 mg). At wk14, GLM50 mg and 100 mg grps had significantly greater improvements in signs and symptoms of RA and physical function vs PBO. Efficacy response was maintained through wk 52. At wk 24, GLM100 mg grp had significantly less radiographic progression (RP) vs PBO. At wk 52, both GLM50 mg and 100 mg grps had significantly less RP vs PBO (table). The proportion of pts with changes in TSS greater than the smallest detectable change (SDC) was lower in GLM50 mg and 100 mg grps than PBO at wk 52. Significantly more GLM100 mg-treated pts had no progression, defined as change in TSS < 0, vs PBO-treated pts at wk 52. The incidence of AEs up to Week 52 was 82.0% (242/295 pts, 973 events) among all GLM-treated pts. Serum GLM levels increased in a dose-proportional manner, with steady state reached at week 12 and it was maintained through wk 52. Among the AEs, the system organ class that showed the highest incidence was "Infections and Infestations". The incidences of serious AEs in PBO, PBO→GLM50 mg, GLM50 mg and 100 mg grps were 2.9%, 7.6%, 5.9%, and 5.9%, respectively. There were no deaths and no tuberculosis. One breast cancer was reported in GLM100 mg grp.

	PBO	GLM	
		50 mg	100 mg
n	105	101	102
Change from BL in TSS Mean ±SD	6.9±12.5	3.3±6.4 p=0.0118	3.2±18.0 p<0.0001
Pts with progression based on TSS >SDC=4.04, n(%)	44(41.9)	28(27.7) p=0.0328	19(18.6) p=0.0003
Pts with change ≤0 in TSS from BL n(%)	37(35.2)	46(45.5) p=0.1316	54(52.9) p=0.0103

Conclusion: Both doses of GLM significantly improved signs and symptoms of RA and physical function compared with PBO. The GLM50 mg and GLM100 mg grps had significantly less RP vs PBO at wks 24 (GLM100 mg only) and 52 (both dose grps). GLM monotherapy was well-tolerated with safety profile similar to other anti-TNF agents.

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Impact of Different Biologic Agents on the Improvement of Fatigue. Anja Strangfeld[1], Matthias Schneider[2], Jörg Kaufmann[3], Andreas Krause[4], Angela Zink[5] and Joachim Listing[6]. [1]Deutsches Rheumaforschungszentrum, Berlin, Germany, [2]Heinrich-Heine-University, Duesseldorf, Germany, [3]Rheumatologist, Ludwigsfelde, Germany, [4]Immanuel Krankenhaus Berlin-Buch, Berlin, Germany, [5]Deutsches Rheumaforschungszentrum and Charité University Medicine, Berlin, Germany, [6]German Rheumatism Research Centre, Berlin, Germany

Background/Purpose: Fatigue is a factor significantly affecting the physical health of patients and limiting their social live. It was reported lately that TNFα leads to prolonged brain activity upon nociceptive stimulation, which is rapidly reversed with TNF-blockade. It was shown that this is not primarily linked to the anti-inflammatory effects of TNF-inhibition. Due to the effects of TNFα in the central nervous system our aim was to examine whether the relative improvement of fatigue is different for the various biologic agents.

Methods: We used data from the German biologics register RABBIT which observes more than 9,500 patients with rheumatoid arthritis (RA) from start of treatment with any approved biologic agent or with a new DMARD. In the current analysis, only patients with a follow-up of at least 6 months and a minimum of two DMARD failures were included. Fatigue was measured on a 0 to 10 numerical rating scale (NRS) at baseline, and after 3 and 6 months. Multiple logistic regression was used to compare the treatment with various

biologic agents to non-biologic DMARD treatment regarding a) the chance of achieving 'no fatigue' (value <= 1) at six months and b) the chance of clinically significant improvement (change in fatigue score of 3 or more) in patients who had a baseline score of at least 3. Adjustment was made for the following baseline variables: fatigue, DAS28, functional capacity (measured by the Hannover Functional Status Questionnaire (FFbH)), co-morbid conditions (4 subgroups), previous treatment with biologics (yes/no), treatment with glucocorticoids (no, <10mg/d >=10mg/d), pain and morning stiffness >=30 minutes.

Results: Data of 5,432 patients with a mean age of 55 years and disease duration of 12 ± 9 years were available for the analysis. At baseline, patients had a mean fatigue score of 5.5 ±2.7, a DAS28 of 5.5 ±1.3 and 59% of full function. Fatigue improved to 4.2 ±2.7 at six months. Patients treated with biologics improved significantly more frequently by a score of 3 or higher than DMARD treated patients. This was also found if patients with similar improvement in DAS28 scores were compared (data not shown). Anti-TNF treated patients had compared to DMARD controls a significantly higher chance of achieving 'no fatigue' already at three months (data not shown) and at six months (Tab).

Table. Adjusted odds ratios (OR) and corresponding adjusted frequencies of patients achieving 'no fatigue' (<= 1 on a 0 to 10 scale) or a clinically significant improvement of ≥ 3 points.

		No fatigue at 6 months		Clin. significant improvement	
	No. of patients	Adj. OR	Adj. frequency (%)	Adj. OR	Adj. frequency (%)
DMARD	1,068	Referent	11.7 [10–14]	Referent	26.6 [23–30]
Etanercept	1,249	1.7 *	18.3 [16–21]	2.1 *	43.8 [40–47]
Infliximab	516	1.6 *	17.4 [14–21]	1.8 *	39.3 [34–45]
Adalimumab	1,389	1.4 *	15.6 [14–18]	1.9 *	40.2 [37–43]
Rituximab	840	1.2	13.8 [11–17]	1.7 *	37.5 [33–43]
Abatacept	182	1.1	13.1 [8–20]	1.6 *	37.0 [28–47]
Tocilizumab	188	1.5	16.6 [12–23]	1.9 *	41.3 [32–51]

* $p < 0.05$

Conclusion: Treatment with a biologic agent improved fatigue significantly more frequently than with a conventional DMARD. This finding is supported by experimental research in which Hess et al (1) observed that blocking TNFα does not only have anti-inflammatory effects but also an impact on processes in the CNS.

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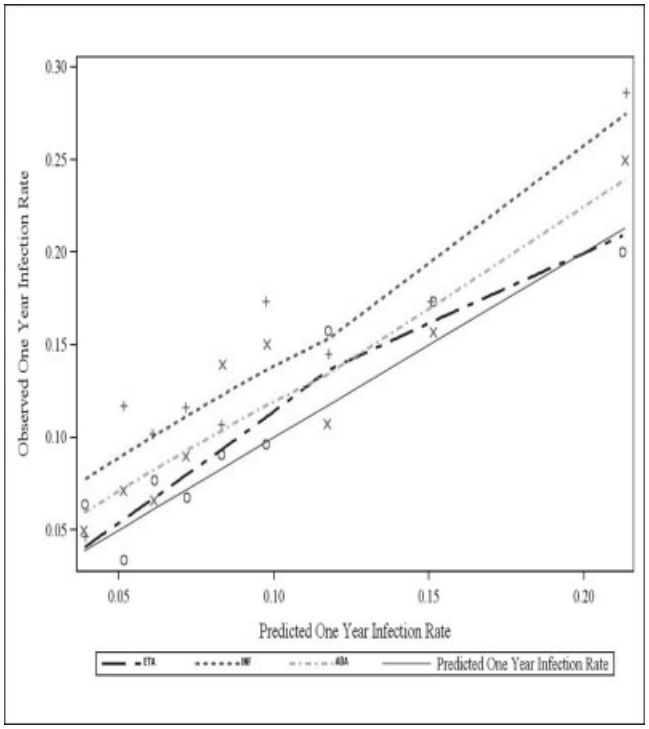
Does the Association Between Anti-TNF Biologics and Serious Infections in Rheumatoid Arthritis Patients Vary by Comorbidity Burden? Jeffrey R. Curtis[1], Fenglong Xie[2], Paul M. Muntner[2], Lang Chen[2], Kenneth G. Saag[2] and Elizabeth S. Delzell[2]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: In many studies, anti-TNF therapy is associated with an increased risk for serious infections. It is unclear whether this risk is incrementally increased for patients with a high baseline infection risk on the basis of older age or comorbidities that are independently associated with infections. We evaluated associations between anti-TNF agents and serious infection according to patients' baseline risk for infection.

Methods: We studied new users of infliximab, etanercept, and adalimumab among RA patients enrolled in Medicare/Medicaid during 2000–2006. Using an infection prediction score, we calculated person-specific 1-year predicted risk of hospitalized infection based upon factors measured in the 1 year prior to biologic use; these factors included age, demographics, comorbidities, and oral glucocorticoids.

The subsequent 1-year observed risk of hospitalized infection was compared among users of etanercept, infliximab and adalimumab and to predicted risk in the absence of anti-TNF exposure. Associations were evaluated on the risk difference and risk ratio scale to evaluate effect modification according to baseline predicted infection risk. Cox proportional hazards models compared the pairwise infection risk for each of the 3 anti-TNF agents, controlling for decile of the infection risk score. The observed and predicted risks of infection were plotted for each decile and smoothed using LOWESS curves.

Results: Among 7537 RA patients initiating inflixiumab (n=3036), etanercept (n=2253) and adalimumab (n=2248), the overall observed one year risk of infection was 15.3, 13.1, and 13.7 per 100 person years, respectively. Infection risk was highest for infliximab users (p = 0.01 for infliximab vs. etanercept, p=0.15 for infliximab vs. adalimumab, and p=0.23 for etanercept vs. adalimumab). Comparing inflixumab to the other two anti-TNF agents and to predicted risk, there was a relative constant risk difference of 2–3 per 100 person-years according to baseline predicted infection risk (Figure). The relative risk ratio varied, ranging from 1.5 at the low end of predicted risk down to 1.0 at the higher end of predicted risk.



Conclusion: The risk of serious infections for anti-TNF agents was incrementally increased by a fixed absolute difference irrespective of age, comorbidities, and other factors that contributed to infection risk. The clinical importance of an increased relative risk for infection is likely to be most relevant for patients with low baseline infection risk; in contrast, the relative risk increase was small for patients with a high baseline risk. Older patients and those with high comorbidity burdens should be reassured that the magnitude of incremental risk with anti-TNF agents does not appear to be greater for them than for lower risk patients.

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A Preliminary Report of Remission Induction with Two Therapeutic Strategies with Infliximab or High Dose Intravenous Steroids for the Treatment of Rheumatoid Arthritis. Jackie L. Nam[1], Edith Villeneuve[2], Philip G. Conaghan[3], Elizabeth Hensor[4], Helen I. Keen[5], Roshan Amarasena[6], Andrew K. Gough[7], Philip Helliwell[3], Ann W. Morgan[3], Mark Quinn[8], Michael J. Green[9], Richard Reece[10], Richard Wakefield[3] and Paul Emery[3]. [1]NIHR Leeds Musculoskeletal Biomedical Research Unit, LIMM, University of Leeds., Leeds, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Unit, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [3]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [4]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [5]UWA, Perth, Australia, [6]Salford Royal Foundation trust, Manchester, United Kingdom, [7]Harrogate District Hospital, Harrogate, United Kingdom, [8]The York Hospital, York Teaching Hospital NHS Foundation Trust, York, United Kingdom, [9]York Teaching Hospital NHS Foundation Trust, Harrogate, United Kingdom, [10]University of Leeds, Leeds, United Kingdom

Background/Purpose: Early intensive treatment strategies have demonstrated good clinical outcomes for patients with rheumatoid arthritis (RA). Infliximab (IFX) and the use of high dose steroids have shown to be effective for remission induction. Objectives**:** To compare the efficacy of methotrexate (MTX) + IFX vs. MTX + high dose intravenous (IV) steroid as induction therapy, together with dose and treatment modification according to predefined disease activity measures in patients with DMARD naïve RA.

Methods: The IDEA study is a 78 week multicentre randomised controlled study of 112 patients with early (symptom duration of >3 and <12 months) DMARD naïve RA (1987 ACR criteria, DAS>2.4). Patients were randomised to one of 2 groups –IFX or steroid/placebo. Treatment was blinded until week 26 then pragmatically guided by disease activity scores according to a pre determined therapeutic regime. The IFX group received: IFX 3mg/kg (weeks 0, 2, 6, 14, 22) + MTX 10mg weekly increasing to 20mg by week 6 with IFX dose modification (increase or stopping) depending on DAS 44 from week 26. The steroid/placebo group received: IV methylprednisolone 250mg at week 0, placebo infusions at weeks 2, 6, 14, 22 + MTX 10mg weekly increasing to 20mg by week 6; from week 26 treatment was escalated stepwise as follows if DAS >2.4: add sulphasalazine (SSZ) and hydroxychloroquine (HCQ), then stop SSZ+ HCQ and add leflunomide (LEF), then one of the following combinations: MTX s/c +LEF or MTX + ciclosporin or MTX+ LEF + prednisolone 5–7.5mg daily. Additional IM methylprednisolone 120mg was administered if DAS >2.4 (weeks 6, 14, 22, 38, 50 and 62) for both groups. Other biologics were also allowed from week 26 according to NICE guidelines. Remission data are reported here.

Results: Baseline characteristics were similar in the 2 patient groups. At week 2 remission (DAS <1.6) was achieved in 22.2% (12/54) in the IFX group and 8.9% (5/56) in steroid/placebo group (p=0.054). At week 26, 33.3% (18/54) and 44.6% (25/56) in the in the IFX and steroid/placebo groups respectively were in remission (p=0.224). At week 50, a greater percentage achieved remission in the IFX group (IFX 51.9% (28/54) vs. steroid/placebo 35.7% (20/56), p=0.088. By week 78, similar remission rates were seen in the two groups (IFX 48.1% (26/54) vs. steroid/ placebo 51.8% (29/56), p= 0.703).

Conclusion: Early and sustained remission rates were achieved using an intensive treatment strategy with IFX as induction therapy. Similar remission rates were achieved using with high dose IV steroids; although some reduction was seen at 50 weeks this was regained at week 78. Analysis of the radiographic data will be of interest in providing further information regarding the effects of the two therapeutic strategies on bone damage.

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The Immunogenicity of Infliximab, Adalimumab and Etanercept in Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Crohn's Disease and Ulcerative Colitis—a Quantitative and a Qualitative Review. Sandra Garcês[1], Jocelyne Demengeot[2], Gj Wolbink[3], L. Aarden[4] and Elizabeth Benito-Garcia[5]. [1]Instituto Gulbenkian Ciência; Hospital Garcia de Orta, Oeiras, Portugal, [2]Instituto Gulbenkian Ciência, Oeiras, Portugal, [3]Reade/Jan van Breemen Institute Research Center, Amsterdam, Netherlands, [4]Sanquin Research and Landsteiner Laboratory, Amsterdam, Netherlands, [5]BioEpi, Research Center, Oeiras, Portugal

Background/Purpose: Despite the beneficial effects of aTNF alpha agents on the systemic rheumatic and inflammatory bowel diseases, a significant proportion of patients cannot sustain a therapeutic response over time. An increasing body of literature highlights immunogenicity as one of the main factors behind therapeutic failure and infusion-related adverse events. Given the recent recommendations by the EMEA to monitor immunogenicity in clinical practice, it is important to reevaluate the impact of anti-biologic antibodies on drug efficacy and safety.

We conducted a meta-analysis to assess the influence antibodies against infliximab, adalimumab and etanercept on therapeutic efficacy/effectiveness and the influence of concomitant immunosuppression in anti-biologic antibodies production, in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn′s disease and ulcerative colitis.

Methods: A systematic literature search of Medline, Embase and Cochrane Library was conducted trough May 2011, complemented with the reference lists of articles and consultation with experts. We included clinical trials and observational studies. Seventeen studies met our inclusion criteria. Fixed-effects models (Mantel-Haenszel method) were initially used for clustering results and random-effects models according to the Laird method were introduced whenever statistically significant heterogeneity existed, examined by calculating the χ^2 test for heterogeneity and the I^2 measure of inconsistency. The effects of individual study and population characteristics were evaluated by meta-regression.

Results: Overall, the presence of anti-biologic antibodies reduced the therapeutic response rate (RR, 95% CI varied from 0.05 to 0.53). Subgroup analysis revealed that the concomitant use of Methothrexate (MTX) was a significant source of heterogeneity. When high proportion of patients was receiving concomitant MTX (≥74%) the effect size reduction was smaller (RR 0.68, 95% CI 0.58 to 0.79) than in studies where a lower proportion of patients were co-treated with MTX (RR 0.20, 95% CI 0.11 to 0.35). The effect is independent of the type of the disease. The concomitant use of immunosupressors reduced the proportion of patients with detectable anti-biologic antibodies by about 50% (RR varied from 0.26 to 0.82). In the subgroup analysis we verified that when RIA was used to detect anti-biologic antibodies the effect size reduction was larger (RR 0.36, 95% CI 0.28 to 0.45) than in studies where the antibodies were detected by ELISA methods (RR 0.66, 95% CI 0.57 to 0.76).

Conclusion: There is evidence of an increased risk of therapeutic failure in patients with anti-biologic antibodies, which although modulated by MTX, remains very significant. Aside from clinical impact, immunogenicity can also alter drug safety profile. Concomitant immunosuppression reduces but do not abrogate anti-biological production. The type of assays employed to assess anti-biologic antibodies can influence the results. Routine assessment of immunogenicity will help us to design more cost-effective strategies, tailored to each patient.

ACR Poster Session A
Sjögren's Syndrome
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Effect of Caphosol® On the Symptoms of Xerostomia Associated with Primary and Secondary Sjögren's Syndrome. Stephanie Mathew[1], Angelique N. Collamer[2], Athena S. Papas[3] and Daniel F. Battafarano[4]. [1]United States Air Force SAUSHEC, Fort Sam Houston, TX, [2]Langley AFB Hospital, Langley AFB, VA, [3]Tufts School of Dental Medicine, Boston, MA, [4]Brooke Army Medical Ctr, San Antonio, TX

Background/Purpose: Sjögren's syndrome is a common autoimmune disorder affecting up to 4% of the general population, resulting in lymphocytic infiltration of exocrine glands and subsequent xerophthalmia and xerostomia. Effective and tolerable therapies for xerostomia are lacking. Caphosol®, a supersaturated calcium and phosphate electrolyte solution, has been successful in treating radiation and chemotherapy induced mucositis and xerostomia. This study evaluated the potential benefit of Caphosol® on Sjögren's syndrome patients reported oral health, quality of life and xerostomia symptoms.

Methods: Rheumatology clinic patients diagnosed with primary or secondary Sjögren's syndrome with symptomatic xerostomia were recruited to participate in an IRB approved study. Prior to enrollment, patients were assessed with a 6 minute un-stimulated salivary flow rate, and were eligible if they produced less than 0.6mL/minute of saliva. Exclusion criteria included those on a highly restricted sodium diet (less than 1 gram per day), inability to provide written consent or self-mix the solution. Patients were allowed to continue all medications, with the exception of other oral solutions used for the purpose of treating dry mouth. During the study period patients could not start new saliva replacement preparations, anticholinergic or antimuscarinic medications. Following the initial evaluation, patients were provided Caphosol® solution, as well as detailed guidance on its administration and instructed to use it 2 to 10 times daily. Enrolled patients answered validated questionnaires (HAQ, SF-36, Xerostomia Inventory and New York Bluestone mouth feel) at baseline and 3 months to assess quality of life and symptoms of xerostomia.

Results: Thirty-eight patients met inclusion criteria and consented to participate, 95% (36/38) were female, 66% (25/38) Caucasian, with a mean age of 56 (range 38–67). Twenty-five patients (66%) had secondary Sjögren's syndrome associated with rheumatoid arthritis (10), scleroderma (5), systemic lupus erythematosis (3), undifferentiated connective tissue disease (3), mixed connective tissue disease (2), relapsing polychondritis (1) and Behçet's disease (1). Twenty-four patients were included in the statistical analysis, 22 used Caphosol® more than 2 times daily. Three patients failed to use the solution, 2 withdrew consent and 7 did not return the questionnaires in the allotted time.

At 3 months, a statistically significant improvement in the symptoms of dry mouth (p 0.05), and ability to swallow problematic foods (p 0.025) when compared to baseline was found in those patients using the solution at least 2 times daily. However, no statistically significant quality of life improvement, as measured by the HAQ and SF-36 questionnaires was found.

Conclusion: In this pilot study, the supersaturated calcium and phosphate electrolyte solution Caphosol® improved symptoms of xerostomia in Sjögren's syndrome patients. Caphosol® is an effective option for the treatment of xerostomia in Sjögren's syndrome. Longer studies may be

necessary to evaluate for potential quality of life improvements with extended Caphosol® use.

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Responsiveness of Disease Activity Indices (ESSPRI, ESSDAI) in Patients with Primary Sjögren's Syndrome Treated with Rituximab. Petra M. Meiners, Suzanne Arends, Elisabeth Brouwer, Arjan Vissink and Hendrika Bootsma. University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: To evaluate the responsiveness of the ESSPRI and ESSDAI in patients with primary Sjögren's syndrome (pSS) treated with rituximab.

Methods: Twenty-eight pSS patients who were treated with rituximab (1000 mg) infusions at days 1 and 15 were included. Clinical data, including ESSPRI and ESSDAI, were collected prospectively at baseline and 16, 24, 36, 48 and 60 weeks after treatment. Internal responsiveness was assessed using standardized response means (SRM) and effect sizes (ES). SRM and ES <0.5 were interpreted as small, between 0.5 and 0.8 as moderate and >0.8 as large. External responsiveness was assessed using Spearman's correlation coefficients.

Results: Median (range) ESSPRI and ESSDAI at baseline were 6.7 (0.3–9.0) and 8 (2–18), respectively. Both indices improved significantly after treatment. SRM and ES for ESSPRI and ESSDAI were ≥ 0.8 at week 16, decreased afterwards and were larger for ESSDAI than for ESSPRI. SRM and ES values for patient (patGDA) and physician (phyGDA) global disease activity, and rheumatoid factor (IgM-Rf) broadly followed the pattern of those of ESSPRI and ESSDAI. SRM and ES for stimulated whole salivary flow were small at all time-points. Furthermore, at baseline and form most change scores, moderate correlations were found between ESSPRI and patGDA and between ESSDAI and phyGDA. No significant correlation was found between ESSPRI and ESSDAI.

Conclusion: This is the first study to demonstrate that the recently developed ESSPRI and ESSDAI are sensitive to measure change in disease activity after therapeutic intervention. This supports the usefulness of these indices for future clinical trials in pSS patients. Responsiveness of ESSPRI was less prominent than for ESSDAI.

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Characterization of Anti Sjögren's Syndrome Nuclear Antigen-1 (SSNA-1) Novel Autoantibody in Patients with Primary Sjögren's Syndrome. Kaori Hiruma[1], Kazuhisa Nozawa[1], Keigo Ikeda[2], Ayako Yamaguci[1], Iwao Sekigawa[2], Edward K.L. Chan[3] and Yoshinari Takasaki[1]. [1]Juntendo University School of Medicine, Tokyo, Japan, [2]Juntendo University Urayasu Hospital, Tomioka, Urayasu, Chiba, Japan, [3]University of Florida, Gainesville, FL

Background/Purpose: Sjogren's syndrome nuclear antigen-1 (SSNA-1)/nuclear antigen of 14 kDa (NA14) is a novel autoantigen which were recently identified. SSNA-1 belongs to a coiled coil protein superfamily and the coiled coil proteins are known to often elicit autoimmune reaction in Sjogren's syndrome. Although we previously have reported that autoantibody against SSNA-1 was often produced in patients sera with primary Sjogren syndrome (pSS), the detailed autoantigen characteristics about the SSNA-1 remains poorly described. Therefore, we conducted the present study to clarify characteristics of SSNA1 regarding clinical association of pSS and mechanism of the autoantibody production.

Methods: Total 332 sera with various rheumatic diseases including pSS positive for standard autoantigens (SS-A/SS-B, centromere, U1-RNP, ds-DNA, Jo-1, and nucleolar related proteins) were obtained from serum bank of our university hospital approved by the local ethics committee. Reactivity for recombinant SSNA-1 protein in these autoimmune sera was measured by direct ELISA and immunoblotting. Statistical analysis was performed by χ^2test compared to those of normal control. SSNA-1, interferon γ inducible protein of 10 kDa (IP-10) and B cell-activating factor belonging to the TNF family (BAFF) expression in human salivary cells line (HSG) was monitored by quantitative real-time PCR. Serum levels of IP-10 and BAFF were measured by sandwich ELISA. IIF analysis was performed to characterize staining pattern of anti-SSNA-1 antibody.

Results: High frequency of positive sera against SSNA-1 was observed in anti- SS-A/SS-B, centromere, and U1-RNP positive autoimmune sera significantly compared to normal controls, and was not observed in anti-ds-DNA, Jo-1 and nucleolar related proteins positive autoimmune sera. Although the anti-SSNA-1 antibody was predominantly recognized in pSS among various systemic rheumatic diseases as we expected, patients with mix connective tissue disease (MCTD) showed high prevalence of anti-SSNA antibody as well as pSS. IIF analysis revealed that anti-SSNA-1 monoclonal antibody stained only G2-M phase mitotic cells and did not stain G1-S phase cells. IFNγ treatment resulted in 10-fold increase of SSNA-1 mRNA expression on the HSG cells. Serum levels of IP-10 and BAFF, which were also positively regulated by IFNγ in HSG cells, were statistically greater in anti-SSNA-1 positive sera with pSS compared to those in the anti-SSNA-1 negative sera.

Conclusion: In the present study, we clarified that anti-SSNA-1 antibody is frequently recognized in anti-SS-A/SS-B, centromere, and U1-RNP positive autoimmune sera. The production of anti-SSNA-1 antibody had unique disease specificity for pSS and MCTD. In addition, SSNA-1 appeared to be classified as novel mitotic apparatus autoantigen. Regarding to an important factors of the anti-SSNA-1 autoantibody production, IP-10 and BAFF played an important role for the autoantibody production. Overexpression of IP-10 and BAFF induced by abnormal IFNγ regulation in pSS may possibly induce autoreactive T cells infiltration and abnormal B cells activation in salivary gland with pSS consequently resulting in anti-SSNA-1 autoantibody production.

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Early Reconstitution of Autoreactive B-Cells After Rituximab Treatment in Primary Sjögren's Syndrome. Wayel H. Abdulahad, Henko Tadema, Arjan Vissink, Minke G. Huitema, Jetske Anema, Petra M. Meiners, Pieter C. Limburg, Cees GM Kallenberg, Frans Kroese and Hendrika Bootsma. University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: B-cell depletion therapy with rituximab (RTX) leads to improvement of salivary and lacrimal gland function for at least 6–9 months in patients with primary Sjögren's syndrome (pSS). However, clinical symptoms of pSS re-appear at the time that B-cells return in the peripheral blood. This observation offers the possibility to analyze the impact of RTX on reconstitution of autoreactive B-cells in pSS-patients. In the present study, we aimed to assess the effect of RTX-treatment on anti-Ro52/60 and anti-La autoantibody-producing B-cells in patients with pSS.

Methods: Seventeen patients with pSS were treated with RTX on days 1 and 15. To study the effect of RTX on depletion/reconstitution of autoreactive B-cells, peripheral blood mononuclear cells (PBMCs) were isolated from pSS-patients (at baseline and 5, 16, 24, 36, 48 and 60 weeks after RTX treatment) and from age- and sex-matched healthy controls (HC, n=12). These PBMCs were stimulated for 12 days with CpG-ODN and IL-2 to induce polyclonal B-cell activation and antibody production. *In vitro* produced autoantibodies to the Ro60-, Ro52-, and La- proteins were measured in supernatants by ImmunoCAP assay. Presence of circulating Ro52/60-specific B-cells was determined by flowcytometry, using APC-conjugated recombinant Ro52/60. To characterize the phenotype of autoreactive B-cells, $CD19^+$ cells were sorted into 4 subsets on the basis of surface expression of IgD and CD27. These 4 subsets were separately co-cultured with autologous B-cell-depleted PBMCs (ratio 1:10 cells), and stimulated with CpG-ODN/IL-2 to analyze the levels of *in vitro* produced autoantibodies. In addition, B-cell numbers and phenotypes were examined by flowcytometry in fresh blood samples at aforementioned time points.

Results: At baseline, B-cells from all pSS-patients produced high levels of anti-Ro60 and low levels of anti-Ro52 autoantibodies, whereas anti-La autoantibodies were detected in 7 out of 17 pSS-patients only. No autoantibody production was observed in HCs. *In vitro* autoantibody production in pSS-patients was disappeared at weeks 5 and 16 after B-cell depletion, reappeared at week 24, and reached baseline levels at week 36 post-RTX-treatment. At 36 weeks, reconstituted B-cell numbers were, however, still decreased as compared to their numbers at baseline. In addition, increased frequencies of Ro60-binding B-cells were observed in peripheral blood of pSS-patients by FACS analysis. Furthermore, B-cell-sorting experiments clearly demonstrated that IgD^- memory B-cells were the major producers of anti-Ro60 autoantibodies.

Conclusion: Circulating autoreactive B-cells in pSS-patients, bearing the phenotype of IgD^- memory cells, produce high levels of anti-Ro60 autoantibodies. These autoreactive B-cells were successfully depleted by RTX, but early reconstituted despite the low numbers of regenerated B-cells. RTX-treatment might induce emerging autoreactive B-cells which in turn could be in favor of a more specific targeting of IgD^- memory B-cells in pSS-patients.

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A Novel Cell-Based Assay for Inhibitory Anti-Muscarinic Type 3 Receptor Antibodies in Patients with Sjögren's Syndrome. Michael W. Jackson[1], Isabell Bastian[1] and Thomas P. Gordon[2]. [1]Flinders University and Flinders Medical Centre, Adelaide, Australia, [2]Flinders Medical Centre, Bedford Park, Australia

Background/Purpose: Primary Sjögren's syndrome (SS) is a systemic autoimmune disorder characterized by exocrine failure and widespread autonomic dysfunction. Functional autoantibodies directed against the muscarinic type 3 receptor (M3R) have been postulated to underpin gastrointestinal, bladder and cardiac dysfunction in SS *(Cai et al, Arthritis Res Ther 2008;10:R31)*, and we have recently demonstrated that SS IgG acts specifically at the M3R to disrupt cholinergic neurotransmission and motility in murine gastrointestinal tissues *(Park et al, Arthritis Rheum, 2011, 63: 1426–34)*. To date, detailed studies correlating the presence in patients of anti-M3R antibodies and symptoms of autonomic dysfunction have been hampered by a lack of suitable screening assays *(Dawson et al, Arthritis Rheum 2004;52:2984–95)*. Hence, the aim of the current study was to develop a cell-based assay to screen patient IgG samples for anti-M3R activity.

Methods: HEK293 cells (2×10^5) were transiently transfected in 96 well culture plates for 24 hours with DNA encoding the human M3R, and with the pGL4.33 vector (Promega) containing a luciferase gene driven by the serum response element promoter. Cells were then incubated for 4 hours in the presence of the cholinergic agonist, carbachol, (0.3 to 100 μM) and patient IgG (4 mg/ml) characterised as positive (M3R+; n = 4) or negative (M3R-; n = 2) for inhibitory anti-M3R activity, as determined by the in vitro bladder strip assay *(Waterman et al, Arthritis Rheum 2000;43:1647–54)*. IgG from healthy donors (n = 6) was used as controls. Luciferase gene activity was determined on a DTX 880 MultiMode Detector (Beckman Coulter).

Results: M3R+ IgG, but not control or M3R- IgG, significantly inhibited carbachol-induced luciferase activity across a range of carbachol concentrations, with a maximum inhibition of approximately 40%. M3R+ IgG had no effect on luciferase activity in the absence of carbachol, or in cells transfected with the pGL4.33 vector alone. The inhibitory action of the autoantibody on carbachol-induced receptor activity was non-competitive, consistent with allosteric modification of receptor signalling.

Conclusion: We have developed a real-time cell-based bioassay incorporating a luciferase reporter to detect inhibitory anti-M3R antibodies in IgG from patients with SS. The assay does not rely on direct detection of immobilised antibody at the receptor, thereby overcoming the limitations of conventional immunological techniques such as ELISA or Western blotting. The results from the cell assay compare favourably with those from whole-tissue in vitro assays (*Waterman et al, Arthritis Rheum 2000;43:1647–54; Cavill et al, Arthritis Rheum 2003;48:3597–02)*, thereby combining the sensitivity of ex-vivo tissues with the convenience of a 96-well assay format. The bioassay should facilitate both detailed pharmacological characterization of the mechanism of antibody action at the M3R, and the screening studies required to establish the role of anti-M3R antibodies in mediating the autonomic dysfunction associated with SS.

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Immunological Differences in Sicca Patients Based on Age. Andreea Coca, Tracey Sanford, Mustimbo Roberts, Jason Englert, Jennifer H. Anolik and Ignacio Sanz. University of Rochester, Rochester, NY

Background/Purpose: Sjogren's syndrome is a chronic autoimmune disease that affects primarily the lacrimal and salivary glands. It may occur as a primary disorder (pSS) or secondary to other autoimmune disease. With a prevalence ranging from 0.1 to 0.6%, it is considered a common immunological disease. Despite the fact that most people develop the disease in mid-life, its presentation at extremes of age is not uncommon. The focus of this study is to analyze the age related disease discrepancies in patients with early and established Sjogren's syndrome.

Methods: Our cohort included patients that fulfill the American European Consensus Group criteria for the diagnosis of Sjogren's syndrome (AECG group). Early sicca (ES) group are patients that have subjective and/or objective dryness, some evidence of autoimmune disregulation (positive ANA, and/or Ro/La) but do not fulfill the AECG criteria. We collected demographic and laboratory data (anti-Ro, anti-La, ANA, RF, IgG, ESR, CBC, % lymphocytes, C3, C4, VAS for subjective oral and ocular dryness, Schirmer test, unstimulated whole sialometry - UWS). We excluded patients with head and neck radiation, hepatitis C infection, AIDS, sarcoidosis, graft vs. host disease, use of anticholinergic drugs. The data was analyzed using unpaired t-test.

Results: We included in the analysis 52 AECG and 33 ES. By breaking down these two groups based on age (< and > than 50 y/o) we observed a trend: younger patients had more immunological activation than older people and less dryness (better Schirmer, better VAS for oral and ocular dryness and UWS in ES only). Younger pSS patients perceived less subjective dryness, but it was the opposite for early disease. As such, more patients with leucopenia ($p=0.02$), higher IgG levels ($p<0.05$) and higher % lymphocytes ($p<0.05$) were observed in younger AECG patients. In the sicca population we observed more statistically significant differences in the population younger than 50 y/o: more patients had increased RF levels, positive anti-Ro, anti-La and the combination of both, as well as higher IgG levels and better Schirmer test higher (all $p<0.05$).

AECG		#	%ANA	%RF	%Ro	%La	WBCs	%Ro La	% hypergam	ESR >30	% lymph	Schirmer	VAS ocular	VAS oral	UWS
	<50	16	87.5	37.5	68.7	50	7.5	50	50	56.2	13.3	4	7.8	10.6	1.2
	>50	36	69.4	41.6	77.7	47.2	5.6	41.6	16.6	27.7	9	3.4	21.3	14.9	1.2
			NS	NS	NS	NS	p=0.02	NS	p<0.05	NS	p<0.05	NS	p=0.07	NS	NS
pre-SS	<50	14	78.5	28.5	64.2	35.7	4.8	35.7	35.7	7.6	14.2	21	11.1	18.3	3.1
	>50	19	57.8	5.2	42.1	0	5.9	0	0.2	15.7	5.2	10.6	9.6	2.1	2.1
			NS	p<0.05	p<0.05	p<0.05	NS	p<0.05	p<0.05	NS	NS	p=0.03	NS	NS	NS

Conclusion: In our cohort of Sjogren's we have observed that those younger than 50 y/o tend to have more of an active immunological disease (higher number had autoantibodies, hypergammaglobulinemia) but less subjective dryness. This trend was more obvious and statistically significant in pre-clinical disease, (higher number of patients with RF, positive anti-Ro, anti-La, and hypergammaglobulinemia). As this active immunological phenotype seems more pronounced early on, it could suggest a "burned-out disease" by the time the classical pSS phenotype establishes itself.

Our main limitation comes from the small number of patients. We are actively recruiting patients into this database, as we recognize the need for larger sample size to validate our results.

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In Vivo Confocal Microscopic Evaluation of Corneal Morphology and Innervation in Primary Sjögren's Syndrome and Non-SS Dry Eye: A Monocentric Cross Sectional Study. Chiara Baldini[1], Giovanna Gabbrielli[2], Pasquale Pepe[1], Valentina Varanini[2], Francesco Ferro[1], Francesca Fanucci[2], Chiara Notarstefano[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Opthalmology Unit, Pisa, Italy

Background/Purpose: To analyse with confocal microscopy (CM) the *in vivo* corneal structure and sub-basal plexus nerves in patients with primary Sjögren's syndrome (pSS) and non-SS dry eye. *Secondary aims*: to correlate CM findings with routinary performed tear function tests (Schirmer-I test, Break up time (BUT), Green Lissamine staining (GLS)); to evaluate the usefulness of CM in the differential diagnosis between pSS and non-SS dry eye..

Methods: Twenty eyes from 10 consecutive patients with pSS (AECG criteria) and 14 eyes from 7 consecutive patients with a diagnosis of non-SS dry eye were investigated in this cross-sectional study. Exclusion criteria included: corneal dystrophy/inflammation; systemic therapies with known corneal toxicity; topical antiglaucoma drugs, steroids, or NSAIDs; use of contact lenses; previous interventions of ophthalmic surgery. Each subject had both eyes examined; the same ophthalmologist analysed all the CM images. Tear function test (Schirmer-I test, BUT, GLS) were performed in all the cases. CM parameters taken into consideration included: basal epithelial integrity (evaluated according to grading (0–2)), pachymetric data, keratocyte activation (evaluated according to grading (0–2)), cell densities of the superficial and basal epithelium, number of nerves (evaluated according to grading (0–5), tortuosity, and fiber reflectivity of the sub-basal plexus (evaluated according to grading (0–4)). Chi-square, ANOVA and t-test were used for statistical analysis.

Results: Table 1 reports patients' demographic, clinical and serological data. Tear function tests and CM parameters are also summarised in Table 1. As expected, we found that clinical and serological data and routinary performed tear function tests had a limited value in differentiating pSS from non-SS dry eyes. On the contrary, CM pachymetric data and the cell densities of the superficial epithelium were significantly lower in pSS vs non-SS dry eye ($p<0.0001$). No correlation was detected between CM data and tear function tests.

	pSS	Non-SS dry eye	p-value
Patients n°	10	7	
Age (M±SD)	53 ± 9	43 ± 15	ns
Xerostomia	8/10	5/7	ns
Salivary Gland Enlargement	2/10	0/7	ns
Arthralgia	7/10	0/7	0.01
Low C3/Low C4	2/10	0/7	ns
Leukopenia	3/10	1/7	ns
Hypergammaglobulinemia	4/10	0/7	0.08
Antinuclear antibodies	10/10	2/7	0.01
Anti-Ro/SSA	4/10	0/7	0.08
Anti-La/SSB	2/10	0/7	ns
Rheumatoid Factor	8/10	0/7	0.003
Schirmer-I test (M±SD)	4.9 ± 2.3	5.6 ± 1.9	ns
BUT	6.2 ± 1.3	6.7 ± 1.3	ns
Green Lissamine (eyes)	8/20	4/14	ns
Corneal tickness (M±SD)	**507 ± 34**	**584 ± 13**	**<0.0001**
Basal epithelium cell density (M±SD)	5918 ± 415	6017 ± 290	ns
Superficial epithelium cell density (M±SD)	**966 ± 44**	**1346 ± 121**	**<0.0001**
Number of nerves (grade≤2)	14/20	8/14	ns
Tortuosity (grade≥3)	10/20	8/14	ns
Reflectivity (grade≥3)	9/20	8/14	ns
Keratocyte activation (grade =2)	1/20	0/14	ns
Basal epithelial integrity (grade =2)	16/20	14/14	ns

Conclusion: This study demonstrated that pSS patients had a reduced corneal tickness and a lower cell density of the superficial corneal epithelium in comparison to non-SS dry eye subjects, shedding new lights on the potential role of CM in the diagnostic armamentarium of the disease.

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Assessment of Minor Salivary Gland Innervation in Sjögren's Syndrome: A Feasibility Study. Alan N. Baer[1], Ying Liu[1], Anthony L. Keyes[2], Jean Kim[1] and Michael Polydefkis[1]. [1]Johns Hopkins University, Baltimore, MD, [2]John Hopkins, Baltimore, MD

Background/Purpose: Salivary gland dysfunction in Sjögren's syndrome (SS) correlates poorly with the severity of sialoadenitis, as assessed by minor salivary (lip) gland biopsy. Impaired innervation of the salivary gland has thus been postulated to contribute to glandular dysfunction in SS. We sought to determine the feasibility of quantifying minor salivary gland innervation in SS and sicca control patients.

Methods: Minor salivary gland lobules were obtained for this study at the time of diagnostic lip biopsy from 7 female patients with suspected SS who had consented to an IRB-approved protocol. One to two glands from each patient were fixed, cryoprotected, and sectioned at 50 μM intervals. Three-five randomly-selected 50 μM sections were stained immunohistochemically with rabbit anti-human polyclonal PGP9.5 antibody. The density of glandular nerve fibers was assessed by an unbiased stereology methodology and the laboratory personnel were blinded to the diagnoses of the patients.

Results: A dense network of small nerve fibers was visualized in each of the minor salivary glands. There were no qualitative differences in nerve fiber morphology. The clinical features and nerve fiber densities of the 7 patients are summarized in the Table.

Patient	Final diagnosis	Age	Lip biopsy	Salivary gland scintigraphy	KCS	Anti-SS-A/ anti-SS-B	Nerve density (mean ± SD)
LS	Primary SS	46	Normal	Minimal dysfunction	+	positive	4.5 ± 1.2
MB	Primary SS	59	FLS, FS=ND	Impaired tracer uptake	+	positive	4.7 ± 1.4
JT	Primary SS	42	FLS, FS=2.4	Impaired tracer uptake and discharge	+	positive	4.0 ± 2.0
NW	Secondary SS	63	FLS, FS=2.9	Not done	+	negative	2.6 ± 1.0
KK	Primary SS	57	FLS, FS=1.3	Impaired tracer uptake	+	positive	2.7 ±1.0
FB	Sicca	47	Non-specific chronic sialoadenitis	(S/P bilateral superficial parotidectomy)	+	negative	4.9 ± 0.8
BH	Sicca	32	normal	Impaired tracer uptake	+	negative	4.7 ± 0.7

KCS: keratoconjunctivitis sicca; FLS: foçal lymphocytic sialoadenitis; FS: focus score; ND: not determined due to surface area <4 mm²

Nerve fiber densities were markedly lower in 2/5 SS patients. The mean nerve fiber densities were 3.7 ± 1.0 for the SS patients and 4.8 ± 0.2 for the sicca control patients (p=0.07).

Conclusion: In this feasibility study, we established a methodology for assessing the innervation of minor salivary gland lobules in patients with SS. The minor salivary gland lobules are richly innervated and significant decreases in nerve fiber density can be detected in select SS patients. More studies are in progress to assess the nerve fiber subtypes and the correlation of nerve fiber density with clinical and histopathologic parameters.

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Improved Assessment of Parotid Gland Dysfunction with Scintigraphy in Sjögren's Syndrome. Anthony L. Keyes, Rebecca L. Manno, Margaret Mills, John Petronis and Alan N. Baer. Johns Hopkins University, Baltimore, MD

Background/Purpose: The optimal method for assessing parotid gland function by scintigraphy has been debated. We chose to compare the initial slope of radiotracer uptake by the parotid glands with more conventional measures of net uptake ratio and maximal count time as a means to differentiate patients with Sjogren's syndrome (SS) from sicca control patients.

Methods: Parotid scintigraphy was performed on 20 patients as part of their evaluation for suspected or established SS. A diagnosis of SS was assigned to 10 of these patients, based on the 2002 AECC criteria. The results of the parotid scintigraphy were not utilized in this classification. For each patient, the time-activity curve of radiotracer uptake by the parotid glands was assessed by the net uptake ratio (ratio of maximum count and the count at 60 seconds) and the maximal count time (time at which the maximum count was reached). These results were referenced to a prior study which defined the range of values in a group of healthy controls (J Nuc Med 1998; 39:1260). The slopes of the time-activity curves to the point of maximal counts were assessed by linear regression.

Results: The mean slopes of radiotracer uptake were 1.03 ± 0.7 counts/sec and 0.97 ± 0.7 counts/sec respectively for the left and right parotid glands of the SS patients and 3.36 ± 2.7 counts/sec and 3.17 ± 0.98 counts/sec respectively for the left and right parotid glands of the sicca control patients. These differences were statistically significant for the left parotid gland (p=0.023, Student t-test) and trended to significance for the right parotid gland (p=0.0548). A slope value of 1.6 counts/sec best differentiated the two groups. Thus, the initial slope for radiotracer uptake was less than 1.6 counts/sec for 8/10 left parotid and 9/10 right parotid scans of the SS patients and more than 1.6 counts/sec for 8/10 left parotid and 8/10 right parotid scans of the sicca controls. Using a published range of values for normal individuals, the net uptake ratios were more than 2 standard deviations from the norm for 8/10 left parotid and 6/10 right parotid scans in the sicca controls and 10/10 left parotid and 9/10 right parotid scans for the SS patients.

Conclusion: Measurement of the initial slope of radiotracer uptake by the parotid glands provided better differentiation of SS from sicca control patients than assessment of net uptake ratios. This observation suggests that the same slope calculation in a group of healthy controls would yield a more narrow range of normal values for radiotracer uptake in parotid scintigraphy and increase the clinical utility of the test.

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Diagnostic Validity of Major Salivary Gland Ultrasonography for Sjogren's Syndrome: Echostructure, Gland Size and Döppler Waveform Analysis. Divi Cornec[1], Sandrine Jousse-Joulin[2], Alain Saraux[1], Luc Bressollette[1], Jacques-Olivier Pers[1], Thierry Marhadour[3], Sylvie Boisramé-Gastrin[1], Pierre Y. Youinou[4] and Valerie Devauchelle-Pensec[5]. [1]Brest Occidentale University, Brest, France, [2]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France, [3]CHU La Cavale Blanche, Brest, France, [4]Brest Univ Medical School, Brest, France, [5]Brest University Medical School, Brest, France

Background/Purpose: Primary Sjögren's syndrome (pSS) is a chronic auto-immune disorder affecting primarily exocrine glands. Ultrasonography (US) coupled with power doppler (PD) is a simple and non-invasive tool, which can be used to assess major salivary gland changes during pSS. Our objective was to define diagnosis performance of US PD in patients suspected for pSS.

Methods: 147 patients with suspected pSS (sicca, parotidomegaly or suggestive extra-glandular features) were prospectively included between

2006 and 2011. Mean age was 57.1±12.7 years, female percentage 91.2%, and mean duration of the symptoms 6.6±6.7 years. 60 patients fulfilled 2002 AECG criteria and were considered as pSS. The other diagnoses were idiopathic sicca (n=54), secondary SS (n=14), drug-induced sicca (n=15) and diabetes (n=4). US was performed in all patients by the same experienced operator, who was blinded to the diagnosis. Both bilateral parotid and submandibular glands were examined. The echostructure of each gland was quoted on a 0–4 scale as previously published, and the maximal score for each patient was considered for analysis, as well as the 0–16 sum of the scores of the 4 glands. Parotid length and width were measured in longitudinal and transversal planes, and submandibular glands in longitudinal plane. The surface of the glands was measured drawing the outlines on the screen, and calculated with the following formula: length*width/2. Parotid blood flow was studied through Döppler waveform analysis of the transverse facial artery, without and during stimulation with lemon juice. Resistive index (RI) was computed as the difference between peak systolic and end-diastolic velocities over the peak systolic velocity.

Results: The mean echostructure score sum was significantly higher in the pSS group than in the non-pSS (6.78±5.79 vs 1.58±3.4, p<0.001). Using ROC curve analysis, we determined ≥5/16 as the ideal cut-off, with 55.0% sensitivity (Se) and 88.6% specificity (Sp). However, the ROC curve of the maximal score of a single gland was very similar, and a cut-off ≥2/4 led to 60.0% Se and 85.2% Sp. The correlation coefficients between the echostructure of the different glands in a given patient were high: right vs left parotid (0.95), right vs left submandibular (0.97), right parotid vs submandibular (0.78), left parotid vs submandibular (0.80). All measures of parotid size were similar between the 2 groups, but the calculated surface of the submandibular glands was significantly lower in pSS patients (1.47±0.68 cm^2 vs 1.66±0.56, p=0.005 for the right side, and 1.47±0.61 vs 1.59±0.60, p=0.047 for the left side). No differences were found between the 2 groups concerning pre- and post-stimulation RI.

Conclusion: The assessment of major salivary gland echostructure represents a non-invasive and easy-to-perform tool for the diagnosis of pSS with good sensitivity and specificity, and should be included in future diagnostic criteria of pSS. Other measurements, including gland size and Döppler analysis of arterial flow, seem to be of less interest.

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Nailfold Capillary Changes in Patients with Primary Sjogren's Syndrome: Comparison to Controls. Richa Mishra[1], Anupama Shahane[1], Liang Wu[2] and Frederick B. Vivino[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]Penn Presbyt Med Ctr, Philadelphia, PA

Background/Purpose: Nailfold capillaroscopy is a reliable way to distinguish between primary Raynaud's phenomenon (RP) and secondary RP associated with systemic sclerosis (SSc). It's role in the diagnosis of Sjögren's syndrome has not been well characterized. Purpose of this study was to assess prevalence of nailfold capillary changes in patients (pts) with primary Sjögren's syndrome (PSS), non autoimmune sicca controls (chronic sialadenitis) and healthy normal controls, which will help us to determine the utility of this technique for the diagnosis of PSS.

Methods: This prospective study was conducted on pts who met the American European Consensus Group (AECG) criteria (Vitali et al, 2002) for PSS (n=61), pts with biopsy proven chronic sialadenitis (n=6) and healthy normal controls (n=35). Healthy normal controls included patients with no sicca symptoms or history of autoimmune disease. Patients with diagnosis of secondary SS were also excluded. All participants filled out medical questionnaires to determine the prevalence of RP, risk factors for cardiovascular disease and other comorbidities. Using a stereo dissecting microscope nailfold capillaries of the 2nd to 5th fingers bilaterally were examined under controlled environmental conditions, photographed and scored.

A semiquantitative rating scale to score each capillary abnormality was adopted (1= Normal, 2= Dilatation >20 and < 50 micrometer, 3= Dilatation >50 micrometer, 4= Hemorrhage, 5= Drop out, 6= Neoangiogenesis). The scores for the eight digits were added together and divided by eight to calculate the total mean capillary score.

Results: A total of 111 patients were included in the study. Nailfold capillaroscopy photmicrographs of 102 patients were analyzed and 9 patients had be excluded because of poor picture quality due to dark skin. Eighty seven % of patients were female.

Table 1.

	Primary Sjögren's syndrome		Chronic sialadenitis		Controls	
	RP+	RP−	RP+	RP−	RP+	RP−
No. of pts	25	36	1	5	2	33
Mean Total Score (±SD)	31 (±10)	28.38 (±11)	14	22 (±12)	19 (±2)	13.27 (±9)
Mean Total Score of the Group (±SD)	29.45 (±11)		20.6 (±12)		13.6 (±9)	

Patients with PSS had the highest prevalence of RP among all 3 groups and significantly higher mean total capillaroscopy scores compared to healthy controls (p <0.0001) and pts with chronic sialadenitis (p = 0.07). The most common abnormality in PSS was capillary drop out.

Conclusion: The prevalence and severity of nailfold capillary changes in pts with PSS is significantly higher than that of nonautoimmune sicca pts and healthy controls. Capillary changes may occur in the presence or absence of RP. These results suggest that diagnostic sensitivity of AECG classification criteria or other criteria sets for PSS could be further improved by addition of simple variable like nailfold capillaroscopy scores.

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A Step Toward New Diagnostic Criteria in Sjögren's Syndrome: Contribution of Major Salivary Gland Ultrasonography and Blood B-Cell Subset Profiling. Divi Cornec[1], Alain Saraux[1], Sandrine Jousse-Joulin[2], Thierry Marhadour[3], Jacques-Olivier Pers[1], Beatrice Cochener[1], Pierre Youinou[1] and Valerie Devauchelle-Pensec[4]. [1]Brest Occidentale University, Brest, France, [2]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France, [3]CHU La Cavale Blanche, Brest, France, [4]Brest Occidentale university, Brest, France

Background/Purpose: The clinical diagnosis of primary Sjögren's Syndrome (pSS) is mainly based on the AECG classification criteria, published in 2002. They do not include salivary gland ultrasonography (SGUS) and B-cell subset profiling, which have recently shown promising performance for the diagnosis of pSS. The aim of this prospective study was to determine their diagnostic value, and to suggest modifications of the classification criteria.

Methods: This study was conducted in a prospective monocentric cohort of patients with suspected pSS (sicca symptoms, parotidomegaly or extraglandular manifestations suggestive of pSS), included between 2006 and 2011. Clinical examination, basic biology, immunological tests and minor labial salivary gland biopsy (SGB) were performed systematically. SGUS was standardized and performed on bilateral parotid and submandibular glands, and their echostructure was quoted on a scale between 0 and 4, as previously published. The maximal score of one of the glands was considered for analysis. For blood B-cell subset profiling, the ratio (Bm2+Bm2')/(eBm5+Bm5) was determined using flow cytometry. A ratio ≥5 has been shown suggestive of pSS. The gold standard for the analysis was a clinical diagnosis of pSS performed by a group of experts blinded to the results ultrasonograophy and Blood B cells.

Results: 185 patients have been included in the study (mean age 56.5±12.9 years, symptoms duration 6.4±6.7 years, 91.4% females). 78 patients had pSS, of whom 62 (79.5%) fulfilled AECG criteria. Other diagnoses were idiopathic sicca (n=54), secondary SS (n=27), drug-induced sicca (n=22) and diabetes (n=4). No differences were found between the 2 groups concerning age, disease duration, and sex ratio. All items of AECG criteria were significantly associated with the diagnosis of pSS. SGUS was performed in 147 patients. ROC analysis determined an ideal cut-off of ≥2 on the 0–4 scale, for a 63.0% sensitivity (Se) and a 97.3% specificity (Sp). 37/72 pSS and 17/98 non-pSS patients had a (Bm2+Bm2')/(eBm5+Bm5) ratio ≥5. The sensibility of this test was 51.4% for a 82.7% specificity. Higher cut-off led to an increased Sp but a lower Se (≥6.5: Se 40.3%, Sp 92.9%; ≥9: Se 26.4%, Sp 98.0%). Logistic regression analysis selected only 5 items independently predictive of pSS diagnosis: xerostomy, Schirmer test, SGB, SSA/SSB positivity and SGUS. A weighted score was constructed using these variables: (Xerostomy × 2) + Schirmer + (SGB × 2) + (SSA/SSAB × 2) + SGUS. After ROC analysis, we found that a score ≥5/8 had a 84.9% Se and a 97.2% Sp, compared to 79.5% and 98.6% for AECG criteria. The area under the ROC curve of our criteria was higher than of AECG criteria (0.966 vs 0.891).

Conclusion: In this study, B-cell subset profiling was suggestive of pSS, but was not independent from other items. SGUS has an important diagnostic value for pSS, and modifications of AECG criteria including this item notably improve their diagnostic performance. The diagnostic value of such criteria have to be confirmed in other studies.

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High Risk of Human Papillomavirus Type 58 Infections and of Cervical Squamous Intraepithelial Lesions in Sjogren 's Syndrome Patients. Miansong Zhao Sr. Beijing Shijitan Hospital,Capital Medical University, Beijing, China

Background/Purpose: To determine rates of human papillomavirus (HPV) infections, abnormal cervical smears, and squamous intraepithelial lesions (SIL) among women with Sjogren 's syndrome.

Methods: We investigated 35 women with Sjogren 's syndrome.

71 with abnormal smears from colposcopy clinics, and 20 community subjects with normal smears. Polymerase chain reaction results for viral DNA and HPV-58 sequencing data were correlated to cytology and colposcopic findings. Ethical permission for this investigation was provided by the Research Ethics Committee of Beijing Shijitan Hospital-,Capital Medical University.

Results: Sjogren 's syndrome and colposcopy patients were more likely (P <0.05) to be HPV positive (20[57%] and 39 [55%] patients, respectively) and HPV-58 DNA positive (22 [63%] and 23 [33%] patients, respectively) than community subjects (0% HPV DNA positive and 0 [0%] HPV-58 DNA positive).Sjogren's syndrome patients were also more likely to be HPV-58 DNA positive than colposcopy patients (P <0.05). Sjogren's syndrome patients with a high HPV-58 viral load more frequently had SIL (n=6) than those with a low HPV-58 viral load (n=1; P <0.05). HPV and HPV-58 DNA positivity were not associated with previous or current drug therapy for Sjogren 's syndrome patients.

Conclusion: Women with a Sjogren 's syndrome diagnosis had elevated levels of HPV infections, abnormal cervical cytology, and SIL.

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Monoclonal Gammapathy Is Associated with Ten-Fold Risk of Hematologic Disorders in Primary Sjögren Syndrome. Anne-Laurence Tomi[1], Raphaèle Seror[2], Stephan Pavy[3], Corinne Miceli-Richard[4] and Xavier Mariette[5]. [1]Bicetre university hospital, Le Kremlin-Bicêtre, France, [2]Bicetre university hospital, LE Kremlin-Bicetre, France, [3]Hopital Bicetre, Paris, France, [4]Hopital Bicêtre, Le Kremlin Bicêtre, France, [5]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: To assess the relationship between the presence of monoclonal gammapathy (MG) and incidence of hematologic disorders in primary Sjögren Syndrome (pSS).

Methods: Three hundred fifty-two pSS patients (from the cohort followed in the Department of Rheumatology of Bicêtre Hospital between 2000 and 2008) according to the 1993 European Classification Criteria were screened for the presence MG using immunofixation technique; 15 (4,3%) had lymphoma and 6 (1,7%) had multiple myeloma (MM). Each patient with MG was paired with 2 age and sex matched pSS controls. Clinical characteristics of patients with and without MG were compared in univariate and multivariate analyses to look for factors associated with MG. The frequency of malignant hematologic disorders was compared between these 2 groups. Also, serum BAFF levels will be measured using ELISA (R&D Systems, Minneapolis, Minnesota) and compared.

Results: Twenty-six (7,4%) patients had MG (88% female, median age of 66,0 [IQR=56,5–76,5] years, median disease duration of 7,8 [IQR=3,1–12,7] years, 85% with sialadenitis [Focus score >1], 69% had anti-Ro/SSA and/or anti-La/SSB antibodies). The MG were Ig G kappa (32%), Ig G lambda (20%), Ig M kappa (16%), Ig M lambda (12%), Ig A kappa (4%), biclonal gammapathy (16%).

Compared with the 52 matched controls, cutaneous involvement (p=0,011), high LDH level (p=0,044), cryoglobulinaemia (p=0,003), low C4 level (p=0,027), and higher gammaglobulin level on serum protein electrophoresis (p=0,037) were significantly associated with the presence of MG in univariate analysis. Multivariate analysis only retained low C4 (aOR= 0.46 per 0,1 unit ;p=0.039) and higher gammaglobulin level (aOR= 1.21 [1,05–1,41]; p=0,011).

Overall, 10 (38,5%) patients with MG had malignant hematologic disorders (4 lymphomas: 1 mantle cell, 1 marginal zone, 1 lymphocytic, 1 hepatic MALT and 6 MM: 4 stage III and 2 stage I) compared with 3 (1 marginal zone lymphoma, 1 ocular MALT lymphoma, 1 chronic lymphoid leukemia) in the control group (p=0,001). At screening, in the MG group, 6 (all the 4 lymphomas and 2 MM) of the 10 hematological disorders were previously known; the 4 remaining MM have been diagnosed during the follow-up upon an increase of the M-component (n=2), appearance of cytopenia (n=1) or bone lesions (n=1) (median follow-up of patients with MG= 4,6 [IQR=1,8-8,1]years). The 3 lymphoid malignancies of the control group have been previously diagnosed and no relapse or new hematologic malignancy was diagnosed during the follow-up (median follow-up= 3,4 [IQR= 0–5,8]years). The frequency of MM in the MG group was significantly higher than in the non MG group (p=0.001). The overall risk of hematologic disorders was estimated: OR=10.21 [2.18–54.22].

The results of the comparison of BAFF levels will be presented at the meeting.

Conclusion: In this cohort, 1.7% of patients with pSS developed MM, supporting the fact that beyond the well-known risk of lymphomas, there is also an increased risk of MM in pSS. MG is a strong risk factor of lymphomas but also MM. Patients with MG should therefore be screened and also carefully followed to look for the presence or emergence of both lymphomas and multiple myelomas.

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Follow up of Primary Sjögren Syndrome Patients Presenting Positive Anti-Cyclic Citrullinated Peptides Antibodies. Yang-Seon Ryu[1], Eun-Ji Kim[1], Ji-Min Kim[1], Jennifer Lee[1], Seung-Ki Kwok[1], Ji Hyeon Ju[2], Sung Hwan Park[3] and Ho-Youn Kim[2]. [1]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul, South Korea, [3]Rhematism Research Center, Seoul, South Korea

Background/Purpose: Anti-cyclic citrullinated peptide antibodies(anti-CCP antibodies) are very useful for the diagnosis of rheumatoid arthritis(RA) and associated with articular erosions. The specificity of anti-CCP antibodies in the diagnosis of RA was reported about 97.4%. Because of its higher specificity to RA, we assessed of clinical features in primary sjögren syndrome patients presenting positive anti-CCP antibodies.

Methods: We conducted a retrospective medical record review of 405 patients who were diagnosed primary primary sjogren syndrome at the first visit in the rheumatology department of Seoul St. Mary's Hospital between June 1996 and June 2011. Patients fulfilled the 2002 American-European consensus group revised criteria for primary sjogren syndrome. An anti-CCP antibody ELISA was performed according to manufacturer's instructions with the cutoff at 20 units. We have followed up 37 of 405(8.9%, mean age 54±10.9 years) patients who initially presented positive anti-CCP antibodies. Presence of arthritis were evaluated by ultrasonographic findings, x-ray and physical examination about swelling, tenderness.

Results: We analysed of 405 patients who were diagnosed primary sjogren syndrome at the first presenting signs, 38 of 405(8.9%) patients were positive anti-CCP antibodies and there was close relationship between anti-CCP antibodies level and arthritis. Its Pearson's correlation coefficients was 0.416(P<0.001). And then we analysed correlation coefficient of rheumatoid factor titer and arthritis, that was shown 0.194(P<0.001). It seemed like anti-CCP antibodies had higher association with arthritis than rheumatoid factor titer in primary sjogren syndrome patients. But 405 primary sjogren syndrome patients have observed, 50(12%) patients have progressed to secondary sjogren's syndrome. 30(7.2%) patients have been progressed to RA who fulfill the 2010 ACR criteria for RA. Patients who have been progressed to RA, their mean duration of progression to RA was 49±31.1 months. 5(16%) of 30 patients were negative anti-CCP antibodies, 23(76.7%) of 30 patients were positive anti-CCP antibodies, 2(6.7%) were not checked. Comparing two goups of progressed RA and not progressed RA whithin positive anti-CCP antibodies patients who were diagnosed primary sjogren syndrome at the first presenting signs, the mean duration of observed was shown shorter, 49±31.1 months to 29±27 months.

Conclusion: There was close relationship between anti-CCP antibody titer and arthritis in primary sjogren syndrome patients. But we have followed up primary sjogren syndrome patients who was positive anti-CCP antibody. About 49 months later, 23(76.7%) patients were progressed to RA who had originally been diagnosed primary sjogren syndrome. Testing for anti-CCP antibodies in primary sjogren syndrome patients presenting arthritis allows the prediction of progression to RA.

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Low Levels of Vitamin-D are Associated with Neuropathy and Lymphoma Among Patients with Sjögren's Syndrome. Nancy Agmon-Levin[1], Howard Amital[2], Athanasios G. Tzioufas[3], Marcus López Hoyos[4], Blaz Rozman[5], Shaye Kivity[1], Ilan Ben Zvi[1], Inga Efes[1], Yinon Shapira[1] and Yehuda Shoenfeld[6]. [1]Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, Tel-Hashomer, Israel, [2]Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, Tel-hashomer, Israel, [3]Medical School-Univ of Athens, Athens, Greece, [4]Servicio Inmunología Hospital Universitario Marqués de Valdecilla Santander Spain, Santander, Spain, [5]University Medical Centre, Ljubljana, Slovenia, [6]Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, Ramat Gan, Israel

Background/Purpose: Primary Sjögren's syndrome (SS) is a chronic autoimmune disease primarily involving the exocrine glands. SS clinical picture ranges from exocrinopathy to systemic disease affecting the lung, kidney, liver, skin, musculockeletal and the nervous system. The morbidity of SS is mainly determined by extraglandular disease and increased prevalence of lymphoma[1]. Environmental and hormonal factors, such as vitamin-D may play a role in the pathogenic process and disease expression[2]. Thus, we aimed to evaluate the association between vitamin-D concentrations and the manifestations of SS.

Methods: Vitamin-D levels were determined in 176 SS patients and 140 matched healthy volunteers utilizing the Liaison chemiluminescent immunoassays (DiaSorin-Italy), and correlated with clinical and serological manifestations of SS.

Results: Vitamin-D levels were comparable between SS patients and control 20.5±10ng/ml and 21.6±10ng/ml respectively. Peripheral neuropathy or neuropathic pain were diagnosed in 23% of patients and associated with lower vitamin-D levels (18.6±5.5ng/ml vs. 22.6±8ng/ml (p=0.04)). Lymphoma was diagnosed in 4.3% of SS patients that showed vitamin-D deficiency 13.2±6.25ng/ml as compared with SS patients without lymphoma (22±8 ng/ml; p=0.03). Other clinical and serological manifestations did not correlate with vitamin-D status.

Conclusion: In this study, low levels of Vitamin-D correlated with the presence of peripheral nerve involvement and lymphoma among SS patients. The link between vitamin-D neuropathy and lymphoma was reported in other conditions, and may support a role for vitamin-D in the pathogenesis of these processes as well as a beneficial effect for vitamin-D supplementation.

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A High-Density Genome-Wide Association Study by the Sjögren's Genetics Network Identifies Five Novel Susceptibility Loci for Primary Sjögren's Syndrome and Confirms Association with *MHC, IRF5,* and *BLK*. Christopher J. Lessard[1], John A. Ice[1], Indra Adrianto[1], Jennifer A. Kelly[1], Roland Jonsson[2], Gabor G. Illei[3], Maureen Rischmueller[4], Gunnel Nordmark[5], Xavier Mariette[6], Corinne Miceli-Richard[6], Marie Wahren Herlenius[7], Torsten Witte[8], Michael T. Brennan[9], Roald Omdal[10], Timothy J. Vyse[11], James A. Lessard[12], Wan-Fai Ng[13], Nelson L. Rhodus[14], Barbara M. Segal[15], R. Hal Scofield[1], Benjamin A. Rybicki for ACCESS[16], Juan-Manuel Anaya[17], John B. Harley[18], Courtney G. Montgomery[1] and Kathy L. Moser[19]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Bergen, Bergen, Norway, [3]NIDCR/ NIH #10 1N110, Bethesda, MD, [4]Queen Elizabeth Hospital, Adelaide, Australia, [5]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden, [6]Bicêtre University Hospital, Le Kremlin Bicêtre, France, [7]Karolinska Institute, Stockholm, Sweden, [8]Hannover Medical School, Hanover, Germany, [9]Carolinas Medical Center, Charlotte, NC, [10]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway, [11]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [12]Valley Bone & Joint Clinic, Grand Forks, ND, [13]Musculoskeletal Research Group Institute of Cellular Medicine, Newcastle University, Newcastle, England, [14]University of Minnesota, Minneapolis, MN, [15]Hennepin County Medical Center, Minneapolis, MN, [16]Henry Ford Hospital, Detroit, MI, [17]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [18]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [19]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Sjögren's syndrome (SS) is a clinically heterogeneous autoimmune disease characterized by exocrine gland dysfunction that involves both innate and adaptive immune responses. A complex genetic architecture has been hypothesized; however, genetic studies to date have been primarily limited to candidate gene studies. We used high-density genotyping arrays to perform a genome-wide association scan (GWAS) in an unbiased manner to identify SS susceptibility loci.

Methods: We have established the Sjögrens Genetics Network (SGENE) to assemble a large cohort of samples for large-scale genetic studies. We used the Illumina OMNI1-Quad arrays containing >1.1 million variants in a discovery cohort of 424 European-derived SS cases and 728 healthy controls. Stringent quality control criteria, adjustments for population stratification, and standard GWA statistical methodologies were used to compare allele frequencies between cases and controls. A total of ~774,000 single nucleotide polymorphisms (SNPs) were tested for association to SS in our final GWA dataset (P_{omni}). A secondary analysis was performed using data from 1398 additional controls from the Illumina iControl database typed on the HumanHap 550 with ~289,000 SNPs in common with the OMNI1-Quad. For replication, we used a DNA pooling approach in an independent collection of 450 cases and controls of European descent, and also genotyped using the OMNI1-Quad arrays (P_{pool}). Weighted Z-scores were used to determine meta-P-values for combined discovery and replication data (P_{meta}).

Results: The most significantly associated region with risk of SS was the major histocompatibility complex (MHC), with 1304 SNPs exceeding a genome-wide significance threshold of 5×10E-8. The peak association was observed in HLA-DRA within P_{omni}=1.68×10E-23 and replicated with P_{pool}=8.47×10E-5, leading to a P_{meta}=6.92×10E-29. Additional results across the extended MHC support association with multiple loci throughout this region. Evidence for novel genetic associations outside of the MHC were also observed. A SNP between PIK3R1 and SLC30A5 was found to be associated with SS in both the discovery and replication cohorts resulting in P_{meta}=7.55×10E-8. Association (P_{meta}<10E-5) with SS was also identified with SNPs in or near CTNNA2, VASP, FGFR1OP2, and LCK. In addition, we observed association with SNPs previously implicated as risk factors for SS, including IRF5 (P_{meta}=2.66×10E-8) and BLK (P_{meta}=6.66×10E-5).

Conclusion: We have performed the first GWAS in SS, and have identified PIK3R1/SLC30A5, CTNNA2, VASP, FGFR1OP2, and LCK as putative risk loci. We have also confirmed associations previously reported with MHC, IRF5, and BLK. Currently, we are genotyping ~1500 SNPs in >3200 subjects to replicate additional effects observed in the discovery phase.

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Sympathetic and Parasympathetic Abnormalities in Primary Sjögren's Syndrome (pSS) Patients Assessed in Outpatients Using Real-Time Digital Autonomic Nervous System (ANS) Monitoring. Nikolay P. Nikolov[1], Stanley R. Pillemer[1], Vladimir Bakalov[2], Lolita Bebris[1], Joe Colombo[3] and Gabor G. Illei[1]. [1]NIDCR/NIH, Bethesda, MD, [2]NIH, Bethesda, MD, [3]Ansar Medical Technologies, Inc, Philadelphia, PA

Background/Purpose: Autonomic nervous system (ANS) function abnormalities have been reported in pSS and may be important in pathogenesis of the disease. The aim of this study was to evaluate cardiovascular (CV) ANS function in pSS by ambulatory real-time digital monitoring.

Methods: Standardized ambulatory ANS testing was done on 109 consecutive pSS patients and 34 age- and sex-matched adult healthy volunteers (HV) using ANX 3.0 (ANSAR, Inc.). Caffeine and ANS active medications were not allowed on the testing day. Beat-to-beat heart rate, brachial blood pressure, and respiratory activity (RA) were recorded at 5 min baseline (BL), sitting and in response to reflex CV challenges of deep breathing (DB) at 6 breaths/min, Valsalva maneuver (VM) and standing for 5 min. Heart rate variability (HRV) was assessed by time-domain and statistical analyses. ANS activity was assessed by combined spectral analysis of HRV and RA to account for vagal (parasympathetic) control of respiration and expressed as inspiration:expiration (I:E) Ratio, Valsalva Ratio and 30:15 Ratio, CV responses to DB, VM, and standing respectively. Sympathetic/Parasympathetic (S/PS) balance was computed as the

ratio of low frequency area (LFa) and high frequency area (RFa) that are measures of S and PS activity respectively. Statistical analysis was performed using non-parametric ANOVA testing and regression models (SAS, Inc).

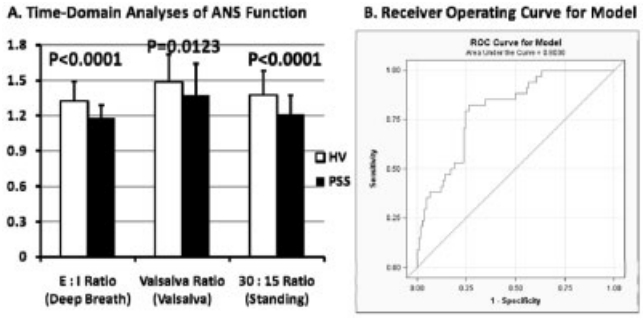
Results: Small significant differences in HRV between HV and pSS were seen for the three main time-domain analysis variables I:E Ratio, Valsalva Ratio, and 30:15 Ratio, (Figure 1A) indicating low cardiovagal tonus.

Both S (LFa) and PS (RFa) CV responses to DB, VM, and Standing challenge were significantly lower in pSS compared with HV (Table 1) while maintaining the S/PS balance (LFa/RFa Ratio).

Table 1. Spectral Analyses, Change from Baseline

	HV (n=34)	PSS (n=109)	Wilcoxon Test, p value
LFa (Sympathetic Function)			
Deep Breathing	6.39	1.55	0.0012
Valsalva	52.75	32.08	NS
Standing	3.45	1.45	0.0117
RFa (Parasympathetic Function)			
Deep Breathing	42.7	15.92	0.0351
Valsalva	5.15	3.32	0.0077
Standing	0.65	−0.04	0.0047

Further, E:I and 30:15 ratios were independently predictive of the diagnosis of pSS by a logistic regression model, also reflected by the area under the receiver operating curve=0.8030 (Figure 1B).



Conclusion: ANS function testing in pSS outpatients identified abnormalities in both S and PS CV function that may reflect a primary failure in one and compensatory decreased output in the other. Unexpectedly, the E:I and 30:15 ratios were found to independently predict the diagnosis of pSS in this cohort that warrants further study.

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Fine Specificity of Antibodies Against Ro52, Ro60, and La Antigens in Sjögren's Patients with Neuropathies and Demyelinating Syndromes. Julius Birnbaum, Livia Casciola-Rosen, Laura Gutierrez and Alan N. Baer. Johns Hopkins University, Baltimore, MD

Background/Purpose: The respective association of neuropathies and demyelinating manifestations in Sjögren's patients with fine antibody specificities against Ro52, Ro60, and La antibodies has not been rigorously assessed. Knowledge of such antibody associations might suggest different immunologic signatures. We therefore sought to compare patterns of antibody specificities for Sjögren's patients with or without neurological complications. We also evaluated patterns and predictors of misclassification, by measuring the clinical laboratory assignment of antibody status, against a "gold standard" of fine antibody specificity assessed by ELISA (for Ro52 and La antibodies), and by immunoprecipitation (for Ro60 antibodies).

Methods: In sera from a prospectively evaluated Sjögren's cohort of 83 patients enriched with neurological disease, Ro52 and La antibodies were assayed using a commercially available ELISA kit (INOVA Diagnostics). 35S-methionine labeled Ro60 was generated from cDNA by in-vitro transcription translation (IVTT) using a commercially available kit (Stratagene). Ro60 antibodies were assayed by immunoprecipitation using 35-S methionine labeled Ro60 generated by IVTT as source material.

Results: There were 19 patients with demyelinating disease (8 patients with Neuromyelitis Optica/NMO), 43 patients with peripheral neuropathies (2 of whom also had demyelinating disease), and 23 "glandular" patients without demyelinating or peripheral neuropathy syndromes. Ro52 or Ro60 antibodies were detected in 100% (8/8) NMO patients, versus 60.9% (14/23) "glandular" patients (p=0.04), versus 65.1% [28/43] neuropathy patients. 85.7% (12/14) "glandular" Sjögren's patients had antibodies concomitantly targeting Ro52 and Ro60, whereas 45.4% (20/44) patients with neurological disease of either subtype had isolated antibody specificities which separately targeted either Ro52 or Ro60 (p=0.04). Antibodies against La were found less frequently in patients with neuropathies and demyelinating syndromes (21.7%, 13/60), compared to "glandular" disease (43.4%, 10/23, p=0.05). The sensitivity/specificity for the commercial laboratory assessment of Ro antibody status (against the "gold standard" assessing for *either* Ro52 or Ro60 by ELISA or immunoprecipitation) was 67.2%/96.0%, with a kappa of 0.52. The sensitivity/specificity for the commercial laboratory assessment of La antibody status (against the gold standard of La by ELISA) was 54.5%/80.4%, with a kappa of 0.35.

Conclusion: "Glandular" Sjögren's patients have antibody specificities usually directed against Ro52 **and** Ro60, whereas patients with neurological disease may have antibodies directed against **either** Ro52 **or** Ro60. NMO in Sjögren's disease is strongly associated with Ro52 and/or Ro60 antibodies. The high misclassification rate of Ro and La antibody status may contribute to the underdiagnosis of Sjögren's in patients with demyelinating syndromes and neuropathies, and may justify inclusion of fine Ro52, Ro60, and La antibody specificities even in routine clinical practice.

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Salivary Genomic Biomarkers for Primary Sjögren's Syndrome: Correlation with Minor Salivary Gland Lymphocyte Focus Score and Serum Interleukin-17, 21, 23 Level. Sung-Hoon Park[1], Ji Hun Kim[1], Seong-Kyu Kim[2], Jung-Yoon Choe[3], Sang-Hyon Kim[4] and Ji-Yoon Kim[5]. [1]Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegu, South Korea, [2]Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegue, South Korea, [3]Arthritis and Autoimmunity Research Center, Catholic university of Daegu, School of mediine, Daegu, [4]Dongsan Medical Center, Keimyung University, Daegu, South Korea, [5]Dongsan Medical Center, Keimyung University, School of medicine, Daegu, South Korea

Background/Purpose: To evaluate the expression level of salivary FCGR3B, GBP-2, GAPDH mRNA in primary Sjögren's syndrome(pSS) and to investigate its correlation with minor salivary gland lymph focus score-(LFS) and serum Interleukin(IL)-17, 21, 23 Level.

Methods: Saliva samples were collected from 8 female patient with pSS(age = 38 ~ 55, mean ± SD = 46.13±6.01) and healthy female controls(age = 33 ~ 45, mean ± SD = 39.75 ± 5.12) using our standardized saliva collection protocols for comparative analysis. Subject should refrain from eating, drinking, or oral hygiene procedures for at least 1 hour prior to collection. After collection, the saliva samples were immediately mixed with RNAprotect Saliva Reagent(Qiagen, Hilden, Germany) to the RNA in the saliva sample was stabilized and then centrifuged at 10,000g for 10 minutes. The supernatant was removed from the pellet, immediately aliquoted, and stored at −80°C. cDNA was synthesized with oligo-d(T), Improm- II TM 5 × reaction buffer, 25mM $MgCl_2$, 10mM dNTP, Improm-II TM reverse transcriptase, 25°C 5min, 42°C 60min, 70°C 15min. cDNAs were analyzed by real time quantitative PCR(RT-PCR) in a Finnzymes DyNAmoTMSYBR green qPCR kit (Finnzymes, Beverly, MA, USA). The primer sequences were FCGR3B forward primer, 5′-CAG TGG TTT CAC AAT GTG AA-3′; FCGR3B reverse primer, 5′-ATG GAC TTC TAG CTG CAC-3′, GBP-2 forward primer, 5′-GGA TAT ATT TGG CCC TTT AGA AGA A-3′; GBP-2 reverse primer, 5′-CTT TTT CCT TTT CTG AGA GTG ACT G-3′, GAPDH forward primer 5′-GAA GGT GAA GGT CGG AGT-3′; GAPDH reverse primer, 5′-GAA GAT GGT GAT GGG ATT TC-3′. The results were analyzed with LightCycler software (Bio-rad).

Results: There was no statistical difference in age between patients and healthy control group. In pSS group, GBP-2 mRNA level was 16.36±35.25 and was significantly correlated with serum IL17 level(94.54±254.65pg/ml, p=0.004) and IL23 level(16.24±22.56pg/ml, p=0.005) by Spearman's

correlation. FCGR3B mRNA level and LFS(3.25±2.55) was not correlated with serum cytokine level. FCGR3B mRNA level was significantly correlated with the patient's age(p=0.003). GAPDH mRNA level was not detectable in the patient group.

Conclusion: GBP-2 mRNA level in saliva of pSS patients was significantly correlated with serum IL17 and IL23 level. Pathophysiologic relevance and possibility of genomic biomarker should be investigated in larger population in the future.

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BLK Polymorphisms Are Associated with Sjogren's Syndrome Only in Patients with Anti-SSA Antibodies. Corinne Miceli-Richard[1], Joanne Nititham[2], Kimberly E. Taylor[3], Céline Verstuyft[1], Laurent Becquemont[1], Ryad Tamouza[4], Xavier Puechal[5], Eric Hachulla[6], Jacques-Eric Gottenberg[7], Lindsey A. Criswell[8] and Xavier Mariette[9]. [1]Hopital Bicêtre, Le Kremlin Bicêtre, France, [2]University of California, CA, [3]University of California, San Francisco, San Francisco, CA, [4]Paris, France, [5]Le Mans General Hospital, Le Mans, France, [6]Internal Medicine, Lille CEDEX, France, [7]Strasbourg University Hospital, Strasbourg, France, [8]University of California San Francisco, San Francisco, CA, [9]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: Primary Sjögren's syndrome (pSS) shares a number of pathogenic mechanisms with systemic lupus erythematosus (SLE), including an IFN type I signature illustrated by genetic association with *STAT4* and *IRF5* in both diseases and involvement of B cells. Polymorphisms of genes involved in B-cell function, such as *BLK,* have been associated with lupus and recently to pSS. Our goal for this study was to determine whether *BLK* polymorphisms are associated with risk of pSS.

Methods: Our study population included 624 pSS patients and 577 control individuals of French Caucasian ancestry. A total of 9 SNPs located within the BLK locus, as well as 48 AIMs (Ancestry Informative Markers), were genotyped among patients and controls. Principal components analysis of the AIM data identified 32 cases and 53 controls with evidence of non-European ancestry and these subjects were removed from subsequent association analyses. Case control association tests were performed among the remaining 592 pSS and 524 controls for the 9 BLK SNPs and tested for independence. Subphenotype analyses were performed to determine whether genetic association results differed substantially according to the presence of anti-SSA auto-antibodies (328 SSA+ and 264 SSA-), systemic manifestations (N=307), cryoglobulinemia (N=60) or lymphoma (N=24).

Results: We observed significant evidence of association with pSS for 3 SNPs within the *BLK* locus. The rs13277113 A allele was the most significantly associated *BLK* variant with an OR of 1.30 (95% CI 1.06–1.58), $p = 9.10^{-3}$. Two other BLK SNPs were associated with pSS: the rs12677843 T allele: OR of 1.29 (95% CI 1.06–1.56), $p = 9.7.10^{-3}$ and the rs2736340 T allele: OR of 1.28 (95% CI 1.05–1.56), $p = 1.2.10^{-2}$. For these 3 SNPs, there were differences between anti-SSA positive and anti-SSA negative patients suggesting that these associations were restricted to anti-SSA positive patients. Comparison of anti-SSA positive patients to controls revealed 2 additional SNPs associated with anti-SSA positive pSS: the rs922483 T allele: OR of 1.28 (95% CI 1.03–1.60), $p = 2.0.10^{-2}$ and the rs12549796 T allele: OR of 1.24 (95% CI 1.01–1.53), $p = 3.7.10^{-2}$. Case-only analyses comparing patients with systemic manifestations, cryoglobulinemia, or lymphoma versus patients without each of these manifestations did not demonstrate significant association. Conditional haplotype analysis suggested that haplotypes comprised of 2 SNPs (rs13277113 and rs1382563) contribute to risk of pSS (p=0.019).

Conclusion: We replicated the study from Nordmark et al (1) and found additional *BLK* SNPs that contribute to the risk of pSS. These results provide an additional example of shared genetic susceptibility to SLE and pSS. BLK is a gene involved in B-cell function and studying functional consequences of these polymorphisms may provide clues to the mechanisms of B cell activation in these 2 autoimmune diseases.

References:

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Interferon-Alpha Activation in Relation to Pro-Inflammatory Cytokines and Anti-Ro/La Response in Primary Sjøgren's Syndrome. Johannes C. Nossent[1], Maureen Rischmueller[2], Andrea Becker-Merok[1] and Sue Lester[2]. [1]University of Tromsø, Tromso, Norway, [2]Queen Elizabeth Hospital, Adelaide, Australia

Background/Purpose: Interferon type I activation is a major pathway in the pathogenesis of systemic autoimmune diseases. While up regulation of type I IFN genes has been described in salivary glands and PBMC, there are few data on circulating IFNa2 in primary Sjøgren's syndrome (pSS). We investigated the frequency, clinical and serological correlates of increased levels of circulating IFNα2 in pSS patients.

Methods: Cross sectional study of patients with established pSS (n= 83). Healthy controls (HC) (n= 27) and patients with Systemic lupus Erythematosus (SLE) (n=87) served as comparators.Cytokine levels were determined on stored sera by a highly sensitive seven-plex bead immunoassay with BAFF measured by commercial ELISA. Associations between increased IFN-a, clinical measures and serological biomarkers were analyzed by nonparametric methods.

Results: IFNα2 was increased in 48.2% of pSS patients versus 64.4% in SLE (p=0.03) and 7.2% in HC (p<0.01). pSS patients with increased IFNα had significantly higher levels of IL-1b, IL-6, IL-10, IL-12, TNFα and GM-CSF, while IL-15 and BAFF did not differ from patients with normal IFNα (51.8%). In pSS patient with increased IFNα2 levels, the mean number of elevated cytokines was five (range 1–8) versus 0.5 (range 0–3) in patients with normal IFNα2 (p<0.001). Increased IFNα2 did not associate with scores for fatigue, sleepiness or urogenital symptoms, low C4 or leucopenia, but was associated with increasing diversity of the anti-Ro/La antibody response (p=0.04 for linear trend) and higher titers of IgG and RF. In the 43 patients with normal IFNα2, there was no activation of other cytokines in 24 (56%) with increased BAFF (30%) and IL-6 (18%) accounting for most cytokine abnormailities in this group.

Conclusion: High circulating levels of IFNα2 are found in nearly half of all pSS patients, where they are accompanied by multiple cytokine activation and a diversified anti-Ro/La response. In the remaining pSS patients cytokine activation is uncommon suggesting a different underlying pathophysiology.

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Cathepsin S Activity Measurements in Tears As a Putative Marker of Sjögren's Syndrome. Jay Zhu[1], Daniel G. Arkfeld[1], W. Stohl[1], Srikanth R. Janga[2], J. Martin Heur[3], John Irvine[3] and Sarah F. Hamm-Alvarez[2]. [1]USC Keck School of Medicine, Los Angeles, CA, [2]University of Southern California School of Pharmacy, Los Angeles, CA, [3]Doheny Eye Institute, Los Angeles, CA

Background/Purpose: Sjögren's syndrome (SjS) is a chronic autoimmune disease characterized by inflammation and destruction of the moisture-producing glands in the body. For 4 million patients in the U.S., this process leads to the landmark symptoms of dry eye and dry mouth as well as many possible systemic complications. Despite the prevalence of SjS, current diagnostic methods remain inexact due to a lack of sensitive and specific testing. It is also difficult to distinguish the autoimmune-mediated keratoconjunctivitis sicca (dry eye) from that associated with other types of dry eye seen extensively in ophthalmology practices. Recent studies performed with non-obese diabetic mice indicated increased expression of the protease, cathepsin S, in the tears and lacrimal glands of this established SjS model[1]. This study seeks to explore the feasibility of measuring cathepsin S (CATS) in the tears of patients as a prelude to exploring its correlation with clinical manifestations of SjS.

Methods: Tears were acquired from 173 patients in an all-comers trial conducted in the USC Rheumatology Clinic and the Doheny Eye Institute Cornea Clinic using extraction onto Schirmer's strips. Tear proteins were eluted from the strips and CATS activity was assayed within 4 hrs. of collection and normalized to sample protein. Control studies indicated there was no loss of catalytic activity during this period.

Results: The average CATS value for all patients in the study was 2142 fluorescence units (FU) per 20 ug of total protein (standard error = 210 FU/20ug protein). The average CATS value for the 8 patients in the study with SjS was 5352 FU/20 ug protein (SE = 1430 FU/20 ug protein), and the average value for all non-SjS patients was 1931 FU/20 ug protein (SE = 198 FU/20 ug protein). This represented a threefold increase for SjS patients over non-SjS patients. The average CATS value for the 57 patients from the rheumatology clinic was 2556 FU/20 ug protein (SE = 410 FU/20 ug protein) while the average CATS value for the 116 patients from the cornea clinic was 1958 FU/protein (SE = 243 FU/20ug protein).

Conclusion: This study shows the feasibility of measuring the enzymatic activity of biomarker proteins in tear samples collected from patients. In particular, they support the potential of CATS as a biomarker indicative of SjS. A new clinical study is ongoing which further explores the validity of this biomarker in a patient population in which SjS patients as well as patients with non-autoimmune keratoconjunctivitis sicca are more extensively represented.

Reference:

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Serum IL-21 Is Increased and Associated with Higher Disease Activity and Higher Serum Levels of Markers of B-Cell Activation in Primary Sjögren's Syndrome. Jacques-Eric Gottenberg[1], Ghada Alsaleh[1], Corinne Miceli-Richard[2], Raphaèle Seror[3], Joelle Benessiano[4], Valerie Devauchelle-Pensec[5], Philippe Dieude[6], Jean Jacques Dubost[7], Anne-Laure Fauchais[8], Vincent Goeb[9], Eric Hachulla[10], Pierre yves Hatron[11], C. Larroche[12], Véronique Le Guern[13], Jacques Morel[14], Aleth Perdriger[15], Xavier Puechal[16], Stephanie Rist[17], Alain Saraux[18], Damien Sène[19], Jean Sibilia[20], Karine Inamo[21], Philippe Ravaud[22] and Xavier Mariette[23]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Hopital Bicêtre, Le Kremlin Bicêtre, France, [3]Bicetre university hospital, LE Kremlin-Bicetre, France, [4]Rheumatology, Paris Unervisity Hospital BICHAT, France, [5]Brest Occidentale university, Brest, France, [6]APHP, Hopital Bichat, Paris, France, [7]CHU Gabriel Montpied, Clermont-Ferrand, France, [8]Hospital, Limoges, France, [9]Rheumatology, Rouen Unervisity Hospital, France, France, [10]Internal Medicine, Lille CEDEX, France, [11]Service de médecine interne, Hôpital Claude Huriez, Université Lille II, Lille, France, Paris, France, [12]Hospital University Bobigny, France, [13]Cochin Hospital, Paris, France, [14]Hopital Lapeyronie, Montpellier, France, [15]Hôpital Sud, Rennes, France, [16]Le Mans General Hospital, Le Mans, France, [17]Hospital University Orléans, France, [18]CHU de la Cavale Blanche, Brest Cedex, France, [19]Pitie-Salpetriere Hospital, Paris, France, [20]Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, Strasbourg, France, [21]Nihon Univ Hikarigoaka Hosp, Nerima-ku Tokyo, Japan, [22]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [23]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: Recent data from animal models and patients with primary Sjögren's syndrome (pSS) suggest that follicular T helper cells (Tfh), which secrete predominantly IL-21, might contribute to the marked B-cell activation observed in pSS. We aimed to investigate serum IL-21 level and its correlation with autoantibody secretion, markers of B-cell activation and disease activity in pSS

Methods: 400 patients with pSS have been included in the 5-year prospective multicenter ASSESS cohort (Assessment of SyStemic features and Evolution of primary Sjögren's Syndrome) since 2006. Clinical data and disease activity using the ESSDAI score have been collected homogeneously. DNA, RNA and serum were collected at inclusion and immediately frozen. Central assessment of serum IL-21 was performed using Ebioscience assay. IL-21 and IL-21R gene polymorphism (rs2221903, rs3093301, rs907715 were genoyped.

Results: Serum IL-21, assessed in 331 patients, was significantly higher in pSS (median: 342 pg/ml, 25^{th}–75^{th}: 181–588) than in healthy controls (82 [55–118] pg/ml, $P< 0.0001$). Patients with either anti-SSA or anti-SSA and SSB antibodies had more frequently detectable IL-21 than patients without anti-SSA nor anti-SSB antibodies (94.9% vs 87.0%, $P= 0.02$). Serum IL-21 was correlated with IgG ($r=0.24$, $P< 0.0001$), kappa ($r= 0.11$, $P= 0.04$) and lambda ($r= 0.15$, $P= 0.006$) free light chains of immunoglobulins, but not with BAFF or beta2-microglobulin. No association was found between IL-21 or IL-21 gene polymorphisms and serum IL-21 level. IL21 was significantly correlated with systemic disease activity assessed by the ESSDAI ($r=0.2$, $P= 0.0009$). In patients with marked systemic disease activity (ESSDAI equal or superior to 7 corresponding to the 75^{th} value of ESSDAI scores of all the patients), serum IL-21 was significantly increased (median 512.6 vs 329.9 pg/ml in patients with ESSDAI<7, $P= 0.009$).

Conclusion: Serum IL-21 level is increased in pSS. This increase is not determined by the assessed gene polymorphisms. The increase of IL-21 is associated with increased systemic disease activity and marked B-cell activation. Targeting IL-21 or follicular T helper cells might therefore represent a promising therapeutic perspective in pSS.

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Gene Expression Profiling in a Cohort of 275 European American Sjögren's Syndrome Patients and Controls. Jennifer A. Kelly[1], Christopher J. Lessard[1], Indra Adrianto[1], John A. Ice[1], He Li[1], Stuart B. Glenn[1], Kimberly Hefner[2], Evan Glenn Vista[3], Donald U. Stone[4], Raj Gopalakrishnan[5], Glen D. Houston[4], David M. Lewis[4], Michael Rohrer[5], Pamela Hughes[5], John B. Harley[6], Courtney G. Montgomery[1], James Chodosh[7], James A. Lessard[8], Juan-Manuel Anaya[9], Barbara M. Segal[10], Nelson L. Rhodus[5], Lida Radfar[4], M. Bart Frank[1], Robert H. Scofield[11] and Kathy L. Moser[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Hefner Eye Care and Optical Center, Oklahoma City, OK, [3]University of Santo Tomas, Taguig City, Philippines, [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]University of Minnesota, Minneapolis, MN, [6]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [7]Harvard Clinical and Translational Science Center, Boston, MA, [8]Valley Bone & Joint Clinic, Grand Forks, ND, [9]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [10]Univ of Minnesota, Minneapolis, MN, [11]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, US Department of Veterans Affairs Medical Center and Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background/Purpose: Sjögren's syndrome (SS) is a progressive, heterogeneous autoimmune exocrinopathy. We chose to perform global gene expression profiling (GEP) in order to better understand the molecular pathways involved in the pathophysiology of SS. We present the largest GEP analysis to date in SS.

Methods: A total of 48803 mRNA transcript levels were measured using the Illumina HumanWG-6 v3.0 Expression BeadChip in 215 European American SS cases and 65 healthy controls. Raw intensity values were background subtracted and probe level analysis was performed using the LUMI package for R. After quantile normalization, Welsh t-tests, q-values (to correct for multiple testing) and fold changes (FC) were calculated. Differentially expressed (DE) genes between cases and controls were selected using 1) maximum expression values > 32, 2) $q<0.05$ and 3) $|FC| >1.25$ or <0.8. Ingenuity Pathway Analysis was utilized to identify canonical pathways among the DE genes.

Results: A total of 1117 genes were DE between SS cases and controls ($7.20\times10E\text{-}24<q<0.05$). Phospholipase A2, group X (PLA2G10) was the most up-regulated gene in SS cases ($FC=84.45$), while transembrane protein 45A (TMEM45A) was the most down-regulated ($FC=-29.17$). Twenty interferon inducible (IFI) genes were among the top 114 DE genes ($q<1\times10E\text{-}10$), of which interferon alpha-inducible protein 27 (IFI27) demonstrated the greatest fold change ($FC=22.4$; $q=1.0\times10E\text{-}17$). Indeed, the top canonical pathway was the interferon signaling pathway,

with 13 of this 34 pathway's genes (38%) DE in our dataset (Fishers p=4.85×10E-12) (Table 1). Another disregulated pathway included genes involved in recognition of bacteria and viruses with 16.9% of this pathway's genes DE in our dataset (Fishers p=3.73×10E-7). Top ranked genes previously implicated in SS included TAP2, an antigen presentation gene reportedly associated with SS in Japanese and Columbian cases (rank 69; q=3.2×10–13; FC=1.44); CXCL10, a Th1-chemokine that regulates immune responses and is up-regulated in SS salivary glands (rank 79; q=1×10E-12;FC=2.69); and MUC1, a human mucin previously found to be associated with dry eyes and dry mouth (rank 104; q=3.66×10E-11; FC=1.54). Common functions observed included cellular movement, growth and proliferation, development, function and maintenance and cellular death. Genes implicated in liver hepatitis as well as cardiac and renal necrosis were also up-regulated in SS cases.

Table 1. Genes in top SS canonical pathways

Pathway	Gene Symbol	Gene Name	Fold Change	FDR q-value
Interferon Signaling	IFIT3	interferon-induced protein with tetratricopeptide repeats 3	3.08	5.82E-19
	OAS1	2',5'-oligoadenylate synthetase 1, 40/46kDa	2.91	2.77E-11
	IFIT1	interferon-induced protein with tetratricopeptide repeats 1	2.89	9.37E-07
	MX1	myxovirus resistance 1, interferon-inducible protein p78	2.49	4.06E-16
	IFI35	interferon-induced protein 35	1.72	1.64E-12
	STAT2	signal transducer and activator of transcription 2, 113kDa	1.60	1.36E-16
	SOCS1	suppressor of cytokine signaling 1	1.58	4.32E-09
	STAT1	signal transducer and activator of transcription 1, 91kDa	1.54	9.13E-18
	BAX	BCL2-associated X protein	1.39	8.49E-04
	JAK2	Janus kinase 2	1.36	3.16E-07
	TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	1.36	1.61E-09
	IRF9	interferon regulatory factor 9	1.33	3.34E-11
	IFITM1	interferon induced transmembrane protein 1 (9–27)	1.30	4.06E-05
Recognition of Viruses and Bacteria	OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa	4.18	1.26E-09
	C1QC	complement component 1, q subcomponent, C chain	2.89	1.97E-05
	OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa	2.15	7.57E-15
	EIF2AK2	eukaryotic translation initiation factor 2-alpha kinase 2	2.05	2.05E-20
	C1QB	complement component 1, q subcomponent, B chain	2.05	1.29E-04
	IFIH1	interferon induced with helicase C domain 1	1.90	1.63E-20
	DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	1.85	1.28E-17
	IRF7	interferon regulatory factor 7	1.85	7.66E-14
	C3AR1	complement component 3a receptor 1	1.77	7.38E-15
	C1QA	complement component 1, q subcomponent, A chain	1.63	5.78E-05
	CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	1.39	2.79E-10
	TICAM1	toll-like receptor adaptor molecule 1	1.31	1.72E-03

Conclusion: The results demonstrate a role for not only innate but also adaptive immunity in SS and overexpression of interferon-related genes continues to play a strong role in this disorder. Additional cellular processes appear to be involved in SS that provide hypotheses to better understand this disorder. Clearly, many of the up-regulated genes are strong candidates for disease biomarkers or susceptibility.

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Cellular microRNAs and Sjögren's Syndrome: Candidate Regulators of Autoimmune Response and Autoantigen Expression. Efstathia K. Kapsogeorgou, Vasiliki C. Gourzi, Nikolaos C. Kyriakidis, Menelaos N. Manoussakis, Haralampos M. Moutsopoulos and Athanasios G. Tzioufas. Pathophysiology Dept, School of Medicine, National University of Athens, Greece, Athens, Greece

Background/Purpose: Sjögren's Syndrome (SS) is characterized by humoral responses against the Ro/SSA and La/SSB ribonucleoproteins, whereas elevated expression of these autoantigens has been described in the salivary glands (SG) and the SG epithelial cells (SGEC) of SS patients. The mechanisms implicated in the regulation of their expression are not defined. Recently, a novel post-transcriptional regulatory mechanism of gene expression, involving small RNA molecules, called microRNAs (miRNAs), has been identified. Deregulated expression of miRNAs has been implicated in the pathogenesis of autoimmune diseases, including SS. Herein, we sought to investigate the role of miRNAs that are predicted to target Ro/SSA and La/SSB autoantigens in SS. Therefore, we studied their expression in SG tissues, SGECs and peripheral blood mononuclear cells (PBMC) of SS patients and controls.

Methods: The miRNAs that target the Ro (Ro52/TRIM21 and Ro60/TROVE2) and La mRNAs were predicted by the miRecords database (http://mirecords.biolead.org), which enables the simultaneous analysis by the 11 most recognized miRNA target prediction programs. The expression of miRNAs was analyzed by real-time PCR in total RNA extracted from SG-tissues, SGECs and PBMC obtained from 14 SS patients and 13 sicca-controls. Statistically significant differences in miRNA expression between SS patients and sicca-controls were evaluated by non-parametric Mann-Whitney analysis.

Results: The miRecords computational analysis identified 430, 1258 and 377 miRNAs that target the Ro52/TRIM21, Ro60/TROVE2 and/or La/SSB mRNAs, respectively. Subsequently, to narrow the number of the miRNAs that target the Ro/SSA and La/SSB mRNAs to an investigable amount, the miRNAS that are predicted to target both Ro (Ro52/TRIM21 and/or Ro60/TROVE2) and La mRNAs, and identified by at least four miRecords-included databases were selected. This approach lead to the identification of eleven miRNAs (let-7b, miR-16, miR-129-5p, miR-153, miR-181a, miR-200b, miR-200b*, miR-223, miR-483-5p, miR-573 and miR-583) that target human Ro/SSA and La/SSB mRNAs. miRs 129-5p, 153, 573 and 583 were not expressed in any of the samples studied, miR-200b* was not found to be expressed in PBMCs. The miRNAs let-7b, miR-16, miR-181a, miR-200b, miR-200b*, miR-223 and miR-483-5p, were expressed in SG tissues, SGECs and PBMCs. Mann-Whitney analysis revealed that miR-181a in SG tissues, miR-200b in SGECs and miR-223 in PBMCs were significantly upregulated in SS patients compared to sicca-controls (mean±SE: 43.89±18.6 *vs* 5.525±1.292, p=0.02, 2426±511.1 *vs* 965±243.3, p=0.03 and 986200±503300 *vs* 50310±13910, p=0.02 in SS *vs* CT, respectively). Finally, down-regulated expression of let-7b mi-RNA was observed in SGECs derived from SS patients that had autoantibodies against Ro/SSA and/or La/SSB proteins compared to negative patients (p=0.02)

Conclusion: Our findings implicate miR-181a, miR-200b, miR-223 and let-7b in SS pathogenesis. However, further functional studies are needed to enlighten the role of the deregulated miRNAs in disease pathogenesis and autoantigen expression.

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Autoantibodies in Primary Sjögren Syndrome Patients Induce Internalization of Muscarinic Type 3 Receptors. Meihong Jin[1], Sung-Min Hwang[1], Alexander J. Davies[1], Yonghwan Shin[1], Jun-Seok Bae[1], Chongho Lee[1], Byoong-Yong Choi[2], Eun Young Lee[2], Yeong Wook Song[2] and Kyungpyo Park[1]. [1]Seoul National University and Dental Research Institute, Seoul, South Korea, [2]Seoul National University Hospital, Seoul, South Korea

Background/Purpose: Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by lymphocyte infiltration into the salivary and lachrymal glands, leading to dry mouth and eyes. The presence of functional autoantibodies against muscarinic type 3 receptor (M3R) in SS has been reported. However, the pathological role of these autoantibodies in the development of SS still remains to be elucidated.

Methods: Purified IgGs were obtained from normal (control) and primary SS patients' sera (pSS IgG). Internalization of M3R and clathrin was analyzed by biochemical assay and immunofluorescence confocal microscopy in human submandibular gland (hSMG) acinar cells. Cytoplasmic free Ca^{2+} concentration ($[Ca^{2+}]_i$) was measured by microspectrofluorimetry.

Results: Incubation of hSMG cells with pSS IgG (1mg/ml) significantly decreased M3R expression levels at the membrane. Carbachol-induced $[Ca^{2+}]_i$ transients (CICTs) in these cells were also inhibited by pSS IgG. In contrast to pSS IgG, control IgG had no effect on both the M3R expression level and CICTs. We found that binding of pSS IgG to M3R induces phosphorylation of M3R, and that pSS IgG-induced M3R internalization is prevented by lysosomal inhibitor, chloroquine. In addition, pSS IgG decreased membrane clathrin expression, which was inhibited by atropine. Our immunofluorescence study further confirmed that pSS IgG induces a co-localization of M3R with clathrin and subsequent internalization of M3R.

Conclusion: pSS IgG induces an internalization of M3R partly through a clathrin-mediated pathway. The results suggest M3R internalization as a potential mechanism to explain the exocrinopathy seen in pSS patients.

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Analysis of M3R Reactive T Cell Epitopes in M3R Induced Autoimmune sialoadenitis. Naomi Matsuo, Hiroto Tsuboi, Mana Iizuka, Yuya Kondo, Isao Matsumoto and Takayuki Sumida. Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan

Background/Purpose: M3 muscarinic acetylcholine receptor (M3R) functions as key receptor for salivary and lacrimal secretion. Recently, M3R has been the focus of our interest for autoantigen of Sjögren syndrome (SS). Our previous studies have shown that Rag1$^{-/-}$mice transferred with splenocytes of M3R$^{-/-}$ mice immunized with M3R peptides mixture (N-terminal, 1st, 2nd, 3rd extracellular loops) developed sialoadenitis like SS (M3R induced autoimmune sialoadenitis; MIS). Moreover, we have shown that M3R reactive T cells play a crucial role in MIS. However, the epitope of M3R reactive T cells remains unclear. This study was carried out to clarify the major T cell epitopes of M3R molecular in MIS.

Methods: 1) M3R$^{-/-}$ mice were immunized with synthesized peptides mixture coding the extracellular domains of murine M3R (N-terminal, 1st, 2nd, 3rd extracellular loops) by intradermal administration. On day 10, these mice were boosted with M3R peptides mixture. On day 20, spleens were isolated from these mice and splenocytes were cultured with each M3R peptide. The cytokines (IL-17, IFN-g and IL-4) production from M3R reactive T cells was measured by ELISA. 2) M3R$^{-/-}$ mice were immunized with M3R 1st extracellular loop peptide alone, which was the candidate for the dominant T cell epitope. On day 10, these mice were boosted with M3R 1st loop peptide. On day 20, spleens were isolated from these mice and splenocytes were cultured with each M3R peptide. The cytokine production from M3R 1st loop reactive T cells was measured by ELISA. 3) The splenocytes of M3R$^{-/-}$ mice immunized with M3R 1st loop peptide were transferred into Rag2$^{-/-}$mice. On day 45 after transfer, Rag2$^{-/-}$mice were sacrificed and the salivary glands were histologically examined by H-E and immunohistochemical stainings. The cervical lymph nodes and splenocytes were cultured with each M3R peptide and the cytokines production from M3R 1st loop reactive T cells was measured by ELISA.

Results

1) The production of IL-17 and IFN-g against M3R 1st extracellular loop in vitro were much higher than that to the other domains of M3R.

2) M3R 1st extracellular loop reactive T cells could produce much more IL-17 and IFN-g but not IL-4.

3) In Rag2$^{-/-}$ mice transferred with splenic T cells immunized with M3R 1st loop developed mild sialoadenitis. M3R 1st extracellular loop reactive T cells in cervical lymph nodes were able to produce IL-17.

Conclusion: We suggested that the major T cell epitope of M3R molecular might be 1st extracellular loop in MIS and IL-17 production may induce autoimmune sialoadenitis.

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The Sjogren's Syndrome-Related Autoantigen Ro52 Is a Pro-Apoptotic Molecule Upon Oxidative Stress. Siti NA Jauharoh[1], Seiji Kawano[1], Jun Saegusa[1], Takeshi Sugimoto[1], Daisuke Sugiyama[1], Osamu Tokuno[1], Chiyo Kurimoto[1], Yumiko Nobuhara[2], Yuji Nakamachi[1], Bambang Ardianto[3] and Shunichi Kumagai[1]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]Saiseikai Nakatsu Hospital, Osaka, Japan, [3]Gadjah Mada University Faculty of Medicine Department of Child Health, Yogyakarta, Indonesia

Background/Purpose: Ro52/TRIM21, is an autoantigen, which has been known to play important roles in the pathogenesis of several systemic autoimmune diseases, such as systemic lupus erythematosus (SLE) and Sjögren's syndrome. Recent studies revealed that Ro52 has an E3 ligase activity and may ubiquitinate cellular, as well as nuclear, proteins important for anti-viral immunity. It has been reported that IFN-a induces Ro52 translocation from the cytoplasm to the nucleus in a p53-dependent manner. We have previously reported that during stress exposure, Ro52 undergoes stimulating agent-specific intracellular translocation.

Methods: In the present study, to investigate the role of Ro52 upon stress exposure, we performed transient transfection with siRNA against Ro52 on HeLa cells. These transfectants were stimulated with H_2O_2, diamide, IFN-α and γ-irradiation, and were then subjected to Annexin-V fluorescent staining and TUNEL assay for apoptosis detection. Furthermore, to elucidate whether the nuclear translocation of Ro52 is required in Ro52-mediated apoptosis, we analyzed the expression of Ro52 protein on the nuclear and cytoplasmic fractions by Western blot analysis.

Results: We found that the Ro52^{low} HeLa cells were significantly more resistant to apoptosis induced by H_2O_2, as well as various other types of stimuli, compared to those of the control HeLa cells. Moreover, we showed that H_2O_2 and IFN-α, but not diamide or γ-irradiation, induced the translocation of Ro52 protein from the cytoplasm to the nucleus.

Conclusion: Our data suggested that Ro52 may be a pro-apoptotic molecule and the nuclear translocation of Ro52 is not necessary in Ro52-associated apoptosis.

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VIP/VPAC System Involved in the Interaction of Primary Sjögren Syndrome Immune Cells and a Human Salivary Gland Epithelial Cell Line. Vanesa C. Hauk[1], Laura Fraccaroli[1], Esteban Grasso[1], Rosanna Ramhorst[1], Alicia Eimon[2], Osvaldo Hubscher[2] and Claudia Perez Leiros[1]. [1]School of Exact and Natural Sciences-CONICET, Buenos Aires, Argentina, [2]CEMIC, Buenos Aires, Argentina

Background/Purpose: Primary Sjögren's syndrome (pSS) is a chronic inflammatory and systemic autoimmune disease with a prevalence of 0.3–0.5%. The clinical hallmark of pSS is a progressive oral and ocular dryness that poorly correlates with the extent of inflammatory infiltrates of exocrine glands. Evidence of aberrant expression of inflammatory mediators and apoptosis of glandular epithelial cells has been proposed as early events in pSS pathogenesis. Vasoactive Intestinal Peptide (VIP) is a pleiotropic secretory and vasodilator neuropeptide with potent immunomodulatory effects in various animal models of chronic inflammation. Also, we have recently proposed an anti-apoptotic effect of VIP on murine acinar epithelial cells through VPAC1 subtype of VIP receptors. The aim of this work was to study the role of VIP / VPAC system in the interaction of monocytes from pSS patients with a human salivary gland epithelial cell line.

Methods: Monocytes were isolated from peripheral blood of women with pSS (Vitali C et al., 2002) (n=26) and age-matched healthy women as the control group (n=10). Mononuclear cells were analyzed by flow cytometry and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) for cytokines, chemokines and VIP receptors before and after activation with lipopolysaccharide (LPS) and also after co-cultures with salivary epithelial cells (HSG cell line) in the presence or absence of 100 nM VIP.

Results: We found an increased expression of VPAC2 subtype of VIP receptors on pSS monocytes compared with healthy control patients ($P<0.05$, Student) that was differentially modulated by LPS and VIP. CD14 positive cells from pSS but not from control subjects showed increased expression of IL-12 after co-culture with epithelial cells which was partially reversed by VIP. Moreover, only pSS cells induced the expression of inflammatory and migration markers on epithelial cells after co-cultures with a 2.2 fold increase of Toll like receptor 4 TLR4 ($P<0.05$ vs. basal expression) and Monocyte chemotactic protein-1 (MCP-1) among other molecules.

Conclusion: These observations support that salivary gland epithelial cells could be actively involved in the priming of peripheral monocytes of pSS patients and that VIP / VPAC system might have a role in this interaction.

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Regulatory T Cell Subset Defect in a Mouse Model of Sjögren Syndrome. Scott M. Lieberman[1], Portia A. Kreiger[2] and Gary A. Koretzky[3]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Nemours/A.I. DuPont Hospital for Children, Wilmington, DE, [3]University of Pennsylvania, Philadelphia, PA

Background/Purpose: CD4$^+$Foxp3$^+$ regulatory T cells (Tregs) are a specialized population of lymphocytes which prevent autoimmunity in normal hosts. Sjögren syndrome is an autoimmune disease characterized by destruction of lacrimal and salivary glands resulting in profound ocular and oral dryness. Studies in Sjögren syndrome demonstrate normal or elevated Treg numbers in peripheral

blood and normal in vitro function, but these assays for global Treg dysfunction fail to detect defects in specific Treg subsets. In the nonobese diabetic (NOD) mouse model of Sjögren syndrome, females develop earlier and more severe sialadenitis while males develop primarily dacryoadenitis. Here, we use a new NOD-based transfer model of Sjögren syndrome to evaluate the role of Treg subset defects in disease development.

Methods: Sjögren-like disease was induced by transfer of cervical lymph node cells, either whole or depleted of Tregs, to immunodeficient NOD-SCID mice that have no lymphocytes and do not develop autoimmunity. Seven weeks following adoptive transfer, dacryoadenitis and sialadenitis were quantified by an experienced, blinded pathologist using a standard focus score.

Results: Transfer of whole cervical lymph node cells from female NOD mice to female NOD-SCID mice resulted in sialadenitis with minimal or no dacryoadenitis, a pattern similar to disease in intact female NOD mice. Interestingly, dacryoadenitis developed in recipients of cervical lymph node cells depleted of the Treg-enriched $CD4^+CD25^+$ population and was abrogated by co-transfer of this population.

Conclusion: Female NOD mice harbor a lacrimal gland-protective (but not salivary gland-protective) Treg subset within the organ-draining cervical lymph nodes, suggesting spontaneous sialadenitis is due to dysfunction of salivary gland-protective Tregs. Whether male NOD mice have a similar, but lacrimal gland-specific, Treg subset defect is under investigation.

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A Chimeric Human-Mouse Model of Sjogren's Syndrome. Nicholas Young, Alexandra Friedman and Wael N. Jarjour. The Ohio State University Medical Center, Columbus, OH

Background/Purpose: Sjogren's Syndrome (SjS) is a chronic autoimmune disorder that results in the persistent inflammation of moisture producing glands. In addition to the lacrimal and salivary gland response, systemic inflammation is also observed to different extents. Despite recent advances in the understanding of this disease, the pathogenic mechanisms remain to be elucidated. Although animal models have been useful in characterizing some disease aspects, an ideal model for early drug discovery is not available.

Methods: In this work, peripheral blood mononuclear cells (PBMCs) from healthy subjects and patients with SjS were isolated and injected into immuno-incompetent mice. This transgenic mouse strain is commonly known as NOD *scid* gamma (NSG) and can not produce functional T cells, B cells, and NK cells due to several induced mutations. Moreover, this mouse has been shown to have more successful engraftment of PBMCs than any other strain. Before initial injection, PBMCs from SjS patients and healthy controls were characterized though flow cytometry with markers directed against major cell subtypes. Upon euthanization, tissue from multiple organs was harvested and heparinized blood was collected for additional cytometric analysis.

Results: Isolated PBMCs from SjS patients were found to contain approximately 65% CD3+ T cells, with approxiametely 55% being CD4+ and 8% CD8+. Monocytes (12%), NK cells (3%), and B cells (7%) were also detected in these samples. Isolated PBMCs were then adoptively transferred into NSG mice. H&E stains of tissues from SjS adoptive transfers revealed a dramatic multi-organ inflammatory response which pronounced infiltrate observed in the lacrimal and salivary glands. Tissue sections of mice transferred with healthy PBMCs showed significantly less infiltrate into these target organs. Interestingly, flow cytometry of the blood collected showed a slightly decreased presence in both CD3+/CD4+ and CD3+/CD8+ cells. However, no monocytes, NK cells, and B cells of human origin were detected. When the salivary and lacrimal glands of mice transferred with SjS PBMCs were examined further with immunohistochemistry (IHC), the infiltrate consisted largely of CD4+ cells with some CD8+ cells present. Notably, B cells were also detected in the infiltrate of these glands, but to a lesser extent. The localization of inflammation to the lacrimal and salivary gland targets may explain the presence of B cells in these organs, while not found using flow cytometry.

Conclusion: This adoptive transfer model of SjS uses PBMCs isolated from patients and displays pronounced target organ infiltrate. Continued efforts with this model will characterize the inflammatory response further, both in cellular infiltrate and organ involvement, and optimize experimental conditions. Ultimately, this novel chimeric human-mouse model using primary human SjS cells will offer a unique experimental environment in which to test therapeutics and investigate disease pathology.

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The Majority of Micrornas in Serum and Saliva Is Concentrated in Exosomes. Alessia Gallo[1], Mayank Tandon[1], Gabor G. Illei[2] and Ilias Alevizos[1]. [1]NIDCR, Bethesda, MD, [2]NIDCR/ NIH #10 1N110, Bethesda, MD

Background/Purpose: MicroRNAs (miRNA) are small regulatory RNA molecules with important roles in a variety of physiological and pathological processes. miRNA signatures from both unfractionated human fluids, like serum and saliva and from exosomes showed promise as diagnostic biomarkers, but the relative contribution of exosomal miRNAs to whole serum microRNAs has not yet been explored.

Methods: We first optimized a protocol to isolate exosomes from a very small amount of fresh and frozen serum and saliva. The isolation of microvescicles was done using different centrifugation and ultra centrifugation steps. The purity of exosome preparations were confirmed by electron microscopy and by Western blot using exosome specific antibodies (CD63, TSG101). The expression of selected microRNAs isolated either from exosomes or the exosome-free supernatant were compared by TaqMan RT-qPCR. We tested miR-150, miR-146a, miR-574, miR101, miR107, miR16, miR678 and miR13 in serum samples and miR202, miR203, miR1273d, and miR22 in saliva samples.

Results: The centrifugation and ultracentrifugation steps allowed to have a very clean isolation of exosomes and subsequently a higher quality miRNA preparation, compared to the whole serum and the supernatant. The expression of all tested miRNAs in the pellet was at least 8 fold higher compared to the supernatant. The difference ranged from 8–128 folds (3–7 cycles). Most miRNAs were either undetectable (Cycles Threshold >35) or detectable at a very low level in the exosome-free supernatant.

Conclusion: These results show that the majority of miRNAs in the serum and saliva is packaged within microvesicles, primarily exosomes and not found free circulating in human samples. Even though, the exosome isolation could mean an extra-step, it is maybe necessary to reliably detect miRNAs which are present at low concentration in human fluids.

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Deep Sequencing of Small RNAs Reveals Novel MicroRNAs in Minor Salivary Glands of Sjögren's Syndrome Patients. Mayank Tandon[1], Alessia Gallo[1], Gabor G. Illei[2] and Ilias Alevizos[2]. [1]NIDCR, Bethesda, MD, [2]NIDCR/ NIH #10 1N110, Bethesda, MD

Background/Purpose: Sjögren's Syndrome (SS) is a complex autoimmune disease of the salivary gland with an unknown etiology, so a thorough characterization of the transcriptome would facilitate our understanding of the disease. We use ultra deep sequencing of small RNAs from Sjögren's patients and healthy volunteers, primarily to identify and discover novel miRNA sequences that may play a role in the disease.

Methods: Total RNA was isolated from minor salivary glands of healthy volunteers (n=3) and patients with either high (n=3) or low (n=3) salivary flow. RNA from individuals was pooled and sequenced on the SOLiD 4 platform using the small RNA protocol from Applied Biosystems. Prediction of mature miRNAs from the sequenced reads was done using miRanalyzer and expression was validated using custom Taqman qPCR assays. Additional validation was performed on several cell lines, including human salivary gland (HSG) cells, Jurkat cells, and primary culture cells from patient salivary glands and fibroblasts.

Results: The number of total reads generated, as well as the reads mapped during each step of the analysis, was greatly varied between samples. The Low Flow sample generated more reads (~26 million) than the Healthy Volunteer sample (~15 million). However, a smaller proportion of those reads was matched to the human genome in Low Flow patients, 3.6% compared to 27.8% in Healthy Volunteers, suggesting an elevated level of exogenous sequences in patients. We also validated the presence of six previously unidentified miRNA sequences in patient samples and in several cell lines, and one shows promise as a biomarker candidate. This novel miRNA is elevated 4.6-fold in patients with high salivary flow and 12.5-fold in patients with low salivary flow when compared to healthy volunteers.

Conclusion: Sequencing small RNAs in the salivary gland is largely unprecedented, but here we show the feasibility of discovering novel miRNAs and disease biomarkers by sequencing the transcriptome of pooled patient samples.

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Subclinical Peripheral Synovitis Detected by ultrasound In Patients with Axial Spondyloarthritis. Pascal Zufferey[1], Cecile Mouly Jr.[1], Hans Rudolf Ziswiler[2] and Jean Dudler[3]. [1]Rheumatology, Lausanne, Switzerland, [2]Rheumatology, Bern, Switzerland, [3]HFR Fribourg-Hôpital Cantonal, Fribourg, Switzerland

Background/Purpose: Peripheral arthritis is considered fairly rare in patients with axial Spondyloarthritis (SpA), with about 30% of them suffering from the classical oligoarthritis. However, many of them complain of pain in the small peripheral joints, in the absence of obvious synovitis. Musculoskeletal ultrasound (US) can demonstrated subclinical synovitis in rheumatoid arthritis (RA), synovitis relevant in term of disease activity and treatment strategies.

The goal of the present study was to determine the prevalence of small joint synovitis in SpA identified by ultrasonography as compared to RA patients and controls, and if those synovitis were relevant in terms of disease activity and function.

Methods: The Swiss Sonography in Arthritis and Rheumatism (SONAR) group has developed a reproducible semi-quantitative score for synovitis in RA using OMERACT criteria. The score includes B mode and Doppler evaluation of metacarpophalangeal and proximal interphalangeal joints 2 to 5, wrist, elbows and knees (22 joints, grade: 0 to 3, maximum of 66 points each).

40 consecutive patients fullfilling the ASAS classification criteria for axial SpA without history of oligoarthritis, 20 gender and age-matched controls without rheumatologic diseases and 40 consecutive RA patients (19 in remission [DAS28 <2.6], 10 in low activity [$2.6 <$ DAS28 > 3.4] and 11 with moderate activity ($3.5 <$ DAS28 >5.1) were evaluated using the SONAR score by ultrasonographer blinded to any clinical parameters. A corresponding 28-joints counts was performed by two investigators in patients and controls, while patients and controls also completed self-evaluation assessments for disease activity (BASDAI), general function (BASFI), hand function (m-SACRAH) and quality of life (HAQ). Furthermore, BASMI and DAS28 were determined in SpA and DAS28 in RA patients.

Results: 34% of SpA patients had significant synovitis by US evaluation using a B mode score > 8 a cut-off value for significance (value set to classify $<$ 10% of controls (mean: 5.9) and $>$ 90% of the active RA (DAS28 $\geq$ 2.6). SpA score remained mostly mild, with a mean B mode score (12) not significantly higher than RA in remission (7.1). Only active RA (DAS >3.5) had significantly higher echographic scores for B mode (17), Doppler score or number of synovitis with grade > 1, compared to all other groups.

In a preliminary analysis, BASDAI, BASFI, BASMI, m-SACRAH, DAS28 and CRP were not significantly different in SpA patients with or without echographic synovitis, and no correlation was found between any variables and the echographic scores, on the contrary to RA patients were echographic synovitis severity did significantly correlate to clinical variables

Conclusion: one third of the patients with axial SpA have significant small joints peripheral synovitis detected by echography. The significance of such demonstration remained undetermined as no clear correlation between the severity of the synovitis and the various parameters was found in SpA patients, on the contrary to RA.

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Cardiometabolic Abnormalities in Moderate-to-Severe Plaque Psoriasis with and without Psoriatic Arthritis: The PRISTINE Trial. M. Elaine Husni[1], Abrar A. Qureshi[2], Annette Szumski[3], Andrew S. Koenig[3] and Debbie H. Robertson[3]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Brigham and Women's Hospital, Boston, MA, [3]Pfizer Inc., Collegeville, PA

Background/Purpose: Individuals with psoriasis and psoriatic arthritis (PsA) have increased morbidity and mortality, which has largely been related to cardiovascular disease (CVD).[1,2] CVD risk factors such as diabetes[3] are more common in patients with psoriasis. In the PRISTINE trial (NCT00663052), a randomized, double-blind, etanercept trial, cardiometabolic parameters were assessed in psoriasis subjects with and without PsA.

Methods: Subjects with moderate-to-severe plaque psoriasis were divided into 2 groups, PsA+ and PsA-, based on patient history. Baseline demographic/disease characteristics were analyzed using one-way ANOVA. Categorical baseline variables were analyzed by a Cochran-Mantel-Haenszel (CMH) test of general association. Associations between baseline frequency of metabolic syndrome and quartiles of the Psoriasis Activity and Severity Index (PASI) were assessed by CMH test. For each PsA+/− subgroup, a logistic model of baseline metabolic syndrome analyzed gender as a predictor, adjusting for baseline PASI. For each subgroup, differences in mean baseline PASI between BMI <30 and ≥ 30 kg/m^2 were assessed by two-sample t test.

Results: Subjects (n=273) were 70% male and 64% white, with mean age 44 y, mean BMI 28.3 kg/m^2 (males)/29.6 kg/m^2 (females), and mean baseline PASI 21; mean psoriasis duration was 17 y and PsA duration was 8 y. The cardiometabolic characteristics of PsA+ and PsA- subjects are shown (table). Metabolic syndrome was seen in 44%, 48%, 44%, and 40% of PsA+ subjects and 42%, 44%, 36%, and 41% of PsA- subjects with PASI <13.7, ≥ 13.7–<18.7, ≥ 18.7–<26.5, and ≥ 26.5, respectively ($P \leq 0.73$ and $P \leq 0.75$, correlations of PsA+ and PsA- vs PASI quartile). Metabolic syndrome was significantly more prevalent in females vs males in the PsA+ subgroup (adjusted OR, 3.2; $P<0.05$) but not in the PsA- subgroup (adjusted OR, 1.3; $P=0.44$). Mean baseline PASI was not significantly different between BMI <30 and ≥ 30 kg/m^2 in either subgroup.

Baseline cardiometabolic parameters in subjects with psoriasis with and without PsA

	Subjects, n (%)		
Cardiometabolic Parameter	**PsA+ (N = 84)**	**PsA− (N = 189)**	**P value**
Metabolic syndrome[a]	37 (44)	77 (41)	0.61
Large waist circumference[b]	61 (73)	130 (70)	0.65
Low HDL cholesterol[c]	21 (25)	48 (25)	0.95
Elevated triglycerides[d]	30 (36)	63 (33)	0.70
Elevated blood pressure[e]	61 (73)	105 (56)	0.01
Elevated glucose[f]	29 (35)	50 (27)	0.18
Diabetes[g]	18 (21)	17 (9)	<0.01
Diabetes + prediabetes[g]	44 (52)	77 (41)	0.07
Hypertension[h]	52 (62)	50 (27)	<0.001
	Mean Score/Level (SD)		
Framingham 10-year % risk	6.3 (6.6)	5.3 (6.1)	0.21
Reynolds 10-year % risk	4.3 (4.5)	3.9 (6.1)	0.01
Plasma NT-proBNP, pg/mL	87.8 (128.0)	57.4 (119.4)	0.06
High sensitivity CRP[i], mg/L	11.5 (17.5)	5.51 (7.7)	0.02

[a]Satisfied 3/5 criteria. [b]Europe: ≥102/≥88 cm (M/F); Asia, Cent/S America: ≥90/≥80 cm (M/F). [c]Fasting HDL-C <1.0/<1.3 mmol/L (M/F) or receiving drug treatment. [d]Fasting triglycerides ≥1.7 mmol/L or receiving drug treatment. [e]SBP ≥130 or DBP ≥85 mm Hg or receiving drug treatment with history of hypertension. [f]Fasting glucose ≥100 mg/dL or on drug treatment. [g]Diabetes = HbA1c >6.4% or medical history or receiving drug treatment; prediabetes = HbA1c 5.7–6.4% (2010 ADA criteria). [h]Medical history or receiving drug treatment. [i]Normal CRP level ≤3.0 mg/L.

Conclusion: Metabolic syndrome and other CVD risk factors were common in psoriasis with and without PsA. Women with PsA were significantly more likely to have this syndrome than men with PsA. A significantly higher proportion of subjects with diabetes and hypertension, and significantly greater Reynolds % risk and C-reactive protein, were observed in PsA+ subjects vs PsA- subjects. No significant associations were seen between the severity of psoriasis and metabolic syndrome or BMI in either subgroup. Clinicians need to be attentive to cardiometabolic biomarkers in those affected by psoriasis and PsA to help reduce overall cardiovascular disease risk.

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Impact of Uveitis On the Phenotype of Patients with Recent Inflammatory Back Pain. Data From the DESIR Cohort. Daniel Wendling[1], Clément Prati[2], Christophe Demattei[3], Corinne Miceli-Richard[4], Jean-Pierre Daures[3] and Maxime Dougados[5]. [1]Minjoz University Hospital, Besancon, France, [2]CHU J Minjoz, Besancon, France, [3]CHU, Nimes, France, [4]Hopital Bicêtre, Le Kremlin Bicêtre, France, [5]Paris-Descartes University, Cochin Hospital, Paris, France

Background/Purpose: Influence of uveitis on clinical, epidemiological and imaging features in patients with inflammatory back pain (IBP) related to spondyloarthritis (SpA) needs to be known.

Objectives: To determine the prevalence of uveitis in patients with recent IBP suggestive of SpA, and to investigate the influence of uveitis on the overall features of patients presenting with recent IBP.

Methods: The DESIR cohort is a prospective, multicenter French cohort of patients with early IBP (Calin or Berlin criteria) (>3 months and <3 years of duration) suggestive of SpA according to the investigator, including 708 patients (mean age 33.8 years, 53.8% female, 57.3% HLA B27 positive). Uveitis was defined by an ophthalmological episode diagnosed as uveitis by an ophthalmologist, or a painful red eye episode of at least 48 hours duration and/or necessitating local steroids. Data on the baseline demographic characteristics, functional status and quality of life, imaging features (standard X-Rays, MRI, Ultrasounds), BMD, and blood tests were compared in patients with and without uveitis. Both the date of the first symptom of IBP and the symptoms of uveitis were recorded, as well as the date of the visit. Factors associated with the presence of uveitis were identified both by uni and multivariate analysis (logistic regression).

Results: The prevalence of uveitis in the DESIR cohort was 8.47% [95%CI 6.58–10.83] (n=60/708 patients). Uveitis occurred after the first symptoms of IBP in 45%, before in 37%, and simultaneously (±1month) in 18% of the cases. Presence of uveitis was significantly associated in univariate analysis with pain in cervical spine, infection preceding (less than 3 months) inflammatory disease, previous diagnosis of inflammatory bowel disease, some dimensions of SF36 (mental and physical health, relation), presence of Achilles enthesitis, elevated leukocyte count, serum creatinin levels, radiological hip involvement, and chronic sacro iliac MRI lesions. Uveitis is not associated with fulfilment of diagnosis criteria, HLA-B27, BASDAI, BASFI, ASDAS, BMD. A stepwise multivariate analysis found an association between uveitis and: pain in cervical spine, infection preceding inflammatory disease, previous diagnosis of inflammatory bowel disease, physical health limitation of SF36 (Table).

	Uveitis (n=60)	No uveitis (n=648)	Adjusted OR	p-value
pain in cervical spine	31 (51.7%)	243 (37.5%)	2.09 [1.17–3.73]	0.01
infection preceding inflammatory disease	8 (13.3%)	22 (3.4%)	5.75 [2.29–14.40]	0.0002
previous diagnosis of inflammatory bowel disease	5 (8.3%)	16 (2.5%)	3.38 [1.07–10.66]	0.04
physical health limitation of SF36	56.7 ± 41.4	44.0 ± 39.1		0.001

Conclusion: In recent IBP suggestive of SpA, uveitis is associated with some particular rheumatologic and extra rheumatologic features. Our data, and in particular the association with IBD and infection might suggest a role of environmental factors in the incidence of uveitis in SpA.

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Cardiovascular Events Are Related to High Levels of HDL-Cholesterol In Ankylosing Spondylitis. Anne Grete Semb[1], Tore K. Kvien[1], Rana Fayyad[2], David A. DeMicco[2], John LaRosa[3], John Betteridge[4], Terje R. Pedersen[5] and Ingar Holme[5]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Pfizer Inc, New York, [3]State University of New York health Science Centre, New York, [4]Middelsex Hospital, London, United Kingdom, [5]Oslo University Hospital-Ullevaal, Oslo, Norway

Background/Purpose: We evaluated lipids and apolipoproteins as predictors of cardiovascular mortality and morbidity (CVMM) in patients with spondyloarthritis (SpA); ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Methods: To obtain patients with AS and PsA who were followed over time and had a CV endpoint, we used a pooled analysis of 2 CV secondary prevention studies (IDEAL and TNT) and a primary CV prevention study (CARDS). Number of participants was 21727. Fifty of these had AS, 36 had PsA, and 21641 did not have AS or PsA (non-SpA). There was no heterogeneity across the 3 trials concerning the proportion of CVMM in the different treatment groups for AS and PsA.

Results: Baseline data were similar across AS, PsA and non-SpA, except that there were more male AS patients. The AS patients used less aspirin and the PsA patients had more hypertension and higher BMI than non-SpA. Atherogenic lipids were lower in AS, but not in PsA, compared to non-SpA. The HR per 1 SD increase in baseline lipids for future CVMM was calculated (Table). Surprisingly, both HDL and ApoA-1 were significantly associated with CVMM in AS, in contrast to PsA and non-SpA. The interaction test for HDL and ApoA-1 in AS vs. non-SpA was highly significant: p<0.0001 and p=0.0003 respectively, but not significant for the atherogenic lipids in AS. None of the interaction tests were significant for PsA (Table).

Table. HR (95% CI) of CVMM for 1 SD increase in baseline lipid/apolipoprotein in subgroups of AS, PsA and non-SpA participating in the IDEAL, TNT and CARDS studies, adjusted for age, gender and treatment

Lipid/ Apolipoprotein	AS (n=50) HR (95% CI)	p-value	PsA (n=36) HR (95% CI)	p-value	nonSpA (n=21641) HR (95% CI)	p-value
Total Cholesterol	1.39 (0.82, 2.40)	0.23	1.01 (0.44, 2.31)	0.98	1.10 (1.07, 1.14)	<0.0001
LDL	1.37 (0.78, 2.41)	0.28	0.94 (0.42, 2.14)	0.89	1.13 (1.09, 1.16)	<0.0001
HDL	3.67 (1.49, 9.06)	0.005	1.03 (0.49, 2.15)	0.94	0.86 (0.84, 0.89)	<0.0001
ApoB	1.19 (0.69, 2.05)	0.54	1.27 (0.62, 2.57)	0.52	1.14 (1.11, 1.18)	<0.0001
ApoA1	1.89 (1.02, 3.54)	0.05	0.79 (0.34, 1.89)	0.60	0.88 (0.85, 0.91)	<0.0001

*Hazard ratio (HR) of CVMM for per 1 SD increase in baseline lipid/apolipoprotein
CVMM=Cardiovascular morbidity and mortality, AS=ankylosing spondylitis, PsA=psoriatic arthritis (PsA), Non-SpA= non-spondyloarthritis, HR=hazard ratio, CI=confidence interval

Conclusion: Increased levels of HDL and ApoA-1 were associated with increased risk of CVMM in patients with AS, whereas these lipids were protective in non-SpA. These observations are preliminary and need confirmation in larger trials.

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The Degree of Spinal Inflammation Is Similar in Patients with Axial Spondyloarthritis Who Report High or Low Levels of Disease Activity— a Cohort Study. Uta Kiltz[1], Xenofon Baraliakos[1], Pantelis Karakostas[1], Manfred Igelmann[2], Ludwig H. Kalthoff[3], Claudia Klink[4], Dietmar MJ Krause[4], Elmar Schmitz-Bortz[5], Martina Floerecke[1], Matthias Bollow[6] and Juergen Braun[1]. [1]Ruhr-University Bochum, Herne, Germany, [2]Private Rheumatology office, Bochum, Germany, [3]Private rheumatology office, Herne, Germany, [4]Private rheumatology office, Gladbeck, Germany, [5]Private rheumatology office, Hattingen, Germany, [6]Augusta Krankenanstalten, Bochum, Germany

Background/Purpose: Patients with axial spondyloarthritis (axSpA) may already have established radiographic changes in the sacroiliac joints, classified as ankylosing spondylitis (AS) or non-radiographic axial SpA (nraxSpA). International recommendations for the management of axSpA have set the cut off for the minimal clinical disease activity required to fulfill criteria for anti-TNF therapy at a BASDAI level of 4 - based on a convention arbitrarily proposed some years ago. However, the level of inflammatory activity as demonstrated by magnetic resonance imaging (MRI) or elevated CRP levels in patients who report moderate disease activity is unknown. The objective of this study was to systematically compare the clinical, laboratory and imaging data of patients with axSpA, stratified by the level of disease activity: BASDAI <4 and ≥4.

Methods: A total of 100 consecutive patients with axSpA who had never been treated with TNF-blockers were included. Data on demographics (gender, age, symptom duration, comorbidities, use of concomitant medication) were collected, and standardized assessment tools (BASDAI, BASFI, ASDAS, NRS pain, physicians′s and patient′s global assessment, ASQoL, SF-36) applied, laboratory parameters (CRP, HLA-B 27 status) measured, and spinal MRI and x-rays performed and quantified with established scoring systems (mSASSS, RASSS and Berlin score). Data were stratified according to the correspondent BASDAI level ≥4 or <4.

Results: AS was diagnosed in 56 and nraxSpA in 44 patients, mean age 40.2±10.4 years; 57% male, mean disease duration 6.4±8.4y, 88% HLA-B27 positivity. Almost all patients took NSAIDs (94%), 54% continuously. More than half of the patients had spinal inflammation to some degree (60%). The stratification based on BASDAI levels showed statistically significant differences in most clinical parameters—but not for inflammation as measured by either CRP or MRI: nraxSpA patients with BASDAI <4 versus (vs) ≥4 had 0.9±1.4 and 0.5±0.6 inflammatory lesions/patient, respectively (p=0.6), while AS patients with BASDAI <4 vs ≥4 had 3.6±3.7 and 2.7±3.0 inflammatory lesions/patient, respectively (p=0.4).

Table. Differences between patients with nraxSpA and AS stratified according to BASDAI level

	BASDAI	AS	nraSpA	p for AS vs. nraSpA	p for BASDAI < vs. ≥4
Patient's global	<4	2.4 ± 1.6	2.1 ± 2.1	0.26	<0.001
	≥4	6.2 ± 2.2	5.7 ± 2.2	0.37	
BASFI	<4	1.2 ± 1.1	0.8 ± 0.7	0.39	<0.001
	≥4	4.8 ± 2.1	3.3 ± 2.2	0.02	
ASQoL	<4	2.0 ± 2.4	2.3 ± 3.1	0.89	<0.001
	≥4	9.0 ± 4.2	8.4 ± 4.1	0.26	
CRP (mg/l)	<4	10.7 ± 8.34	5.7 ± 6.9	0.037	0.824
	≥4	11.6 ± 13.63	5.4 ± 6.8	0.005	
N inflamed lesions/ patient (MRI)	<4	3.5 ± 3.5	1.0 ± 1.4	0.004	0.550
	≥4	2.7 ± 3.0	0.5 ± 0.6	0.008	

Conclusion: The striking result of this study in patients with axSpA is that there is not only no correlation between widely used clinical assessments of disease activity and more objective measurements of inflammation such as CRP serum levels and MRI but that the BASDAI cut-off ≥ 4 needs to be reevaluated. These data clearly challenge the concept of the arbitrarily set clinical cut off BASDAI≥4 since the burden of inflammation and most clinical measures were quite comparable in patients with nraxSpA and established AS - irrespective of BASDAI levels. These data confirm and justify the inclusion of patients with nraxSpA in the recent recommendations for anti-TNF therapy.

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The Swedish Early Psoriatic Arthritis (SwePsA) Registry. 5-Year Follow-up: Higher Disease Activity, Greater Functional Impairment and Worse Outcome for Women Compared to Men. Elke Theander[1], Tomas Husmark[2], Gerd-Marie Alenius[3], Per Larsson[4], Annika Teleman[5], Mats Geijer[6] and Ulla R. C. Lindqvist[7]. [1]Department of Rheumatology, Skåne University Hospital, Lund University, Malmö, Sweden, [2]Depart ment of Rheumatology, Falu Hospital, Falun, Sweden, [3]Department of Public Health and Clinical Medicine, Rheumatology, Umeå University Hospital, Umeå, Sweden, [4]Department of Rheumatology, Karolinska University Hospital, Stockholm, Sweden, [5]Spenshult Rheumatological Hospital, Oskarstrom, Sweden, [6]Department of Radiology, Skåne University Hospital, Lund University, Lund, Sweden, [7]Department of Medical Scie nces, Rheumatology, University Hospital, Uppsala university, Uppsala, Sweden

Background/Purpose: SwePsA intends to describe the course of disease during early psoriatic arthritis (PsA) in a real life clinical setting in Sweden. Here we present results from a 5-year follow-up of 206 patients and analyse predictors of unfavourable outcome.

Methods: In 6 Swedish centres patients with signs suggestive of PsA were included in the registry within 2 years from symptom onset. Two-hundred and six patients fulfilling CASPAR (1) or ASAS (2) criteria who had passed the 5-year follow-up visit were included. DAS-28 and DAPSA (3) were used as disease activity measures. Clinical remission (defined as no tender or swollen joints and normal ESR and CRP) and Minimal Disease Activity (MDA) (4) were used as outcome measures. Patterns of joint involvement and medication were assessed.

Results: Mean age at baseline:46 years, younger in male (n=88) than female (n=118) patients (48 vs 43 years).

DAS-28 was 3.4 at baseline and 2.6 at 5-year follow-up, significantly higher in women (3.7 and 2.9) than in men (2.9 and 2.1) at both visits. Likewise DAPSA scores were significantly higher in women (22.9 and 14.0) than in men (14.9 and 9.9) at both visits. The degree of improvement (delta DAS-28 and delta DAPSA) was similar in women and men. A larger proportion of men were in MDA state or remission at 5-year follow-up (50% vs 30% and 36% vs 23%). While women had significantly more often polyarticular disease at baseline (52% vs 33%) and also kept that pattern over the 5 years (21%), men had more often axial or mono/oligoarticular disease at baseline or converted to it during follow-up.

Despite higher disease activity in women there was a trend towards less DMARD treatment (40% of women vs 34% of men had never been treated with DMARDs). The use of biologics did not differ (7% vs 6%).

Predictors of MDA or remission at 5-year follow-up were male gender, low HAQ and short delay between symptom onset and inclusion, mono/oligoarticular or axial disease pattern at baseline, for MDA also low DAS-28, DAPSA, TJC, PGA and pain VAS. In multivariate analysis male gender, axial disease, shorter delay between symptom onset and inclusion and preserved physical functioning at inclusion independently predicted better outcome. Exclusion of patients with axial disease only did not change the results.

Conclusion: In early PsA male gender, axial disease, short delay between symptom onset and diagnosis, as well as preserved function at diagnosis are predictors of favourable outcome at 5-year follow-up. Early recognition of PsA and active treatment may be important particularly in women with polyarticular disease.

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Gender Differences in the Correlation of Self-Reported Functional Status with Spinal Mobility in Patients with Ankylosing Spondylitis. Pooja N. Patel[1], Roozbeh Sharif[2], Shervin Assassi[3], Lianne S. Gensler[4], Laura A. Diekman[5], Thomas J. Learch[6], Michael H. Weisman[7], Michael M. Ward[8] and John D. Reveille[2]. [1]University of Texas, Houston, Houston, TX, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]Univ of Texas Health Science, Houston, TX, [4]UCSF, San Francisco, CA, [5]UT Health Science Center, Houston, TX, [6]Cedars-Sinai, Los Angeles, CA, [7]Cedars Sinai Med Ctr, Los Angeles, CA, [8]NIAMS/NIH, Bethesda, MD

Background/Purpose: Spinal damage in patients with ankylosing spondylitis (AS) can result in physical limitation. Previous studies have reported clinical and psychological factors correlate with self-reported functional status in AS patients. In the current study, the association of functional status with measurements of spinal mobility (AS-Metrology) was evaluated. Also examined was the the impact of gender, disease duration, and anti-tumor necrosis factor (TNF)α treatment on this association.

Methods: Patients enrolled in the **P**rospective **S**tudy of **O**utcomes in **A**nkylosing **S**pondylitis (PSOAS) cohort were studied. PSOAS is a multi-ethnic, multi-center cohort of patients with AS in the United States. The study investigators performed the following measurements of spinal mobility: cervical rotation and flexion, occiput-to-wall distance, chest expansion, modified Schober, lateral lumbar flexion, and hip internal/external rotation. In addition, the patients' perceived functional limitation was recorded by the Bath AS Functional Index (BASFI). Linear regression was used to examine the association of the BASFI score with concomitantly recorded spinal mobility measures at enrollment. Considering potential effect modifiers, the interaction term of BASFI with the following variables was examined: disease duration, gender, and anti-TNF α treatment.

Results: Overall, 436 patients were included in the analysis: median age of 42.3 years, 70% male, 77% Caucasian, and median disease duration of 16.3 years. HLA-B27 was detected in 85% of subjects. BASFI score correlated with AS-Metrology ($p<0.001$). The analysis of potential effect modifiers indicated the presence of a statistically significant interaction between gender and BASFI with regard to its association with AS-Metrology ($p<0.05$). Subgroup analysis based on the gender indicated male patients have a stronger correlation between BASFI and AS-Metrology, compared to female patients (table-1). Though some of the AS-Metrology variables were not normally distributed, analysis of log transformed variables did not affect the results.

Conclusion: AS-Metrology is associated with BASFI score and this correlation is statistically stronger among men compared to women. These findings support the hypothesis that other factors might play an important role in perceived functional status among women with AS.

Table 1. Subgroup analysis of correlation between BASFI and AS metrology based on gender

	BASFI* score			
	Male		Female	
Clinical measurements	*Correlation coefficient*	*p-value*	*Correlation coefficient*	*p-value*
Cervical rotation	*−0.53*	***<0.001***	*−0.43*	***<0.001***
Cervical flexion	*−0.37*	***<0.001***	*−0.36*	***<0.001***
Occiput-to-wall distance	*0.48***	***<0.001***	*0.24*	***0.011***
Chest expansion	*−0.50***	***<0.001***	*−0.29*	***0.002***
Modified Schober	*−0.41***	***<0.001***	*−0.19*	***0.048***
Lateral flexion	*−0.49*	***<0.001***	*−0.48*	***<0.001***
Hip external rotation	*−0.29***	***<0.001***	*−0.08*	*0.422*
Hip internal rotation	*−0.36***	***<0.001***	*−0.14*	*0.168*

** BASFI: Bath Ankylosing Spondylitis Functional Index;** The magnitude of effect is statistically higher in men, compared to women*

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Patients with Non-Radiographic Axial Spondyloarthritis Differ From Patients with Ankylosing Spondylitis in Several aspects—Results of a Cross-Sectional Cohort Study. Uta Kiltz[1], Xenofon Baraliakos[2], Pantelis Karakostas[2], Manfred Igelmann[3], Ludwig H. Kalthoff[4], Claudia Klink[5], Dietmar MJ Krause[6], Elmar Schmitz-Bortz[7], Martina Floerecke[2], Matthias Bollow[8] and Juergen Braun[2]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Ruhr-University Bochum, Herne, Germany, [3]Private Rheumatology office, Bochum, Germany, [4]Private rheumatology office, Herne, Germany, [5]Private rheumatology office, Gladbeck, Germany, [6]Gladbeck, Germany, [7]Private rheumatology office, Hattingen, Germany, [8]Augusta Krankenanstalten, Bochum, Germany

Background/Purpose: Patients with axial spondyloarthritis (SpA) may already have established radiographic changes in the sacroiliac joints and the spine or not—the former are classified as having ankylosing spondylitis (AS), the latter as pre- or non-radiographic axial SpA (nraxSpA) according to the ASAS criteria. The nature and the relationship of these subentities are incompletely understood. The objective of this stufy was to study the patients' clinical data and their view of the current disease status in relation to laboratory markers and spinal inflammation (MRI) in patients with AS and nraxSpA.

Methods: A total of 100 consecutive patients with a diagnosis of axial SpA who had never been treated with TNF antagonists were studied and the results compared to those of laboratory parameters, spinal x-rays and MRIs which were scored by the mSASSS and the Berlin score, respectively. Standardized clinical assessment tools were used (NRS pain, BASDAI, ASDAS, BASFI, ASQoL, SF-36).

Results: AS was diagnosed in 56 and nraxSpA in 44 patients. Patients with established nraxSpA and AS did not differ much in many clinical variables (BASDAI, BASFI, ASQoL) but the proportion of males (32% vs 72%) and the extent of inflammation were clearly lower in nraxSpA vs AS patients: CRP (5.7±6.6 vs 11.6±12.6), ASDAS (2.2±0.8 vs 2.9±0.9), Berlin score (0.8±1.2 vs 3.1±3.2) and mSASSS: 2.4±3.5 vs 13.2±20.7 (all $p<0.01$). The frequency of typical comorbidities (uveitis, psoriasis, CED or enthesitis), nor in the actual medication regarding NSAIDs or sulfasalazine differed between the groups. These results were confirmed by multivariate analyses adjusted for gender, CRP and mSASSS at baseline.

Table 1. Comparison between the two analyzed subgroups for all measured parameters.

	nraSpA	AS	p
Age (y)	39.1 ± 9.8	41.2 ± 10.9	0.455
Symptom duration (y)	9.4 ± 9.5	12.8 ± 10.7	0.085
NRS pain	4.0 ± 2.1	4.7 ± 2.7	0.244
Physician′s global assessment	2.7 ± 1.7	3.5 ± 1.9	0.064
Patient′s global assessment	4.0 ± 2.7	4.6 ± 2.7	0.265
BASDAI	3.6 ± 1.7	4.2 ± 2.2	0.194
BASFI	2.4 ± 2.1	3.2 ± 2.4	0.054
SF-36 MCS	45.0 ± 12.3	47.5 ± 11.5	0.382
SF-36 PCS	39.0 ± 9.0	36.5 ± 10.2	0.192
ASQoL	5.6 ± 4.8	6.0 ± 4.8	0.712

Conclusion: These data largely confirm earlier data showing that the disease burden in nraxSpA and established AS is similar. Interestingly, these subgroups did not differ much in clinical variables but in CRP levels and the extension of inflammation detected by MRI – both were higher in patients with AS. Expectedly, male patients were more prone to develop structural changes. Although this study was 'only' cross-sectional the data shows that a large group of patients with axSpA has not developed structural changes after almost 10 years of symptom duration. We propose that patients with nraxSpA should not be regarded as pre-radiographic AS but rather as non-radiographic axial SpA – a subgroup that is less prone to develop new bone formatio It will be interesting to see whether and how many of these patients will develop AS in the further disease course.

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Performance of the Ankylosing Spondylitis Disease Activity Score (ASDAS) in Patients Under Biological Therapies in Daily Practice—Results From the Portuguese Register Reuma.Pt. Sofia Ramiro[1], Pedro Machado[2], Raquel Roque[3], Helena Santos[4], Joaquim Polido-Pereira[5], Daniela Peixoto[6], Cátia Duarte[7], Fernando Pimentel-Santos[8], Cândida Silva[4], J. E. Fonseca[5], Filipa Teixeira[6], Andrea Marques[7], Filipe Araújo[8], Jaime C. Branco[8], José Pereira Da-Silva[7], José Costa[6], Jose A. Pereira Da Silva[9], Luis Cunha Miranda[4], J. Canas da Silva[3], Helena Canhão[5], A.M. Van Tubergen[10], Desirée van der Heijde[11], Robert Landewé[12] and MJ Santos[3]. [1]Hospital Garcia de Orta, Almada, Portugal and Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Hospitais da Universidade de Coimbra, Coimbra, Portugal and Leiden University Medical Center, Leiden, Netherlands, [3]Hospital Garcia de Orta, Almada, Portugal, [4]Instituto Português de Reumatologia, Lisboa, Portugal, [5]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisboa, Portugal, [6]Centro Hospitalar do Alto Minho, Hospital de Ponte de Lima, Ponte de Lima, Portugal, [7]Hospitais da Universidade de Coimbra, Coimbra, Portugal, [8]Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal, [9]Centro Hospitalar de Lisboa Norte, Hospital de Santa Maria, Lisboa, Portugal, [10]Maastricht University Medical Center, Maastricht, Netherlands, [11]Leiden University Medical Center, Leiden, Netherlands, [12]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: The Ankylosing Spondylitis Disease Activity Score (ASDAS) is the new index to measure disease activity in Ankylosing Spondylitis (AS). Our aim was to address validity and discriminatory aspects of the ASDAS, as well as to analyse the performance of the ASDAS disease activity states and response criteria in the setting of an observational cohort of patients with AS starting biological therapies.

Methods: Patients with AS under biological therapy and followed in the Portuguese register of rheumatic diseases (Reuma.pt) were included in this analysis. Reuma.pt is used as an electronic medical record and assessments are performed by rheumatologists. All patients with baseline data were used for cross-sectional analysis (n = 264). For the longitudinal analyses, follow-up visits at 12 and 24 weeks and with an ASDAS-CRP available were required (n = 109). Pearson coefficients were calculated to establish the correlation between disease activity measurements at baseline. Discrimination between patients with low versus high disease activity according to the patient's global assessment (PGA) was analysed as the standardised mean difference (SMD). The percentage of patients within each ASDAS disease activity state at each time point and the percentage of patients achieving ASDAS improvement criteria at 12 and 24 weeks were determined and the latter were compared with other response measures.

Results: The ASDAS showed a good correlation with the PGA (0.66), and simultaneously a good correlation with acute phase reactants (CPR 0.61; ESR 0.52). The ASDAS was discriminatory, with similar SMDs to the ones from BASDAI. Results were consistent for the whole population as well as in subgroups of baseline CRP (at a cutoff of 5g/l) and disease duration (at a cutoff of 5 years). ASDAS disease activity in states showed a clinically meaningful shift from high to low over time (Table 1). The same pattern was found in the subgroups of CRP and disease duration. The ASDAS improvement criteria identified more patients with clinically meaningful improvement than the classical criteria did (Table 2), and the same results were also found in the subgroups of CRP and disease duration.

Table 1. Longitudinal evolution of ASDAS disease activity states

Time point	N	ASDAS < 1.3 N (%)	1.3 ≤ ASDAS < 2.1 N (%)	2.1 ≤ ASDAS < 3.5 N (%)	ASDAS > 3.5 N (%)
Baseline	109	0 (0%)	3 (2.8%)	46 (42.2%)	60 (55.0%)
12 weeks	109	33 (30.3%)	25 (22.9%)	42 (38.5%)	9 (8.3%)
24 weeks	109	30 (27.5%)	29 (26.6%)	40 (36.7%)	10 (9.2%)

Table 2. Percentage of patients achieving different improvement criteria

	12 weeks (n = 91)	24 weeks (n = 91)
Δ ASDAS ≥ 1.1	57 (62.6%)	55 (60.4%)
Δ ASDAS ≥ 2.0	36 (39.6%)	34 (37.4%)
Δ BASDAI ≥ 2.0	46 (50.6%)	46 (50.6%)
BASDAI50	40 (44.0%)	37 (40.7%)
ASAS20	51 (56.0%)	51 (56.0%)
ASAS40	42 (46.2%)	44 (48.4%)

Conclusion: The ASDAS is a discriminatory instrument for disease activity in the setting of usual clinical practice.

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Prevalence and Treatment Patterns of Psoriatic Arthritis in the Health Improvement Network. Alexis Ogdie[1], Thorvardur Love[2], Kevin Haynes[3], Yiding Yu[3], Nicole Seminara[3], Hyon K. Choi[4] and Joel Gelfand[3]. [1]University of Pennsylvania, Philadelphia, PA, [2]Landspitali University Hospital, Reykjavík, Iceland, [3]University of Pennsylvania., Philadelphia, PA, [4]Boston University School of Medicine, Boston, MA

Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. Prevalence in the general population has been estimated at 0.1–0.25% but large population-based studies have not been performed. The Health Improvement Network (THIN) is an electronic medical record database representative of the UK general population and can be used to perform high quality, population-based epidemiology studies. We aimed to determine the prevalence of PsA in THIN and describe the therapies prescribed.

Methods: Seven Read codes (similar to ICD9 codes) for PsA and 26 codes for psoriasis were identified. Patients were considered to have PsA or psoriasis if they ever had a code consistent with that diagnosis. Cohort entry occurred at the PsA diagnosis. Multilex drug codes for disease modifying antirheumatic drugs (DMARDs) on or after cohort entry were analyzed using STATA 11.0 (College Station, TX).

Results: Of 8.05 million patients (all ages) registered with a THIN practice between 1995–2009, 8586 patients had at least one Read code for PsA recorded and 165,903 at least one Read code for psoriasis. The prevalence of PsA in THIN was 0.11% (95%CI: 0.10–0.11) and among psoriasis patients was 5.2% (95%CI: 5.1–5.3). Of the 8586 patients, 6855 (79.8%) were between age 18–90, 51.5% were male and 48.5% were female. Prescription records indicated that of the 6855, 3492 patients (50.9%) had received a DMARD on or after cohort entry; 2461 (35.9%) had received methotrexate, 1827 (26.7%) sulfasalazine, 389 (4.9%) leflunamide, 174 (2.5%) cyclosporine, 135 (2.0%) azathioprine, and 16 (0.2%) TNF-alpha inhibitors. Of patients receiving DMARDs, 64.9% have only ever been prescribed one DMARD. Aside from DMARDs, 5427 (79.2%) had received non-steroidal anti-inflammatory agents, 1618 (23.6%) oral corticosteroids, 1349 (19.7%) tramadol, and 287 (4.2%) received opiates.

Conclusion: This is the largest population based study of PsA to date. The prevalence of PsA and DMARD use are consistent with previous population based estimates in the US and Northern Europe. Limitations include the unclear recording of biologic medications in THIN (only 0.2% of patients have a recorded biologic) and a definition of PsA based on a diagnostic code rather than CASPAR criteria. The code for psoriasis has a positive predictive value of 90%; work to confirm that a code reflects the true clinical state in PsA is ongoing. Given the large population of PsA patients, THIN is an important resource for the study of PsA.

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The Risk of Malignancy in a Large Cohort of Patients with Psoriatic Arthritis. Rachel L. Gross[1], Julie S. Schwartzman-Morris[1], Michael Krathen[2], George Reed[3], Hong Chang[2], Katherine C. Saunders[4], Mark C. Fisher[5], Chaim Putterman[1], Philip J. Mease[6], Alice B. Gottlieb[2] and Anna R. Broder[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Tufts Medical Center, Boston, MA, [3]University of Massachusetts, Worcester, MA, [4]CORRONA, Inc., Southborough, MA, [5]Massachusetts General Hospital, Boston, MA, [6]Seattle Rheumatology Associate, Seattle, WA

Background/Purpose: There are few studies examining malignancy incidence in patients with Psoriatic Arthritis (PsA), and an increased malignancy risk in this population is often extrapolated from studies of patients with Rheumatoid Arthritis (RA) and Psoriasis. Knowledge of malignancy risk can help providers in counseling patients and aid in treatment decisions regarding the use of immunomodulatory medications. Therefore, we sought to determine the incidence rate and patient characteristics predictive of malignancy in a large observational cohort of patients with PsA, the CORRONA registry.

Methods: We included all patients with a diagnosis of PsA followed by CORRONA from 8/2003 to 8/2010. Patients with a previous history of malignancy and those with less than two CORRONA study visits for PsA were excluded. All cases of malignancy reported at CORRONA visits underwent an independent medical record review by two study investigators, and only confirmed cases were included in the analysis. Malignancy incidence rates with 95% confidence intervals were calculated. We then used Poisson regression models to determine patient specific variables predictive of first malignancy.

Results: Of the 4428 patients enrolled in CORRONA, 2977 (mean age 51.2 ±12.5 years, 51.7% female) were eligible for our analysis, with 40 confirmed cases of malignancy during a total of 7156 patient-years of follow-up. The overall incidence rate (IR) of malignancy was 5.59 (95% CI 3.99–7.61) per 1000 patient years of follow-up, as compared to an IR of 5.44 (95% CI 4.56–6.32) in the RA CORRONA cohort[1]. The IR of lymphoma was 0.42 (95% CI 0.086–1.23) and of non-melanoma skin cancer was 2.10 (95% CI 1.17–3.46), versus 0.70 (95% 0.39–1.02) and 1.89 (95% CI 1.37–2.41) respectively in the RA CORRONA cohort[1]. Incidence rates by cancer type are summarized in Table 1. In our Poisson regression model, both older age of onset of PsA ($p<0.001$, IRR=1.06, 95% CI 1.03–1.09) and longer disease duration ($p<0.001$, IRR=1.07, 95% CI=1.03–1.11) were predictive of first malignancy. CDAI and history of either methotrexate or anti-tumor necrosis factor use were not significant predictors.

Table 1. Incidence of Malignancy in CORRONA PsA Cohort

Cancer type	Events	IR per 1000 patient years (95% CI's)
All cancers	40	5.59 (3.99, 7.61)
Non-Melanoma Skin Cancer (NMSC)	15	2.10 (1.17, 3.46)
All cancers excluding NMSC	25	3.49 (2.26, 5.16)
Solid	20	2.80 (1.71, 4.32)
Hematologic	5	0.70 (0.23, 1.63)
Breast	7	1.94 (0.78, 4.00)
Prostate	3	0.85 (0.18, 2.49)
Lymphoma	3	0.42 (0.086, 1.23)
Colorectal	3	0.42 (0.086, 1.23)
Melanoma	3	0.42 (0.086, 1.23)

Conclusion: This is the first study to investigate malignancy incidence in a large U.S. cohort of patients with PsA. The incidence rate of malignancy in PsA patients appears similar to patients with Rheumatoid Arthritis in the CORRONA registry, and future analysis is planned to formally compare incidence rates between these two groups and with U.S. general population databases. Both older age of onset of PsA and longer disease duration were independent risk factors for development of malignancy in this Psoriatic Arthritis cohort.

Reference:
Solomon D, et al. *Ann Rheum Dis* 2010;69(Suppl3):519. Abstract SAT0100

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Hand Bone Loss in Patients with Psoriatic Arthritis: Sub Analysis From IMPACT-2 Study Comparing Infliximab and Placebo. Mari Hoff[1], Arthur Kavanaugh[2] and Glenn Haugeberg[3]. [1]PhD, Trondheim, Norway, [2]University of California San Diego, San Diego, CA, [3]PhD, Kristiansand, Norway

Background/Purpose: The hallmark of bone involvement in rheumatoid arthritis (RA) is bone loss presenting on X-rays as erosions and periarticular osteoporosis, both features driven by osteoclast activation. In contrast, X-ray changes in psoriatic arthritis (PSA) can include both new bone formation and bone destruction, indicating that both osteoblasts and osteoclasts are activated. In RA, anti-TNF treatment has been shown to reduce the rate of hand bone loss. To our knowledge there are no data on the effect of anti-TNF treatment on hand bone loss in PsA. The objective was to examine changes in hand bone loss at 24 and 54 weeks in patient with PsA treated with infliximab or placebo.

Methods: The IMPACT study compared the efficacy of infliximab (INFX) to placebo (PLA) in patients with PSA [1]. Patients with persistent disease activity could enter early escape at week 16, and all remaining placebo patients crossed over to infliximab at week 24. The present sub analyses included a subset of 37 patients from the 60 patients with the

largest radiographic changes at 24 weeks, equally divided according to treatment and positive/negative X-ray changes. Hand bone loss was assessed by digital X-ray radiogrammetry bone mineral density (DXR-BMD), calculated from digitized radiographs (Sectra, Sweden) [2]. DXR-BMD percentage change from baseline to 24 and 52 weeks was evaluated. Non-parametric group comparisons and correlation analyses were performed.

Results: Mean age was 46.8 yrs, 42% were females and mean disease duration was 8.1 yrs. 53% were using methotrexate and 13% oral steroids at baseline. Patients had a high disease activity with mean CRP of 3.47 mg/dl. The median changes in DXR-BMD for all patients were −0.38% at 24 weeks (N=37) and −0.04% at 54 weeks (N=26). While stratifying for treatment there was a suggestion at 24 weeks that the infliximab group lost less bone than the placebo group (−0.24% INFX vs. −0.50% PLA, p=0.50) while at 54 weeks there was greater difference in DXR-BMD change between the two groups (+0.41 % INFX vs. −0.51% PLA, p=0.06). In the placebo group, four patients went trough early escape. There were no significant correlation between radiographic change and DXR-BMD loss at 24 weeks (r= 0.02, p=0.90) or at 54 weeks (r=−0.04, P=0.87).

Conclusion: Our data indicate that hand bone loss in PsA patients treated with anti-TNF is not only arrested but may in fact ameliorate. These findings are in contrast to what has been reported in RA where bone loss only has been shown to be reduced. The results from our study support the hypothesis that both osteoclasts and osteoblasts are involved in the pathophysiological mechanisms of bone involvement in PsA.

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Early Disease Characteristics of Enthesitis-Related Arthritis Reveals Elevated TGF-Beta. Hemalatha Srinivasalu[1], Michael Barnes[2], Gerlinde Layh-Schmitt[3], Michael M. Ward[4] and Robert A. Colbert[3]. [1]NIAMS NIH, Nemours/Alfred I duPont Hospital for Children, Bethesda, MD, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]NIAMS NIH, Bethesda, MD, [4]NIAMS/NIH, Bethesda, MD

Background/Purpose: Enthesitis-related arthritis (ERA) is a subtype of Juvenile idiopathic arthritis (JIA) as defined by ILAR. Most ERA cohorts have been established retrospectively, and consequently there is a paucity of data on early disease characteristics of ERA. The purpose of this study was to examine an inception cohort of ERA and determine correlation between serum cytokine levels and disease manifestations.

Methods: Thirty-seven patients who satisfied ILAR criteria for ERA were included in the study. At their baseline visit, information about demographics, active joint & enthesis count, Schober, presence of eye disease, family history of HLA-B27-associated disease, CHAQ score, physician global, lab analyses including CBC, ESR, CRP, HLA-B27, ANA, RF and imaging studies when indicated, were collected. Serum collected at the baseline visit from patients and healthy controls were analyzed by ELISA for IL-22, IL-23, GM-CSF, IFN-gamma, IL-6, IL-10, IL-12p70, MCP-1, TNF-alpha, G-CSF, IL-17, IP-10, MIP-1alpha and TGF-beta1. Mann-Whitney U tests, one-way ANOVA, and Tukey's multiple comparison tests were performed for statistical analyses.

Results: The median interval from disease onset to enrollment was 5.4 months (IQR 2.05–9.8). Seventy eight percent were males, median age 12 years (IQR 10.15–13.65) and 89% were Caucasian. Positivity of HLA-B27 was 59% (19 of 32 tested) and that of ANA was 25% (4 of 16 tested). The median ESR was 8 (IQR 4–17), CRP 0.3 (IQR 0.3–0.7). The median active joint count was 1 (IQR 0–4) and the median enthesis count was 4 (IQR 2–6). One patient had acute anterior uveitis. Radiological evidence of arthritis was present in 35% of patients; only one patient had sacroiliitis. One patient (2.7%) had back pain and 2 patients (5.4%) had SI joint pain. Ninety three percent of patients were on NSAIDs and 33% had GI complaints at their baseline visit. There was a prior history of joint injection in 27% of patients and a family history of HLA-B27-associated disease in 16% of patients. Levels of IL-22 were lower in ERA patients compared with controls (p=0.0397). TGF-beta1 was elevated in ERA patients compared to controls (p=0.0075). Further, levels of TGF-beta1 were significantly elevated in patients with a history of GI complaints when compared to healthy controls (p=0.0082) and when compared to patients without GI complaints ($p<0.05$). Levels of TGF-beta1 were elevated in patients without arthritis when compared to controls ($p<0.05$). There was no difference in TGF-beta1 levels on comparing patients by presence of enthesitis, HLA-B27 status and inflammatory markers.

Conclusion: This study informs us on the early disease characteristics of ERA. TGF-beta1 has been reported to be elevated in the serum of patients with ankylosing spondylitis. To our knowledge, this is the first study reporting elevation of serum TGF-beta1 in patients with ERA. This finding correlates with earlier studies we have published on evidence for a TGF-beta1 peripheral blood gene expression signature in ERA patients. Additionally, TGF-beta is known to be elevated in chronic gut inflammation; its elevation in patients with GI complaints seen in our cohort suggests a role of gut inflammation in early ERA.

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Clinical Predictors Associated with Severe Radiographic Sacroilitis in Axial Spondyloarthritis. Grace Yoon[1], Thomas J. Learch[2], John C. Davis[3] and Lianne S. Gensler[4]. [1]UCSF, San Franciscao, CA, [2]Cedars-Sinai, Los Angeles, CA, [3]Genentech Inc, South San Francisco, CA, [4]UCSF, San Francisco, CA

Background/Purpose: Sacroilitis is the hallmark radiographic feature of Axial Spondyloarthritis (ASpA). To date, there has been little published on the predictors of radiographic severity of sacroilitis. The objective of this study was to determine if there were clinical predictors of severe sacroilitis, as defined by completely fused sacroiliac joints (grade 4 according to the New York classification scale).

Methods: We studied 151 consecutive ASpA subjects who met Assessment of SpondyloArthritis (ASAS) criteria for axial SpA. All subjects underwent radiographic imaging using the anterior-posterior pelvis view. Right and left sacroiliac joints were scored by 2 of the investigators (LG, TL). The average of the scores was then calculated and used in the analysis. Forty two patients were found to have bilateral grade 4 sacroilitis and 109 patients were calculated to have less than grade 4 sacroilitis. Demographics and clinical variables were collected at the time the radiograph was obtained. Statistical analysis was performed using the student t-test and wilcoxan ranksum for continuous variables and a chi-square analysis for dichotomous variables. A multivariate logistic regression was performed adjusting for age and gender.

Results: Severe sacroilitis was significantly associated with non-Caucasian ethnicity, disease duration and a history of total hip arthroplasty. Having a first degree relative with Ankylosing Spondylitis (AS) was also a predictor of severe sacroilitis as was smoking tobacco as measured by pack years (Table 2).

Table 1. Univariate Analysis

Predictor	Sacroilitis < grade 4 (n = 109)	Sacroilitis = grade 4 (n = 42)	P value
Age (years)	37.7 ± 10.0	41.9 ± 13.2	.16
Gender (% male)	64	79	.09
Ethnicity (% non-Caucasian)	**34**	**57**	**.009**
% Modified NY criteria	64	100	<.0001
Disease duration (years)	**13.3 ± 9.8**	**20.1 ± 11.4**	**.0007**
HLA B27 positivity (%)	81	89	.25
Age at onset	**24.4 ± 9.3**	**21.8 ± 8.5**	**.05**
History of Uveitis (%)	47	40.5	.46
History of peripheral symptoms (%)	58	49	.32
Total hip arthroplasty (%)	**3**	**14**	**.008**
Family history of AS in a first degree relative (FDR) (%)	**10**	**32**	**.002**
On biologic (%)	31	41	.28
Smoking (pack years)	**1.4 ± 4.3**	**6.2 ± 12.8**	**.04**
Employed (%)	83	73	.19
Education (years)	16.6 ± 2.5	15.2 ± 3.9	.1
BASDAI (0–100)	37.3 ± 24.6	38.3 ± 20.5	.67
Inflammation score (0–100)	41.3 ± 31	33.1 ± 24.5	.2
ASDAS (ESR)	15 ± 10.3	14 ± 8.1	.85
ASDAS (CRP)	14.1 ± 9.52	13.8 ± 8.4	.99
BASFI (0–100)	**23.3 ± 24.3**	**33.4 ± 26**	**.02**
ESR (mm/hour)	15.9 ± 20.9	17.3 ± 16.6	.29
CRP (g/dL)	**6.7 ± 12.3**	**9.9 ± 11.4**	**.006**

Table 2. Multivariate Logistic Regression (after adjustment for age and gender)

Predictor	Odds ratio	P value	95% Confidence Interval
Non-Caucasian ethnicity	3.3	.02	1.26; 8.79
Disease duration	1.07	.05	1; 1.13
Total hip arthroplasty	27.9	.0004	2.84; 274.3
Family history of AS (in a FDR)	4.65	.01	1.44; 15
Smoking (pack years)	1.13	.006	1.04; 1.23

Conclusion: Severe radiographic sacroilitis appears to be associated with predictable characteristics like disease duration and total hip arthroplasty, but also appears to be associated with less reported characteristics such as familial AS and tobacco use. Smoking may be a modifiable risk factor for the development of severe radiographic AS.

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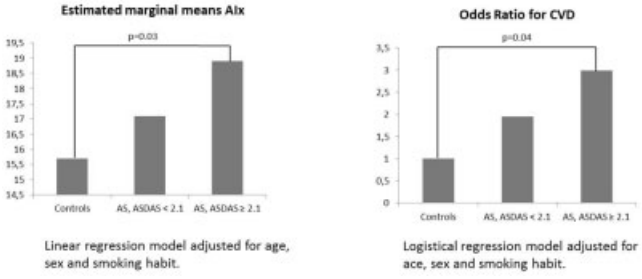
Increased Risk of Cardiovascular Disease in Patients with Active Ankylosing Spondylitis. Inger Jorid Berg[1], Sella Provan[2], Hanne Dagfinrud[3], D.M.F.M. van der Heijde[4], Tore K. Kvien[3] and Anne Grete Semb[3]. [1]Diakonhjemmet Hospital, 0319 Oslo, Norway, [2]Diakonhjemmet hospital, Oslo, Norway, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: The increased risk of cardiovascular disease (CVD) in inflammatory joint diseases cannot be explained by traditional risk factors. There are studies suggesting a higher risk of CVD in patients with ankylosing spondylitis (AS). The aim of this study was to compare prevalence of established CVD and levels of Augmentation Index (AIx), a surrogate marker of CVD risk, between a cohort of AS patients and a population control group and to evaluate the influence of disease activity measured by the ankylosing spondylitis disease activity score (ASDAS).

Methods: In 2008–2010 161 patients from the Oslo area with AS and 134 controls were examined. The AS patients were evaluated as a part of the 5-year longitudinal follow-up of a cohort of hospital-recruited patients diagnosed according to the New York classification criteria. The control population was randomly selected by Statistics Norway. AIx estimation, measuring arterial stiffness, was performed using the Sphygmocor apparatus. The ASDAS score was calculated using the appropriate BASDAI questions and CRP levels. The ASDAS cutoff was set at 2.1 dividing patients into low-moderate and high-very high disease activity. Statistical analyses were performed in SPSS 17.0 using bivariate tests as appropriate. Validity of the results was confirmed in logistical and linear regression models adjusted for age, sex and smoking habits.

Results: The groups were comparable regarding demographic data (AS vs. controls): age (50.7 vs. 52.6 p=0.17), gender/male (61.9% vs. 58.5% p=0.52) and smoking (56.4% vs. 60.4% p=0.48), but as expected there were significant differences regarding ESR (16 vs. 8 p<0.001) and CRP (3 vs.1 p<0.001). Total cholesterol was significant lower in the AS group compared to controls: (mean±SD) 5.41± 1.12mmol/l vs. 5.75±0.96mmol/l p=0.008. In subgroup analyses AIx was significantly higher in the high-very high ASDAS compared to controls 19 (CI 16.9–21.0) vs16 (CI 14.7–17.6). Odds ratio for CVD was 3.0 (CI 1.04–8.62) in high-very high ASDAS compared to controls. The subgroup analyses are presented in Figure 1.

Figure 1
Levels of AIx and OR for CVD compared across AS disease activity, measured by ASDAS, and population controls.



Linear regression model adjusted for age, sex and smoking habit.

Logistical regression model adjusted for ace, sex and smoking habit.

Conclusion: We found significantly higher odds ratio (OR) for established CVD among patients with active AS despite the total AS group having significantly lower total cholesterol. The increased risk of CVD was further confirmed by a significantly increased AIx in patients with high ASDAS. The results indicate that there might be a higher risk of CVD in AS patients with the most active disease.

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Differences Between Women and Men with Recent Onset Axial Spondyloarthritis: Results From the DESIR Cohort. Anne Tournadre[1], Bruno Pereira[1], Agnes Lhoste[1], Jean Jacques Dubost[1], Jean Michel Ristori[1], Pascal Claudepierre[2], Maxime Dougados[3] and Martin Soubrier[1]. [1]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [2]Paris-Est University; LIC EA4393; APHP, Henri Mondor Hospital, Creteil, France, [3]Paris-Descartes University, Medicine Faculty; UPRES EA-4058; APHP, Cochin Hospital, Paris, France

Background/Purpose: To characterize clinical and imaging differences between men and women with early axial spondyloarthritis (SpA).

Methods: 708 patients with recent inflammatory back pain and possible diagnosis of SpA were included in the DEvenir des Spondylathropathies Indifférenciées Récentes (DESIR) cohort, a prospective longitudinal multicentric cohort in France. Clinical and imaging features between men and women fulfilling the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA were compared using univariate analysis. Significant variables in univariate analysis were re-tested as dependent variables in multivariate regression models adjusted for age.

Results: The table shows significant differences (p values < 0.05) between men and women with SpA according ASAS classification criteria. Mean duration of axial symptoms, HLA B27 status, response to NSAID, history or current symptoms suggestive of peripheral joint arthritis, presence of enthesiopathy, extraarticular involvement, spinal mobility assessed by the the Bath Ankylosing Spondylitis Metrology Index, and the Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) were not different.

Table. Comparison of baseline characteristics between men and women with SpA. (mean ± SD or % of patients)

	Men (n=239)	Women (n=236)	p-value
age (years)	31.92 ± 8.4	34.05 ± 8.7	<0.05
BASG	45 ± 2.6	52.5 ± 2.65	0.004
BASDAI	39.59 ± 20.44	46.52 ± 19.87	<0.001
BASDAI fatigue	49.7 ± 0.15	60.8 ± 0.15	<0.001
Intensity of axial pain (NRS*)	4.25 ± 2.8	5.18 ± 2.76	0.001
Intensity of peripheral joint pain (NRS*)	2.78 ± 2.76	3.32 ± 2.81	<0.05
Localization of symptoms to cervical spine	29.3%	44.1%	<0.05
Localization of symptoms to buttock	69.9%	79.7%	<0.05
BASFI	26.84 ± 21.23	32.66 ± 23.28	<0.05
SF-36 Mental Health score	55.06 ± 21.35	47.9 ± 19.72	0.001
SF-36 Physical Health score	52.58 ± 21.03	45.16 ± 19.20	<0.001
HAQ-AS	0.47 ± 0.39	0.61 ± 0.44	<0.001
AS-Qol	7.96 ± 4.99	10.23 ± 4.79	<0.001
Radiological sacroiliitis (Obvious change and/or fusion)	45.1%	32.9%	<0.05
MRI inflammatory lesions of the sacroiliac joints	58.9%	40.3%	<0.001
MRI inflammatory lesions of the spine:			
− Lumbar spine	−23.3%	−9.9%	<0.001
− Thoracic spine	−27%	−10.9%	<0.001
− Cervical spine	−6.1%	−2.3%	<0.05

* NRS, numerical rating scale

Conclusion: Women with early axial SpA according to ASAS classification criteria had less radiological and MRI abnormalities than men despite higher functional impairment. Differences in the disease expression in women may be confounding factors to establish the diagnosis of SpA and to assess the disease activity.

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Poor Agreement Between Enthesitis on Whole-Body Magnetic Resonance Imaging and Enthesitis on Clinical Examination in Patients with Early Axial Spondyloarthritis—Results From the ESTHER Trial At Baseline. In-Ho Song[1], Kay-Geert Hermann[2], Hildrun Haibel[1], Christian Althoff[2], Denis Poddubnyy[1], Joachim Listing[3], Anja Weiβ[3], Bruce Freundlich[4], Martin Rudwaleit[5] and Joachim Sieper[1]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Charite Medical School, Berlin, Germany, [3]German Rheumatism Research Centre, Berlin, Germany, [4]University of Pennsylvania, Philadelphia, PA, [5]Ev. Krankenhaus Hagen-Haspe, Hagen, Germany

Background/Purpose: In patients with early axial spondyloarthritis (SpA) with a disease duration of < 5 years to assess the agreement between enthesitis on whole-body magnetic resonance imaging (MRI) and enthesitis by clinical examination.

Methods: At baseline 76 patients with early axial SpA were examined for enthesitis by clinical examination and by whole-body MRI. The following 7 enthesitis sites were assessed by MRI (M) and clinical examination (C): manubriosternal synchondrosis (M)/ first costosternal joint (C) (1 site), lower rip insertions at the sternum (M)/ 7th costochondral joints (C) (2 sites, each left and right), pelvic rim (M)/ iliac crest (C) (2 sites, each left and right), proximal insertion of Achilles tendon/ plantar fascia (M/C) (2 sites, each left and right). Kappa values were calculated to assess agreement between MRI findings and clinical examination. MRI enthesitis assessment was performed by two radiologists in consensus approach.

Results: By clinical enthesitis assessment in the above described locations 108 enthesitic sites were found in 40 out of 76 (60.5%) patients. The most frequently affected location was the iliac crest (45 sites in 30 patients) followed by the 7th costosternal joint (26 sites in 16 patients), the insertion of the Achilles tendon/plantar fascia (22 sites in 14 patients) and the 1st costosternal joint (15 sites in 15 patients) (table 1).

Table 1.

MRI enthesitis location	Clinical examination enthesitis location	Number of positive enthesitic sites on MRI	Number of positive enthesitic sites on clinical examination	Agreement*
Synchondrosis manubriosternalis	First Costosternal joint	3 sites in 3 patients	15 sites in 15 patients	1
Lower rip insertions at the sternum (Rip)	Seventh Costosternal joint	Right: 0 sites in 0 patients	11 sites in 11 patients	0
		Left: 0 sites in 0 patients	15 sites in patients	0
		Both: 0 sites in 0 patients	26 sites in 16 patients	0
Pelvic rim (Bec)	Crista iliaca/ Spina iliaca anterior superior/Spina iliaca posterior superior	Right: 1 site in 1 patient	23 sites in 23 patients	1
		Left: 1 site in 1 patient	22 sites in 22 pts	0
		Both: 2 sites in 1 patient	45 sites in 30 patients	1
Achilles tendon insertion (Ach)	Prox. Achilles tendon insertion	Right: 2 sites in 2 patients	9 sites in 9 pts	0
		Left: 2 sites in 2 patients	13 sites in 13 pts	1
		Both: 4 sites in 3 patient	22 sites in 14 patients	1

* 1= yes, 0= no.

Of MRI examination in the above described locations 9 enthesitic sites were found in 6 out of the 76 patients. The most frequently affected sites were the manubriosternal synchondrosis (3 sites in 3 patients), followed by the Achilles tendon insertion (4 sites in 3 patients).

67 out of 76 patients scored the enthesitis question (BASDAI question 4) of the BASDAI ≥1.

The kappa values in terms of single enthesitic sites between MRI and clinical examination was only 0.038. The kappa value on a patient level was also only −0.011. Kappa between clinical examination and self-assessment by BASDAI question 4 was 0.1. In all patients enthesitic only 3 enthesitic sites were found to be positive in both by MRI and clinical examination at the same time.

Conclusion: Clinical and MRI enthesitis was found in 52.6% and 7.9% of patients in the above mentioned enthesitis sites with early axial SpA, respectively. The agreement between clinical and MRI enthesitis assessment was poor.

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Difference in Clinical Presentation of Patients with Spondyloarthritis with a Positive MRI of the SI Joints and/or HLA-B27 Positivity. R. van den Berg, M. Reijnierse, T.W.J. Huizinga and D.M.F.M. van der Heijde. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: The SPondyloArthritis Caught Early (SPACE)-cohort is set-up in the Leiden University Medical Center (LUMC) aiming to diagnose and treat patients with axial spondyloarthritis (SpA) early. Unlike previous criteria sets, the new ASAS axial SpA criteria rely importantly on the presence of active MRI abnormalities of the SI-joints and on HLA-B27 positivity. The goal is to investigate the difference in presentation of patients with an abnormal vs. a normal MRI of the SI-joints and presence vs. absence of HLA-B27.

Methods: All patients with back pain (>3 months, but <2 years; onset <45 years) were included and underwent a diagnostic work-up; MRI and X-rays of the SI-joints and laboratory assessments. All patients were classified according to various classification criteria (ESSG, Amor, ASAS axial SpA, and modified New York criteria). A comparison was made between the patients presenting with a positive vs. a negative MRI of the SI-joints; and between HLA-B27 positive and HLA-B27 negative patients.

Results: In 6/133 patients no MRI was made and they were excluded from further analyses. 3/38 patients not fulfilling any classification criteria set had a positive MRI as only SpA-feature, and 2/38 had only one other SpA-feature in addition to HLA-B27 positivity. The remaining 95 patients fulfilled one or more classification criteria sets. Male patients had more frequently sacroiliitis on MRI than female patients (p=0.04), but were not more frequently HLA-B27 positive (p=0.27). Sacroiliitis on X-ray was more frequently present in patients with MRI+ than in patients with MRI- (p<0.001). Therefore, more patients in the MRI+ group fulfilled the modified New York criteria than in the MRI- group (p=0.003). HLA-B27+ patients had more frequently a positive family history and a history of uveitis than HLA-B27- patients (p<0.001 and p=0.01 respectively). Also, more HLA-B27+ patients fulfilled the ESSG and Amor criteria than HLA-B27- patients (p=0.03 and p=0.004 respectively). The distribution of other SpA-features and the level of disease activity among MRI+ and MRI- patients, and among HLA-B27+ and HLA-B27- patients was remarkably similar (table 1).

Variable	MRI+ group N=28 vs MRI− group N=99		HLA-B27+ group N=42 vs HLA-B27− group N=85	
Male, N (%)	***14 (50.0)***	***29 (29.3)***	17 (40.5)	26 (30.6)
Age (years) onset back pain, mean ± SD	32.5 ± 8.5	29.2 ± 8.9	27.9 ± 8.3	30.0 ± 9.0
Duration (months) back pain, mean ± SD	15.0 ± 7.1	13.1 ± 7.5	12.6 ± 7.6	14.0 ± 7.3
HLA-B27 positive, N (%)	11 (39.3)	31 (31.3)	–	–
Pos. fam. history SpA, N (%)	7 (25.0)	38 (38.4)	***26 (61.9)***	***19 (22.4)***
Uveitis, N (%)	0 (0.0)	10 (10.1)	***7 (16.7)***	***3 (3.5)***
SI-itis MRI, N (%)	–	–	11 (26.2)	17 (20.0)
SI-itis X-ray, N (%)	***8 (29.6)***	***5 (5.1)***	7 (15.6)	7 (8.1)
IBP, N (%)	18 (64.3)	68 (68.7)	32 (76.2)	54 (63.5)
Enthesitis, N (%)	2 (7.1)	13 (13.1)	5 (11.9)	10 (11.8)
Dactylitis, N (%)	1 (3.6)	2 (2.0)	0 (0.0)	3 (3.5)
IBD, N (%)	3 (10.7)	5 (5.1)	1 (2.4)	7 (8.2)
Good response to NSAIDs, N (%)	9 (32.1)	31 (31.3)	14 (33.3)	26 (30.6)
Elevated ESR/CRP, N (%)	5 (17.9)	18 (18.2)	10 (23.8)	13 (15.3)
Preceding infection, N (%)	0 (0.0)	4 (4.0)	2 (4.8)	2 (2.4)
Peripheral arthritis, N (%)	4 (14.3)	15 (15.2)	6 (14.0)	14 (16.7)
Psoriasis, N (%)	3 (10.7)	10 (10.1)	4 (9.5)	9 (10.6)
Alternating buttock pain, N (%)	7 (28.0)	14 (14.4)	8 (20.0)	13 (15.9)
BASDAI mean ± SD (N=126)	4.4 ± 2.2	4.5 ± 2.0	4.1 ± 2.3	4.6 ± 1.9
ASDAS mean ± SD (N=126)	2.7 ± 0.9	2.8 ± 0.9	2.6 ± 1.0	2.8 ± 0.8
ESSG, N (%)	11 (39.3)	56 (56.6)	***28 (66.7)***	***39 (45.9)***
AMOR (6 pnt), N (%)	12 (42.9)	35 (35.4)	***23 (54.8)***	***24 (28.2)***
ASAS axial, N (%)	***24 (85.7)***	***31 (31.3)***	***39 (92.9)***	***16 (18.8)***
Modified New York, N (%)	***6 (21.4)***	***4 (4.0)***	5 (11.9)	5 (5.9)

Italics are statistically significantly different.

Conclusion: The presence and distribution of SpA-features as well as the level of disease activity in MRI+ and MRI-patients and in HLA-B27+ and HLA-B27- patients is similar. Sacroiliitis on X-ray and male gender are associated with MRI positivity; a positive family history and uveitis are associated with HLA-B27 positivity. ESSG and AMOR criteria are associated with HLA-B27 positivity but not MRI+, modified New York criteria with MRI+, and ASAS axial SpA criteria with both MRI+ and HLA-B27 positivity.

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Comparing 2 Referral Strategies to Diagnose Axial Spondyloarthritis: The Recognizing and Diagnosing Ankylosing Spondylitis Reliably Study. J. Sieper[1], S. Srinivasan[2], O. Zamani[3], H. Mielants[4], D. Choquette[5], Karel Pavelka[6], Anne Gitte Loft[7], P. Gehér[8], D. Danda[9], T. Reitblat[10], Fabrizio Cantini[11], C. Ancuta[12], S. Erdes[13], H. Raffayova[14], AC Keat[15], JS Hill Gaston[16] and N. Vastesaeger[17]. [1]Charitè Berlin, Campus Benjamin Franklin, Berlin, Germany, [2]Merck, Sharp & Dohme Corporation, Rahway, NJ, [3]Rheumazentrum Favoriten, Wien, Austria, [4]University Hospital, Gent, Belgium, [5]Institute of Rheumatology of Montreal, Montreal, QC, [6]1Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [7]Vejle Hospital, Vejle, Denmark, [8]Semmelweis University, Budapest, Hungary, [9]Christian Medical College, Vellore, India, [10]Barzilai Medical Centre, Ashkelon, Israel, [11]Stabilimento Ospedaliero Misericordia, Prato, Italy, [12]G.T. Popa Center for Biomedical Research, Iasi, Romania, [13]Scientific Institute of Rheumatology, Moscow, Russia, [14]National Institute of Rheumatic Diseases, Pieš □ any, Slovakia, [15]Northwick Park Hospital, Harrow, United Kingdom, [16]Univ of Cambridge/Clin Med, Cambridge, United Kingdom, [17]Merck, Sharp & Dohme Corporation, Brussels, Belgium

Background/Purpose: Improved referral from primary care (PC) allows shortening the time to diagnosis of axial spondyloarthritis (SpA), which may lead to better treatment and improved prognosis. The objective of the RecognizIng and Diagnosing Ankylosing Spondylitis Reliably(RADAR) study was to determine which of 2 referral strategies, when used by physicians for chronic back pain (CBP) patients, is superior in diagnosing definite axial SpA by rheumatologists.

Methods: Primary-care referral sites in 16 countries were randomized (1:1) to refer CBP patients to a rheumatologist according to 1 of 2 referral strategies: *Strategy I*, 1 of 3 criteria—inflammatory BP (IBP), HLA-B27+, sacroiliitis on imaging (SI); or *Strategy II*, 2 of 6 criteria—IBP, HLA-B27+, SI, family history, good response to NSAIDs, extra-articular manifestations (EAMs). The rheumatologist then established a diagnosis. The primary analysis compared the proportion of patients diagnosed with axial SpA depending on the referral strategy used. Reported are: usage of referral criteria in PC, concordance with rheumatologist, sensitivity, specificity, predictive values (PV), and likelihood ratio of the criteria to make a diagnosis.

Results: Subjects had CBP of unknown origin >3 months, onset before age 45, and no diagnosis of axial SpA or ankylosing spondylitis established yet. Strategy I was used at 135 primary-care sites to refer 504 subjects of which 35.6 were diagnosed with axial SpA. Strategy II was used at 143 primary-care sites to refer 568 subjects of which 39.8% were diagnosed with axial SpA. (For both strategies: delta: 4.40%, 95%CI: –7.09% to 15.89%, ns.) IBP was the most used referral criterion, and rheumatologist concordance was high (Table). PV for SI, HLA-B27, or EAMs judged positive by PC physicians were 72.5, 76.1, and 55.6%, respectively, and +/– 40% for other criteria. Negative PV and sensitivity of IBP judged by rheumatologists was >85%, but positive PV and specificity was <50%. NPV and/or sensitivity of any other single criterion was <80%. Analysis of alternative strategies showed that referral on 2 of 2 criteria performed poorly, whereas many 2 of 3 strategies, most of which included SI, performed well. But only the strategy with SI, HLA-B27, and IBP had sensitivity, specificity, NPV, and PPV >80%.

Referral Criteria and Rheumatologist Results

Criterion	Usage by Referring Physician			Concordance with Rheumatologist		
	Strategy 1 (%)	*Strategy 2 (%)*	*Combined (%)*	*Strategy 1 (%)*	*Strategy 2 (%)*	*Combined (%)*
SI	137 (27.2)	204 (35.9)	341 (31.8%)	90 (68.2)	120 (61.5)	210 (64.2)
HLA-B27	87 (17.3)	97 (17.1)	184 (17.2)	82 (97.6)	87 (96.7)	169 (97.1)
IBP	469 (93.1)	546 (96.1)	1015 (94.7)	376 (84.5)	425 (86.2)	801 (85.4)
EAMs		112 (19.7%)			98 (89.1)	
Family history		66 (6.2)			42 (76.4)	
NSAID response		428 (75.4)			240 (60.2)	

Conclusion: This is the first international randomized study to show that a referral strategy for CBP based on 3 criteria performs as well as one with 6 and leads to diagnosis of axial SpA in >35% of patients. IBP was nearly always used, showed good concordance with rheumatologists, and had high sensitivity and NPV. Combining IBP with other criteria such as HLA-B27 and SI increases the likelihood of diagnosis.

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Associations Between Axial and Peripheral Signs of Ankylosing Spondylitis and the Acute Phase Response: A Prospective Longitudinal Study in 411 Patients. Siddharth Bethi[1], Abhijit Dasgupta[1], Michael H. Weisman[2], Thomas J. Learch[3], Lianne S. Gensler[4], John C. Davis[5], John D. Reveille[6] and Michael M. Ward[1]. [1]NIAMS/NIH, Bethesda, MD, [2]Cedars Sinai Med Ctr, Los Angeles, CA, [3]Cedars-Sinai, Los Angeles, CA, [4]UCSF, San Francisco, CA, [5]Genentech Inc, South San Francisco, CA, [6]University of Texas Health Science Center at Houston, Houston, TX

Background/Purpose: The value of acute phase reactants as outcome measures in ankylosing spondylitis (AS) is often questioned. Although erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are associated with peripheral joint involvement, it is not clear if they are also associated with axial manifestations. We investigated associations between musculoskeletal exam findings and ESR and CRP in AS. The objectives were to investigate whether the acute phase response was associated with axial signs, with peripheral signs, or with both; to determine if signs were associated with ESR and CRP accounting for BASDAI; and to determine if the ESR or CRP had a stronger association with physical signs of AS.

Methods: We examined 411 patients with AS in a prospective longitudinal study at 4 centers. Patients were examined at intervals of 4 to 6 months for up to 5 years. On each visit, we scored the number of swollen and tender joints, number of tender entheses, and measured cervical rotation and lateral flexion, chest expansion, hip rotation, Schober test, and lumbar lateral flexion. ESR and CRP were measured at each visit. We tested associations between each physical exam sign and ESR and CRP longitudinally using mixed linear models, adjusted for age, gender, months from study entry, ethnicity, education level, duration of AS and examining rheumatologist. Analyses used log-transformed ESR and CRP as the dependent variables, so models estimate the % change in median ESR (or CRP) with 1 unit change in the physical exam measure.

Results: Patients (69% men; median age 40.1 years; median duration of AS 13.8 years) had a median of 3 visits (range 1–6; total visits 1620). There was substantial intra-patient variation in ESR and CRP levels. The exam feature most strongly associated with acute phase response was the swollen joint count. In patients with 3 or more swollen joints, the median ESR was 17.5% higher and the median CRP was 74.5% higher than in those with no swollen joints (table). Less hip rotation was associated with higher ESR but not CRP. Tender joint count and enthesis count were not associated with ESR or CRP. Axial signs were associated with ESR and CRP independent of peripheral signs and BASDAI. Patients with a higher chest expansion had a lower acute phase response: with every 1 cm increase in chest expansion the median ESR was 3.4% lower and CRP was 12.2% lower. Lumbar lateral flexion was associated with both ESR and CRP, while cervical flexion and Schober test were also associated with CRP. Adjusting for physical signs, neither BASDAI item was associated with ESR, but BASDAI 5+6 was associated with CRP.

Measures	% Change in median ESR	P	% Change in median CRP	P
Cervical rotation (per 10 degrees)	0.3%	0.60	3.6%	0.10
Cervical lateral flexion (per 10 degrees)	−0.6%	0.31	**−5.8%**	0.005
Occiput to wall (per cm)	−0.2%	0.53	−1.0%	0.32
Chest expansion (per cm)	**−3.4%**	<0.0001	−12.2%	<0.0001
Schober (per cm)	−0.5%	0.46	**−5.9%**	0.04
Lateral flexion (per cm)	**−1.1%**	0.003	−4.3%	0.0006
Hip rotation (per 10 degrees)	**−2.8%**	0.007	4.8%	0.29
Enthesis	−0.3%	0.57	−3.1%	0.13
Bad hip=1 vs. 0	−7.5%	0.31	−7.4%	0.75
Bad hip=2 vs. 0	−6.4%	0.41	−3.0%	0.89
Bad hip=3 vs. 0	−10.4%	0.21	13.5%	0.65
Tender joints=1 vs. 0	0.8%	0.76	−1.9%	0.88
Tender joints=2 vs. 0	−3.2%	0.31	−1.7%	0.90
Tender joints=3+ vs. 0	−1.1%	0.81	9.9%	0.53
Swollen joints=1 vs.0	2.8%	0.61	20.6%	0.24
Swollen joints=2 vs. 0	−3.0%	0.66	**56.2%**	0.03
Swollen joints=3+ vs. 0	**17.5%**	0.05	74.5%	0.02
BASDAI2	0.9%	0.12	0.9%	0.69
BASDAI 5+6	0.9%	0.17	**4.6%**	0.05

Conclusion: Acute phase response is associated with both axial and peripheral signs of AS. These associations were above and beyond patient

reported symptoms. CRP had stronger associations than ESR and was associated with more axial signs, suggesting it is the preferred measure.

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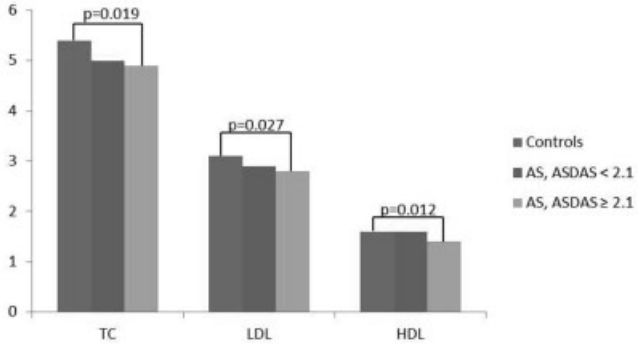
Low Lipid Levels are related to Disease activity in Ankylosing Spondylitis. Inger Jorid Berg[1], Anne Grete Semb[2], Désirée van der Heijde[3], Hanne Dagfinrud[2], Sella Provan[4] and Tore K. Kvien[2]. [1]Diakonhjemmet Hospital, 0319 Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [4]Diakonhjemmet hospital, Oslo, Norway

Background/Purpose: Despite an increased risk of cardiovascular disease in ankylosing spondylitis (AS), low lipid levels have been reported. The aim of this study was to evaluate the assosiations between disease activity measured by the AS disease activity score (ASDAS) and lipid levels.

Methods: In 2008–2010 161 patients from the Oslo area with AS and 134 controls were examined. The AS patients were evaluated as a part of the 5-year longitudinal follow-up of a cohort of hospital-recruited patients diagnosed according to the mNew York classification criteria. The control population was randomly selected by the Statistics Norway. Both groups underwent the same examinations. The ASDAS score was calculated using the appropriate BASDAI questions and CRP levels. The ASDAS cut off was set at 2.1 between low-moderate and high-very high disease activity. Statistical analyses were preformed in SPSS 17.0. Bivariate tests were used to compare the groups. Lipid levels were compared between patients and controls by linear regression models adjusted for age, sex and use of statins and the estimated marginal means were calculated.

Results: The groups were comparable regarding demographic data (AS vs controls): age (years) (50.7 vs. 52.6 p=0.17), gender/male (61.9% vs 58.5% p=0.52) and use of statins (13.5% vs 12.1% p=0.74), but levels of acute phase reactants were as expected different (ESR 16 vs. 8 p<0.001; CRP 3 vs. 1, p=0.001). In adjusted analysis atherogenic lipids were lower in the whole AS group compared to controls: Total cholesterol 5.10mmol/l (CI 4.89–5.30) vs. 5.33mmol/l (CI 5.11–5.55), p=0.05 and LDL 2.87mmol/l (CI 2.68–3.06) vs. 3.11mmol/l (CI 2.91–3.32), p=0.03, whilst there was no significant difference in HDL levels between AS and controls (1.54mmol/l (CI 1.45–1.63) vs. 1.56mmol/l (CI 1.47–1.66), p=0.73). Within the AS patients, lipid levels were lower in patients with high-very high ASDAS vs. low-moderate ASDAS. This difference was significant for HDL; 1.43mmol/l (1.31–1.55) vs. 1.61mmol/l (CI 1.48–1.64), p=0.01, but not significant for total cholesterol; 4.91mmol/l (CI 4.61–5.21) vs. 5.05mmol/l (CI 4.74–5.37), p=0.42 and LDL; 2.74mmol/l (CI 2.46–3.02) vs. 2.80mmol/l (2.51–3.09), p=0.71. The estimated marginal means lipid levels split across disease activity levels are presented in figure 1.



Conclusion: Patients with AS have lower lipids than controls. We also found a trend in the direction of lower lipid levels in patients with high disease activity measured by ASDAS.

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Circulating Mediators of Bone Remodelling in Patients with Psoriatic and Rheumatoid Arthritis Treated with Anti-TNF-Alpha Therapy. Agnes Szentpetery[1], Harjit P. Bhattoa[2], Peter Antal-Szalmas[2], Zoltan Szekanecz[3] and Oliver M. FitzGerald[1]. [1]St. Vincent's University Hospital, Dublin, Ireland, [2]University of Debrecen, Medical and Health Science Center, Debrecen, Hungary, [3]University of Debrecen Medical and Health Sciences Center, Debrecen, Hungary

Background/Purpose: Dickkopf-1 (Dkk-1), an inhibitor of Wnt signalling, receptor activator of nuclear factor kappa B ligand (RANKL), an osteoclast differentiation factor and its soluble inhibitor osteoprotegerin (OPG) are key regulators of bone remodelling activity. Both rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are characterised by bone erosion; but bone formation is also a feature in PsA. The molecular basis of the different patterns of bone remodelling is unknown. It has been shown that TNF-alpha inhibits bone formation by up-regulating Dkk-1 and promotes osteoclastogenesis by stimulating RANKL production. The effect of anti-TNF-alpha on soluble mediators of bone remodelling in RA and PsA has not previously been compared in a prospective study design.

The aim of this study was to: (1) compare both the very early (1 month) and more long-term (12 months) effects of anti-TNF-alpha treatment on serum Dkk-1, RANKL and OPG in patients with RA and PsA; and (2) to explore associations between circulating mediators of bone remodelling and measurements of clinical parameters.

Methods: RA and PsA patients with active disease were recruited following a decision to start anti-TNF-alpha therapy. Serum was analysed for Dkk-1, RANKL and OPG by ELISA at baseline, 1 month and 12 months. Clinical assessments including ESR, CRP, and DAS28-CRP were recorded at all time points.

Results: 62 patients (35 RA, 27 PsA) were recruited. Mean disease duration was 9 years. Serum Dkk-1 and RANKL levels did not change in either RA or PsA during the course of the study. OPG levels were significantly higher at 1 year compared to 1 month in RA (p=0.03) whilst there was no significant difference in OPG observed in PsA during the study. Dkk-1 and RANKL levels were not significantly different comparing RA with PsA at any time point while Dkk-1 levels were lower at 1 year approaching significance (p=0.08). RANKL levels were lower at all time points in PsA. OPG levels were lower in PsA compared to RA at all time points with a significant reduction at 1 year (p=0.01). OPG/RANKL ratio reflecting remodelling balance was similar and did not change significantly in either RA or PsA during the course of the study.

OPG levels were correlated with ESR (r=0.42, p=0.04) and CRP levels (r=0.46, p=0.02) at baseline in PsA, whilst OPG levels were associated with ESR (r=0.43, p=0.04) and CRP (r=0.46, p=0.03) at 1 year in RA. No correlations were found between Dkk-1 and RANKL and markers of disease activity.

Conclusion: This study indicates differences in the regulation of bone remodelling between RA and PsA. Dkk-1 and RANKL levels may be lower in PsA consistent with both the fewer erosions and the accelerated bone formation seen in this disease. OPG, but not Dkk-1 and RANKL, is associated with markers of systemic inflammation in RA and PsA but increases further with effective treatment in RA suggesting that there is uncoupling between factors that drive inflammation and those responsible for erosive change.

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Spondyloarthritis: A Clinical Comparison Between Men and Women. Jacqueline E. Paramarta, Leen E. De Rycke, Carmen A. Ambarus, Paul P. Tak and Dominique L. Baeten. Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Many studies report a male predominance in ankylosing spondylitis (AS), the most prevalent and typical form of spondyloarthritis (SpA). As AS represents only part of the SpA spectrum, an alternative explanation is that the disease has no gender bias but is less typical or severe (including progression towards new bone formation) in females. With the recent treatment advances it becomes increasingly important to recognize also less typical presentations as early as possible in the disease course. The aim of this study was to assess whether gender affects the clinical presentation of SpA in terms of prevalence, symptoms and severity.

Methods: 175 patients presenting on a dedicated SpA outpatient clinic fulfilling the European Spondyloarthropathy Study Group (ESSG) criteria were recruited in a prospective inception cohort. The patient's and physician's global assessment of disease activity visual analogue scale (VAS), Bath Ankylosing Spondylitis Disease Activity (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), 68 swollen and tender joint count, Schober, ESR and CRP were measured. Parametric tests were used for normally distributed data and non-parametric tests for non-normally distributed data.

Results: The demographic and clinical characteristics are shown in Table 1. The cohort included 93 men and 82 women, who had a comparable age and disease duration. The prevalence of the SpA subtypes AS, undifferentiated

spondyloarthritis (USpA), inflammatory bowel disease related SpA (IBD-SpA) and reactive arthritis (ReA) was not significantly different between men and women. Only psoriatic arthritis (PsA) was significantly more common in men (32% vs. 18%). Classification into axial versus peripheral SpA showed no gender difference as axial disease was more common in both genders. Also HLA-B27 positivity (47% and 48%, respectively) and sacroiliitis on conventional X-ray (61% and 56%, respectively) were similar in males and females. The BASDAI (4.3 in men and 5.3 in women) and ESR (7 mm/h in men and 14 mm/h in women) were slightly but significantly higher in females. The other disease activity parameters were comparable. This trend towards higher disease activity in women was found in all SpA subtypes. Accordingly, anti-TNF therapy was more often initiated in women (39%) than in men (26%) during follow-up.

Table 1. Demographic and clinical characteristics

	Men (n=93)	Women (n=82)	*P*
Age, mean (SD) years	44.1 (12.3)	45.5 (13.2)	NS
Age at disease onset, median (range) years	34.0 (9.1–62.1)	38.6 (17.2–75.6)	NS
Disease duration, median (range) years	4.0 (0.0–46.8)	3.0 (0.0–31.1)	NS
AS, %	46.2	37.8	NS
PsA, %	32.3	18.3	0.035
USpA, %	18.3	28.0	NS
ReA, %	3.2	0.0	NS
IBD-SpA, %	11.8	22.0	NS
HLA-B27 positive, %	47.1	47.9	NS
Inflammatory back pain, %	74.2	81.7	NS
Peripheral arthritis, %	60.2	57.3	NS
Sacroiliitis low grade, %	15.1	17.1	NS
Sacroiliitis high grade, %	46.2	39.0	NS
Patient's global assessment VAS, median (range)	48 (0–98)	57.5 (4–100)	NS
Physician's global assessment VAS, median (range)	38.5 (2–90)	42.5 (1–81)	NS
BASDAI, median (range)	4.3 (0.0–8.5)	5.3 (0.4–9.2)	0.011
BASDAI ≥4, %	53.3	70.5	0.023
ASDAS <1.3 (inactive disease), %	23.7	20.3	NS
1.3≤ ASDAS <2.1 (moderate disease activity), %	32.9	18.8	NS
2.1≤ ASDAS≤3.5 (high disease activity), %	42.1	57.8	NS
ASDAS >3.5 (very high disease activity), %	1.3	3.1	NS
Swollen joint count, median (range) 0–66 joints	0 (0–26)	0 (0–8)	NS
Tender joint count, median (range), 0–66 joints	0 (0–34)	0 (0–21)	NS
Schober, mean (SD) centimetres	4.1 (1.3)	3.8 (1.0)	NS
ESR, median (range) mm/h	7 (1–55)	14 (2–61)	0.001
CRP, median (range) mg/l	2.6 (1.0–73.6)	4.0 (1.0–209.3)	NS

Conclusion: Gender does not profoundly affect the clinical presentation of SpA, with exception of a male predominance in the PsA subtype and slightly higher disease activity in females. These data emphasize the need for early diagnosis and adequate treatment of SpA independently of the gender of patients.

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Evidence for a Link Between Inflammation and Radiographic Progression in Ankylosing Spondylitis. Nigil Haroon[1], Nathalie Morency[2], Richard J. Cook[3], Ker-Ai Lee[3], Stephanie Wichuk[2], Proton Rahman[4], Dafna D. Gladman[1], Robert D. Inman[1] and Walter P. Maksymowych[2]. [1]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [2]University of Alberta, Edmonton, AB, [3]University of Waterloo, Waterloo, ON, [4]St. Claires Mercy Hospital, St. Johns, NF

Background/Purpose: Controversy exists as to the possible link between inflammation and the development of radiographic progression in ankylosing spondylitis (AS). Studies of tumor necrosis factor (TNF) blockers have shown no impact while prospective cohort data have as yet not shown consistent associations between markers of inflammation and progression. Imaging data suggest that new bone may develop following resolution of inflammation with TNF blockers. This hypothesis formed the basis for this prospective analysis aimed at assessing not only baseline CRP but also the change in CRP following TNF blocker therapy as a predictor of radiographic progression over 2 years in patients with SpA.

Methods: The Spondyloarthritis Research Consortium of Canada (SPARCC) cohort comprises patients with AS followed prospectively with clinical and radiographic outcomes. Readers scored X-rays obtained at baseline and year 2 using the mSASSS method. Pre-specified dependent variables were: 1) change in mSASSS >0 and >2 units from baseline through 2 years, 2) development of new syndesmophytes at year 2, 3) spur and ankylosis score (SAS: score for ankylosis = 3 and spur = 2 per vertebral corner). Multivariate analyses were controlled for age, sex, disease duration, biologic treatment, and baseline radiographic score.

Results: Baseline and 2-year radiographs were available on 241 patients with AS according to the modified New York criteria. Mean (SD) age was 40.5 (13.3) years, males 81.1%, mean (SD) disease duration 20 (11.2) years), 48.9% received TNF blockers, and 51.1% received standard therapies. At baseline, mean (SD) mSASSS was 15.1 (20.7) and mean (SD) SAS was 12.3 (20.7). Mean (SD) change in mSASSS and SAS over 2 years was 1.8 (3.8) and 1.9 (4.9), respectively, 20.6% had mSASSS progression > 2 units, and 28.6% developed ≥1 new syndesmophyte. The mean (SD) baseline and 2-year CRP were 13.85 (20.6) and 7.11 (12.5) respectively. The mean (SD) 2-year change in CRP in the standard therapy group was −1.69 (11.56) and −11.02 (26.12) in those on TNF blockers (p = 0.0023). Multivariate linear regression analysis with either the mSASSS or the SAS as dependent variable showed that both CRP and 2-year reduction in CRP were independent predictors of progression in patients receiving TNF blocker therapy but not in patients on standard therapies (Table).

	Dependent variable	Multivariate Full Model Est	95%CI	P value
Baseline CRP	**SAS**	0.18	0.04, 0.31	0.01
Δ CRP	**SAS**	0.20	0.04, 0.36	0.01
Baseline CRP	**mSASSS**	0.15	0.02, 0.27	0.02
Δ CRP	**mSASSS**	0.14	−0.03, 0.29	0.05

Conclusion: Our data not only support a link between inflammation, as measured by CRP, and radiographic progression but are also consistent with the hypothesis that progression may follow resolution of inflammation.

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Serum Levels of Adiponectin and Insulin Resistance Are Increased in Patients with Psoriatic Arthritis Compared to Those with Psoriasis Alone. Lihi Eder[1], Remy Pollock[1], Fawnda Pellett[2], Jai Jayakar[3], Arane Thavaneswaran[1], Daniel Pereira[2], Cheryl Rosen[2], Vinod Chandran[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]University of Western Ontario, London, ON

Background/Purpose: The metabolic syndrome (MetS), a cluster of metabolically interrelated cardiovascular and diabetic risk factors, has become a major public health challenge worldwide. The prevalence of MetS is higher in patients with Psoriatic Arthritis (PsA) and psoriasis compared to healthy controls. The aim of this study was to compare the levels of biomarkers related to the MetS in patients with PsA and cutaneous psoriasis without arthritis (PsC).

Methods: This cross-sectional study included two groups of patients: those with PsA who met the CASPAR criteria and patients with PsC who were diagnosed by a dermatologist. All patients with PsC were assessed by a rheumatologist to rule out inflammatory arthritis. The presence of MetS was determined according to the IDF criteria[1]. Fasting serum levels of insulin, adiponectin and leptin were measured. The HOmeostasis Model Assessment for Insulin Resistance (HOMA-IR) was calculated as follows: [fasting insulin (μU/ml) × fasting glucose (mmol/L)]/22.5. Information about smoking status, alcohol consumption and psoriasis activity (by Psoriasis Area and Severity Index (PASI)) was collected. HOMA-IR, adiponectin and leptin were log-transformed. Continuous variables were compared using the t-test and Chi square test was used for discrete variables. Multivariate regression models were used to compare the association of MetS, adiponectin and HOMA-IR with PsA compared to PsC after adjusting for age, gender, race, use of Disease Modifying Anti-Rheumatic Drugs (DMARDs), anti-TNFα agents, alcohol consumption, smoking and PASI score.

Results: 251 PsA and 173 PsC patients were analyzed. Their mean age

was 51.8±12.8 and 40.8% of them were females. The mean duration of psoriasis and PsA was 23.1±14.7 and 14.9±11.2, respectively. 26.2% of the patients were using anti-TNFα agents and 40.1% of them were using DMARDs. The prevalence of obesity (BMI>30) was higher in the PsA group (39.7% vs. 30.2%, p<0.05). The prevalence of MetS was higher in PsA patients compared to PsC however, did not reach statistical significance (40.2% vs. 32.4%, p=0.1). The HOMA-IR and adiponectin level were higher in PsA patients compared to PsC (HOMA-IR (mmol/L × μU/ml)): 3.37±2.95 vs. 2.74±2.84, p=0.04, adiponectin (μg/ml): 8.81±5.19 vs. 7.45±4.51, p=0.009). Serum levels of leptin were not significantly different between the two groups. In multivariate regression analysis PASI score (OR 1.8, 95% CI 1.2–2.7, p=0.005) and the use of anti-TNFα agents (OR 1.8, 95% CI 1.1–2.9, p=0.02) were associated with MetS. HOMA-IR was significantly associated with PsA (p=0.01), use of anti-TNFα agents (p=0.02), age (p=0.04) and male gender (p=0.05). Adiponectin was significantly associated with PsA (p=0.004), female gender (p<0.001) and age (p=0.005).

Conclusion: The occurrence of MetS is associated with anti-TNFα therapy and severity of psoriasis. Serum adiponectin levels and insulin resistance are increased in PsA patients compared to PsC.

[1]Alberti KG et al. The metabolic syndrome – a new worldwide definition. Lancet 2005;366:1059–62

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Anti TNFα Agents Are More Effective Than Methotrexate in Preventing Radiographic Joint Damage Among Patients with Psoriatic Arthritis in a Clinic Setting. Lihi Eder[1], Arane Thavaneswaran[1], Vinod Chandran[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Clinical trials have demonstrated that anti TNFα agents reduce the progression of radiographic joint damage in patients with psoriatic arthritis (PsA). This effect has not been evaluated in observational studies that reflect clinical practice. The aim of this study was to determine whether anti TNFα agents are more effective than methotrexate (MTX) in preventing the progression of radiographic joint damage in patients with PsA in a clinic setting.

Methods: A cohort analysis of patients followed prospectively from 1978 to 2010 at a large PsA clinic was performed. Patients were followed at 6–12 month intervals according to a standard protocol. Patients who received an anti TNFα agent were compared to those treated with MTX. In order to minimize selection bias, only patients who started to receive MTX prior to the year 2000 (before anti TNFα agents were available in Canada) were selected. Additional inclusion criteria included: 1) the presence of joint erosions 2) the presence of inflammatory peripheral arthritis at baseline. Patients who discontinued their treatment before the completion of 1 year were excluded. Radiographs of the hands and feet were performed at baseline (less than 12 month prior to the initiation of the medication), 1–2 years (Time 1) and 3–4 years (Time 2). Radiographic joint damage in 42 joints was scored according to the modified Steinbrocker score (mSBS).The outcome variable was an increase in mSBS (defined as >1 in mSBS units). Multivariate logistic regression analysis was used to compare progression in radiographic joint damage between the two treatment groups after adjustment for potential confounders.

Results: 65 patients treated with an anti TNFα agent and 70 patients treated with MTX were analyzed. Their mean age was 46.8±12.5 years, 37.7% were females and the mean duration of PsA at initiation of treatment was 11.9±9.1 years. 70.1% of the patients were treated with etanercept, 12.3% with infliximab, 12.3% with adalimumab and 4.6% with golimumab. The proportion of patients who demonstrated progression of radiographic damage score at Time 1 and Time 2 compared to baseline was higher in the MTX group compared to the anti TNFα group (Time 1: 34/50 (68%) vs. 22/39 (56.4%) p=0.03, Time 2: 42/50 (84%) vs. 27/36 (75%), p=0.005, respectively). The multivariate regression analyses showed that MTX treatment was associated with an increase in radiographic damage compared to anti TNFα therapy (Time 1: Odds Ratio (OR) 3.53, 95% Confidence Interval (CI) 1.29–9.65, p=0.03, Time 2: OR 4.66, 95% CI 1.57–13.81 p=0.004) after adjusting for age, sex, duration of PsA, active and swollen joint counts, baseline mSBS and duration of follow-up.

Conclusion: In a clinic setting, PsA patients receiving anti TNF treatment had a better radiographic outcome compared to those treated with MTX.

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Association Between Clinical Factors and Radiographic Severity in Ankylosing Spondylitis. Tae-Jong Kim[1], Seung-Hun Lee[2], Kyung-Bin Joo[3] and Tae-Hwan Kim[4]. [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]South Korea, [3]Hanynag University, Seoul, South Korea, [4]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

Background/Purpose: The most characteristic bony changes in ankylosing spondylitis (AS) are growth of new bone and formation of syndesmophytes, possibly leading to ankylosis and spinal fusion. The objective of this study was to examine the association between clinical factors and radiographic severity in AS

Methods: A total of 1000 AS patients who met the modified New York criteria were recruited. To use the modified Stoke AS Spinal Score (mSASSS), cervical and lumbar spinal radiographs were examined by two experienced bone and joint radiologists (KB Joo, SH Lee) to validate the results. The inter-observer variability was also assessed. A review of the clinical parameters was conducted to investigate the associations between clinical factors and the radiographic progression.

Results: The mean age was 35.1(8.7), and the mean disease duration was 11.9(6.9) years. 85.9% were men and 945 patients (94.5%) were HLA-B27 positive. The frequency of juvenile onset AS and peripheral arthritis were 28.1% and 40.7%, respectively. The scores of mSASSS were different between gender (male 22.0±18.9, female 12.6±11.2, p=0.009). As expected, symptom duration has a good relationships with radiographic changes (r=0.412, p<0.001) after age and gender adjusted. The mSASSS of adult onset AS was higher, comparing to Juvenile onset (15.3±10.2, 11.4±8.5, p < 0.05). The patients with peripheral arthritis have lower radiologic scores, comparing to ones without arthritis (11.2±5.2, 16.3±8.5, p < 0.05). Multiple linear regression analysis showed that gender, type of onset, peripheral arthritis, and symptom duration still had an influence on radiographic change score. Unfortunately, no correlations were found between radiographic score and clinical parameters, such as uveitis, B27 positivity, familial history, and use of biologic agent.

Conclusion: Radiographic spinal changes in patients with AS are seen more often in men and those with long symptom duration. Clinical factors such as, juvenile onset AS and peripheral arthritis are negative predictors of radiographic progression in AS. More long term follow up studies are needed to assess the clinical predictors of radiographic change

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Rheumatologist's Expert Opinion Is An Important Determinant of Tumor Necrosis Factor Blocking Agent Prescription in Axial Spondyloarthritis: Results From the Swiss Clinical Quality Management Axial Spondyloarthritis Cohort. Almut Scherer[1], Ulrich Weber[2], Pascale Exer[3], Juerg Bernhard[4], Jean Dudler[5], Giorgio Tamborrini[6], Bettina Weiss[2], Ruediger Mueller[7], Beat A. Michel[6], Rudolf O. Kissling[2], Adrian Ciurea[6] and on behalf of the SCQM Rheumatologists[8]. [1]SCQM Foundation, Zurich, Switzerland, [2]Balgrist University Hospital, Zurich, Switzerland, [3]Private Rheumatology Practice, Basel, Switzerland, [4]Buergerspital, Solothurn, Switzerland, [5]Hôpital Cantonal, Fribourg, Switzerland, [6]Department of Rheumatology, University Hospital, Zurich, Switzerland, [7]Cantonal Hospital, St. Gallen, Switzerland, [8]Scqm, Switzerland

Background/Purpose: To investigate the determinants of anti-TNF agent (aTNF) prescription in patients (pts) with non-radiographic spondyloarthritis (nrSpA) and definite ankylosing spondylitis (AS) if the fulfillment of the modified NY criteria (mNYc) is not mandatory and a BASDAI >=4 not required for reimbursement.

Methods: 741 pts fulfilled the mNYc (AS), while 162 mNYc-negative pts fulfilled the ASAS axial SpA criteria (nrSpA) in the Swiss Clinical Quality Management (SCQM) axial SpA cohort. Pts were recruited by rheumatologists in private practice (53%), non-academic (28%) and academic (19%) centers since 2004. Data on demographics, medication, ESR and CRP levels were collected and standardized assessment tools applied. A similar proportion of AS and nrSpA pts were treated with aTNF in SCQM-SpA (74% [95% CI 70–77] vs. 71% [64–77]). Two logistic multiple regression models of potential determinants for aTNF prescription were performed with the following variables: age, disease duration, classification as AS or nrSpA, sick leave, BASFI, BASMI, physician's global assessment (PhysGA), peripheral arthritis, and quality of life (EuroQol). BASDAI and CRP were additionally included as

continuous variables in model 1, ASDAS was included in model 2. We controlled for gender and type of recruiting center.

Results: 497 pts had complete data sets for all the evaluated variables (239 AS and 51 nrSpA pts with aTNF start after enrollment and 149 AS and 40 nrSpA pts without biologic treatment at two consecutive observations in the cohort). The percentage of pts with BASDAI>=4 was slightly higher in treated nrSpA than in AS pts (82% vs. 75%, n.s.). In the group without aTNF, 52% of nrSpA and 48% of AS pts had a BASDAI >=4. Mean BASDAI was 4.8 in AS and 5.1 in nrSpA pts (p=0.2). Mean ASDAS was 4.2 in AS and 3.9 in nrSpA pts (p=0.05). The logistic regression model 1 revealed that rheumatologists assigned aTNF preferentially to pts with peripheral arthritis and higher BASDAI, CRP and PhysGA levels, with the lowest contribution for BASDAI (Table). ASDAS, arthritis and PhysGA were strongly associated with aTNF start in model 2.

Table. Predictors of aTNF initiation in two regression models

	Variables	OR	95% CI	p Value
Model 1	BASDAI	1.22	1.04–1.45	0.018
	CRP	1.03	1.01–1.05	0.006
	PhysGA	1.40	1.23–1.60	<0.00001
	Arthritis	2.27	1.42–3.69	0.0007
Model 2	ASDAS	1.50	1.21–1.87	0.0002
	PhysGA	1.40	1.23–1.60	<0.00001
	Arthritis	2.39	1.50–3.88	0.0003

Conclusion: In the context of non-restrictive reimbursement criteria, comparable proportions of nrSpA and AS pts are treated with aTNF, matching similar levels of disease activity in the two groups. The determinants of aTNF initiation found here represent a more comprehensive concept of disease activity including the rheumatologist's expert opinion and reflect the predictive factors of a good treatment response.[1] ASDAS seems moreover to better determine aTNF prescription than BASDAI.

Reference

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Dyslipidemia in Patients with Seronegative Spondyloarthropathies. Charalampos Papagoras[1], Theodora E. Markatseli[1], Ioanna Saougou[1], Haralampos J. Milionis[2] and Alexandros A. Drosos[3]. [1]Fellow in Rheumatology, Ioannina, Greece, [2]Assistant Professor of Internal Medicine, Ioannina, Greece, [3]Professor of Medicine/Rheumatology, Ioannina, Greece

Background/Purpose: Chronic arthritis, particularly rheumatoid arthritis (RA), has been associated with a pro-atherogenic lipid profile and premature atherosclerosis. Patients with seronegative spondyloarthropathies (SpA) also seem to be in greater risk for cardiovascular disease than the general population. However, data on the serum lipid levels of patients with SpA are far less than for RA.

Methods: We studied the serum lipid profile of patients with SpA and compared it with non-SpA controls. A case-control study was conducted in which cases were non-diabetic patients with SpA and controls were age and sex-matched apparently healthy volunteers. In all study participants, we measured serum levels of total cholesterol (Chol), triglycerides (Trg), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), Apolipoprotein AI (ApoAI), ApoB, ApoE and lipoprotein (α) [Lp(α)], while body mass index (BMI) and waist-to-hip ratio (WHR) were also calculated. In SpA patients, disease activity markers (ESR, CRP, BASDAI, BASFI, DAS28 and PASI, when applicable) were recorded as well.

Results: One hundred and fifty SpA patients [73 with ankylosing spondylitis (AS), 71 with psoriatic arthritis (PsA) and 6 with other forms of SpA] and 150 controls were studied. As shown in Table, SpA patients had significantly greater WHR, lower levels of Chol, Trg, HDL, a higher Chol/HDL ratio, lower levels of ApoB, ApoE, Lp(α) and a lower ApoB/ApoAI ratio. Focusing separately on the PsA and AS subgroups, a particular pattern of dyslipidemia involving lower HDL and a higher Chol/HDL ratio is a persistent finding. In the SpA group, correlation analysis revealed a statistically significant association of ESR with HDL (r=−0.222, p=0.003), ApoAI (r=−0.224, p=0.003) and ApoB/ApoAI ratio (r=0.221, p=0.004). In the PsA subgroup, significant correlations also emerged between ESR and HDL (r=−0.362, p<0.001), Chol/HDL (r=0.236, p=0.023), ApoAI (r=−0.338, p=0.001) and ApoB/ApoAI (r=0.315, p=0.003). Similar associations were observed between CRP and the above parameters as well. In the AS subgroup, a correlation of CRP with HDL (r=−0.223, p=0.049) and ApoAI (r=−0.31, p=0.007) was found. Except DAS28 which correlated significantly with HDL (r=−0.312, p=0.042), ApoAI (r=−0.352, p=0.026) and ApoB/ApoAI (r=0.334, p=0.035) in the PsA subgroup, no other significant correlations between BASDAI, BASFI or PASI and lipid parameters were observed.

Table. An thropometric measures and serum lipid levels in SpA patients, AS and PsA subgroups and the corresponding control groups

Parameter	*SpA (N=150)*	*Controls (N=150)*	*AS (N=73)*	*Controls (N=73)*	*PsA (N=71)*	*Controls (N=71)*
Male/Female	112/38	112/38	66/7	66/7	43/28	43/28
Age	46.3 ± 12.8	46.9 ± 13.6	44.9 ± 11.2	45.9 ± 12.7	48.9 ± 13.5	49 ± 14
BMI	27 ± 4.6	27.1 ± 4.2	25.7 ± 3.9	26.7 ± 3.8	28.6 ± 4.9	27.4 ± 4.7
WHR	0.933 ± 0.091*	0.869 ± 0.099	0.939 ± 0.093	0.911 ± 0.064	0.933 ± 0.088*	0.848 ± 0.108
Chol	207.8 ± 36.7†	217.3 ± 39.3	210 ± 37.2	215.3 ± 38.2	208.7 ± 34.3	219.1 ± 41.1
Trg	122.3 ± 90.8†	127.4 ± 53.6	118.8 ± 112.7†	118.6 ± 45.2	130.2 ± 64.3	135.3 ± 61.1
HDL	50.7 ± 12.9*	56.7 ± 11.7	50.6 ± 11.6*	56.3 ± 11.8	50.4 ± 13.6*	57 ± 12
LDL	132.7 ± 33.3	135.1 ± 35.4	135.7 ± 36.5	135.2 ± 34.6	132.2 ± 27.9	135 ± 36.2
Chol/HDL	4.287 ± 1.085**	3.948 ± 0.913	4.327 ± 1.123¶	3.949 ± 0.938	4.328 ± 1.028†	3.947 ± 0.889
ApoAI	142.4 ± 26.4	146.7 ± 30.2	141.8 ± 22.3	141.5 ± 31.4	143.9 ± 30.8†	154.7 ± 27.7
ApoB	92.6 ± 23.8*	108.8 ± 32.2	94.1 ± 25.8*	115.3 ± 31.6	92.9 ± 21.2	100.8 ± 31.9
ApoE	39.3 ± 21.3*	45.7 ± 15.9	38.3 ± 25.5*	44.6 ± 14.1	41.3 ± 16.8	46.7 ± 18.6
Lp(α)	13.033 ± 16.734†	15.772 ± 19.975	11.984 ± 12.572†	17.252 ± 20.022	14.971 ± 20.662	13.449 ± 19.859
ApoB/ApoAI	0.671 ± 0.208**	0.774 ± 0.275	0.682 ± 0.219*	0.855 ± 0.29	0.671 ± 0.201	0.665 ± 0.218

*p≤0.001, **p<0.01, †p<0.05, ¶ p=0.059, for comparison of patients versus age-and-sex matched controls

Conclusion: SpA patients show several metabolic disturbances, spanning from increased abdominal fat to lipoprotein level perturbations. The most consistent alteration encountered in most patients is a lower level of HDL and an unfavorable Chol/HDL ratio. Many of these alterations correlate significantly with inflammatory markers or DAS28.

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Body Mass Index Influences the Response to Infliximab in Ankylosing Spondylitis. Sébastien Ottaviani[1], Yannick Allanore[2], Florence Tubach[3], Blandine Pasquet[3], Olivier Meyer[4] and Philippe Dieude[5]. [1]APHP, Paris, France, [2]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [3]APHP, Hôpital Bichat, Paris, France, [4]Hopital Bichat, Paris, France, [5]APHP, Hopital Bichat, Paris, France

Background/Purpose: The excess of adipose tissue in obese individuals may have immunomodulating properties and pharmacokinetics consequences. The aim of this study was to determine whether body mass index (BMI) affects response to infliximab (IFX) in ankylosing spondylitis (AS) patients.

Methods: In 155 patients retrospectively included with active AS, the BMI was calculated before initiation of IFX treatment (5 mg/kg intravenously). After 6 months of treatment, change from baseline in BASDAI, VAS pain, CRP level and total dose of NSAID was dichotomized with a threshold corresponding to a decrease of 50% of initial level of the measure, into binary variables assessing response to IFX (namely, VAS50, CRP50, NSAID50). Whether BMI was predictive of response to therapy according to theses different definitions was assessed with logistic regression.

Results: Multivariate analysis revealed that a lower BMI was associated with a positive BASDAI50 response after 6 month of IFX therapy (P = 0.0003). When analyses were performed according to the 3 WHO BMI categories, similar results were observed when response to IFX was defined by BASDAI50 ($P < 0.0001$), VAS50 ($P < 0.0001$), CRP50 ($P = 0.0279$) and NSAID50 ($P = 0.0077$).

Conclusion: This study provides the first evidence that a higher BMI negatively influences the response to IFX in AS. These data are in line with recent findings observed in rheumatoid arthritis. They raise the points of the consideration of BMI to assess to response to IFX and the pharmacological impact of fat tissue.

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The Role of CRP and Peripheral Disease in Achieving ASDAS Response to Anti-TNF Therapy in 397 Patients with Ankylosing Spondylitis. Karen Minde Fagerli[1], Elisabeth Lie[2], D.M.F.M. van der Heijde[3], Marte S. Heiberg[1], Erik Rødevand[4], Cecillie Kaufmann[5], Knut Mikkelsen[6], Synnøve Kalstad[7] and Tore K. Kvien[2]. [1]Diakonhjemmet hospital, Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Trondheim, Norway, [5]Vestre Viken, Drammen, Norway, [6]Lillehammer Hosp for Rheumatic Diseases, Lillehammer, Norway, [7]Tromsø, Norway

Background/Purpose: BASDAI has been the most commonly used outcome measure for assessing efficacy of TNF-inhibitors (TNFi) in ankylosing spondylitis (AS). However, BASDAI is solely patient-reported. ASDAS is a recently developed composite disease activity score incorporating an inflammatory marker (CRP or ESR). It has not been well studied if ASDAS performs similarly in patients with elevated CRP vs. normal CRP and patients with swollen joints vs. patients without swollen joints.

Objectives: To compare the response to TNFi according to different response criteria in patients with and without swollen joints as well as with and without elevated CRP.

Methods: Data for these analyses were extracted from the NOR-DMARD register where adult patients with inflammatory arthropathies starting a new DMARD treatment have been consecutively included and followed longitudinally with assessments at 3, 6 and 12 months and then yearly. Patients with AS starting a TNFi who had complete data for calculating ASDAS-CRP at baseline and 3 months were selected for the current analyses. Cut-point for elevated CRP was selected as 10 mg/L. The presence of a swollen joint was based on evaluation of the 28-joint count as well as feet. Selected response criteria were ASDAS clinically important improvement ($\Delta \geq 1.1$), ASDAS major improvement ($\Delta \geq 2.0$), ASAS20, ASAS40, BASDAI50, BASDAI 2-point change and BASDAI response (BASDAI50 and/or BASDAI 2-point change).

Results: 397 patients starting a TNFi were included in the analyses (70.2% males, 91.2% HLA B27 positive, mean (SD) age 42.7 (11.2) yrs, disease duration 11.8 (11.2) yrs, BASDAI 5.4 (2.1) and ASDAS 3.4 (1.1), median (IQR) CRP 9.0 (5.0–20.5) mg/L). 42.8% of patients had CRP levels ≥ 10 and 21.3% had at least one swollen joint. A significantly higher proportion of patients with a CRP ≥ 10 showed a response as compared to patients with a CRP < 10 with all response criteria (table). This difference was most pronounced using ASDAS response criteria, but the % with ASDAS clinically important improvement in the patients with CRP < 10 was still in the same range as picked up with other response measures. When comparing the patients with or without swollen joints there was only a significant difference in achieving ASDAS major improvement.

Table. Percentages achieving response according to different criteria

	Overall	CRP (mg/L)			Swollen joints		
		≥10	<10	p-value*	Present	Absent	p-value*
ASDAS clinically important improvement	52.4	75.3	35.2	<0.001	56.1	50.2	0.38
ASDAS major improvement	26.7	44.1	13.7	<0.001	39.0	22.8	0.004
ASAS 20	61.4	61.8	43.6	<0.001	53.7	50.2	0.62
ASAS 40	36.0	44.1	30.0	0.004	40.2	34.7	0.37
BASDAI 50	43.1	50.6	37.4	0.01	43.2	40.2	0.71
BASDAI 2 points	49.4	57.6	43.2	0.005	56.1	46.9	0.17
BASDAI response	54.2	61.8	48.5	0.01	57.3	52.5	0.46

* Chi-square test.

Conclusion: AS patients starting a TNFi who had a baseline CRP ≥ 10 more frequently achieved a response compared to patients with CRP < 10. These findings were seen for ASDAS responses but also for measures that do not include inflammatory markers. The response rate for ASDAS clinically important improvement was similar to responses for other measures and the findings support the use of ASDAS as a response measure also in patients with normal CRP and without swollen joints.

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Prevalence of Psoriatic Arthritis in Dermatological Patients with Psoriasis. Joerg C. Henes[1], Michael Eisfelder[2], Anette Adamczyk[3], Björn Knaudt[3], Felix Jacob[3], Eva-Maria Zuipa[1], Ralf Denfeld[4], Jürgen Lux[5], Armin Philipp[4], Carolin Steigleder[4], Martin Kleinhans[4], Nicole Oster[4], Gerhard Fierlbeck[3] and Ina Kötter[6]. [1]University Hospital Tuebingen, Tuebingen, Germany, [2]Private practice, Rottweil, Rottweil, Germany, [3]University Hospital Tuebingen, Department of dermatology, Tuebingen, Germany, [4]Private practice, Stuttgart, Germany, [5]Private practice, Tuebingen, Germany, [6]Department of Internal Medicine II, Rheumatology Division, Tübingen, Germany

Background/Purpose: The existing data on prevalence of psoriatic arthritis (PsA) among patients with psoriasis in the literature vary between 5.8 and 40%. Recently, a new screening questionnaire in German language has been validated by Haerle et al.. This GEPARD (German Psoriasis Arthritis Diagnostic questionnaire) has a sensitivity and specificity of 89% and 69.1% for ≥4 questions answered "yes".

Methods: Two dermatologic hospitals and 9 private dermatologic practices were involved. All consecutive patients with psoriasis were asked to fill out the questionnaire without the help of the physician and send them to the study centre. All patients with ≥4 positive questions were invited for a rheumatological examination. Patients with known PsA (question 7 answered "yes") received a second questionnaire with regard to the history and treatment of PsA. 30% of patients with known arthritis were interviewed by a telephone call and if diagnosis was uncertain were invited for a rheumatological evaluation. Those patients with a positive questionnaire who denied coming were considered as having no arthritis. The rheumatologic assessment consisted of physical examination and laboratory tests including inflammatory markers, rheumatoid factor, anti-CCP antibodies and HLA B27. All patients with peripheral arthralgia received ultrasound of the joints including Doppler and X-ray of hands, feet and affected joints. In those patients with marginal changes or spinal complaints magnetic resonance imaging (MRI) was added. The CASPAR criteria were used for the diagnosis of PsA.

Results: 404 questionnaires were evaluated. 204 patients (50.5%) had answered ≥4 questions with "yes" of whom 38.2% (n=78) had a known PsA. 126 patients were invited for a clinical examination and 23% (n=29) refused to come. 98 patients with suspected PsA had a clinical evaluation at the study centre. In 49% (n=48) the CASPAR criteria were not fulfilled and in 44.9% (n=44) a new PsA was diagnosed. In two patients anti-CCP antibodies and a symmetrical arthritis made the diagnosis rheumatoid arthritis more plausible. 6.1% already had the diagnosis of PsA. In addition to the clinical evaluation the diagnosis was confirmed by radiological assessment using X-ray in 69.4% (n=68), powerdoppler ultrasound in 83.7% and MRI in 39.8%. All together, of the 404 patients 44 (10.9%) were newly diagnosed having a PsA and 78 (19.3%) had a known PsA whereas 282 (69.8%) were found to have no signs of PsA. Thus the prevalence PsA among patients with psoriasis in this study was 30.2%. There were no significant differences in the patients with or without definite arthritis regarding CRP or ESR, HLAB27, gender or severity of psoriasis. Only dactylitis was significantly associated with definite PsA.

Conclusion: This study uses a validated questionnaire in the forefront of a clinical evaluation in patients with suspected PsA. By using this approach the prevalence of PsA was higher than that in recent studies in Germany, UK and the United States and supports findings from Scandinavia. With nearly 50% positive questionnaires for patients without PsA the specificity should be improved.

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Predictors of ASDAS Major Improvement in Patients with Ankylosing Spondylitis Receiving Their First TNF Inhibitor. Results From a Longitudinal Observational Study. Karen Minde Fagerli[1], Elisabeth Lie[2], Marte S. Heiberg[1], D.M.F.M. van der Heijde[3], Synnøve Kalstad[4], Knut Mikkelsen[5], Cecillie Kaufmann[6], Erik Rødevand[7] and Tore K. Kvien[2]. [1]Diakonhjemmet hospital, Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Tromsø, Norway, [5]Lillehammer Hosp for Rheumatic Diseases, Lillehammer, Norway, [6]Vestre Viken, Drammen, Norway, [7]Trondheim, Norway

Background/Purpose: TNF inhibitors (TNFi) have been proven highly efficacious in reducing symptoms and inflammation in patients with AS. However, not all patients show a good response to therapy, while treatment is expensive and has potentially serious side effects. Identification of predictors of a good response might aid decision-making and improve the benefit/risk ratio in patients selected to start TNFi.

Objectives: To determine predictors of ASDAS major improvement ($\Delta \geq 2.0$) after 3 months of treatment with TNFi in TNFi-naive patients.

Methods: Data was extracted from the NOR-DMARD register where adult patients with inflammatory arthropathies starting a new DMARD treatment are consecutively included and followed longitudinally in 5 rheumatology departments in Norway. For this analysis AS patients who were treated with their first TNFi and who had complete data for calculation of ASDAS at baseline and 3 months were included [N=249; 90.7 % HLA B27 positive, 67.9 % males, mean (SD) age 41.9 (11.1) years, disease duration 10.1 (10.8) years, BASDAI 5.36 (1.98) BASFI 4.30 (2.20) and ASDAS 3.38 (0.96)]. The following variables were selected for univariate logistic regression analyses with 3-month ASDAS major improvement as the dependent variable: age, sex, disease duration, baseline CRP, HLA B27 status, smoking (ever/never), educational level, presence of swollen peripheral joints (28 joints + feet), and BASDAI, BASFI, physician and patient global assessments. Variables yielding a p-value < 0.25 were included in a subsequent multivariate logistic regression analysis, and non-significant variables were removed from the model one at the time (starting with the least significant variable), checking for confounding. Clinically relevant interactions were tested in the final main-effects model. Appropriate tests for linearity and goodness of fit were performed.

Results: ASDAS major improvement was achieved by 32.1 % of the patients at 3 months. All variables except disease duration, smoking and level of education

were significant predictors in univariate analyses and included as covariates. BASDAI was excluded from multivariate analysis due its correlation with patient global and BASFI. Age, sex, baseline CRP level, HLA B27 status and higher baseline patient global assessment were independent predictors of ASDAS major response at 3 months, and constituted the final logistic regression model. The fit of the model was satisfactory (Hosmer-Lemeshow goodness of fit test: p=0.50) and model accuracy was 79.0%.

Table. Logistic regression model for predictors of ASDAS major response at 3 months.

Variable	Odds ratio	95 % CI	p-value
Age	0.96*	0.92–0.99	0.021
Male sex	4.70	1.99–11.1	<0.001
CRP ≥10	7.77	2.28–9.93	<0.001
HLA B27 positivity	6.64	1.39–31.7	0.018
Patient global	1.78**	1.46–2.17	<0.001

* Odds ratio for one year increase in age. ** Odds ratio for a 10-mm increase on a 0–100 mm VAS.

Conclusion: Lower age, male sex, CRP ≥10, HLA B27 positivity and higher baseline patient global assessment were identified as independent predictors of achieving ASDAS major improvement at 3 months for AS patients starting their first TNFi.

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Differences in Comorbidities Related to Rheumatoid Arthritis and Psoriatic-Arthritis: Data From Large Prospectiv Observational Studies. Frank Behrens[1], Diamant Thaci[2], Hanns-Martin Lorenz[3], Brigitte Krummel-Lorenz[4], Lothar Meier[5], Holger Gnann[6], Gerd Greger[7], Bianca Wittig[7] and Harald Burkhardt[1]. [1]CIRI/Rheumatology, J.W. Goethe University, Frankfurt/Main, Germany, [2]Klinik für Dermatologie, Venerologie und Allergologie, J.W. Goethe University, Frankfurt/Main, Germany, [3]Medizinische Klinik und Poliklinik, Universität, Heidelberg, Germany, [4]CIRI/Endokrinologikum, Frankfurt/Main, Germany, [5]CIRI/Rheumatologische Schwerpunktpraxis, Hofheim, Germany, [6]Abteilung Biostatistik, GKM Gesellschaft für Therapieforschung mbH, München, Germany, [7]Abbott GmbH & Co KG, Wiesbaden, Germany

Background/Purpose: To examine the impact of Rheumatoid Arthritis and Psoriatic Arthritis on the prevalence of type II diabetes, obesity, and osteoporosis.

Methods: Cross-sectional comparative analyses of baseline characteristics of two cohorts of patients with long-lasting rheumatoid arthritis (RA), and psoriatic arthritis (PsA) enrolled in prospective observational multi-centre studies. Patients with active RA (n= 4640) or PsA (n=1467) and either an inadequate response or intolerance to conventional or biologic disease-modifying therapy who had enrolled in observational studies of adalimumab. Baseline prevalence rates of type II diabetes, obesity, and osteoporosis and the odds ratios with 95% confidence intervals (CI) for identified risk factors were calculated.

Results: Prevalence rates revealed a discordant relationship between type II diabetes and osteoporosis in RA compared with PsA. Whereas the PsA cohort exhibited a higher rate of type II diabetes than the RA cohort, particularly in patients over 60 years of age (19.1% vs 10.9%; P=.0003), the frequency of osteoporosis was reduced (6.0% vs 21.8%; P<.0001) in PsA independent of age and gender. Systemic inflammation is unlikely to be the sole explanation for these differences, as the diabetes prevalence was higher in PsA while the RA patient cohort exhibited more severe inflammatory disease as evidenced by serologic and clinical parameters of inflammation. An impact of constitutional factors on comorbidity is indicated by a significantly higher mean body mass index (BMI) independent of age or gender in PsA. Logistic regression uncovered rheumatoid factor seropositivity as a previously unidentified serological marker for increased risk of osteoporosis in PsA patients (odds ratio= 3.319 [95% CI, 1.822 to 6.045]).

Conclusion: Patients with PsA have a higher rate of type II diabetes and an elevated BMI, but reduced levels of systemic inflammation and a lower prevalence of osteoporosis than patients with RA. The observed differences between RA and PsA patients do not support the concept of systemically released proinflammatory mediators as a dominant contributor to comorbidities in distinct inflammatory disorders. Our data thus suggest that disease-specific factors beyond inflammation impact the development of comorbidities in patients with inflammatory disorders.

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Sustained Improvement of Spinal Mobility, Physical Function, and Quality of Life in Patients with Ankylosing Spondylitis: 5-Year Results. Désirée van der Heijde[1], Maxime A. Breban[2], Dale G. Halter[3], Gino DiVittorio[4], Johan Bratt[5], Fabrizio Cantini[6], Sonja Kary[7], L. Steven Brown[8], Hartmut Kupper[7], Tracy F. Nicholson[9] and Philip J. Mease[10]. [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Hopital Ambroise Pare, Boulogne, France, [3]Houston, TX, [4]Mobile, AL, [5]Karolinska Univ Hosp Huddinge, Stockholm, Sweden, [6]Stabilimento Ospedaliero Misericordia, Prato, Italy, [7]Abbott GmBH & Co KG, Ludwigshafen, Germany, [8]Abbott Laboratories, Abbott Park, IL, [9]Abbott Laboratories, [10]Seattle Rheumatology Associate, Seattle, WA

Background/Purpose: Ankylosing Spondylitis (AS) is a chronic, inflammatory disease of the axial skeleton characterized by back pain and radiographic sacroiliitis that can progressively restrict spinal mobility. In patients (pts) with AS treated with adalimumab (ADA), previous reports demonstrated improved spinal mobility, physical function, and quality of life as early as 12 and 24 wks. [1,2] In this post hoc analysis, the long-term maintenance of those improvements was assessed through 5 yrs and the correlation between spinal mobility and clinical, functional, and quality-of-life outcomes were evaluated.

Methods: ATLAS was a phase 3, multicenter, double-blind trial of pts with active AS randomized to ADA 40 mg every other week or placebo (PBO) for 24 wks followed by an open-label extension up to 5 yrs. Improvements in spinal mobility were evaluated using linear BASMI($_{ln}$), including individual assessment of cervical rotation in degrees, lumbar flexion, lumbar side flexion, intermalleolar distance, and tragus-to-wall distance in cm. Additional outcomes included BASDAI, total back pain, CRP, BASFI, SF-36 Physical Component Summary (PCS), and the AS Quality of Life (ASQOL) questionnaire. Spearman's rank correlation was used to evaluate the relationship between BASMI$_{ln}$ and clinical, functional, and quality-of-life outcomes at 12 wks and 5 yrs of exposure.

Results: A total of 315 pts (208 ADA/107 PBO) were randomized, of which 311 received at least one dose of ADA. Improvements in BASMI$_{ln}$ were sustained through 5 yrs (table), with a mean change of −0.6 from baseline. Of the individual components, lumbar side flexion, cervical rotation, and intermalleolar distance appeared to drive change in overall BASMI$_{ln}$. Improvements in disease activity, function, and quality of life were also sustained through 5 yrs. BASMI$_{ln}$ was significantly correlated with all evaluated clinical outcomes (P<0.001), with the highest correlation observed between BASMI$_{ln}$ and BASFI at 12 wks and 5 yrs, (r=0.51 and 0.64, respectively).

Table. Spinal Mobility, Disease Activity, Physical Function and Quality of Life with Long-Term Adalimumab

Assessments (N=BL/Wk12/Yr1/Yr3/Yr 5)	Exposure to Adalimumab mean (SD)				
	Baseline*	Week 12	Year 1	Year 3	Year 5
BASMI$_{ln}$ (N=309/309/282/233/124)	4.4 (1.7)	4.0 (1.8)	3.8 (1.8)	3.7 (1.8)	3.7 (1.8)
Lumbar flexion, cm (N=309/309/282/233/124)	3.9 (3.4)	4.0 (3.2)	4.0 (2.8)	3.9 (2.8)	3.7 (2.2)
Lumbar side flexion, cm (N=306/306/279/230/120)	9.5 (5.4)	10.9 (5.9)	11.5 (5.9)	11.7 (6.1)	11.8 (6.2)
Cervical rotation, degrees (N=307/307/282/233/125)	46.3 (22.1)	50.1 (21.5)	53.7 (22.1)	54.9 (22.9)	57.2 (23.7)
Intermalleolar distance, cm (N=305/305/279/231/123)	93.9 (25.8)	100.4 (28.8)	103.9 (27.7)	106.1 (23.6)	105.5 (24.1)
Tragus to wall distance, cm (N=307/307/280/231/124)	15.8 (6.1)	15.5 (5.7)	15.6 (5.6)	15.5 (6.1)	16.0 (6.3)
BASDAI, 0–10 cm VAS (N=310/310/282/234/124)	6.0 (2.0)	3.6 (2.5)	2.8 (2.4)	2.5 (3.3)	1.8 (1.9)
Total back pain, 0–100 mm VAS (N=310/310/282/234/125)	62.0 (23.9)	37.5 (29.1)	28.1 (26.8)	22.8 (24.4)	16.4 (20.5)
CRP, mg/dL (N=308/308/279/230/123)	1.8 (2.3)	0.6 (1.2)	0.6 (1.1)	0.5 (1.1)	0.4 (0.7)
BASFI, 0–100 mm VAS (N=310/310/282/234/125)	51.7 (23.7)	35.5 (25.8)	29.0 (25.3)	24.3 (23.7)	20.9 (21.0)
SF-36 PCS (N=278/278/278/230/165)	32.6 (8.0)	39.5 (10.1)	42.2 (10.7)	44.5 (9.8)	44.4 (10.0)
ASQOL, 0–18 (N=284/284/281/233/169)	10.3 (4.4)	7.1 (5.3)	5.6 (5.0)	4.7 (4.7)	4.8 (4.8)

*Baseline is last observation prior to first dose of ADA. Baseline summarized for those that have at least 12 weeks of exposure to ADA.

Conclusion: Treatment with ADA up to 5 yrs demonstrated sustained benefits in spinal mobility, disease activity, physical function, and quality of life in pts with active AS. The results of this analysis suggest that early and long-term improvements in mobility with ADA treatment may correlate with improved functional ability.

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Adenosine Receptor Signaling in Keratinocyte Proliferation and Implications for Caffeine and Methotrexate Therapy. Gideon Smith[1], Andrew G. Franks[2], Bruce N. Cronstein[3] and Edwin SL Chan[1]. [1]New York University School of Medicine, New York, NY, [2]New York University, New York, NY, [3]New York Univ Medical Center, New York, NY

Background/Purpose: Methotrexate is highly effective in psoriasis, the classic disorder of keratinocyte proliferation. However, the mechanisms of methotrexate's antiproliferative effects in keratinocytes remains unclear. We previously demonstrated that adenosine mediates the anti-inflammatory effects of methotrexate. Here we investigate whether adenosine directly affects keratinocyte proliferation.

Methods: Normal adult human primary epidermal keratinocytes were cultured in dermal cell basal medium (37C, in 5% CO2). Cultures were supplemented with keratinocyte growth kit. Once 70–80% confluent, cell cultures were starved for 24 hours and then incubated with test substances. Proliferation was assessed by ELISA calorimetry of BrdU uptake.

Results: Incubation of keratinocytes with methotrexate produced a statistically significant reduction in proliferation versus control (DMSO) (1μM, 24 hrs, 57.8+/−2.1%, vs control, n=4, p<0.001). This was partially reversed via pre-treatment with the A2A antagonist ZM241385 (1μM, 24hrs, 78.8+/−2.2%, vs control n=4, p<0.001) or caffeine, a non-selective adenosine receptor antagonist (1μM, 24hrs, 74.1+/−0.9%, vs control n=4, p<0.05). This was also statistically significantly different from methotrexate alone (ZM241385, p<0.001). However, there was no effect on the anti-proliferative effects of methotrexate when pre-treated with the A2B antagonist MRS1754 (1μM, 24 hrs, 57.6+/−1.1% vs control, n=4, p<0.001).

Keratinocyte proliferation was also inhibited by incubation with the adenosine A2A receptor agonist CGS21680 (56.8+/−12.9% vs control, n=4, p<0.001). This effect was again blocked by pre-treatment with ZM241385 and caffeine. However, BAY60–6583, an A2B agonist, also reduced keratinocyte proliferation (1μM, 24hrs for each, 40.8+/−5.1% vs control, n=4, p<0.001), an effect blocked by MRS1754 and caffeine.

Conclusion: While methotrexate may act in psoriasis and psoriatic arthritis through its anti-inflammatory effects on lymphocytes, it also has direct anti-proliferative effects on keratinocytes acting via the A2A receptor. More importantly, we have also demonstrated that keratinocytes are also inhibited by A2B stimulation suggesting a new target for purinergic therapy development. In addition we have provided a potential mechanism for methotrexate therapeutic failure in psoriatic patients with high caffeine intake.

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The Prevalence of Carotid Artery Plaques Is Higher in Patients with Psoriatic Arthritis Compared to Those with Psoriasis Alone. Lihi Eder[1], Jai Jayakar[2], Sutharshini Shanmugarajah[2], Arane Thavaneswaran[1], Daniel Pereira[2], Vinod Chandran[2], Cheryl Rosen[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Cardiovascular morbidity is increased in patients with psoriatic arthritis (PsA) and psoriasis. Carotid Intima-Media Thickness (cIMT) and Carotid Plaque Area (CPA) serve as surrogate measures for cardiovascular diseases. No study to date has compared the extent of sub-clinical atherosclerosis between PsA and cutaneous psoriasis without arthritis (PsC). We hypothesize that PsA patients are at increased cardiovascular risk compared to PsC.

To compare the extent of atherosclerosis, as measured by cIMT and CPA, in patients with PsA and PsC.

Methods: In this cross-sectional study we compared patients with PsA from a large clinic to those with PsC. Psoriasis patients underwent an assessment by a rheumatologist to exclude inflammatory arthritis. Ultrasonographic measurements of CPA and c-IMT were performed using a high resolution optimized ultrasound system for carotid imaging. The area of each plaque was measured by tracing the perimeter with a cursor around the borders of each atherosclerotic plaque. Total plaque area was recorded as the sum of all plaques in the right and left carotid arteries. cIMT was measured as the distance between the intima-lumen interface and the media-adventitia border. PsA and psoriasis patients were matched by age and gender. The outcome variables were transformed into log of c-IMT and square root of CPA. Linear regression model for paired data was used to compare the outcome variables between the two groups. Multivariate regression analysis was used to adjust for the following variables: weight, smoking, systolic and diastolic blood pressure, serum levels of glucose, cholesterol and triglyceride and the use of antihypertensive, glucose-lowering and lipid-lowering medications.

Results: Overall, 107 matched pairs of PsA and PsC patients were included in the study. The mean age of the study population was 53±11.4 years and 45.8% were females. There was no significant difference in the prevalence of hypertension, diabetes mellitus, dyslipidemia, weight and smoking between the two groups. Both measures of atherosclerosis were higher in PsA patients compared to PsC (cIMT: matched difference of 0.02 (Log of μm), p=0.05, CPA: matched difference 0.077 (cm^2), p=0.01). However after adjustment for cardiovascular risk factors only CPA remained significantly increased in PsA compared to PsC (estimate 0.075, p=0.04). There was no significant association between measures of disease activity/damage and atherosclerosis although there was a trend for an increase in cIMT with the use of biologic agents (estimate 0.025, p=0.07).

Conclusion: Ultrasonographic measures of carotid atherosclerosis are increased in patients with PsA compared to those with PsC.

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Sclerostin Predicts Radiographic Progression in Patients with Ankylosing Spondylitis on Standard Therapies but Not in Patients on Tumor Necrosis Factor Blockers. Walter P. Maksymowych[1], Nathalie Morency[1], Stephanie Wichuk[1], Barbara Conner-Spady[1] and Georg Schett[2]. [1]University of Alberta, Edmonton, AB, [2]University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Sclerostin (SCL) is a potent suppressor of new bone formation and lower levels have been reported in ankylosing spondylitis (AS) compared to healthy controls. One report also suggests that lower levels are linked to structural progression in AS[1]. This was a limited analysis that only assessed 46 patients on standard therapies and did not address age, sex, disease duration, or treatment as confounders in the regression model. A preliminary report has also implicated bone specific alkaline phospahatse (BAP) as predictive of progression in SpA but is limited for the same reasons[2]. In this prospective study, we aimed to assess the predictive capacity of SCL and BAP in a broader spectrum of patients with AS that includes those on TNF blocker therapies.

Methods: The study cohort comprised 190 patients with SpA, 82 (43.2%) on TNF blocker therapy, followed prospectively with clinical and radiographic outcomes. Controls were 50 age and sex-matched healthy individuals. SCL and BAP were measured by enzyme-linked immunosorbent assay (ELISA). We analyzed the effect of TNF blocker therapy on levels of SCL (n = 66) and BAP (n = 100). Readers scored X-rays obtained at baseline and year 2 using the mSASSS method. Pre-specified dependent variables were: 1) 2-year change in mSASSS, 2) development of new syndesmophytes at 2 years, 3) mSASSS rate of progression. Multivariate regression analyses were controlled for age, sex, disease duration, TNF blocker treatment, and baseline radiographic score.

Results: BAP was significantly increased in patients versus controls (p = 0.0004) while comparisons between patients and controls for SCL were not significant. SCL correlated with age in SpA patients (r = 0.45, p<0.0001) and correlated inversely with BAP in controls (r = 0.37, p = 0.009). Mean (SD) level (pg/ml) of SCL increased significantly from 0.59 (0.24) to 0.66 (0.27) (p = 0.0002) while BAP increased significantly from 20.8 (8.8) to 23.08 (9.4) (p<0.0001) after TNF blocker therapy. SCL correlated significantly with baseline mSASSS score (r = 0.25, p = 0.007) in the entire cohort. SCL was a significant independent predictor of mSASSS progression in patients on standard, but not TNF blocker, therapy while BAP predicted progression only in the TNF therapy group (Table). The ratio of BAP/SCL was the best predictor of progression in patients on standard therapies. Change in SCL or BAP after TNF blocker therapy was not predictive of progression.

Biomarker	Treatment	Coefficient (95%CI)	P value
SCL	Standard	−0.96 (−1.74–0.19	0.02
BAP/SCL ratio	Standard	0.02 (0.01–0.03)	0.003
BAP	TNF	−0.10 (−0.19–0.01)	0.04

Conclusion: The assessment of SCL as a prognostic indicator in SpA is confounded by age and treatment. SCL predicts progression only in patients on standard therapies. Future studies must fully explore the effects of confounders.

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Clinical Features of Pustulotic Arthro-Osteitis. Jun-ichi Fukushi, Yasuharu Nakashima, Ken Okazaki, Taro Mawatari, Masanobu Ohishi, Yasutaka Tashiro and Yukihide Iwamoto. Kyushu University, Fukuoka, Japan

Background/Purpose: Palmoplantar pustulosis (PPP) is a chronic skin lesion associated with intraepidermal sterile pustules of the palms and soles. Bone lesions of PPP are known as pustulotic arthro-osteitis (PAO). PAO is found in about 10% of Japanese patients with PPP, and has also been reported in rare cases in Caucasians. However, the characteristic features of PAO, including the most effective therapy, have not yet been clarified.

Methods: We reviewed 54 cases with PAO who were treated at Kyushu University Hospital within the past 15 years. Patients without the typical skin rash, even if they had anterior chest pain, were excluded from the study. There were 19 males and 35 females, with an age range at onset from 18 to 75 years (mean: 47.2 years). The average follow-up period was 18 months.

Results: The onset of skin lesions preceded arthro-osteitis in 25 cases, and it was simultaneous in 17 cases. In 4 cases, arthro-osteitis preceded the skin lesions. Elevations in CRP, ESR and ALP were seen in 75%, 70% and 21% of the cases, respectively. Arthro-osteitis was observed in the anterior chest wall in 44 cases (81%). Peripheral arthritis and spinal lesions were observed in 14 (26%) and 9 (16%) cases, respectively. Twenty-six cases (48%) were treated with NSAIDs alone, which was effective in most of the cases. NSAIDs were also used in combination with predonisone in 5 cases. In 9 cases who did not respond to NSAIDs, salazosulfapyridine was used, and 6 of these cases showed improvement of pain and a decrease in CRP.

Conclusion: We reviewed 54 cases with PAO. The skin lesions preceded, or occurred simultaneously, with arthro-osteitis in most of the cases. In addition to anterior chest wall lesions, which were the most common finding, peripheral arthritis and spinal lesions were also observed in about 20% of the cases. NSAIDs were effective in about half of all the cases. Salazosulfapyridine and oral steroids may therefore be a potentially useful treatment regimen for cases refractory to NSAIDs.

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High Prevalence of Spondyloarthritis Among First Degree Relatives of Patients with Familial Mediterranean Fever: Further Evidence for a Link Between the Two Disorders. Servet Akar[1], Ozgul Soysal[2], Dilek Solmaz[2], Vedat Gerdan[2], Fatos Onen[1] and Nurullah Akkoc[1]. [1]Professor, Izmir, Turkey, [2]MD, Izmir, Turkey

Background/Purpose: Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever and serositis. It is associated with the missense variations of Meditteranean fever (MEFV) gene. There is some evidence that spondyloarthritis (SpA) including ankylosing spondylitis (AS) is more prevalent in FMF patients. Moreover we and other groups showed M694V, the most penetrant MEFV variation, may be an additional susceptibility factor for AS. Therefore in the present study we investigated the prevalence of SpA and AS in first-degree relatives (FDRs) of FMF patients.

Methods: The FDRs (> 16 years old) of 201 consecutive unrelated FMF patients were invited to the outpatient clinic. They were examined according to a standard protocol to capture patients with SpA. Presence of inflammatory back pain (IBP) was judged according to the Calin and Berlin criteria. Standard pelvic X-rays of the sacroiliac joints (SIJ) were performed in all patients. The diagnosis of SpA and AS were made based on the European Spondyloarthritis Study Group (ESSG) and the modified New York (mNY) criteria, respectively.

Results: The 201 probands had 1039 FDRs, who were over 16 years-old. Of them, 892 were alive. Ninety-six FDRs who could not be reached after at least three attempts and 84 FDRs with FMF were not included in the study. Of the remaining 712 FDRs, 319 agreed to participate of whom 233 (73%) reported back pain. IBP was present in 32 patients (13.7%) according to Calin criteria and in 20 patients (8.6%) according to Berlin criteria. Thirty-six FDRs were diagnosed as having SpA and five of them as having AS. One additional patient with AS was identified when the medical records of the 393 non-attending invitees were reviewed. The prevalence of SpA and AS among 712 FDRs were calculated as 5.1% and 0.8%, respectively. Based on a prevalence of 1.09% of SpA and 0.49% of AS found in a previous study conducted in our region, the risk ratio was estimated as 4.6 (95%CI; 2.9 to 7.4) for SpA and 1.7 (95%CI; 0.7 to 4.3) for AS in all the relatives. When only the parents (n=275) were considered, the risk ratios for SpA and AS, were 6.9 (95%CI; 4.1 to 11.9) and 2.94 (95% CI; 1.02 to 8.41). Furthermore, two patients with Behcet's syndrome, two patients with rheumatoid arthritis and one patient with un-differentiated arthritis were detected in the study population.

Conclusion: The higher frequency of SpA among the FDRs of the FMF patients and the higher prevalence of AS among the parents, are in line with the previously published studies which have reported high prevalence of sacroiliitis or SpA in FMF patients.

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The Presence of HLA-B15 Determines the Clinical Presentation and Outcome in Colombian's Patients with Spondyloarthropathies. John Londono[1], Paola Peña[2], Ana Santos[3], Wilson Bautista-Molano[2], Consuelo Romero Sanchez[2], Mabel Avila[4], Marlon Porras[4], Calos Jaramillo[3], G. Vargas-Alarcon[5] and Rafael Valle-Oñate[6]. [1]Universidad de La Sabana, Chía, Colombia, [2]Spondyloarthritis Group. Rheumatology Division. Hospital Militar Central/Universidad de La Sabana. Bogotá. Colombia, Bogotá, Colombia, [3]Universidad de Los Andes, Bogota, Colombia, [4]Spondyloarthritis Group. Rheumatology Division. Hospital Militar Central/Universidad de La Sabana. Bogotá. Colombia, Bogota, Colombia, [5]Instituto Nacional de Cardiologia Ignacio Chavez, Ciudad de Mexico DF, Mexico, [6]Spondyloarthritis Group. Rheumatology Division. Hospital Militar Central/Universidad de La Sabana, Bogotá, Colombia

Background/Purpose: In patients with Spondyloarthropathies (SpA) the association with the HLA-B15 has been previously established: 35/228 patients were positive for this allele, while only was present in 2/100 controls: OR 5.3CI95%: 1.8–17.6. (EULAR2011–4847).To determine differences in clinical presentation and outcomes of the disease among HLA-B15+, HLA-B27+ and non B27-B15 patients.

Methods: 435 of a total of 574 patients with SpA according to ESSG classification criteria and had completed HLA typing were selected. Comparisons with HLA-B27+, B15 and non B27-B15 were made to the main clinical features; disease-related background and the commitment level of the sacroiliac joints.

Results: The main findings are presented in the table:

VARIABLE	HLA-B15(+) n=52	HLA-B27(+) n=179	OTHER HLA-B n=203
Age (y)	31.8 ± 10.6	34.9 ± 10.1	35.5 ± 13.03
Age of onset (y)	26.9 ± 9.2	27.3 ± 10.4	29.2 ± 10.6
Evolution (y)	4.7 ± 5.2*	7.9 ± 10.3	6.4 ± 8.6
Sex(M/F)	33/19 1.7:1*	145/34 4.2:1	128/76 1.6:1
u-SpA	25 (48.1%)*	35 (19.6%)	102 (50.2%)
AS	10 (19.2%)	92 (51.4%)*	43 (21.2%)
ReA	17 (32.7%)*	51 (28.5%)	47 (23.2%)
PsA	0 (0%)	1 (0.1%)	11 (5.4%)
Family history for SpA	5 (9.6%)*	10 (5.6%)	12 (5.9%)
Inflammatory back pain	11 (21.1%)	50 (27.9%)	60 (29.5%)
SCHOBER	15.4 ± 3.7	14.7 ± 2.9	14.7 ± 2.1
X-ray Sacroilitis <II	26 (50%)*	51 (28.6%)	151 (74.4%)
X-ray Sacroilitis ≥II	26 (50%)	128 (71.4%)*	52 (25.6%)
Occiput to wall distance (cm)	0.2 ± 1.4	1.3 ± 3.5	0.5 ± 1.7
ASAS Axial criteria	36 (69.2%)	178 (99.4%)*	84 (41.4%)
ASAS Peripheral criteria	41 (78.8%)	161 (89.9%)	203 (100%)

Conclusion: Patients HLA-B15 positive initiated the disease at an earlier age and had a shorter time of evolution, the predominance of males was lower, with a greater proportion of patients with u-SpA and a lower degree of compromise of sacroiliacs joint. This seems to be a pattern of presentation of the disease.

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Rituximab (RTX) Therapy for Psoriatic Arthritis (PsA). M. Esther Jimenez Boj[1], Jozef Rovensky[2], Tanja A. Stamm[1], H. Raffayova[3], Burkhard F. Leeb[4], Klaus P. Machold[5] and Josef Smolen[6]. [1]Medical University of Vienna, Vienna, Austria, [2]Vurch, Piestany, [3]National Institute of Rheumatic Diseases, Piestany, Slovakia, [4]State Hospital Weinviertel,Lower Austrian Centre for Rheumatology, Stockerau, Austria, [5]Vienna Med Univ, Vienna, Austria, [6]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Psoriatic arthritis is a chronic and frequently destructive arthropathy which, in contrast to rheumatoid arthritis (RA), is usually negative for autoantibodies including rheumatoid factor (RF). The current treatment armamentarium comprises several synthetic disease modifying antirheumatic drugs (DMARDs) and TNF inhibitors. In contrast, several other biological agents are available for the treatment of RA. RTX is one of them but is apparently primarily effective in RF-positive patients, although some efficacy has been reported also in RF-negative individuals. It has not yet been assessed in PsA and there have been reports on reactivation of psoriasis in some RTX treated patients. Therefore it deemed appropriate to assess the potential benefit of RTX in PsA initially in an open label study. Here we evaluated the efficacy and safety of RTX in an exploratory, open label study of patients with PsA.

Methods: Nine patients with PsA underwent RTX at 1000mg twice within 14 days and were evaluated, among other traditional variables, by DAS28, DAPSA, BASDAI, HAQ and PASI. Patients were followed monthly for 6 months. Changes in scores were calculated using Kruskal-Wallis test.

Results: Baseline demographics showed an age of 50±11, disease duration of arthritis 9±7 and psoriasis of 12 ± 7 years; mean swollen and tender joint counts (SJC 66, TJC68) were 12±7 and 23±10, respectively. RTX was tolerated well and there were no serious adverse events. Over 6 months, DAS28 improved from a median (IQR) of 6.2 (5,9;6.4) to 4.9 (4.3;5.4), DAPSA from 52.0 (39.5;58.5) to 32.5 (21.5;54.3) and HAQ from 1.5 (1.3;1.6) to 1.0 (0.75;1.6) (all $p \leq 0.05$). C-reactive protein and PASI did not change signicantly. BASDAI decreased from 6.2 (5.2; 7.4) to 5.3 (3.8; 6.9; p=n.s).

Conclusion: In this exploratory, open label study, RTX therapy exhibited significant efficacy in PsA patients with long-standing disease. In particular, composite scores decreased and physical function improved beyond the minimal clinically important difference. Over the 6 months of observation, RTX was well tolerated and there was no reactivation of psoriasis. These data suggest that RTX may have efficacy in PSA and warrant testing this hypothesis in a double blind controlled clinical trial.

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Expression of Dendritic Cell-Specific Transmembrane Protein (DC-STAMP) and Osteoclast Precursor (OCP) Frequency in Psoriasis (PsC) Patients Who Develop Psoriatic Arthritis (PsA). Yahui Grace Chiu[1], Sutharshini Shanmugarajah[2], Dafna D. Gladman[2], Ben Panepento[1], Sharon Moorehead[1], Lihi Eder[2], Vinod Chandran[2], Rick Barrett[1] and Christopher Ritchlin[1]. [1]University of Rochester, Rochester, NY, [2]Toronto Western Hospital, Toronto, ON.

Background/Purpose: Approximately 20% of psoriasis (PsC) patients (pts) develop psoriatic arthritis (PsA) within 10 years after PsC onset. Identification of an arthritis biomarker in PsC would facilitate early intervention with the potential to delay and/or prevent the onset of psoriatic arthritis (PsA). Previously, we reported an increased frequency of circulating osteoclast precursors (OCP) in one third of PsC pts, and examined the potential of Dendritic Cell-Specific Transmembrane Protein (DC-STAMP), a transmembrane protein required for monocyte fusion during osteoclast (OC) formation, as an arthritis susceptibility biomarker in PsC. Four major DC-STAMP expression patterns were identified in human PBMC, in which OC counts increase from pattern I to pattern IV. Healthy controls usually belong to DC-STAMP pattern I, whereas PsA pts manifest DC-STAMP patterns II-IV. Herein we present the data on DC-STAMP and OCP on 10 PsC pts who developed PsA in the International Research Team (IRT) registry..

Methods: PsC and PsA pts were diagnosed by rheumatologists according to a standard criterion and enrolled in the IRT registry. Patients were evaluated annually or earlier if they developed joint pain. Diagnosis of new PsA onset was based on the Classified Criteria for Psoriatic Arthritis (CASPAR) criteria. The DC-STAMP pattern and OCP frequencies were examined in pts by flow cytometry and cell culture.

Results: Between 2006 and 2011, 516 PsC pts were enrolled in the IRT registry and 22 pts developed PsA. The DC-STAMP and OCP frequency were analyzed on 43 PsC pts who did not develop PsA and 10 pts who developed PsA as shown in the table below. For 10 pts who developed PsA, 3 samples were collected before PsA onset and 7 samples were collected on or after PsA diagnosis. Among these 7 subjects, 3 pts were on methotrexate and 1 was on etanercept at the time of blood draw.

Pattern		I	II	III	IV
DC-STAMP	PsC	12	15	11	5
	PsA	2	1	5	2
OCP frequency	PsC	629 + 1036	839 + 1213	286 + 353	1039 + 1064
	PsA	28 + 40	850 + 0	360 + 318	775 + 576

70% of PsC pts who developed PsA had patterns III or IV compared to 37% of PsC patients who had not developed PsA. Consistent with our previous finding, DC-STAMP pattern IV was associated with the highest OCP frequencies.. Nail disease and increased PASI score were two risk factors associated with PsA onset.

Conclusion: These data suggest that DC-STAMP may be a susceptibility marker for arthritis in PsC patients. The lower levels of circulating OCP in some PsA compared to PsC pts may reflect increased migration of these cells into inflamed joints. Additional studies with these biomarkers on PsC pts at risk for arthritis in the IRT registry are in progress.

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Radiographic Progression in Ankylosing Spondylitis – Results After up to 8 Years of Infliximab Treatment. Xenofon Baraliakos[1], Hildrun Haibel[2], Joachim Listing[3], Joachim Sieper[4] and Juergen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [3]German Rheumatism Research Centre, Berlin, Germany, [4]Charité – Campus Benjamin Franklin, Berlin, Germany

Background/Purpose: Therapy with TNF-blockers is clinically efficacious in patients with active AS. Improvement of spinal inflammation was demonstrated by MRI but inhibition of radiographic progression has not been shown. Hypothetical considerations have suggested TNF blockers could worsen structural changes. Baseline (BL) radiographic damage is the only significant predictor for further radiographic progression in AS. We compared the long-term course of radiographic changes in AS patients treated with infliximab ('aTNF') vs. a historical cohort (Herne cohort, 'HC') with retrospectively collected patients who were never treated with TNF blockers.

Methods: Overall, 22 patients were included in aTNF and 34 in HC, based on the availability of lateral x-rays of the cervical and lumbar spine at BL and after 8 years. The radiographs, mostly performed in 2-year intervals, were scored by two blinded readers using the mSASSS in concealed time order. The expectation-maximation (EM) algorithm was used to impute missing radiographs at year 4. Mann-Whitney test was used for simple comparisons between both cohorts. ANCOVA was applied to compare radiographic progression between both cohorts after adjustment for BL status. The progression between year 4 and year 8 was compared by means of non-parametric ANCOVA and by taking the status at BL and the radiographic progression between BL and 4y into account.

Results: Patients in the aTNF group had higher BASDAI (6.2±1.4 vs 4.3±1.4 in HC) and BASFI (5.3±1.4 vs. 3.4±1.5, both $p<0.0001$) levels at BL. HC patients were older, had a longer disease duration and were less frequently HLA B27-positive. The degree of baseline radiographic damage was similar in both groups (13.2± 17.6 in aTNF vs. 14.2± 13.8 in HC, p=0.26). Both groups showed significant radiographic progression after 8y (20.2±21.4 in aTNF and 25.9±17.8 in HC (both $p<0.001$). Similar radiographic progression was seen in the groups between BL and 4y (4.1 units in aTNF and 4.3 in HC (p=0.51). After adjustment for baseline mSASSS and for the rate of radiographic progression during the first 4y, less radiographic progression between 4y and 8y was found in aTNF (2.9 units), vs. HC (7.4 units) (p=0.029). In contrast, adjusting for age (p=0.61), symptom duration (p=0.42), HLA-B27 (p=0.10), BASDAI (p=0.53) and BASFI (p=0.38) at BL did not significantly influence radiographic progression. The number of new syndesmophytes/patient after 8y in patients without BL-syndesmophytes did not differ between groups (0.8±1.6 in aTNF vs. 2.6±4.7 in HC, p=0.36). This was in contrast to the patients with BL-syndesmophytes: less new syndesmophytes developed in the aTNF group (1.3±4.5) vs. HC (3.3±1.9), (p=0.032).

Conclusion: This study shows ongoing radiographic progression in patients with established AS over 8 years. Taking into account the relatively low patient numbers and the nature of the historical cohort, these data show no evidence that continuous anti-TNF therapy leads to increased radiographic progression in AS. It seems even possible that long-term anti-TNF therapy may decrease radiographic damage. This is also backed by the result that less new syndesmophytes developed in anti-TNF treated patients.

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Cardio-Metabolic Risk Profile of Patients with Psoriatic Arthritis and Psoriasis. Yih Chang Lin[1], Kiyoko Uno[1], Neil J. Korman[2], Neil Borkar[2], Katherine Wolski[1], Danielle Brennan[1], Vaibhav Pawar[2], Stephen J. Nicholls[3] and M. Elaine Husni[1]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]University Hospitals-Case Medical Center, Cleveland, OH, [3]Cleveland Clinic Foundation, Cleveland

Background/Purpose: Incremental increase in inflammatory pathways in psoriatic arthritis (PsA) may contribute to an even higher cardiovascular (CV) risk and metabolic syndrome (MetSyn) as compared to psoriasis (PsO) alone. This study aims to establish if presence of inflammatory joint disease in patients with psoriasis is a risk factor for MetSyn.

Methods: 252 patients with psoriatic diseases were prospectively recruited from two tertiary care referral centers. PsA was diagnosed after satisfying the CASPAR criteria and confirmed by board certified rheumatologist, while PsO was diagnosed by a board certified dermatologist. The clinical database was used to determine prevalence of conventional CV risk factors and MetSyn profiles for patients with and without DMARD therapy (both non-biologic and biologics). MetSyn was defined by NCEP/ATP III criteria. Comparisons between PsA and PsO were tested using t-tests and chi-squares. Univariable and multivariable odds ratios (ORs) were calculated to determine the association of PsA and MetSyn.

Results: 145 PsO patients (58%) and 107 PsA patients (42%) were included in the study. There was similar gender distribution (p 0.784), prior CV event (p-value 0.891), and family history of CV risk (p 0.161). However, there was difference in age distribution (p 0.004) and disease duration (p <0.001). PsA patients have significantly higher prevalence of hypertension, obesity, CRP, hypertriglyceridemia, hyperglycemia, and MetSyn with p <0.011, <0.01, 0.03, <0.02, 0.01, <0.01 respectively compared with PsO. In addition, PsA patients who are not on active DMARDs therapy have significantly higher prevalence of MetSyn (p <0.001) and increased Framingham risk score (p 0.005) as compared to PsO. However, the significance was lost when patients were analyzed on DMARDs treatment (p 0.568 and 0.717 respectively). PsO with inflammatory joint disease was found to be a risk factor for MetSyn (unadjusted OR 2.658 (95% CI [1.518–4.653])). After adjustment for age, family history of CV risk, CRP, and treatment with DMARDs, inflammatory arthritis remained significant risk factor for MetSyn (OR 3.423, 95% CI [1.431–8.189]).

Table 1. Adjusted ORs for MetSyn risk factors

Covariates	Adjusted ORs (95% CI)	p-value
PsA vs. PsO	3.423 (1.431, 8.189)	0.006
Age	1.033 (1.005, 1.061)	0.020
Family history of CV risk	3.568 (1.368, 9.305)	0.009
log CRP	1.590 (1.169, 2.164)	0.003
DMARDs (Biologic and Non biologic)	2.336 (1.049, 5.200)	0.038

Conclusion: Our results suggest that presence of inflammatory joint disease in patients with psoriasis is a significant risk factor for MetSyn. PsA patients also have significantly higher prevalence of conventional CV risk factors and higher Framingham risk scores as compared to PsO. However, there is no significant difference once patients are on active DMARDs treatment for psoriatic diseases.

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Approaching Psoriatic Arthritis - Comparing the Patients's Perspective to Physicians' Evaluations. Matthias Englbrecht, Stefan W. H. Dandorfer, Monika R. Ronneberger, Veronika Lang and Georg Schett. University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: To date, we hardly now anything about the comparability of physician's to patient's evaluation of disease related-symptoms in psoriatic arthritis (PsA). To investigate the relation of physician's to patient's evaluation of symptoms in PsA.

Methods: We examined 55 outpatients by referring to the GRAPPA core set of disease related symptoms for PsA including visual analogue scales for general pain, global status, arthritis and psoriasis related symptoms (i.e. status of peripheral joints, spinal involvement, enthesitis, involvement of the skin and the nails) and other symptoms (fatigue & sleep disorders). The second part of the questionnaire consisted of symptom interrelations of arthritis and psoriasis according to the individually experienced magnitude and patients were asked to complete the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The corresponding physician evaluated the patient's condition by using VAS for global status, disease activity of arthritis and psoriasis, and additional comparative measures (i.e. TJC68/SJC66, the Psoriasis Area and Severity Index, the Nail Psoriasis Severity Index and the Maastricht Ankylosing Spondylitis Enthesitis Score with gradation for tendon specific pain). After transformation for better comparability of scores, these measures where compared to the corresponding VAS-ratings of the patient by calculating 95% confidence intervals of differences.

Results: On average, when comparing the magnitude of interrelations, patients evaluated symptoms of arthritis [95%CI:4.29; 5.71] to be worse than symptoms of psoriasis [95%CI:1.58; 3.00] or additional symptoms such as fatigue or sleep disorders [95%CI:2.19; 3.20]. When looking at 95%CI of average differences of VAS evaluations between patients and physicians for global status, arthritis and psoriasis, appraisals differed considerably with patients stating higher ratings (indicated by 95%CI > 0; global status: [95%CI:0.66; 1.79], rheumatic disorders: [95%CI:0.30; 1.33], psoriatic disorders: [95%CI:0.54; 1.58]). These results where confirmed in corresponding 95%CIs and t-tests with respect to physician-patient comparisons when applying comparative measures ($p \leq 0.02$, see Table 1).

Table 1 Comparison of average ratings on patient's VAS and comparative measures

	Dimension 1	Dimension 2	Dimension 3	Dimension 4	Dimension 5	Dimension 6
Comparative measures (Mean ± SD)	TJC68 (1.92 ± 2.15)	SJC66 (0.62 ± 0.75)	BASDAI (3.92 ± 2.28)	MASES (1.35 ± 1.69)	PASI (0.2 ± 0.29)	NAPSI (0.64 ± 1.13)
Patient VAS (Mean ± SD)	Global Pain (3.81 ± 2.82)	Disorders of joints (3.87 ± 2.72)	Global disease activity (3.99 ± 2.80)	Enthesitis (2.57 ± 2.76)	Skin disease activity (2.1 ± 2.58)	Nail disease activity (1.21 ± 1.83)
p-value of dependent samples t-test (p-value)	7.15 (< 0.001)***	18.46 (< 0.001)***	0.38 (0.70)	3.73 (< 0.001)***	5.76 (< 0.001)***	2.41 (0.02)*
95% CIs of difference (VAS – comparative measure)	[1.40; 2.48]	[2.67; 3.84]	[-0.43; 0.83]	[0.58; 1.91]	[1.24; 2.57]	[0.09; 1.62]

Conclusion: In general, patients gave significantly higher ratings to some disease-related symptoms than physicians did. Hence, when investigating the perceived disease impact it seems necessary to take into account both sides of the coin—the patient's as well as the physician's perspective.

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Radiological Characteristics of the Calcaneal Spurs in Psoriatic Arthritis. Mohammed Abufayyah[1], David Salonen[2], Arane Thavaneswaran[3], Vinod Chandran[1] and Dafna D. Gladman[3] [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]University Health Network, Toronto, ON, [3]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Inflammation at the entheses is a distinguishing feature of psoriatic arthritis (PsA). Enthesitis at the heel is the most common location; irregular spiculated calcifications often at sites of enthesis such as the Achilles and plantar fascia insertions on the calcaneous. This study aimed to 1) describe the morphological features and measurements of plantar calcaneal spurs on weight bearing lateral foot radiographs in subjects with PsA and controls and 2) determine radiological features that differentiate between inflammatory & non-inflammatory calcaneal spurs.

Methods: Weight bearing lateral foot radiographs of 101 subjects with PsA and 38 control subjects without inflammatory arthritis were examined for plantar calcaneal and Achilles spurs. Three measurements were taken from each radiograph: plantar spur base, mid-segment, and length in millimeters as shown in Figure 1. The differences in radiographic measurements, and the presence of fluffy periostitis of the plantar spurs were then compared between PsA patients and controls.

Results: Of the 101 subjects with PsA, 76 (75%) had at least one plantar calcaneal spur and 32 (31.5%) had at least one Achilles tendon spur, compared to 18 (47%) and 3 (8%) respectively in control group (p=0.004). The presence of fluffy plantar periostitis was identified in 14 PsA subjects but in none of the controls (p=0.01). The dimensions of plantar spurs were significantly different between groups (table 1); Logistic regression identified that gender and mid-segment distinguished patients with PsA from controls.

Table 1. Demographics, Radiological characteristics and Measurement of Calcaneal Spurs:

Variable	Mean (stdev) or Frequency (%) PsA n=101	Controls n=38	p-value
Gender (M/ F)	65 (64.4%)/36 (35.6%)	15 (39.5%)/23 (60.5%)	0.008
Age	41.1 (10.8)	49.2 (14.7)	0.003
Obesity	42 (44.7%)	6 (46.1%)	0.92
DISH	4 (4.0%)	0 (0.0%)	0.21
Achilles Spurs	32 (31.5%)	3 (8%)	0.004
Plantar Spurs	76 (75.0%)	18 (47.5%)	0.002
Bilateral	56	11	
Unilateral	20	7	
Fluffy plantar periostitis	14 (8.4%)	0 (0.0%_)	0.01
Base (mm)	7.1 (2.8)	4.6 (1.5)	<0.0001
Mid (mm)	4.9 (2.2)	2.3 (0.9)	<0.0001
Length (mm)	4.5 (2.1)	4.2 (1.7)	0.57

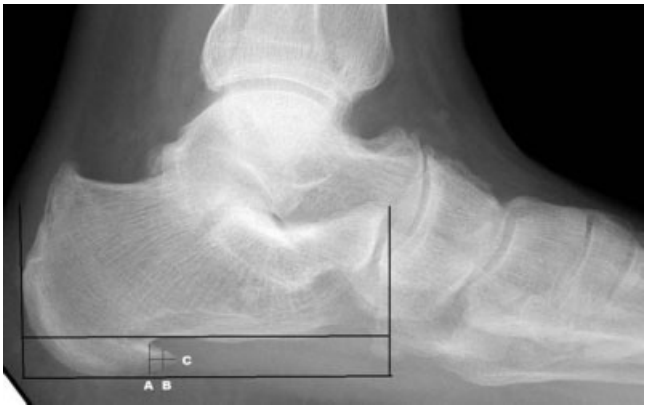

Figure 1. Lateral radiograph with measured dimensions of plantar spur; (A) Spur base; (B) Mid-segment; and (C) Spur length.

Conclusion: In this observational study we found that calcaneal spurs are more common in subjects with PsA, and that a higher midsegment measurement was associated with PsA. This study provides radiological differentiating features between inflammatory and non-inflammatory spurs including the presence of fluffy plantar periostitis and broad based and mid-segment dimensions.

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Smoking Is Associated with Syndesmophyte Development in Ankylosing Spondylitis. Dilek Solmaz[1], Servet Akar[2], Ismail Sari[3], Ozgul Soysal[1], Vedat Gerdan[1], Fatos Onen[2] and Nurullah Akkoc[2]. [1]MD, Izmir, Turkey, [2]Professor, Izmir, Turkey, [3]Dokuz Eylul University School of Medicine, Izmir, Turkey

Background/Purpose: Information on risk factors for the severity of spinal involvement in ankylosing spondylitis (AS) is limited. In this cross-sectional study we examined the association of the presence of syndesmophytes with smoking, which has been suggested to be related to a more severe disease course by some authors, and with the presence of calcaneal enthesophytes, which may be an indicator of a tendency to bone formation in AS.

Methods: We included 114 patients with AS (77 male [67.5%] with a mean age of 40.7 ± 11.4 years) who had available lateral heel radiographs and vertebral X-rays for review. All patients fulfilled the modified New York criteria. Two independent readers evaluated the vertebral and lateral heel radiographs for the presence of syndesmophytes and enthesophytes at the insertion of the *achilles* tendon or *plantar* fascia. In cases of disagreement consensus was reached by second reading session. All clinical and demographic data, including disease activity (BASDAI), functional (BASFI) and mobility (BASMI) scores at the time of radiographic examination and the highest available ESR and CRP levels as well as the smoking status were obtained from the medical records. The relation of the variables with syndesmophyte formation was evaluated with phi coefficient or Spearman's rho. Logistic regression model was used to identify the independent risk factors for the presence of vertebral syndesmopytes.

Results: Clinical and demographic features of the patients are summarized in table 1. A total of 61 (53.5%) patients had syndesmophytes and 73 (64%) had calcaneal enthesophytes. There were moderate and substantial agreement between the two readers in regard with the presence of vertebral syndesmophytes (k=0.706) and calcaneal enthesophytes (k=0.846). Univariate analysis revealed the presence of syndesmophytes was associated with smoking status, the presence of calcaneal enthesophytes as well as age, sex, highest available ESR, BASFI and BASMI (table 2). After multivariate logistic analysis smoking status, male sex, BASMI score and age remained significantly associated with the presence of syndesmophytes (table 2).

Table 1. Characteristics of the study group

	AS patients (n=114)
Age, mean ± SD	40.7 ± 11.4
Male sex: n (%)	77 (67.5)
Disease duration, mean ± SD (years)	6.7 ± 7.9
Symptom duration, mean ± SD (years)	15.1 ± 10.1
Ever-smoker: n (%)	81 (71.7)
Education Level, mean ± SD (years)	9.2 ± 4.0
ESR, mean ± SD	43.2 ± 28.6
CRP, mean ± SD	33.6 ± 42.1
BASDAI, mean ± SD	3.1 ± 2.6
BASFI, mean ± SD	3.5 ± 2.2
BASMI, mean ± SD	3.8 ± 1.9
ASDAS ESR, mean ± SD	2.7 ± 1.1
ASDAS CRP, mean ± SD	2.7 ± 1.1

Table 2. Factors associated with and independently predict the presence of syndesmophyte formation.

Variables	The presence of vertebral syndesmophyte *Rho or phi*	*p*	OR (95% CI)	*P*
Age	0.394	<0.001	1.09 (1.02–1.7)	0.008
Sex	0.218	0.020	4.95 (1.3–18.7)	0.018
Ever-Smoker	0.236	0.012	6.26 (1.46–26.73)	0.013
ESR	0.277	0.003	1.01 (0.99–1.03)	0.102
BASFI	0.314	0.001	1.07 (0.85–1.34)	0.534
BASMI	0.467	<0.001	1.63 (1.16–2.30)	0.005
Calcaneal entesophytes	0.254	0.007	1.53 (0.47–4.97)	0.472

Conclusion: Smoking, male sex, age and BASMI scores are independently associated with structural damage in AS. The association between the presence of calcaneal enthesophytes and syndesmophytes, which was present in univariate analysis but which disappeared after multivariate logistic regression analysis, needs to be further explored in future prospective studies.

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Three Phenotype Profiles Are Revealed by Cluster Analysis in Early Inflammatory Back Pain Suggestive of Spondyloarthritis (SPA). Results From the DEvenir Des Spondyloarthropathies Indifferenciées Récentes (DESIR) Cohort. Maria-Antonietta D'Agostino[1], Philippe Aegerter[2], Maxime A. Breban[3] and Maxime Dougados[4]. [1]Versailles-Saint Quentin en Yvelines University- APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, France, [2]Versailles-Saint Quentin en Yvelines University- APHP, Ambroise-Paré Hospital,, Boulogne-Billancourt,, France, [3]Hopital Ambroise Pare, Boulogne, France, [4]Paris-Descartes University, Paris, France

Background/Purpose: SPA spectrum refers to a variety of skeletal and extra-articular inflammatory manifestations that may combine differently among patients. The objective of the study was to examine whether SPA disease manifestations at baseline would combine according to an ordered or random pattern in patients with early inflammatory low back pain (IBP) and suggestive of SPA.

Methods: Baseline clinical and demographic characteristics, as well as imaging (i.e. pelvic X-rays, pelvic MRI and peripheral entheses ultrasound) and biological data (including HLA-B27) of patients included in the French multicenter DESIR cohort of early (< 3 yrs duration) IBP suggestive of SPA were analysed by multiple correspondence analysis in order to graphically assess the association between the studied manifes-

tations. Several methods of cluster analysis using those variables were then performed to identify subgroups of patients with similar characteristics.

Results: Seven hundred and eight patients were included into the Cohort. Among the 700 analysed patients cluster analysis allowed us to classify 688 patients in 3 major groups (table 1). Cluster A contained a majority of men, with predominant isolated axial manifestations, and higher frequency of uveitis and positivity of HLA-B27. Cluster B predominantly consisted of women, with higher frequency of peripheral signs (including vascularisation at entheses by power Doppler ultrasound (PDUS)), psoriasis and younger onset of disease symptoms. Cluster C was composed by patients with predominant axial symptoms, equal distribution of sex, highest presence of pelvic X-rays and MRI positivity, and lower prevalence of HLA-B27 positivity.

Table 1.

Characteristics	Cluster A (n = 163)	Cluster B (n = 209)	Cluster C (n = 316)	Global P^+
Sex (% of men)	61%	28%	49%	<0.0001
Age at onset (<40 ys)	76%	69%	88%	0.0027
Duration of symptoms (>24 months)	31%	24%	37%	0.007
Arthritis (% of yes)	45%	95%	40%	<0.0001
Enthesitis (% of yes)	40%	82%	32%	<0.0001
Dactylitis (% of yes)	13%	31%	2%	<0.0001
Uveitis (% of yes)	14%	9%	5%	0.003
Psoriasis (% of yes)	14%	32%	7%	<0.0001
IBD* (% of yes)	1.2%	4%	2%	ns
HLA-B27 + (% yes)	61%	36%	28%	<0.0001
X Rays sacroiliitis (% of yes)	16%	21%	36%	<0.0001
MRI sacroiliitis (% of yes)	34%	24%	47%	<0.0001
Vascularized PDUS enthesitis°(% of yes)	15.7%	23%	8.5%	0.004

* IBD=inflammatory bowel diseases; °at least one; $^+$Kruskal-Wallis test.

Funding: The DESIR cohort is supported by an unrestricted grant from PFIZER France

Conclusion: Cluster analysis of SPA manifestations among patients with early IBP allowed us to clearly identify at baseline 3 different groups of clinical phenotypes. Ongoing follow up will allow to determine whether these clusters may correspond to different severity patterns.

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Atherosclerotic Burden In Patients with Psoriatic Arthritis and Psoriasis: Do They Differ? Yih Chang Lin[1], Kiyoko Uno[1], Neil Borkar[2], Danielle Brennan[1], Vaibhav Pawar[2], Katherine Wolski[1], Neil J. Korman[2], Stephen J. Nicholls[3], Soo Hyun Kim[4] and M. Elaine Husni[1]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]University Hospitals - Case Medical Center, Cleveland, OH, [3]Cleveland Clinic Foundation, Cleveland, [4]Cleveland Clinic, Cleveland, OH

Background/Purpose: Both psoriatic arthritis (PsA) and psoriasis (PsO) has each been shown to have increased cardiovascular (CV) morbidity. This study was aimed to identify the presence of atherosclerotic burden in patients with PsA and PsO. We investigated the hypotheses that the incremental inflammatory pathways in PsA of both skin and joint will have greater atherosclerotic burden than PsO alone.

Methods: 178 patients with psoriatic disease were prospectively enrolled from two tertiary-care referral centers. PsA was diagnosed after satisfying the CASPAR criteria and confirmed by board certified rheumatologist, while PsO was diagnosed by a board certified dermatologist. Common carotid intima media thickness (cIMT) was measured using high resolution B mode ultrasonography. cIMT was summarized with means ± SD or medians (Q1-Q3). Comparisons were made using Student's t-test and Wilcoxon rank-sum test.

Results: Our study cohort included 59 PsA patients and 119 PsO patients. The groups were comparable with regards to gender distribution, smoking history, alcohol use, diabetes status, and CV co-morbid diseases (stroke, MI, PVD, diabetes and other cardiovascular diseases). As anticipated, PsO patients were younger compared to PsA patients ($p < 0.01$). cIMT measurements were significantly higher in patients with PsA showing greater mean cIMT (0.70 vs. 0.66, p 0.048) and maximum cIMT (1.13 vs. 0.98, p 0.01).

Conclusion: Our patients with PsA demonstrated a greater carotid intima thickness compared with PsO patients. PsA affecting both skin and joint may increase their atherosclerotic burden compared to PsO alone. Further study is needed to elucidate the mechanism that inflammatory arthritis may contribute a greater risk than skin alone.

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Inhibition of Hyaluronan Synthesis with 4-Methylumbelliferone In NZBWF1/J Mice Is Associated with Improved Renal Function and Reduced Renal Inflammation. Susan Yung, Wan Wai Tse, Mel Chau and Tak Mao Chan. The University of Hong Kong, Hong Kong SAR, Hong Kong

Background/Purpose: Lupus nephritis is a severe complication of systemic lupus erythematosus and an important cause of renal failure. We have previously demonstrated that hyaluronan (HA), an important extracellular matrix component that possesses inflammatory activities, is increased in the kidneys of patients with lupus nephritis. To delineate the role of HA in the pathogenesis of lupus nephritis, this study investigated the effect of 4-methylumbelliferone, a specific inhibitor of HA synthesis, on clinical, serologic and expression of inflammatory mediators in a murine lupus nephritis model.

Methods: Female NZBWF1/J mice with established nephritis and proteinuria >3g/l were randomized to receive treatment with sterile PBS, vehicle alone (1% Arabic Gum in PBS) or 4-methylumbelliferone in 1% Arabic Gum (4-MU, 3g/kg/day) for 2, 4, 8 and 12 weeks by oral gavage (n=6 for all time points for each group), after which time mice were sacrificed and blood collected for the assessment of serum levels of creatinine and urea. Kidneys were harvested for histologic assessment and expression of inflammatory mediators. Spot urine was obtained for the measurement of albumin-to-creatinine ratios. Six mice with established disease were also sacrificed at the beginning of the study to obtain baseline clinical, serologic and histologic data.

Results: Overall survival of mice treated with PBS, Arabic Gum and 4-MU was 75.5%, 78.8% and 90.0% respectively after 12 weeks treatment (P=NS). Serum HA levels increased in a time-dependent manner in PBS and vehicle treated mice, which was associated with increased periglomerular and tubulointerstitial expression of HA. Treatment of mice with 4-MU for 12 weeks reduced serum HA levels by 30% and reduced HA expression to near normal levels in both renal compartments. Urine albumin-to-creatinine ratio and serum levels of urea and creatinine increased in both PBS and vehicle treated mice with increasing progression of disease, whilst these abnormalities were significantly decreased in 4-MU treated mice after 12 weeks treatment ($P<0.05$ for all compared to both control groups). Suppression of HA synthesis in MU-treated mice was associated with reduced IgG and C3 deposition in glomeruli and decreased expression of $CD4^+$ T cells, $CD19^+$ B cells, and macrophages compared to PBS and Arabic Gum treated mice.

Conclusion: These results suggest that hyaluronan plays an important role in the pathogenesis of lupus nephritis and suppression of its synthesis can ameliorate disease manifestations in lupus nephritis.

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Carabin, a Negative Regulator of B Cells, Points Out a New Defective Biological Pathway In Systemic Lupus Erythematosus. Jean-Nicolas Schickel[1], Jean-Louis Pasquali[1], Anne Soley[1], Anne-Marie Knapp[1], Marion Decossas[1], Luc Marcellin[2], Anne-Sophie Korganow[1], Thierry Martin[1] and Pauline Soulas-Sprauel[1]. [1]IBMC, Strasbourg, France, [2]Hôpitaux Universitaires de Strasbourg, Strasbourg, France

Background/Purpose: The mechanisms of B-cell dependent autoimmunity are not entirely elucidated, but could notably result from a faulty negative regulation of mature B cells. Indeed, intrinsic defects of several B-cell negative regulators lead to the development in mice of a systemic lupus erythematosus (SLE)-like disease, with production of antinuclear autoantibodies, sometimes associated to the development of a glomerulonephritis (GN). Carabin is a known negative regulator of T cells that inhibits calcineurin and Ras pathways. Considering the important molecular similarities of antigen receptor signaling in T and B cells, including the role of Ras and Calcineurin pathways in BCR signaling, we decided to evaluate the role of Carabin in B cells, which is currently unknown, and to look for signs of autoimmunity in Carabin deficient mice.

Methods: We analyzed the phenotype of Carabin knock-down (KD) A20 B cells, we generated Carabin knock-out (KO) and B cell specific conditional KO mice, and analyzed B cell functions and autoimmune symptoms in these animals.

Results: Upon BCR stimulation, Carabin deficient B cells accelerate Erk phosphorylation. In vivo, Carabin is not involved in B cell development and in the basal secretion of immunoglobulins. However, Carabin deficiency

clearly impacts on the function of mature Carabin deficient B cells. Indeed, Carabin deficient mice speed up both T-dependent and T-independent B cell responses. Moreover, CpG-DNA treatment of non autoimmune-prone Carabin deficient mice induces a prolonged overproduction of anti-DNA autoantibodies and a lupus-like mesangial type II glomerulonephritis, with large immune deposits. Finally, B cell Carabin expression is low in young (NZB/NZW)F1 mice (spontaneous model of lupus) before the appearance of the disease, is associated with increased Erk phosphorylation, and is also low in a subset of lupus patients.

Conclusion: Our results support the idea that Carabin is a negative regulator of early B cell responses, and that its deficiency in mice can lead to autoimmunity, providing a dual stimulation of the BCR and TLR pathways. In addition, we show that Carabin expression is low in B cells from (NZBxNZW)F1 mice and from a subgroup of patients with quiescent SLE. Taken together, these results depict Carabin as a new player in autoimmunity.

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TWEAK/Fn14 Pathway Blockade Attenuates Renal Disease In Autoantibody-Induced Nephritis. Yumin Xia[1], Sean Campbell[1], Leal Herlitz[2], Jennifer S. Michaelson[3], Linda C. Burkly[3] and Chaim Putterman[4]. [1]Albert Einstein College of Med, Bronx, NY, [2]Columbia Presbyterian Medical Center, [3]Biogen Idec, Cambridge, MA, [4]Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: TNF-superfamily (TNFSF) members are instrumental in the pathogenesis of lupus and lupus nephritis. Previously, we found that TWEAK (TNFSF12)-mediated activation of its receptor, Fn14, stimulates the secretion of MCP-1, RANTES and IP-10 by mesangial cells and podocytes. TWEAK also modulates renal cell survival and proliferation. Thus, we hypothesized that TWEAK blockade may be therapeutically beneficial in autoantibody-mediated nephritis.

Methods: Nephrotoxic serum nephritis (NTN), a murine model for lupus nephritis, was used to study the relevance of the TWEAK/Fn14 pathway in the pathogenesis of renal disease induced by pathogenic antibodies.

Results: We induced NTN by passive transfer of pre-formed nephritogenic rabbit antibodies into 129 Fn14 knockout (KO) and wildtype (WT) mice. On days 7, 14, and 21 after antibody transfer, Fn14 KO mice had significantly decreased levels of proteinuria as compared to Fn14 WT mice (day 7: 61±24 vs 220±42 mg/dl, $p<0.01$; day 14: 99±50 vs. 678±205 mg/dl, $p=0.02$; and day 21: 101±49 vs. 678±205 mg/dl, $p=0.02$). Moreover, crescent formation and tubular dilatation were significantly decreased in Fn14 KO vs. WT mice (**Figure 1**), as were MCP-1, RANTES, and IP-10 kidney mRNA expression levels. To confirm the protective effect of TWEAK inhibition with a pharmacological approach, we induced nephrotoxic nephritis in 129 Fn14 WT mice and initiated treatment with an anti-TWEAK monoclonal antibody (mAb) or an isotype matched control Ig. Similar to the results in the Fn14 KO mice, significant amelioration of proteinuria and improvement in renal histology was observed in mice with induced nephritis receiving treatment with an anti-TWEAK mAb. Anti-TWEAK mAb treatment did not appear to affect the systemic immune response, as no alteration in the murine anti-rabbit IgG subclass antibody titers was evident.

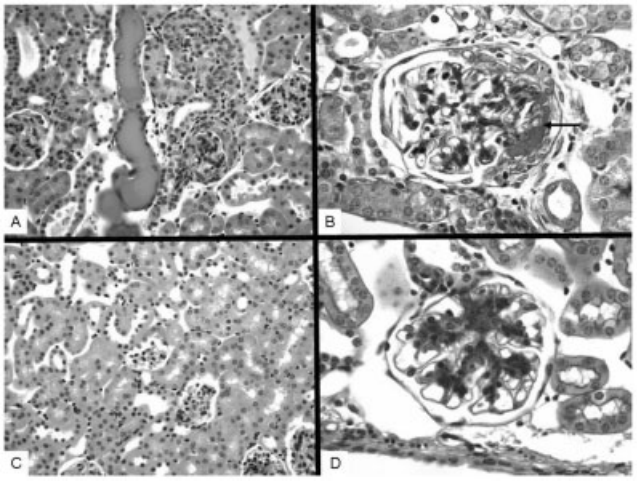

Figure 1. NTN induced in Fn14WT (A & B) and Fn14KO mice (C &D). Panel A shows a large proteinaceous tubular cast as well as mild interstitial inflammation. Also present are 3 glomeruli, one of which shows a crescent. Panel B shows a glomerulus with a large PAS-positive immune deposit (arrow) as well as a segmental overlying cellular crescent. Panel C shows a representative picture of the essentially normal tubulointerstitium seen in Fn14KO mice, with only occasional proteinaceous casts. Panel D shows a representative glomerulus from a Fn14KO mouse. While PAS positive immune deposits are seen in the mesangium, endocapillary proliferation and crescent formation were rare.

Conclusion: TWEAK/Fn14 interactions promote the pathogenesis of nephritis in the NTN model, apparently playing an important role in the cascade of pathologic events locally in the kidney rather than by impacting the systemic immune response. Therefore, disrupting TWEAK/Fn14 interactions may be an innovative approach for the treatment of lupus and other antibody-induced renal diseases.

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Deficiency of the TWEAK Receptor Fn14 Is Protective In the MRL-Lpr/Lpr Mouse Model of Lupus Nephritis. Yumin Xia[1], Jing Wen[1], Jennifer S. Michaelson[2], Linda C. Burkly[2] and Chaim Putterman[3]. [1]Albert Einstein College of Med, Bronx, NY, [2]Biogen Idec, Cambridge, MA, [3]Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: Inhibition of various TNF superfamily (TNFSF) ligand-receptor interactions has proven to have significant therapeutic effects in murine models of lupus and in human disease. Previously we showed that TWEAK (TNFSF12)/ Fn14 (TNFRSF12a) interactions may play a role in the pathogenesis of lupus nephritis (LN). Renal mesangial cells, podocytes, and tubular cells express Fn14, the receptor for TWEAK. TWEAK engagement of Fn14 induces these kidney resident cells to produce multiple inflammatory mediators including MCP-1 and RANTES, which have been conclusively shown to play a role in the pathogenesis of experimental LN. In the chronic graft versus host (cGVH) model, transfer of alloreactive splenocytes to B6 mice results in anti-nuclear antibody generation and renal Ig deposition leading to glomerular proteinuria reminiscent of lupus. In this model, genetic deficiency of Fn14, or treatment with an anti-TWEAK mAb, decreased kidney inflammation and proteinuria without affecting systemic autoantibodies. These studies suggested that inhibition of TWEAK/Fn14 interactions might be efficacious in spontaneous models of lupus.

Methods: We assessed the role of the TWEAK/Fn14 pathway in the pathogenesis of LN by evaluating the effect of Fn14 deficiency in the well-established MRL/lpr spontaneous mouse model of lupus.

Results: We found that kidney Fn14 expression was significantly increased in MRL/lpr mice at 26 as compared to 7 weeks of age, while splenic Fn14 expression actually decreased over time. Kidney TWEAK mRNA expression in MRL/lpr mice was also increased over time, significantly higher by 19 as compared to 7 weeks of age, and further increased and significantly higher in MRL/lpr as compared to MRL/+ mice by 26 weeks of age.

At 26 weeks of age, MRL/lpr Fn14 WT mice (n=10) had significantly higher levels of proteinuria (1022±317 mg/dl) as compared to MRL/lpr Fn14KO (n=9) (38±8 mg/dl, $p=0.01$) (**Figure 1**).

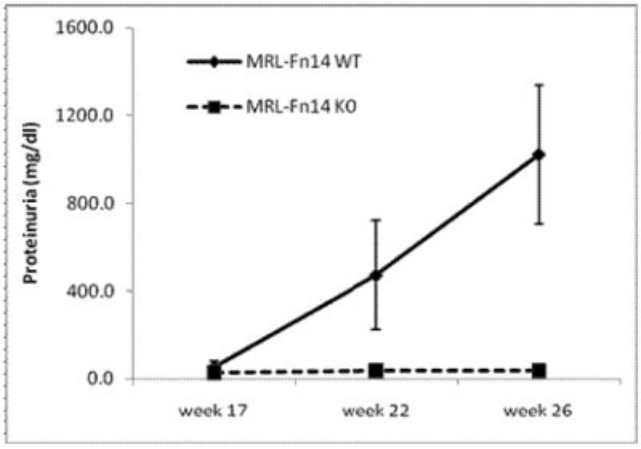

Figure 1.

To determine whether reduced severity of nephritis was due to a decrease in the titer of circulating antibodies, we compared serum autoantibody titers

in MRL/lpr Fn14 WT and KO mice. There were no differences between the groups in anti-dsDNA antibody titers at the various time points, suggesting that TWEAK likely acts by modulating events locally in the kidney.

Conclusion: TWEAK/Fn14 interactions are instrumental in the pathogenesis of LN in the MRL/lpr mouse model. Our results suggest that blocking the effects of TWEAK may be a novel therapeutic approach to the treatment of the kidney disease associated with SLE without inducing systemic immunosuppression.

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Interferon Regulatory Factor-4 deficient Lupus-Prone MRL/*Lpr*Mice Show Strong Propensity for Th1 Polarity and Develop Granulomatous Lesions in Multiple Organs. Hidemaru Sekine[1], Takeshi Machida[1], Eiji Suzuki[2], Christopher Reilly[3], Xian Zhang[4], Phil Ruiz[5] and Gary S. Gilkeson[6]. [1]Fukushima Medical University, Fukushima, Japan, [2]Medical University of South Carolina, Charleston, SC, [3]Virginia Tech, Blacksburg, VA, [4]Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, SC, [5]University of Miami, Miami, FL, [6]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC

Background/Purpose: The transcription factor interferon regulatory factor-4 (IRF-4) is a member of the IRF family of transcription regulators and required for Ig-production/maturation of B cells and development of Th2 and Th17 cells. Previously, we found *Irf4* gene deficient MRL/*lpr* lupus-prone mice develop dermatitis, ear necrosis and diffuse proliferative glomerulonephritis without serum autoantibodies and glomerular immune complex (IC)/C3 depositions. Furthermore, the mice exhibited significantly increased $CD4^+$ T cells with enhanced IFN-γ producing Th1 cells in their spleens. These results suggested a skewed Th1 phenotype in $Irf4^{-/-}$ MRL/*lpr* mice.

Methods: To further define the mechanisms of the disease in $Irf4^{-/-}$ MRL/*lpr* mice, we performed kinetic analysis of splenocyte populations in 6, 12, and 24 weeks old $Irf4^{-/-}$ and $Irf4^{+/+}$ (w.t.) MRL/*lpr* and C57BL/6 mice by flow cytometry. Splenocytes from 12-week-old mice were sorted into $CD4^+$ naïve ($CD44^{low}CD62L^{high}$), memory ($CD44^{high}$ $CD62L^{high}$), and effector ($CD44^{high}CD62L^{low}$) T cells, and stimulated with PNA/ionomycin. Cytokine production was detected by intracellular cytokine staining and flow cytometry. Histopathological analysis of livers, lungs, and spleens in 24 week old animals was performed in addition to analysis of their kidneys, skin, and ears.

Results: By 24 weeks-of-age, all $Irf4^{-/-}$ MRL/*lpr* mice developed whitish spleens characterized by formation of fibrous areas between the lymphoid areas, expansion of lymphoid populations in white pulp area with loss of architecture, and histiocyte proliferation. In addition, 5 of the 10 $Irf4^{-/-}$ MRL/*lpr* mice developed multiple granulomatous lesions in their livers and/or lungs characterized by infiltration of lymphocytes and formation of multinucleated giant cells including Langhans-type giant cells. In contrast, neither whitish spleen nor granulomatous lesion was observed in age-matched w.t. MRL/*lpr,* $Irf4^{-/-}$C57BL/6 or w.t. C57BL/6 mice. At 12 weeks-of-age, $Irf4^{-/-}$ MRL/*lpr* mice had significantly increased splenic $CD4^+$ T cells with differentiation into memory $CD4^+$ T cells (12 wks; $5.9\pm1.9\times10^7$ vs $1.1\pm0.3\times10^7$, $p = 0.021$) and effector $CD4^+$ T cells (12 wks; $3.6\pm1.1\times10^7$ vs $1.1\pm0.3\times10^7$, $p = 0.038$) compared to age-matched w.t. MRL/*lpr* controls. Similar trends were observed between 24 weeks old $Irf4^{-/-}$ and w.t. C57BL/6 mice. Intracellular cytokine analysis showed a significantly increased population of IFN-γ-producing memory $CD4^+$ T cells in the spleens of $Irf4^{-/-}$ MRL/*lpr* mice compared to w.t. MRL/*lpr* mice ($47.5\pm3.3\%$ vs $33.4\pm2.4\%$, $p = 0.026$). Furthermore, we found significant IFN-γ production in naïve $CD4^+$ T cells from $Irf4^{-/-}$ MRL/*lpr* mice, while minimal to no IFN-γ production was noted in naïve $CD4^+$ T cells from MRL/*lpr* mice ($33.1\pm6.5\%$ vs $0.96\pm0.4\%$, $p = 0.008$).

Conclusion: Our results indicate that IRF-4 plays an important role in the regulation of Th1 polarity and affects disease expression in MRL/*lpr* mice. Our results also indicate that their pathogenesis in $Irf4^{-/-}$ MRL/*lpr* mice is independent of autoantibodies/IC-mediated mechanisms, and is most likely dependent on autoreactive Th1 cell-mediated mechanisms.

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TNFα Inhibition Prevents Peri-Glomerular Resident Renal Macrophage Accumulation and Activation in SLE Nephritis. Ramalingam Bethunaickan[1], Yiting Tang[2] and Anne Davidson[3]. [1]Feinstein Institute for Medical research, Manhasset, NY, [2]Feinstein Institute for Medical Research, Manhasset, [3]Feinstein Institute for Medical Research, Manhasset, NY

Background/Purpose: TNFα antagonists are therapeutic in several autoimmune diseases but they may also precipitate SLE. In mouse models of SLE, TNFα is protective in the early disease stages but it is overexpressed in inflamed kidneys in late disease and contributes to renal damage. Consistent with both protective and pro-inflammatory roles of TNFα in SLE, TNFα blockade improved proteinuria in patients with SLE nephritis but increased autoantibody titers. The purpose of our experiments was to investigate the mechanism for efficacy of TNFα inhibition in a murine model SLE nephritis.

Methods: NZB/W mice were treated with a low dose of IFNα-expressing adenovirus at the age of 12 weeks. Once autoantibodies appeared in the serum at Day 21, treatment was started with fully murine TNFR2-Ig, 50ug three times per week. Mice were monitored at two week intervals for proteinuria and serum autoantibodies. Groups of mice were sacrificed at intervals after treatment and systemic immune activation was evaluated by flow cytometry of spleen cells and ELISpot for autoantibody producing B cells. Renal disease was evaluated by histology, immunohistochemistry, flow cytometry and real-time PCR quantitation of inflammatory mediators.

Results: TNFR2-Ig did not prevent the onset of proteinuria, but the proteinuria followed a remitting relapsing course and longevity of the mice was remarkably prolonged compared with untreated controls. Treatment did not decrease titers of autoantibodies, the percentage or numbers of activated T and B cells in the spleens, or the number of autoantibody producing B cells as assessed by ELISpot assay and there was no change in renal immune complex deposition. The onset of proteinuria in NZB/W mice is associated with an increase in renal macrophages ($CD11b/F4/80^{hi}/CD11c^{int}$) and an influx of dendritic cells ($CD11b/F4/80^{lo}/CD11c^{hi}$) together with marked upregulation of CD11b on resident renal $F4/80^{hi}$ macrophages. Kidneys from TNFR2-Ig treated mice had a significant decrease in the percentage and total number of renal $F4/80^{hi}$ cells, but not $CD11c^{hi}$ cells. In NZB/W mice, renal dendritic cells are located only in lymphoid cell aggregates whereas macrophages are located in the peri-glomerular region and in a cuff around lymphoid aggregates. Kidneys from TNFR2-Ig treated mice retained lymphoid aggregates containing $CD11c^{hi}$ and $F4/80^{hi}$ cuffs but peri-glomerular accumulation of $F4/80^{hi}$ macrophages was virtually absent. Real-time PCR analysis revealed a significant decrease in renal expression of chemokines CCL2 and CCL5, of the endothelial activation marker VCAM-1, of genes involved in tissue remodeling and of the markers of proximal tubule damage LCN2 and KIM-1.

Conclusion: TNFα decreases the renal inflammatory response to immune complex deposition by inhibiting the glomerular expression of chemokines and endothelial activation. This decreases the recruitment of peri-glomerular and interstitial renal macrophages that play a role in tissue remodeling and prevents the activation of renal tubular cells that follows exposure to an inflammatory urinary ultrafiltrate. Lymphoid aggregates appear to accumulate in the kidneys in a TNFα independent manner and are not sufficient to induce terminal renal damage.

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Increased Expression of Ribonuclease Prolongs Survival in Murine Lupus. Xizhang Sun[1], Nalini Agrawal[1], Lena Tanaka[1], Martha Hayden-Ledbetter[1], Kelly L. Hudkins[1], Charles E. Alpers[1], Silvia Bolland[2], Jeffrey A. Ledbetter[1] and Keith B. Elkon[1]. [1]University of Washington, Seattle, WA, [2]NIH, NIAID, Rockville, MD

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease characterized by the presence of high titer autoantibodies directed against self nucleoproteins. These antibodies interact with antigens to form immune complexes (ICs) that deposit in the kidneys, skin and vasculature. In addition to directly inducing tissue injury, nucleoprotein containing ICs are endocytosed by plamacytoid dendritic cells (pDC) and, following activation of intracellular TLR 7 and 9, stimulate the production of type 1 interferon (IFN). Evidence supporting the pre-eminence of TLR7 as the main inducer of IFN-a in mice include increased expression of TLR7 in BXSB mice and amelioration of disease in MRL/lpr mice deficient in TLR7 but not TLR9. In humans with SLE, the importance of TLR7 is also evident because the IFN signature is best correlated with anti-RNP containing autoantibodies and polymorphisms associated with increased TLR7 expression are observed in males with SLE.

Goals: Since i) RNA is the critical component of ICs that stimulate TLR7 to induce IFN-a and ii) degradation of RNA with RNase attenuates IFN-a production in an *in vitro* bioassay, we asked whether increasing RNase concentrations *in vivo* would be effective in ameliorating disease in lupus-prone mice.

Methods: C57BL/6 (B6) mice that overexpress TLR7 (TLR7 transgenic (Tg) mice) develop a lupus-like disease with autoantibodies and the deposi-

tion of ICs in the kidneys. They have a median survival of ~ 6 months). We created a mouse strain, JLC, on the B6 background that overexpressed bovine RNase. The mice were healthy and exhibited no apparent changes in lymphoid composition in the spleen or lymph nodes. We then crossed the JLC mice to TLR7 transgenic mice (TLR7 Tg) to create RNase × TLR7 doubleTg (DTg) mice. Two cohorts were studied: Cohort A was sacrificed at 3–4 months for immunological studies and cohort B was a survival study (n = 20 in each group) that was terminated at 12 months. Kidneys were examined by light microscopy, Mac2 staining as well as indirect immunofluorescence for IgG and C3 deposition.

Results: In both single RNAse Tg as well as DTg mice, RNase was secreted into the serum and increased expression levels were detected by an ELISA as well as by a functional enzyme assay in RNA coated agar gels (serum enzyme diffusion or SRED). In Cohort A mice sacrificed at 3–4 months, we observed statistically significant reductions in PAS staining, glomerular tuft size as well as less macrophage infiltration (all $p < 0.05$) in the kidneys. In Cohort B, there was a statistically significant increase in survival in DTg as compared to TLR7 Tg mice (mean survival of 6 and 9 months for single versus DTg respectively, $p < 0.01$). When the study was terminated at 12 months, examination of the kidneys revealed that there was reduced IgG and C3 deposition in DTg as opposed to single TLR7 Tg mice in surviving mice ($p < 0.05$).

Conclusion: Our results indicate that increased expression of RNase significantly attenuates kidney damage in a lupus mouse model and also significantly improves survival. This novel form of treatment encourages nuclease based therapies to be considered for ameliorating SLE in the future.

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Laquinimod Inhibits Disease Severity and Progression in Mouse Models of Lupus: Alone and in Combination with Standard of Care Agents. Joel F. Kaye, Revital Etzyoni, Rotem Keshet-Katz, Emanuel Raymond and Eran Blaugrund. Teva Pharmaceuticals Ltd, Netanya, Israel

Background/Purpose: Laquinimod (LAQ; TV-5600) is a synthetic compound being developed by Teva for the treatment of multiple sclerosis (MS). Laquinimod has demonstrated therapeutic effect in various experimental autoimmune models, including animal models of Experimental Encephalitis (EAE), Inflammatory Bowel Disease, Guillain-Barré Syndrome and Type I Diabetes. The mechanism of action of laquinimod in these models includes the reduction of leukocyte infiltration and modulation of the cytokine milieu. Furthermore, gene expression studies from MS patients have shown that laquinimod modulates the expression of genes related to inflammation and antigen presentation. These promising findings indicate that laquinimod acts as an immunomodulator, targeting a pivotal pathway of autoimmunity, and prompted the present study to evaluate its effect on disease progression in mouse models of SLE.

Methods: Female (NZBxNZW) F1 and MRL/lpr mice were obtained from The Jackson Laboratory (Bar Harbor, ME). Proteinuria (PU) was measured by a semi-quantitative procedure using reagent strips for urine analysis (Albustix, Bayer). Once PU was present in at least 20% of mice, the mice were divided into experimental groups and treatment was initiated. Mice were treated with LAQ (PO daily), Cyclophosphamide (CTX; 50mg/kg IP weekly), Mycophenolate mofetil (MMF; 30 or 100mg/kg IP daily)) or Dexamethasone (Dexa; 0.5mg/kg IP daily). The levels of proteinuria and serum anti-dsDNA antibodies were measured over the treatment period. At study termination, organs were removed for histopathology as well as analysis of immune complex deposition (ICD) in the kidneys.

Results: Treatment with LAQ (0.2, 1, 5 & 25mg/kg) in NZB/W mice resulted in dose dependent reduction of anti-dsDNA antibody levels, almost complete inhibition of proteinuria from as low as 0.2mg/kg, and significant dose dependent prolongation of survival. Analysis of ICD in the kidneys of mice following 12 weeks of treatment showed that mice treated with laquinimod (5mg/kg) had significantly less deposits than vehicle- or CTX-treated animals. Finally, we explored the effect of combining LAQ with either MMF or Dexa. In both of these studies, combining 1mg/kg LAQ with a low dose (30mg/kg) of MMF or with Dexa enhanced the effect of each compound alone. Conversely, neither compound interferes with the potency of laquinimod.

In the MRL/lpr model of lupus, animals were monitored until their urine proteinuria reached >200 mg/dL at which time they were enrolled in the study and treated with either 1 or 5 mg/kg of LAQ or 100 mg/kg MMF for 12 weeks. LAQ treatment resulted in reduction of proteinuria and anti-dsDNA levels throughout the study. Histopathological analysis of organs showed that laquinimod treatment reduced glomerulonephritis, salivary gland inflammation, splenomegaly and symptoms of lupus arthritis.

Conclusion: Here we show that laquinimod effectively inhibits disease progression in both NZB/W and MRL/lpr spontaneous mouse model of lupus. These data suggest that the immunomodulator laquinimod is a promising new oral drug for treating SLE, and as such we have commenced clinical trials in both Lupus Nephritis and Lupus Arthritis.

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Impaired Inhibition on B Cell Activation by Bone Marrow-Derived Mesenchymal Stem Cells with Decreased CCL2 Expression in MRL/Lpr Mice. Nan Che, Xia Li and Lingyun Sun. the Affiliated Drum Tower Hospital of Nanjing University Medical School, Jiangsu 210008, China P.R, Nanjing, China

Background/Purpose: Bone marrow–derived mesenchymal stem cells (BM-MSCs) are multipotent cells characterized by immunomodulatory properties and are therefore considered a promising cell therapy for autoimmune diseases. It has been shown that BM-MSCs from healthy donors are able to inhibit the activation of B cells in vitro and in vivo. Our previous study revealed that BM-MSCs from patients with systemic lupus erythematosus (SLE) possessed some dysfunctions. This study aimed to assess whether inhibition on B cell activation by BM-MSCs in MRL/lpr mice, an animal model of SLE, was impaired and the possible mechanisms involved in this process.

Methods: BM-MSCs were isolated and expanded from either C57BL/6J or MRL/lpr mice. The effects of BM-MSCs on the proliferation and differentiation to plasma cells of normal splenic B cell isolated from C57BL/6J mice were evaluated in vitro. And the differential expression of CCL2 on BM-MSCs from C57BL/6J or MRL/lpr mice was detected. Lupus mice were treated with these two different BM-MSCs respectively, and the levels of serum autoantibodies and immunoglobulin deposition in the kidney were monitored.

Results: BM-MSCs from C57BL/6J mice inhibited the proliferation and differentiation to plasma cells of B cells in vitro. This inhibitory effect was mediated by soluble factors, including CCL2, as neutralizing CCL2 could abolish the suppressive effect on B cells mediated by normal BM-MSCs. Inhibition on B-cell proliferation and differentiation by BM-MSCs from MRL/lpr mice was impaired, partially resulted from down-regulated expression of CCL2. The addition of processed CCL2 restored inhibitory effects of BM-MSCs from MRL/lpr mice on B-cells. In vivo treatment with BM-MSCs from MRL/lpr mice did not reduce the levels of serum pathological antibody production and immunoglobulin deposition in the kidney compared with treatment with BM-MSCs from C57BL/6J mice.

Conclusion: Our findings suggest that inhibitory effects of BM-MSCs on B-cell are mediated by soluble factors including CCL2. Impaired inhibition of BM-MSCs from MRL/lpr mice on B-cell maybe attributes to the down-regulation of CCL2 expression, which may play an important role in the pathogenesis of SLE.

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***Yaa*-Mutation Induces Phenotype Shift From Rheumatoid Arthritis to Systemic Lupus Erythematosus in FcgRIIB-Deficient B6 Mice.** Hirofumi Amano, Shinya Kawano, Toshiyuki Kaneko, Aya Sato-Hayashizaki, Lin Qingshun, Yoshinari Takasaki and Sachiko Hirose. Juntendo University School of Medicine, Tokyo, Japan

Background/Purpose: We previously obtained a FcγRIIB-deficient C57BL/6 (B6) congenic strain of mice, which spontaneously developed severe rheumatoid arthritis (RA). The development of systemic lupus is accelerated by the *Yaa* (*Y-linked autoimmune acceleration*) mutation, which is a consequence of a translocation from the telomeric end of the X chromosome containing the *Tlr7* gene onto the Y chromosome. To examine the effect of the *Yaa* mutation on the autoimmune disease phenotype in this strain, we established B6.FcγRIIB$^{-/-}$.*Yaa* mice by introducing *Yaa* mutation into the RA-prone FcγRIIB-deficient B6 mice.

Methods: The *Yaa* mutation was introduced into FcγRIIB$^{-/-}$ mice from B6.*Yaa* mice. Serum levels of RF, IgG antibodies against double-stranded DNA and chromatin were measured using ELISA. The severity of renal disease was monitored by biweekly testing for proteinuria.Histopathological examination was also performed.

Results: The disease phenotype shifted from RA to SLE in B6.FcγRIIB$^{-/-}$.*Yaa* mice.They did not develop RA, instead they showed the marked increase in serum levels of rheumatoid factor and SLE-related autoantibodies such as anti-chromatin and anti-ds DNA antibodies. These developed glomerulonephritis with the high incidence of positive proteinuria even at 6 months of age.

Conclusion: The present studies suggest that the common genetic pathways play a role in the disease process shared by RA and SLE, and the environmental factors such as the stimulation of innate immune system may control separate autoimmune diseases RA and SLE.

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Anti-Interleukin 23 Antibody Alleviates Nephritis in MRL/*Lpr*lupus-Prone Mice. Ourania Kampagianni, George C. Tsokos and Vasileios C. Kyttaris. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background/Purpose: Interleukin-23 (IL-23) dependent IL-17$^+$ T helper lymphocytes (Th17) are potent inducers of tissue inflammation and have been associated with autoimmunity. We have previously shown the importance of IL-23/IL-17 axis in development of lupus nephritis and demonstrated that IL-23 receptor deficiency prevents the development of nephritis in lupus-prone mice. The aim of this study is to determine whether treatment of lupus-prone mice with an anti-IL-23 blocking antibody mitigates nephritis.

Methods: 9-week old MRL/*lpr* lupus-prone mice were injected intraperitoneally three times a week with 20 μg of rat anti-mouse IL-23 antibody, or equal amount of rat anti-mouse IgG as control, for 7 weeks. Proteinuria was monitored by weekly urine collection. Serum samples were obtained at three different time points (start, middle and at the end of treatment). The mice (N=3 for each group) were subsequently sacrificed and spleen and lymph nodes were extracted for cell cultures, where cytokine production and gene expression were analyzed.

Results: The anti-IL-23-treated mice (treated group) had significantly less proteinuria at the end of the study when compared to IgG treated (control group) (average albumin/creatinine ratio; treated: 4.1 mg/gr vs. control: 14.6 mg/gr). After 7 weeks, spleen and lymph nodes lymphocytes were activated *in vitro* with anti-CD3 and anti-CD28 antibodies; the supernatants were collected 24 hours later and tested for cytokine concentration. The anti-IL-23 antibody treatment decreased the production of IL-17A (treated: 208.6±69.1 pg/mL vs. control: 632.0±366.4 pg/mL) and IL-6 (treated: 427.8±114.7 pg/mL vs. control: 820.3±82.3 pg/mL). On the contrary IFNγ did not differ between the groups.

Using targeted mRNA screening for inflammation related genes, we found that anti-IL-23 treatment resulted in a decrease by 79% of the levels of the chemokine receptor CCR2 in T cells, suggesting that IL-23 plays a significant role in lymphocyte trafficking in these mice.

Immunoglobulin and anti-dsDNA levels, which were already very high at the beginning of the treatment, did not change with this short anti-IL-23 treatment.

Conclusion: Treatment of lupus-prone mice with anti-IL-23 antibody leads to decreased production of Th17 related cytokines and amelioration of kidney disease. These results urge the development of IL-23 targeting therapeutic regimens in systemic lupus erythematosus patients.

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Dysregulation of Clade A Serine Protease Inhibitor Expression in Murine and Human Lupus. Jack Hutcheson[1], Kamala Vanarsa[1], Soyoun Min[1], Tianfu Wu[1] and Chandra Mohan[2]. [1]University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, [2]University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: The serine protease inhibitor (Serpin) superfamily acts to limit tissue damage and excess apoptosis caused by proteases by irreversibly binding their targets. Defects in serpin function have been associated with a number of diseases including alpha 1-trypsin deficiency, Alzheimer's disease, prostate cancer, and Crohn's disease. SerpinA3 is an interferon-mediated acute phase inflammatory response protein which binds certain cathepsins, kallikreins and other serine proteases. Despite its documented role in acute inflammation, the exact role of serpinA3 in a chronic inflammatory condition such as systemic lupus erythematosus (SLE) is unclear.

Methods: To investigate disease pathways in lupus, spleens were collected from 6-month-old MRL/lpr, NZM2410, and B6.Sle1.Sle3 lupus-prone and B6 lupus-resistant strains of mice, and subjected to a microarray transcriptomic analysis. To confirm the results from the microarray analysis, quantitative real-time PCR (qPCR), western blot, and immunofluorescence assays were performed. To determine if these data were of clinical relevance, sera from adult patients with mild non-renal (n=21), severe non-renal (n=4), or active renal (n=43) SLE were screened by ELISA. Matched healthy adults served as controls (n=10).

Results: Several clade A serpins were shown by microarray to be upregulated in the spleens of MRL/lpr lupus-prone mice as compared to lupus-resistant B6 mice. One serpin in particular, serpinA3g (serpinA3 in humans, or alpha 1-antichymotrypsin), has successfully been validated by qPCR, where gene expression was 4.56-fold higher in MRL/lpr spleen as compared to B6 mice (P=0.003) and expression was 3.54-fold higher than lupus-prone B6.Sle1.Sle3 mice (P=0.005). Protein levels of serpinA3g were confirmed to be increased in the spleens, kidneys, and livers of MRL/lpr mice as compared to B6 mice, while B6.Sle1.Sle3 mice displayed intermediate expression, by western blot and confocal microscopy. The latter experiment revealed multiple splenic cells expressing SerpinA3, including macrophages and neutrophils, as well as some B cells. Further investigation of serpinA3 levels in SLE patient sera revealed a 1.67-fold (P=0.0002), 1.41-fold (P=0.08), and 1.87-fold (P<0.0001) increase in mild non-renal, severe non-renal, or active renal SLE patients, respectively, as compared to healthy controls. However, serpinA3 levels did not correlate with the SLE disease activity index.

Conclusion: The serine protease inhibitor serpinA3 (serpinA3g in mice) is increased in both patients and mice with SLE. Whether serpinA3 is elevated in a disease-causative manner or whether it is elevated in response to increased inflammation (and serine proteases) is yet to be determined. The molecular mechanism for this increase in lupus and its role within the kidneys are under further investigation.

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IL-21R Is Required for the Systemic Accumulation of Activated B and T Lymphocytes in MRL^{lpr}Mice. Andrew L. Rankin[1], Tatyana Andreyeva[1], Yijun Carrier[2], Mary Collins[3], Cheryl L. Nickerson-Nutter[3], Deborah Young[2] and Kyri Dunussi-Joannopoulos[3]. [1]Pfizer, Inc., Cambridge, MA, [2]Colleague, Cambridge, MA, [3]Pfizer, Cambridge, MA

Background/Purpose: IL-21 is a pleiotropic cytokine that can influence the activation and proliferation of both B and T cells. We previously showed that the development of lupus-like disease manifestations in MRL^{lpr} mice could be prevented by blocking IL-21 pharmacologically. We generated IL-21R deficient MRL^{lpr} mice to examine the impact of loss of IL-21R signaling on the systemic lymphocyte activation and accumulation observed in MRL^{lpr} mice.

Methods: C57Bl/6.IL-21R$^{-/-}$ mice were backcrossed with MRL^{lpr} mice to generate MRL^{lpr}.IL-21R$^{-/-}$ mice. Disease development in MRL^{lpr}.IL-21R$^{-/-}$ mice was monitored in a time-course study that included assessment of proteinuria (Albustix, Bayer), histologic examination of renal pathology and gross evaluation of skin lesions. B and CD4$^+$ T cell activation status was examined using standard flow cytometric based methods.

Results: MRL^{lpr}.IL-21R$^{-/-}$ mice exhibited significantly decreased proteinuria, lymphadenopathy and reduced severity of cutaneous lesions and renal inflammatory infiltrates. Splenomegaly was reduced in MRL^{lpr}.IL-21R$^{-/-}$ and resulted from a profound reduction in CD4$^+$ T cells, B cells and DN T cells. The vast majority of CD4$^+$ T cells in MRL^{lpr} mice bore an activated cell surface phenotype (CD44^{hi} CD62^{lo}), which was significantly reduced in MRL^{lpr}.IL-21R$^{-/-}$ mice. Significantly reduced titers of anti-dsDNA antibodes were present in MRL^{lpr}.IL-21R$^{-/-}$ mice and correlated with a dramatic reduction in numbers of splenic germinal center B cells and plasma cells. In addition, both T follicular help and T extrafollicular helper cells, which are key promoters of antibody responses, were significantly reduced in MRL^{lpr}.IL-21R$^{-/-}$ mice.

Conclusion: IL-21R is required for the development of inflammatory lesions in both the kidney and skin of MRL^{lpr} mice. Moreover, the systemic lymphoaccumulation observed in MRL^{lpr} mice is dependent on signals delivered via IL-21R. Our data demonstrate that multiple populations of activated B and T lymphocytes depend on IL-21R for their accumulation. The profound dampening of lymphocyte effector activation in the absence of IL-21R signaling suggests that blockade of the IL-21 pathway may be a promising therapy B and T cell mediated autoimmune diseases such as SLE.

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Role of CD5 $^+$ B Cells in the Suppression of Fatal Autoimmunity in Lupus-Prone Mice. Yuriy Baglaenko[1], Nan-Hua Chang[2], Evelyn Pau[3] and Joan E. Wither[2]. [1]University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, University Health Network, Toronto, ON, [3]Toronto Western Research Institute, Toronto, ON

Background/Purpose: Although mapping studies suggest the presence of a lupus-susceptibility locus on NZB chromosome 4 (c4), introgression of

this interval onto the B6 background leads to expansion of Natural Killer T (NKT) and $CD5^+$ B cells in the absence of autoimmunity. To further investigate the role of this locus in autoimmunity, bicongenic mice were produced with the c4 locus and a NZB c1 interval previously shown to promote high titre anti-nuclear antibodies (ANAs) and fatal renal disease. Surprisingly, bicongenic c1c4 mice had increased survival, reduced renal disease and a bias towards less-pathogenic IgG1 autoantibodies when compared to c1 mice. Notably, c1c4 mice retained the expansion of NKT and $CD5^+$ B cells. Previous studies with NKT cell knockout mice revealed no effect on disease suppression in c4 mice, and examination of NKT cell activation in c1c4 mice showed no differences in the majority of mice. These findings suggested that NKT cells may have a limited role in disease suppression. Since a functional deficiency of $CD5^+$ regulatory B cells has been proposed to promote autoimmunity in SLE patients, we sought to investigate their role in suppressed c1c4 mice.

Methods: Splenocytes from 4 month old B6, c1, c4, and c1c4 mice were stimulated for 4.5 hours with LPS, PMA, and ionomycin in the presence of GolgiStop. Freshly isolated or stimulated cells were stained for cell surface markers that discriminate between various cell subsets, fixed, permiabilized, and then stained for intracellular IL-10 or Foxp3. Serum levels of anti-ssDNA IgG antibodies were measured by ELISA.

Results: There was a significant increase ($p<0.05$) in IL-10 producing B cells in c4 and c1c4 mice when compared to c1 and B6 controls. These cells were predominantly $CD5^+CD1d^{int}CD19^{hi}$. This finding suggests that the $CD5^+$ B cells in c1c4 and c4 mice may play a suppressive role. Notably, the IL-10 producing B cells in c1c4 mice are phenotypically distinct from previously documented regulatory populations that are reported to have a $CD5^+CD1d^{hi}CD19^{hi}$ phenotype. To further investigate the possible role of IL-10 producing B cells in the regulation of autoimmunity in c1c4 mice, the relationship between the frequency of IL-10 producing B cells and autoantibody levels was examined. There was a significant negative correlation ($r2 = 0.63$, $p = 0.0196$) between the levels of IgG anti-ssDNA IgG and the frequency of IL-10 producing B cells in c1c4 but not B6 mice. No correlation was seen between autoantibody levels and the proportion of NKT cells. Since B regulatory cells have been implicated in the expansion of $CD25^+$ $Foxp3^+$ T regulatory cells, the proportion of these cells was quantified. c4 and c1c4 mice had similar levels of T regulatory cells to c1 mice. There was no correlation with autoantibody levels in c1c4 mice. These data suggests that if the IL-10 producing cells in our model are regulating autoimmunity they are acting independently of T regulatory cells.

Conclusion: Taken together, these data indicate the presence of a phenotypically novel IL-10 producing B cell population in c4 mice that may play a role in suppressing fatal autoimmunity in c1c4 mice.

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Effects of Fasudil Treatment on Lupus Pathogenesis in NZB/W F1 Female Mice. Roslynn A. Stirzaker[1], Partha S. Biswas[1], Sanjay Gupta[1], Weijia Yuan[1], Li Song[1], Uma Chandrasekaran[1], Govind Bhagat[2] and Alessandra B. Pernis[1]. [1]Hospital for Special Surgery, New York, NY, [2]Columbia University, New York, NY

Background/Purpose: The serine-threonine kinase ROCK2 becomes activated in wild-type $CD4^+$ T cells under T_H17 skewing conditions and phosphorylates IRF4, a transcription factor absolutely required for production of IL-17 and IL-21, two cytokines implicated in the pathogenesis of lupus. In contrast to T cells from non-autoimmune mice, $CD4^+$ T cells from mice that spontaneously develop lupus such as MRL/lpr mice aberrantly activate ROCK2 under neutral conditions. We previously found that treatment of MRL/lpr mice with the ROCK inhibitor Fasudil reduces IL-17 and IL-21 production, and ameliorates autoimmune symptoms, including anti-dsDNA antibody production, immune-complex deposition, and proteinuria. To evaluate whether ROCK inhibition could be broadly effective for the treatment of lupus we have investigated whether administration of Fasudil could also ameliorate lupus in NZB/W F1 mice, another well-established lupus model. We hypothesized that Fasudil would have a protective effect on the spontaneous development and/or progression of lupus in NZB/W F1 mice by inhibiting the activation of immune cells.

Methods: Female NZB/W F1 mice were administered Fasudil Monohydrochloride Salt (100mg/kg) continuously in their drinking water starting at 18 or 24 weeks of age, or were left untreated ($n=10$ per group). Development of nephritis was monitored by regular screening for the presence of proteinuria, and animals underwent regular weighing to monitor weight gain/loss and ensure equivalent water intake amongst the three groups. Surviving mice were sacrificed at the cessation of treatment at 44 weeks of age, and kidneys and spleen were harvested for histopathological analysis. Flow cytometry was used to examine lymphocyte subsets in spleens, and IL-17 and IL-21 gene expression was evaluated by real-time RT-PCR of spleen samples. Serum anti-dsDNA levels and specific Ig isotypes were measured by ELISA.

Results: Fasudil treatment of female NZB/W F1 mice resulted in significantly reduced number of plasma cells compared to untreated mice. No differences in the expression levels of splenic IL-17 and IL-21 were noted. Strikingly, Fasudil treatment caused a significant decrease in the levels of serum anti-dsDNA antibodies and of all serum Ig isotypes investigated (IgG_1, IgG_{2a}, IgG_{2b}, IgG_3, IgM and IgA), and there was a modest but significant decrease in IgG and C3 deposition and in the degree of glomerulonephritis. Importantly the development of severe proteinuria and mortality was significantly reduced in Fasudil treated mice when treatment was started at 18 weeks of age.

Conclusion: This pilot study demonstrates that administration of Fasudil to lupus-prone NZB/W F1 female mice improves a number of pathological features, and may represent a potential treatment for SLE. Further studies are required to further characterize the precise mechanisms by which ROCK inhibition ameliorates lupus pathogenesis in NZB/W F1 mice.

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The PD-1 Pathway Promotes Survival and Continuing Function of $CD4^+$ regulatory T Cells in (New Zealand Black × New Zealand White) F_1 Lupus-Prone Mice. Maida Wong[1], Antonio La Cava[2] and Bevra H. Hahn[3]. [1]UCLA, Los Angeles, CA, [2]Univ of California Los Angeles, Los Angeles, CA, [3]UCLA David Geffen School of Medicine, Los Angeles, CA

Background/Purpose: Programmed death-1 (PD-1) has been regarded as a negative regulatory signal in T cells. Previously, we have induced tolerance by administration of pConsensus (pCons), an autoantibody Ig-based peptide, which induces both $CD4^+$ and $CD8^+$ $Foxp3^+$ regulatory T cells (T_{reg}), which decrease nephritis and prolong survival. In particular, $CD4^+$ T_{reg} have reduced expression of PD-1 compared to untreated controls. PD-1 is important in T cell regulation of autoimmunity, as young BWF_1 females treated with a neutralizing antibody against PD-1 resulted in reduced anti-dsDNA production, delayed onset of proteinuria and improved survival. We hypothesized that regulation of signaling through PD-1 is required for maintenance of functional T_{reg} and subsequent control of autoimmunity in BWF_1 lupus mice, and that regulatory capacity of the cells is sustained at least in part by resistance to apoptosis, resulting in T_{reg} survival.

Methods: Antibody against PD-1 or control isotype-matched IgG were injected i.p. into naïve vs. pCons-treated BWF_1 mice. Foxp3, PD-1 and Fas expression, were assessed by flow cytometry. Signaling pathway array was performed on the $CD4^+$ T_{reg} at the mRNA level.

Results: In contrast to naïve BWF_1 mice (where numbers of $CD4^+$ T_{reg} decline over time), anti-PD-1 or pCons treatments maintained total numbers of functional suppressive $Foxp3^+CD4^+CD25^+$ T cells between 10 and 40 weeks of age. These $CD4^+$ T_{reg} from the anti-PD-1 or pCons treated mice had decreased PD-1 expression by MFI. Fas was one of the candidate molecules in the apoptotic pathways that was downregulated in splenic $CD4^+$ T_{reg} upon pCons-tolerization or blockade of PD-1. Fewer of these $CD4^+$ T_{reg} had Fas expression, and they were more resistant to spontaneous apoptosis. They suppressed $CD4^+CD25^-$ T cell proliferation and induced apoptosis in B cells, resulting in suppression of autoantibodies.

Conclusion: These data suggest that PD-1 is central in control of at least some regulatory T cells that suppress autoimmunity. Low expression of PD-1 correlated with resistance to apoptosis with decreased Fas expression on the $CD4^+$ regulatory T cells. It is likely that expression of PD-1 on regulatory/suppressor T cells must be finely tuned to permit the cells to survive and retain suppressive capacities. One mechanism by which PD-1 sustains these T_{reg} is by reducing their susceptibility to apoptosis, which may relate to alteration of expression of the Fas/FasL pathway.

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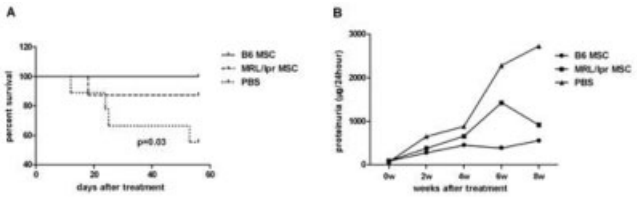
Differential Effect of Autologous Versus Allogeneic Mesenchymal Stem Cell Transplantation in Lupus Prone Mice. Fei Gu[1], Ivan Molano[2], Lingyun Sun[3] and Gary S. Gilkeson[4]. [1]Division of Rheumatology and Immunology,Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina, Charleston, SC, [3]The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [4]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC

Background/Purpose: Lupus is a systemic autoimmune disease characterized by the production of autoantibodies and end organ damage from

immune complex deposition. Mesenchymal stem cells (MSCs), multipotent non-haematopoietic stem cells, support haematopoiesis and can differentiate into cells of the mesenchymal lineage. MSCs home to areas of tissue injury and participate in tissue repair, and possess anti-inflammatory and immunosuppressive properties. Defects in MSCs function are reported in cells derived from lupus prone mice and lupus patients. Thus, a key question in the use of MSCs in autoimmune diseases is whether MSCs from lupus donors are defective and thus not suitable for autologous transplantation.

Methods: MRL/*lpr* mice were treated with a single intravenous injection of 10^6 allogeneic C57BL/6J MSCs (n=8), MRL/*lpr* MSCs (n=8), or phosphate buffered saline (PBS) (n=10) at 17 to 20 weeks of age at during active disease. All mice were sacrificed at 8 weeks after treatment and bone marrow and kidneys were harvested. Serum anti-dsDNA antibody and 24 hour proteinuria were assessed by enzyme-linked immunosorbent assay. Bone marrow IgG-secreting plasma cells were characterized by flow cytometry as identified by surface CD138 and intracellular IgG expression. Kidney pathological slides were stained with haematoxylin and eosin (H&E) and scored in a blinded fashion. The average intensity of glomerular immune complex deposition in five independent fields of one kidney section per animal was quantitated. Data are summarized as mean±SE. Statistical analysis was performed using GraphPad Prism version 5.0. The statistical significance value was set at $p<0.05$.

Results: MSCs transplanted from B6 donors, but not MRL/*lpr* donors, significantly enhanced survival in MRL/*lpr* mice compared to control PBS injected animals ($p=0.03$) (Fig.A). B6-derived MSCs significantly decreased 24 hour proteinuria at 8 weeks after treatment compared to control ($p<0.01$), but MRL/*lpr*-derived MSCs did not (Fig.B). Neither source of MSCs impacted serum anti-dsDNA antibody levels. B6-derived MSCs-treated animals, but not MRL/*lpr*-derived MSCs treated animals, had significantly fewer plasma cells in bone marrow and reduced C3 deposits in glomeruli compared to control ($p<0.05$). MSCs administration did not significantly impact the overall renal pathology scores, though there was a trend towards lower scores in the B6 group versus the other two.



Conclusion: B6-derived MSCs significantly improved MRL/*lpr* survival when given at peak disease activity. B6-derived MSCs transplantation led to less proteinuria, decreased plasma cells in the bone marrow, and reduced C3 deposits in glomeruli. These results indicate MSCs transplantation at time of peak disease does impact disease and suggest that allogeneic sources of MSCs may be preferred to autologous sources.

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Enhanced Survival of Anergic Self-Reactive B Cells in New Zealand Black Chromosome 1 Congenic Mice. Nan-Hua Chang, Christina Loh, Evelyn Pau, Yuriy Baglaenko and Joan E. Wither. Toronto Western Research Institute, University Health Network, Toronto, ON

Background/Purpose: Lupus is characterized by loss of B cell tolerance to nuclear antigens leading to auto-antibody (Ab) production. In this study we have explored the mechanisms leading to this loss of tolerance using B6.NZBc1(96–100cM) (c1) mice. These mice have a homozygous NZB interval containing the *Nba2* locus that results in production of anti-nuclear Abs. To determine the mechanism leading to this breach of tolerance, soluble hen egg white lysozyme (sHEL) and anti-HEL immunoglobulin (Ig) transgenes (Tg) were bred onto the c1 background to generate IgTg or double transgenic (dTg) mice. We previously showed that c1 dTg mice produce anti-HEL Ab, indicating a breach of anergy. In this study we investigated the immune mechanisms leading to this breach.

Methods: Splenocytes from dTg mice were stimulated with anti-IgM $F(ab)'_2$ Ab or HEL for 18 hrs and B cell apoptosis was measured. Mixed hematopoietic chimeric mice (MC) were produced by mixing B6.CD45.1.Ig and c1.Ig bone marrow (BM) in a 1:1 ratio and injecting into irradiated sHEL or non-Tg (B6.CD45.1 × c1)F_1 recipient mice. Mice were analyzed 12 weeks later by flow cytometry of splenic and BM cells. Ab producing cells were measured by ELISpot. Calcium mobilization was assessed using Indo-1 labeled immature IgTg B cells obtained from culture of BM cells with IL-7 for 5 days.

Results: In dTg c1 mice, anergic B cells demonstrated altered function with enhanced upregulation of CD86 following anti-IgM stimualtion, decreased apoptosis in response to anti-IgM or sHEL stimulation, and increased PI3 kinase signaling. These findings suggest that an intrinsic B cell defect breaches anergy, however the presence of IgG anti-HEL antibodies in dTg mice raised the possibility that abnormal T cell help also contributes to this process. To determine the relative role of B and T cell defects in the breach of tolerance in dTg mice, MC mice were produced where both B6 and c1 B cells are exposed to the same environment. Increased numbers of IgM^{a+} and anti-HEL Ab producing cells were found in the spleens of sHEL MC mice as compared control sHEL mice reconstituted with just B6 IgTg BM cells, suggesting a breach of B cell tolerance in MC mice. Although the proportion of B6 B cells in the BM of sHEL MC mice was equivalent to or slightly increased over the proportion of c1 B cells, there was a 1.5 to 3 fold increase in IgTg c1 vs. B6 splenic B cells. Consistent with enhanced survival of c1 anergic B cells, the proportion of freshly isolated IgTg B cells that were PI^+ in sHEL MC mice was significantly higher for B6 vs. c1 cells. Notably, both B6 and c1 splenic B cell populations had similar proportions of T1, T2, follicular, and marginal zone cell subsets, and in mice where there were significant numbers of endogenous F_1 non-Tg B cells, anergic cells were appropriate excluded from the mature B cell repertoire. Nevertheless, c1 B cells in sHEL MC mice expressed increased levels of costimulatory molecules vs. B6 B cells. In support of intrinsically altered B cell function in c1 mice, immature IgTg c1 B cells mobilized less calcium than IgTg B cells.

Conclusion: Intrinsic B cell signaling abnormalities that lead to enhanced survival of anergic B cells contribute to the breach of tolerance in c1 mice.

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Mirna-Let-7a Increases IL-6 Production in Mouse Mesangial Cells. Cristen Chafin, Nicole Regna and Christopher Reilly. Virginia Tech, Blacksburg, VA

Background/Purpose: Recent evidence supports a role for epigenetic alterations in the pathogenesis of systemic lupus erythematosus (SLE). MicroRNAs (miRNAs) are endogenous epigenetic regulators of gene repression whose expression is altered in many diseases, including SLE. We sought to determine the miRNA expression pattern in mesangial cells from NZB/W and NZW mice to determine if alterations in miRNAs contribute to disease pathogenesis. We found many consistent differences between the responses to aging in each mouse strain and chose to further define the role of the miRNA-let-7a in mesangial cell function. It is predicted that IL-6, which contains the binding site of miR-let-7a in its 3' untranslated region (UTR), is regulated by miR-let-7a.

Methods: Mouse mesangial cells were isolated from 8 week old New Zealand Black/White (NZB/W) and New Zealand White (NZW) mice using kidney dissection, differential sieving, collagenase digestion, and antibody labeling followed by magnetic separation. A purified mesangial cell population was obtained by magnetic cell separation using anti-integrin $\alpha 8$ which is specific for mesangial cells in the glomerular tissue. Next, miRNAs were isolated using the *mir*Vana miRNA isolation kit (Applied Biosystems, TX, USA). Microarray analyses were performed using mouse miRNA array chips (Chip ID miRMouse 10.0 version). RT-PCR was used to confirm miRNA gene chip expression data using the endogenous miRNA snoRNA202 as a control. We found miR-let-7a to be increased in NZB/W mice compared to NZW mice. MiR-let-7a inhibitors and mimics were transfected into cultured mesangial cells for 24 hours after which the cells were stimulated with LPS and IFN-γ. The supernatants and the cells were collected after 24 hours of stimulation. The supernatants were analyzed by ELISA and the microRNAs were isolated and analyzed by RT-PCR.

Results: The mesangial cells of pre-diseased NZB/W mice expressed higher levels of miR-let-7a (4.8 fold by microarray; 5.5 fold by RT-PCR) than age-matched NZW mice. Using computational target ranking systems, we identified IL-6 as a potential regulatory target of miR-let-7a. The mimic-transfected mesangial cells expressed higher levels of miR-let-7a while the inhibitor-transfected cells expressed levels less than base line (7.7 fold and 0.8 fold, respectively). Intriguingly, overexpression of miR-let-7a mimics in cultured mesangial cells induced greater IL-6 production than the miR-let-7a inhibitor when stimulated with LPS/IFN-γ.

Conclusion: These data show that NZB/W mice have higher miR-let-7a expression than the parental NZW strain. In addition, increased miR-let-7a expression increases IL-6 production in stimulated cells but not in non-stimulated cells. Overexpression of miR-let-7a in mesangial cells can result in upregulation of IL-6 expression which in turn can contribute to the proin-

flammatory microenvironment of the kidney. Because miR-let-7a binds to the 3' UTR of IL-6, further investigations using IL-6 reporter transfection assays will be performed to confirm the interaction of miR-let-7a on IL-6 production. Our findings suggest the inhibition of miR-let-7a may be a possible therapeutic for the dysregulation of IL-6 in lupus patients.

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Oral Delivery of a Tolerogenic Peptide Reduces Disease Severity and Prolongs Survival in SLE-Prone Mice. Brian Skaggs, Elaine Lourenco and Bevra H. Hahn. UCLA David Geffen School of Medicine, Los Angeles, CA

Background/Purpose: Most therapeutic agents currently in use to treat SLE are predominantly immunosuppressive agents with limited specificities. More specific therapies that target defined pathogenic mechanisms that drive SLE could be more effective and safer therapeutic options. Multiple groups have illustrated that inducing tolerance in SLE-prone mice with a variety of molecules ameliorates disease symptoms and increases survival. We examined if oral administration of various forms of a tolerogenic peptide could affect SLE disease progression and survival. Our laboratory has shown that this peptide is effective at slowing disease progression when delivered intravenously, but we wanted to see if it would be effective when delivered orally as this method of drug delivery would allow for easier clinical translation.

Methods: The pCons peptide, based on heavy chain protein sequences of anti-double stranded DNA antibodies, induces tolerance when administered intravenously through upregulation of regulatory T cells. Six different forms of pCons, including multiple antigenic peptides (MAP) and cyclic peptides (cyc) made up of both L- and D-amino acids, at three different concentrations (10, 100 and 500 micrograms), were fed to BWF1 SLE-susceptible mice (8/group) once per week for 30 weeks. D-amino acids were utilized to avoid gut peptidase/protease digestion, and the MAP and cyc forms were used to increase pCons stability. Proteinuria was measured weekly. Serum was collected monthly and tested for the presence of anti-DNA antibodies, total IgG, and transforming growth factor beta expression. Survival was measured through 47 weeks of age.

Results: Mice fed 100 micrograms of L-MAP or D-MAP had significantly less cumulative proteinuria, less serum anti-dsDNA antibody levels, and less serum IgG than controls. In addition, animals in these groups also survived significantly longer than controls with a corresponding increase in serum TGFbeta, implying a protective role for pCons-induced regulatory T cells.

Conclusion: Oral administration of a tolerogenic peptide is a safe, effective method for ameliorating SLE disease manifestations and prolonging survival in SLE-prone mice. Induction of oral tolerance using modified pCons peptides could lead to a novel method of targeted therapy for human SLE.

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Negative Regulatory Role of TCR zeta Chain in the Pathogenesis of Systemic Lupus Erythematosus Through Lipid Rafts. Guo-Min Deng, Jessica Beltran and George C. Tsokos. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by high production of autoantibodies and multi-organ tissue damages. T cells have been revealed to exert a crucial role in the pathogenesis of SLE. The phenomenon of T cell receptor (TCR) zeta chain down-regulation has been described in SLE and other diseases including rheumatoid arthritis, cancer, and infectious diseases. However, the role of TCR zeta chain in the pathogenesis of SLE is unknown.

Methods: To understand the role of TCR zeta chain, we have developed an in vivo experimental system by using TCR zeta chain knockout mice to determine the role of TCR zeta chain in the pathogenesis of immune diseases.

Results: We found that TCR zeta chain deficient mice can spontaneously develop inflammation in multi-organ tissues. Poly: (ic) treatment promotes development of multi-organ tissue damages in TCR zeta chain knockout mice. Furthermore, we observed that more severe inflammation developed in TCR zeta chain knockout mice than wild mice with transplant of Bm 12 mouse splenocytes in graft-versus-host disease model. We also found that Bm12 mice with transplant of splenocytes from TCR zeta chain mouse develop more severe multi-organ tissue inflammation than splenocytes from wild type mouse. We discovered that cellular immunity not humoral immunity plays an important role in development of multi-organ tissue inflammation. T cells with TCR zeta chain deficiency spontaneously develop high levels of lipid raft clustering and high expression of CD44 and IFN-gamma.

Conclusion: This indicates that TCR zeta chain plays a negative regulatory role in the pathogenesis of SLE and other immune-mediated diseases through lipid rafts.

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Leptin Impinges on the Clearance of Autoimmune T Cells in Murine Lupus. Gil Amarilyo[1], Noriko Iikuni[2], Bevra H. Hahn[3] and Antonio La Cava[4]. [1]University of California, Los Angeles, Los Angeles, CA, [2]UCLA, CA, [3]UCLA David Geffen School of Medicine, Los Angeles, CA, [4]Univ of California Los Angeles, Los Angeles, CA

Background/Purpose: Leptin, a pro-inflammatory adipokine, is elevated in systemic lupus erythematosus (SLE) patients and accelerates proteinuria in lupus-prone (NZB × NZW)F1 (BWF1) mice. However, the role of leptin in the induction and maintenance of autoimmune response in SLE has been only partially explored. Since the availability of self antigen through apoptotic material has been shown to play a key role in the autoimmune pathogenesis of SLE, we investigated whether leptin can influence phagocytosis and clearance of apoptotic T cells in SLE.

Methods: We investigated the ability of BWF1 mice to phagocyte apoptotic cells in vivo. Labeled apoptotic T cells were injected into the intraperitoneal cavity of BWF1 mice pretreated with thioglycolate for the activation of local macrophages. A group of recipient mice received leptin, another group received leptin blockers, and a third group that received vehicle served as control. Macrophages were isolated from the peritoneal fluid and the ingestion of apoptotic cells by macrophages was evaluated via costaining in flow cytometry and confocal microscopy. Parallel in vitro experiments using macrophages of thyoglycolate-treated BWF1 mice incubated in vitro with labeled apoptotic T cells in the presence or not of scalar doses of leptin were also performed.

Results: In vitro and in vivo experiments showed that leptin facilitated the phagocytic uptake of apoptotic cells by inflammatory macrophages in BWF1 lupus mice, thus providing an increased availability of autoantigen (uptake of apoptotic cells in the peritoneal macrophages was 2.6± 2.1% versus 13.4 ± 3.2% in the no leptin vs leptin-treated, $P<0.02$). Leptin treatment also modulated apoptotic cell clearance, possibly contributing to the maintenance of the autoimmune process ($P<0.03$ in the comparison between leptin treated mice versus controls).

Conclusion: Leptin modulates phagocytosis and clearance of apoptotic cells in lupus-prone BWF1 mice. Ongoing experiments are exploring the possibility that a differential role of leptin in young mice vs old animals could lead to excess free autoantigen that would favor the development of humoral immune responses to self antigens in an earlier stage. Later in life, the increased phagocytosis of apoptotic cells could favor self-antigen availability to the adaptive immune system, and thus the perpetuation of autoimmunity.

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Dispensability of APRIL to Development of Systemic Lupus Erythematosus (SLE) In SLE-Prone NZM 2328 Mice. Chaim O. Jacob[1], Shunhua Guo[1], Noam Jacob[1], Rahul Pawar[2], Chaim Putterman[3], William J. Quinn III[4], Michael P. Cancro[4], Thi-Sau Migone[5] and William Stohl[1]. [1]University of Southern California Keck School of Medicine, Los Angeles, CA, [2]Albert Einstein College of Med, Bronx, NY, [3]Albert Einstein College of Medicine, Bronx, NY, [4]University of Pennsylvania School of Medicine, Philadelphia, PA, [5]Human Genome Sciences, Rockville, MD

Background/Purpose: In contrast to the large body of evidence that links BAFF with SLE, the evidence linking the closely related APRIL to SLE is limited at most. Given that APRIL can co-stimulate B cells, induce Ig class switching, and promote plasma cell (PC) survival, APRIL, *a priori*, may be an important (co-)contributor to SLE pathogenesis and, thereby, represent an appropriate therapeutic target in SLE. To date, there have been no studies in either murine or human SLE that have solely targeted APRIL. Accordingly, we sought to determine the role for APRIL in the development of SLE by studying SLE-prone NZM 2328 (NZM) mice genetically deficient in APRIL.

Methods: NZM.*April*$^{-/-}$ and NZM.*Baff*$^{-/-}$ mice were generated by introgressing the *April*$^{-/-}$ and *Baff*$^{-/-}$ genotypes, respectively, into SLE-prone NZM wild-type (WT) mice by a marker-assisted selection protocol that included markers for those regions identified as SLE susceptibility loci in NZM mice. NZM.*Baff*$^{-/-}$.*April*$^{-/-}$ mice were generated by intercrossing NZM.*Baff*$^{-/-}$ and NZM.*April*$^{-/-}$ mice. Mice were evaluated for lymphocyte

phenotype by flow cytometry; for serum total IgG and IgG autoantibody levels by ELISA; for serum BAFF levels by ELISA; for glomerular deposition of IgG and C3 by immunofluorescence; for renal histopathology by staining with H&E, periodic acid-Schiff, Masson's trichrome, and Jones' silver methenamine; and for clinical disease, as assessed by development of severe proteinuria (≥3+ by dipstick on 2 consecutive evaluations).

Results: Despite identical serum BAFF levels, NZM.*April*$^{-/-}$ mice, in comparison to WT mice, harbored increased spleen B cells, T cells, and PC; increased serum levels of IgG anti-chromatin antibodies; and decreased numbers of bone marrow (BM) PC. At 5 months and 8 months of age, glomerular deposition of IgG and C3 was similar in NZM.*April*$^{-/-}$ and WT mice, whereas renal histopathology tended to be more severe in NZM.*April*$^{-/-}$ mice than in WT mice. Development of clinical disease was identical in NZM.*April*$^{-/-}$ and WT mice, with severe proteinuria starting to develop at 5 months of age and 50% of the mice in each cohort being affected by 7–8 months of age. Despite being identically deficient in BAFF, BM (but not spleen) PC and serum IgG anti-chromatin and anti-dsDNA antibody levels were lower in NZM.*Baff*$^{-/-}$.*April*$^{-/-}$ mice than in NZM.*Baff*$^{-/-}$ mice, whereas renal immunopathology in each cohort was equally mild. Clinical disease did not develop in either NZM.*Baff*$^{-/-}$.*April*$^{-/-}$ or NZM.*Baff*$^{-/-}$ mice through the time of sacrifice (8 months of age).

Conclusion: APRIL is dispensable for development of full-blown SLE in NZM mice. Moreover, the elimination of both APRIL and BAFF had no discernable effect on development of renal immunopathology or clinical disease beyond that of elimination of BAFF alone. The reduction in BM PC in hosts doubly-deficient in APRIL and BAFF beyond that in hosts deficient only in BAFF raises concern that combined antagonism of APRIL and BAFF may lead to greater immunosuppression without concomitant increase in clinical efficacy.

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Fn14 Deficiency Ameliorates Neuropsychiatric Disease In MRL-Lpr/Lpr Lupus Prone Mice. Jing Wen[1], Yumin Xia[1], Jennifer S. Michaelson[2], Linda C. Burkly[2], Maria Gulinello[1] and Chaim Putterman[3]. [1]Albert Einstein College of Med, Bronx, NY, [2]Biogen Idec, Cambridge, MA, [3]Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: Neuropsychiatric disease in SLE (NPSLE) is one of the earliest manifestations of human lupus, with 60% of patients developing NPSLE symptoms within the first year of diagnosis. Brain involvement is thought to be a primary manifestation of SLE activity, given this early disease onset and the potential for patients to respond to immunosuppressive therapy. However, optimal treatment for NPSLE has yet to be determined.

TWEAK is a TNF superfamily ligand that mediates pleiotropic effects through its receptor, Fn14, including the stimulation of proinflammatory cytokine expression by astrocytes, as well as endothelial, epithelial, and other non-hematopoeitic cell types. TWEAK also induces neuronal death, and increases blood brain barrier permeability. Furthermore, TWEAK-inducible mediators, including MCP-1, MMP-9, and IL-6, are implicated in NPSLE. Thus, we hypothesized that the TWEAK/Fn14 pathway may be involved in the pathogenesis of NPSLE.

Methods: 129 Fn14 knockout (KO) mice were backcrossed 8 generations onto MRL-lpr/lpr (MRL/lpr) mice to generate MRL-lpr, Fn14 deficient (Fn14KO) mice. Female MRL/lpr Fn14KO mice were compared to age and gender matched MRL/lpr wild type (Fn14WT) and MRL/+ mice at young (10–20 weeks old) and older (20–40 weeks old) ages. The development of neuropsychiatric disease was investigated using a comprehensive neurobehavioral assessment battery, including forced swim, anhedonia, open field, object recognition, object placement, and social preference tests. In addition, serum and urine were serially obtained for measurement of autoantibodies and proteinuria, respectively, and CSF was obtained at sacrifice.

Results: There were no abnormalities in the behavior of MRL/lpr Fn14 WT and KO mice or differences between the strains in total and center track distances in the open field, indicating no major sickness behavior or musculoskeletal disability at the time points tested. One manifestation of NPSLE is depression-like behavior, which can be assessed as increased immobility in the forced swim test. While MRL-lpr Fn14 WT mice displayed significant depressive like behavior, immobility was significantly decreased in MRL/lpr Fn14 KO mice and was no different from MRL/+ controls. Ahedonia, as evaluated by a lack of the normal preference for sweetened drinks and which was evident in MRL-lpr Fn14 WT mice, was also normalized in MRL/lpr Fn14 KO mice. Finally, while MRL/lpr Fn14 WT mice displayed impaired cognitive function in the object placement test, MRL/lpr Fn14 KO mice performed normally. Interestingly, the observed neurobehavioral abnormalities were selective, with no evidence of anxiety or loss of social preference in MRL/lpr Fn14 WT mice. At the time neurobehavioral deficits were observed in the younger mice, there were no significant differences in autoantibody titers or renal function between MRL-lpr Fn14 WT and KO mice.

Conclusion: Fn14 deficient MRL/lpr mice exhibit improved neurobehavioral characteristics, suggesting that the TWEAK/Fn14 interactions are instrumental in the pathogenesis of neuropsychiatric disease in MRL-lpr mice. Furthermore, blockade of the TWEAK/Fn14 pathway may represent a novel therapeutic approach for the treatment of primary NPSLE.

ACR Poster Session A
Systemic Lupus Erythematosus - Clinical Aspects I
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Restoration of Regulatory T Cells-Th17 Cells Balance in Systemic Lupus Erythematosus Through Vitamin D Supplementation. Benjamin Terrier[1], Yoland Schoindre[2], Guillaume Geri[3], David Saadoun[4], Kubéraka Mariampillai[5], Michelle Rosenzwajg[6], David Klatzmann[6], Jean-Charles Piette[3], Patrice Cacoub[3] and Nathalie Costedoat-Chalumeau[3]. [1]Pitié-Salpêtrière Hospital, Paris, France, [2]Foch Hospital, Suresnes, France, [3]CHU Pitié-Salpêtrière, Paris, France, [4]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [5]Pitié-Salpétrière Hospital, Paris, France, [6]Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Paris, France

Background/Purpose: Systemic lupus erythematosus (SLE) is associated with perturbations in regulatory T cells (Tregs), T helper lymphocytes producing interleukin (IL)-17 (Th17 cells) and B cells. Immunomodulatory effects of vitamin D were recently described in vitro, notably the expansion of Tregs able to suppress inflammatory responses and the decrease of Th17 cells. Objective. To evaluate tolerance and immunologic and clinical effects of vitamin D supplementation in SLE.

Methods: In this monocenter prospective study, we measured vitamin D level in SLE patients (according to the revised ACR criteria). Patients with hypovitaminosis D (< 30 ng/mL) and stable dosage of prednisone and/or immunosuppressant agents received vitamin D supplementation: 100 000 UI of cholecalciferol per week for 4 weeks, followed by 100 000 UI per month for 6 months. Patients were screened at day 0 (D0) and at month 2 (M2) and 6 (M6) after the beginning of vitamin D supplementation. The end points were tolerance, immunologic effects and clinical efficacy.

Results: Among 24 patients, 20 (20 women, age 31±8 years) had low vitamin D levels and received vitamin D supplementation. Treatment was safe with no hypercalcemia or lithiasis. Serum 25(OH)D levels dramatically increased from 18.7±6.7 at D0 to 51.4±14.1 ($p<0.001$) at M2 and 41.5±10.1 ng/mL ($p<0.001$) at M6. Disease activity assessed by the SLEDAI was 2.9±2.5 at D0, 2.6±2.5 at M2 ($p=0.67$) and 1.9±1.8 at M6 ($p=0.16$). Anti-DNA levels decreased from 177±63 at D0 to 124±67 at M2 ($p<0.05$) and 103±36 UI/mL at M6 ($p<0.01$). The percentage of Tregs (CD4+CD25hiCD127-FoxP3+) increased under vitamin D supplementation (3.5±1.2% at D0 to 4.6±1.3% at M2 and 4.3±1.4% at M6, $p<0.001$ and $p<0.01$, respectively) with a similar trend between naïve and activated memory Tregs. This was associated with an increased expression of molecules associated with suppression of Tregs (i.e. GITR and LAP). A decrease in Th17 (2.0±1.1% at D0 to 1.6±0.9% at M2 and 2.0±1.3% at M6, $p<0.01$ and $p=0.81$, respectively) and Th1 cells (16.9±6.7% at D0 to 11.0±5.1% at M2 and 13.6±6.5% at M6, $p<0.01$ and $p<0.05$, respectively) was observed mainly after 2 months of vitamin D supplementation. We also observed a decrease in class-switched memory B cells (28.1±14.5% at D0 to 24.7±12.6% at M2 and 27.6±14.6% at M6, $p<0.05$ and $p=0.65$, respectively) and HLA-DR+ CD8+ T cells (46.0±15.0% at D0 to 40.8±16.8% at M2 and 36.1±18.2% at M6, $p=0.12$ and $p<0.001$, respectively).

Conclusion: This is the first study to report the immunologic effects of vitamin D supplementation in vivo during SLE. Vitamin D modulates the Tregs-Th17 balance by increasing Tregs and decreasing the Th17 cells, and decreases Th1 cells and memory B cells. This study suggests the beneficial

role of vitamin D in SLE which needs to be confirmed in randomized controlled trials.

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Safety Profile of Belimumab, a B-Lymphocyte Stimulator–Specific Inhibitor, in Phase 2 and 3 Clinical Trials of Patients with Active Systemic Lupus Erythematosus. D.J. Wallace[1], S. Navarra[2], M. Petri[3], A. Gallacher[4], R. Gúzman[5], M. Thomas[6], R.A. Furie[7], O. Zamani[8], R.A. Levy[9], R.F. van Vollenhoven[10], S. Cooper[11], Z.J. Zhong[11], W. Freimuth[11], L. Pineda[11], R. Cervera[12] and BLISS-52 and -76 and LBSL02/99 Study Groups[13]. [1]Cedars-Sinai/UCLA, Los Angeles, CA, [2]University of Santo Tomas Hospital, Manila, Philippines, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]Hospital Británico de Buenos Aires, Buenos Aires, Argentina, [5]IDEARG, SaludCoop, Bogotá, Colombia, [6]Kerala Institute of Medical Sciences, Kerala, India, [7]North Shore-LIJ Health System, Lake Success, NY, [8]Rheumazentrum Favoriten, Wien, Austria, [9]Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil, [10]The Karolinska Institute, Stockholm, Sweden, [11]Human Genome Sciences, Inc., Rockville, MD, [12]Hospital Clinic, Barcelona, Spain, [13]Multicenter

Background/Purpose: To present integrated safety data of belimumab in 3 double-blind studies of systemic lupus erythematosus (SLE), including the full wk-76 data from BLISS-76.

Methods: Safety data from 2133 patients with SLE who participated in one phase 2 (LBSL02, N=449) and two phase 3 (BLISS-52, N = 865; BLISS-76, N = 819), multicenter, double-blind, clinical studies of belimumab were evaluated. Belimumab (1 and 10 mg/kg in all studies; 4 mg/kg in LBSL02 only) or placebo was given by intravenous (IV) infusion on days 0, 14, and 28, and q28d thereafter for 52 weeks in LBSL02, 48 weeks in BLISS-52, and 72 weeks in BLISS-76. All patients received ≥1 standard therapy (or a combination), eg, corticosteroids, antimalarials, immunosuppressants, and nonsteroidal anti-inflammatory drugs. Clinical and laboratory assessments were performed during scheduled visits and adverse events (AEs) were evaluated as they occurred. AE rates were based on the double-blind, placebo-controlled phase 2 and phase 3 studies. Malignancy rate was based on exposure to belimumab in all SLE studies (phases 1–3 and open-label continuation; IV and subcutaneous routes).

Results: Rates of AEs overall, by severity and seriousness, and as the cause of discontinuations were similar between placebo and belimumab. Depression was more common with belimumab 1 and 10 mg vs standard therapy alone (6.1% and 5.2% vs 3.7%, respectively). The suicidality rate was the same across treatment groups (0.1%). Infection rates, including lower respiratory infections, as well as infusion/hypersensitivity reactions were numerically higher with belimumab, while all others were comparable with placebo. In all belimumab SLE studies (double-blind and continuation), the rate/100 patient-years (pt-y) of malignancy (excluding nonmelanoma skin cancer) was 0.45, and of mortality was 0.55. No single cause of death predominated; etiologies included infection, cardiovascular disease, and suicide.

Table. Integrated Safety Data Through Wk 76[a]

	Standard Therapy Plus		
	Placebo (N = 675) % Patients	Belimumab 1 mg/kg (N = 673) % Patients	Belimumab 10 mg/kg (N = 674) % Patients
AE in general	92.7	93.3	93.0
Discontinuation due to AE	7.4	6.4	6.8
Serious/severe AE	22.4	24.1	23.3
Death	0.4	0.7	0.9
Infection in general	67.4	71.9	70.8
Discontinuation due to infection	1.2	0.7	0.6
Serious/severe infection	6.8	7.6	6.1
Infection of special interest			
Cellulitis	6.7	8.9	6.4
Sepsis	0.4	0.6	0.7
Fungal	3.4	3.1	2.5
Herpes virus	8.0	8.3	6.8
All respiratory	49.5	52.0	53.0
Lower respiratory	8.9	11.9	12.3
Possible opportunistic[b]	0	0	0.3
Serious/severe infusion/hypersensitivity reactions	0.6	1.2	1.2
Malignant neoplasm	0.3	0.7	0.4

Malignant Neoplasm/Mortality With Belimumab vs Placebo

	Phase 2/3 Double-blind, Placebo-Controlled		All SLE Studies (Double-blind and Continuation)	
	Placebo (N = 675) (692 pt-y)	Belimumab (N = 1458) (1516 pt-y)	Placebo (N = 688) (702 pt-y)	Belimumab (N = 1982)[f] (3976 pt-y)
Malignant Neoplasm[c,d]				
Patients with events, n (%)	2 (0.3)	3 (0.2)	2 (0.3)	18 (0.9)
Rate/100 patient-years (95% CI)	0.29 (0.04–1.04)	0.20 (0.04–0.58)	0.28 (0.03–1.03)	0.45 (0.27–0.72)
Mortality[e]				
Patients with events, n (%)	3 (0.4)	11 (0.75)	3 (0.4)	22 (1.1)
Rate/100 patient-years (95% CI)	0.43 (0.09–1.27)	0.73 (0.36–1.30)	0.43 (0.09–1.25)	0.55 (0.35–0.84)

[a] Pooled data of belimumab 1 and 10 mg/kg compared with placebo; the 4-mg/kg dose (n = 111) was included only in LBSL02, where its safety profile was similar to that of placebo and belimumab 1 and 10 mg/kg in LBSL02; no malignancy, death, or hypersensitivity was reported with the 4-mg/kg dose; [b]there were 2 cases of latent tuberculosis (TB), 1 extrapulmonary TB, 2 *Mycobacterium* non-TB (1 atypical extrapulmonary and 1 avium complex pulmonary), 1 cytomegalovirus pneumonia, 1 coccidioidomycosis, and 1 *Acinetobacter* sepsis after day 0; [c]excludes non-melanoma skin cancer; [d]malignancy rate/100 pt-y of 0.53 (95% CI: 0.48, 0.59) was reported in an international SLE cohort followed for an average of 8 y (76,948 pt-y) (Bernatsky S, Boivin JF, Joseph L, et al. An international cohort study of cancer in systemic lupus erythematosus. *Arthritis Rheum*. 2005;52:1481–90); [e]mortality rate/100 pt-y of 1.63 (1.54, 1.72) was reported in an international SLE cohort followed for an average of 8 y (76,948 pt-y) (Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum*. 2006;54:2550–7); [f]includes phases 1–3 and open-label continuation studies in SLE as of February 2011.

Conclusion: Based on data from 2133 patients (with >4600 pt-y of exposure), belimumab was generally well tolerated when used in combination with a wide range of standard SLE therapy. (ClinicalTrials.gov: NCT00071487/00583362; NCT00424476; NCT00410384.)

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Safety of a Quadrivalent Human Papillomavirus (HPV) Vaccine in Patients with Systemic Lupus Erythematosus. Chi Chiu Mok[1], Pak To Chan[1], Ling Yin Ho[2], Ka Lung Yu[1] and Chi Hung To[1]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Tuen Mun Hospital, Hong Kong SAR, Hong Kong

Background/Purpose: The quadrivalent human papillomavirus (HPV) vaccine (GARDASIL) is a recombinant vaccine which provides protection against infection of the HPV serotypes 6,11,16 and 18. The objective of the current study is to evaluate the safety of GARDASIL in patients with SLE in terms of disease flares and adverse effects.

Methods: Patients who fulfilled ³4 ACR criteria for SLE were recruited to receive vaccination of GARDASIL. Inclusion criteria: (1) age between 18 and 35 years; (2) Having received a stable dose of prednisolone and/or other immunosuppressive agents within 3 months of study entry; (3) informed consent could be obtained. The vaccine was given by intramuscular injection at baseline, 2 months and 6 months. Disease activity scores (SLEDAI), physicians' global assessment scores (PGA) on disease activity, disease flares (SELENA flare instrument) and levels of C3, C4, anti-dsDNA were assessed at baseline, month 2 and month 6. Adverse events reported by the patients were also recorded.

Results: Fifty female patients were recruited. The mean age was 25.8±3.9 years and the mean disease duration was 6.6±4.5 years. The median SLEDAI score at study entry was 4 (IQR 1.75–4.0). None of the patients had SELENA flares at baseline compared to preceding status. The mean anti-dsDNA, C3, C4 and anti-C1q levels were 131±112IU/mL (NR<50), 0.80±0.23g/dL (NR0.75–1.61), 0.15±0.07g/dL (NR0.14–0.44) and 16.0±18.9RU/mL (NR<20), respectively. At month 12, the seroconversion rates of antibodies to HPV types 6,11,16 and 18 in SLE patients and controls were 82%, 89%, 95%, 76% and 98%, 98%, 98%, 80%, respectively. In SLE patients, there were no significant changes in the titers of anti-dsDNA, complements, anti-ENA index, anti-C1q, SLEDAI and PGA scores from baseline to month 2, 7 and 12. There were 1 mild/moderate lupus flare at month 0–2, 2 mild/moderate lupus flares at month 3–6 and 7 mild/moderate lupus flares at month 7–12, which were controlled with usual treatment regimens. The overall rate of disease flares (0.2/patient/year) of the SLE participants was similar to that of 50 SLE controls matched for age and disease duration who did not participate in this study (0.2/patient/year; p>0.99). Erythema and pain at injection sites was the commonest adverse event (AE) (5% of participants) and the frequency of AEs experienced by SLE patients and controls was similar.

Conclusion: The quadrivalent HPV vaccine (GARDASIL) is effective and safe in patients with inactive SLE, and does not induce an increase in serological activity or clinical lupus flares.

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A Risk Management Program Led by a Nurse Improves Cardiovascular and Osteoporosis Risk Management in a Specialized Lupus Clinic. Anne Cymet[1], Carolina Landolt-Marticorena[2], Dafna D. Gladman[3], Paul R. Fortin[2] and Murray B. Urowitz[2]. [1]University Health Network, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease associated with significant morbidity and mortality. Individuals with lupus develop premature cardiovascular disease and osteoporosis. The purpose of this study was to examine whether a risk management program given by a nurse and integrated with lupus medical care improved cardiovascular and osteoporosis risk management.

Methods: Patients prospectively followed at the Lupus Clinic were divided into two groups: 1) those receiving a nurse led intensive risk factor assessment and modification intervention and 2) those receiving usual care. Patients in group 1 underwent cardiovascular and osteoporosis risk assessment and were counseled on risk reduction strategies according to their needs. Cardiovascular risk reduction consisted of lifestyle modifications including smoking cessation, dietary changes and weight management. Hypertension and abnormal lipid levels were monitored and treatment initiated by physician per clinic guidelines The osteoporosis program consisted of documentation of bone mineral density (BMD) by DEXA scan, determination of vitamin D levels and risk reduction strategies included optimization of vitamin D and calcium intake, recommendations about the use of osteoporosis preventive medication and encouragement of weight bearing exercises.

Results: The study cohort consisted of 786 patients: 458 patients seen by the nurse and 328 receiving usual care. The two groups had similar demographics, disease duration and activity. The group receiving the nurse led risk management program showed significant improvement in a number of domains when compared to the usual care group. Appropriate initiation of lipid lowering therapy was significantly higher in the risk management group (33.9% vs 11.5%, $p < 0.0001$). In patients seen by the nurse 49.2% underwent BMD scans and 85.3 % were initiated on Vitamin D whilst in the control population only 24.1 % ($p < 0.0001$) underwent imaging and 72.2% were placed on vitamin supplementation ($p < 0.0001$).

Conclusion: A risk management program led by a dedicated nurse improves adherence to lupus cardiovascular and osteoporosis risk modification strategies. The impact of this intervention in reducing long term risk stratification, cardiovascular and osteoporotic complications, and long-term adherence to preventive strategies will be assessed in future studies.

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Antimalarials: A Window of Opportunity to Improve the Influenza A/H1N1 Vaccine Response in Lupus Patients Under Immunosuppressive Agents. Eduardo F. Borba[1], Carla G.S. Saad[1], Sandra G. Pasoto[1], Ana L. G. Calich[1], Nadia E. Aikawa[1], Ana C. M. Ribeiro[2], Julio C. B. Moraes[2], Elaine P. Leon[1], Luciana P.C. Seguro[1], Lissiane K. N. Guedes[1], Clovis A. Silva[1], Celio Goncalves[2], Ricardo Fuller[3], Suzimara A. Oliveira[1], Maria A. Ishida[4], Alexander R. Precioso[5] and Eloisa Bonfa[6]. [1]University of Sao Paulo, Sao Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]University of Sao Paulo, São Paulo, Brazil, [4]Adolfo Lutz Institute, Sao Paulo, Brazil, [5]Butantan Institute, Sao Paulo, Brazil, [6]Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil

Background/Purpose: The recent WHO recommendation that the 2010–2011 trivalent seasonal influenza vaccine must contain the A/California/7/2009/H1N1–like virus reinforces the need for an extensive evaluation of its immunogenicity and safety in systemic lupus erythematosus (SLE) patients, particularly those under immunosuppressive therapy.

Methods: A total of 555 SLE patients and 170 healthy controls were vaccinated with a single dose of a nonadjuvanted preparation. Clinical/laboratory data, treatment and adverse events were monitored prevaccination and 21 days postvaccination. Anti-H1N1 titres, the percentages of seroprotection (SP), and seroconversion (SC) were evaluated.

Results: After immunisation, lower SP (64.7%; 95%CI 60.7–68.7 vs. 84.1%; 95%CI 78.6–89.6; $p<0.0001$) and SC rates (60.7%; 95%CI 56.7–64.8 vs. 80.0%; 95%CI 74.0–86.0; $p<0.0001$) were observed in SLE compared to controls, whereas an equivalent response was detected for the SLE no therapy group (SP, 74.7%; 95%CI 64.8–84.5; $p=0.10$; and SC, 72.0%; 95%CI 61.8–82.1; $p=0.18$). A treatment analysis comparing the SLE no therapy group revealed analogous SP (vs. 78.0%; 95%CI 70.1–85.9, $p=0.60$) and SC (vs. 69.5%; 95%CI 60.7–78.3, $p=0.75$) for antimalarial monotherapy. Regarding those without antimalarials, a reduced response for prednisone (SC, $p=0.04$), prednisone daily dose >20 mg (SC, $p=0.028$), immunosuppressors (SP, $p=0.037$; and SC, $p=0.035$) and for the concomitant use of prednisone >20 mg + immunosuppressors (SC, $p=0.038$) was observed. In contrast, the association of antimalarials with prednisone >20 mg (SC, $p=1.00$), with immunosuppressors (SC, $p=0.54$) and with prednisone >20 mg + immunosuppressors (SC, $p=0.09$) resulted in a comparable immunoresponse for the SLE therapy group.

Conclusion: Antimalarials may be a promising, inexpensive candidate to improve pandemic influenza A H1N1/2009 response in lupus patients under immunosuppressive therapy. This finding predicts a window of opportunity for other autoimmune conditions (ClinicalTrials.gov, number NCT01151644).

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Defensins and Cardiovascular Disease In Systemic Lupus Erythematosus. Stefan Vordenbäumen, Oliver Sander, Ellen Bleck, Matthias Schneider and Rebecca Fischer-Betz. Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

Background/Purpose: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with an increased long-term mortality mostly due to arteriosclerosis. Besides traditional risk factors, SLE inherent mechanisms which are not yet identified contribute to arteriosclerosis. In an attempt to identify such a putative factor, we analyzed if defensins are related to cardiovascular disease in SLE. Defensins are immunomodulatory peptides which were recently suggested to modulate angiogenesis and whose blood levels were reported to be elevated in SLE.

Methods: 72 SLE patients fulfilling the 1982 ACR criteria were prospectively evaluated over 6 years. At baseline, serum levels of human beta defensin 2 (hBD2) and the neutrophil alpha defensins (human neutrophil peptides, HNP) were determined by ELISA from stored samples. Cardiovascular risk factors were assessed and the occurrence of cardiovascular events (CVE: stroke, claudication, angina pectoris, myocardial infarction) was recorded. Measurement of the intima media thickness (IMT) and of the extent of plaques of the carotid arteries was carried out by ultrasound in 42 of 72 patients at baseline and at 4 years. Log-transformed defensin levels (log-hBD2 and log-HNP) showed normal distribution according to Kolmogorov-Smirnov test and were used for further analyses.

Results: SLE patients who experienced a CVE (n = 13) had significantly higher log-hBD2 values (3.73 vs. 3.40 log(ng/ml), $p <.05$). According to receiver-operating-characteristics analysis, log-hBD2 was moderately discriminative (AUC 0.68). At the cut-off point (3.3 log(ng/ml)), the likelihood-ratio for CVE was 2.23, specificity 85% and sensitivity 34%. In order to identify other variables predictive of CVE, bivariate linear regression analysis was carried out and the number of traditional cardiovascular risk factors (dyslipidemia, hypertension, positive family history, age, smoking, diabetes) was identified to correlate to the incidence of CVE (r^2 0.35, $p <.05$). In a binary logistic regression analysis, log-hBD2 contributed to a model also incorporating the amount of cardiovascular risk factors as explanatory variables for the incidence of CVE (regression coefficient 1.84, odds-ratio 6.3, $p <.05$, likelihood ratio test for the model X^2 13.56, $p <.005$). Employing this model to the population tested, 81.9% of events were predicted correctly. Moreover, SLE patients with progressive IMT (n = 10) showed increased log-hBD2 and log-HNP values (3.76 vs. 3.37 log(ng/ml) and 2.52 vs. 2.36 ng/ml respectively, $p <.05$). Both defensin-levels also showed some correlation to the extent of plaques at baseline (hBD2: r^2 0.10; HNP r^2 0.12, $p <.05$). Neither log-hBD2 nor log-HNP were correlated to traditional cardiovascular risk factors, suggesting an independent effect.

Conclusion: The determination of serum HNP and especially hBD2 may be an indicator of arteriosclerosis and of progressive cardiovascular disease in SLE patients independent of traditional cardiovascular risk factors. Further studies involving more subjects and repeated measurement of defensin-levels are warranted.

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Differences Between Male and Female Systemic Lupus Erythematosus In a Multi-Ethnic Population. Tan Tze Chin[1], Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Male systemic lupus erythematosus (SLE) has been thought to be similar to female SLE, but there is lack of consensus in past studies. Comparisons between male and female SLE in a large SLE cohort were made.

Methods: 1979 patients in a longitudinal cohort were included in the analysis. The results were based on the chi-square test (SAS Institute, Cary, NC, USA). A p-value ≤ 0.05 was considered statistically significant.

Results: The cohort consisted of 157 men (66% Caucasian, 34% African-American) and 1822 women (60% Caucasian, 40% African-American). The mean followup was 6.02 (range: 0–23.73) years. Men were more likely to have renal, hematological, serological and thrombotic events than women. Renal and cardiovascular damage were more prevalent in men. In both African-American and Caucasian SLE, men were more likely to have cardiac and renal damage. In general, differences between males and females were more numerous and striking in Caucasians, especially in term of men having more lupus nephritis, more abnormal serologies, and more thrombosis.

Table 1. Comparison between Male and Female SLE

Characteristics/ Manifestations	Male (n=157) n	Male (n=157) %	Female (n=1822) n	Female (n=1822) %	p-value	Odds Ratio (95% Confidence Interval)‡	Adjusted p value‡
Ethnic group							
African-American	53	33.8	732	40.2	0.1147	N.A	N.A
Caucasian	104	66.2	1090	59.8			
Age at onset (years)							
Less than 30	67	43.2	1093	60.7	<0.0001	N.A	N.A
More than 30	88	56.8	708				39.3
Age at diagnosis (years)							
Less than 30	51	32.7	928	51.1	<0.0001	N.A	N.A
More than 30	105	67.3	887	48.9			
Education level (years)							
Less than 12	68	46.6	627	36.2	0.0127	0.6 (0.4, 0.9)[1]	0.0077
More than 12	78	53.4	1105	63.8			
Clinical Features							
Malar rash	62	39.7	953	52.4	0.0024	0.7 (0.5, 0.9)	0.0173
Photosensitivity	63	40.4	1007	55.5	0.0003	0.5 (0.4, 0.7)	0.0003
Oral ulcer	53	34.0	961	52.9	<0.0001	0.4 (0.3, 0.6)	<0.0001
Alopecia	44	28.2	1023	56.3	<0.0001	0.3 (0.2, 0.4)	<0.0001
Raynauds	56	35.7	987	54.4	<0.0001	0.5 (0.3, 0.7)	<0.0001
Arthralgias	137	87.3	1688	92.7	0.0133	0.5 (0.3, 0.9)	0.0256
Proteinuria	78	50	732	40.4	0.0197	1.9 (1.4, 2.8)	0.0002
Nephrotic syndrome	36	23.8	299	16.6	0.0245	2.0 (1.3, 3.1)	0.0010
Hematuria	54	34.8	492	27.2	0.0407	1.7 (1.2, 2.5)	0.0030
Renal insufficiency	49	34.1	343	18.9	0.0002	2.2 (1.5, 3.2)	<0.0001
Renal failure	15.3	24	138	7.6	0.0008	2.7 (1.6, 4.4)	0.0001
Lymphopenia	77	49.4	698	38.8	0.0097	1.5 (1.1, 2.1)	0.0169
Thrombocytopenia	45	28.8	353	19.5	0.0051	1.9 (1.3, 2.7)	0.0014
Laboratory							
Coombs positivity	35	26.9	281	19.6	0.0450	1.7 (1.1, 2.7)	0.0125
Lupus anticoagulant	62	41.3	446	25.3	<0.0001	2.1 (1.5, 2.9)	<0.0001
Anti-Sm	36	23.5	308	17.5	0.0640	1.8 (1.2, 2.7)	0.0065
Anti-dsDNA	107	68.2	1120	61.7	0.1082	1.6 (1.1, 2.2)	0.0167
Low C3	94	60.3	967	53.2	0.0894	1.6 (1.1, 2.3)	0.0095
Hypertension	103	65.6	944	51.9	0.0010	1.8 (1.2, 2.6)	0.0026
Deep Vein Thrombosis	31	19.9	242	13.3	0.0229	1.7 (1.1, 2.6)	0.0127

‡ Adjusted for ethnicity, age at last assessment, and duration of SLE at last assessment.
[1] The ratio of the odds of the event "more than 12" occurring in males to the odds of it occurring in females

Table 2. SLICC/ACR Damage Index Comparison between Male and Female SLE (n=1979)

Damage	Male (n = 157) n	Male (n = 157) %	Female (n = 1822) n	Female (n = 1822) %	p-value*	Odds Ratio (95% Confidence Interval)§	Adjusted p value§
Neuropsychiatric							
Seizures requiring therapy for 6 months	14	9.0	81	4.5	0.0117	2.3 (1.3, 4.2)	0.0071
Renal							
GFR <50%	21	13.5	105	5.8	0.0002	2.8 (1.7, 4.9)	0.0001
Proteinuria > 3.5g/ day	22	14.3	130	7.2	0.0017	2.6 (1.5, 4.5)	0.0005
End-Stage Renal Disease	13	8.4	85	4.7	0.0444	2.3 (1.2, 4.4)	0.0113
Cardiovascular							
Angina	12	7.7	56	3.1	0.0026	2.3 (1.2, 4.5)	0.0181
Myocardial Infarction	17	11.0	68	3.8	<0.0001	2.9 (1.6, 5.4)	0.0007
Left ventricular hypertrophy	18	11.8	106	6.1	0.0064	2.3 (1.3, 4.0)	0.0040
Hypertension	69	45.4	614	34.3	0.0061	1.6 (1.1, 2.2)	0.0164
Peripheral Vascular							
Venous Thrombosis	14	9.0	65	3.6	0.0010	2.8 (1.5, 5.1)	0.0010

* Fisher's exact test was used for expected counts less than 5.
§ Adjusted for ethnicity, age at last assessment, and duration of SLE at last assessment.

Conclusion: Our study suggests that there are major clinical differences between male and female SLE. Surprisingly, the differences between male and female SLE also depend on ethnicity. Future SLE studies will need to consider both ethnicity and gender to understand these differences.

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Sustained Disease Improvement and Safety Profile Over the 1500 Patient-Year Experience (6 years) with Belimumab in Patients with Systemic Lupus Erythematosus. J.T. Merrill[1], R.A. Furie[2], D.J. Wallace[3], W. Stohl[4], W. Chatham[5], A. Weinstein[6], J. Mckay[7], E.M. Ginzler[8], Z.J. Zhong[9], L. Pineda[9], J. Klein[9], W. Freimuth[9], M. Petri[10] and LBSL02/99 Study Group[11]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]North Shore-LIJ Health System, Lake Success, NY, [3]Cedars-Sinai/UCLA, Los Angeles, CA, [4]USC/Keck School of Medicine, Los Angeles, CA, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Washington Hospital Center, Washington, DC, [7]Oklahoma State University Center for Health Sciences, Tulsa, OK, [8]SUNY Downstate Medical Center, Brooklyn, NY, [9]Human Genome Sciences, Inc., Rockville, MD, [10]Johns Hopkins University School of Medicine, Baltimore, MD, [11]Multicenter

Background/Purpose: To update belimumab safety and efficacy data over 6 y in patients with active SLE.

Methods: 449 SLE patients with SELENA-SLEDAI score ≥ 4 were enrolled in a phase 2 study of belimumab 1, 4, or 10 mg/kg, vs placebo, plus standard of care for 52 wk. All placebo patients switched to belimumab 10 mg/kg at wk 56; prior belimumab patients continued on the same dose or switched to 10 mg/kg. At wk 80, all patients electing to enter a continuation study received belimumab 10 mg/kg. Adverse events (AEs) were assessed in all patients at each study visit. Analyses of disease activity included SLE Responder Index (post-hoc analysis: improvement in SELENA-SLEDAI [≥ 4 points], no new BILAG A or 2 new BILAG B scores, and no Physician's Global Assessment worsening [<0.3 points] vs baseline), BILAG A/B flares, SELENA-SLEDAI Flare Index (SFI), and biomarker changes. Efficacy assessments were limited to patients who were autoantibody-positive (antinuclear antibody titer $\geq 1:80$ or anti-double-stranded DNA ≥ 30 IU/mL) at baseline. All results are presented by 1-y intervals through 6 y of belimumab treatment.

Results: 296 of the original 449 patients (66%) entered the continuation trial. At the end of the 6-y interval, 208 patients remained on study. Total belimumab exposure was approximately 1500 patient-y. Rates of AEs/100 patient-y remained stable/decreased over 6 y (table). Five patients treated with belimumab died over 6 y; no single cause predominated and etiologies included aspiration pneumonia with subsequent sepsis and respiratory failure, infection, cardiovascular disease, and suicide. The SRI rate with belimumab was 46% at wk 52 (vs 29% with placebo; $p < 0.05$), increasing to 55%–61% through 6 y of open-label

treatment. The frequency of 1 new BILAG A or 2 new B flares with belimumab was 38% at 1 y vs 44% with placebo, decreasing to 11% at 6 y of open-label treatment. The frequency of all SFI flares with belimumab was 84% (severe 17%) at 1 y vs 85% (severe 19%) with placebo, decreasing to 42% (severe 5%) at 6 y. Patients on belimumab had increases in complement (C3 or C4) levels over 6 y. Autoantibody levels (anti-Smith, anti-double-stranded DNA, anticardiolipin-immunoglobulin-G) generally decreased over time. In 283 patients taking corticosteroids at baseline, corticosteroid use decreased over time with a mean reduction of 34% and an absolute reduction of 4.7 mg/d at 6 y vs baseline.

AE Incidence (rate per 100 patient-y) in Patients Treated With Belimumab[a]

	Interval[b]					
	1 (0−1 y)	2 (1 −2 y)	3 (2 −3 y)	4 (3 − 4 y)	5 (4 −5 y)	6 (5 −6 y)
Patients, n [patient-y]	336 [320.1]	339 [299.1]	274 [258.1]	248 [234.2]	223 [215.8]	208 [171.9]
Overall AEs	326 (101.8)	322 (107.7)	260 (100.8)	237 (101.2)	211 (97.8)	167 (97.2)
Serious AEs	55 (17.2)	52 (17.4)	49 (19.0)	31 (13.2)	41 (19.0)	25 (14.5)
Overall infections	254 (79.4)	237 (79.2)	192 (74.4)	181 (77.3)	145 (67.2)	104 (60.5)
Serious infections	17 (5.3)	14 (4.7)	8 (3.1)	8 (3.4)	6 (2.8)	7 (4.1)
Malignancies[c]	0	2 (0.7)	1 (0.4)	1 (0.4)	3 (1.4)	2 (1.2)
Mortality	3 (0.8)	0	1 (0.4)	1 (0.4)	0	0

[a]Data presented as no. of patients with AE (no./100 patient-y) unless specified; [b]interval 1 includes only patients treated with belimumab (and not placebo) during the 52-wk, double-blind study (except mortality data includes 2 deaths during the 52-wk, double-blind period and 1 death during the extension period); intervals 2–6 (and interval-1 mortality data; n = 424, 374.0 patient-y) include all belimumab-treated patients, including those originally randomized to placebo who subsequently switched to belimumab; [c]excluding nonmelanoma skin cancer; including unspecified malignancy of lungs.

Conclusion: Belimumab added to standard SLE therapy was well tolerated for its intended indication in patients remaining on treatment over 6 y in an open-label study. Five patients died over 6 y; no single cause predominated. Autoantibody-positive patients treated with belimumab showed sustained improvement in disease activity, and declines in BILAG and SFI flares over 6 y accompanied by reductions in corticosteroid use and autoantibody levels. (NCT00071487/NCT00583362.)

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Association between B-Cell Activating Factor Gene Expression and Disease Characteristics in Systemic Lupus Erythematosus. Michelle Petri[1], Wenzheng Hu[1], Hong Fang[1], Jie Xu[1], Jadwiga Bienkowska[2], Norm Allaire[2], John Carulli[2] and Matthew D. Linnik[3]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Biogen Idec Inc., Cambridge, MA, [3]Biogen Idec Inc., Solana Beach, CA

Background/Purpose: Multiple gene expression signatures occur in SLE. Because of the interest in anti-BAFF therapy in SLE, we explored the association between BAFF gene expression and clinical observations in SLE patients.

Methods: 292 SLE patients (58.9% Caucasian, 33.9% African-American, 91.1% female, mean age 46.0±11.9 years) were enrolled in a prospective observational study. At baseline, the BAFF gene expression levels were determined in peripheral blood RNA using Affymetrix chips. Clinical associations, based on the cumulative history and the same-day visit disease activity, were then determined. The results were based on the chi-square test (SAS Institute, Cary, NC, USA). P-values were then adjusted for race. A p-value ≤0.05 was considered statistically significant.

BAFF gene expression was high (> 11.4) in 28.8%, medium (10.7–11.4) in 37.7% and low (<10.7) in 33.6%. Medium to high signature was more common in African-Americans than Caucasians. Clinically, the gene signature was associated with more leukopenia and serologically with Coombs, more autoantibodies (anti-dsDNA, anti-Sm, anti-Ro, anti-La, and anti-RNP) and low complement. However, it was not associated with antiphospholipid antibodies (not shown in the table). The same-day visit disease activity was found to be higher in higher BAFF group. In terms of SLICC/ACR Damage Index, the gene expression was associated with less cataract, cognitive impairment and chronic seizure but not associated with other organ damage (not shown in the table).

Results:

Table 1. Association between cumulative history characteristics and BAFF in SLE

Variable	Low BAFF (<10.7) (%, N=98)	Med BAFF (10.7–11.4) (%, N=110)	High BAFF (>11.4) (%, N=84)	P-value	Adjusted P-value for Race
Race African-American	27.6	39.1	34.5	0.005	N.A.
Caucasian	70.4	54.6	51.2		
Other	2.0	6.4	14.3		
Malar rash	51.0	56.4	45.2	0.31	0.30
Discoid rash	15.3	21.8	16.7	0.44	0.61
Photosensitivity	61.2	51.8	50.0	0.25	0.47
Oral Ulcer	63.3	48.2	48.8	0.057	0.13
Arthritis	76.5	74.6	71.4	0.73	0.61
Serositis	46.9	51.8	44.1	0.55	0.60
Neurologic disorder	13.3	12.7	3.6	0.056	0.042
Hematologic disorder	64.3	76.4	70.2	0.16	0.16
Immunologic disorder	82.7	84.6	86.9	0.73	0.87
ANA	95.9	98.2	98.8	0.39	0.50
Proteinuria	34.7	45.5	52.4	0.05	0.25
Hematuria	22.5	35.5	34.5	0.09	0.20
Seizure	11.2	10.0	2.4	0.066	0.065
Hemolytic anemia	10.2	9.1	9.5	0.96	0.87
Coombs	6.1	22.0	25.0	0.0011	0.0005
Leukopenia	33.7	48.2	58.3	0.0035	0.0064
Anti-dsDNA	48.0	65.5	73.8	0.0010	0.0043
Anti-Sm	9.2	20.0	27.7	0.0054	0.026
Anti-Ro	11.2	32.7	51.2	<.0001	<.0001
Anti-La	5.1	13.6	22.9	0.0022	0.0019
Anti-RNP	9.2	29.1	37.4	<.0001	0.0002
Low C3	45.9	53.6	71.4	0.002	0.012
Low C4	32.7	46.4	64.3	0.0001	0.0005
Increased ESR	64.3	77.3	75.0	0.091	0.30

Table 2. Association between same-day visit disease activity and BAFF in SLE

Variable	Low BAFF (<10.7) (%, N=98)	Med BAFF (10.7–11.4) (%, N=110)	High BAFF (>11.4) (%, N=84)	P-value	Adjusted P-value for Race
Physician global assessment >1	9.2	20.9	27.4	0.006	0.026
SLEDAI ≥2	35.7	66.4	71.4	<.0001	<.0001
Age at visit ≤ 30	7.1	12.7	16.7	0.14	0.27
> 30	92.9	87.3	83.3		
Urine Protein/Creatinine Ratio (≥0.5)	3.1	13.6	15.5	0.011	0.058
Anti-dsDNA ≥ 10	10.2	19.1	39.3	<.0001	<.0001
C3 <79	5.1	13.6	19.1	0.015	0.011
C4 <12	4.1	11.8	17.9	0.012	0.0064
ESR >20	36.5	54.7	63.1	0.001	0.0077

Table 3. Association between SLICC/ACR Damage Index and BAFF in SLE

Variable	Low BAFF (<10.7) (%, N=98)	Med BAFF (10.7–11.4) (%, N=110)	High BAFF (>11.4) (%, N=84)	P-value	Adjusted P-value for Race
Cataract	30.6	23.6	9.5	0.0024	0.0011
Cognitive impairment	16.3	7.3	2.4	0.0033	0.0027
Seizure	9.2	4.6	1.2	0.048	0.078

Conclusion: BAFF gene expression level is strongly associated with Coombs positivity, leukopenia, autoantibodies and low complement. Surprisingly, it is negatively associated with neurological damage. The associations between BAFF gene expression and clinical characteristics were studied at the RNA level and need to be verified at the protein level.

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Decreased Breast Cancer Risk In SLE: Can a Genetic Basis Be Determined? Sasha Bernatsky[1], Douglas Easton[2], Alison M. Dunning[2], Rosalind Ramsey-Goldman[3], Caroline Gordon[4], William Foulkes[5], Kyriaki Michailidou[2] and Ann E. Clarke[6]. [1]McGill UHC/RVH, Montreal, QC, [2]University of Cambridge, United Kingdom, [3]Northwestern University, Chicago, IL, [4]University of Birmingham, Birmingham, United Kingdom, [5]McGill University, Montreal, QC, [6]Research Institute of the McGill Univ. Health, Montreal, QC

Background/Purpose: Recent work has also demonstrated an important decrease in certain non-hematologic cancers, such as breast cancers in

women with SLE. The reason behind this phenomenon is unknown. Our purpose was to explore whether risk alleles of the SNPs predisposing to SLE might be protective against breast cancer (in women in the general population).

Methods: The literature was reviewed and 17 SLE SNPs were identified as of potential interest. We assessed these SNPs, which are known to be associated with SLE risk, in terms of the available data on their occurrence in women with breast cancer, in the general population. To do this we used the most up to date breast cancer GWAS data, involving 37,012 cases and 40,069 controls from 33 studies in the National Cancer Institute Cancer Genetic Markers of Susceptibility (CGEMS) collaboration and the United Kingdom Breast Cancer Association Consortium (BCAC).

Results: Only two of the SLE-related SNPs that we studied appeared to be negatively associated with breast cancer in the GWAS data. This was rs1801274 (on chromosome 1, position 159746369), with an odds ratio, OR of 0.936687 (p-value 0.037549); and rs9888739 (on 16, position 31220754) with an OR of 0.907551 (p value 0.049899).

Conclusion: Population-based GWAS breast cancer data suggest possible protective roles for two lupus-related SNPs. This is hypothesis-generating only; due to multiple testing, the significance of the associations remains unclear. Future work will use the reverse approach in GWAS of SLE populations, to determine if SNPs known to be associated with breast cancer are in fact represented less often in SLE than in the general population.

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Cystatin C Is Associated with Inflammation but Not Atherosclerosis In Systemic Lupus Erythematosus. Ratchaya Lertnawapan[1], Aihua Bian[2], Young Hee Rho[1], Paolo Raggi[3], Annette Oeser[4], Joseph F. Solus[4], Tebeb Gebretsadik[2], Ayumi Shintani[2] and C. Michael Stein[4]. [1]Div.of Clinical Pharmacology and Rheumatology, Dept.of Medicine and Pharmocology, School of Medicine, Vanderbilt University, Nashville, TN, [2]Vanderbilt Medical Center, Nashville, TN, [3]Div.of Cardiology, Emory University, Atlanta, GA, [4]Vanderbilt University, Nashville, TN

Background/Purpose: Even mild renal impairment is associated with increased atherosclerosis and cardiovascular mortality. Cystatin C, a novel measure of renal function, is more sensitive than conventional creatinine-based measures for the detection of subtle renal impairment. Increased cystatin concentrations are also associated with cardiovascular risk, independent of conventional measures of renal function. We examined the hypothesis that cystatin C is elevated in systemic lupus erythematosus (SLE) and is associated with coronary atherosclerosis.

Methods: We measured serum cystatin C, creatinine, TNF- α and IL-6 concentrations, coronary artery calcium score (CACS), Framingham risk score (FRS), Modified Diet in Renal Disease estimated glomerular filtration rate (MDRD-eGFR) and other clinical parameters in 118 patients with SLE and 83 control subjects. The independent association between concentrations of cystatin C and SLE was evaluated using multivariable linear regression models, and the relationship between renal measures and coronary calcium was assessed with multivariable proportional odds logistic regression models.

Results: Cystatin C concentrations, but not serum creatinine or MDRD-eGFR, were significantly higher in patients with SLE than controls (1.11 [IQR: 0.84–1.31] mg/L vs. 0.89 [IQR: 0.76–0.99]mg/L; $P<0.001$ after adjusting for age, race and sex and MDRD-eGFR). In SLE cystatin C was significantly correlated with SLEDAI ($P=0.05$), SLICC ($P=0.04$), ESR ($P=0.001$), CRP ($P=0.04$), TNF-α ($P=0.008$) and IL-6 concentrations ($P=0.01$) after adjustment for age, race and sex. However, cystatin C was not significantly correlated with coronary calcium score in SLE (unadjusted $P= 0.31$; after adjustment for age, race, sex and Framingham risk score $P=0.98$).

Conclusion: Cystatin C concentrations were higher in patients with SLE than control subjects even after adjustment for a conventional creatinine-based measure of GFR. Cystatin C was significantly correlated with several markers of inflammation in SLE but was not associated with coronary atherosclerosis. Subtle renal dysfunction does not appear to be directly associated with accelerated atherosclerosis in SLE.

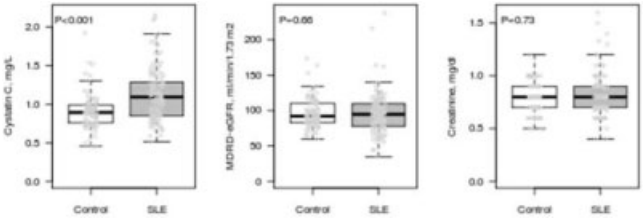

Figure 1. Concentrations of Cystatin C, Creatinine and MDRD-eGFR in Control Subjects and Patients with SLE.

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A New 30-Year Cardiovascular Risk Prediction Score Does Not Differ in Women with Systemic Lupus Erythematosus and Control Subjects. Vivian K. Kawai[1], Joseph F. Solus[1], Annette Oeser[1], Young Hee Rho[1], Paolo Raggi[2], Aihua Bian[3], Tebeb Gebretsadik[3], Ayumi Shintani[3] and C. Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]Div.of Cardiology, Emory University, Atlanta, GA, [3]Vanderbilt Medical Center, Nashville, TN

Background/Purpose: Lupus primarily affects young women and is associated with accelerated atherosclerosis and increased risk of coronary heart disease (CHD). Conventional 10-year CHD risk prediction scores, such as the Framingham risk score, perform poorly and are not different in patients with SLE and controls. Long-term cardiovascular risk scores that take into account the cumulative effect of risk factors present in early adulthood have been developed specifically to assess CHD risk in younger populations and could be more suitable for risk prediction in SLE. We examined the hypothesis that a new long-term cardiovascular risk prediction model, the Framingham Heart Study 30-year risk score, is higher in women with lupus compared to controls. Age is the strongest risk factor for coronary atherosclerosis. Thus, we also examined the hypothesis that the 30-year risk score predicts the presence of subclinical coronary atherosclerosis better than age in women with SLE.

Methods: We performed a cross-sectional, case-control study of 121 women with lupus and 65 control subjects matched for age, sex and race. Subjects with diabetes or CHD were excluded. Demographic, clinical and laboratory data and coronary artery calcium scores (CACS) were recorded and 30-year risk scores were calculated. The 30-year risk score estimates the probability of having a cardiovascular event (%) in the next 30 years. The Wilcoxon rank sum test was used to compare the 30-year risk score in lupus and controls, and in lupus patients with and without CAC. We used the area under the receiver operating characteristic curve (AUC) to quantify the ability of the 30-year risk model to discriminate subclinical atherosclerosis (presence of CAC) in SLE and we compared it with AUC for age.

Results: The 30-year risk score did not differ significantly in women with lupus and controls (5.0 [2.7–9.5] % vs. 6.3 [2.2–11.5] %, $p=0.75$, Fig 1) despite the more frequent presence of CAC in lupus (21/121, 17%) compared to controls (4/65, 6%) ($p=0.033$). SLE patients with CAC had higher 30-year risk scores than those without (14.5 [6.5–17.9] % vs. 4.5 [2.4–7.6] %, $p<0.001$); however, the ability of the 30-year risk model to identify patients with CAC did not differ significantly from that of age alone (AUC 0.746, 95% CI (0.616, 0.875) vs. AUC=0.773, 95% CI (0.660, 0.886), $p=0.41$ (Fig. 2).

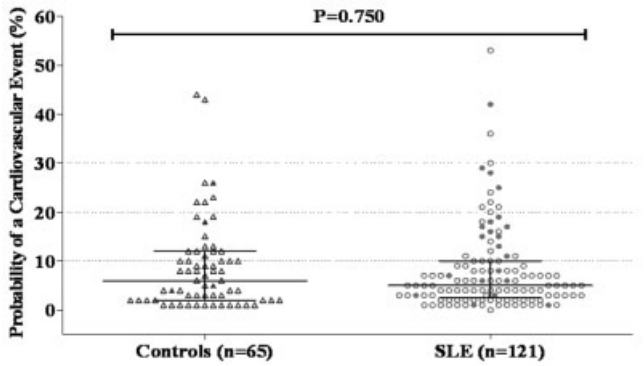

Figure 1.

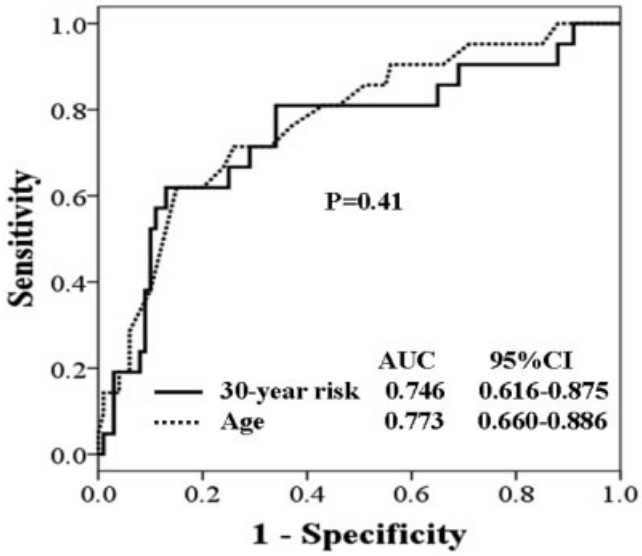

Figure 2.

Conclusion: The 30-year CHD risk prediction score is not different in patients with SLE and controls and its ability to predict subclinical atherosclerosis in SLE is similar to that of age alone.

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Development of Damage and Death in a Large Cohort of SLE Patients. Chee-Seng Yee[1], Deva Situnayake[2], Simon J. Bowman[3], Veronica Toescu[1], Richard A. Hickman[1] and Caroline Gordon[1]. [1]University of Birmingham, Birmingham, United Kingdom, [2]Sandwell and West Birmingham NHS Trust, Birmingham, United Kingdom, [3]University Hospital Birmingham, Birmingham, United Kingdom

Background/Purpose: To determine the development of damage and death in a large cohort of SLE patients.

Methods: This was a prospective longitudinal study of SLE patients under regular follow-up at a single centre, that was set up in 1989. SLE patients were included if they achieved the 4th ACR criteria for SLE within 3 years at the time of recruitment. Data were collected on damage (SLICC/ACR damage index) every 12 months. Information on death was provided by the Office for National Statistics. The censure date for analysis was 31st December 2007. Analysis was with survival analysis and standardised mortality ratio (SMR) was calculated. Cox proportional hazards model was used to determine predictors of damage and death (results in hazards ratio (HR)).

Results: There were 382 patients (92.4% women, 51.6% Caucasian, 22% South Asian, 20.7% Afro-Caribbean). Median follow-up was 5.1 years (range 0.2–18.1) and mean age at recruitment was 36.3 years (SD 13.3). There were 26 deaths and 266 items of damage occurring in 123 (32.2%) patients. For those who died, the mean age was 51.4 years (SD 18.8) and mean disease duration was 5.8 years (SD 3.9). The causes of death were infection 10 (38.4%), cardiovascular 8 (30.8%), cancer 3 (11.5%), ARDS 2 (7.7%), active SLE 1 (3.8%), cardiac tamponade 1 (3.8%) and pulmonary hypertension 1 (3.8%). SMR for this cohort was 1.6 (95% CI: 1.1, 2.3), being highest in the younger age group and there is decreasing trend with age towards the general population rate after menopause (Table 1). The distribution of damage was musculoskeletal 59 (22.2%), neuropsychiatric 54 (20.3%), ophthalmic 33 (12.4%), renal 21 (7.9%), pulmonary 20 (7.5%), cardiac 19 (7.1%), cutaneous 18 (6.8%), gastrointestinal 15 (5.6%), malignancy 10 (3.8%), vascular 7 (2.6%), diabetes mellitus 7 (2.6%) and premature menopause 3 (1.1%). The rate of development of damage or death appears to be stable throughout the period of follow-up (Table 2). Prior damage (HR 1.37, 95% CI: 1.26, 1.48) and older age at diagnosis (HR 1.03, 95% CI: 1.02, 1.04) were predictive of development of damage or death, while gender and ethnicity were not.

Table 1. Standardised mortality ratio for cohort of SLE patients

Age group (years)	SMR (95% CI)
20–24	5.3 (1.3, 21.1)
25–34	3.7 (1.4, 9.8)
35–44	1.6 (0.5, 5.0)
45–54	2.6 (1.2, 5.4)
55–64	0.8 (0.3, 2.6)
65–74	1.3 (0.5, 3.3)
75–84	1.1 (0.3, 4.4)
≥85	15.2 (2.1, 107.6)

Table 2. Incidence rate of development of damage or death over period of follow-up at 3 yearly intervals

Period of follow-up (year)	Person-years at risk	Number of death or new items of damage	Incidence rate, per 1000 person-years (95% CI)
0–3	984.6	126	128.0 (107.5, 152.4)
3–6	627.9	70	111.5 (88.2, 140.9)
6–9	403.3	32	79.4 (56.1, 112.2)
9–12	228.0	26	114.0 (77.6, 167.5)
12–15	96.8	8	82.6 (41.3, 165.2)
15–18	37.7	5	132.5 (55.2, 318.4)

Conclusion: In this cohort, SLE patients have premature mortality as compared to general population and the risk is highest in the younger age group. The most common causes of death were infections and cardiovascular disease. The development of damage and death appears to be stable throughout follow-up. The most common damage was in the musculoskeletal, neuropsychiatric and ophthalmic systems.

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Depression in Systemic Lupus Erythematosus, Dependent or Independent of Severity of Disease. Eric van Exel[1], Jonathan Jacobs[1], Lindy-Anne Korswagen[1], Alexandre Voskuyl[1], Max Stek[1], Joost Dekker[2] and Irene Bultink[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Reade, Centre for Rehabilitation and Rheumatology, VU University Medical Centre, Department of Rehabilitation Medicine, EMGO Institute and Department of Psychiatry, Amsterdam, Netherlands

Background/Purpose: Depression is one of the most commonly reported neuropsychiatric symptoms in systemic lupus erythematosus (SLE) patients. We set out to further unravel the relation between depression and SLE, hypothesizing that presence of depression in patients with SLE is due to increased severity of SLE.

Methods: We studied 102 patients with SLE (mean age 44.4 yrs, 88% female, mean disease duration 7.8 yrs), all fulfilling the ACR classification criteria for SLE. Severity of SLE was determined with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaborative Clinics Damage Index (SDI), representing disease activity and organ damage. We used the Beck Depression Inventory score, a validated screening instrument able to detect major depression and to estimate the prevalence of depression. A cut off score of 14 points or higher represents presence of major depression. As a proxy for treatment of depression we assessed the number of patients using anti-depressants.

Results: The mean Beck Depression Inventory score was higher in SLE patients ($n=102$) compared to the Beck Depression Inventory scores derived from an European population based study (ODIN study, $n=7934$), (10.1 points in patients with SLE vs 5.6 points in subjects from ODIN, $p<0.001$). 27.5% of all SLE patients had a major depression ($n=28$). Only 7% of these depressed patients used anti-depressant medication.

There was no difference in disease characteristics, disease activity score (SLEDAI) and organ damage index (SDI) between SLE patients with and without depression (all $p>0.1$). The number of years of education was significantly lower in SLE patients with a depression compared to those without a depression (9.5 yrs. vs 12.2 yrs, $p=0.004$).

Conclusion: The mean Beck Depression Inventory score, i.e. a proxy for prevalence of depression, is almost doubled in SLE patients compared to the mean Beck Depression Inventory score from a large pan European population based study. Surprisingly, we found no association between

disease characteristics or severity of SLE and presence of depression, determined with the Beck Depression Inventory score.

Finally, we found that the number of depressed SLE patients treated with anti-depressant medication is very low, suggesting that depressed SLE patients are not adequately recognized and treated for depression. For depressed SLE patients, this study provides clues that screening for depression in SLE patients should be done routinely, and that psychiatric counseling for these patients should be readily available.

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A Prospective Study of Seizures in Systemic Lupus Erythematosus. John G. Hanly[1], Murray B. Urowitz[2], Li Su[3], Caroline Gordon[4], Sang-Cheol Bae[5], Jorge Sanchez-Guerrero[6], Juanita Romero-Diaz[7], Daniel Wallace[8], Ann Clarke[9], Sasha Bernatsky[10], E.M. Ginzler[11], Joan T. Merrill[12], David A. Isenberg[13], Anisur Rahman[13], M. Petri[14], Paul R. Fortin[15], Dafna D. Gladman[16], Ian N. Bruce[17], Kristjan Steinsson[18], M.A. Dooley[19], Munther A. Khamashta[20], Graciela S. Alarcon[21], Barri J. Fessler[21], Rosalind Ramsey-Goldman[22] and Susan Manzi[23]. [1]Dalhousie University, Halifax, NS, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, UK, Cambridge, United Kingdom, [4]University of Birmingham, Birmingham, United Kingdom, [5]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [6]Mount Sinai Hospital/ University Health Network, Toronto, ON, [7]INCMNSZ, Mexico city, Mexico, [8]Cedars-Sinai/UCLA, Los Angeles, CA, [9]Montreal General Hospital, Montreal, QC, [10]McGill UHC/RVH, Montreal, QC, [11]SUNY-Downstate Medical Center, Brooklyn, NY, [12]Oklahoma Medical Research Foundation, Oklahoma City, OK, [13]University College London, London, United Kingdom, [14]Johns Hopkins University School of Medicine, Baltimore, MD, [15]Toronto Western Hospital, Toronto, ON, [16]Toronto Western Hospital, University of Toronto, Toronto, ON, [17]A, Manchester, United Kingdom, [18]Landspital Univ Hospital, Reykjavik, Iceland, [19]University of North Carolina at Chapel Hill, Chapel Hill, NC, [20]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [21]University of Alabama at Birmingham, Birmingham, AL, [22]Northwestern University Feinberg School of Medicine, Chicago, IL, [23]Allegheny Singer Research Institute, Pittsburgh, PA

Background/Purpose: Seizure disorders are serious manifestations of neuropsychiatric systemic lupus erythematosus (NPSLE). We wished to determine the frequency, attribution and outcome of seizures in a long-term study of SLE.

Methods: The study was conducted by an international research network of academic centers. Patients were enrolled close to the time of SLE diagnosis and assessed annually for up to 10 years for the occurrence of seizures and other NP events using the ACR case definitions. The attribution of seizures to SLE and non-SLE causes was determined centrally using a priori decision rules. Physician outcome scores of seizure disorders were recorded on a 7 point Likert scale. Patient outcomes were derived from the mental (MCS) and physical (PCS) component summary scores of the SF-36. Statistical analyses included Cox regression for time-to-seizure resolution (adjusting for correlation of multiple seizures in the same patient) and linear regression for MCS and PCS summary scores by generalised estimating equations (adjusting for correlation between multiple MCS and PCS measurements for the same patient).

Results: Of the 1631 enrolled patients 89.4% were female and the mean ($\pm$ SD) age was 35.0 $\pm$ 13.4 years. The mean disease duration at enrollment was 5.6 $\pm$ 4.8 months and the mean length of followup was 3.5 $\pm$ 2.9 years. A total of 75/1631 (4.6%) patients had $\geq$ 1 seizure with the majority (79%) having a single event. In these 75 patients there were a total of 91 seizures (66% generalized; 34% focal) of which 78/91 (86%) were attributed to SLE. Although seizures occurred over the entire observation period, the majority presented early in the disease course with a median (range) interval from the time of diagnosis of SLE to onset of first seizure of 0.14 (-0.50 – 7.57) years. More patients with seizures attributed to SLE stopped taking anti-seizure drugs at the first followup assessment compared to patients with seizures attributed to non-SLE causes (19/66=29% vs. 2/12=17%) and similarly by the second followup assessment (32% vs. 11%). Using physician assessment, those seizures attributed to SLE were more likely to resolve (59/78, (76%)) compared to seizures attributed to non-SLE causes (7/13, (54%)). Using patient self-report the mean ($\pm$ SD) MCS score in patients with seizures and no other NP events was comparable to patients without NP events (45$\pm$13.1 vs. 48.5 $\pm$ 10.9; p=0.21). A similar outcome was seen in the mean ($\pm$ SD) PCS scores (40.0 $\pm$ 10.8 vs. 42.8 $\pm$ 11.2; p=0.34).

Conclusion: Most seizures in SLE patients are attributable to lupus and occur in close proximity to the time of diagnosis of SLE. In the majority of cases the seizures resolve, do not require long-term anti-seizure medication and are not associated with a negative impact on mental or physical health-related quality of life.

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Predictors of Seizures in Systemic Lupus Erythematosus. John G. Hanly[1], Murray B. Urowitz[2], Li Su[3], Caroline Gordon[4], Sang-Cheol Bae[5], Jorge Sanchez-Guerrero[6], Juanita Romero-Diaz[7], Daniel Wallace[8], Ann E. Clarke[9], Sasha Bernatsky[10], E.M. Ginzler[11], Joan T. Merrill[12], David A. Isenberg[13], Anisur Rahman[13], M. Petri[14], Paul R. Fortin[15], Dafna D. Gladman[16], Ian N. Bruce[17], Kristjan Steinsson[18], M.A. Dooley[19], Munther A. Khamashta[20], Graciela S. Alarcon[21], Barri J. Fessler[21], Rosalind Ramsey-Goldman[22] and Susan Manzi[23]. [1]Dalhousie University and Capital Health, Halifax, NS, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, UK, Cambridge, United Kingdom, [4]University of Birmingham, Birmingham, United Kingdom, [5]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [6]Mount Sinai Hospital/University Health Network, Toronto, ON, [7]INCMNSZ, Mexico city, Mexico, [8]Cedars-Sinai/UCLA, Los Angeles, CA, [9]Research Institute of the McGill Univ. Health, Montreal, QC, [10]McGill UHC/RVH, Montreal, QC, [11]SUNY-Downstate Medical Center, Brooklyn, NY, [12]Oklahoma Medical Research Foundation, Oklahoma City, OK, [13]University College London, London, United Kingdom, [14]Johns Hopkins University School of Medicine, Baltimore, MD, [15]Toronto Western Hospital, Toronto, ON, [16]Toronto Western Hospital, University of Toronto, Toronto, ON, [17]A, Manchester, United Kingdom, [18]Landspital Univ Hospital, Reykjavik, Iceland, [19]University of North Carolina at Chapel Hill, Chapel Hill, NC, [20]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [21]University of Alabama at Birmingham, Birmingham, AL, [22]Northwestern University Feinberg School of Medicine, Chicago, IL, [23]Allegheny Singer Research Institute, Pittsburgh, PA

Background/Purpose: Neuropsychiatric (NP) manifestations of SLE include seizure disorders. Our objective was to determine which clinical and laboratory variables were associated with seizures in a long-term prospective study of SLE patients.

Methods: A multi-center, international, research network enrolled patients within 15 months of fulfilling ACR criteria for SLE and performed annual assessments for up to 10 years. Seizures and other NP manifestations were recorded using the ACR case definitions. Decision rules determined the attribution of seizures to SLE and non-SLE causes. Clinical variables included demographic characteristics, disease duration, educational status, medication utilization, global SLE disease activity (SLEDAI-2K) and cumulative organ damage (SLICC/ACR Damage Index (SDI)) computed with and without NP variables. Plasma/serum samples were available at enrollment for the determination of the following autoantibodies: lupus anticoagulant, anticardiolipin, anti-β_2 glycoprotein-I, anti-ribosomal P and anti-NR2 glutamate receptor antibodies. The association between clinical and serological variables and the risk of the first occurrence of seizures was examined by univariate and multivariate Cox regression analysis.

Results: The 1631 enrolled patients were predominantly female (89.4%) with a mean ($\pm$ SD) age of 35.0 $\pm$ 13.4 years and mean disease duration of 5.6 $\pm$ 4.8 months. The mean followup was 3.5 $\pm$ 2.9 years. Over this period 75/1631 (4.6%) patients had $\geq$ 1 seizure with a total of 91 seizures of which 78/91 (86%) were attributed to SLE. Multivariate analysis indicated a significantly higher risk of seizures with African race/ethnicity (HR (CI): 1.97 (1.07–3.63); p=0.02) and lack of post-secondary education (1.97 (1.21–3.19); p<0.01) after adjustment for age at diagnosis and gender. In order to examine the effect of prior organ damage and medication use, the analysis was restricted to those seizures

occurring after the enrollment visit (n=20). In these patients higher SDI scores calculated without NP variables were associated with an increased risk of subsequent seizures (SDI=1: 3.71(1.38–9.95); SDI=2or3: 1.33(0.27–6.46); SDI≥4: 6.44(0.72–57.2); p=0.04). After adjustment for prior medication, this risk was less significant (p=0.07) demonstrating some confounding between disease severity and medication. Prior use of anti-malarial drugs in the absence of immunosuppressive agents was the most notable treatment effect on seizures (0.07 (0.01–0.66); p=0.02). There was no association with SLEDAI scores or between any of the autoantibodies detected at enrollment with subsequent seizures.

Conclusion: The risk of seizures in SLE patients is higher in patients of African race/ethnicity, lower educational status and organ damage outside of the nervous system. The association with lupus related therapies is complex but anti-malarial drugs may have a protective effect.

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Plasma Levels of Osteopontin Identify Patients At Risk for Organ Damage in Systemic Lupus Erythematosus. Ornella J. Rullo[1], Jennifer MP Woo[1], Alice DC Hoftman[1], Miriam F. Parsa[1], David Elashoff[2], Paul Maranian[3], Jennifer M. Grossman[4], Bevra H. Hahn[4], Maureen A. McMahon[3], Deborah K. McCurdy[1] and Betty P. Tsao[3]. [1]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [2]University of California, Los Angeles, Los Angeles, CA, [3]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [4]UCLA David Geffen School of Medicine, Los Angeles, CA

Background/Purpose: Osteopontin (OPN) is involved in adhesion and migration of monocytes and T cells, and has been implicated in post-inflammatory fibrosis of lung and kidney. We have established that circulating plasma OPN (cOPN) is increased in pediatric SLE patients (pSLE; age of onset <18 years; n = 72), compared with healthy controls (p = 0.0007), and that cOPN is associated with ACR/SLICC damage index (SDI) scores >0 (p = 0.006). This study assessed whether increased cOPN might precede the development of organ damage in pSLE.

Methods: 23 pSLE patients have been followed for 12 months with cOPN measured by ELISA at 6 month intervals, SLEDAI at 3 month intervals and disease flare, and SDI at every 6 months. An adult cohort of 23 SLE patients with plasma, SLEDAI and SDI collected at 6 month intervals was obtained for confirmation. Time-adjusted cumulative disease activity (adjusted-mean SLEDAI, or AMS) was calculated using area under the curve of serial SLEDAI measurements. Statistical analysis was performed using Student's t test, Pearson's correlation, Fisher's exact test, multivariate regression modeling, and receiver operator characteristic (ROC) curves.

Results: By logistic regression, independent risk factors for active SLE (SLEDAI ≥ 4) at study enrollment for both cohorts were: increased cOPN (OR = 1.5, p = 0.002) and shorter disease duration (OR = 0.9, p = 0.05), but not gender or C4. Baseline cOPN of highest versus lowest quartile was associated with increased cumulative disease activity at 6 months (AMS = 9.6 vs. 2.2, p = 0.0003 in pSLE; and 4.6 vs. 2.7, p = 0.01 in adult SLE). This association was strongly supported by the positive correlation between baseline cOPN with 6-month AMS: r = 0.67 (p = 0.0002) in pSLE and r = 0.54 (p = 0.01) in adult SLE. Furthermore, in multivariate linear regression models of the combined cohort, baseline cOPN levels were independent predictors of AMS over the subsequent 6 months (p = 0.01) and 12 months (p = 0.002), but gender, disease duration, C4, lifetime prednisone dose, and non-white race were not. Increased baseline cOPN were associated with pSLE and adult SLE patients exhibiting increased SDI (n = 5 and 4, respectively) over the 12 month period compared to those with a stable SDI (t-test p = 0.003 and 0.1, respectively). Cumulative disease activity was associated with increases in SDI in pSLE (mean AMS of 8.2 in SDI>0 vs. 2.2 in SDI=0; p < 0.0001) and adult SLE (4.8 vs. 2.8; p = 0.03). The area under the ROC curve for cOPN as predictor of AMS (score ≥ 4) at 12 months was 0.828 (Figure 1). By logistic regression, independent risk factors for change in SDI at 12 months were: cOPN (OR 1.3, p = 0.02), AMS (OR 1.05, p = 0.03), and cumulative prednisone exposure (OR 1.15, p = 0.03), but not disease duration and gender.

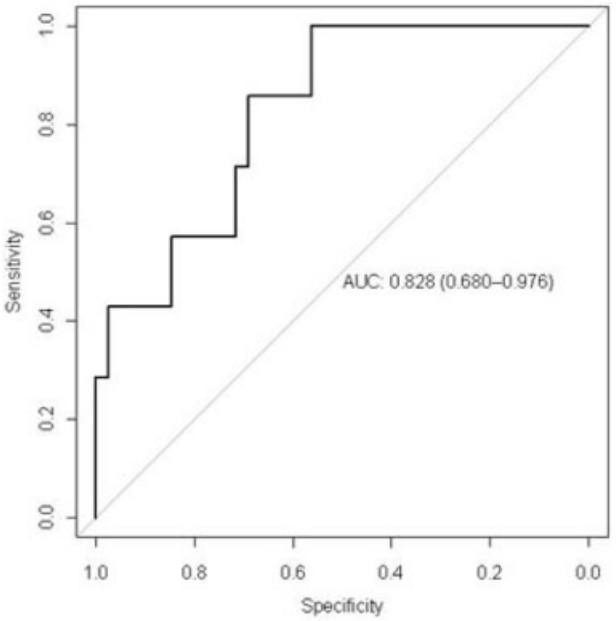

Figure 1. Receiver-operating characteristic (ROC) curve of baseline cOPN sensitivity and specificity to indicate SLE patients (total n = 46) with high cumulative disease activity (AMS ≥ 4; n = 7). A cut-off of cOPN = 19.1 ng/ml (2 standard deviations above the mean for young, healthy controls) has a sensitivity of 86% and specificity of 67% for determining high AMS, with a negative predictive value of 96%.

Conclusion: High circulating OPN levels predicted increased cumulative disease activity and organ damage in both pediatric and adult SLE patients.

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All-Trans Retinoic Acid Sustains the Stability and Function of Natural Regulatory T Cells From Human and Patients with SLE. Qin Lan[1], Julie Wang[1], Hui-Ming Fan[2], David Brand[3], Hejian Zou[4], Zhong-Min Liu[2] and Song G. Zheng[1]. [1]University of Southern California, Los Angeles, CA, [2]Shanghai East Hospital, Tonji University, Shanghai, China, [3]VA Medical Center, Memphis, TN, [4]Huashan Hospital, Shanghai, China

Background/Purpose: CD4+Foxp3+ natural regulatory T cells (nTregs) play a key role in the prevention of autoimmune diseases. However, recent studies have also demonstrated nTregs are instable in the inflammatory milieu and therapeutic effect of nTregs to the established autoimmune diseases was unsatisfactory. We previously reported that nTregs pretreated with all-trans retinoic acid (atRA) become stable and functional in the inflammatory condition in animal model. It is unclear whether atRA treated nTregs from healthy subjects and patients with SLE could sustain the stability and functionality of nTregs.

Methods: $CD4^+CD25^+CD127^-$ nTregs sorted from PBMCs of healthy donors and SLE patients were expanded *in vitro* with anti-CD3/CD28-coated beads (1 bead to 3 cells) and IL-2 (300U/ml) in the presence or absence of IL-1β (10ng/ml) and IL-6 (10ng/ml) for 3 days. atRA (100nM) or DMSO control was added to some wells. In other experiments, nTregs pretreated with atRA or DMSO for five days, then were widely washed and re-stimulated with IL-1 and IL-6 for three days. Intracellular and soluble productions of IL-17 and IFN-γ were measured by FACS and Elisa respectively. IL-1βRI, IL-6R and related signaling molecule expression was analyzed by FACS and western blot. Foxp3 and other regulatory T cells related phenotypes were measured by FACS. Suppressive activities of these cells *in vitro* and *in vivo* were measured by a standard assay and xeno-GVHD humanized animal model as we previously reported.

Results: We found that nTregs mostly lost Foxp3 expression and suppressive activities *in vitro* and *in vivo* when they were stimulated with IL-1β and IL-6. Some of nTregs become Th1, or Th17 or both Th1/Th17 cells. However, addition of atRA to the cultures, or nTregs that had been primed with atRA, enabled the nTregs to be resistant to T effector cell conversion, sustain Foxp3 expression and suppressive activity. Adoptive transfer of these cells to SCID γ common chain KO mice markedly prolonged the survival of these mice received human PBMC compared to mice received PBMC alone and PBMC + control nTregs. Similarly, atRA primed nTregs isolated from active SLE patients also displayed stable phenotypic and functional characteristics with nTregs from healthy controls.

Conclusion: We suggest that addition of atRA to the nTregs expanded *in vitro* may represent a novel strategy to manipulate nTregs for treating SLE and other human autoimmune diseases.

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Monocyte Chemoattractant Protein-1 and Pentraxin in Systemic Lupus Erythematosus. Adnan Kiani[1], Thor Ueland[2], Pal Aukrust[2], Laurence S. Magder[3], Ivana Hollan[4] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]The Oslo University, Oslo, Norway, [3]University of Maryland, Baltimore, MD, [4]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway

Background/Purpose: Pentraxin 3 (PTX3), a member of the same family as C reactive protein, has been shown to be associated with vascular inflammation. Monocyte Chemoattractant Protein-1 (MCP-1) is a chemokine also associated with atherosclerosis. We determined the association of these potential biomarkers with subclinical atherosclerosis measured by coronary artery calcium (CAC), carotid intima-media thickness (IMT) and carotid plaque in SLE at two years followup.

Methods: 148 SLE patients (91% female, 64% Caucasian, 31% African-American, 5% others, mean age 45 yrs) had measurement of subclinical atherosclerosis (coronary artery calcium CAC, carotid intima-media thickness (IMT) and carotid plaque.

Results: Values of MCP-1 ranged from 34–668pg/ml (mean=183, SD=101) and PTX3 from 0.16–25ng/ml (mean=2.2, SD=2.6).

Table 1. Shows the association between MCP-1, PTX3 and coronary calcium at baseline.

	Proportion (%) with detectable coronary calcium at baseline	p-value
MCP-1 level (n=148)	17/31 (35%)	0.41
Low	25/53 (47%)	
Medium	22/47 (47%)	
High		
PTX3 level (n=148)	21/51 (41%)	0.75
Low	22/46 (48%)	
Medium	21/51 (41%)	
High		

The lowest rate of CAC was among those with low levels of MCP-1, but this difference was not statistically significant.

Table 2. Shows the association between MCP-1, PTX3 and the mean carotid IMT.

	Baseline IMT		Change in IMT	
	Mean IMT	P-value	Mean change from baseline to follow-up	P-value
MCP-1 level	0.57	0.70	0.08	0.88
Low	0.59		0.09	
Medium	0.57		0.09	
High				
PTX3 level	0.58	0.38	0.10	0.69
Low	0.58		0.09	
Medium	0.56		0.08	
High				

Table 3. Shows the association between MCP-1, PTX3 and carotid plaque.

	Proportion (%) with carotid plaque at baseline	p-value	Proportion (%) with carotid plaque at follow-up[1]	p-value
MCP-level	7/47 (15%)	0.71	7/37 (19%)	0.72
Low	11/52 (21%)		8/39 (21%)	
Medium	8/47 (17%)		9/34 (26%)	
High				
PTX3 level	13/51 (25%)	0.14[2]	8/34 (24%)	0.93
Low	8/46 (17%)		8/36 (22%)	
Medium	5/49 (10%)		8/40 (20%)	
High				

[1] Among those who were negative for carotid plaque at baseline.
[2] P=0.046 for the test for trend providing modest evidence that the proportion with carotid plaque decreases as PTX levels increases.

Conclusion: MCP-1 and PTX3 have been associated with atherosclerosis in the general population. In general, the PTX3 levels seen in this study were equivalent to those seen in controls in other studies. MCP-1 and PTX3 in SLE were not associated with any marker of subclinical atherosclerosis. In fact, PTX3 even appeared to be protective against carotid plaque.

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Increase In Vitamin D Improves Urine Protein/Creatinine Ratio and Complement In Systemic Lupus Erythematosus. Michelle Petri[1], Kayode J. Bello[1], Hong Fang[1] and Laurence S. Magder[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Vitamin D deficiency has been associated with a number of chronic and autoimmune conditions including systemic lupus erythematosus (SLE). We investigated whether a change in vitamin D levels was associated with disease activity, in vitamin D deficient SLE patients on vitamin D supplements, after a follow-up period of 68 weeks (July 2009 – December 2010).

Methods: 802 SLE patients were followed for 68 weeks. Serum vitamin D levels were measured as part of routine clinical care. SLE patients determined to have low levels of 25 OH Vitamin D (<40 ng/mL) were supplemented with 50,000 units Vitamin D weekly, with Ca/D 200 units twice daily. The physician's global assessment (PGA) and SLEDAI were measured at all visits and routine laboratory tests were also done. Linear regression models were used to estimate the association between change in vitamin D and change in various measures of disease activity. The dependent variables analyzed in the models were change in PGA, SLEDAI, urine protein/creatinine Ratio, C3, C4, anti-dsDNA, and prednisone dose. The independent variable was change in Vitamin D. Generalized estimating equations were used to account for repeated observations from the same patients.

Results: The SLE patients were 91% female, mean age 44.9, 54% Caucasian, 38% African-American, 8% other ethnicity. At baseline, the mean PGA (0–3 VAS) was 0.6 $\pm$ 0.7 and mean SELENA-SLEDAI was 2.2 $\pm$ 2.9. The mean 25 OH Vitamin D at baseline was 29.7 $\pm$ 14.4.

Vitamin D levels were not associated with PGA and SLEDAI. However, there was significant improvement in the urine protein/creatinine ratio, serum C3 and C4.

Table. Effect of change in Vitamin D on disease activity by univariate analysis

	Estimated change in variable per 10 units increase in 25 (OH) Vit D	P-Value
Physician Global Assessment	-0.010 ± 0.007	0.16
SELENA-SLEDAI	-0.017 ± 0.034	0.61
Urine Protein/Creatinine Ratio	-0.020 ± 0.008	0.009
Serum C3 (mg/dL)	0.796 ± 0.266	0.003
Serum C4 (mg/dL)	0.206 ± 0.063	0.001
Anti-dsDNA	-0.075 ± 1.109	0.95
Prednisone (mg)	-0.133 ± 0.070	0.057

Conclusion: In this SLE population, there was no change in global clinical disease activity even with long follow-up. However, we found a statistically significant improvement in urine protein/creatinine ratio and low complement. The analysis suggests that Vitamin D supplementation in SLE patients may have beneficial effects on lupus nephritis that deserve future study.

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The Contribution of Cell Bound Complement Activation Products to the Diagnosis of Systemic Lupus Erythematosus. Kenneth C. Kalunian[1], W. Chatham[2], Elena M. Massarotti[3], Cole Harris[4], R.A. Furie[5], Jill P. Buyon[6], Eliza F. Chakravarty[7], Emily C. Somers[8], Puja Chitkara[9], Rachel L. Gross[10], Kyriakos A. Kirou[11], Joyce Reyes-Thomas[12], Rosalind Ramsey-Goldman[13], Christine Hsieh[14], Chaim Putterman[15], Thierry Dervieux[16] and A. Weinstein[17]. [1]UCSD School of Medicine, La Jolla, CA, [2]UAB Arthritis Clinical Intervention Program, Birmingham, AL, [3]Brigham and Women's Hospital, Boston, MA, [4]Exagen Diagnostics, [5]North Shore-LIJ Health System, Lake Success, NY, [6]NYU School of Medicine, New York, NY, [7]Stanford University, Palo Alto, CA, [8]University of Michigan, Ann Arbor, MI, [9]SDAMC, San Diego, CA, [10]Albert Einstein College of Medicine, New York, NY, [11]Mary Kirkland Center for Lupus Care, Hospital for Special Surgery, New York, NY, [12]Albert Einstein College of Med, Bronx, NY, [13]Northwestern University Feinberg School of Medicine, Chicago, IL, [14]University of Chicago, Chicago, IL, [15]Albert Einstein College of Medicine, Bronx, NY, [16]Exagen Diagnostics, Albuquerque, NM, [17]Washington Hospital Center, Washington, DC

Background/Purpose: Previous studies have established the utility of cell-bound complement activation products (CB-CAPS) as diagnostic biomarkers for systemic lupus erythematosus (SLE). The purpose of this study was to demonstrate the value of CB-CAPs in combination with antinuclear (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies for the diagnosis of SLE.

Methods: Fourteen centers participated in this cross-sectional study that enrolled SLE patients who met the ACR classification criteria, patients with other rheumatic diseases and healthy subjects. Serological markers (ANA, anti-dsDNA and anti-mutated citrullinated vimentin antibodies [anti-MCV]) were measured using enzyme-linked immunosorbent assays. Complement receptor 1 levels on erythrocytes (E-CR1) as well as complement C4d levels on erythrocytes (E-C4d), platelets (PC4d), and B cells (BC4d) were determined by flow cytometry. Statistical analyses utilized multivariate logistic regression, area under receiver operating characteristic (ROC) curves, and calculations of diagnostic sensitivity and specificity.

Results: A total of 210 SLE patients (90.5% females, mean age 42y), 178 patients with other rheumatic diseases (80.3% females, mean age 57y), and 205 healthy individuals (65.8% females, mean age 41y) participated. The group of patients with other rheumatic diseases consisted mainly of rheumatoid arthritis patients (n=120, 67%) and patients with systemic sclerosis (n=21, 12%). Table I indicates the percentage positivity for serological markers together with EC4d, BC4d, PC4d and ECR1 net mean fluorescence intensity (MFI) in each of the three groups.

Table. Diagnostic assay results among SLE, other diseases and healthy subjects. (Net MFI: Net Mean Fluorescence intensity).

	SLE	Other diseases	Normal Healthy
ANA >20 units (normal ≤ 20)	88.5%	41.0%	9.3%
anti-dsDNA > 301 units (normal ≤ 301)	29.5%	3.9%	0.5%
Anti-MCV >70 units (normal ≤ 70)	1.9%	36.0%	0.5%
EC4d Net MFI (CI 95%)	17.6 (15.2–20.0)	6.3 (5.7–6.8)	5.3 (4.6–6.1)
BC4d Net MFI (CI 95%)	110.4 (96.3–124.5)	34.9 (26.1–41.6)	23.5 (21.4–25.6)
PC4d Net MFI (CI 95%)	16.2 (12.0–20.5)	3.6 (3.0–4.2)	2.0 (1.2–2.8)
ECR1 Net MFI (CI 95%)	13.3 (12.4–14.1)	16.1 (15.1–17.1)	20.7 (19.6–21.7)

Anti-dsDNA was an insensitive (29.5%) yet highly specific (>95%) marker for SLE. Among 523 anti-anti-dsDNA negative individuals, a multivariate logistic regression analysis revealed that SLE was associated with ANA positivity ($p<0.001$), anti-MCV negativity ($p<0.001$), and elevation of both EC4d and BC4d ($p<0.001$) (ROC area=0.907). An Index score corresponding to a weighted sum of these four markers was 0.80 (CI95%: 0.45;1.15) in SLE, −2.91 (CI95%: −3.21;−2.61) in other rheumatic diseases, and −2.87 (CI95%: −3.03;−2.71) in healthy subjects. A combination of anti-dsDNA positivity and the Index score (using a cutoff of zero) yielded 81% sensitivity for SLE, and 86.0% specificity in distinguishing SLE from other rheumatic diseases (97.1% specificity in distinguishing SLE from healthy subjects).

Conclusion: This multicenter study demonstrates that an assay panel combining anti-dsDNA, ANA, anti-MCV, EC4d and BC4d is highly sensitive and specific for the diagnosis of SLE.

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Predictors of Organ Damage At the Time of Systemic Lupus Erythematosus Diagnosis, and of Rates of Increase in Damage After Diagnosis. Sneha Purvey[1], Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: The SLICC/ACR Damage Index (SDI) has become the accepted measure of permanent organ damage in SLE. Multiple cross-sectional and several prospective studies have examined predictors or associates of damage. We now report a new statistical analysis of the damage experience of patients in the Hopkins Lupus Cohort.

Methods: 2063 SLE patients (92.4% female, 56.3% Caucasian, 37% African-American, mean age 48.1 years) were included. The SLICC/ACRDamage Index was calculated from diagnosis onwards in a prospective cohort. We explored predictors of damage at the time of diagnosis, and predictors of change in damage score over time after diagnosis using two linear regression models.

Results: The mean SDI score of the cohort at diagnosis was estimated to be 0.82 and the mean rate of progression in SDI score was 0.10 per year. The variables associated with greater rate of progression in organ damage were male gender ($P=0.0015$), African-American ethnicity ($P=0.0001$), lower income ($P=0.0001$), higher disease activity at first cohort visit (by SLEDAI) ($P=0.0001$), higher SDI score at diagnosis ($P=0.0001$), lupus anticoagulant ($P=0.0001$), hypertension ($P=0.0001$), proteinuria ($P=0.0001$), corticosteroid use ($P=0.0001$), and immunosuppressive use ($P=0.0001$). In the multivariate analysis, higher age at diagnosis, low income, lupus anticoagulant, hypertension, proteinuria, corticosteroid use, and immunosuppressant use remained independent predictors. Hydroxychloroquine use was protective ($P=0.0001$).

Conclusion: The most important demographic predictors of progression were low income, older age at diagnosis, male gender, and low education. The serologic test associated with progression was the lupus anticoagulant, not anti-dsDNA or other antiphospholipid antibodies. Patients already damaged at diagnosis had a higher rate of progression. Disease activity and corticosteroid use clearly increased the rate of progression, as expected. Hydroxycholoquine use was protective against damage progression. These data clearly point to the need for effective prophylactic therapy for the lupus anticoagulant and the need for tight control of disease activity, without reliance on corticosteroids.

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Time to Recovery From Proteinuria in Lupus Nephritis Patients Receiving Standard of Care Treatment. Zahi Touma[1], Murray B. Urowitz[1], Dominique Ibanez[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: The level of proteinuria is an important measure to document improvement in lupus nephritis. The recovery time from abnormal levels of proteinuria has not been well described with standard treatment.

To determine the recovery time from proteinuria in lupus nephritis patients receiving standard treatment. To determine whether the initial level of proteinuria predicts the percentage of patients who improve and the time to improvement.

Methods: We studied all lupus nephritis patients registered at the Lupus Clinic; 1970–2011. Proteinuria was defined as ≥0.5g/24 hours as defined by SLEDAI-2K.

Patients with proteinuria and at least one of the urinary sediments (hematuria, pyuria or casts) present for 2 consecutive visits were enrolled. Patients were grouped into: group 1 as 0.5–0.9g/day, group 2 as 1–2g/day and group 3 as ≥2g/day. Recovery from proteinuria was defined as proteinuria <0.5g/24 hours. We determined the time to recovery from proteinuria in all patients and in each of the 3 groups separately with Kaplan-Meier curve.

Results: 244 patients (F 85%) were identified. 58% were Caucasian, 17% Black, 14% Asian, and 11% other. Age at diagnosis of lupus was 28.0±12.4 years, age and duration of lupus at start of study was 34.0±12.2 and 6.0±6.5 years, respectively. The mean length of follow-up period was 2.3±2.7 years. SLEDAI-2K was 16.9±6.8 at the start and 7.9±7.2 at the end of the study.

53% of the patients recovered from proteinuria within 2 years while 74% recovered within 5 years (Table 1 and Figure 1).

Table 1. Time to recovery from proteinuria

Patients	Time	1 Year	2 Year	3 Year	4 Year	5 Year
All (n=244)		30%	53%	63%	70%	74%
Proteinuria 0.5–0.9g/d (n=29)		45%	77%	86%	91%	91%
Proteinuria 1–1.9g/day (n=74)		38%	54%	64%	72%	72%
Proteinuria ≥2g/day (n=111)		16%	42%	50%	60%	67%
Proteinuria≥1 g/day (n=185)		25%	47%	55%	65%	69%

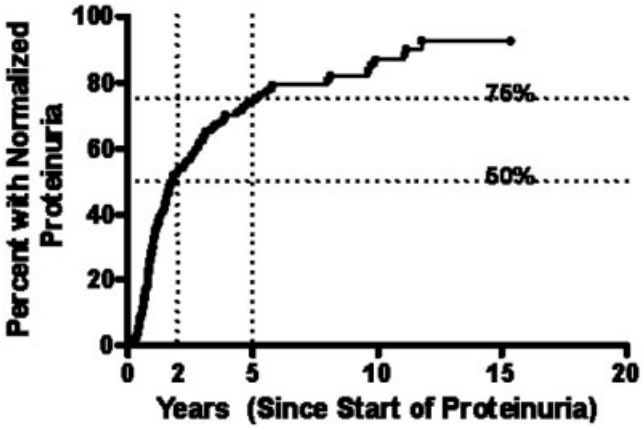

Figure 1. Kaplan-Meier curve for time to recovery from proteinuria in all patients.

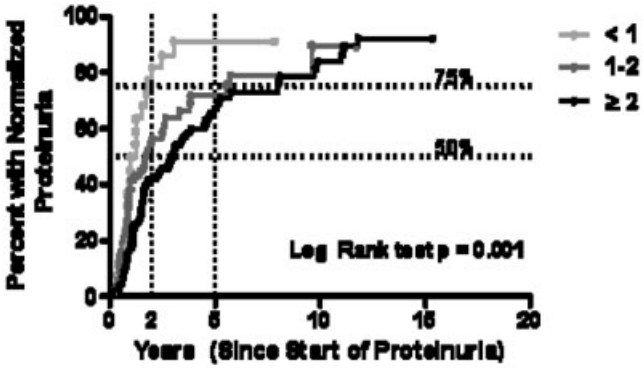

Figure 2. Kaplan-Meier curve for time to recovery from proteinuria in 3 groups.

The level of proteinuria at baseline visit predicted the time to improvement and the percentage of patients who improved. Patients with a higher level of proteinuria at baseline needed a longer time to normalize their proteinuria (Table 1 and Figure 2).

Conclusion: Almost 50% of the lupus nephritis patients normalize their proteinuria by year 2 and others continue to improve over time; 74% recovered by year 5. The level of proteinuria at baseline visit predicts the percent of patients who respond over time and also the time to improvement.

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Proposal for a Reliable and Feasible Algorithm for the Identification of Antinuclear Antibodies. Kaline M.C. Pereira, Alessandra Dellavance and Luis E. C. Andrade. Universidade Federal de São Paulo and Fleury Health and Medicine Laboratories, Sao Paulo, Brazil

Background/Purpose: Antibodies to Sm, RNP, SS-A/Ro, SS-B/La, Scl-70 and Jo-1 (known as extractable nuclear antigens - ENA) are particularly relevant in the diagnosis of systemic autoimmune rheumatic diseases (SARD). The known clinical associations of anti-ENA antibodies were originally defined on the basis of double immunodiffusion (DID) assay, which is cost-effective and extremely specific, but has limited sensitivity, is time-consuming, needs qualified personnel and is not appropriate for automation. Solid phase assays (ELISA and similar), in turn, are highly sensitive and ready for automation, but show variable diagnostic performance and often yield unexpected positive results. The present study analyzed the diagnostic performance of six ELISA kits and DID for determination of anti-ENA antibodies and proposes an algorithm combining ELISA and DID for efficient high throughput.

Methods: 290 serum samples from patients with well characterized autoimmune (ACR criteria) and non-autoimmune rheumatic diseases, chronic viral hepatitis, and healthy controls were tested for anti-ENA antibodies by DID and six ELISA kits according to manufacturer's instructions. Clinical diagnosis was the gold standard for determining the diagnostic performance of each assay. An algorithm combining a screening step by ELISA and a confirmatory step by DID was applied to 16,485 samples for which anti-ENA antibodies had been ordered in a large clinical laboratory.

Results: The sensitivity of ELISA tests for the detection of anti-ENA was higher than DID for all ELISA kits. The sensitivity of anti-Sm for the diagnosis of systemic lupus erythematosus (SLE) was 6.7% in DID and ranged from 18.6% to 44.2% in ELISA kits. The same was observed with anti-Scl-70 regarding the diagnosis of systemic sclerosis (SSc) (13.8% sensitivity by DID; 28.6 to 37.9% by ELISA) and anti-Jo-1 for polymyositis (PM) (5.9% sensitivity by DID; 9.5 to 17.7% by ELISA). In contrast the positive predictive value (PPV) of antibodies to Sm, Scl-70, and Jo-1, was 100% for SLE, SSc and PM, respectively, when assayed by DID, but had an average of 52.2% (ranging from 0 to 100%), when assayed by ELISA. ELISA, but not DID, yielded several anti-ENA positive results in non-SARD patients, such as those with chronic hepatitis, ankylosing spondylitis and osteoarthritis, and even in healthy individuals. No sample with a positive result in DID was negative in ELISA, what allowed the proposal of a two-step algorithm based on ELISA screening and confirmation by DID. With such algorithm only 17% of 16,485 samples were positive by ELISA and required confirmation by DID. In comparison to the standard one-step DID operation, this strategy resulted in a 60% reduction in the operation cost, and a significant reduction in the turn-around time from 96h to 24h in over 80% of the samples.

Conclusion: The proposed algorithm, whose effectiveness was demonstrated in the autoantibody routine of a large clinical laboratory, takes advantage of the best features of each method, ie, speed, automation and higher sensitivity of the EIA and the high specificity and positive predictive value of DID, allowing the report of highly reliable positive results with genuine value to the clinician.

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Longitudinal Assessment of SLE Disease Activity: BILAG-2004, SLEDAI-2000 or Both? Chee-Seng Yee[1], Caroline Gordon[1], David A. Isenberg[2], Bridget Griffiths[3], Lee- Suan Teh[4], Ian N. Bruce[5], Yasmeen Ahmad[6], Anisur Rahman[7], Athiveeraramapandian Prabu[1], Mohammed Akil[8], Neil J. McHugh[9], Christopher Edwards[10], DP. D'Cruz[11], Munther A. Khamashta[12] and Vernon Farewell[13]. [1]University of Birmingham, Birmingham, United Kingdom, [2]University College London, London WC1E 6JF, United Kingdom, [3]Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [4]Royal Blackburn Hospital, Blackburn, United Kingdom, [5]A, Manchester, United Kingdom, [6]The Department of Rheumatology, Betsi Cadwaladr University Health Board (West), Llandudno, LL30 1LB, UK, Wales, United Kingdom, [7]University College London, London, United Kingdom, [8]Sheffield Center Rheumatic Dis, Sheffield South Yorkshire, United Kingdom, [9]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [10]Southhampton General Hospital, Southampton, United Kingdom, [11]St. Thomas' Hospital, London, United Kingdom, [12]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [13]MRC Biostatistics Unit, Cambridge, United Kingdom

Background/Purpose: This analysis was to compare the responsiveness of BILAG-2004 and SLEDAI-2000 indices and to determine if there was any added value in combining the two indices.

Methods: This was an analysis of a longitudinal study of SLE patients where data were collected on BILAG-2004, SLEDAI-2000 and therapy at every visit. The external responsiveness of the indices was assessed by determining the relationship between change in disease activity and change in therapy between two consecutive visits. The indices were compared by assessing the main effects of the indices using logistic regression. The recently developed new methods of analysing BILAG-2004 system scores, BILAG-2004 systems tally (BST) and simplified BST (sBST), were also assessed. Receiver operating characteristics (ROC) curves analyses were used to describe the performance of these indices individually or in various combinations of the two. Sensitivity, specificity, PPV, NPV and AUC were estimated.

Results: There were 1414 observations from 347 patients. Both indices maintained an independent relationship with change in therapy when com-

pared. Tables 1 and 2 summarises the performance of the two indices and various combinations of the two, as dichotomous variables.

Table 1. Sensitivity, specificity, PPV, NPV and AUC of deterioration in disease activity on increase in therapy

Deterioration in score	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	AUC
BILAG-2004 deterioration in score	53.9 (48.6, 59.1)	92.8 (90.7, 94.4)	68.7 (62.4, 74.3)	87.3 (85.0, 89.2)	0.73
SLEDAI-2000 Increase ≥ 1	47.4 (41.6, 53.2)	82.4 (80.0, 84.6)	44.2 (39.0, 49.5)	84.2 (81.6, 86.5)	0.65
SLEDAI-2000 Increase ≥ 3	28.7 (23.7, 34.2)	95.4 (94.0, 96.5)	64.8 (56.8, 72.0)	82.0 (79.5, 84.3)	0.62
BILAG-2004 deterioration in score or SLEDAI-2000 Increase ≥ 1	65.1 (59.4, 70.4)	79.2 (76.5, 81.7)	47.9 (43.2, 52.7)	88.5 (86.1, 90.6)	0.72
BILAG-2004 deterioration in score or SLEDAI-2000 Increase ≥ 3	58.3 (52.7, 63.6)	90.6 (88.4, 92.4)	64.5 (58.8, 69.8)	88.1 (85.8, 90.0)	0.74

Table 2. Sensitivity, specificity, PPV, NPV and AUC of improvement in disease activity on decrease in therapy

Improvement in score	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	AUC
BILAG-2004 improvements (with no deterioration)	54.1 (49.4, 58.7)	65.2 (62.2, 68.0)	48.0 (43.6, 52.4)	70.5 (66.7, 74.0)	0.60
BILAG-2004 improvement to C/D (with no deterioration)	52.8 (48.1, 57.3)	66.1 (63.1, 68.9)	48.0 (43.5, 52.5)	70.2 (66.4, 73.7)	0.59
SLEDAI-2000 Decrease ≥ 1	38.7 (34.7, 42.9)	77.0 (74.2, 79.6)	50.0 (45.1, 54.9)	67.9 (64.4, 71.2)	0.58
SLEDAI-2000 Decrease ≥ 4	18.8 (15.4, 22.7)	90.3 (88.2, 92.1)	53.5 (46.2, 60.6)	65.2 (62.0, 68.3)	0.55
SLEDAI-2000 Decrease ≥ 4 with no BILAG-2004 deterioration (similar to SRI)	1.5 (0.8, 2.9)	98.9 (97.9, 99.4)	44.4 (23.5, 67.6)	62.8 (59.8, 65.7)	0.50
BILAG-2004 improvements with no SLEDAI-2000 increase ≥ 1	48.2 (43.8, 52.6)	70.0 (67.2, 72.7)	48.8 (44.2, 53.5)	69.5 (65.9, 72.8)	0.59
BILAG-2004 improvements (and no deterioration) with no SLEDAI-2000 increase ≥ 1	48.2 (43.8, 52.6)	70.0 (67.2, 72.7)	48.8 (44.2, 53.5)	69.5 (65.9, 72.8)	0.59
BILAG-2004 improvements (and no deterioration) with no SLEDAI-2000 increase ≥ 3	52.9 (48.3, 57.5)	66.3 (63.3, 69.1)	48.3 (43.8, 52.8)	70.3 (66.6, 73.8)	0.60
BILAG-2004 improvement to C/D (and no deterioration) with no SLEDAI-2000 increase ≥ 1	47.1 (42.8, 51.4)	70.8 (68.0, 73.5)	48.9 (44.2, 53.6)	69.2 (65.7, 72.6)	0.59
BILAG-2004 improvement to C/D (and no deterioration) with no SLEDAI-2000 increase ≥ 3	51.6 (47.0, 56.2)	67.2 (64.2, 70.0)	48.3 (43.8, 52.9)	70.0 (66.3, 73.5)	0.59

Both indices had better performance when analysed as non-dichotomous variables (predominantly counts or continuous variables). The AUC from ROC analysis for increase in therapy are: BILAG-2004 system scores 0.75, BST 0.83, sBST 0.81, SLEDAI-2000 variables (change in score and previous visit score) 0.76, combination of BST and SLEDAI-2000 variables 0.84, and combination of sBST and SLEDAI-2000 variables 0.83. The AUC from ROC analysis for decrease in therapy are: BILAG-2004 system scores 0.65, BST 0.66, sBST 0.65, SLEDAI-2000 variables 0.63, combination of BST and SLEDAI-2000 variables 0.67, and combination of sBST and SLEDAI-2000 variables 0.67. There was minimal improvement in the performance when SLEDAI-2000 variables were combined with BST or sBST.

Conclusion: We recommend the use of counts or continuous variables, due to improved efficiency and performance over dichotomous variables, in clinical trials. BST and sBST appear to have better performance than SLEDAI-2000 in assessment of SLE disease activity longitudinally, especially for deterioration in disease activity. There is minimal benefit in combining the indices. These findings should be investigated further with trial data.

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Post Hoc British Isles Lupus Assessment Group Index Mucocutaneous Organ Domain Item Analysis of Systemic Lupus Erythematosus Patients Treated in Phase 3 Belimumab Clinical Trials. Susan Manzi[1], Dafna Gladman[2], Sandra Navarra[3], Jorge Sanchez-Guerrero[4], David D'Cruz[5], William Freimuth[6], Z. John Zhong[6], Greg Keenan[6] and BLISS-52 and BLISS-76 Study Groups[7]. [1]Allegheny Singer Research Institute, Pittsburgh, PA, [2]Toronto Western Hospital, Toronto, ON, [3]University of Santo Tomas Hospital, Manila, Philippines, [4]University Health Network/Mount Sinai Hospital, Toronto, ON, [5]St. Thomas' Hospital, London, United Kingdom, [6]Human Genome Sciences, Inc., Rockville, MD, [7]Multicenter

Background/Purpose: To determine the belimumab treatment effect on the individual mucocutaneous organ system items of the Classic British Isles Lupus Assessment Group Index (BILAG) data from the BLISS studies.

Methods: The BILAG index is made up of 8 organ system domains. The focus of this analysis is on the mucocutaneous organ system, one of the most common organ systems involved in systemic lupus erythematosus (SLE). The data from BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) studies were pooled by treatment cohort (placebo, 1 mg/kg, and 10 mg/kg) to evaluate the effect of belimumab treatment in combination with standard therapy relative to standard therapy alone. The overall mucocutaneous organ system results showed more improvement for patients treated with belimumab and standard therapy compared to those treated with standard therapy alone, so to identify those items contributing to this effect each of the 18 items within the mucocutaneous organ system examination and symptom recording tool were analyzed. The post hoc analysis included only subjects who had an item scored as present at baseline and each item required a minimum of 20 subject observations per arm to be able to make any comparisons. The analysis evaluated each item for subjects scored not-present at week 52 among subjects with the same, worsening, or new/recurrent disease at baseline (dropout=failure). This analysis showed the number of subjects who had mucocutaneous organ system item involvement at baseline that were able to resolve these manifestations by week 52.

Results: The improvement in the overall mucocutaneous organ system domain results were 39.1%, 47.9%, and 47.6%, for placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg respectively. The results from the 7 items that met the threshold criteria are shown in Table 1.

Table 1. Mucocutaneous Item Scored as Improvement (Not Present) at Week 52 Among Patients With Mucocutaneous Disease at Baseline (dropout = failure)

	Placebo	*Belimumab 1 mg/kg*	*Belimumab 10 mg/kg*
BILAG Mucocutaneous Organ System Domain	(39.1%)	(47.9%)	(47.6%)
P-value[1]		<0.05	<0.05
BILAG Mucocutaneous Item			
Maculopapular Eruption-mild	38/118 (32.2%)	76/143 (53.1%)	61/136 (44.9%)
P-value[1]		0.0006	0.0386
Active Discoid Lupus Localized	21/66 (31.8%)	24/55 (43.6%)	30/60 (50.0%)
P-value[1]		0.1805	0.0374
Alopecia - Severe, Active	12/31 (38.7%)	13/27 (48.1%)	21/33 (63.6%)
P-value[1]		0.4690	0.0450
Alopecia - Mild	94/252 (37.3%)	110/256 (43.0%)	119/251 (47.4%)
P-value[1]		0.1925	0.0217
Small Mucosal Ulceration	67/116 (57.8%)	59/92 (64.1%)	67/111 (60.4%)
P-value[1]		0.3496	0.6903
Malar Erythema	103/258 (39.9%)	90/231 (39.0%)	97/225 (43.1%)
P-value[1]		0.8281	0.4780
Periungual Erythema	19/51 (37.3%)	35/52 (67.3%)	18/38 (47.4%)
P-value[1]		0.0021	0.3386

[1]P-values are nominal and were obtained from the likelihood ratio test from the comparison between the placebo group and each of the belimumab groups.

Conclusion: This post hoc analysis provides directional perspective on the effect of belimumab treatment on some of the items in one of the most common organ systems involved in SLE. The favorable responses are consistent with the response in the overall mucocutaneous organ system. A larger study with more subjects with baseline involvement would be needed to more thoroughly elucidate more of the individual mucocutaneous items. Further analyses of the other BILAG organ domains are planned.

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Vascular Cell Adhesion Molecule-1 and Neutrophil Gelatinase-Associated Lipocalin in Systemic Lupus Erythematosus. Adnan Kiani[1], Hong Fang[1], Tianfu Wu[2], Laurence S. Magder[3], Chandra Mohan[4] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, [3]University of Maryland, Baltimore, MD, [4]University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: Vascular cell adhesion molecule-1 (VCAM-1), an adhesion molecule, is involved in the progression of glomerular and tubulointerstitial injury. Neutrophil gelatinase-associated lipocalin (NGAL), a member of the lipocalin superfamily, has been shown to rise in both acute and chronic kidney damage. Both VCAM-1 and NGAL have been found at high levels in the urine of patients with active lupus nephritis. We investigated both as potential biomarkers for lupus nephritis.

Methods: VCAM-1 and NGAL were measured during 1 to 8 clinic visits in 107 SLE patients (91% female, 51% African-American, 36% Caucasian, 4% Asian, 4% Hispanic and 5% others) for a total of 190 visits by ELISA (R&D). Mean age was 41 years. We analyzed the relationship between these potential urine biomarkers and the urine protein/creatinine atio (urine Pr/Cr), the SLICC Renal Activity Score, SLEDAI renal descriptors and other clinical variables.

Results: VCAM-1 levels were strongly associated with the physician's global estimate of disease activity (0.0002), the renal Visual Analog Scale (<0.0001), the urine protein/creatinine ratio (p<0.0001) and SLICC Renal Activity Score (p<0.0001). VCAM-1 levels were also associated with a urine pr/cr ≥0.5

(<0.0001). NGAL was not associated with any measure of disease activity, nor with lupus serologies (Table 1).

Table 1. Mean (SD) Log-transformed and Normalized (by urine creatinine) VCAM-1 and NGAL, by Clinical Variables at Each Visit

Clinical Variables at Each Visit	VCAM-1		NGAL	
	Mean (SD)	P-value*	Mean (SD)	P-value*
Age, years	0.21 (0.40)	0.07	0.17 (0.40)	0.43
21–44 (n=115)	0.11 (0.17)		0.12 (0.17)	
45–70 (n=75)				
Sex	0.17 (0.34)	0.79	0.16 (0.31)	0.31
Female (n=175)	0.14 (0.15)		0.07 (0.15)	
Male (n=15)				
Ethnicity	0.15 (0.20)	0.66	0.11 (0.16)	0.46
Caucasian (n=62)	0.17 (0.39)		0.18 (0.37)	
African American (n=108)	0.23 (0.34)		0.11 (0.13)	
Other (n=20)				
Physician's Global Assessment	0.27 (0.45)	0.0002	0.18 (0.39)	0.23
>=1.5 (n=89)	0.08 (0.11)		0.12 (0.17)	
<1.5 (n=101)				
Renal activity (VAS)	0.31 (0.47)	<0.0001	0.19 (0.42)	0.19
>=1.5 (n=75)	0.08 (0.10)		0.12 (0.16)	
<1.5 (n=115)				
Hematuria	0.20 (0.14)	0.73	0.13 (0.12)	0.80
Present (n=20)	0.17 (0.35)		0.15 (0.31)	
Absent (n=170)				
Proteinuria	0.27 (0.29)	0.15	0.13(0.14)	0.48
Present (n=28)	0.15 (0.33)		0.15 (0.32)	
Absent (n=162)				
Pyuria	0.20 (0.13)	0.76	0.18 (0.14)	0.74
Present (n=8)	0.17 (0.34)		0.15 (0.30)	
Absent (n=182)				
Anti-dsDNA	0.18 (0.20)	0.75	0.13 (0.12)	0.44
Present (n=64)	0.17 (0.38)		0.16 (0.36)	
Absent (n=126)				
Low C3 or C4	0.20 (0.25)	0.46	0.12 (0.13)	0.21
Present (n=84)	0.15 (0.38)		0.17 (0.38)	
Absent (n=105)				
Leukopenia	0.22 (0.22)	0.64	0.18 (0.10)	0.82
Present (n=5)	0.17 (0.33)		0.15 (0.30)	
Absent (n=185)				
Urine Protein/Creatinine Ratio	0.26 (0.24)	<0.0001	0.14 (0.15)	0.34
>=0.5 (n=76)	0.07 (0.10)		0.13 (0.17)	
<0.5 (n=106)				
Renal Failure	0.11 (0.15)	0.57	0.15 (0.17)	0.95
Ever (n=15)	0.18 (0.34)		0.15 (0.31)	
Never (n=175)				
Hydroxychloroquine	0.17 (0.36)	0.97	0.16(0.33)	0.48
Yes (n=146)	0.18 (0.23)		0.11 (0.12)	
No (n=44)				
Diabetes mellitus	0.08 (0.08)	0.30	0.17 (0.22)	0.69
Present (n=20)	0.18 (0.34)		0.15 (0.31)	
Absent (n=170)				
Use of ACE/ARB inhibitor	0.14 (0.15)	0.0488	0.13 (0.16)	0.16
Yes (n=132)	0.24 (0.55)		0.20 (0.48)	
No (n=58)				
SLICC Renal Activity Score	0.26 (0.25)	<0.0001	0.14 (0.14)	0.17
>=4 (n=64)	0.09 (0.13)		0.12 (0.15)	
<4 (n=107)				

* P-values are based on a mixed effects model to account for the fact that some patients contributed multiple observations.

Conclusion: Urine VCAM-1 had a strong association with measures of disease activity, including multiple renal activity descriptors. Use of ACE inhibitors or ARB may reduce it. However, in contrast to previous SLE studies, NGAL failed to show any association with lupus nephritis. Further study of urinary VCAM-1 with long-term renal outcomes is justified.

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Chinese Systemic Lupus Erythematosus Treatment and Research Group Registry: Prevalence and Risk Factors of Pulmonary Arterial Hypertension and Interstitial Lung Disease in Chinese Patients with Systemic Lupus Erythematosus. Qian Wang Jr.[1], Mengtao Li[1], Jiuliang Zhao[1], Xiaofeng Zeng[2] and Chinese SLE Treatment and Research Group (CSTAR)[3]. [1]Peking Union Medical College Hospital, Beijing, China, [2]Peking Union Medical College Hospital, Peking Union Medical College, Beijing, China, [3]Beijing, China

Background/Purpose: Pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are associated with high morbidity and mortality in patients with systemic lupus erythematosus (SLE), while large population-based data are lacking. The Chinese SLE Treatment and Research Group (CSTAR) has developed a network registry for SLE patients. We aimed to investigate the prevalence and risk factors of PAH and ILD in a large cohort of Chinese SLE patients in CSTAR database.

Methods: Detailed records of registered SLE patients were investigated. Data related to PAH and ILD were extracted. Patients were assigned into PAH group when estimated systolic pulmonary artery pressure by echocardiography was over 36mmHg as well as valvular disease, cardiomyopathy and ILD were excluded. Patients were assigned into ILD group when specific features (grand-glass, bibasilar reticulonodular or symmetric fibrotic opacities) were demonstrated on high resolution computerized tomography without alternative etiology. Potential risk factors were assessed by multivariate logistic regression analysis.

Results: Among 1980 patients included for PAH evaluation, 77 (3.9%) met the diagnostic criteria of PAH. The incidences of lupus nephritis, pleuritis, pericarditis, hypocomplementemia, anti-SSA and anti-ribonucleoprotein (RNP) were significantly higher than those without PAH. SLE disease activity index (SLEDAI) was significantly higher in PAH group than controls. Pericarditis, pleuritis, and anti-RNP were independent risk factors for PAH. (Table 1.)

Table 1. Risk factors for SLE associated PAH

	PAH group (n=77)	Non-PAH group (n=1903)	*P*-value (univariate analysis)	Odds radio (95% CI)	*P*-value (multivariate analysis)
Lupus nephritis	42 (56.8%)	726 (39.1%)	0.002		
Pleuritis	27 (36.5%)	146 (7.9%)	<0.001	2.834 (1.459–5.505)	0.002
Pericarditis	30 (40.5%)	157 (8.4%)	<0.001	4.609 (2.432–8.735)	<0.001
Hypocomplementemia	61 (82.4%)	1222 (65.7%)	0.003		
Anti-RNP	12 (15.6%)	160(8.4%)	0.028	2.229 (1.080–4.563)	0.030
Anti-SSA	29 (37.7%)	440(23.1%)	0.003		
SLEDAI	12.78 ± 7.08	9.50 ± 7.12	<0.001		

PAH = pulmonary arterial hypertension; anti-RNP = anti-ribonucleoprotein; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; PGA = physician global assessment.

86 (4.2%) out of 2024 included patients were diagnosed by ILD. ILD group had higher incidences of initial renal and respiratory symptoms, higher incidences of oral ulcer, pleuritis and proteinuria and lower incidence of lupus-specific rash on registration and higher SLEDAI than controls with statistic significance. Oral ulcer, pleuritis, proteinuria were independent risk factors, while lupus-specific rash was protective factor for SLE associated ILD. (Table 2.)

Table 2. Risk factors for SLE associated ILD

	ILD group (n=86)	Non-ILD group (n=1938)	*P*-value (univariate analysis)	Odds radio (95% CI)	*P*-value (multivariate analysis)
Initial renal symptoms	32 (37.2%)	454 (25.8%)	0.024		
Inial respiratory symptoms	9 (10.5%)	78 (4.4%)	0.017		
Oral ulcer	29 (33.7%)	381 (21.6%)	0.011	2.007 (1.257–3.205)	0.004
Pleuritis	15 (17.4%)	116 (6.6%)	0.001	2.511 (1.356–4.651)	0.003
Protenuria	41 (47.7%)	591 (33.6%)	0.010	1.637 (1.041–2.574)	0.033
Lupus rash	21 (24.4%)	668 (38.0%)	0.012	0.529 (0.319–0.879)	0.014
SLEDAI	11.02 ± 6.99	9.32 ± 7.01	0.028		

ILD = interstitial lung disease; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

Conclusion: The prevalence of PAH and ILD was low in Chinese SLE patients from CSTAR database. Higher disease activity, as demonstrated by serositis, proteinura and oral ulcer, may contribute to the development of PAH and ILD in SLE and thus prompt immunosuppressive therapy may be warranted.

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The BILAG-2004 Systems Tally—a Novel Way of Analysing the BILAG-2004 Scores. Chee-Seng Yee[1], Caroline Gordon[1], David A. Isenberg[2], Bridget Griffiths[3], Lee- Suan Teh[4], Ian N. Bruce[5], Yasmeen Ahmad[6], Anisur Rahman[7], Athiveeraramapandian Prabu[1], Mohammed Akil[8], Neil J. McHugh[9], Christopher Edwards[10], DP. D'Cruz[11], Munther A. Khamashta[12] and Vernon Farewell[13]. [1]University of Birmingham, Birmingham, United Kingdom, [2]University College London, London WC1E 6JF, United Kingdom, [3]Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [4]Royal Blackburn Hospital, Blackburn, United Kingdom, [5]A, Manchester, United Kingdom, [6]The Department of Rheumatology, Betsi Cadwaladr University Health Board (West), Llandudno, LL30 1LB, UK, Wales, United Kingdom, [7]University College London, London, United Kingdom, [8]Sheffield Center Rheumatic Dis, Sheffield South Yorkshire, United Kingdom, [9]Royal National Hospital, Bath, United Kingdom, [10]University of Southampton, Southampton, United Kingdom, [11]St. Thomas' Hospital, London, United Kingdom, [12]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [13]MRC Biostatistics Unit, Cambridge, United Kingdom

Background/Purpose: The BILAG-2004 index has 9 separate categorical system scores which pose a challenge to longitudinal analysis of

disease activity in clinical studies. We propose a novel method to record the number of systems in which activity increases, decreases or remains the same between two time points and express this as a tally (BILAG-2004 systems tally, BST). The aim of this exploratory analysis was to assess the appropriateness and performance of this novel method.

Methods: This was an analysis of a multi-centre longitudinal study of SLE patients where data were collected on the BILAG-2004 index and therapy at every visit. External responsiveness with multinomial logistic regression was used to examine the appropriateness of BST with change in therapy as the reference standard. It was anticipated that the tally of worsening or persistently active disease would be significantly associated with treatment increase and the tally of improving activity would be significantly associated with treatment reduction. Results were reported in coefficient and 95%CI. Receiver operating characteristics (ROC) curves analysis was used to assess the performance of this approach.

Results: There were 1414 observations from 347 patients. BST was a data driven simplification of the BILAG-2004 system scores and its derivation was suggested from external responsiveness analysis of the original 9 system scores. It had 6 components (Table) and showed the expected significant association with change in therapy. This was further simplified into 3 components (simplified BST, sBST), by combining persistent significant activity and deteriorations (major and minor) into one category (number of systems with active/worsening disease), and combining the improvements (major and minor) into another category (number of systems with improving disease). Similarly, sBST showed the expected significant association with change in therapy: active/worsening disease component with treatment increase (coefficient 2.08, 95%CI: 1.72–2.43) and improving disease component with treatment reduction (coefficient 0.43, 95%CI: 0.21–0.65). ROC curves analyses demonstrated that both versions had similar good performance characteristics in predicting increase in therapy with area under curve (AUC) for BST 0.83 and sBST 0.81, whereas the AUC for the original BILAG-2004 index systems score was 0.75.

Table. External responsiveness of the BILAG-2004 systems tally with multinomial logistic regression

BILAG-2004 systems tally	Number of Observations	Increase in Therapy Coefficient (95% CI)	Decrease in Therapy Coefficient (95% CI)
Number of systems with major deterioration (change of Grade B/C/D/E to A or Grade D/E to B)	170	2.82 (2.34, 3.30)	−0.22 (−0.79, 0.35)
Number of systems with minor deterioration (change of Grade C to B)	103	1.88 (1.22, 2.55)	
Number of systems with persistent significant activity (no change from Grade A or B)	79	1.64 (1.21, 2.06)	−0.02 (−0.63, 0.59)
Numbers of systems with minor improvement (change of Grade A to B or B to C)	188	−0.28 (−0.73, 0.17)	−0.38 (−0.79, 0.03)
Number of systems with major improvement (change of Grade A to C/D or Grade B to D)	173	0.18 (−0.26, 0.63)	0.33 (0.04, 0.62)
Number of systems with persistent minimal or no activity (change of Grade C/D/E to C/D/E)	1414	0	0

Conclusion: The novel BST and sBST provide an alternative method to analyse BILAG-2004 disease activity longitudinally. Both are clinically relevant and meaningful which may provide a more efficient way of analysing clinical trials results. With better efficiency, fewer patients will be required in trials without jeopardising the power of the study and this will reduce the cost of running such studies.

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Seasonal Variation In the Activity of Systemic Lupus Erythematosus. Alí Duarte-García[1], Hong Fang[1], Chi Hung To[2], Laurence S. Magder[3] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Chelsea Heights, Hong Kong, Hong Kong, [3]University of Maryland, Baltimore, MD

Background/Purpose: To determine if there is any seasonal influence on the activity of systemic lupus erythematosus (SLE) overall and by individual organs.

Methods: The study group comprised 2,102 patients with SLE who were recruited to participate in a prospective longitudinal cohort study. In this cohort, 92.3% of the patients were women, the mean + SD age of the patients was 47.9 + 13.9 years, 56.3% were Caucasian, 37.1% were African-American and 3.1% were Asian. Global disease activity was recorded by the SELENA SLEDAI and the Visual Analog Scales for each organ system on a 0 to 3 scale. Mean disease activity scores were computed for each month of the year, and a p-value assessing the hypothesis of no monthly differences was calculated. For those with evidence of significant monthly differences we identified the months with highest levels of disease activity.

Results: Photosensitive rash was more frequent in spring and summer months ($P<0.0001$). There was significantly more activity of arthritis in spring and summer by both SELENA SLEDAI ($P=0.0057$) and joints Visual Analog Scale ($P=0.0045$). A decrease in renal activity was found in the summer months, compared to the rest of the year ($P=0.0397$). Serositis captured by the Visual Analog Scale had higher activity in August to October ($P=0.0019$). Anti-dsDNA levels were significantly higher during October and November ($P<0.0001$). There was significant variation of anticardiolipin levels and lupus anticoagulant ($P<0.0001$ and $P=0.0003$ respectively). We found a significant variation in activity through the year captured by SELENA SLEDAI ($P=0.0484$).

Table. Seasonal variation in activity of SLE

	P-value for monthly differences in disease activity	Months with highest levels of activity
Photosensitive rash		
SELENA SLEDAI	<.0001	April to September
Visual Analog Scale	0.0015	April to September
Arthritis		
SELENA SLEDAI	0.0057	May to October
Visual Analog Scale	0.0045	May to October
Central nervous system		
SELENA SLEDAI	0.0638	August to November
Serositis		
Visual Analog Scale	0.0340	August to October
Raynaud's	<.0001	November to May
Renal activity	0.0397	November to May
Anti-dsDNA	<.0001	September to November
Low complement	<.0001	March to June
Lupus anticoagulant	0.0003	October, November

Conclusion: In this cohort, joint activity is also increased during the spring and summer, lagging behind skin by one month. However, renal activity is opposite, being lower in the summer months. Anti-dsDNA and renal activity appear to peak in the fall-winter (in concert with a similar peak in infections). These seasonal variations likely reflect environmental factors that influence disease activity, including ultraviolet light and infections.

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Predictors of Corticosteroid Tapering in Systemic Lupus Erythematosus Patients. Zaki Abou Zahr[1], Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Organ damage in SLE patients is highly associated with the use of corticosteroids. Doses of prednisone below 6 mg daily are associated with reduced organ damage. We now report on the largest prospective cohort study of predictors of prednisone tapering in SLE patients who are on just 5 mg daily.

Methods: 866 SLE patients (91% female, 50% Caucasian, 43% African-American, mean age 43 years) who consented for a cohort study from 1987 through 2009 were included. The analysis was based on patient visits when the previously prescribed dose of prednisone was 5 mg/day. We then examined the proportion of times the patient's dose was reduced to below 5 mg/day ("tapering"). Among those patients who tapered and were followed for at least one year thereafter, we examined the proportion whose prednisone dose remained below 5mg/day for at least one year ("Successful Tapering"). Rates of tapering and successful tapering were calculated for patient subsets based on demographic and clinical characteristics.

Results: The analyses showed that Caucasians, younger patients, patients with a higher level of education, lower disease activity, or absence of urine protein were more likely to have a taper. However, successful tapering was not dependent on age, ethnicity, or education. As expected, successful tapering was more frequent in those with lower disease activity. Successful tapering was achieved more often after the year 2000.

Table 1. Proportion of Visits that Resulted in Prednisone Tapering, by Patient Characteristics.

Variable	Group	Proportion (%) Tapering	P-value
Sex	Male	56/683 (8%)	.33
	Female	765/6934 (11%)	
Ethnicity	African-American	365/3942 (9%)	.0014
	Caucasian	407/3319 (12%)	
	Other	49/356 (14%)	
Year	1988–1994	89/978 (9%)	.28
	1995–1999	220/1831 (12%)	
	2000–2004	248/2239 (11%)	
	2005–2009	264/2569 (10%)	
Age Group	18–29	165/2272 (14%)	.0029[1]
	30–44	348/3116 (11%)	
	45–59	235/2552 (9%)	
	60+	55/660 (8%)	
Years of Education	<=12	346/3715 (9%)	.0139
	12–15	217/1814 (12%)	
	16+	253/2042 (12%)	
Physical Global Assessment	<.5	373/2470 (15%)	<.0001[1]
	5–1	371/3549 (10%)	
	>1	77/1598 (5%)	
SELENA SLEDAI	0	328/2478 (13%)	<.0001[1]
	1–2	218/1876 (12%)	
	3+	275/3261 (8%)	
C3	Low	643/5851 (11%)	.087
	Normal	172/1749 (10%)	
C4	Low	670/6266 (11%)	.37
	Normal	145/1330 (11%)	
Anti-dsDNA	Absent	570/5203 (11%)	.83
	Present	245/2380 (10%)	
Urine Protein	Absent	663/5769 (11%)	<.0001[1]
	Present	147/1806 (8%)	

[1] Based on a model that treats the predictors as continuous variables.

Table 2. Proportion of Times Tapering was Successful, by Patient Characteristics.

Variable	Group	Proportion (%) Successful	P-value
Sex	Male	29/47 (62%)	0.36
	Female	348/639 (54%)	
Ethnicity	African-American	162/311 (52%)	0.42
	Caucasian	191/335 (57%)	
	Other	24/40 (609%)	
Year	1988–1994	35/73 (48%)	0.0008
	1995–1999	86/191 (45%)	
	2000–2004	140/220 (64%)	
	2005–2009	116/202 (57%)	
Age Group	18–29	65/122 (53%)	0.641
	30–44	160/286 (56%)	
	45–59	109/207 (53%)	
	60+	28/44 (64%)	
Years of Education	<=12	154/295 (52%)	0.38
	12–15	98/177 (55%)	
	16+	124/211 (59%)	
Physician Global Assessment	<.5	195/303 (64%)	0.00031
	5–1	155/320 (48%)	
	>1	26/61 (43%)	
SELENA SLEDAI	0	159/262 (61%)	0.0121
	1–2	105/190 (55%)	
	3+	112/233 (48%)	
C3	Low	92/182 (51%)	0.2
	Normal	280/494 (57%)	
C4	Low	70/140 (50%)	0.25
	Normal	302/534 (57%)	
Anti-dsDNA	Absent	267/467 (57%)	0.07
	Present	104/219 (50%)	
Urine Protein	Absent	304/549 (55%)	0.501
	Present	64/121 (53%)	

[1] Based on a model that treats the predictors as continuous variables.

Conclusion: Our study suggest that successful tapering of prednisone below 5 mg has increased since the year 2000, which may reflect the greater knowledge of the long term harm of chronic corticosteroid use. Caucasians, younger age, higher level of education, and absence of proteinuria predicted tapering, but not successful tapering. Lower disease activity was the only major clinical variable that significantly predicted successful tapering to a dose of less than 5 mg.

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Results of a French Multicenter Randomized Prospective Study (the PLUS Study) on Reduction of Systemic Lupus Erythematosus Flares Through Adaptation of the Dosage of Hydroxychloroquine to Its Whole-Blood Concentration. Nathalie Costedoat-Chalumeau[1], L. Galicier[1], O. Aumaitre[1], C. Francès[1], Véronique Le Guern[2], F. Lioté[1], A. Smail[1], N. Limal[1], L. Perard[1], H. Desmurs-Clavel[1], B. Asli[1], C. Grandpeix[1], Olivier Pourrat[3], F. Ackermann[1], T. Papo[1], B. Brihaye[1], O. Fain[1], J. Stirnemann[1], Moez Jallouli[1], J. Cohen[1], Marie-Laure Tanguy[1], Js Hulot[1], L. Musset[1], Zahir Amoura[1] and the investigators of the PLUS study[1]. [1]CHU Pitié-Salpêtrière, Paris, France, [2]Cochin Hospital, Paris, France, [3]CHU poitiers, Poitiers, France

Background/Purpose: Blood Hydroxychloroquine concentration [HCQ] varies widely among patients. We have previously demonstrated that low blood HCQ concentration [HCQ] is a marker for and a predictor of systemic lupus erythematosus (SLE) flares [Costedoat-Chalumeau, Arthritis Rheum, 2006]. These findings led us to perform a prospective study to determine the potential benefits of individualizing HCQ dosing schedules aimed at maintaining the [HCQ] · 1000 ng/ml.

Methods: SLE patients treated with HCQ for at least 6 months, with stable disease and a SELENA-SLEDAI ≤12, and without neither known retinopathy nor suspected non adherence, were included in this randomized, double-blind, placebo-controlled, multicenter (n=37) trial and had a centralised [HCQ] dosage. Patients with [HCQ] ranging between 100 and 750 ng/ml were eligible for randomisation between no daily dosage change (group 1) and increased HCQ dosage to obtain a [HCQ] · 1000 ng/ml (group 2). All randomised patients received 4 tablets/day (including HCQ and placebo), and were followed-up at 1, 3, 5, and 7 months.

Results: 573 subjects were included. At day 0, the median SLEDAI was 2.02 ± 2.4. The median [HCQ] was 857 [0–3316] ng/ml. There was an inverse correlation between [HCQ] and disease activity measured by SELENA-SLEDAI (p=0.023).

10 patients were excluded for major non-adherence ([HCQ]<100 ng/ml), 354 had early study discontinuation ([HCQ]>750 ng/ml), and 209 were eligible for randomisation (100< [HCQ] <750 ng/ml). 33 patients were not randomised due to patient refusal (n=11), contra-indications (ophthalmological n=8, and renal insufficiency n=1), SLE flares between inclusion and randomization (n=4), non-adherence recognition (n=4), pregnancy (n=2) or other causes (n=3). 5 dropped out just after randomization. Then, 171 patients were analyzed.

Median [HCQ] significantly increased between inclusion and randomisation (548 [102–749] to 613 [35–2005]; P<0,001), meaning before any therapeutic action. Median [HCQ] were similar between group 1 (n = 84) and group 2 (n = 87) at randomization (623 [193–1610] versus 591 [35–2005]; p = 0.2), and were significantly higher in group 2 at M1 (1250 [9–3253] vs 733 [185–1700]; p<0.001), M3 (1362 [44–4005] vs 661 [239–1797]; p <0.001), M5 (1428 [33–3282] vs 718 [194–2013]; p <0.001) and M7 (1271 [13–3311] vs 665 [80–1578]; p <0.001).

The number of SLE flares was similar in both groups (26.2% vs 27.6%; p = 0.83). Many patients in group 1 had [HCQ] in the therapeutic range and conversely, XXX patients in group 2 had low [HCQ]. When we mixed both groups, the comparison of patients with [HCQ] < 1000 and those with [HCQ] · 1000 during the 7 months of follow-up showed a rate of SLE flares of 18/53 (34%) and 8/36 (22%) respectively (p=0.23).

Conclusion: We confirm that low [HCQ] is associated with higher SLE activity. We failed to demonstrate that the adaptation of HCQ dosage reduces SLE flares in patients with low [HCQ]. However, the knowledge of low [HCQ] and the inclusion in the study improved treatment

adherence, allowing many patients to reach higher [HCQ]. Patients with higher [HCQ] during the study had a trend toward a reduction of SLE flares although not statistically significant.

ClinicalTrials.gov: NCT00413361

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Biologics use in SLE in 23 Centers - Data from the International Registry for Biologics In SLE (IRBIS). R.F. van Vollenhoven[1], Søren Jacobsen[2], Daniel Wallace[3], John G. Hanly[4], Michelle Petri[5], David A. Isenberg[6], Sasha Bernatsky[7], Sang-Cheol Bae[8], Manuel Ramos-Casals[9], Guillermo Ruiz-Irastorza[10], Francisco J. García-Hernández[11], Luis Saez[12], José Luis Callejas[13], Javier Rascón[14], Enrique de Ramón[15], M[a] Mar Ayala-Gutiérrez[15], Maite Camps[15], Melinda Mild[16], Murat Inanç[17], Bahar Artim-Esen[17], Rosalind Ramsey-Goldman[18], Christine A. Peschken[19], Danilo Squatrito[20], László Kovács[21], Andrea Doria[22], Zoltan Szekanecz[23], Elisa Gremese[24] and Emilia I. Sato[25]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]Rigshospitalet - 4242, Copenhagen, Denmark, [3]Cedars-Sinai/UCLA, Los Angeles, CA, [4]Dalhousie University and Capital Health, Halifax, NS, [5]Johns Hopkins Hospital, Baltimore, MD, [6]University College London, London WC1E 6JF, United Kingdom, [7]McGill UHC/RVH, Montreal, QC, [8]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [9]Hospital Clínic, Barcelona, Spain, [10]Hospital de Cruces, Bizkaia, Spain, [11]Hospital Virgen del Rocío, Sevilla, Spain, [12]Hospital Miguel Servet, Zaragoza, Spain, [13]Hospital San Cecilio, Granada, Spain, [14]Hospital Son Dureta, Palma de Mallorca, Spain, [15]Hospital Carlos Haya, Málaga, Spain, [16]Karolinska Institutet, Stockholm, Sweden, [17]Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey, [18]Northwestern University Feinberg School of Medicine, Chicago, IL, [19]Univ of Manitoba, Winnipeg, MB, [20]Careggi Hospital- Florence, Florence, Italy, [21]University of Szeged, Szeged, Hungary, [22]University of Padova, Padova, Italy, [23]University of Debrecen Medical and Health Sciences Center, Debrecen, Hungary, [24]Rheumatology Unit, Catholic University, Roma, Italy, [25]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil

Background/Purpose: Only one biologic agent has been approved for use in SLE, but some are used off-label in various settings. In order to obtain information systematically regarding this, members of the SLICC group initiated the International Registry for Biologics in SLE (IRBIS). The objective of this study was to analyse the use of biologics in SLE, and assess results achieved with the most commonly used off-label biologic, rituximab (RTX).

Methods: IRBIS investigators were asked to provide retrospective data on all patients treated with a biologic for SLE at their center. Standardized case report forms were used to collect demographic, disease-specific and treatment data at the time of biologic initiation and at yearly follow-up. Data from the first 23 reporting centers are presented.

Results: 359 patients were treated off-label with RTX, and additional groups of patients were exposed to belimumab (n=44, trial-extension), epratuzumab (n=21, trial-extension), abatacept (n=4), etanercept (n=3) and adalimumab (n=1). For the RTX treated group, age (mean±SD) was 41.3±13.3 and 91% were female. The majority (76 %) were Caucasian, and smaller proportions were Southeast Asian, Asian/Indian, African-American, Latino, Afro-Caribbean or other (each <10%). Disease duration when RTX was initiated was 9.2±7.8 years. SLEDAI at start was 11.3±7.6, SLICC-damage index 1.4±1.5 and glucocorticoid dosage 17.0±15.2 mg. At baseline, concomitant glucocorticoids were used in 91% of the patients compared to 75% at follow-up. Previous treatments (n=300) include cyclophosphamide (n=144), mycophenolate mofetil (n=117), azathioprine (n=114), methotrexate (n=56) and other immunosuppressives (ISs, n=76). Most patients (78%) had been treated with one or two different ISs prior to RTX, 20% had been treated with three ISs and the remaining 2% with four or five ISs. Two different dosing regimens for RTX were used: 375 mg/m2 × 4 (52%) and 1000 mg × 2 (48%). Concomitant cyclophosphamide was used in 39% of patients. The major organ manifestations leading to RTX treatment were lupus nephritis (LN, 48%), hematological (21%), musculoskeletal (9%), skin disease (9%), CNS (4%) and other (9%). Disease-control (n=84%) and disease-control plus steroid-sparing (16%) were given as reasons for choosing a biologic. At 1-year follow-up (n=123, 1 year ±3.5 months) both SLEDAI and GC dose had decreased to 4.2±3.5 (n=106) and 7.9±7.0 mg (n=89), respectively (paired samples, p<0.0001 for both comparisons). Exclusion of patients started on additional immunosuppressives (n=24) did not change SLEDAI or GC dose significantly. SLEDAI at baseline was higher in LN than in non-LN patients but similar at follow-up. Overall, 1000 mg × 2 was used more often but both dosing regimens appeared equally effective in LN.

Conclusion: Rituximab was the off-label biologic used most commonly in this multi-center international lupus cohort and was used for LN as well as for a range of other SLE manifestations. At one-year follow-up both lupus activity and concomitant glucocorticoid dosage had decreased even when no other immunosuppressive treatments had been introduced. The two RTX dosing regimes appeared equally effective for LN treatment.

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Differences in Autoantibody Profiles, Disease Activity (SLEDAI) and Damage (SDI) Scores Between Childhood-Onset Lupus and Adult-Onset Lupus: A Meta-Analysis. Brieanna Livingston[1], Ashley Bonner[2] and Janet E. Pope[3]. [1]University of Western Ontario, London, ON, [2]McMaster University, Hamilton, ON, [3]St. Joseph Health Care London, London, ON

Background/Purpose: In systemic lupus erythematosus (SLE), autoantibodies and other lab tests are used for diagnosis, correlate with clinical manifestations, and provide important prognostic information. Age at disease onset impacts the autoantibody profile, lab test results, disease activity and damage in SLE. Two commonly used indices, SLEDAI and SDI, measure disease activity and damage respectively. Our objectives were to conduct a systemic literature review and meta-analysis of all studies that directly compared childhood-onset SLE (cSLE) to adult-onset SLE (aSLE) to: (1) determine which autoantibodies and lab tests vary with age at disease onset, and (2) quantify the differences in SLEDAI and SDI scores between cSLE and aSLE.

Methods: A literature search of the MEDLINE/PubMed, EMBASE, CINAHL, and SCOPUS databases until January 2011 was conducted to identify relevant articles. Study quality was assessed using the STROBE checklist. Two independent reviewers determined eligibility criteria. Study sample characteristics, autoantibody profiles, lab test results and SLEDAI and SDI scores were extracted from each study. Pooled odds ratios and mean differences were calculated assuming random effects, and between-study heterogeneity was estimated using the I^2 statistic.

Results: Of the 484 studies identified, 19 were eligible. The total number of SLE patients was 7519. Mean trial quality was 18/32, ranging from 8 to 29. Several statistically significant differences were found: anti-dsDNA antibody (OR 1.97; P=0.001) and IgG/IgM antiocardiolipin antibody (OR 1.66; P=0.002) were more common in cSLE. Rheumatoid factor was less frequent in cSLE (OR 0.53; P=0.01). Children had higher disease activity {SLEDAI} (OR 4.73; P=0.0004), but damage {SDI} was not different between cSLE and aSLE (OR 0.50; 95% CI −0.13 to 1.14).

Conclusion: The results of this meta-analysis suggest that cSLE may have different autoantibody profiles, laboratory tests, and more disease activity than aSLE.

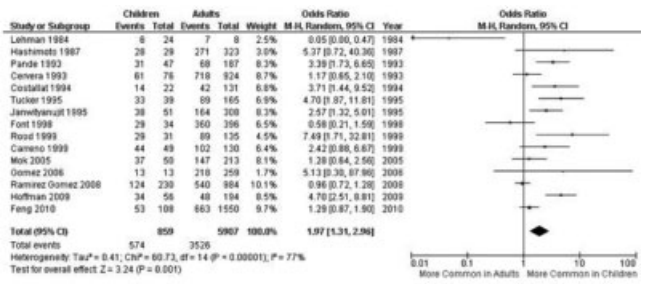

Figure 1. Anti-dsDNA antibody in Adult vs. Child Onset SLE

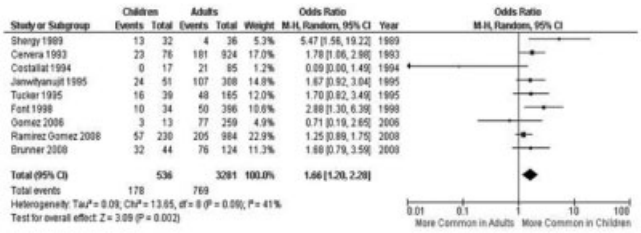

Figure 2. Fig 2 Antiocardiolipin antibody in Adult vs. Child Onset SLE

Figure 3. Fig 3 Rheumatoid factor in Adult vs. Child Onset SLE

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Why Do Lupus Patients Go to the Emergency Department in the United States? Marina Scolnik[1], Ajitha Mannalithara[2], Enrique R. Soriano[1] and Gurkirpal Singh[2]. [1]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Stanford University School of Medicine, Palo Alto, CA

Background/Purpose: Patients with systemic lupus erythematosus (SLE) are often seen in the Emergency Department (ED) and hospitalized for complications of their disease. While there are several studies on reasons for hospitalization in SLE patients, there is little information on epidemiology, causes or economics of ED visits in these patients.

Methods: The US Nationwide Emergency Department Sample (NEDS) is a stratified random sample of all ED visits in community hospitals in the US. It contains almost 28 million records annually for ED visits from over 980 hospitals that can be weighted to produce reliable national estimates of the 125 million annual ED visits. We recognized SLE ED visits using International Classification of Diseases (ICD-9) code 710.0. CDC's Clinical classification software (CCS) diagnoses of consultation and hospitalization were identified. Comorbidities were analized through ICD-9 codes. SLE ED visits were compared with ED visits from other causes in the general population.

Results: A total of 81,378 ED visits in SLE patients were identified in 2008. 91.2% of lupus ED visits were in women, with a mean age 40.2 years (Table 1). SLE patients had more hypertension and chronic renal failure (23.2% vs 15.7% and 9.1 % vs 2.1%) and smoked more (11.1% vs 8.8%). They were hospitalized significantly more often than general ED population (34.2% vs 16.8%) and males were hospitalized more often than females with lupus (42.99% vs 33.83%, $p<0.0001$). However, mortality at ED or after hospitalization was lower than the general population (0.25% vs 0.61%). Main CCS diagnoses at ED visit are shown in table 2, stratified by age and gender. 25.1% of SLE patients (n= 20391) went to ED because of the disease itself and this was also the principal cause of hospitalization (36.6% of hospitalizations). Non specific chest pain, headache, infections (pneumonia, skin or urinary) and musculoskeletal complains followed as other diagnoses. Cardiovascular events were only seen in older lupus patients. Sickle cell anemia appeared in association with lupus in male children. Costs per ED visit were higher for SLE patients (1864.9 vs 1674.8 US dollars) (table 1).

Table 1. Patients' characteristics

	Lupus patients	Non lupus patients
Total number of visits, n	81378	124863886
Mean age, years	40.2 (CI 95% 39.8–40.7)	38.3 (CI 95% 37.8–38.9)
Female, n (%)	74244 (91.2%)	68554644 (54.9%)
Comorbidities		
Hypertension, n (%)	18863 (23.18%) (CI 95% 21.02–25.33)	19640951 (15.73%) (CI 95% 14.91–16.55)
Diabetes, n (%)	6193 (7.61%) (CI 95% 6.76–8.46)	10917997 (8.74%) (CI 95% 8.29–9.19)
Dyslipidemia, n (%)	4616 (5.67%) (CI 95% 5.05–6.3)	7738400 (6.2%) (CI 95% 5.81–6.58)
Smoking, n (%)	8997 (11.06%) (CI 95% 9.91–12.2)	11025395 (8.83%) (CI 95% 8.08–9.58)
COPD, n (%)	2077 (2.55%) (CI 95% 2.19–2.91)	4667468 (3.74%) (CI 95% 3.54–3.94)
CRF, n (%)	7434 (9.14%) (CI 95% 8.03–10.24)	2554895 (2.05%) (CI 95% 1.92–2.17)
Hospitalization, n (%)	28182 (34.22%)	21016909 (16.83%)
Female, n (% of total F)	25115 (33.83%F)	11211011 (16.35% F)
Male, n (% of total M)	3067 (42.99%M)	9805898 (17,42% M)
Mortality	202 (0.25%)	756851 (0.61%)
Female, n (% of total F)	189 (0.26% F)	358629 (0.53% F)
Male, n (% of total M)	13 (0.18% M)	398064 (0.71%M)
Total ED visits cost, US dollars	117529976 (CI 95% 105494592–129565359)	171554271390 (CI 95% 159802715755–183305827025)
Average cost per ED visit, US dollars	1864.9 (CI 95% 1760.3–1969.5)	1674.82 (CI 95% 1608.1 – 1741.6)
Payment source Medicare, n (%)	17906 (22.05%)	25463357 (20.49%)
Medicaid, n (%)	21553 (26.54%)	27680568 (22.28%)
Private, n (%)	28741 (35.39%)	43317150 (34.86%)
Others, n (%)	13012 (16.02%)	27799407 (22.37%)

Table 2. Primary 10 lupus patients' CCS diagnosis of ED consultation

	FEMALES (n=74244)				MALES (n=7134)			
	0–17 y (n=2233)	18–40 y (n=35673)	41–64 y (n=32002)	+65 y (n=4336)	0–17 y (n=465)	18–40 y (n=3184)	41–64 y (n=2949)	+65 y (n=536)
1	**Lupus** (43.6%)	**Lupus** (29.7%)	**Lupus** (19.1%)	**Lupus** (16.4%)	**Lupus** (47.9%)	**Lupus** (34.1%)	**Lupus** (19.5%)	**Lupus** (20.3%)
2	**Non Specific Chest Pain** (4.7%)	**Headache** (4.6%)	**Non Specific Chest Pain** (6.8%)	**Non Specific Chest Pain** (4.5%)	**Epilepsy, convulsions** (4.1%)	**Non Specific Chest Pain** (4.5%)	**Non Specific Chest Pain** (5.5%)	**Pneumonia** (7.3%)
3	**Headache** (4.2%)	**Non Specific Chest Pain** (4.3%)	**Headache** (4.4%)	**Pneumonia** (3.3%)	**Fever of unknown origin** (4.1%)	**Non traumatic joint disorders** (3.6%)	**Skin and subcutaneous tissue infection** (3.2%)	**Non Specific Chest Pain** (5.8%)
4	**Other connective tissue diseases** (2.02%)	**Abdominal pain** (4.1%)	**Other connective tissue diseases** (3.5%)	**COPD and bronchiectasis** (2.8%)	**Skin and subcutaneous tissue infection** (3.4%)	**Other connective tissue diseases** (2.98%)	**Other connective tissue diseases** (2.95%)	**Back problems** (4.5%)
5	**Superficial injury, contusion** (1.8%)	**Other connective tissue diseases** (3.3%)	**Abdominal pain** (3.02%)	**Urinary tract infection** (2.5%)	**Sickle cell anemia** (3.4%)	**Back problems** (2.9%)	**Abdominal pain** (2.9%)	**Other connective tissue diseases** (3.7%)
6	**Urinary tract infection** (1.8%)	**Urinary tract infection** (2.8%)	**Back problem** (2.8%)	**Cardiac dysrhythmias** (2.3%)	**Other skin disorders** (3.01%)	**Abdominal pain** (2.7%)	**Pneumonia** (2.7%)	**Cardiac dysrhythmias** (3.2%)
7	**Skin and subcutaneous tissue infection** (1.7%)	**Non traumatic joint disorders** (2.5%)	**Skin and subcutaneous tissue infection** (2.8%)	**Superficial injury, contusion** (2.3%)	**Pneumonia** (2.8%)	**Skin and subcutaneous tissue infection** (2.3%)	**Non traumatic joint disorders** (2.6%)	**Coronary atherosclerosis and other heart disease** (2.8%)
8	**Essential hypertension** (1.7%)	**Skin and subcutaneous tissue infection** (2.4%)	**Non traumatic joint disorders** (2.3%)	**Fracture of upper limb** (2.03%)	**Abdominal pain** (2.4%)	**Pneumonia** (2.1%)	**Other nervous system disorders** (2.6%)	**Acute myocardial infarction** (2.4%)
9	**Other lower respiratory diseases** (1.7%)	**Sprains and strains** (1.9%)	**Sprains and strains** (2.2%)	**Back problems** (1.9%)	**Sprains and strains** (2.4%)	**Epilepsy, convulsion** (2.1%)	**Back problems** (2.3%)	**Transient cerebral ischemia** (2.2%)
10	**Fever of unknown origin** (1.2%)	**Back problems** (1.9%)	**Urinary tract infection** (2.1%)	**Abdominal pain** (1.9%)	—(less than 10 patients)	**Residual codes, unclassified** (2.1%)	**Mood disorders** (2.2%)	**Abdominal pain** (2.2%)

Conclusion: ED visits in SLE patients resulted in hospitalization in a high proportion. SLE itself was the main diagnosis at ED visits and admissions.

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Achieving Consensus on Quality Indicators for Pediatric Systemic Lupus Erythematosus. Joshua D. Pendl[1], Matthew C. Hollander[2], Shannen L. Nelson[1], Xolti Morgan[3], Nicolino Ruperto[4], Michael W. Beresford[5], Marisa Klein-Gitelman[6], Marilynn G. Punaro[7], Anne M. Stevens[2], Tadej Avcin[8], Graciela Espada[9], Tsz-Leung Lee[10], Yu-Lung Lau[10], Jennifer L. Huggins[1], Esi Morgan Dewitt[1] and Hermine Brunner[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Seattle Children's Hospital, Seattle, WA, [3]University of Cincinnati, Cincinnati, OH, [4]PRINTO-IRCCS, Genova, Italy, [5]Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [6]Children's Memorial Hospital, Chicago, IL, [7]Texas Scottish Rite Hospital, Dallas, TX, [8]University Children's Hospital Ljubljana, Ljubljana, Slovenia, [9]Childrens Hosp Ricardo Gutierrez, Buenos Aires, Argentina, [10]The University of Hong Kong, Hong Kong, Hong Kong

Background/Purpose: Quality Indicators (QI) are retrospectively measurable elements of practice performance for which there is evidence or consensus that can be used to assess the quality of care provided. Consensus-derived QI for pediatric systemic lupus erythematosus (pSLE) could serve as international benchmarks to assess the quality of patient care. By regularly monitoring adherence to QI in a clinical setting, targeted interventions may be implemented to improve the quality of medical care that patients with pSLE receive.

Methods: Based on the medical literature, a Delphi survey was created and distributed to the physician membership of PRES, PANLAR, CARRA and the ACR via e-mail. Consensus was considered 80% agreement or higher.

Results: There was consensus (97%) among the 297 respondents that simply applying QI developed by the ACR and EULAR for adults with SLE was insufficient and that distinct QI for pSLE were needed. Respondents concurred that 5 of the 20 ACR and 5 of the 23 EULAR adult QI are also suitable for pSLE in their current form (Table 1). An additional 14 ACR and 17 EULAR adult QI might be useful for pSLE after modifications. Consensus (>80% agreement) or near consensus (>70% agreement) was reached among respondents that all categories of adult QI are still useful for children with the exceptions of "Pregnancy" and "Reproductive Health," which achieved lower levels of agreement (Table 2).

Table 1. Consensus on ACR and EULAR adult SLE Quality Indicators that are useful to pSLE in their current form

Quality Indicator	ACR/EULAR
IF a patient has a flare after having achieved remission of kidney disease, THEN diligent follow-up of renal disease is needed.	EULAR
IF a patient with pSLE is on immunosuppressive therapy, THEN an inactivated influenza vaccination should be administered annually, unless contraindicated.	ACR
IF a patient with pSLE is pregnant, THEN anti-SSA, anti-SSB, and anti-phospholipid antibodies should be documented in the medical record.	ACR
IF a patient is prescribed a new medication for pSLE (e.g., NSAIDs, DMARDs, or glucocorticoids), THEN a discussion with the patient about the risks versus benefits of the chosen therapy should be documented.	ACR
IF a patient has pSLE, THEN lifestyle modifications (smoking cessation, weight control, exercise) are likely to be beneficial for patient outcomes and should be encouraged.	EULAR
IF a patient with pSLE has proliferative lupus nephritis, THEN glucocorticoids in combination with immunosuppressive agents (cyclophosphamide, mycophenolate mofetil) should be used for treatment.	EULAR
IF a patient has newly diagnosed lupus nephritis, THEN renal biopsy, urine sediment analysis, proteinuria, and kidney function should all be assessed.	EULAR
IF a patient has pSLE, THEN education about sun avoidance should be documented at least once in the medical record (e.g., wearing protective clothing, applying sunscreens whenever outdoors, and avoiding sunbathing).	ACR
IF a patient is diagnosed with proliferative pSLE nephritis (WHO or ISN/RPS class III or IV), THEN therapy with corticosteroids combined with another immunosuppressant agent should be provided and documented within 1 month of this diagnosis, unless contraindicated.	ACR
IF a patient with pSLE has major neuropsychiatric manifestations (optic neuritis, acute confusional state/coma, cranial or peripheral neuropathy, psychosis, and transverse myelitis/myelopathy), THEN immunosuppressive therapy should be considered.	EULAR

Table 2. Percentage of expert respondents (n=297) who agreed that the following categories of QI for adults with SLE were still applicable to children with pSLE

Quality Indicator Domain	% Agreement
Renal Disease/Lupus Nephritis	88%
Growth and Development	88%
Quality of Life Including School Function	88%
Drug Monitoring	87%
Diagnosis	86%
Control of Overall Disease Activity	85%
Neuropsychiatric Lupus	82%
Anti-Phospholipid Antibodies	81%
General Preventative Strategies	77%
Avoidance of Overall Disease Damage	76%
Contraception/Reproductive Counseling	76%
Osteoporosis	73%
Cardiovascular Disease	72%
Reproductive Health	65%
Pregnancy	41%

Conclusion: There is great demand among pediatric rheumatologists to develop QI for pSLE. Initial agreement has been reached about the types and domains of QI for pSLE, but additional discussion and consensus formation under consideration of the medical evidence is needed to finalize a set of QI for pSLE. This distinct set of QI could be used to define and improve standard of care treatment for children and adolescents with pSLE.

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Effect of Hydroxychloroquine and Statin Therapy on Pro-Inflammatory Cytokines and Disease Activity in a Lupus Cohort. Rohan Willis[1], Praveen Jajoria[1], Brock E. Harper[1], Emilio B. Gonzalez[1], M. Petri[2], Ehtisham Akhter[2], Hong Fang[2] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Multiple cytokines play a role in the immune dysregulation seen in SLE and the local inflammatory responses that ultimately lead to tissue injury. IL6, TNFα, sCD40L, IFNα and IFN inducible cytokines such as MCP1 and IP10 are correlated with disease activity as measured by the SLEDAI, SLAM-R, ESR and anti-dsDNA antibody titres. Elevated VEGF and IL1β levels have been demonstrated in patients (pts) with antiphospholipid syndrome.

Both hydroxychloroquine (HCQ) and statins have proven clinical efficacy in treating SLE patients. There is however limited data highlighting the effect HCQ and statins have on biomarkers of disease activity in SLE. As such we sought to determine the proinflammatory biomarkers elevated in these pts and the effect that HCQ or statin therapy has on their levels and on disease activity.

Methods: Pts were selected from a longitudinal cohort and were included if placed on HCQ or statin therapy during follow-up and had stored serum or plasma samples taken before and after commencement of therapy at least 6 months apart. Serum samples from age and sex matched controls with no evidence of inflammatory disease were used for comparison. Concurrent use of prednisone greater than 10mg/day or change in use or dose of other immunosuppressive agents precluded inclusion. Samples from 30 controls and 61 paired samples from SLE pts were analyzed. IFNα2, IL1β, IL6, IL8, IP10, MCP1, TNFα, VEGF and sCD40L levels were determined by the MILLIPLEXMAP human cytokine/chemokine panel assay (Millipore, Billerica, MA). This assay utilizes flow cytometry, microspheres, lasers, digital signal processing and traditional chemistry in a multiplex format. Disease activity was assessed using SLEDAI scores.

Results: VEGF, IP10, sCD40L, IFNα2 and TNFα were significantly elevated (p= <0.0001 – 0.0478) in SLE pts compared to controls while MCP1 and IL8 were significantly lower. No difference was seen with IL6 and IL1β. Both statin and HCQ therapy resulted in decreased SLEDAI scores although these were not statistically significant (p= 0.07 and 0.30 respectively). Elevated VEGF, IP10, sCD40L, IFNα2 or TNFα at baseline were reduced by 16.3 – 41.0% as a result of statin therapy and by 15.4 – 44.9% as a result of HCQ therapy. When considering all subjects in the SLE cohort, the changes in biomarkers were not statistically significant.

Conclusion: This study shows that proinflammatory cytokines in SLE patients are significantly elevated when compared to controls. Although the treatment with HCQ or with statins produced a decrease in the levels of cytokines in the subjects where those markers were elevated at baseline, no differences were seen in SLEDAI scores after the treatment with HCQ or statins, possibly due to the limited sample size (due to a strict inclusion/exclusion criteria) and/or the relatively low disease activity scores of the subjects in this lupus cohort.

Cytokines	Ctrls/ Median	SLE/ Median	p-value	# elevated baseline samples HCQ therapy(%)	% reduction in elevated samples after HCQ/mean	# elevated baseline samples statin therapy(%)	% reduction in elevated samples after statin/mean
IL8	27.4	3.44	<0.0001	3/33 (9.1)	93.9 ± 5.2	4/28 (14.2)	72.5 ± 48.4
IL6	0	0	0.2971	10/33 (30.3)	39.6 ± 50.1	5/28 (17.9)	58.82 ± 53.73
VEGF	88.3	146.27	0.0178	20/33 (60.6)	18.6 ± 29.7	15/28 (53.6)	16.3 ± 21.6
MCP1	884.28	230.08	<0.0001	2/33 (6.0)	39.2 ± 55.5	0	0
IP10	96.22	335.51	<0.0001	30/33 (90.9)	20.7 ± 27.1	25/28 (89.3)	14.7 ± 24.0
sCD40L	16.39	719.95	<0.0001	31/33 (93.9)	44.9 ± 41.6	28/28 (100)	35.1 ± 43.1
INFα2	0	9.22	0.0478	14/33 (42.4)	15.4 ± 32.5	11/28 (39.3)	39.6±48.5
IL1β	0	0	0.5442	8/33 (24.2)	60.5 ± 44.7	8/28 (28.6)	65.6 ± 46.9
TNFα	0	6.93	<0.0001	20/33 (60.6)	32.9 ± 34.2	18/28 (64.3)	41.0 ± 39.6

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Increased Disease Activity Measure in Systemic Lupus Erythematosus Is Adversely Associated with Pregnancy and Pregnancy Outcomes. Lisa A. Davis[1], Vincent M. Davis[1], Laura Trupin[2], Jinoos Yazdany[3], Edward Yelin[4] and Joann Zell[5]. [1]Univ of Colorado School of Med, Aurora, CO, [2]UC San Francisco, San Francisco, CA, [3]University of California San Francisco, San Francisco, CA, [4]UCSF, San Francisco, CA, [5]National Jewish Health, Denver, CO

Background/Purpose: Systemic lupus erythematosus (SLE) is a disease that primarily affects women of childbearing age. Issues surrounding pregnancy are therefore of vital importance in caring for these patients. We studied women with a diagnosis of SLE in a prospective manner to examine factors associated with pregnancy and risk factors for poor pregnancy outcomes.

Methods: The Lupus Outcomes Study (LOS) is a large, yearly telephone questionnaire administered to a community-based sample of patients who meet the American College of Rheumatology criteria for SLE. We used data from 2003 through 2009 to identify pregnancies among women <50 years of age who did not report a hysterectomy, resulting in 2065 person-years of observation among 595 women. Each observation was treated as an independent observation in the analyses. We examined the following primary outcome variables: individual instances of pregnancies, live births, and miscarriages/stillbirths. Predictor variables from the year that the pregnancies occurred were used and included: demographics [age, poverty, smoking]; disease activity/severity measures [Systemic Lupus Activity Questionnaire (SLAQ) score, anti-phospholipid antibodies (aPL), and the presence of renal disease]; and use of medications [hydroxychloroquine (HCQ), etc.]. Logistic regression was used to examine factors associated with pregnancy (N=526 observations). Among those who reported a pregnancy, we used logistic regression to investigate factors associated with live births (N=51) and with miscarriage/stillbirth (N=50).

Results: We prospectively captured 55 individual pregnancies, which resulted in 8 induced abortions, 3 tubal pregnancies, 33 live births and 11 miscarriage/ stillbirths. Pregnancy was inversely associated with age, SLAQ score, and use of HCQ, and pregnancy was associated with being married (see Table). Only SLAQ score was inversely associated with incident live births. SLAQ score was also associated with miscarriage/stillbirth.

Table. Predictors of pregnancy, live births, and miscarriage/stillbirth in the LOS cohort

	Predictors of pregnancy amongst reproductive-aged women, N=526				Predictors of live births amongst women with incident pregnancies, N=51				Predictors of miscarriage/stillbirth amongst women with incident pregnancies, N=50			
Variable	OR	95% CI		p-value	OR	95% CI		p-value	OR	95% CI		p-value
Age	0.85	0.80	0.90	**0.00**	0.98	0.88	1.08	0.64	0.95	0.82	1.11	0.53
Married	3.00	1.59	5.67	**0.00**								
Positive aPL lab	1.51	0.76	3.00	0.24								
History of renal disease	0.56	0.20	1.56	0.27								
Smoking status	1.77	0.49	6.48	0.39								
SLAQ score	0.94	0.88	0.99	**0.03**	0.93	0.86	1.01	**0.08**	1.18	1.03	1.35	**0.02**
Below poverty line	1.02	0.35	2.98	0.97								
Use of HCQ in the last year	0.47	0.23	0.95	**0.04**								

*Key: aPL = anti-phospholipid antibody laboratory, at least one lab value positive; SLAQ = Systemic Lupus Activity Questionnaire measure; HCQ = hydroxychloroquine

Conclusion: Live birth rates among individual instances of pregnancy observed in the LOS (70.2%) were similar to other studies (71–92%). The inverse association of SLAQ scores with pregnancy and pregnancy outcomes may be due to a biological etiology, or it may reflect that those who have active disease avoid pregnancy and/or choose to end pregnancies. Surprisingly, we found that the use of hydroxychloroquine was inversely associated with the total number of individual pregnancies. The reasons for this association are unclear, but one hypothesis that requires exploration is that this finding represents the practice of rheumatologists and/or patients avoiding HCQ when conception is planned.

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Urinary λ Free Light Chain Concentration Is Associated with Disease Activity and Response to Treatment in Proliferative Lupus Nephritis. Masanori Hanaoka, Takahisa Gono, Yasushi Kawaguchi, Hirotaka Kaneko, Yumi Koseki, Yasuhiro Katsumata, Kae Takagi, Hisae Ichida, Sayumi Baba, Yuko Okamoto, Yuko Ota, Sayuri Kataoka and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: The aim of the present study was to evaluate whether serum or urinary free light chain (FLC) is a useful biomarker for proliferative lupus nephritis (PLN) in patients with systemic lupus erythematosus (SLE).

Methods: Forty-three patients in whom renal biopsy was performed at our institute from 2004 to 2006 were consecutively enrolled in the present study. All patients were diagnosed with SLE based on the classification criteria of the American College of Rheumatology and suffered from some active SLE-associated symptoms. The evaluation of clinical parameters included renal markers (24 h-creatinine clearance [CCr] and quantification of proteinuria), immunological markers (IgG, complement component 3 and anti-dsDNA antibody), SLE disease activity index (SLEDAI) (with and without renal score), and serum and urinary FLC. Enrolled patients were divided into the following two subsets: a PLN group (WHO class III and IV) and non-PLN group (WHO class I, II and V). Clinical characteristics were compared between the two subsets. In addition, serum and urinary FLC were measured before and after immunosuppressive treatment in a separate group of 8 patients who were prospectively enrolled from 2009 to 2010 in the present study.

Results: The frequencies of WHO class I, class II, class III, class IV and class V lupus nephritis were 9 (21%), 7 (16%), 8 (19%), 10 (23%) and 9 (21%), respectively, in 43 retrospectively enrolled patients. Hypoalbuminemia ($P = 0.0077$), hypocomplementemia ($P = 0.0083$), elevation of anti-dsDNA antibody ($P < 0.0001$), SLEDAI ($P = 0.0013$) and SLEDAI without renal score ($P = 0.0013$) were significantly higher in the PLN group compared to the non-PLN group. Both serum and urinary FLC were not significantly correlated with SLEDAI in either subset, although significant correlation was found between anti-dsDNA antibody titer and SLEDAI. Urinary λ-FLC concentrations were significantly ($P = 0.008$) higher in the PLN group than the non-PLN group, although serum κ-FLC and λ-FLC, serum IgG and urinary κ-FLC concentrations did not differ significantly between the two subsets. Although complement, anti-dsDNA antibody and CCr were not associated with the quantification of proteinuria in both the subsets, urinary λ-FLC was significantly correlated ($R^2 = 0.35$. $P = 0.0096$) with the quantification of proteinuria in the PLN group. In contrast, there was no significant association between the quantification of proteinuria and urinary λ-FLC in the non-PLN group. To evaluate the association between the response to immunosuppressive treatment and serum or urinary FLC concentrations, a separate group of 8 patients (1 patient with WHO class II, 6 patients with WHO class III and 1 patient with WHO class V) were prospectively enrolled in the present study. The decline index in urinary λ-FLC was more significant after treatment, compared with those in anti-dsDNA antibody ($P = 0.0156$) and serum λ-FLC ($P = 0.0039$). Moreover, urinary λ-FLC was not detected after treatment in any patient.

Conclusion: Urinary λ-FLC, but not serum FLC, not only is associated with disease activity but is also useful for the evaluation of response to treatment for PLN.

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Lymphoproliferative Disorders in Patients with Systemic Lupus Erythematosus At the University of Michigan. Jason S. Knight and Emily C. Somers. University of Michigan, Ann Arbor, MI

Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at higher risk of lymphoproliferative disorders (LD), in particular non-Hodgkin's lymphoma, than the general population. Most reports focus on LD diagnosed *after* SLE, and exclude concurrent and preceding LD. We performed this study to better characterize the timing, histopathology, and therapy of LD in patients with SLE.

Methods: We identified 13,296 cases of LD in the University of Michigan (UM) tumor registry (diagnosed 1980–2008) and 10,539 potential SLE patients from the UM billing/lab databases (data available 1988-present) with either an ICD-9-CM code for SLE or anti-double-stranded DNA (dsDNA) autoantibodies. Forty-five patients were confirmed to have *both* LD by histopathology and SLE by ACR (≥4) criteria.

Results: Of the 45 patients diagnosed with both LD and SLE, 38 (84%) were female and 38 (84%) white; 7 (16%) had co-existing Sjogren's syndrome and 2 (4%) end-stage renal disease (with kidney transplant) secondary to SLE. Autoantibodies were positive as follows: anti-dsDNA in 24/41 (59%), anti-Smith 2/35 (6%), and anti-phospholipid 21/40 (53%). Of these 45 patients, 29 (64%) were diagnosed with LD ≥1 year *after* diagnosis with SLE and 16 (36%) LD *before (or concurrent with)* SLE. Of the 29 patients with LD after SLE, 27 (93%) had hematologic manifestations of SLE and 7 (24%) lupus nephritis; prior to diagnosis with LD, 15 (52%) were treated with any immunosuppression and 8 (28%) cyclophosphamide specifically. Among these 29 patients, malignant diagnoses were as follows: 13 (45%) with diffuse large B-cell lymphoma (DLBCL), 6 (21%) indolent lymphoma, 4 (14%) leukemia or a related disorder, 3 (10%) Hodgkin's disease, and 1 (3%) each Burkitt's lymphoma, T-cell lymphoma, and multiple myeloma. Of the 13 patients with DLBCL, 10 (77%) presented with stage IV disease and 11 (85%) extranodal disease. Eleven DLBCL patients were treated with CHOP or R-CHOP; 6 (55%) died (all within 14 months), 1 (9%) had active disease at last follow-up (11 months), and 4 (36%) achieved durable remission. Of the 16 patients diagnosed with LD *before* (or *concurrent with)* SLE, 9 (56%) were diagnosed with LD >2 years before SLE; these patients tended to have early-stage LD and were in remission prior to SLE diagnosis. Seven patients (44%) were diagnosed with LD and SLE concurrently; no particular type of LD predominated. All 7 patients had serology consistent with SLE, and 6 (86%) were treated with hydroxychloroquine; only 1 (14%) required immunosuppression (methotrexate) targeted at SLE. In terms of their LD, 6/7 (86%) achieved remission or stable disease.

Conclusion: Almost two-thirds of patients were diagnosed with LD ≥1 year *after* diagnosis with SLE; DLBCL was the most common type of LD in this group, and the DLBCL patients usually presented with advanced-stage disease. One-third of patients were diagnosed with LD *before (or concurrent with)* SLE; these patients tended to have early-stage LD and an excellent response to therapy. In the patients diagnosed concurrently, the SLE symptoms may have brought their LD to clinical attention early, possibly resulting in better outcomes.

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Disease Activity and Quality of Life in Refractory Cutaneous Lupus Erythematosus Patients Initiated on Immunosuppressive Therapy. Aileen Y. Chang[1], Elizabeth Ghazi[2], Joyce Okawa[1] and Victoria P. Werth[1]. [1]Perelman School of Medicine at the University of Pennsylvania and Philadelphia V.A. Medical Center, Philadelphia, PA, [2]UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ

Background/Purpose: Immunosuppressives are used as systemic therapy for antimalarial-refractory cutaneous lupus erythematosus (CLE), despite limited evidence for their use. This study aimed to demonstrate response to immunosuppressives in a cohort of CLE patients using a disease-specific activity measure and a skin-specific quality of life measure.

Methods: This longitudinal cohort study prospectively evaluated response to antimetabolite immunosuppressives in CLE patients using a validated disease outcome measure, the CLE Disease Area and Severity Index (CLASI), and a validated skin-specific quality of life measure, the Skindex-29. Patients eligible for the study were those who presented from January 2007 to July 2010 at a university's cutaneous autoimmune disease clinic, met criteria for having CLE, and had at least 2 visits with CLASI activity scores measured. Of these eligible patients, those initiated on an antimetabolite (methotrexate, mycophenolate, or azathioprine) with pre- and post-treatment (Tx) CLASI scores were identified. Patients who had previously failed an antimetabolite or non-antimalarial systemic therapy were excluded. Response was defined as either a 4-point or 20% decrease in CLASI score and was determined by comparing the score at the pre-Tx visit with the first post-Tx visit. Skindex-29 subscale scores (Emotions, Functioning, Symptoms) were also assessed.

Results: 128 eligible patients were identified. Of 5 patients initiated on methotrexate, 4 (80%) demonstrated response at their first post-Tx visit with a decrease in median (interquartile range [IQR]) CLASI activity score from 24 (14–33) to 12 (5–17) ($p=0.07$), over a median (IQR) Tx duration of 3.7 (2.1–3.9) months. Of 4 patients initiated on mycophenolate, 2 (50%) demonstrated response at their first post-Tx visit with a decrease in median (IQR) CLASI score from 4.5 (2.0–7.0) to 1.0 (0.0–2.0) ($p=0.18$), over a median (IQR) Tx duration of 4.0 (2.7–4.5) months. Of 4 patients initiated on azathioprine, 0 demonstrated response at their first post-Tx visit, over a median (IQR) Tx duration of 3.4 (2.6–5.6) months. For 6 responders out of 13 patients initiated on an antimetabolite, the mean (95% confidence interval [CI]) Emotions score decreased from 64.2 (32.5, 95.8) to 39.1 (18.5, 59.8) ($p=0.04$), Functioning score decreased from 53.0 (26.8, 79.2) to 28.1 (10.6, 45.6) ($p=0.07$), and Symptoms score decreased from 55.4 (31.1, 79.6) to 36.3 (20.3, 52.3) ($p=0.07$). For the 7 non-responders, the mean (95% CI) Emotions, Functioning, and Symptoms score were unchanged: 65.4 (41.1, 89.3) to 64.6 (43.5, 85.8) ($p=0.89$); 39.0 (19.7, 58.2) to 41.1 (19.7, 62.4) ($p=0.69$); 57.7 (42.0, 73.3) to 56.1 (27.6, 84,6) ($p=0.81$), respectively. Differences in pre-Tx CLASI score, age, sex, smoking status, and Tx duration between responders and non-responders were not statistically significant.

Conclusion: Half of CLE patients with antimalarial-refractory disease responded to the addition of an antimetabolite. Response in disease activity was accompanied by an improvement in skin-specific quality of life measures. Larger studies of systemic therapies that focus on both disease and quality of life outcomes in CLE are needed.

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Higher Education Level is Associated with Decreased Compliance in an Urban Multi-Ethnic Lupus Cohort. Rachel L. Gross, Dawn M. Wahezi, Chaim Putterman and Irene Blanco. Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: Systemic Lupus Erythematosus (SLE) disproportionably affects non-whites. Worse disease outcomes in minorities may not be adequately explained by genetic or environmental factors, and compliance with treatment may account for such disparities. Our aim was to determine rates and predictors of medication compliance in our cohort of SLE patients.

Methods: Patients were recruited from the Einstein Lupus Cohort, a multi-ethnic cohort followed at the university hospitals of Albert Einstein College of Medicine. Medication compliance was assessed using a validated 19-item questionnaire, the Compliance Questionnaire Rheumatology (CQR). Patients with medication compliance of ≥80% as predicted by the weighted questionnaire responses were categorized as compliant. Participants also completed self-reported measures of compliance and the Beliefs about Medicine Questionnaire (BMQ) to determine factors influencing compliance. Demographic and clinical characteristics of compliant and non-compliant participants underwent bivariate analysis using the Chi square test for categorical variables and the Mann-Whitney U test for continuous variables. Variables of interest from the bivariate analysis and those with a p-value< 0.20 were further evaluated using a multivariate logistic regression model.

Results: 89 patients (42 Hispanic, 43 Blacks, 4 other races; 92% female) who met 4/11 ACR criteria for SLE were included in the analysis with a median age of 37y (IQR 25–48) and disease duration of 8y (IQR 3–15). 48% (43/89) of patients (52% (22/42) Hispanics, 44% (19/43) Blacks) were compliant with medications as measured by the CQR. Several factors were associated with non-compliance on bivariate analysis. Non-compliant patients had more concerns regarding their medications as measured by a higher mean BMQ-concerns score (14.5± 4.1 v. 12.3± 3.8; $p=0.02$). Other factors that trended towards predicting decreased compliance include: education level above high school (OR=0.43, $p=0.06$), yearly income < $15,000 (OR=0.48, $p=0.13$), and the use of mycophenylate mofetil (OR=0.31, $p=0.12$). Age, race, gender, disease duration, SLEDAI score, self-reported compliance, insurance status, total number of medications and steroid dose were not associated with compliance.

In our multivariate analysis, patients with more than a high school education were 78% less likely to be compliant (OR=0.22, $p=0.01$). Patients with higher BMQ concerns score also trended towards being less compliant (OR=0.86, $p=0.058$). In addition, non-English speakers (OR 12.4, $p=0.04$) and those with an annual income > $15,000 (OR=3.5, $p = 0.045$) were more likely to be compliant.

Conclusion: Non-compliance with medication was common in this urban minority lupus cohort, and is associated with higher education levels, low income, primary language, and increased medication concerns. This surprising finding of lower compliance among more educated SLE patients may be due to more independent decision making, or less trust of physicians in this population. These factors suggest areas of intervention that may improve compliance.

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Distribution of Urine Protein/Creatinine Ratio by Urinalysis Protein Dipstick Score In Systemic Lupus Erythematosus. Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Lupus nephritis occurs in over 50% of patients with systemic lupus erythematosus (SLE). As a traditional rapid screening test, the urinalysis protein by dipstick is limited in that it does not quantify proteinuria. In this study, we investigated the distribution of urine protein/creatinine ratios with a simultaneous urine dipstick score in SLE patients.

Methods: 1277 SLE patients (92% female, 55% Caucasian, 36% African-American, 8% other ethnicities, mean age at entry 41.6 years) were included. Univariate analysis was used to determine the distribution of urine protein/creatinine ratio by urine dipstick score. The urine dipstick protein scores were 0 (n=6980), trace (n=2381), 1+ (n=1887), 2+ (n=808), 3+ (n=437), and 4+ (n=36).

Results:

Table 1. Distribution of Urine Protein/Creatinine Ratio by Urinalysis Protein Dipstick

	Urine Pr/Cr Ratio				
Urine Dipstick Score	5% Quantile	25% Quantile	50% Quantile (Median)	75% Quantile	95% Quantile
0	0	0	0.06	0.10	0.21
trace	0	0.06	0.09	0.14	0.34
1	0	0.05	0.15	0.34	0.90
2	0.09	0.45	0.89	1.59	3.43
3	0.50	1.28	2.44	4.17	10.14
4	0.17	1.34	2.10	4.00	8.18

Table 2. Proportion of Urine Protein/Creatinine greater than 0.5 by Urinalysis Protein Dipstick

Urine Dipstick Score	Proportion (%) with Urine Pr/Cr Ratio ≥ 0.5
0	0.7%
Trace	2.4%
1	15.5%
2	71.9%
3	95.2%
4	94.4%

Conclusion: This study demonstrated the wide distribution of urine protein/creatinine ratio for any urine dipstick of 1+ or greater. Given the current standard that 0.500 grams of urine protein would trigger a renal biopsy for lupus nephritis, the data show that a urinalysis dipstick of 1+ could include that range. Thus, any urinalysis dipstick protein of 1+ or higher should lead to quantification with a spot urine protein/creatinine ratio or to a 24 hour urine protein/creatinine ratio.

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Avoidance of Major Bleeding Complications Post Renal Biopsy In Lupus Nephritis Patients with Co-Existing Antiphospholipid Syndrome. Natasha Jordan, Ahlem I. Chaib, Shirish Sangle, Fahim Tungekar, Munther Khamastha, Tarun Sabharwal, Ian Abbs and David P. D'Cruz. Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom

Background/Purpose: Renal biopsy remains the gold standard investigation of lupus nephritis. However it is not without potentially significant complications. In a previous retrospective review of 148 renal biopsies in 137 lupus nephritis patients at our centre over an 8 year period (1999–2007), 8.1% experienced minor bleeding and 7.4% developed major haemorrhagic complications. Major bleeding complications were significantly more common in those with coexisting Antiphospholipid syndrome and/or antiphospholipid antibodies (aPL).

Modification of our renal biopsy protocol was undertaken implementing strict management of anticoagulation, hypertensive control and biopsy tract plugging with gelofoam. The purpose of this study was to examine the current rate of bleeding complications post renal biopsy.

Methods: A prospective review of post biopsy bleeding complications following 48 renal biopsies (2007–2010) was undertaken. All biopsies were performed on native kidneys by an experienced radiologist. Prior to biopsy, coagulation parameters were checked and anaemia and thrombocytopenia were corrected. Following biopsy, patients were maintained under observation for 24 hours, monitoring for hypotension, tachycardia, gross haematuria, and abdominal pain. Anticoagulation was strictly monitored with switching from warfarin to heparin one week prior to the procedure until two weeks post biopsy. Renal biopsy was only performed when patients were normotensive (<140/90).

Major complications were defined as those requiring post procedural intervention such as blood transfusion, surgical revision of hematoma, embolisation, nephrectomy or death. Minor complications including subcapsular hematomas, perinephric hematomas or hematuria requiring close observation only.

Results: 47 lupus nephritis patients underwent renal biopsy (48 biopsies) since implementation of the new renal biopsy protocol. Minor bleeding occurred in 6 patients (12.5%) with 3 events in SLE patients, 3 in SLE/aPL and none in SLE/APS. There were no major bleeding complications.

Table 1. Patient demographics pre and post modification of renal biopsy protocol.

	Renal biopsies 1999–March 2007	Renal biopsies April 2007–present
	148 biopsies (137 patients)	48 biopsies (47 patients)
Gender	119 females 18 males	40 females 8 males
Mean age	35.31 years	35.04 years
SLE	49 (33.1%)	25 (52.1%)
SLE/APS	35 (23.7%)	8 (16.7%)
SLE/APL	64 (43.2%)	15 (31.2%)
Hypertension	67 (45.3%)	15 (31.25%)
Mean serum creatinine (mg/dl):		
Bleeding group	188.91	130.33
Non-bleeding group	117.79	93.92
Warfarin therapy	35 (23.6%)	6 (12.5%)
Aspirin therapy	33 (22.3%)	17 (35.4%)

Table 2. Rate of bleeding complications pre and post modification of renal biopsy protocol.

	Bleeding complications prior to protocol modification			
	No bleeding complication	Overall Bleeding Rate	% Minor Bleed	% Major Bleed
SLE	46	3 (6.1%)	2 (4.1%)	1 (2.0%)
SLE/APL	53	11 (17.2%)	6 (9.4%)	5 (7.8%)
SLE/APS	26	9 (25.7%)	4 (11.4%)	5 (14.3%)
Total	125	23 (15.5%)	12 (8.1%)	11 (7.4%)

	Bleeding complications post protocol modification			
	No bleeding complication	Overall Bleeding Rate	% Minor Bleed	% Major Bleed
SLE	22	3 (12%)	3 (12%)	0%
SLE/APL	12	3 (20%)	3 (20%)	0%
SLE/APS	8	0%	0%	0%
Total	42	6 (12.5%)	6 (12.5%)	0%

Conclusion: A significant finding in this study is the higher rate of serious bleeding events in SLE/aPL patients and SLE/APS compared to the SLE patient group post renal biopsy. Identification of these at risk patients prior to renal biopsy and close clinical monitoring minimizing procedure associated morbidity and mortality.

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Serum Macrophage Migration Inhibitory Factor In Systemic Lupus Erythematosus with Long-Term Remission and Its Relationship to Chronic Glucocorticoid Exposure. Yoko Wada[1], Hiroe Sato[1], Daisuke Kobayashi[1], Takeshi Nakatsue[1], Shuichi Murakami[1], Takeshi Kuroda[1], Masaaki Nakano[2] and Ichiei Narita[1]. [1]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Niigata University School of Medicine, Niigata, Japan

Background/Purpose: Macrophage migration inhibitory factor (MIF) is a unique pro-inflammatory cytokine that can be induced by glucocorticoid, and acts as a physiological counter-regulator of the anti-inflammatory effects of glucocorticoid. It is thought to be involved in the development and progression of atherosclerosis, and also plays a potent role in the onset of autoimmune disorders including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Although a positive correlation between the serum level of MIF and disease activity has already been reported in patients with SLE, the role of this inflammatory cytokine in SLE patients who achieve long-term remission remains unknown in terms of chronic glucocorticoid exposure and the association of chronic complications such as dyslipidemia and accelerated atherosclerosis. We examined the contribution of MIF in SLE patients with long-term remission, especially in terms of inflammatory status, serum lipid profile, atherosclerosis, and chronic glucocorticoid exposure.

Methods: Sixty-five patients who had achieved long-term remission of SLE were recruited. All of them fulfilled the American College of Rheumatology criteria for the classification of SLE, their daily dosage of prednisolone had been fixed at less than 15 mg for more than 12 months, and there had been no signs of SLE flare-up for more than 3 years. Written informed consent was obtained from each participant. Serum levels of MIF, acute inflammatory reactants including highly sensitive C-reactive protein (HS-CRP) and serum amyloid-A protein (SAA), serum lipid profiles, common carotid artery intima-media thickness (CCA-IMT), and cumulative and current dosage of prednisolone were examined in each subject, and analyzed using Pearson's correlation coefficient and stepwise multiple regression. Sex- and age-matched normal subjects (n=20) and patients just diagnosed as having SLE before glucocorticoid administration (n=20) were also recruited as controls.

Results: The level of serum MIF was 9.86 ± 8.44 ng/ml (mean ± SD) in the SLE patients with long-term remission, being significantly higher than that in normal subjects (4.07 ± 1.87 ng/ml, p=0.0025), and lower than that in SLE patients with active disease (16.7 ± 16.6ng/ml, p=0.02). In the SLE patients with long-term remission, the serum MIF level was correlated with serum triglyceride (correlation coefficient = 0.267, p=0.03) and the cumulative dosage of prednisolone (correlation coefficient = −0.268, p=0.03), but had no association with CCA-IMT, other serum lipids, or acute inflammatory reactants. Stepwise multiple regression analysis also selected serum triglyceride as a positive independent variable (rho = 0.295) and the cumulative dosage of prednisolone as a negative independent variable (rho = −0.281).

Conclusion: The serum MIF level does not reflect acute inflammatory status or current atherosclerosis, but is affected by the level of serum triglyceride and the cumulative, but not current, dosage of prednisolone in SLE patients with long-term remission.

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Association of Lupus Nephritis Class with Poor Longterm Outcomes. Michelle Petri and Hong Fang. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Lupus nephritis is a common manifestation of SLE. We investigated the association between renal biopsies by the International Society of Nephrology (ISN) class in SLE and poor renal outcome, defined not just by renal failure, but also by nephrotic syndrome and thrombosis.

Methods: 503 SLE patients (39.4% Caucasian, 49.5% African-American, 89.5% female, mean age of diagnosis 28.8 ± 12.0) with biopsy-proven lupus nephritis (LN) were selected as the study population in a longitudinal cohort study. The renal biopsies were classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) as class I (minimal mesangial lupus nephritis), class II (mesangial proliferative lupus nephritis), class III (focal lupus nephritis), class IV (diffuse lupus nephritis), class V (membranous lupus nephritis) and class VI (advanced sclerosing lupus nephritis).

Results:

Table. Association of outcome with renal biopsy

Class of renal biopsy	All	Caucasian	African-American	% Nephrotic Syndrome	% Renal failure	% Any thrombosis
II	44 (8.8%)	17 (38.6%)	27 (61.4%)	20 (45.5%)	9 (20.5%)	14 (31.8%)
III	80 (15.9%)	35 (43.8%)	35 (43.8%)	32 (40.5%)	10 (12.5%)	19 (23.8%)
IV	166 (33.0%)	69 (41.6%)	68 (41.0%)	99 (60.4%)	58 (34.9%)	53 (31.9%)
V	97 (19.3%)	35 (36.1%)	57 (58.8%)	56 (58.3%)	8 (8.3%)	31 (32.0%)
II,III	8 (2.0%)	3 (37.5%)	4 (50.0%)	5 (62.5%)	2 (25.0%)	5 (62.5%)
II,III,V	4 (0.8%)	2 (50.0%)	2 (50.0%)	4 (100%)	1 (25.0%)	1 (25.0%)
II,IV	10 (2.0%)	5 (50.0%)	5 (50.0%)	4 (40.0%)	2 (20.0%)	4 (40.0%)
II,IV,V	4 (0.8%)	1 (25.0%)	2 (50.0%)	4 (100%)	0 (0%)	1 (25.0%)
II,V	12 (2.4%)	7 (58.3%)	5 (41.7%)	9 (75.0%)	2 (16.7%)	6 (50.0%)
III,V	42 (8.4%)	13 (31.0%)	23 (54.8%)	24 (58.5%)	6 (14.3%)	11 (26.2%)
IV,V	36 (7.2%)	11 (30.6%)	21 (58.3%)	25 (73.5%)	17 (47.2%)	13 (36.1%)

503 patients were classified into 11 different groups based on the findings of the first biopsy. African-Americans were more likely to have Class V (P=0.044).

Conclusion: In lupus nephritis, the most common class was class IV. Class IV either as the sole class or as a mixed class had the greatest risk of renal failure. However, nephrotic syndrome and thrombosis were common regardless of ISN class. Reliance on renal failure as the only outcome would miss these other important longterm consequences of lupus nephritis.

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Ultrasound Assessment of Erosive hand arthritis In Systemic Lupus Erythematosus. Elisabeth M.A Ball[1], Madeleine Rooney[2] and Aubrey Bell[3]. [1]Musgrave Park Hospital/Queens' University, Belfast, United Kingdom, [2]Arthritis Research Group, Queen's University, Belfast, United Kingdom, [3]Musgrave Park Hospital/Queens' University, Belfast, Ireland

Background/Purpose: Joint involvement in Systemic Lupus Erythematosus is common and affects up to 90% of patients at some stage in their disease and has a significant impact on quality of life. Despite this lupus arthritis remains largely understudied in comparison to the abundance of research that exists surrounding rheumatoid arthritis. The traditional idea that lupus patients develop a non-erosive arthropathy with reducible deformities is being challenged by newer imaging techniques which have the potential to provide a framework for a well-defined classification system.

Methods: 31 patients who fulfilled the ACR criteria for the diagnosis of SLE and who complained of painful hands for > 1 year were recruited and included in the study. 12 patients with rheumatoid arthritis were also recruited as a comparator group. Baseline immunological tests were performed; lupus disease activity was measured and clinical examination was carried out to assess joint deformities. All patients underwent ultrasonography by the same sonographer and the presence of synovitis, erosions, tenosynovitis and Doppler signal were noted and scored according to a recognised scoring system[1].

Results:

	SLE patients (n = 31)	RA patients (n = 12)
Clinical deformity	12 (38%)	8 (67%)
Wrist synovitis	15 (48%)	10 (83%)
Erosive disease (wrist or 2nd/3rd MCP joint)	9 (29%)	10 (83%)
Tenosynovitis (Extensor Carpi Ulnaris or 2nd/3rd finger flexor tendon)	9 (29%)	5 (41%)
Anti-CCP antibody	1 (3.2%)	11 (91%)
Rheumatoid factor	3 (9.6%)	12 (100%)
Anti- ds DNA antibody	18 (58%)	0 (0%)
CRP > 20mg/l	5 (16%)	2 (16%)

Conclusion: Arthritis with radiological erosion similar to the pattern in rheumatoid arthritis is thought to be less common in SLE and has been estimated to be < 5% of patients. Our small study has shown that ultrasound may reveal a higher percentage of erosions than previously thought. The role of the anti-CCP antibody in SLE arthritis remains controversial. Some studies have identified a link with erosive disease as in rheumatoid arthritis however our results are in keeping with other studies to date which have identified no link [2].

While data is accumulating gradually our current understanding of lupus arthritis remains incomplete and a well-defined classification system does not yet exist. It is clear that developments in imaging including MRI and ultrasound are reshaping our understanding of the processes of erosion and joint pathology in the spectrum of rheumatic diseases as a whole. Future continued application of these developments to SLE arthritis will continue to provide answers to several important questions.

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624

Human CD8 regulatory T cells generated *Ex-Vivo* have Potent Protective Activity *In Vivo*. Qin Lan, Stephanie Pan, Dixon Gray, Julie Wang, Song G. Zheng and David A. Horwitz. USC Keck School of Medicine, Los Angeles, CA

Background/Purpose: In addition to CD4+ cells, CD8+ cells can also be induced to become regulatory/suppressor cells ex-vivo. Here we asked whether various CD8+ induced Treg subsets have potent protective activity *in vivo* in humanized mice.

Methods: Human blood CD8+ cells were stimulated with anti-CD3/28 coated beads and IL-2± TGF-β alone or with all-trans retinoic acid (atRA), rapamycin (rapa) or both for 3 to 9 days. Their phenotype and functional activity were assessed. *In vivo* Treg activity was assessed by protection of NOD SCID cγ chain $^{-/-}$ (NOG) mice from the xeno-GVHD induced by human PBMC (p values by log rank test).

Results: CD8+ cells activated with IL-2 only rapidly expressed CD25, GITR, CTLA-4, TNFR-2, PDL-1, Granzyme A, and 30±2% (mean ±SEM) expressed Foxp3. The addition of TGF-β significantly increased Foxp3 (48±2%), CD122, PD-1 and CD103, but decreased Granzyme A. The addition of atRA did not enhance TGF-β effects, but did enhance downregulation of CD127. Approximately 40% of control activated CD8+cells secreted IL-2 and this decreased only slightly with CD8+ cells activated with TGF-β ± atRA. TGF-β decreased IFN-γ production and adding atRA resulted en even less IFN-γ. All previously activated CD8 subsets tested proliferated poorly after restimulation, and had significant suppressive activity in vitro in ratios of 1 Treg per 10 responder cells. In assays without APC, suppression CD8 cells activated with TGF-β was greater than CD8 cells stimulated with IL-2 only. Studies with 7-ADD and annexin V indicated that none of the activated CD8 subsets killed CD4 responder cells or monocytes. Separation of the CD8 cell subsets into TNF-R2 and PDL-1 bright and dim cells revealed that suppressive activity was concentrated in the former. The *in vivo* studies revealed that all activated CD8+ cells added to human PBMC in a ratio of 1:4 significantly enhanced survival of NOG mice. Remarkably, unlike CD4+Foxp3+ Tregs we studied previously

which can double or triple survival, the CD8regs could increase survival five fold.

Conclusion: Similar to findings with CD4+ cells, polyclonal activation of CD8+ cells with IL-2 and TGF-β enhances Foxp3 expression. However, CD4+ cells require other agents for them to rapidly acquire protective suppressive activity. By contrast, CD8+ cells activated with IL-2 only that strongly expressed TNFR2 and PDL-1 had significant suppressive activity both *in vitro* and *in vivo*. Although TGF-β addition resulted in enhanced suppressive activity *in vitro*, to date TGF-β with or without atRA or rapa has not resulted in significant enhancement of protective activity *in vivo*. Consistent with recent reports of *in vivo* suppressive effects of CD8+ cells in mouse and human SLE, our studies suggest that CD8 regs induced ex-vivo deserve consideration in future clinical trials with Tregs in SLE.

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Higher Frequency and Worse Outcome of Lupus Nephritis in Korean Male. Jiwon Hwang[1], Jaejoon Lee[1], Joong Kyong Ahn[2], Chan Hong Jeon[3], Hoon-Suk Cha[1] and Eun-Mi Koh[1]. [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Soonchunhyang University College of Medicine, Bucheon, South Korea

Background/Purpose: Female preponderance is a well-known characteristic of systemic lupus erythematosus (SLE), and gender may influence the clinical features and outcome of SLE patients. In this study, we investigated the clinical characteristics and outcome in Korean male SLE patients compared to female patients.

Methods: We performed a retrospective analysis using medical records at a single tertiary hospital between August 1994 and May 2010. Each male patient was matched with 3 female SLE patients for age and disease duration. Clinical and serologic features at the disease onset and during the course of disease were compared between the groups. SLE severity was assessed using the Severity of Disease Index (SDI). The assessment of organ damage was made using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI).

Results: Among total of 632 patients with SLE, 57 males were identified. The ratio of female to male was 11.6:1. The mean time to SLE diagnosis was 23.2 $\pm$ 43.3 months for males and 8.9 $\pm$ 10.5 months for females ($p = 0.001$). The mean age at diagnosis was 32.7 $\pm$ 12.1 years-old and the mean duration of follow-up was 55.3 $\pm$ 51.1 months for both groups. The 5- and 10- year survival rates of male lupus were 90% and 90% compared to 95.9% and 94.2% of female lupus ($p = 0.11$). Male lupus patients had less discoid rash ($p = 0.005$), alopecia ($p = 0.010$), leucopenia ($p < 0.001$) and anti-Ro ($p < 0.001$) at the onset of disease but renal disorder was more prevalent in male lupus ($p < 0.001$). The adjusted odds ratio (OR) demonstrated a significant gender difference for discoid rash (OR 0.34, 95% confidence interval (CI) 0.14 – 0.81) and renal disorder (OR 3.26, 95% CI 1.62 – 6.57). In male lupus, high-dose of corticosteroid and immunosuppressive agents for disease control were used more frequently compared to female (62.7% vs. 32.7, $p < 0.001$ and 74.5% vs. 46.7%, $p = 0.001$). Male lupus patients had a higher percentage of diffuse proliferative lupus nephritis ($p = 0.025$) and end-stage renal disease (ESRD) which required dialysis ($p < 0.001$) during the course and the risk for dialysis were significantly elevated (OR 4.02, 95% CI 1.07 – 15.06). There was no difference in the neuropsychiatric and cardiovascular damage between male and female lupus ($p = 0.62$ and $p = 0.52$). In male lupus, the mean SDI and SLICC/ACR DI were significantly higher (4.44 $\pm$ 2.69 vs. 3.45 $\pm$ 2.03, $p = 0.011$ and 1.55 $\pm$ 1.35 vs. 1.02 $\pm$ 1.57, $p = 0.028$).

Conclusion: Our data shows a significant gender effect in the clinical features and outcome of Korean male SLE. Delayed diagnosis was observed in male SLE patients and higher frequency of renal disorder including diffuse proliferative lupus nephritis and dialysis-required ESRD was demonstrated. Male SLE was more severe and more organ damage was present in male SLE.

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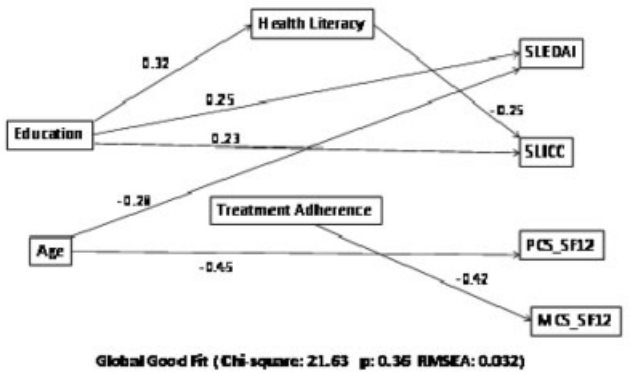
Impact of Health Literacy on Treatment Adherence and Clinical Outcomes in Patients with Systemic Lupus Erythematosus. Maria F. Marengo[1], Michael A. Kallen[1], Sofia De Achaval[2], Vanessa Cox[1], Araceli Garcia[3], Marsha Richardson[4] and Maria E. Suarez-Almazor[5]. [1]UT MD Anderson Cancer Center, Houston, TX, [2]U.T. MD Anderson Cancer Center, Houston, TX, [3]UT MD Anderson, Houston, [4]UT MD Anderson, Houston, TX, [5]University of Texas. M.D Anderson Cancer Center, Houston, TX

Background/Purpose: Limited Health Literacy (HL) has been associated with poorer health outcomes and higher cost; however, little is known about the effects of low health literacy among patients with rheumatic diseases.The objective of our study was to measure the level of HL among patients with Systemic Lupus Erythematosus (SLE) and evaluate its impact on treatment adherence and clinical outcomes.

Methods: This study was part of a 2– year prospective cohort study of 110 patients with SLE from 2 publicly-funded county hospitals; 85 SLE patients completed the HL assessment. HL was measured using the numeracy score (0–50) related to health care issues from the Test of Functional Health Literacy in Adults (TOFHLA) and the reading comprehension score (0–50) from TOFHLA-Short. A total score (0–100) was obtained (total TOFHLA), with 0 being the worst HL. Patients were categorized as having low or adequate HL using the traditional cutoff ($\geq$60). Patient information was collected at baseline, 12, and 24 months, including disease activity (SLEDAI), organ damage (SLICC), physical (PCS-SF12) and mental component scales (MCS-SF12) of quality of life and treatment adherence (AAGTG). 85% of patients completed the 2-years' follow-up. A conceptual casual model was developed, with demographic variables predicting HL and adherence, all of which predicted disease activity, organ chronic damage, and quality of life. Path analysis was conducted to test the model. Statistical analyses were carried out using STATA 11.1 and LISREL 8.8.

Results: 90% of patients were female, 38.2% Hispanic, and 55.4% African-American; mean age was 36.3y ($\pm$12), disease duration 5.8y ($\pm$5.1), SLEDAI 2.7 ($\pm$2.7), SLICC 1.1 ($\pm$1.3), PCS-SF12 36 ($\pm$9.9), MCS-SF12 42 ($\pm$9.7) and AACTG 0.67 ($\pm$ 0.48). Mean total TOFHLA was 85.2 ($\pm$14.5); mean numeracy was 40.4($\pm$7.6) and mean reading comprehension 44.4 ($\pm$9.1). Of 85 patients, 12 (14.1%) had low HL; these patients were more frequently Spanish-only speakers ($p=0.02$), with lower education ($p<0.01$) and higher SLEDAI ($p=<0.01$). In the path analysis (Graph1), age was found to have a significant negative direct effect on SLEDAI and PCS-SF12. Education had significant positive direct effects on HL, SLEDAI, and SLICC. HL had only a negative direct effect on SLICC and no effect on treatment adherence, SLEDAI, or SF-12. Treatment adherence had a negative direct effect on MCS-SF12. Overall, the path analytic model displayed good fit to the data (chi-square= 21.6, $p=0.36$, RMSEA= 0.032). No differences were obtained when this model was applied in subpopulations differing by gender or ethnicity.

Graph 1:Model in SLE patients



Conclusion: Low HL level was relatively frequent among SLE patients. In our population, higher education is associated with higher HL, which is related to lower chronic organ damage; however, this education effect is not mediated via disease activity or treatment adherence.

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Risk Factors to Predict the Development of Chronic Kidney Disease In Patients with Lupus Nephritis. Dong-Jin Park[1], Sung-Ji Lee[1], Tae-Jong Kim[2], Yong-Wook Park[2] and Shin-Seok Lee[1]. [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Chonnam National University Medical School and Hospital, Gwangju, South Korea

Background/Purpose: Although the outcome in patients with lupus nephritis (LN) has improved with the availability of more effective and better tolerated immunosuppressive drugs, a significant proportion of patients still progress to chronic kidney disease (CKD) and end-stage renal disease. The consequences of CKD include not only progression to kidney failure but also increased risks for cardiovascular disease and premature death. It is important to identify risk factors capable of predicting progression to CKD in LN patients in order to develop strategies for its prevention, detection, and treatment. Here, we aimed to find prognostic factors for the development of CKD in ethnically homogeneous Korean patients with LN.

Methods: Eighty-nine LN patients were included in this study based on availability of kidney biopsy specimens. Sociodemographic, clinical, laboratory, and treatment-related data at the time of kidney biopsy and during follow-up were obtained by reviewing patients' charts. Renal biopsy specimens were reclassified according to the ISN-RPS classification, by a renal pathologist blinded to the previous classification. CKD was defined as a glomerular filtration rate <60 mL/min/1.73 m^2 for 3 or more months, as recommended by the Kidney Disease Quality Outcome Initiative. Univariate and multivariate analyses were performed using the Cox proportional hazard regression model to identify independent risk factors for CKD in LN patients.

Results: Eighteen of 89 patients (20%) developed CKD during a mean follow-up of 41.9 months (range: 12–86 months). Patients who developed CKD were older at onset of LN ($P = 0.010$), less educated ($P < 0.001$), and more likely to have hypertension ($P = 0.005$); they had a lower serum albumin level ($P = 0.019$), lower platelet level ($P = 0.008$), higher serum creatinine level ($P < 0.001$), lower estimated glomerular filtration rate (eGFR, $P < 0.001$), higher chronicity index ($P = 0.010$), lower frequency of anti-ribosomal P antibodies ($P = 0.012$), and they were less likely to be in complete remission (CR) in the 1st year ($P = 0.006$). The incidence of CKD was lower in patients treated with hydroxychloroquine at the onset of LN than in those not taking hydroxychloroquine ($P = 0.039$). In stepwise multivariable analyses, hypertension ($P = 0.004$), eGFR ($P = 0.017$), and failure to achieve CR in the 1st year of treatment ($P = 0.032$) were significant predictors of the development of CKD in LN patients.

Conclusion: These findings suggest that patients with hypertension and decreased kidney function at the onset of LN and showing a poor response to immunosuppressive drugs in the 1st year should be monitored carefully and managed aggressively to avoid deterioration of kidney function.

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Emergency Room Visits and Hospitalizations in Systemic Lupus Erythematosus. Jie Xu, Hong Fang and Michelle Petri. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: SLE has a profound effect on medical care costs (Clark et al.). We quantified the frequency and clinical associations of ER visits and hospitalizations.

Methods: A medical resource use questionnaire that covered the last 3 months was distributed to 386 SLE patients. They were 91% female, mean age 45.7±12.3, 55% Caucasian, 36% African American. Exclusion criteria were diagnosis with SLE less than 6 months, age younger than 18 or older than 75, pregnant at baseline, and active HIV patients.

Results: 9% were hospitalized and 13.5% had an ER visit during the 3 month period. Of the hospitalizations, 57% were due to SLE. Of the emergency visits, 52% were due to SLE.

Table 1. SLE Characteristics Associated with Hospitalizations

Variable	No hospitalizations (%, N=351)	Hospitalizations (%, N=35)	P-value
Age at visit (years)			
≤35	24.8	34.3	0.22
>35	75.2	65.7	
Race			
African-American	35.3	45.7	0.30
Caucasian	56.4	42.9	
Other	8.3	11.4	
Education (years)			
<12	31.6	25.7	1.47
≥12	68.4	74.3	
Income ($)			
≤50K	47.3	48.6	0.89
>50K	52.7	51.4	
Smoking	11.7	5.7	0.28
Physician Global Assessment of Activity >1 (0 to 3 VAS)	12.5	28.6	0.018
SLEDAI ≥ 4	22.2	34.3	0.11
Low C3	14.8	11.4	0.59
Low C4	14.3	11.4	0.65
Anti-dsDNA	21.4	28.6	0.33
Urine protein/cr ≥ 0.5	6.0	20.0	0.008
Prednisone	36.5	62.9	0.002
ESR > 20	42.9	67.7	0.006

Table 2. SLE Characteristics Associated with ER visits

Variable	No ER visits (%, N=334)	ER visits (%, N=52)	P-value
Age at visit (years)			
≤35	22.5	46.2	0.0003
>35	77.5	53.9	
Race			
African-American	35	44.2	0.44
Caucasian	56.3	48.1	
Other	8.7	7.7	
Education (years)			
<12	30.2	36.5	0.36
≥12	69.8	63.5	
Income ($)			
≤50K	45.5	59.6	0.058
>50K	54.5	40.4	
Smoking	9.3	23.1	0.003
Physician Global Assessment of Activity >1 (0 to 3 VAS)	11.1	32.7	<.0001
SLEDAI · 4	21.9	32.7	0.086
Low C3	15.3	9.6	0.28
Low C4	14.4	11.5	0.58
Anti-dsDNA	20.1	34.6	0.019
Urine protein/cr ≥ 0.5	5.7	17.3	0.007
Prednisone	35	63.5	<.0001
ESR > 20	43.3	56.9	0.071

Conclusion: Hospitalizations and ER visits were very frequent. Young age was associated with ER visits but not hospitalizations. Surprisingly, race, education, and income were not associated with hospitalizations or ER visits. Smoking was strongly associated with ER visits. The physician global assessment of disease activity (but not SLEDAI) was associated with both hospitalization risk and ER visits. Of individual organ systems, only lupus nephritis was associated with hospitalizations and ER visits. These data can be used to predict subsets with higher future costs and indicate that effective therapies for lupus nephritis will limit costs.

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Eltrombopag As Steroid Sparing Therapy for Immune Thrombocytopenic Purpura (ITP) in Systemic Lupus Erythemathosus (SLE), Report of Three Cases. Marie Claire Maroun[1], Rosanne Ososki[2], Judith Andersen[1], Frank B. Vasey[1] and J. Patricia Dhar[1]. [1]Wayne State University, Detroit, MI, [2]Detroit Medical Center, Detroit, MI

Background/Purpose: To review the efficacy of eltrompobag, as a steroid sparing therapy for ITP associated with SLE.

Eltrobopag activates the thrombopoietin (TPO)surface receptor on the megakaryocyte, which increases the production of platelets, and rapidly improves circulating platelet numbers in patients with ITP. This allows for rapid tapering and/or cessation of corticosteroid therapy. Less is known about the platelet response to this drug in ITP associated with SLE.

Methods: Retrospective review was performed of the clinical course of 3 consecutive patients, each with SLE-associated ITP who were initially treated with corticosteroids or other immunomodulatory therapy. These patients were treated with eltrombopag at the DMC Center for Bleeding Disorders and Thrombosis. Eltrompopag was administered according the package insert, with an initial dose of 50 mg daily, with weekly, then monthly monitoring of platelet counts and dose adjustments. Some immunomodulatory agents (*e.g.* hydroxychloroquine) were continued to control non hematologic SLE manifestions..

Results: All 3 patients maintained acceptable platelet counts ($>$ 50,000/μL, (see graphs) for $>$ 6 months following tapering and cessation of corticosteroids. The drug was well-tolerated and there were no adverse events, and specifically no thrombotic events.

Conclusion: Eltrombopag is effective as a rapidly acting corticosteroid sparing therapy for patients with ITP associated with SLE. This is important in reducing corticosteroid related side effects and morbidities in treating SLE patients with ITP. Larger studies are needed to ascertain safety and efficacy of eltrombopag in SLE patients with ITP, particularly those with coexisting antiphospholipid antibodies.

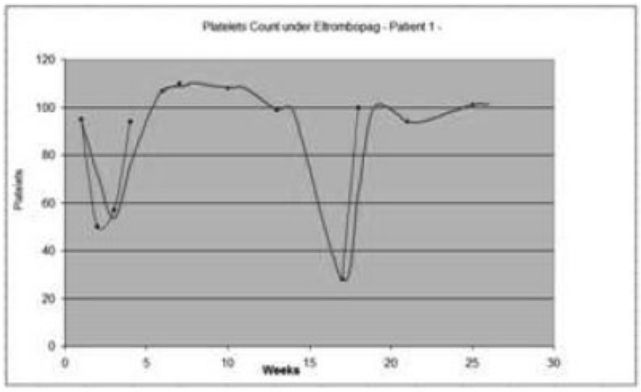
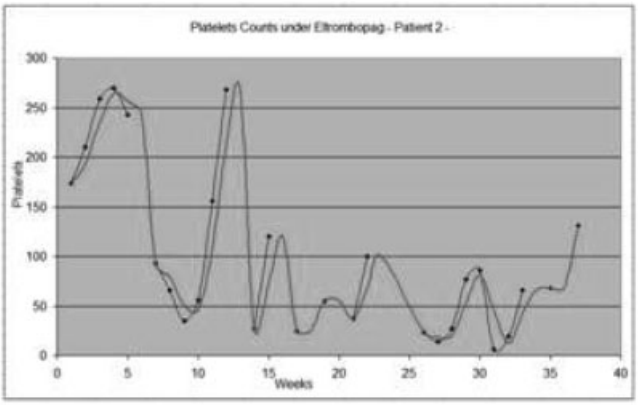
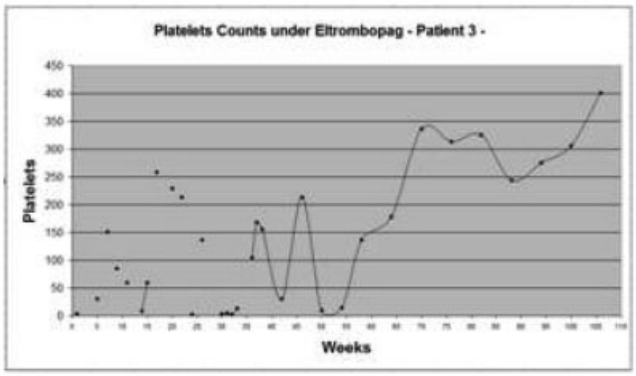


Figure. Platelets Counts under Eltrombopag





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How Does Cutaneous Lupus Disease Area and Severity Index (CLASI) Compare with Physician Assessments of Cutaneous Activity and Damage in Lupus? Meenakshi Jolly, Nazia Kazmi, Rachel A. Mikolaitis and Joel A. Block. Rush University Medical Center, Chicago, IL

Background/Purpose: The purpose of this study was to validate Cutaneous Lupus disease Area and Severity Index (CLASI) against physician assessments of itemized and total cutaneous disease activity and damage in patients with cutaneous manifestations of lupus (CLE) or Systemic Lupus Erythematosus (SLE). Additionally, we sought to determine its relationship with patient reported health assessments (LupusPRO, EQ5D and Body Image Quality of Life Index-BIQLI).

Methods: 29 consecutive SLE and CLE patients seen in our lupus clinic were self-administered demographics, LupusPRO, EQ5D VAS, and BIQLI. A physician then completed the CLASI, and assessed disease activity (SLEDAI) and damage (SLICC/SDI) during the study visit.

Results: Mean age (SD) was 42.4 (13.2) yrs. 25/29 had SLE. Ninety seven percent were women and 46% had a flare at the time of the study. Mean (SD) total scores were CLASI activity 8.8 (5.6), CLASI damage 9.6 (9.1), PGA 1.1 (0.8), SLEDAI 4.5 (4.1) and SDI 1.8 (2.2). Fifty-nine percent patients were on prednisone and 66% on hydroxy-chloroquine. Mean (SD) EQ5D VAS was 73 (15.1), and BIQLI 0.39 (1.5).

CLASI activity score correlated with SLEDAI-rash item (r 0.46, p=0.01), LupusPRO Lupus Symptom item on skin flare (r 0.37, p=0.05), EQ5D VAS (r −0.49, p=0.04), but not with PGA (r 0.35, p=0.08) or total SLEDAI (r 0.19, p=0.33). CLASI damage score correlated with age (r 0.45, p=0.02), SDI items on cutaneous skin scarring/alopecia (r 0.51, p=0.001), skin extensive scarring/panniculum (r 0.51, p=0.01) and skin ulceration (r 0.37, p=0.05) and total SDI score (r 0.53, p=0.001).

BIQLI was not associated with CLASI activity or damage score. However, CLASI face activity adversely affected patient's interactions with people of their own sex (r −0.53, p=0.001), interactions with people of opposite sex (r −0.49, p=0.01), experiences when they met new people (r −0.36, p=0.05), experiences at work/school (r −0.45, p=0.01), relationships with friends (r −0.40, p=0.03) and relationships with family members (r −0.39, p=0.04).

Conclusion: CLASI has good validity against physician assessed itemized cutaneous disease activity and damage, and overall damage in SLE. Furthermore, visible cutaneous activity adversely affects lupus patient's interactions, life experiences and relationships.

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Clinical Outcomes In SLE Patients Since the introduction of the 2003 ISN/RPS Classification of Lupus Nephritis. Natasha Jordan, Shirish Sangle, Yousuf Karim, Fahim Tungekar, Ian Abbs and David P. D'Cruz. Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom

Background/Purpose: Lupus nephritis affects approximately 60% of Systemic Lupus Erythematosus (SLE) patients and is associated with significant morbidity and mortality. The 2003 International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification is currently used to histologically define lupus nephritis classes.

The objectives of this research were to determine the rate of progression to end-stage renal disease in lupus nephritis patients who have undergone renal biopsy since the introduction of the 2003 ISN/RPS classification and to identify risk factors associated with poor outcome.

Methods: We retrospectively reviewed the clinical data of 84 lupus nephritis patients who underwent renal biopsy since the introduction of 2003 ISN/RPS classification. Data collected included demographic details, autoantibody profiles, co-existence of Antiphospholipid Syn-

drome, activity and chronicity indices on renal biopsy and renal outcomes.

Results: 99 renal biopsies were performed in 84 SLE patients since the introduction of 2003 ISN/RPS classification. 83% of those biopsied were female (n=70) and 17% were male (n=14). The mean age at renal biopsy in female patients was 35 years (range 10–64 years) and 26 years in male patients (range 14–50 years). 41.6% of patients biopsied were of Caucasian origin (n=35), 32% were of Afro-Caribbean descent (n=27) and 21.4% of Asian extraction (n=18). 7% of our cohort progressed to advanced renal impairment requiring dialysis or renal transplantation.

Afro-Caribbean ancestry was associated with an increased likelihood of developing advanced renal disease (p=0.053). Younger age at renal biopsy was also associated with a worse outcome. Patients with class IV-G on biopsy were more likely to develop renal impairment (p=0.049). No particular autoantibody profile was associated with an adverse outcome. The presence of anti-cardiolipin antibodies, lupus anticoagulant or thrombotic microangiopathy on biopsy were not associated with disease progression in this cohort. High chronicity index on renal biopsy was significantly associated progression to end-stage renal impairment (p=0.001). High activity index on renal biopsy was not associated with the development of renal failure.

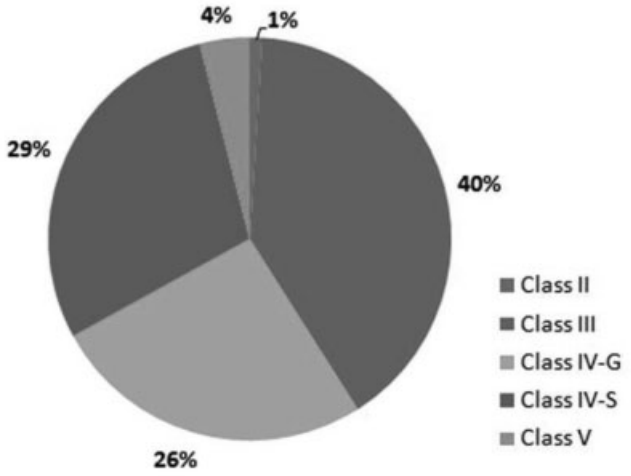

Figure 1. Frequency of lupus nephritis classes seen on renal biopsy

Degree of renal impairment	Class III	Class IV-G	Class IV-S	Class V	
Normal renal function GFR>90	12	5	7	2	37% (n=26)
GFR 60-89	9	4	11	1	35% (n=25)
GFR 30-59	7	7	1	0	21% (n=15)
GFR 15-29	1	0	0	0	1% (n=1)
GFR <15	0	3	1	O	6% (n=4)

Figure 2. Clinical outcomes in ISN/RPS lupus nephritis classes based on KDOQI (kidney disease outcomes quality initiative) stages of kidney disease. GFR (glomerular filtration rate)

Conclusion: Despite advances in the clinical management of lupus nephritis with earlier recognition of disease and improved immunosuppressive regimens, a proportion of patients still progress to end-stage renal failure. In our cohort 7% of patients progressed to advanced renal disease. In our cohort patients with proliferative nephritis were more likely to require renal replacement therapy particularly those with class IV-G nephritis. The association with high chronicity indices on biopsy and progression to renal impairment emphasizes the importance of prompt diagnosis and initiation of appropriate therapy.

ACR Poster Session A
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis I: Susceptibility and Pathogenic Mechanisms
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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Phenotypic Associations of Genetic Susceptibility Loci In Systemic Lupus Erythematosus. Elena Sanchez[1], Ajay Nadig[1], Bruce C. Richardson[2], Barry I. Freedman[3], Kenneth Kaufman[4], Timothy B. Niewold[5], Diane L. Kamen[6], Gary S. Gilkeson[7], Carl D. Langefeld[3], Robert P. Kimberly[8], J.T. Merrill[1], Juan-Manuel Anaya[9], Judith A. James[10], Bernardo Pons-Estel[11], Javier Martin[12], Sang-Cheol Bae[13], Kathy L. Moser[14], Tomothy J. Vyse[15], Lindsey A. Criswell[16], Patrick M. Gaffney[14], Betty P. Tsao[17], Chaim O. Jacob[18], John B. Harley[19], Marta E. Alarcon-Riquelme on behalf of BIOLUPUS and GENLES[20] and Amr H. Sawalha[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Michigan, Ann Arbor, MI, [3]Wake Forest University Health Sciences, Winston-Salem, NC, [4]Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [5]University of Chicago, Chicago, IL, [6]Medical University of SC, Charleston, SC, [7]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [8]University of Alabama at Birmingham, Birmingham, AL, [9]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [10]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [11]Rosario, Argentina, [12]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [13]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [14]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [15]King's College London, Guy's Hospital, London, United Kingdom, [16]University of California San Francisco, San Francisco, CA, [17]UCLA School of Medicine, Los Angeles, CA, [18]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [19]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [20]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK

Background/Purpose: Systemic lupus erythematosus is a clinically-heterogeneous autoimmune disease characterized by antinuclear antibody production. A number of genetic loci that increase lupus susceptibility have been established. Herein, we examine if these genetic loci also contribute to the clinical heterogeneity in lupus.

Methods: A total of 4,001 European-derived, 1,547 Hispanic, 1,590 African-American, and 1,191 Asian lupus patients were genotyped for tag SNPs within 16 confirmed lupus susceptibility loci. Ancestry informative markers were genotyped to calculate and adjust for admixture proportions in each population. The association between the risk allele in each locus was determined and compared in patients with and without the various clinical manifestations included in the ACR criteria.

Results: Significant associations were found between clinical manifestations and the *FCGR2A*, *ITGAM*, *STAT4*, *TNSF4*, and *IL21* genes. Renal disorder was significantly correlated with the lupus risk allele in *ITGAM* ($P = 5.0 \times 10^{-6}$, OR= 1.25 95%CI 1.12–1.35) and in *TNFSF4* (P= 0.0013, OR= 1.14 95%CI 1.07–1.25). Other significant findings include the association between the risk alleles in *FCGR2A* and malar rash (P= 0.0031, OR= 1.11 95%CI 1.17–1.33), *ITGAM* and discoid rash (P= 0.0020, OR= 1.20 95%CI 1.06–1.33), *STAT4* and the protection from oral ulcers (P= 0.0027, OR= 0.89 95%CI 0.83–0.96), and *IL21* and hematologic disorder (P= 0.0027, OR= 1.13 95%CI 1.04–1.22). All

these associations are significant with a false discovery rate of <0.05 and pass the significance threshold using Bonferroni correction for multiple testing.

Conclusion: We analyzed the association between genetic risk loci and clinical manifestations in lupus using a large multi-ethnic cohort of lupus patients. Our findings suggest that genetic profiling might be a useful tool to predict disease manifestations in lupus patients in the future.

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Genetic Associations with Serologic Autoimmunity in a Large Multi-Ancestral Systemic Lupus Erythematosus Cohort. Silvia Kariuki[1], Beverly S. Franek[1], Akaash A. Kumar[1], Marissa Kumabe[1], Kenneth M. Kaufman[2], Juan-Manuel Anaya[3], Marta E. Alarcón-Riquelme[4], Sang-Cheol Bae[5], Elizabeth E. Brown[6], Barry I. Freedman[7], Gary S. Gilkeson[8], Chaim O. Jacob[9], Judith A. James[10], Robert P. Kimberly[11], Javier Martin[12], Joan T. Merrill[13], Bernardo Pons-Estel[14], Betty P. Tsao[15], Timothy J. Vyse[16], Carl D. Langefeld[7], John B. Harley[17], Kathy L. Moser[18], Patrick M. Gaffney[18], Andrew D. Skol[1] and Timothy B. Niewold[1]. [1]University of Chicago, Chicago, IL, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation and US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [3]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [4]Oklahoma Medical Research Foundation and Centro de Genómica e Investigación Oncológica Pfizer-Universidad de Granada-Junta de Andalucía (GENYO), Granada, Spain, on behalf of the BIOLUPUS and GENLES networks, Oklahoma City, OK, [5]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [6]Department of Medicine and Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [7]Wake Forest School of Medicine, Winston-Salem, NC, [8]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [9]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [10]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [11]University of Alabama at Birmingham, Birmingham, AL, [12]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [13]Oklahoma Medical Research Foundation, Oklahoma City, OK, [14]Sanatorio Parque, Rosario, Argentina, [15]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [16]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [17]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [18]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Systemic lupus erythematosus (SLE) is a highly heterogeneous disorder characterized by production of autoantibodies directed at particular self-antigens in the cell nucleus. Similar to other autoimmune diseases, the genetic basis of SLE appears to vary in different serologic groups. We followed up loci from a case-only GWAS study which were associated with particular autoantibodies.

Methods: We genotyped 43 tag SNPs from 10 regions identified in the above GWAS in a multi-ancestral SLE cohort of over 8000 patients split between African-American, European, Hispanic, and Asian ancestral backgrounds. For each SNP and by ethnic group, we computed admixture adjusted logistic regression analyses among cases for association between the SNPs and the presence or absence of the autoantibodies. P-values less than 1.2×10^{-3} withstand Bonferroni correction for the number of SNPs tested.

Results: In African-Americans, the rs310230 SNP in JAK1 was strongly associated with anti-dsDNA and anti-RNP antibodies in an additive manner (OR=1.63, $p=6.20\times10^{-05}$). Additionally, a SNP in KLHL6 demonstrated evidence for association in the anti-RNP positive, anti-Sm negative group ($p=2.1\times10^{-3}$). In Asian ancestry, MAPK4 rs7242442 was associated with anti-Ro antibodies (OR=1.68, $p=4.49\times10^{-05}$). In Hispanic subjects, the strongest serologic association was also with the MAPK4 rs7242442 SNP, although it was associated with anti-RNP in this background (OR=1.47, $p=3.9\times10^{-3}$). In European ancestry, the strongest evidence for a SNP-antibody association was observed between a different MAPK4 tag SNP and anti-Ro antibodies (OR=1.23, $p=5.3\times10^{-3}$).

Conclusion: We demonstrate association of SNPs within the JAK1, KLHL6, and MAPK4 genes with SLE-specific autoantibodies. Serologic autoimmunity differs greatly by ancestral background in SLE, and different autoantibodies have been associated with important clinical differences in patients. This study begins to genetically map this aspect of SLE across multiple ancestral backgrounds.

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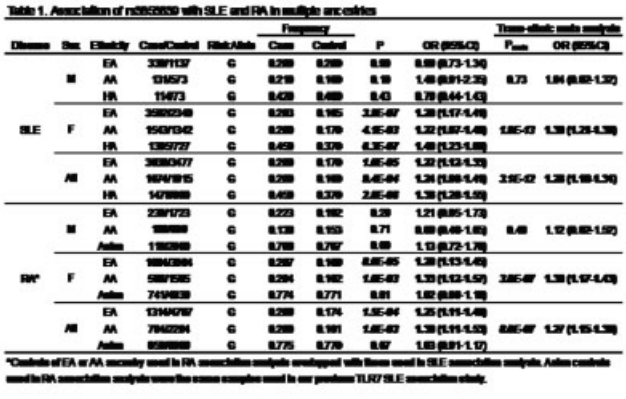
Association of a Functional Variant in *TLR7* with Systemic Lupus Erythematosus and Rheumatoid Arthritis in Multiple Ancestries. Yun Deng[1], Jian Zhao[1], Wenfeng Tan[1], Kenneth M. Kaufman[2], Elizabeth E. Brown[3], Jeffrey C. Edberg[4], Diane L. Kamen[5], Gary S. Gilkeson[6], Chaim O. Jacob[7], Robert H. Scofield[8], Robert P. Kimberly on behalf of PROFILE investigators[4], Carl D. Langefeld[9], Marta E. Alarcón-Riquelme on behalf of the BIOLUPUS and GENLES[10], John B. Harley[11], Timothy J. Vyse[12], Patrick M. Gaffney[13], Kathy L. Moser[13], Judith A. James[14], Ji-Yih Chen[15], Ted R. Mikuls[16], Nancy A. Shadick[17], Michael E. Weinblatt[17], S. Louis Bridges Jr.[18], Harold E. Paulus[1] and Betty P. Tsao[1]. [1]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation and US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [3]Department of Medicine and Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [4]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [5]Medical University of SC, Charleston, SC, [6]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [7]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [8]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, US Department of Veterans Affairs Medical Center and Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [9]Department of Biostatistical Sciences, Wake Forest University Health Sciences, Winston-Salem, NC, [10]Center for Genomics and Oncological Research, Pfizer-University of Granada-Junta de Andalucia, Granada, Spain and Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [11]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [12]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [13]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [14]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [15]Division of Allergy, Immunology and Rheumatology, Chang Gung Memorial Hospital, Taipei, Taiwan, [16]Omaha VA and University of Nebraska, Omaha, NE, [17]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [18]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: We have established an X-linked *TLR7* 3'UTR SNP (rs3853839) as a risk locus for SLE in 9,274 Eastern Asians (OR = 1.27 [1.17–1.36], $p = 6.5\times10^{-10}$). The aim of this study was to seek replication of SLE-associated SNP(s) in 13,275 SLE case-control subjects including European Americans (EA), African Americans (AA), and Hispanics enriched for the Amerindian-European admixture (HS), to assess whether SLE-risk SNP(s) also predispose to RA in 2,877 RA subjects of EA, AA and Asian ancestries, and to explore functional consequences of disease-associated SNP(s).

Methods: We genotyped 47 SNPs and imputed genotypes for SNPs in the HapMap Phase III and Immunochip. Each SNP was assessed for the association with SLE. Then, identified SLE-risk SNPs were genotyped and assessed for the association with RA. We performed χ^2 testing to identify disease-associated SNPs, and Mantel-Haenszel testing to generate a trans-ancestral meta-analysis *P* value. We performed RT-PCR and reporter gene assay to measure gene expression level, pyrosequencing and mRNA stability assay to measure allelic variations in mRNA level and stability.

Results: The previously identified *TLR7* 3'UTR SNP (rs3853839) was the only independent variant across all 3 replication populations, exhibiting significant association with SLE below a Bonferroni-corrected $P < 4.17\times10^{-3}$ (Table 1). Trans-ancestral meta-analysis extended our previous finding to 13,275 subjects of EA, AA and HS ancestries ($P = 3.1\times10^{-12}$, OR [95%CI] =1.26 [1.18–1.34]). Additionally, the SLE-risk G allele of rs3853839 was associated with susceptibility of RA in EA and AA populations, but not in Asians ($P = 1.5\times10^{-4}$ in EA, 1.0×10^{-3} in

AA, and 0.67 in Asians). Compared to the C allele, disease-associated G allele conferred elevated expression of *TLR7* mRNA in PBMCs from healthy individuals of European ancestry ($P = 0.01$ and 0.02 for men and women respectively), and enhanced transcriptional activity in transfected HEK 293 cells ($P = 0.026$). Allelic specific expression confirmed a higher level of G allele-containing *TLR7* transcripts in PBMCs from European heterozygote women. PBMCs from heterozygote women exhibited a higher G/C allele ratio in *TLR7* transcripts after 4 hours of incubation with actinomycin D (transcriptional inhibitor) than with vehicle control ($P = 0.047$), suggesting a slower degradation of the G allele-containing transcripts.



Conclusion: The G allele of *TLR7* 3'UTR SNP that confers elevated mRNA level through a slower degradation predisposes to SLE and RA in multiple ancestries, highlighting the importance of TLR signaling pathway in the pathogenesis of autoimmune diseases.

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The Association Between the TNFAIP3 Gene Polymorphisms and Systemic Lupus Erythematosus: A Meta-Analysis. Young Ho Lee[1], Sung Jae Choi[1], Jong Dae Ji[1] and Gwan Gyu Song[2]. [1]Korea University Medical Center, Seoul, South Korea, [2]Korea University Medical Center, Seoul

Background/Purpose: The tumor necrosis factor alpha inducible protein 3 (TNFAIP3) gene, located at 6q23 region, has been associated with susceptibility to multiple autoimmune diseases. The aim of this study was to determine whether tumor necrosis factor alpha inducible protein 3 (TNFAIP3) polymorphisms confer susceptibility to systemic lupus erythematosus (SLE) in ethnically different populations.

Methods: A meta-analysis was conducted on the TNFAIP3 polymorphisms across eight comparative studies that include 6,311 SLE subjects and 6,492 subjects. We examined the contrast of the allelic effect of 2 (the minor allele) versus 1 (the common allele). The random effects model was used in the presence of significant between-study heterogeneity. Otherwise, the fixed effects model was applied.

Results: Meta-analysis showed an association between the 2 allele of the rs2230926 and SLE in all subjects (OR [odds ratio] 1.848, 95% confidence interval [CI] 1.547, 2.208, $p < 1.0 \times 10^{-9}$). Analysis after stratification by ethnicity indicated that the 2 allele of the rs2230926 was significantly associated with SLE in Asians and Europeans (OR 1.821, 95% CI 1.495, 2.219, $p < 1.0 \times 10^{-9}$; OR 2.251, 95% CI 1.830, 2.768, $p < 1.0 \times 10^{-9}$). Meta-analysis revealed a significant association between the 2 allele of the rs5029939 polymorphism and the risk of developing SLE in overall group and Europeans (OR 1.804, 95% CI 1.255, 2.592, $p = 0.001$; OR 2.145, 95% CI 1.731, 2.658, $p < 1.0 \times 10^{-9}$). Meta-analysis revealed an association between the 2 allele of the rs3757173 and SLE in all subjects (OR 1.540, 95% CI 1.017, 2.331, $p = 0.041$). However, no association was found between SLE susceptibility and rs6922466 by meta-analysis (OR 0.953, 95% CI 0.812, 1.120, $p = 0.561$).

Conclusion: This meta-analysis confirms that the TNFAIP3 polymorphisms are associated with SLE susceptibility in different ethnic groups such as Asians and Europeans.

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A Single Risk Haplotype in the Region of UBE2L3 Is Associated with Systemic Lupus Erythematosus in Multiple Ethnic Populations. Shaofeng Wang[1], Indra Adrianto[1], Graham B. Wiley[1], Kenneth M. Kaufman[2], Juan-Manuel Anaya[3], Marta E. Alarcón-Riquelme on behalf of the BIOLUPUS and GENLES networ[4], Sang-Cheol Bae[5], Elizabeth E. Brown[6], Barry I. Freedman[7], Gary S. Gilkeson[8], Chaim O. Jacob[9], Judith A. James[10], Robert P. Kimberly on behalf of PROFILE investigators[11], Javier Martin[12], Joan T. Merrill[1], Timothy B. Niewold[13], Bernardo Pons-Estel[14], Betty P. Tsao[15], Tomothy J. Vyse[16], Carl D. Langefeld[7], John B. Harley[17], Edward Wakeland[18], Kathy L. Moser[19], Courtney G. Montgomery[1] and Patrick M. Gaffney[19]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation and US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [3]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [4]Oklahoma Medical Research Foundation; Center for Genomics and Oncological Research, Oklahoma City; Granada, Spain, OK, [5]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [6]University of Alabama at Birmingham, Birmingham, AL, [7]Wake Forest School of Medicine, Winston-Salem, NC, [8]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [9]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [10]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [11]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [12]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [13]University of Chicago, Chicago, IL, [14]Sanatorio Parque, Rosario, Argentina, [15]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [16]King's College London, Guy's Hospital, London, United Kingdom, [17]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [18]Univ of Texas SW Med Ctr, Dallas, TX, [19]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease with diverse clinical manifestations characterized by the development of pathogenic autoantibodies and target tissue damage. Genome-wide association (GWA) studies have identified genetic variants in the *UBE2L3* region that are associated with SLE in subjects of European and Asian ancestry. *UBE2L3* encodes an ubiquitin-conjugating enzyme, UBcH7, involved in cell proliferation and immune function. In this study, we sought to further characterize the genetic association in the region of *UBE2L3* and use molecular methods to determine the functional effect of the risk haplotype.

Methods: The IlluminaiSelect platform was employed to genotype SNPs within the *UBE2L3* region in 8,922 cases and 8,077 controls, including: African-Americans (1,569 cases/1,893 controls), Asians (1,328 cases/1,348 controls), Europeans (4,248 cases/3,818 controls), Gullah (155 cases/131 controls), and Hispanics enriched for Amerindian-European admixture (1,622 cases/887 controls). Imputation was performed using IMPUTE2 and the 1000 Genomes Project reference panels. The single marker association analyses were calculated using the logistic regression function in PLINK adjusting for gender and global ancestry estimates. Haploview version 4.2 was used to generate probable haplotypes and calculate haplotypic association for all haplotypes formed by the associated markers. Eight EBV-transformed B cell lines with risk haplotype and 16 with non-risk haplotype were used to study the effect on *UBE2L3* mRNA and UBcH7 protein expression. Quantitative RT-PCR and western blotting was performed to compare the mRNA and protein expression level of *UBE2L3*, respectively.

Results: We identified strong associations between variants in *UBE2L3* and SLE in Europeans (86 SNPs with $P < 1 \times 10^{-4}$), Asians (71 SNPs with $P < 1 \times 10^{-3}$), and modest association in African-Americans (24 SNPs with $P < 0.01$), and Hispanics (17 SNPs with $P < 0.01$). A single risk haplotype was observed in subjects of European-ancestry ($P = 2.07 \times 10^{-7}$), and the other associated populations. However, due to strong LD across the region we were not able to narrow the risk interval using genetic methods ($r^2 > 0.8$). Previous studies suggested that variants in the region of *UBE2L3* influence *UBE2L3* transcript expression. To evaluate if the SLE risk haplotype carries variants that influence *UBE2L3* transcript or UBcH7 protein levels, we used quantitative-PCR and western blotting. Our results demonstrate that individuals harboring the risk haplotype display a significant increase in both mRNA expression ($P < 0.001$) and UBcH7 protein expression ($P = 0.001$). These results suggest

the variants carried on the SLE associated *UBE2L3* risk haplotype influence autoimmunity by modulating UBcH7 expression.

Conclusion: *UBE2L3* is an SLE risk locus present in multiple ethnic groups. Our data demonstrate a single risk haplotype with strong linkage disequilibrium that resists further genetic refinement. The *UBE2L3* risk haplotype results in increased expression of both *UBE2L3* mRNA and UBcH7 protein.

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A Functional Haplotype in the Region of *TNIP1* Is Associated with Systemic Lupus Erythematosus in Multiple Populations. Indra Adrianto[1], Graham B. Wiley[1], Shaofeng Wang[1], Kenneth M. Kaufman[2], Juan-Manuel Anaya[3], Marta E. Alarcón-Riquelme on behalf of BIOLUPUS and GENLES networks[4], Sang-Cheol Bae[5], Elizabeth E. Brown for PROFILE[6], Barry I. Freedman[7], Gary S. Gilkeson[8], Chaim O. Jacob[9], Judith A. James[10], Robert P. Kimberly[6], Javier Martin[11], Joan T. Merrill[1], Timothy B. Niewold[12], Betty P. Tsao[13], Timothy J. Vyse[14], Carl D. Langefeld[7], John B. Harley[15], Edward K. Wakeland[16], Kathy L. Moser[17], Courtney G. Montgomery[1] and Patrick M. Gaffney[17]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation and US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [3]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [4]Oklahoma Medical Research Foundation and Centro de Genómica e Investigación Oncológica Pfizer-Universidad de Granada-Junta de Andalucía (GENYO), Granada, Spain, Oklahoma City, OK, [5]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [6]University of Alabama at Birmingham, Birmingham, AL, [7]Wake Forest School of Medicine, Winston-Salem, NC, [8]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [9]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [10]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [11]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [12]University of Chicago, Chicago, IL, [13]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [14]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [15]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [16]Univ of Texas SW Med Ctr, Dallas, TX, [17]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Recent genome-wide association studies (GWAS) in Asian and European-ancestry (EA) populations have revealed genetic variants in the vicinity of *TNIP1* to be associated with systemic lupus erythematosus (SLE), an autoimmune disease characterized by loss of tolerance to self-antigens and dysregulated interferon responses. *TNIP1* encodes for the adapter protein ABIN1 that recruits A20 to polyubiquitinated NEMO (IKKγ) facilitating NEMO deubiquitination and restriction of NF-κB signaling. To fully characterize the variants in *TNIP1* responsible for association with SLE, we performed fine mapping, resequencing, and imputation using single-nucleotide polymorphisms (SNPs) within *TNIP1* on chromosome 5q33 in five ethnically diverse populations.

Methods: Genotyping was performed on the Illumina iSelect platform for 83 SNPs within *TNIP1* in the following cases and controls: African-American (AA) (1,569/1,893), Asian (1,328/1,348), EA (4,248/3,818), Gullah (155/131) and Hispanic (1,622/887) populations. Imputation was conducted using IMPUTE2 and the 1000 Genomes Project haplotypes. Imputation using targeted resequencing data from 187 EA and 46 AA individuals was also performed in order to improve ascertainment of causal alleles enriched in SLE patients. The single marker association analyses were performed using logistic regression in PLINK. Conditional analyses adjusting for each haplotype-tagging variant were done using logistic regression. Haplotypes were estimated followed by haplotypic association using Haploview. Western blotting was performed to compare the basal protein expression level of ABIN1 in the EBV-transformed B cell lines of 9 individuals with risk haplotypes and 7 individuals with non-risk haplotype.

Results: The peak associations of variants within *TNIP1* were observed in EA ($P = 2.24 \times 10^{-11}$), Hispanic ($P = 8.00 \times 10^{-7}$), and AA ($P = 1.15 \times 10^{-5}$) populations, respectively. We saw more modest association in Asians ($P = 2.53 \times 10^{-4}$), but no association in Gullah. In the EA population, we were able to dissect two independent risk haplotypes (H1 and H2) with $P = 1.54 \times 10^{-6}$ and $P = 7.49 \times 10^{-6}$ by conditional analyses. Interestingly, the H1 haplotype was also present in AAs and Hispanics, but we saw no evidence of the H2 haplotype in other populations. To determine if these risk haplotypes carry variants that influence the expression of ABIN1 protein, we used Western blotting in lysates from resting EBV transformed lymphocytes harboring either haplotype. We observed a significant decrease in ABIN1 protein expression ($P = 0.0029$) in 7 individuals with the H1 haplotype suggesting functional variants present on this haplotype influence susceptibility to autoimmunity by restricting ABIN1 expression.

Conclusion: We have comprehensively characterized the variants present within *TNIP1* in five populations. In the EA population, we observed two risk haplotypes one of which was also seen in AAs and Hispanics. Variants present on this haplotype result in decreased ABIN1 protein expression. Further functional studies to investigate the role of *TNIP1* in regulating autoimmunity are ongoing.

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The Role of *Bsm*I and *Fok* I Vitamin D Receptor Gene Polymorphisms and Serum 25-Hydroxyvitamin D in Systemic Lupus Erythematosus. Odirlei A. Monticielo[1], Jose A. B. Chies[1], Guilherme G. Rucatti[2], Maria G. F. Longo[1], R. Scalco[3], João Carlos T. Brenol[1] and Ricardo M. Xavier[1]. [1]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]Universidade Federal do Rio Grande do Sul, Porto A legre, Brazil, [3]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Background/Purpose: Vitamin D has pleiotropic actions on many chronic diseases. The expression of the VDR (vitamin D receptor) in various cells of the immune system strengthens the possible influence of vitamin D on systemic lupus erythematosus (SLE). Genetic polymorphisms located in *VDR* gene may determine changes in the mechanisms of action of vitamin D, but with results still unknown. The *Bsm*I *VDR* polymorphism was associated with SLE in Asian patients and more studies are needed to further clarification.

Methods: A case-control study with 195 SLE patients and 201 health controls was performed to investigate the influence of *Bsm*I and *Fok*I *VDR* gene polymorphisms on the susceptibility to SLE. Serum 25-hydroxyvitamin D [25(OH)D)] levels were measured in the cases. Genotyping was performed by Restriction Fragment Length Polymorphism-Polymerase Chain Reaction (RFLP-PCR), using primers and restriction enzymes specific for each polymorphism. The measurement of 25(OH)D was performed by chemiluminescence.

Results: There was no statistically significant difference in genotypic and allelic frequencies of *Bsm*I and *Fok*I polymorphisms among European-derived cases and controls. There was no association between clinical and laboratory features in SLE patients and the studied polymorphisms. The mean serum levels of 25(OH)D were 25.51±11.43 ng/ml in SLE patients. When patients were classified according to vitamin D status, the following distribution was observed: 55 (30.4%) had normal ($\geq$30 ng/ml), 63 (34.8%) insufficient (20–30 ng/ml), 52 (28.7%) deficient ($<$20 ng/ml) and 11 (6,1%) critically low serum levels ($<$10 ng/ml). Fifty six percent of patients with deficiency received at least 800 IU of vitamin D per day. Based on genotype distribution, 25(OH)D levels were significantly higher in patients carrying the f/f genotype, when compared to patients carrying the F/F genotype (31.6±14.1 ng/ml versus 23.0±9.2 ng/ml, p=0.004). Vitamin D levels were not associated with clinical and laboratory features of SLE.

Conclusion: The *Fok*I polymorphism showed significant influence on 25(OH)D levels, reinforcing its role in functional activity of VDR. This finding may be considered in future clinical and experimental studies involving vitamin D measurements. Serum concentrations of 25(OH)D required to maintain optimal musculoskeletal, cardiovascular and immune health should be individualized for each patient and new guidelines about vitamin D supplementation may have to take into consideration the individual genetic background. Genetic-specific definitions of ideal levels of vitamin D in SLE should therefore be established in future studies.

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SLE-Risk Alleles of SNPs in the *NMNAT2*/*SMG7* Region Are Associated with Lower mRNA Levels of *SMG7*. Jian Zhao[1], Daisuke Sakurai[1], Yun Deng[1], Andrea L. Sestak[2], Carl D. Langefeld[3], Kenneth M. Kaufman[4], Jennifer A. Kelly[5], Patrick M. Gaffney[6], Kathy L. Moser[6], Marta E. Alarcón-Riquelme on behalf of BIOLUPUS and GENLES network[7], John B. Harley[8], Sang-Cheol Bae[9], Timothy J. Vyse[10], Chaim O. Jacob[11], Robert P. Kimberly on behalf of PROFILE investigators[12], Lindsey A. Criswell[13], Judith A. James[14], Gary S. Gilkeson[15], Juan-Manuel Anaya[16], Deh-Ming Chang[17], Yeong W. Song[18], Jennifer M. Grossman[19], Bevra H. Hahn[19], Rita M. Cantor[20] and Betty P. Tsao[1]. [1]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Wake Forest University Health Sciences, Winston-Salem, NC, [4]US Department of Veterans Affairs Medical Center and Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]Centro de Genómica e Investigación Oncológica Pfizer-Universidad de Granada-Junta de Andalucía (GENYO), Granada, Spain and Oklahoma Medical Research Foundation, Oklahoma City, OK, [8]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [9]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [10]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [11]Keck School of Medicine University of Southern California, Los Angeles, CA, [12]University of Alabama Birmingham, Birmingham, AL, [13]Rosalind Russell Medical Research Center for Arthritis, Department of Medicine, University of California San Francisco, San Francisco, CA, [14]Department of Medicine, University of Oklahoma Health Sciences Center and Oklahoma Medical Research Foundation, Oklahoma City, OK, [15]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [16]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [17]National Defense Medical Center, Taipei, [18]Seoul National University, Seoul, [19]UCLA David Geffen School of Medicine, Los Angeles, CA, [20]University of California Los Angeles, Los Angeles, CA

Background/Purpose: Within the 1q25 region, rs2022013 located in *NMNAT2* (encoding a central enzyme of the NAD biosynthesis pathway expressed mainly in neurons) was associated with SLE in the SLEGEN genome-wide association study (GWAS) and a replication study conducted in subjects of European ancestry, which indicates the *NMNAT2* region is a risk locus for SLE. Here we sought to fine map the *NMNAT2* region to identify underlying causal variants predisposing to SLE.

Methods: We genotyped 34 *NMNAT2* SNPs and 347 ancestry informative markers (AIMs) in 15,292 case-control subjects including European Americans (EA, 3438 cases vs. 3417 controls not used in SLEGEN GWAS), African Americans (AA, 1679 vs. 1934), Asians (AS, 1265 vs. 1260) and Hispanics enriched for the Amerindian-European admixture (HS, 1492 vs. 807). AIMs were used to estimate global ancestry for each subject and eliminate genetic outliers. *NMNAT2* SNPs were assessed for the association with SLE under a logistic regression model adjusted for sex and global ancestry. We also imputed genotypes for SNPs in the 1000 Genomes Project and assessed them for the association with SLE. In addition, we performed conditional analysis to distinguish independent association signals, meta-analysis to calculate combined *P* value and RT-PCR to measure gene expression levels.

Results: We detected significant association signals (defined as $P<0.05/34=1.5\times10^{-3}$) in EA and HS but not in AA and AS. Previously reported association of rs2022013 with SLE was confirmed in EA ($P=3.9\times10^{-7}$, OR=0.83). After imputation, 163 SNPs in EA and 10 SNPs in HS, spanning 239 kb from *NMNAT2* to *SMG7*, were significantly associated with SLE, of which 68 SNPs showed consistent association in EA and HS ($P<0.05$). These association signals could be explained by 4 groups of SNPs (group 1: rs12146097, $P_{meta}=6.4\times10^{-13}$, OR=1.40; group 2: proxy SNP rs12410472, $P_{meta}=1.6\times10^{-6}$, OR=0.77; group 3: proxy SNP rs2702178, $P_{meta}=7.9\times10^{-10}$, OR=1.22; group 4: proxy SNP rs536586, $P_{meta}=1.5\times10^{-7}$, OR=1.18). Group 1, 2 and 4 SNPs are all located in intron 1 of *NMNAT2* long isoform, but multiple group 3 SNPs are located in the *SMG7* region. SMG7 is an ubiquitously expressed key component of the nonsense-mediated mRNA decay (NMD) pathway, which mainly functions in controlling mRNA quality and expression levels and is coupled with alternative splicing to regulate core spliceosomal proteins such as Sm and snRNP. In the Genevar eQTL database, SLE-risk alleles of group 1, 3 and 4 SNPs were associated with lower expression levels of *SMG7* rather than *NMNAT2* or other genes within 250 kb. We confirmed that the risk allele of group 3 SNPs showed dosage-dependent association with lower mRNA levels of *SMG7* in PBMCs of 34 SLE patients and 33 healthy controls of European ancestry ($P<1.0\times10^{-4}$), in which *SMG7* levels were negatively associated with known ANA titers of 26 of the 34 SLE patients ($r=-0.43$, $P=0.03$).

Conclusion: We identified SLE-associated SNPs, exceeding GWAS significance level of $P<5.0\times10^{-8}$, in the *NMNAT2*/*SMG7* region and showed that these SNPs might confer risk of SLE, at least in part, by influencing the expression of *SMG7*. These findings implicate a novel mechanism by which the NMD pathway may be involved in the pathogenesis of SLE.

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Association of Androgen Receptor Gene Polymorphism with Damage in Systemic Lupus Erythematosus. Yun Deng[1], Jennifer M. Grossman[2], Qiong Fu[1], William Martin[1], Matthew Quirk[1], Ornella J. Rullo[3], Susan A. Boackle[4], Chaim Putterman[5], Jane E. Salmon[6], Vasileios C. Kyttaris[7], George C. Tsokos[7], Erika Magdangal[1], Lori Sahakian[2], Weiling Chen[1], Jennifer MP Woo[3], Deborah K. McCurdy[3], Chack-Yung Yu[8], Bevra H. Hahn[2], Maureen A. McMahon[1] and Betty P. Tsao[1]. [1]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [2]UCLA David Geffen School of Medicine, Los Angeles, CA, [3]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [4]University of Colorado Denver School of Medicine, Aurora, CO, [5]Albert Einstein College of Medicine, Bronx, NY, [6]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [7]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [8]7Center for Molecular and Human Genetics, The Research Institute at Nationwide Children's Hospital and The Ohio State University, Columbus, OH

Background/Purpose: Organ damage predicts physical function and mortality of SLE. The exploration of genes contributing to risk for damage in SLE has been limited. Since men with SLE tend to accrue damage more rapidly, we investigated whether an X-linked androgen receptor (*AR*) polyGLN polymorphism that impacts androgen receptor transactivation activity correlated with damage assessed by the SLICC/ACR Damage Index (SDI) in SLE.

Methods: A retrospective chart review was performed to collect the clinical data. The damage score was calculated using SDI, a standardized, validated damage instrument. Length of CAG repeat in exon 1 of *AR* genotyped by PCR was assessed for association with SDI using the Spearman correlation test, Chi square test, and logistic regression analysis.

Results: Men with SLE (n = 129) had a shorter disease duration than 422 women with SLE (median [interquartile range] = 5.5 [2–11] vs. 8.5 [3–16] years, $p = 0.007$), but similar composition of ancestry background, age at onset and cumulative prednisone dose. The proportion of patients who had accrued any damage was higher among men than women in the first 5 years of disease (63.5% vs.39.5%, $p = 0.004$). Both genders had similar damage accrual in the general SDI categories, except for the renal and pulmonary system in which men were more likely to accrue damage ($p = 0.0002$ and 0.01, respectively). For AR analysis, CAG repeat length ranged from 12 to 31 in men and 11 to 26 in women with SLE. Combined both genders, the number of CAG repeats varied with ethnicity that the interquartile range was 17–21 in European or Hispanic, 16–19.5 in African, and 18.5–22 in Asian ancestry ($p < 0.0001$). The lowest quartile of CAG repeat length ($n \leq 17$) was significantly associated with more damage (SDI ≥ 2) in women (OR = 2.49 [1.57–3.94], $p = 0.0001$), but only in men within the top quartile of disease duration (>16 years) (OR = 3.71 [1.10–12.56], $p = 0.04$). Using logistic regression analysis, independent risk factors for increased damage (SDI ≥ 2) in the combined 551 SLE patients were short CAG repeat length ($n \leq 17$) (OR = 2.17 [1.36–3.47], $p = 0.001$), higher cumulative prednisone dosage (OR = 2.13 [1.62–2.79], $p<0.0001$), and longer disease duration (OR = 1.06 [1.04–1.09], $p<0.0001$), but not male gender, non-European ancestry and age at onset which were previously observed to be associated with more organ damage (Table 1).

Table 1. Independent risk factors for increased damage (SDI≥2) in SLE

Independent factors*	OR	95% CI	*p*
Short CAG repeat (≤17)	2.71	1.36–3.47	0.001
Cumulative prednisone dose	2.13	1.62–2.79	*<0.0001*
Disease duration (yrs)	1.06	1.04–1.09	*<0.0001*
Male gender	1.52	0.86–2.67	0.13
Non-European ancestry	1.52	0.97–2.40	0.15
Age at onset (yrs)	1.01	0.99–1.02	0.11

*In this logistic regression model, disease duration and age at onset were entered as a continuous variable, whereas others as categorical variables. Cumulative prednisone dose was defined as: 0=0–10 grams; 1=10–20 grams; 2=>20 grams.

Conclusion: Compared to women, men with SLE in this study had accelerated damage accrual particularly in the early course of disease and a higher risk of developing renal and pulmonary damage. The short CAG repeat (≤17), which confers an enhanced androgen transactivation activity resulting in a heightened response of testosterone and DHEA binding might be a prognostic marker for SLE damage in both genders, particularly during the second decade after disease onset. These data support a potential role for androgen signaling in the development of damage in SLE.

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Association of Reactive Intermediate Genes with Systemic Lupus Erythematosus (SLE) Varies Across Populations with Different African Ancestries. Paula S. Ramos[1], James C. Oates[2], Diane L. Kamen[2], Patrick M. Gaffney[3], Carl D. Langefeld[1], Jennifer A. Kelly[3], Kenneth M. Kaufman[3], Robert P. Kimberly[4], Timothy B. Niewold[5], Chaim O. Jacob[6], Betty P. Tsao[7], Elizabeth Brown for PROFILE[4], Judith A. James[8], Joel Guthridge[3], Joan T. Merrill[3], Susan A. Boackle[9], Barry I. Freedman[1], R. Hal Scofield[3], Anne M. Stevens[10], Timothy J. Vyse[11], Lindsey A. Criswell[12], Kathy L. Moser[3], Marta E. Alarcon-Riquelme[13], John B. Harley[14] and Gary S. Gilkeson[2]. [1]Wake Forest School of Medicine, Winston-Salem, NC, [2]Medical University of South Carolina, Charleston, SC, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]University of Alabama at Birmingham, Birmingham, AL, [5]University of Chicago, Chicago, IL, [6]Keck School of Medicine, University of Southern California, Los Angeles, CA, [7]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, [8]Oklahoma Medical Research Foundation and Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [9]University of Colorado Denver School of Medicine, Aurora, CO, [10]University of Washington, Seattle, WA, [11]King's College London, Guy's Hospital, London, United Kingdom, [12]University of California San Francisco, San Francisco, CA, [13]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [14]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH

Background/Purpose: Very little is known about the genetic etiology of systemic lupus erythematosus (SLE) in individuals of African ancestry – in spite of its higher prevalence, incidence, disease severity, and mortality rates in African Americans (AA). Overproduction of nitric oxide (NO) has been implicated in its pathogenesis and correlated with disease severity, making NO synthases and other reactive intermediate genes biological candidates for disease susceptibility. Here, we report a comprehensive analysis of reactive intermediate genes for their association with SLE in populations of African ancestry. One such population is the Gullah of the Sea Islands of South Carolina: a population isolate with limited and well defined ancestral diversity. Such reduced genetic heterogeneity may increase the power to detect associations in this population. In addition, their higher familial disease prevalence might reflect a stronger genetic component to the disease.

Methods: We analyzed 279 SNPs from 55 regions in 133 Gullah cases and 112 Gullah controls, as well as in other 1432 AA cases and 1575 AA controls. These and approximately 300 additional ancestry informative markers were genotyped on an Illumina custom array; principal components analysis and admixture estimates were computed and adjusted for in association analyses.

Results: While the *glutathione reductase G*SR (rs2253409, P=0.0014, odds ratio (OR) [95% confidence interval (CI)]=1.26 [1.09–1.44]) and *paraoxonase PON3* (rs17879114, P=0.0016, OR [95%CI]=0.79 [0.68–0.91]) were the most significant single-SNP associations in AA, in the Gullah the *NADH dehydrogenase NDUFS4* (rs381575, P=0.0065, OR [95%CI]=2.10 [1.23–3.59]) and *nitric oxide synthase NOS1* (rs561712, P=0.0072, OR [95%CI]=0.62 [0.44–0.88]) were the most strongly associate with SLE. When analyzed together, *GSR* remained the most significant effect (rs2253409, P=0.00072, OR [95%CI]=1.26 [1.10–1.44]). Haplotype analyses revealed a significant 3-SNP haplotype in *NOS1* in AA (rs3741476-rs10774909, P=0.00029, OR=1.32), as well as in the joint cohorts together (P=0.00074, OR=1.28). Two-loci interaction analysis uncovered significant interactions between *NDUFS2* (rs4656993) and the *minichromosome maintenance complex component MCM5* (rs4645794) in AA (P=9.74E-05, OR [95%CI]=1.40 [1.32–1.48]), between the *ring finger protein RNF157* (rs11099897) and the *toll-like receptor TLR7* (rs5741880) in the Gullah (P=6.61E-05, OR [95%CI]=4.10 [1.54–10.91]), and between *PON3* (rs13226149) and *TLR7* (rs1731479) in the joint cohort (P=0.0003, OR [95%CI]=1.41 [1.32–1.50]).

Conclusion: These results suggest that different variants in reactive intermediate genes in different African ancestries may be associated with SLE.

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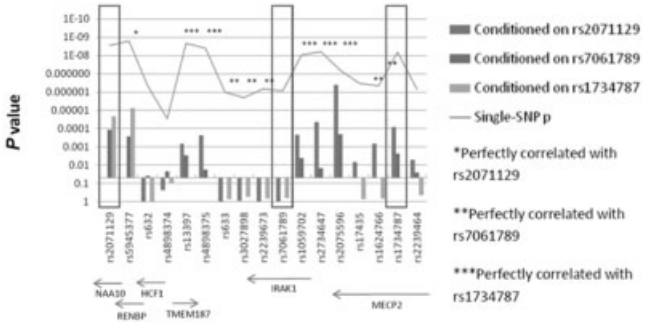
Fine Mapping of Xq28: Both *MECP2/IRAK1* and *NAA10/RENBP* Contribute to Risk for SLE in Multiple Ancestral Groups. Kenneth M. Kaufman[1], Jennifer A. Kelly[2], Travis Hughes[2], Adam Adler[2], Elena Sanchez[2], Joshua O. Ojwang[2], Carl D. Langefeld[3], Julie T. Ziegler[3], Judith A. James[4], Elizabeth E. Brown[5], Robert P. Kimberly[6], Jeffrey C. Edberg[7], Lindsey A. Criswell[8], Deh-Ming Chang[9], Gary S. Gilkeson[10], Timothy B. Niewold[11], Sang-Cheol Bae[12], Marta E. Alarcón-Riquelme[13], Chaim O. Jacob[14], Kathy L. Moser[15], Patrick M. Gaffney[15], John B. Harley[16], Amr H. Sawalha[2] and Betty P. Tsao[17]. [1]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation and US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Wake Forest University Health Sciences, Winston-Salem, NC, [4]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [5]Department of Medicine and Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [6]University of Alabama at Birmingham, Birmingham, AL, [7]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [8]University of California San Francisco, San Francisco, CA, [9]National Defense Medical Center, Taipei, [10]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [11]University of Chicago, Chicago, IL, [12]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [13]Oklahoma Medical Research Foundation and Centro de Genómica e Investigación Oncológica Pfizer-Universidad de Granada-Junta de Andalucía (GENYO), Granada, Spain, on behalf of the BIOLUPUS and GENLES networks, Oklahoma City, OK, [14]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [15]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [16]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [17]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA

Objectives: Previous studies have identified genetic associations of SLE with *IRAK1* (interleukin-1 receptor associated kinase-1) and its adjacent gene, *MECP2* (Methyl-CpG-binding protein 2) located on chromosome Xq28. To further our understanding of Xq28, we assessed a 215 kb region, including *IRAK1, MECP2,* and 6 other genes, in a trans-ancestral approach using >15,000 case-control samples of European, African, Asian and Hispanic descent.

Methods: We genotyped 55 SNPs spanning 8 genes on Xq28 and 347 ancestry informative markers (AIMs) using a customized Illumina array on the iSCAN instrument. Association tests were calculated using logistic regression, as implemented in PLINK, while adjusting for the four admixture proportions (west African, Indigenous American, Asian and European) using AIMs. Standard haplotype analyses were performed using Haploview 4.2. A trans-ancestral meta-analysis was conducted on the 23 SNPs that produced clean data for the European, Asian and Hispanic samples using METAL. Conditional haplotype-based likelihood ratio test statistics were calculated to localize genetic effects observed at Xq28.

Results: Stratification based on gender identified association in Xq28 in both males and females, however the number of males analyzed was smaller due to lupus being a predominately female disease. Robust associations of SNPs located in genomic region containing *NAA10, RENBP, HCFC1, TMEM187, IRAK1*, and *MECP2* with SLE in samples of European (4248 cases vs. 3818 controls), Asian (1328 vs. 1348) and Hispanic (961 vs. 336) populations surpassing genome wide significance were detected ($p<5\times10^{-8}$;

n=7, 12, and 4 SNPs, respectively), but no association after adjustment for multiple testing was detected in African descent (1569 vs. 1893). Located ~70 kb upstream of the *IRAK1/MECP2* locus, the *NAA10* (N-alpha-acetyltransferase 10)/*RENBP* (rennin binding protein) locus also exhibited strong linkage disequilibrium between the two neighboring genes, and the strongest association was observed at rs5945377 of *RENBP* in the European samples ($p=1.58\times10^{-9}$, OR= 1.35) and supported in both Asian and Hispanic samples ($p=1.76\times10^{-5}$and 7.36×10^{-5}, OR=1.32 and 1.30, respectively). A trans-ancestral meta-analysis of European, Asian, and Hispanic derived samples showed $p_{meta}=5.85\times10^{-17}$, $p_{meta}=1.95\times10^{-22}$ and $=2.68\times10^{-21}$ at *NAA10/RENBP*, *MECP2* and *IRAK1,* respectively. In the largest dataset of Europeans, haplotype-based likelihood ratio test statistics showed that the *NAA10/RENBP* effect (proxy SNP rs2071129) appeared to be independent of *IRAK1* (rs7061789) and *MECP2* (rs1734787), and the *MECP2* association was stronger than that of *IRAK1* in lupus susceptibility (Figure 1).



Conclusion: We confirmed strong association of *MECP2* and *IRAK1* with SLE in European, Asian, and Hispanic ancestries, and identified the *NAA10/RENBP* region as a novel lupus susceptibility locus within Xq28.

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Triple X Syndrome (47,XXX) Increases the Risk and Accelerates the Onset of Systemic Lupus Erythematosus and Sjögren's Syndrome: Support for a Gene-Dose Effect From the X Chromosome. Skyler P. Dillon[1], Lydia Kao[1], Kenneth M. Kaufman[2], John A. Ice[2], Roald Omdal[3], Xavier Mariette[4], Torsten Witte[5], Gabor G. Illei[6], Maureen Rischmueller[7], Gunnel Nordmark[8], Roland Jonsson[9], Marie Wahren Herlenius[10], Timothy J. Vyse[11], Michael T. Brennan[12], Benjamin A. Rybicki[13], Wan-Fai Ng[14], Barbara M. Segal[15], Nelson L. Rhodus[16], Joan T. Merrill[2], Courtney G. Montgomery[2], Christopher J. Lessard[2], John B. Harley[17], Kathy L. Moser[18], Patrick M. Gaffney[18] and R. Hal Scofield[2]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway, [4]Université Paris-Sud, Le Kremlin Bicetre, France, [5]Hannover Medical School, Hanover, Germany, [6]NIDCR/NIH #10 1N110, Bethesda, MD, [7]Queen Elizabeth Hospital, Adelaide, Australia, [8]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden, [9]University of Bergen, Bergen, Norway, [10]CMM L8204 Karolinska Hosp, Stockholm, Sweden, [11]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [12]Carolinas Medical Center, Charlotte, NC, [13]Henry Ford Health System, Detroit, MI, [14]Newcastle University, Newcastle upon Tyne, United Kingdom, [15]Hennepin County Medical Center, Minneapolis, MN, [16]University of Minnesota, Minneapolis, MN, [17]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [18]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Autoimmune diseases are a common cause of death among young women, but not men. Women are ~8 times more likely to have systemic lupus erythemstosus (SLE) and ~14 times more likely to have Sjögren's syndrome (SS). This gender bias has long been suspected to be caused by sex hormones. However, on the contrary, men who have an extra X chromosome (47,XXY Klinefelter's syndrome) are ~11 times more likely to have lupus, even though their circulating sex hormone profile is closer to a man's than a woman's. This observation lead to the hypothesis that the extra X chromosome may be the culprit behind female biased autoimmune diseases, instead of circulating sex hormones. In order to further test this hypothesis, here we looked to see if triple X syndrome (47,XXX), which has a hormone profile comparable to 46,XX females, is increased among lupus and Sjögren's patients.

Methods: All patients either met the 1997 ACR criteria for SLE or the 2002 revised European criteria for SS. Genotyping of at least 200k SNPs was performed on each DNA sample from 2,137 lupus women, 1,483 Sjögren's women, and 2,902 control women. Samples with abnormal SNP allele frequencies for chromosome X were confirmed by interphase FISH and/or quantitative PCR. The prevalence of Turner syndrome (45,X), triple X syndrome (47,XXX), mosaicism, and Down syndrome in the patients and controls were statistically compared using Fisher's exact test.

Results: Triple X syndrome (47,XXX) and its variants were found in 9 of 2,137 lupus patients and in 5 of 1,483 Sjögren's patients, but not in any of the 2,902 control women (RR=∞ (2.30-∞), P<0.001; and RR=∞ (1.69-∞), P=0.004; respectively). We estimate that there is 1 lupus and ~8 Sjögren's women among every ~453 women with 47,XXX. The average age of lupus onset in women with 47,XXX was 23.2yrs vs. 35.5yrs for the rest of the lupus cohort (P=0.044, Mann-Whitney U test). Classic Turner syndrome (45,X) was not found in any lupus or Sjögren's patient, but in one control (P=1.00). Down syndrome (47,XX,+21) was not found in anyone, contrary to case reports suggesting its association with lupus.

Conclusion: The prevalence of lupus and Sjögren's in triple X syndrome (47,XXX) was estimated to be ~3 and ~4 times higher than in 46,XX women and ~25 and ~52 times higher than in 46,XY men, respectively. Interestingly, the lupus patients with a 47,XXX genotype developed the disease on average ~13yrs earlier than the other patients in the cohort. Furthermore, no lupus or Sjögren's patient was found with a 45,X genotype. These results along with our results showing increased Klinefelter's (47,XXY) in SLE, imply that X chromosome number, independent of circulating sex hormone levels, explains the sex-bias of SLE and SS.

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Effects of OAZ In Regulating B-Cell Proliferation by Mesenchymal Stem Cells From Patients with Systemic Lupus Erythematosus. Xuebing Feng[1], Yan Liu[1], Nan Che[1], Dandan Wang[1], Betty P. Tsao[2] and Lingyun Sun[1]. [1]Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]UCLA School of Medicine, Los Angeles, CA

Background/Purpose: Allogeneic mesenchymal stem cell transplantation (MSCT) has shown some benefits in patients with refractory systemic lupus erythematosus (SLE). However, the underlying mechanism is still unclear. Our data indicate that Olf1/EBF associated zinc finger protein (OAZ), a novel lupus susceptibility gene down-regulated after MSCT, is involved in the production of antinuclear antibody (ANA). Because this gene is highly expressed in MSCs, the role of OAZ in MSC-B cell regulation is explored.

Methods: Study protocol was approved by the hospital's Ethics Committee. MSCs isolated and expanded after culturing for 3 passages from bone marrow of 4 female SLE patients, were incubated with siRNAs targeting OAZ or non-targeting sequence. Three days later, cells were collected for measuring mRNA levels of OAZ and ID1–3, downstream genes of OAZ, using quantitative real-time polymerase chain reaction (qPCR) and levels of cytokines and chemokines in cultured supernatants were detected by ELISA. Splenic B cells from C57BL/6 mice were purified using anti-CD43 antibody, co-cultured with SLE MSCs at 10: 1 ratio in the presence or absence of OAZ siRNAs, and then harvested for the detection of proliferation by using BrdU assay.

Results: Silencing OAZ in SLE MSCs 1) significantly reduced mRNA levels of OAZ and its downstream ID1–3 by 67.9 ± 7.2% and ~50% respectively, 2) significantly increased expression levels of CCL2, a MSC-derived chemokine involved in plasmablast proliferation, in both mRNA and protein of cultured supernatants, and had no effects in IL-21 levels. Figure 1 showed LPS stimulated proliferation of mouse B cells was not affected by co-culturing with human MSCs at 1:10 ratio (28 ± 0.4% vs 31 ± 0.8%,n= 3 and $p > 0.05$), but was impaired (18 ± 1.6%, $p < 0.05$) by the addition of siRNAs targeting human OAZ gene in the co-cultures. Interestingly, when anti-CCL2 neutralizing antibody (1ng/ml) was added to MSC-B cell co-cultures, the ability of B cell proliferation was fully restored.

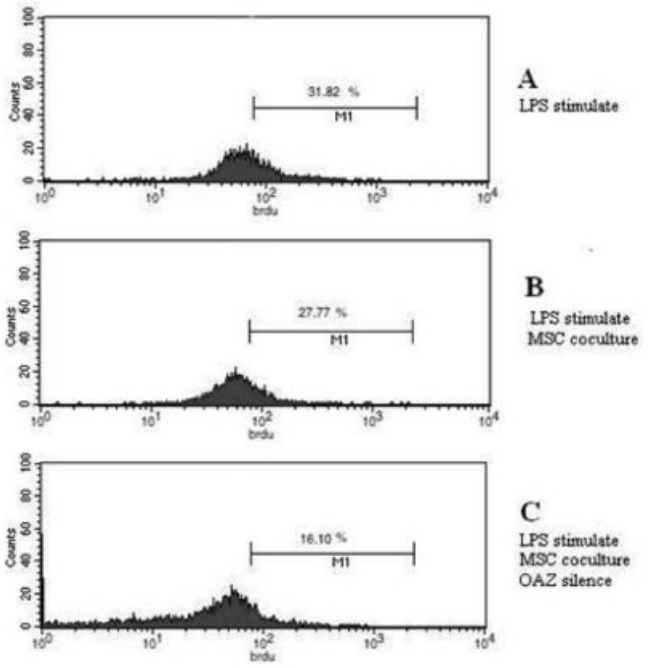

Figure 1. Representative result of proliferated B cells measured by BrdU. A, B cell cultured with LPS stimulation. B, B cell- MSC co-culture, with LPS stimulation. C, B cell-MSC co-culture in the presence of OAZ siRNAs, with LPS stimulation.

Conclusion: Down-regulating of OAZ in MSCs increases CCL2 levels and inhibits B cells proliferation in MSC-B cell co-cultures, implicating a role of OAZ in SLE MSCT.

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Differential DNA Methylation Associated with Anti-dsDNA Autoantibody Production In Systemic Lupus Erythematosus. Sharon A. Chung[1], Kimberly E. Taylor[1], Hong L. Quach[2], Lisa F. Barcellos[2] and Lindsey A. Criswell[1]. [1]University of California, San Francisco, San Francisco, CA, [2]University of California, Berkeley, Berkeley, CA

Background/Purpose: Aberrant DNA methylation has been implicated in the pathogenesis of systemic lupus erythematosus (SLE), with less DNA methylation observed in SLE patients compared to healthy controls. We conducted this study to identify differences in DNA methylation across the genome associated with anti-dsDNA autoantibody production, a clinically relevant autoantibody associated with kidney damage and more severe disease in SLE.

Methods: Genomic DNA from peripheral blood leukocytes was isolated from 104 pairs of SLE cases (n=208 cases total). All SLE cases were female, of European descent, and had never smoked. Case pairs were discordant for anti-dsDNA autoantibody production status (positive vs. negative), and were matched (within 5 years) on age at DNA sample collection and SLE disease duration. Using the Illumina HumanMethylation27 Beadchip, the methylation status of 27,568 CpG sites across the genome were interrogated in all SLE cases. Paired t-tests were used to identify site-specific methylation differences associated with anti-dsDNA autoantibody production. P-values less than 1.8×10^{-6} (Bonferroni corrected) were considered statistically significant.

Results: Overall, less methylation was observed in the anti-dsDNA positive group. Mean methylation levels were decreased in the anti-dsDNA positive cases when compared to anti-dsDNA negative cases for 63% of the CpG sites investigated (n=17,286). Increased methylation of two CpG sites in *PRIC285*, a transcriptional co-activator for nuclear receptors, was significantly associated with anti-dsDNA autoantibody production ($p=1.9 \times 10^{-7}$ and 3.4×10^{-7}). Decreased methylation of a CpG site near *SOCS2* ($p=3.5 \times 10^{-7}$), an inhibitor of the STAT family of transcription factors, was also associated with anti-dsDNA autoantibody production. No evidence of interaction ($p>0.05$) was found between methylation of the associated *SOCS2* CpG site and rs7574865 of *STAT4*, a known SLE susceptibility and anti-dsDNA propensity locus.

Conclusion: Similar to comparisons between SLE cases and controls, DNA from autoantibody positive SLE cases appears to be less methylated than autoantibody negative SLE cases. Abnormal methylation of specific genes such as *PRIC285* and *SOCS2* may contribute to autoantibody production in SLE. Lastly, studies of DNA methylation and other epigenetic modifications may identify additional biologic mechanisms involved in the pathogenesis of SLE.

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Circulating T Helper Cells in Patients with Systemic Lupus Erythematosus Share the Phenotypic Property with Lymphoid T Follicular Helper Cells. Elvira Lindwall[1], Carl Gauthier[1], Anika Alarakhia[1], Gwendoline Menga[1], Jerald M. Zakem[1], William E. Davis[1], Tamika A. Webb-Detiege[1], Young Sung Choi[1], Robert Quinet[2] and Xin Zhang[1]. [1]Ochsner Medical Center, New Orleans, LA, [2]Ochsner Medical Center - New Orleans, New Orleans, LA

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by autoreactive B cells and autoantibody (autoAb) production. These autoAbs bind to self-antigens, leading to multi-system disease. T follicular helper (T_{FH}) cells, a T cell subset located in germinal center in secondary lymphoid organs, have emerged as a key participant that controls B cell peripheral tolerance and Ab production. Previously we have found that circulating T_{FH} (cT_{FH}) cells are expanded in SLE patients. To identify the origin and the role of cT_{FH} cells in SLE, we compared the phenotypic property of cTFH cells in SLE patients with lymphoid T_{FH} cells in the secondary lymphoid organ (tonsil), and correlated the percentage of cT_{FH} cells with autoAb production and disease activity in SLE patients.

Methods: Eighteen SLE patients diagnosed according to the ACR criteria were recruited. The disease activity was determined by SLEDAI. Blood from these lupus patients and eighteen age, gender-matched healthy controls was obtained. Mononuclear cells were isolated by Ficoll density-gradient centrifuge, and stained with fluorescent-conjugated Abs. T_{FH} cells were defined by their signature surface markers ($CD4^+CXCR5^+ICOS^+CD57^+$) via flow cytometry and analyzed using FlowJo software. The cT_{FH} cells, non- cT_{FH} cells from SLE patients, and lymphoid T_{FH} cells from tonsils were purified by MACS columns, and the purities were above 90%. The expression levels of cytokines of these cells were measured by RT-PCR and intracellular staining. Plasmablasts were identified by surface $CD20^{lo}CD38^{hi}$expression. Levels of anti-dsDNA Ab, anti-nuclear Ab (ANA), C3 and C4 were also collected. Statistical analysis was carried out using GraphPad Prism software and the significance was evaluated by *t* test. Correlation analysis was determined by Spearman's rank correlation test as *r* value.

Results: The frequency of cT_{FH} cells was significantly increased in SLE patients compared to healthy controls ($P<0.01$). This elevated frequency of cT_{FH} cells had a positive correlation with levels of circulating plasmablasts, serum anti-dsDNA Ab and ANA, but no correlation with serum C3 and C4. In addition, cT_{FH} cells from SLE patients shared similar phenotype and frequency with lymphoid T_{FH} cells, with less intense expression of co-stimulatory molecules CXCR5, CD57, and ICOS. Both the cT_{FH} cells from SLE patient and lymphoid T_{FH} cells expressed significant higher amounts of IL-21, IL-6 and IL-10 than non-T_{FH} cells in lupus patients and T helper cells from healthy donors. These cytokines are known to drive B cells to differentiate into IgG-secreting plasma cells *in vitro*.

Conclusion: The increased frequency of ectopically located cT_{FH} cells in SLE patients share a similar phenotype with lymphoid T_{FH}, and may derive from lymphoid organs. By secreting plasma cell driving cytokines (IL-21, IL-10, and IL-6), these accumulated cT_{FH} cells may ensure that self-reactive B cell clones further differentiate to plasmablasts producing autoAbs in the periphery, thus serve as perpetrators in the pathogenesis in SLE patients and a possible mechanism for treatment.

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Microarray Analysis of the autologous Hematopoietic Stem Cell Transplantation Induced Remission Associated CD8 Treg Cells Gene Expression Profile. Li Zhang, Anne M. Bertucci, Richard K. Burt and Syamal K. Datta. Northwestern University FSM, Chicago, IL

Background/Purpose: Our previous work demonstrated that autologous hematopoietic stem cell transplantation (HSCT) can induce true Immunologic Remission in refractory lupus by generating a newly differentiated population of FoxP3+, $LAP^{high}CD103^{high}CD8^{TGF\text{-}beta}$ Treg cells, which is lacking in

patients with conventional drug treated "clinical remission" (SLEDAI = 0). With the unique opportunity provided by HSCT, here we begin to characterize the genes for generation and mechanism of action of the unusual CD8+ Treg subset of post-transplant lupus patients.

Methods: Microarray analysis was conducted with Illumina Human HT12 Chip. The RNA was isolated from the autologous CD8+ T cell lines which were derived from the **same lupus patients** pre- and post-transplantation. RNA from the healthy subjects' CD8 T cell lines were included to compare with genes expression of post-transplant CD8 Treg cells, since both showed potent suppressive function. The data was analyzed with functional gene networks and gene set enrichment analysis to select the interesting genes.

Results: There were marked differences in the gene expression profiles between autologous pre- and post- transplantation CD8 line T cells. At the level of a ≥ 2-fold change, there were **314** genes showing an increase or decrease in expression in common among all three patients on comparing pre-transplant with their autologous post-transplant CD8 T cells that were cultured with IL-2 for 6 hours before the RNA was isolated. Among these **314** genes, **136** showed a consistent increase, and **85** genes showed a consistent decrease in expression among all three **pre**-transplant CD8 T cell samples when compared with their autologous **post**-transplant CD8 T cell lines, and also when compared with three different **normal** CD8 T cells lines from unrelated subjects, at two different time points (cultured with IL-2 for 6 or 12 hours before RNA isolation). After confirming with real time PCR, we narrowed down interesting genes which belong to pathways of immune response, inflammatory cytokine/chemokine, immunomodulation, TGF-β signal transduction, apoptosis pathways, DNA replication, cell cycle, and mitochondrial energy metabolism.

Conclusion: Gene expression microarray analysis of the autologous pre- and post-transplant CD8 line T cells derived from **same lupus patients** reveal interesting candidate genes, which may provide insight into the mechanisms of *human* lupus development (including how the pre-transplant CD8 line T cells "help" CD4 T cell reactivity to autoantigens) and understanding how the post-transplant CD8 Treg cells maintain patients in true *immunological remission* and how they are generated by HSCT, as well as to identify new cell surface markers of CD8 Treg cells.

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Peptides Inducing Potent Autoantigen-Specific Treg Cells in Human Lupus. Li Zhang[1], Anne M. Bertucci[1], Rosalind Ramsey-Goldman[2], Richard K. Burt[1] and Syamal K. Datta[1]. [1]Northwestern University FSM, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: To develop a natural, non-toxic therapy that generates potent Treg cells and devise a screening assay for therapeutic peptides to maintain lupus patients in remission.

Methods: PBMC from 15 lupus patients (5 active and 10 remission, 20–60 years), and 8 healthy subjects (23–57 years) were isolated and cultured with low doses of nucleosomal histone peptide autoepitopes: H1(22–42), H3(115–135), H3 (82–105), H4(16–32), and H4(71–94), as well as control peptides for 7 days, along with 50 U/ml of hIL-2. Then the percentage of *STABLE* CD4 and CD8 FoxP3+ Treg cells were analyzed by flow cytometry. The expression of TGFβ precursor-Latency Associated Peptide (LAP), CD103 and CD39 in T cells induced by peptides were also measured. The optimal culture conditions, and the effect of anti-inflammatory drugs on peptide induction of Treg cells, such as Dexamethasone (DEX), hydroxychloroquine (HCQ) and anti-IL6 were determined. The relation of FoxP3 expression with TGF-β/ALK-5/Smad signaling pathway in induced Treg cells was also explored.

Results: CD4+CD25highFoxP3+ cells, CD4+CD45RA+FoxP3low cells (induced Treg cells), CD8+CD25+FoxP3+ cells were all significantly increased in PBMCs when cells were cultured with very low dose histone peptide in vitro for 7 days, compared with control peptide pConA or with medium only ($P < 0.01$). These histone peptides can induce stable FoxP3 positive Treg cells in vitro in PBMC from active and remission lupus patients as well as healthy subjects. LAP expression on CD4 and CD8 T cells was also increased when cells were cultured with histone peptides, but CD103, CD39 expression did not increase significantly. Anti-inflammatory drugs DEX, HCQ could enhance the effect of peptides in inducing Treg cells, but anti-IL6 did not show such enhancing effects although it could increase CD25 expression on T cells remarkably. Interestingly, pSmad 2/3 expression in CD4 T cells was also induced by these low dose peptide epitopes and the number of peptide induced FoxP3 positive cells was significantly reduced when ALK-5 inhibitor (SB-431542), to block TGF-β signaling was added.

Conclusion: Very low dose histone peptide epitopes can induce stable CD4+ and CD8+ Treg cells in vitro in both active and remission lupus patients through TGF-β/ALK-5/Smad signaling pathway. In animal models, similar peptide-induced Treg cells can block accelerated lupus disease. This study would be useful for screening therapeutic peptides and developing approaches for maintaining lupus patients in remission by inducing autoantigen-specific Treg cells in vivo, or by adoptive transfer of in vitro generated Treg cells.

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Genome-Wide Association Scan of Antigenic Epitopes of Lupus Specific Autoantibodies in European Americans. Chee Paul Lin[1], Indra Adrianto[1], Jessica J. Hale[1], Jennifer A. Kelly[1], Stuart B. Glenn[1], Jourdan Anderson[1], Kenneth M. Kaufman[2], John B. Harley[3], Tomothy J. Vyse[4], Robert P. Kimberly[5], Marta E. Alarcón-Riquelme[1], Carl D. Langefeld[6], Betty P. Tsao[7], Lindsey A. Criswell[8], Chaim O. Jacob[9], Patrick M. Gaffney[1], Kathy L. Moser[1], Judith A. James[1] and Courtney G. Montgomery[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Cincinnati, OK, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]King's College London, Guy's Hospital, London, United Kingdom, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Wake Forest University Health Sciences, Winston-Salem, NC, [7]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [8]Rosalind Russell Medical Research Center for Arthritis, Department of Medicine, University of California San Francisco, San Francisco, CA, [9]Keck School of Medicine University of Southern California, Los Angeles, CA

Background/Purpose: Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease characterized by multi-organ-system involvement and the production of autoantibodies that can lead to tissue inflammation, destruction of cells and even end-organ damage. Susceptibility to SLE is likely to arise from a complex network of gene-environment interactions. Several studies support these contributions of environmental exposure to the development of disease. A temporal sequence of specific immune targets of select autoantibodies is observed in patients prior to disease classification and in phases of early pathogenesis. Curiously these autoantibodies are closely related to the antibodies that emerge in some lupus patients in response to viral infection, specifically Epstein-Barr Virus (EBV). In this study, we conduct a genome-wide association study (GWAS) of the three initial humoral antigenic epitopes of Sm B' (PPPGMRPP), Sm D1 (a Gly-Arg repeat) and 60kD Ro (amino acids 169–180) to evaluate the genetic influence on the production of these early autoimmune antigenic structures in SLE cases.

Methods: A sample of 703 independent SLE patients of European descent was recruited from multiple institutions and their genotypes were obtained from several large-scale genetic studies. Sera of these patients were tested for antibodies directed against early humoral epitopes of Sm B' (PPPGMRPP), Sm D1 (GRGRGRGR) and 60kD Ro (TKYKQRNWSHK) constructed on poly-lysine backbones. We used enzyme-linked immunosorbent assays (ELISA) to quantify levels of autoantibody response directed against each epitope. Box and Cox transformation was applied to epitope variables that did not fulfill the normality assumption. Genome-wide imputation was performed using IMPUTE2 and the phase III Hapmap panel for 659,676 observed single-nucleotide polymorphisms (SNPs). After quality control, the final genotype sample comprised 581,509 SNPs. We tested for association between the epitopes as quantitative traits and the genetic variants using multiple linear regression under an additive model, adjusting for gender and global ancestry.

Results: After performing stringent quality control, no effects met the Bonferroni corrected threshold of $p < 8.60\times10^{-8}$. However, several regions were significant at a suggestive level ($p< 1\times10^{-4}$) in *RYR2* ($p=1.95\times10^{-6}$), *GTDC1* ($p=1.06\times10^{-5}$) and *NAALADL2* ($p=1.72\times10^{-6}$) for anti-Sm B', anti-Sm D1 and anti-60kD Ro epitopes, respectively. Genes previously shown to be associated with SLE were also evident in the study, particularly *JAZF1* ($p=0.000456$) for anti-Sm B', *KIAA1542* ($p=0.000204$) and *XKR6* ($p=0.0001$) for anti-Sm D1 and *PXK* ($p=0.00058$) for anti-60kD Ro epitopes.

Conclusion: Our results demonstrate the potential power gained by examining more precise phenotypes and refines the association of previously reported SLE genes to the production of these antigenic responses. Overall, our study presents the first evidence of genetic associations with early lupus autoimmunity. It also highlights the importance of examining sub-phenotypes of a complex disease and further supports the involvement of gene by environment interactions toward initiating specific lupus autoimmune responses.

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Inhibited Expression of HPK1 Associated with Loss of JMJD3 Promoter Binding Contributes to Autoimmunity in Systemic Lupus Erythematosus. Qing Zhang, Hai Long, Jieyue Liao, Ming Zhao, Gongping Liang, Xiaoyan Wu, Peng Zhang, Shu Ding, Shuangyan Luo and Qianjin Lu. Second Xiangya Hospital, Central South University; Hunan Key Laboratory of Medical Epigenomics, Changsha, China

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by T cell overactivation and B cell hyperstimulation. Hematopoietic progenitor kinase 1 (HPK1, also called MAP4K1) negatively regulates T cell-mediated immune responses. However, the role of HPK1 in the development of SLE remains poorly understood. This study investigated whether HPK1 played roles in the pathogenesis of SLE and what regulated HPK1 expression.

Methods: HPK1 and JMJD3 mRNA and protein levels were determined by real-time RT-PCR and western blotting. Detection of IFN-α and IgG levels were performed by ELISA. Cell proliferations were evaluated with MTT assay. Amounts of histone H3 lysine 27 trimethylation (H3K27me3), JMJD3, and EZH2 within the HPK1 promoter were analyzed by chromatin immunoprecipitation (ChIP) and real-time PCR.

Results: We found that HPK1 mRNA and protein levels were significantly decreased in CD4+ T cells of patients with SLE, and that down-regulation of HPK1 in healthy CD4+ T cells significantly accelerated T cell proliferation and production of IFNα and IgG. Consistent with these findings, overexpressing HPK1 in SLE CD4+ T cells caused the opposite phenotypes. In addition, we found that H3K27me3 enrichment at the HPK1 promoter was significantly higher in SLE CD4+ T cells than in healthy controls. We also observed a decrease in JMJD3 binding, but no marked change in EZH2 binding at the HPK1 promoter region in SLE CD4+ T cells compared to healthy controls. Knocking down JMJD3 with siRNA in healthy CD4+ T cells led to decreased JMJD3 binding and increased H3K27me3 enrichment at the HPK1 promoter, thus inhibiting the expression of HPK1. Concordantly, plasmid-induced overexpression of JMJD3 in SLE CD4+ T cells had the opposite effect.

Conclusion: These findings indicate that inhibited HPK1 expression in SLE CD4+ T cells is associated with loss of JMJD3 binding and increased H3K27me3 enrichment at the HPK1 promoter, contributing to T cell overactivation and B cell overstimulation in SLE.

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Increased IL-21R Expression and Signaling in B Cells From Patients with Systemic Lupus Erythematosus. Vinh Nguyen[1], Horea Rus[2] and Violeta Rus[2]. [1]Univ of Maryland Schl of Med, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD

Background/Purpose: IL-21 exerts an autocrine effect on T follicular B helper cells (TFH) cells and also stimulates B cell proliferation, plasma cell (PC) differentiation and germinal center (GC) expansion. Studies in murine models of lupus have indicated increased production of IL-21 and attenuation of autoimmune features following IL-21 blockade. Recent studies have also revealed a strong association between genetic polymorphisms in IL-21 and IL-21R and systemic lupus erythematosus (SLE), suggesting a role for IL-21 in human SLE. We have previously reported elevated serum levels of IL-21 and increased mRNA and intracellular expression of IL-21 in CD4+ T cells from patients with SLE. These data implicate IL-21 in disease pathogenesis and suggest that IL-21 blockade may be an attractive therapeutic option in SLE. However, there are limited data on the effect of IL-21/IL-21R interaction on B cells in patients with SLE. To address this issue we analyzed the expression and binding availability of IL-21R on subsets of B cells from lupus patients compared to controls as well as the response of lupus B cells to exogenous or endogenous IL-21 with respect to proliferation, STAT-3 phosphorylation and PC differentiation.

Methods: The expression of IL-21R in purified B cells was detected by flow cytometry and PCR. Levels of IL-21R available for binding were detected on naïve and memory B cells by flow cytometry using biotinylated rhIL-21. Phosphorylation of STAT-3, the major signaling molecule induced by IL-21, was detected by intracellular staining of purified B cells incubated for 30 minutes with 0.1, 1 or 10 ng/ml rhIL-21. In vitro proliferation and PC differentiation of purified B cells stimulated with anti-CD40 in the presence or absence of rhIL-21 or in coculture with purified CD4 T cells stimulated with anti-CD3 were detected by thymidine incorporation and flow cytometry, respectively.

Results: IL-21R mRNA expression was 1.5 fold higher in lupus patients vs. controls and displayed a trend toward increased surface expression, although the difference was not statistically significant. Similarly, the total available receptors for binding IL-21 were increased on both naive and memory B cells from lupus patients suggesting that increased serum levels of IL-21 and IL-21/IL-21R interactions do not alter the availability of IL-21R on B cells. Phosphorylation of STAT-3 was increased in lupus B cells vs. controls and reached statistical significance at the lowest dose ($p=0.03$). In concordance with the increased surface expression and enhanced signaling through IL-21R, lupus B cells exhibited higher proliferation rates in coculture with anti-CD3 stimulated CD4 T cells or in response to rhIL-21, ($p<0.05$). In addition, anti-CD40 induced PC differentiation was significantly higher in the presence of IL-21 in patients compared to controls ($p=0.02$).

Conclusion: These results suggest that the IL-21/IL-21R pathway is aberrantly expressed in patients with lupus through both increased production of IL-21 by CD4 cells and increased expression, availability and responsiveness of IL-21R by lupus B cells. These data suggest that IL-21 can be targeted therapeutically in SLE.

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High Plasma Microparticle-IgG Burden Characterizes Systemic Lupus Erythematosus Patients and Is Associated with Autoantibodies Against DNA and C1q and Activation of the Complement System. Christoffer T. Nielsen[1], Ole Østergaard[2], Line Stener[1], Line V. Iversen[1], Lennart T. Truedsson[3], Søren Jacobsen[4] and Niels H.H. Heegaard[1]. [1]Statens Serum Institut, Copenhagen S, Denmark, [2]Statens Serum Institute, Copenhagen S, Denmark, [3]Dept of Clinical Sciences Lund, Section of Microbiology, Immunology and Glycobiology, Lund, Sweden, [4]Rigshospitalet - 4242, Copenhagen, Denmark

Background/Purpose: Circulating plasma microparticles (MPs), a heterogenous pool of submicron cell-derived membranous vesicles, is suspected as carriers of autoantigens and precursors of immune complexes (ICs) triggering the immune system in systemic lupus erythematosus (SLE). We wanted to characterize immunoglobulins and complement on circulating cell-derived microparticles (MPs) in systemic lupus erythematosus (SLE) and explore correlations between the MP-immunoglobulin burden and clinical and serological parameters.

Methods: IgG on MPs was characterized by flow cytometry in samples from 68 clinically well-characterized SLE patients and 38 healthy controls (HCs). MPs with IgG-, IgM- and C1q were analyzed using both flow cytometry and quantitative mass spectrometry in a subset of SLE and patients and in control samples from HCs, systemic sclerosis (SSc), and rheumatoid arthritis (RA) patients.

Results: SLE patients had significantly increased total and relative numbers of IgG-positive MPs ($p=0.0004$) with a much higher average IgG-load/MP ($p<0.0001$) than HCs. In subset analyses, IgG-positive MPs were also more numerous in SLE than in RA samples ($p=0.03$). In both RA and SSc the average IgG-load/MP was significantly lower than in SLE ($p=0.006$ and 0.05, respectively). Also the IgM and C1q-loads/MP were higher in SLE than in all the controls ($p<0.05$) except for IgM in the RA-group. Mass spectrometry confirmed increased MP-associated IgG, IgM and C1q in SLE. IgG-positive MPs were significantly associated with the presence of anti-dsDNA, with total IgG levels, and with decreased leukocyte levels. The average IgG-load/MP was associated with lower total concentrations of MPs, presence of anti-C1q, and highly significantly with the consumption of complement components.

Conclusion: Circulating cell-derived MPs in SLE carry significantly increased loads of IgG, IgM, and C1q. This is likely to be important for disease etiology and for the sustained systemic pro-inflammatory activities characteristic of SLE.

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Enhanced Apoptosis and Senescence of Bone Marrow-Derived Mesenchymal Stem Cells From Patients with Systemic Lupus Erythematosus. Lei Liu, Defang Meng, Xia Li and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: Previous studies have indicated that bone marrow mesenchymal stem cells (BMSCs) from patients with systemic lupus erythematosus (SLE) exhibit impaired capacities of proliferation, differentiation, secretion of cytokines and immune modulation. In this study, we aimed to investigate whether apoptosis and senescence of BMSCs from SLE patients were dysregulated.

Methods: BMSCs were isolated from bone marrow of SLE patients and healthy controls by density centrifugation and adhesive culture in vitro. TNF-a was added to detect its effect on the activation of apoptosis. The apoptosis of BMSCs was evaluated by TUNEL assay and Annexin

V-FITC/PI Apoptosis Detection. Real-time PCR technique was used to determine the gene expressions of Fas, Bcl-2, Bax, Bcl-w, Caspase 8 and TNFR or without with TNF-a. Cytochrome C was detected by immunocytochemistry. Western blot was used to detect the expressions of Fas, TNFR and Caspase 8. The expressions of Fas, Bcl-2 and the activity of Caspase 8 were detected by flow cytometry. Meanwhile, serum levels of FasL and TNF-a were measured by ELISA.

Results: The frequencies of apoptotic and ageing BMSCs from SLE patients were significantly increased in culture when compared with those of healthy controls. Notably, levels of Bcl-2 expression in BMSCs from SLE patients were markedly deceased both at mRNA and protein levels. When BMSCs were induced to apoptosis in vitro stimulated by TNF-a, the Bax and Caspase 8 expressions in BMSCs from SLE patients were significantly inceased at mRNA levels. The activity of Caspase 8 was enhanced in BMSCs from SLE patients. More cytochrome C positive pellets in the cytosolic fraction were detected in BMSCs from SLE patients compared with healthy controls. The expressions of Fas and TNFR1 on BMSCs from SLE patients were significantly upregulated compared to healthy controls as well as serum level of FasL and TNF-a. Moreover, intracellular ROS levels of BMSCs from SLE patients were higher than those of healthy controls characterized with the activation of PI3K/AKT/FoxO3 signaling pathway.

Conclusion: Our results have demonstrated increased apoptosis and senescence in BMSCs from SLE patients, which may be associated with the pathogenesis of SLE.

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Activated NF-Kb in Mesenchymal Cells From SLE Patients Inhibits Osteogenic Differentiation Through Down-Regulating Smad Signaling. Yu Tang, Jiyun Zhang and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: The osteoporosis of patients with systemic lupus erythematosus (SLE) is thought to be the results of over-osteoclastogenesis induced by pro-inflammatory cytokines such as TNF-a. However, the osteoblastogenesis in SLE patients is unclear. We investigated the (Bone morphogeneic protein) BMP-2-induced osteoblastic capacity of bone marrow-derived mesenchymal stem cells (BMMSCs) from SLE patients and the TNF signaling system in determining BMP-2-induced the regulatory pathways.

Methods: BMMSCs were differentiated into osteoblasts in vitro stimulated by BMP-2 and the osteogenic capacity was quantitated. cDNA microarray was performed between BMMSCs from four SLE patients and four healthy controls, and differentially expressed genes in BMP/TGF-β signaling pathway were analyzed. The activation of BMP/Smad and NF-κB signaling pathways in SLE-BMMSCs were evaluated by detecting the phosphorylated Smad1/5/8 (p Smad1/5/8) and I-κB. TNF-a was added and its effect on the activation of pSmad1/5/8 and BMP-2-induced osteogenic differentiation of normal BMMSCs was determined, while PDTC, a NF-κB inhibitor, was used to examine its effect on that of SLE-BMMSCs. Finally, BMP-2 level in the serum from SLE patients were detected by ELISA.

Results: The capacity of osteogenic differentiation of BMMSCs from SLE patients reduced as compared with that from healthy controls. The NF-κB signaling was active, while the BMP/Smad pathway was repressed in the BMMSCs from SLE patients. TNF-a activated NF-kB pathway and inhibited the phosphorylation of Smad 1/5/8 and BMP-2-induced osteoblastic differentiation in normal BMMSCs, while addition of PDTC to SLE-BMMSCs could partially restore them. The BMP-2 level was lower in the serum of SLE patients.

Conclusion: Our findings suggest that the activated NF-κB pathway in SLE-BMMSCs inhibits the BMP-2-induced osteoblastic differentiation through BMP/Smad signaling pathway. The inadequate osteoblastic differentiation may participate in the pathology of osteoporosis in SLE patients.

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High Oxidation Status Induced the Rearrangement of F-Actin Cytoskeleton of Bone Marrow-Derived Mesenchymal Stem Cells in Patients with Systemic Lupus Erythematosus Via Downregulation of RhoA Signaling Pathway. Dongyan Shi, Xia Li and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: Systemic lupus erythematosus (SLE) is described as a hematopoietic stem cell disorder and bone marrow-derived mesenchymal stem cells (BMMSCs) from SLE patients is proved to be abnormal in their functions. This study was undertaken to determine the effect of oxidation status on F-actin cytoskeleton and RhoA signaling pathway in BMMSCs from SLE patients

Methods: The F-actin cytoskeleton was observed by fluorescence microscopy after staining with Alexa Fluor 594 phalloidin. Transwell system was performed to determine the migration ratio of MSCs. RT-PCR and western blot were carried out to detect changes of RhoA signaling pathway. Serum level of SOD-1 was examined by ELISA and ROS level of MSCs was tested by flow cytometry. In order to investigate the effect of oxidation status on F-actin cytoskeleton of MSCs, 20mM H_2O_2 was added into the growth medium of normal MSCs 1h before testing and 0.2mM NAC, an antioxidant, was added into the growth medium of SLE MSCs.

Results: F-actin cytoskeleton of MSCs was rearranged in SLE patients. The percentage of abnormal MSCs was significantly higher in SLE patients than that of normal controls and increased as they were passaged. The migration capacity was also impaired as passaged. Both of the mRNA level and protein expressions of RhoA, which participates in a main regulatory signaling pathway of F-actin cytoskeleton and cell migration, were downregulated in SLE MSCs. Reduced serum SOD-1 level and higher intracellular ROS level suggested high oxidation status in SLE patients. H_2O_2, as an exogenous oxidant, induced upregulation of ROS level in normal MSCs. As a result, the F-actin cytoskeleton was rearranged and subsequently reduced migration ratio. While NAC, which downregulated ROS level, reversed the rearrangement of F-actin cytoskeleton and the impairment of migration capacity of SLE MSCs. RhoA expression was downregulated by H_2O_2 while upregulated by NAC.

Conclusion: These experimental findings suggest that the rearrangement of F-actin cytoskeleton of MSCs in SLE patients leads to the impairment of their migration capacity, which may result from the high oxidation status via downregulation of RhoA.

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A Paradoxical Increase in Th17 Cells in Patients with High Interferon Activity in Systemic Lupus Erythematosus. Vivian V. Stone, Thomas H. Teal, Pradipta Ghosh, Jeffrey A. Ledbetter and Keith B. Elkon. University of Washington, Seattle, WA

Background/Purpose: Increased expression of type I interferons (IFN) is reported in ~60% of SLE patients and is strongly implicated in the pathogenesis of SLE. Recently, several groups have reported that some SLE patients, particularly those with nephritis, have increased numbers of Th17 cells in the blood and kidneys. An increase in the number of Th17 cells in SLE is surprising because type 1 IFN suppresses Th17 proliferation and differentiation *in vitro*. Furthermore, type 1 IFN is widely used for the treatment of multiple sclerosis where its mechanism of action is thought to be suppression of Th17 cells. Based on these findings, we tested the hypothesis that increased Th17 cells are predominantly observed in SLE patients with a low IFN score.

Methods: IFN activity was measured using real-time quantitative PCR to determine mRNA expression of three interferon stimulated genes (ISG)—MX1, CXCL10 and PKR—in peripheral blood mononuclear cells obtained from 68 lupus patients and 23 healthy controls. Interferon stimulated gene (ISG) scores were calculated as the number of standard deviations (SD) above the mean of the controls and total IFN score was calculated as the sum of the 3 ISG scores. A high IFN score is defined as >2 SDs above mean control score. Th1 and Th17 cells were quantified by intracellular staining for IFN-g and IL-17 by flow cytometry following PMA/Ionomycin stimulation in 50 SLE patients and 27 controls. A high %Th17 cells is defined as >2 SDs above the mean of the controls. Disease activity was assessed at the time of blood collection using the SELENA-SLEDAI disease activity index (active disease = SLEDAI>5).

Results: High IFN scores were found in 73% of lupus patients. Patients with high IFN scores trended to more active disease ($p=0.05$). A higher %Th17, but not Th1, T cells was also found in SLE patients compared to controls ($p<0.05$), and patients with high Th17 cells had more active disease ($p<0.05$). Higher %Th17 cells were found in patients with active disease ($p<0.01$), renal disease ($p<0.001$), and low complement ($p<0.01$) compared with controls. Contrary to expectations, higher %Th17 cells were found in lupus patients with high IFN scores compared to controls ($p<0.01$). To define more precisely the relationship between Th17 cells, IFN-a and their clinical correlates, patients were divided into 4 groups: 1) high IFN only (n=14), 2) high Th17 only (n=1), 3) high in both cytokines (n=9), and 4) low in both cytokines (n=9). Patients with elevations in both IFN and Th17 had the

highest percentage (45%) of renal disease; while patients with only high IFN had the highest percentages of skin and joint disease (30% in each group).

Conclusion: There are four main conclusions: 1) Increased %Th17 cells are more strongly associated with active disease than IFN scores. 2) The paradoxically higher percentages of Th17 cells in patients with high IFN scores suggests that in some SLE patients, type I IFN fails to suppress the Th17 pathway. 3) Evaluation of cytokine combinations is likely to be more powerful correlates and, perhaps, predictors of clinical subsets of disease. 4) SLE therapy may need to target more than one cytokine in individual patients, especially those with renal disease.

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Abnormal Electron Transport Chain Activity in Mitochondria of Peripheral Blood Lymphocytes From Patients with Systemic Lupus Erythematosus. Edward Doherty[1] and Andras Perl[2]. [1]SUNY Upstate, Syracuse, NY, [2]Upstate Medical University, Syracuse, NY

Background/Purpose: T cells from patients with systemic lupus erythematosus (SLE) exhibit an elevation of the mitochondrial transmembrane potential ($\Delta\Psi_m$) or mitochondrial hyperpolarization (MHP) and increased mitochondrial mass which have been linked to increased production of nitric oxide (NO) and reactive oxygen intermediates (ROI). Here, we investigated the role of the electron transport chain (ETC) in MHP of patients with SLE.

Methods: We studied peripheral blood lymphocytes (PBL) from 17 SLE subjects and from 10 healthy subjects, matched for age within ten years, gender and ethnicity of the patients. Mitochondrial O_2 consumption was measured in 1) freshly isolated PBL, 2) PBL rested overnight, and 3) PBL stimulated overnight through CD3/CD28, using Clark-type O_2 electrode (Hansatech, Norfok, UK). Cell viability, mitochondrial mass, $\Delta\Psi_m$, NO, ROI, and Ca^{2+} were assessed by flow cytometry.

Results: Freshly isolated lupus PBL exhibit moderately decreased O_2 consumption through complex II (−18% ±0.30; p=0.011). However, after resting overnight in culture medium, lupus PBL show increased O_2 consumption through complex II (+38% ±0.31; p=0.015). Following overnight stimulation with anti-CD3, O_2 consumption is increased by lupus mitochondria through complexes I (2.26-fold ±0.27; p=0.001) and IV (+14% ±0.57; p=0.040). In accordance with our earlier findings, resting SLE T cells have increased $\Delta\Psi_m$ (DiOC6: 19% ±0.07; p=0.022), mass (NAO: +10% ±0.09; p=0.037), Ca^{2+} (Rhod-2: +10% ±0.06), NO (DAF-FM: +9% ±0.06), nitrite (DAR-4M: +10% ± 0.06), and H_2O_2 levels (DCF-DA: +10% ±0.04; p=0.035). There was a negative correlation between 1) NO production and O_2 consumption through Complex II (r= −0.559; p = 0.011) and 2) H_2O_2levels and O_2 consumption through Complex IV (r = −0.364; p = 0.035). O_2 consumption through complex I by CD3-stimulated PBL negatively correlated with increased NO (r = −0.143; p = 0.036). O_2 consumption through complex IV by CD3-stimulated PBL positively correlated with $\Delta\Psi_m$ (r = 0.591; p = 0.002) and mitochondrial mass (r = 0.267; p = 0.036). In vitro addition of 600μM NOC-18, an NO donor, directly inhibited O_2 consumption through complex I in healthy but not in lupus PBL.

Conclusion: The results suggest that MHP and increased mitochondrial mass are associated with increased ETC activity by mitochondria of SLE PBL. The negative correlation of O_2 consumption with increased NO production and H_2O_2levels indicate that these two metabolites may impair ETC activity and enhance mitochondrial biogenesis in lupus PBL. Along this line, blockade of ETC activity by NO in healthy but not by lupus mitochondria indicate pre-existing damage in patients with SLE. Such ETC defect may underlie the MHP and altered T cell activation in SLE.

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The Monitoring of FoxP3 Expressing CD4+ T Cell Subsets May Be Helpful for the Prediction of Systemic Lupus Erythematosus Flares. Makoto Miyara[1], Alexis Mathian[1], Julien Haroche[1], Laurent Arnaud[2], Driss Chader[1], Lucile Musset[1], Guy Gorochov[1] and Zahir Amoura[1]. [1]CHU Pitié-Salpêtrière, Paris, France, [2]Paris, France

Background/Purpose: Based on the functional delineation of FoxP3 expressing $CD4^+$ T cell subsets that we defined recently, we have shown that perturbation in Treg cell homeostasis may participate in the immunopathogenic mechanisms that lead to SLE flares. Whether modifications in FoxP3 expressing $CD4^+$ T cell subsets are observed in patients before they develop SLE flares has not been determinde yet.

Methods: Patients with inactive SLE (SLEDAI <6, n=45) were included for a 6 month follow-up. Clinical and biological evaluation of SLE activity and analysis of the proportions of FoxP3 expressing subsets were performed every 2 months. Normal values of each FoxP3 expressing $CD4^+$ T cell subsets were defined in a cohort of 50 healthy donors as follows: naïve Treg cells (nTreg) defined as $CD4^+FoxP3^{low}CD45RA^+$ cells: 2.4% (1–4.5%), effector Treg cells (eTreg) as $CD4^+FoxP3^{high}CD45RA^-$ cells: 1.55% (1–3%) and FoxP3 non Treg cells ($FoxP3^+$nonTreg) defined as $CD4^+FoxP3^{low}CD45RA^-$: 3.05% (1.3–5.8%).

Results: 20 patients (44.4 %) had normal proportions of nTreg, eTreg and $FoxP3^+$nonTregs at inclusion. The most frequent anomaly was an isolated increase in the proportion of $FoxP3^+$nonTregs (n=11, 24.4%). Other anomalies were: decrease in eTreg (n=2, 4.4%), decrease in nTreg cells (n=2, 4.4%), increase in nTreg cells (n=2, 4.4%), increases in both $FoxP3^+$nonTreg and nTreg (n=4, 8.8%), combination of increase in FoxP3+nonTreg and decrease in nTreg, (n=3, 6.6%), decrease in both nTreg and in eTreg (n=1, 2.2%). Increase in $FoxP3^+$nonTreg was thus observed in 18 patients (40%), decrease in nTreg in 6 (13%), increase in nTreg in 6 (13%) and decrease in eTreg cells in 3 patients (6.7 %).

Only one patient among the patient that did not display anomalies in any FoxP3 expressing subset at inclusion developed a mild flare (arthritis, 5%) while, among those with anomalies, 5 patients developed SLE flares including 2 nephritis (20%). The most prevalent anomaly observed before flares was an increase in $FoxP3^+$nonTreg (n=4) while an increase in nTreg was observed in 3 patients, a decrease in nTreg in 2 and a decrease in eTreg cells in 3.

Among the 25 patients that had anomalies at inclusion, only 4 of them returned to normal proportions. None of them developped SLE flare. Among the 21 patients that kept anomalies, 5 of them developed SLE flares (25%). Most patients without anomalies at inclusion (n=20) developed a new anomaly 6 months later (n=12, 60%) that was mainly an increase in FoxP3+nonTreg (n=8, 75%). Of note, the last patient that developed a mild SLE flare belonged to this group. Thus, 8 patients kept normal proportions of FoxP3 expressing subsets and did not develop SLE flare.

Conclusion: Although phenotypically similar, inactive SLE patients have different patterns in the proportions of FoxP3 expressing $CD4^+$ T cell subsets. Most patients that developed SLE flares during the 6 month follow-up had anomalies in FoxP3 expressing $CD4^+$ T cells subset before flares while those who maintained the absence of anomaly did not develop flares. The monitoring of $FoxP3^+$ $CD4^+$ T cell subsets may be a novel efficient parameter for the prediction of SLE flares in SLE outpatients.

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Hypermethylation of CD3*Z* Promoter CpG Islands in Patients with Autoimmune Diseases Including Systemic Lupus Erythematosus. Kyeong-Man Hong[1], Hyun-Kyoung Kim[1], Seong-Yeol Park[1], Yong-Bock Choi[1], Mi-Kyeong Kim[1], Ji Ah Park[2], Eun Young Lee[2], Eun Bong Lee[2] and Yeong Wook Song[2]. [1]National Cancer Center, Goyang, South Korea, [2]Seoul National University Hospital, Seoul, South Korea

Background/Purpose: To assess the role of epigenetic factors in autoimmune disease, systemic lupus erythematosus (SLE) was used as a model system because lots of epigenetic importance has been demonstrated.

Methods: microarray analysis and quantitative measurements of methylated promoters in whole blood DNAs of patients with autoimmune disease including SLE, rheumatoid arthritis and systemic sclerosis

Results: A significantly increased *CD3Z* promoter methylation was found in SLE patients (n=114) compared to healthy control (n=105, p <0.0001 with OR = 20.6). Increased methylation levels were also observed in affected discordant monozygotic twins (4 pairs). Moreover, the level of methylation was significantly higher in active SLE patients (n=108) than inactive cases (n=6, p=0.0075). In patients with rheumatoid arthritis (n=19) or systemic sclerosis (n=18), increased *CD3Z* promoter methylation was also observed, suggesting increased *CD3Z* methylation is a common phenomenon in autoimmune disease. In addition to *CD3Z*, increased promoter methylations of two other genes, *ADA* and

VHL, were also found in blood cell DNAs from patients with autoimmune diseases.

Conclusion: Our results not only indicate that epigenetic components in blood cells might be fluctuating more profoundly and often especially in disease status, but also provide a model system to support the importance of epigenetic changes for the clinical manifestation of disease.

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Comprehensive Screening for Primary Immunodeficiencies Shows Unexpectedly High Frequency of Selective IgM Deficiency in Systemic Lupus Erythematosus. Sandro F. Perazzio[1], Neusa P. Silva[2], Reinaldo Salomao[1] and Luis Eduardo C. Andrade[3]. [1]Federal University of Sao Paulo, Sao Paulo, Brazil, [2]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo and Fleury Health and Medicine Laboratories, Sao Paulo Brazil, Sao Paulo, Brazil

Background/Purpose: Systemic Lupus Erythematosus (SLE) is known to be associated with deficiency of C1q, C4, and C2. There is high frequency of discoid lesions (2.7%) and SLE (0.5%) in Chronic Granulomatosus Disease (CGD). Selective IgA Deficiency (SIgAD) has been associated with juvenile (5.2%) and adult (2.6%) SLE. About 25% of patients with Common Variable Immunodeficiency (CVID) develop autoimmune manifestation, including SLE. Although there are reports of individual primary immunodeficiency (PID) in SLE, there is no systematic study estimating the fraction of SLE patients presenting a comprehensive array of PID. We present preliminary results of an ongoing study aimed to estimate the prevalence of overall PID in a cohort of SLE patients and age- and gender-matched healthy controls, and to compare the clinical characteristics of the SLE patients with and without PID.

Methods: 265 SLE patients and 215 controls recruited among blood donors underwent clinical examination and were evaluated for C2, C3, mannose binding lectin (MBL), immunoglobulin isotypes, and quantification of the oxidative burst in neutrophils. Those who presented any laboratory indication of PID were submitted to a novel examination within 60 days for confirmation. Cases under disease activity were followed and submitted to novel examinations after the end of the flare or excluded if no remission was attained up to the end of the project. PID was established after confirmation of abnormal results in a second evaluation and after disease remission.

Results: Altogether there were 27 SLE patients and four controls with established diagnosis of PID ($p<0.01$). PIDs in SLE patients included Selective IgM Deficiency (SIgMD) (n=19), SIgAD (n=2), SIgGD (n=6, all due to lower IgG1 serum component). No patient presented evidence of Hyper-IgM Syndrome, MBL deficiency, CVID, and CGD. There was one female patient with neutrophil oxidative burst compatible with CGD gene carrier status. There was isolated reduction of C2 or C3 in eight patients but these were not classified as PID at this moment because these results must be confirmed by genotyping. As expected, there was higher frequency of hypergammaglobulinemia (high IgA and IgG levels) in SLE (40%) as compared to controls (6%) ($p<0.001$). SLE patients with and without evidence for PID did not differ with respect to clinical manifestations, immunosuppressant use, infection rate and severity, SLEDAI, and age at disease onset.

Conclusion: These preliminary findings demonstrate high frequency of overall PID in SLE, suggesting that an immunodeficient state PID might represent a risk factor for SLE development. The unexpected high frequency of SIgMD appears to indicate an intriguing aspect of SLE pathophysiology since IgM is important for immunocomplex and pathogen clearance. Therefore, low IgM levels might induce a state of frequent and persistent immunological stimulation, which may culminate in autoimmunity development.

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Altered Selection Leads to Expansion of the Anergic IgM$^-$ B Cell Population in SLE. Julie Kim[1], Nan-Hua Chang[1], Murray B. Urowitz[2], Dafna D. Gladman[3], Paul R. Fortin[2] and Joan E. Wither[1]. [1]Toronto Western Research Institute, University Health Network, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Recently, the IgM$^-$IgD$^+$ naïve B cell population in healthy humans was identified as a naturally auto-reactive subset that is functionally anergic. Here, we examined this population in SLE patients and controls.

Methods: Patients (N=75) satisfying at least 4 ACR criteria for SLE and 37 healthy age-matched controls without a family history of systemic autoimmune disease were recruited. Naïve B cells (CD19$^+$CD27$^-$IgD$^+$) that were categorized to be mature (CD38$^+$, CD24$^+$ or CD10$^+$) or transitional (CD38^{++}, CD24^{++} or CD10^{++}) were identified by flow cytometry following staining of PBMC. Identification of IgM$^-$and CD86$^+$ populations was determined by FMO controls. The IgM$^+$ population was stratified into two groups (IgM^{lo} and IgM^{hi}) based on contour plots. B cell signaling was examined using Phosflow.

Results: There was an increased proportion of IgM$^-$cells within the mature naïve and transitional B cell compartments of SLE patients vs. controls (mature $p = 0.003$; transitional $p = 0.020$). In SLE patients and controls there was a significant trend to increased proportions of CD86$^+$ cells with decreasing levels of IgM ($p < 0.0001$). Although increased proportions of CD86$^+$cells were seen in SLE vs. controls for all IgM populations, this only achieved significance for the mature IgM^{lo} subset. Notably, a substantial (0–80%) proportion of IgM$^-$ mature B cells expressed CD86, suggesting that they had been recently activated. Consistent with this possibility, basal levels of pPLCγ2 were elevated in a significant proportion of these cells. To determine whether the IgM$^-$ cell population was anergic, cells were stimulated with anti-IgD. The proportion of cells that upregulated pPLCγ2$^+$ following anti-IgD stimulation was significantly reduced with decreased cell surface expression of IgM. Nevertheless, some upregulation of pPLCγ2 following anti-IgD stimulation was retained in IgM$^-$ cells, which was slightly reduced in SLE patients. To investigate whether the expanded IgM$^-$ population in SLE results from an altered B cell signaling threshold, the correlation between the proportion of IgM$^-$ cells and upregulation of pSYK$^+$ or pPLCγ2$^+$ with anti-IgM or -IgD stimulation was examined. No association was seen. However, comparison of the proportion of IgM$^-$ cells in the transitional vs. mature naïve subsets indicated that SLE patients with high proportions of IgM$^-$ cells within their transitional subset also had high proportions of IgM$^-$ cells in their mature subset, whereas for controls the proportion of IgM$^-$ cells in the mature B cell subset became normalized.

Conclusion: The IgM$^-$ naïve B cell population is equivalently refractory to activation in SLE patients and controls. Some of these cells appear to recently activated, rather than anergic cells. The expansion of the IgM$^-$ population in SLE patients may result from altered selection at the transitional to mature stage of B cell development.

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Auto-Reactive IgEs and Basophils in Systemic Lupus Erythematosus. Barbara Dema[1], Sarfaraz A. Hasni[2], Chao Jiang[1], Donna F. Hardwick[3], Nicolas Charles[4], Gabor G. Illei[5] and Juan Rivera[1]. [1]Laboratory of Molecular Immunogenetics, NIAMS, NIH, Bethesda, MD, [2]National Institutes of Health, Bethesda, MD, [3]NIH MSC 1616, Bethesda, MD, [4]Institut national de la Sante et de la Reserche Medicale, Paris, France, [5]NIDCR/ NIH #10 1N110, Bethesda, MD

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder that can lead to kidney failure as a consequence of the deposition of immune complexes (ICs) in the glomeruli. Previous studies in mice deficient in the Src family protein tyrosine kinase Lyn, which develop a lupus nephritis-like phenotype, indicated an involvement of basophils in the development of this disease. IgE present in the circulating ICs of these mice promoted the activation of basophils, IL-4 production and thus, autoantibody production and disease amplification. Furthermore, the presence of circulating anti-dsDNA IgE in a small cohort of SLE patients was found to be associated with active lupus nephritis and with the presence of activated basophils in secondary lymphoid tissue. In the current study we first explore whether auto-reactive IgE is found in other mouse models of spontaneous lupus-like disease. We also investigate the role of auto-reactive IgE and basophils in a larger population of SLE patients. In addition, we investigate if IgE's with other antigen specificities play a role in disease development.

Methods: Blood samples from healthy blood donors (n=75) and patients that fulfilled the American College of Rheumatology classification criteria for SLE (n=99) were collected under a current NIH protocol after prior written informed consent. Disease activity was measured using SLE Disease Activity Index (SLEDAI) scores. Serum auto-reactive IgE antibodies were measured by ELISA and basophil markers were measured by flow cytometry (BD FACSCanto II, BDBioscience).

Results: Auto-reactive IgE and total IgE were significantly elevated in the *FcgRII*$^{-/-}$*.Yaa* mouse model of spontaneous lupus demonstrating the presence of auto-reactive IgE in this innate driven lupus model. In SLE patients, the levels of dsDNA and Sm/RNP specific IgE were significantly elevated when compared to healthy individuals. A stronger association was evident

with higher disease activity (SLEDAI≥4) when compared to patients with lower disease activity (SLEDAI <4). The levels of anti-dsDNA IgE correlated with the anti-dsDNA IgG, anti-Sm IgG and anti-Sm IgE in SLE patients. Moreover, we detected increased expression of the basophil activation marker (CD203c) and of the homing marker for secondary lymphoid tissues (CD62L or L-Selectin) on the surface of basophils from patients with modest to high disease activity (SLEDAI ≥4). This was consistent with a reduced proportion of circulating basophils in patients with modest to high disease activity.

Conclusion: Auto-reactive IgEs are present in a least two mouse models of spontaneous lupus; the previously reported *lyn*$^{-/-}$ mice and the herein reported *FcgRII*$^{-/-}$.*Yaa* mice. In patients, these IgE autoantibodies (dsDNA and Sm/RNP) are associated with increased disease activity. Other antigen specificities may also be important and this possibility is under investigation. Activated basophils may also amplify autoantibody production through their presence in secondary lymphoid organs and expression of markers that support T and B cell function. Our findings are consistent with a role for auto-reactive IgE and basophils in the development of lupus.

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ZAS3 Is Overexpressed in Peripheral Blood Mononuclear Cells in Systemic Lupus Erythematosus Patients and Is Regulated by Estrogen: A Cause of the Dysreguated IL-2 Response? Nicholas Young, Alexandra Friedman, Francesca Madiai, Benjamin Kaffenberger, Lai-Chu Wu and Wael N. Jarjour. The Ohio State University Medical Center, Columbus, OH

Background/Purpose: Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by significant gender bias. Previous studies have demonstrated some of the contributions of hormones to SLE pathogenesis. Estrogen (E2) has been shown to regulate the expression of multiple genes by binding and activating estrogen receptors (ER) alpha and beta. While many ER-target genes have been previously described, recent evidence indicates that many others remain to be characterized. ZAS3 is a member of the Zas family of zinc-finger transcription factors. This subtype is rapidly degraded in primary lymphocytes ex vivo and thought to be involved in controlling cellular growth and inflammation. Studies have shown that ZAS3 expression inhibits nuclear translocation and DNA binding of NF-kB. Similarly, abnormal NF-kB activity has also been observed through cross-talk with hormone receptors and when SLE PBMCs are compared to healthy controls. Consequently, IL-2 production is decreased in SLE patients since NF-kB contributes to the transcriptional regulation of this promoter. To this accord, recent work has shown that transfection of p65 can restore IL-2 production in SLE T cells.

Methods: PBMCs of SLE patients and healthy controls were isolated to examine resting ZAS3 expression. ZAS3 was then measured with or without treatment with a physiological dose of E2 in these PBMCs and in cell lines. EMSA was performed with nuclear extracts to examine DNA-protein interactions in the ZAS3 genomic region. The *in vivo* effect on ZAS3 expression with E2 treatment was investigated through subcutaneous injections into wild-type B6 mice. Wild-type and ZAS3 −/− mice were challenged with LPS and IL-2 production was measured through cytokine assays of collected serum.

Results: Elevated ZAS3 mRNA levels were observed from PBMCs in whole blood samples of SLE patients when compared to healthy controls. In order to study the influence of E2 over ZAS3 expression, healthy human PBMCs were examined and displayed significantly induced ZAS3 expression with E2 treatment. This E2-induction was found to be dose dependent and endogenous ZAS3 was expressed primarily in T, B and breast cancer cell lines. In order to establish the validity of these *in vitro* observations, the *in vivo* E2-induced expression of ZAS3 was examined in B6 mice. Increased ZAS3 protein expression, by indirect immunofluorescence, was observed not only in lymph nodes and spleen but also the mammary gland. Mechanistic evidence of the direct role of E2 in the induction of ZAS3 expression was shown through EMSA analysis. Here, differential DNA binding in the ZAS3 region with the treatment of E2 was observed. LPS stimulation of wild-type and ZAS3 −/− mice illustrated the knockout of ZAS3 resulted in significantly elevated levels of IL-2.

Conclusion: ZAS3 expression is upregulated in resting PBMCs of SLE patients and is induced by E2. This was shown to be a direct E2 effect in a breast cancer cell line. Furthermore, a higher expression of ZAS3 was associated with a lower IL-2 production. Taken together, these data suggest that ZAS3 upregulation plays a significant role in SLE pathology by inhibiting NF-kB binding activity.

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Elevated IgE Anti-Ds-DNA Levels Are Associated with Serological Disease Activity in Patients with SLE: Potential for a New Treatment Target. Sarfaraz A. Hasni[1], Barbara Dema[2], Donna F. Hardwick[3], Gema Souto-Adeva[4], Chao Jiang[5], Juan Rivera[2] and Gabor G. Illei[4]. [1]National Institutes of Health, Bethesda, MD, [2]Laboratory of Molecular Immunogenetics, NIAMS, NIH, Bethesda, MD, [3]NIH MSC 1616, Bethesda, MD, [4]NIDCR/ NIH #10 1N110, Bethesda, MD, [5]Laboratory of Immunogenetics, NIAMS, NIH, Bethesda, MD

Background/Purpose: Autoreactive IgE leads to activation of basophils and lupus-like nephritis in lyn −/− mice. Prior studies in subjects with Systemic Lupus Erythematosus (SLE) showed increased levels of IgE directed against ds-DNA. In this study we explored the correlation between IgE anti-ds-DNA levels and lupus disease activity.

Methods: We collected blood samples over a period of 8 months from patients followed under SLE natural history protocol. Demographic information, clinical manifestations, current medications and laboratory data were collected; disease activity was measured using SLE Disease Activity Index SELENA modification (SELENA/SLEDAI) scores. Serum IgE anti-ds-DNA was measured by our internally standardized ELISA. Statistical analysis was done using SAS Enterprise Guide 4.2 software (SAS Institute Inc. Cary, NC).

Results: In this cross-sectional study IgE anti-ds-DNA was measured on sera from 92 patients and 66 healthy controls. The average age of the patients was 41.5 yrs, 81/92 patients were females, 30 African-American, 31 white, 18 Hispanics and 13 were Asian. Mean SLEDAI score was 2 (min-max:0–37). Average serum IgE anti-ds-DNA level was 546.58 A.U. ±1760.32 (mean±SD) in patients and 22.71 A.U. ±93.32 (mean±SD) in healthy controls. Total serum IgE levels and IgE anti-ds-DNA levels did not correlate (Spearman Correlation Coefficient: 0.32) in a subset of 67 patients with available total serum IgE. IgE anti-ds-DNA levels correlated modestly with SLEDAI scores (Spearman correlation coefficient: 0.46). Median IgE anti-ds-DNA levels were higher (56.52 A.U.) in patients with SLEDAI≥4 (N=33) compared to those with SLEDAI<4 (0 A.U.)(N=59)(p value<.0001). In contrast to our previous findings, there was no difference in IgE anti-ds-DNA levels in patients with or without lupus nephritis (p-value 0.23). Levels of IgE-ds-DNA correlated modestly with IgG-ds-DNA (Spearman correlation coefficient:0.49). Complement proteins C3 and C4 trended inversely with IgE-ds-DNA levels(Spearman correlation coefficient:−0.44 and−0.42 respectively). Patients with hypocomplementemia (26/92) had a higher IgE anti-ds-DNA level (median 247.99 A.U.) compared to those with normal complement levels (median 1.19 A.U.) (p-value <0.0001).

Conclusion: Our results indicate that serologic activity in SLE includes increased production of IgE anti-ds-DNA antibodies. Levels of these autoreactive antibodies correlate with disease activity index and hypocomplementemia; suggestive of their role in disease pathogenesis. Based on this data we are planning a pilot treatment study using an anti-IgE monoclonal antibody.

ACR Poster Session A
Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics I
Sunday, November 6, 2011, 9:00 AM–6:00 PM

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SELF-Administered Systemic Sclerosis Questionnaire. Validation of A SPANISH Version (SYSQ) In Mexicans. Maria Pilar Cruz-Dominguez[1], Moises Casarrubias-Ramirez[1], Victor Gasca Martínez[1], Olga Lidia Vera Lastra[1], Luis J. Jara Quezada[2] and Daniel Hector Montes-Cortes[3]. [1]Hospital de Especialidades CMN La Raza, IMSS, Mexico, DF, Mexico, [2]Hospital de Especialidades CMN La Raza, IMSS, Mexico City, Mexico, [3]Hospital General CMN La Raza, IMSS, Mexico DF, Mexico

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease, characterized by systemic progressive fibrosis and frecuently severe functional alterations.

The purpose of this study was validate a Spanish version of The self-administered systemic sclerosis questionnaire (SySQ) to evaluate functional performance in patients with systemic sclerosis.

Methods: We conducted a trans-cultural and translation-retranslation validation of the original german version of the questionnaire. The second spanish version was submmitted to a panel of experts for face and content validity, and then used in a pilot test for final modifications. Type of study. Prospective, observational, cross-sectional and analytical study. We included patients with

diagnosis of scleroderma according to the criteria of The American College of Rheumatology, who signed informed consent and had complete clinical information to be evaluated with the severity scleroderma scale. We established a sample size of 50 subjects. Reliability analysis of SySQ, and severity index was done with Cronbach alpha (for each domain and the full questionnaire). The convergent construct validity was performed with a correlation analysis between SySQ and the severity scale for scleroderma. An $r \geq 0.4$ was considered good correlation with a significance level ≤ 0.05 (two-tailed).

Results: We included a total of 53 patients for the study. Age range was 17 to 81 years (mean ± SD.: 50.45 ± 14.05 years). α Cronbach's for the full questionnaire was 0.961. The Spearman's correlation coefficient was 0.526 between both instruments ($p<0.0001$)

Conclusion: The SySQ for scleroderma is a reliable and valid measure for functional performance in a Mexican sample of patients with scleroderma.

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Marital Status in Systemic Sclerosis: Association with Pulmonary Function and Skin Involvement. Brock E. Harper[1], Shervin Assassi[2], Giovanni Geslani[3], Joanna Leung[3], Holly Bentz[1], Emilio B. Gonzalez[1], Hilda T. Draeger[4], Deepthi Nair[2] and Maureen D. Mayes[2]. [1]University of Texas Medical Branch, Galveston, TX, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]Galveston, TX, [4]Univ of TX Health Sci Ctr, San Antonio, TX

Background/Purpose: Systemic sclerosis (SSc) is a chronic autoimmune disease associated with fatigue, depression, and work disability. Previous studies have shown that non-married SSc patients report more unmet psychosocial needs and feelings of disability compared to their married counterparts. Being married has been associated with less frequent work disability in other rheumatic diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). No study to date has investigated the relationship between SSc and marital status. The goal of this study is to assess possible determinants of marital status in SSc.

Methods: Demographic data including age, gender, ethnicity, marital status (married, not married but living in a marriage-like relationship, divorced, separated, widowed and never married) and clinical data including extent of skin involvement as measured by modified Rodnan Skin Score (mRSS), forced vital capacity (FVC), disease type, and presence of anti-centromere and anti-topoisomerase I antibodies were collected at enrollment in the Genetics versus ENvironment In Scleroderma Outcome Study (GENISOS). Widowed patients were subsequently excluded from the analysis. Multivariate logistic regression analysis controlling for age, gender and ethnicity was performed comparing patients in a union (married or in a marriage-like relationship) to patients who were not in a union (separated, divorced, or never married.)

Results: Data from 303 patients with SSc were analyzed. Among women with scleroderma, 128 (50.6%) were married, 11 (4.4%) were living in a marriage-like relationship, 10 (4.0%) were separated, 59 (23.3%) were divorced, 14 (5.5%) were widowed and 31 (12.3%) were never married. Among men with scleroderma, 32 (65.3%) were married, 8 (16.3%) were separated, 1 (2.0%) was widowed and 8 (16.3%) were divorced. Multivariable logistic regression analysis revealed significant associations of FVC <50% and higher mRSS with lower likelihood of being in a union with patients with FVC <50% being 1/3 as likely of being in a union as patients with normal FVC.(Table 1) No other significant associations were identified.

Table 1. Correlation of Being In a Union with Clinical and Serologic Features of SSc

	Multivariable Logistic Regression OR (95% CI)	p
Limited Skin Involvement	1.1781 (0.7159, 1.9388)	0.519
Topo +/−	0.9792 (0.5003, 1.916)	0.951
Centromere +/−	0.9140 (0.4323, 1.9323)	0.814
mRSS	0.9787 (0.9582, 0.9995)	0.045
Disease duration	0.9935 (0.8485, 1.1634)	0.936
FVC < 50 % pred	0.3355 (0.1200, 0.9378)	0.037

Conclusion: At baseline, more severe skin involvement and interstitial lung disease were associated with lower likelihood of being married or in a marriage-like relationship. Further identification of factors contributing to loss of marital support may provide strategies for preserving these relationships and better overall quality of life and coping for patients with SSc.

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Cancer in Systemic Sclerosis: Results From a Single Centre Cohort Report. Giuseppina Abignano, Hannah Lee Evans, Paul Emery, Francesco Del Galdo and Maya H. Buch. University of Leeds, Leeds, United Kingdom

Background/Purpose: Malignancy has been reported in 3.6–10.7 % of patients with systemic sclerosis (SSc) (1) with lung and breast being the most commonly reported types. The aim of this study was to determine the incidence of cancer in our SSc cohort, describe their demographic and clinical features and any cancer risk factors.

Methods: The medical records of 191 patients admitted to our centre and diagnosed with SSc between 1985 and 2010, all fulfilling the ACR classification criteria, were retrospectively reviewed. Patients with overlap syndrome and mixed connective tissue disease were excluded from the analysis. The epidemiological and clinical information and any risk factors of the patients with cancer history were compared to those of a gender-matched control group, randomly selected from our scleroderma database. Continuous variables were expressed as mean and standard deviation. Unpaired two-tailed t-test was used to compare groups. Qualitative variables were compared using Fisher's exact test. Data were analysed using GraphPad Prism software.

Results: Of 191 SSc patients, 18 (9.4%) were found to have a history of cancer. Twenty-one primary cancers were identified. Breast cancer was the most frequent (7 cases, 3.6 %), followed by non-melanoma skin cancer (4 cases, 2.1 %; 3 basal cell carcinoma, 1 squamous cell carcinoma), lung cancer (3 cases, 1.6%), non-Hodgkin's lymphoma (3 cases, 1.6 %), melanoma (1 case, 0.5 %), myeloma (1 case, 0.5.%), colon (1 case, 0.5 %) and parotid cancer (1 case, 0.5%). In 2 patients cancer preceded the SSc onset (1 breast cancer, 1 non-Hodgkin's lymphoma). One patient had 2 primary cancers, breast and colon, before and after the SSc onset, respectively. Comparing the 2 groups with gender-matched controls, we found that cancer diagnosis occurred at a younger age in patients that developed SSc after the malignancy ($p = 0.02$). Patients with cancer developed SSc at an older age compared to controls ($p = 0.0123$). No difference was found in any risk factors. The risk associated to the cyclophosphamide (CYC) therapy in SSc patients with cancer was nearly significant ($p = 0.075$) (table).

Parameters	Post-SSc cancer (n=15)	Pre-SSc cancer (n=2)	Post-SSc cancer vs pre-SSc cancer (p value)	Pre- and post SSc cancer (n=1)	SSc no cancer (n=18)	All SSc-cancer (n=18) vs control (p-value)
Gender (M/F)	2/13	0/2	1	0/1	2/16	–
Subset, L/D	12/3	2/0	1	1/0	13/5	0.69
ANA +	14 (93.3%)	2 (100%)	1	1 (100%)	17 (94.4%)	1.5
ACA +	7 (46.6%)	0 (0%)	0.48	1 (100%)	5 (27.7%)	0.49
AntiScl-70 +	3 (20%)	1 (50%)	0.43	0	6 (33.3%)	0.71
Age at SSc onset (mean ± sd)	52.9 ± 17	47.5 ± 3.5	0.67	65	37.9 ± 18.2	0.0123
Age at cancer dx (mean ± sd)	63.4 ± 11.3	42 ± 4.2	0.02	41, 78	–	–
Family malignancy history	1 (6.6%)	1 (50%)	0.23	0	3 (16.7%)	1
ILD	7 (46.6%)	0 (0%)	0.49	0	5 (27.7%)	0.72
tobacco	5 (33.3%)	1 (50%)	1	0	4 (22.2%)	0.71
alcohol	0 (0%)	0 (0%)	–	0	1 (5.55%)	1
CYC	8 (53.3%)	1 (50%)	1	0	3 (16.6%)	0.075
MMF	2 (13.3%)	1 (50%)	0.33	0	2 (11.1%)	1
AZA	0 (0%)	0 (0%)	–	0	0 (0%)	–
MTX	0 (0%)	1 (50%)	0.12	0	2 (11.1%)	1

Conclusion: In line with previous reports, we found breast and lung cancer among the most common types of malignancy in our SSc patients. High incidence of cases of non-Hodgkin's lymphoma cases was also observed. Although not mostly associated in SSc patients, a relatively high incidence of non-melanoma skin cancers was noted in in our cohort; the small studied population may underlie these findings. With the limitations of a case-control study, no risk factors were identified, except for the nearly significant risk associated to the CYC therapy.

References:

1. Wooten M. Southern Medical journal 2008

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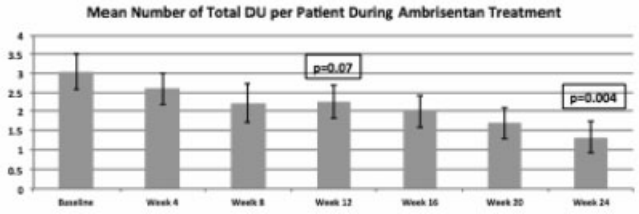
Effect of the ET_A Selective Endothelin Receptor Antagonist Ambrisentan on Digital Ulcers in Patients with Systemic Sclerosis: Results of a Prospective Pilot Study. Lorinda Chung[1], Kait Arefiev[2], Aaliya Yaqub[2], Deborah Strahs[2], Bharathi Lingala[2] and David Fiorentino[1]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]Stanford Univ Medical Center, Palo Alto

Background/Purpose: Previous studies have shown that the dual endothelin receptor antagonist (ETRA) bosentan is useful in the prevention of new digital

ulcers (DU) in patients with systemic sclerosis (SSc), but has no effect on the healing of existing DU. We sought to evaluate the effect of the relatively ET_A selective ETRA ambrisentan on the prevention and healing of DU.

Methods: This was a prospective open-label single-center study enrolling patients with limited or diffuse cutaneous SSc with at least one active DU located at or distal to the proximal interphalangeal joint. Patients with functional class III or IV pulmonary hypertension and those receiving phosphodiesterase-5 inhibitors, ETRAs, or prostacyclins within 4 weeks of screening were excluded. The primary endpoint was the difference in number of new DU that developed in the preceding 4 weeks after 24 weeks of therapy compared with baseline. Secondary endpoints included the % of patients who experienced complete healing of baseline DU; change in number and mean diameter of DU; change in physician global assessment of DU severity by visual analogue scale (VAS); and change in patient assessment of severity of DU and Raynaud's by VAS. A completers analysis was performed.

Results: 20 patients (80% female, mean age 49.3±13.8 years, 65% dcSSc) with a mean disease duration since first Raynaud symptom of 12.7±10.8 years were enrolled. 12 (60%) received stable doses of a calcium channel blocker and/or other vasodilator throughout the study. 16 patients completed 24 weeks of therapy. 2 withdrew due to lower extremity edema, 2 for scheduling conflicts. The mean number of new DU that developed 4 weeks prior to week 24 was not different from baseline (0.44±0.81 vs. 0.45±0.69). However, 14 (88%) patients had complete healing of all baseline DU at week 24. Of the 19 patients who completed 12 weeks of therapy, 7 (37%) had healed all baseline DU and 12 (63%) had healed at least 50% of baseline DU by week 12. The total number of DU decreased from 3.1±2.1 to 1.3±1.6 at week 24 ($p=0.004$) (Figure). For DU that did not heal, the mean diameter decreased from 3.3±1.6 mm to 1.6±1.5 mm ($p<0.0001$). Physician and patient assessments of DU severity were significantly improved at week 24 ($p=0.015$ for both), but patient assessment of Raynaud severity was not significantly different. The most common adverse events (AE) were lower extremity edema (50%), anemia (50%), and DU infection (40%). There were 3 serious AEs: 1 patient had a myocardial infarction and developed pulmonary edema; 1 patient was hospitalized for worsening of underlying SSc lung disease; and 1 patient had a severe Raynaud attack after an angiogram.



Conclusion: Ambrisentan may be useful in reducing ulcer burden and healing DU in SSc patients. A larger randomized double-blind placebo-controlled trial is warranted to further evaluate the efficacy of ambrisentan in the prevention and treatment of DU.

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Successful Pregnancies but Higher Risk of Preterm Delivery in Systemic Sclerosis Women. IMPRESS: The Italian Multicentric Study on Pregnancy in Systemic Sclerosis.. A. Brucato[1], Mara Taraborelli[2], Véronique Ramoni[3] and Angela Tincani[4]. [1]Ospedali Riuniti, Bergamo, Italy, [2]University of Brescia and Spedali Civili, Brescia, Italy, [3]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [4]Rheumathology Unit, University of Brescia, Brescia, Italy, Brescia, Italy

Background/Purpose: To assess fetal and maternal outcomes in Systemic Sclerosis (SSc) women.

Methods: Prospective collected data were retrospectively analyzed according to an uniform protocol. 100 SSc women were observed in 25 Italian referral Centres during their 109 pregnancies (years 2000–2011) and compared to general obstetrical population (GOP, 3939 deliveries). Gestational outcomes and the course of the disease were recorded. Maternal mean age at conception was 31.8 (SD:5,3) years and median disease duration was 67 months (range 2–193).

Results: In SSc patients preterm deliveries (26% vs 12%) and severe (<34 weeks) preterm delivery (10% vs 5%), intrauterine growth restriction (6% vs 1%) and very low birth weight babies (5% vs 1%) were significantly more frequent than in GOP. Patients with a preterm delivery were taking folic acid supplementation in a smaller proportion (36%) than those who had a term delivery (68%) ($p< 0.01$). Antitopoisomerase and anticentromere antibodies were not significantly associated with different pregnancy outcomes, such as diffuse and limited disease. The disease remained stable in most SSc patients, but we observed 4 cases of disease evolution within 1 year from delivery, all in antitopoisomerase positive patients.

Conclusion: SSc patients can have successful pregnancies, but they have an increased risk of preterm delivery, intrauterine growth restriction and very low birth weight babies. A disease evolution during or after pregnancy is a rare but possible event. High-risk management should be standard in these patients and pregnancy should be avoided in cases of severe organ damage and postponed in early diffuse SSc.

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Increased Risk of Osteoporosis and Fracture in Patients with Systemic Sclerosis. A Comparison to Rheumatoid Arthritis. Jérôme Avouac, Eugénie Koumakis, Emese Toth, Marine Meunier, Emilie Maury, Catherine Cormier, Andre Kahan and Yannick Allanore. Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France

Background/Purpose: To investigate whether patients with systemic sclerosis (SSc) have increased risk of osteoporosis (OP) and fractures compared to a "high risk" population with rheumatoid arthritis (RA)

Methods: Cross-sectional study with successive inclusion of SSc and RA patients matched for age and sex on a 12-month period. Risk factors for OP and fractures, including age, menopausal status, calcium/vitamin D intake, family history, comorbidity and steroid use, were collected for all patients. Bone mineral density (BMD) was assessed at AP lumbar spine (L1-L4), femoral neck, and total hip region with DXA Prodigy (GE-Lunar) or QDR4500 (Hologic). We included 75 successive patients with SSc (70 women, 93%) and 147 (139 women, 94%) with RA. The mean ± standard deviation, SD, age of SSc patients was 62±12 years; the mean ± SD disease duration was 10±9 years; 52 (69%) had the limited cutaneous subset and 23 (31%) the diffuse. The mean ± SD age of RA patients was 61±11 years and their mean ± SD disease duration was 18±13 years. RA Patients were more likely to receive corticosteroids than SSc patients (137 (93%) vs. 45 (60%), $p<0.0001$). Cumulative dose of corticosteroids and CRP were significantly higher in patients with RA than SSc (39554±29661 mg *vs.* 19392±19333 mg, $p<0.0001$ and 12±16 mg/l *vs.* 7±7.9 mg/l, $p=0.01$).

Results: The point prevalence of OP (T-score <−2.5) was 28% and 32% in SSc and RA, respectively (p=NS). Bone mineral density measured on lumbar spine, femoral neck and total hip was not different between SSc and RA patients. The point prevalence of fractures was 33% and 32% in SSc and RA, respectively (p=NS). The frequency of vertebral (24% vs. 17%) and non-vertebral fracture (23% vs. 21%) did not differ between the two groups. In multivariate logistic regression analysis, patients with SSc and OP (n=21) were more likely to have longer disease duration than patients without osteoporosis (odds ratio, OR: 1.11, 95% confidence interval, CI: 1.03–1.21). There was no association between OP and treatment with corticosteroid, systemic inflammation (CRP >10mg/l) or any SSc feature. In multivariate analysis, patients with SSc and fractures (n=25) were more likely to be older (OR: 1.10, 95% CI 1.03–1.18) and to have vitamin D deficiency (OR: 95% CI: 5.04 1.27–20.02). In comparison, patients with RA and OP (n=47) were more likely to be older (OR: 1.04, 95% CI: 1.01–1.09) and treated with corticosteroids than patients without OP (OR: 3.30, 95% CI: 1.02–10.70). Cumulative dose of corticosteroids negatively correlated with BMD measured at lumbar spine ($r=0.38$, $p=0.01$) and total hip ($r=0.49$, $p=0.008$) in RA patients. In addition, age (OR: 1.07, 95% CI: 1.02–1.12) and vitamin D

deficiency (OR: 4.97, 95% CI: 1.53–16.13) were associated with fractures in RA patients.

Conclusion: The prevalence of OP and fracture in SSc patients was comparable to those with RA, highlighting an increased risk of OP and fracture. Age and vitamin D deficiency were found to be important factors. Our results indicated that BMD in SSc was similar to patients with RA. Increasing the awareness to perform BMD measurements and supply vitamin D in patients with SSc may be warranted based on our results, especially for older patients.

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Serum Estradiol and Estrone Levels in Patients with Systemic Sclerosis: Relationship to Disease Specific Clinical Manifestations. Christine Peoples[1], Mary Lucas[1], Yona Cloonan[2], Thomas A. Medsger Jr.[1] and Carol A. Feghali-Bostwick[1]. [1]University of Pittsburgh Scleroderma Center, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Systemic sclerosis (SSc) is a chronic, multisystem autoimmune disease which affects the connective tissues. The female to male ratio in SSc is 3:1, but the difference is accentuated during childbearing years with a ratio of 10:1, suggesting that female sex hormones such as estrogen may play a role in disease pathogenesis. There are three main estrogens: estradiol, estrone, and estriol. Estradiol and estrone are the estrogens found in non-pregnant women while estriol is the estrogen of pregnancy. Estrogens induce production of collagen, fibronectin, and a fibrotic phenotype. We propose that abnormal levels of estrogens may be a marker for, or participate in, the pathogenesis of fibrosis in SSc.

Methods: Serum levels of estradiol (68 patients) and estrone (50 patients) were measured by mass spectrometry in post-menopausal SSc patients with diffuse cutaneous (dc) involvement and disease duration less than 3 years who did not receive any hormone replacement therapy (HRT) and age-matched, healthy, post-menopausal controls who similarly did not receive HRT. The levels of estradiol and estrone were analyzed by SSc duration (early vs. late) at the time of the serum sample and by disease specific clinical manifestations occurring at any time during the illness, including severity of skin disease, frequency of internal organ involvement, and serum autoantibody profile. High levels of estradiol were defined as those 5+ pg/mL and high levels of estrone were defined as those 47+ pg/mL. Two separate sets of analyses were performed: case vs. control comparisons of estrone and estradiol and case-only comparisons of clinical manifestations based on high vs. low estrone and high vs. low estradiol among cases. For the comparisons, we utilized the Wilcoxon rank-sum test and Chi-square test of proportions where appropriate.

Results: 34% of SSc patients had high levels of estradiol compared to 21% of controls. Patients with higher estradiol levels had a shorter duration of disease from first symptom to first visit. 32% of patients with high estradiol levels had renal crisis compared to 18% of patients with low estradiol levels. Serum levels of estrone were significantly higher in SSc patients compared to controls (<0.01), with 40% of SSc patients having high estrone compared to 13% of controls. 42% of patients with high estrone had gastrointestinal (GI) involvement compared to 17% of patients with low estrone. 44% of SSc patients with high estrone levels had an anti-Scl 70 antibody as compared to 25% in the low estrone group.

Conclusion: Circulating estradiol and estrone levels are elevated in post-menopausal patients with dcSSc compared with healthy post-menopausal women, and these elevations are associated with renal crisis, GI involvement, and the presence of anti-Scl 70 antibodies. These estrogen compounds may participate in the production of the excessive fibrosis which occurs in the early phase of dcSSc.

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Burden of Disease in Dutch Patients with Systemic Sclerosis and Digital Ulcers; Data From Thedata From the Dutch National Registry. Madelon C. Vonk[1], Alexandre E. Voskuyl[2], Michel Walravens[3], Pieter Paassen[4] and Annemie Schuerwegh[5]. [1]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Maasstad hospital, Rotterdam, Netherlands, [4]University Medical Centre Maastricht, Maastricht, Netherlands, [5]Leids Univ Medisch Centrum, Leiden, Netherlands

Background/Purpose: Digital ulcers (DU) are a frequent complication of systemic sclerosis (SSc) with a negative impact on quality of life. The Dutch incidence, prevalence and natural history of DU in SSc patients are largely unknown. Furthermore, clinical management varies, as international guidelines for the management of DU are not available. RESIDU is a Dutch national observational study, designed to collect cross-sectional and longitudinal epidemiological data in SSc-DU patients. RESIDU aims to describe demographic data, clinical characteristics and Dutch management practice.

Methods: Known Dutch SSc-treating physicians were invited to participate in RESIDU. Upon EC approval in participating centres, all SSc-patient charts were screened for a history of DU and/or pitting scars (PS) and data were collected in an online disease registry.

Results: In June 2011, 28 Dutch hospitals participated in RESIDU. As most larger hospitals participated, RESIDU is estimated to represent approximately half of the Dutch SSc population. In total 1,304 patient charts were screened; 547 patients (42%) had a history of DU. Data of 439 patients were included in RESIDU. The actual number of patients is given for each item, to account for missing data.

Patient inclusion per site ranged from 6 to 301 SSc patients and the incidence of DU varied between 5% and 63%. Smaller sites showed a larger variation in incidence of DU, probably caused by different policies for patient referral to specialized sites.

The average age at first Raynaud phenomenon (RP) occurrence was 43 ± 15 years (n=378) and at first DU 49 ± 15 years (n=315). Time between first RP and DU was 4.4 years (n=287). Other SSc manifestations were gastro-intestinal involvement (57.1%, n=424), lung fibrosis (31.4%, n=424), PAH/PH (9.9%, n=424), heart involvement (6.4%, n=424) and kidney involvement (4.7%, n=424). The most important DU complications were gangrene (29.2%, n=432), soft tissue infection requiring antibiotics (19.3%, n=409), auto-amputation (6.7%, n=406) and osteomyelitis (3.7%, n=432). Hospitalization was needed in 41.5% of patients (n=427), mainly due to need for parenteral prostanoids (38.2%).

Conclusion: The RESIDU database represents half of the Dutch SSc-DU population and therefore gives a good estimate of Dutch DU epidemiology. Furthermore, it offers clear opportunities for evaluation of patient management practices. The current data show that DU patients suffer from a considerable burden of disease.

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Development and Validation of a New Clinical Prediction Rule for 5-Year Survival in Early Scleroderma, a EUSTAR Study. Delia diaconu-Popa[1], Madelon C. Vonk[2], Roger Hesselstrand[3], Patricia E. Carreira[4], Gabriele Valentini[5], Lorenzo Beretta[6], Paolo Airo[7], Murat Inanc[8], Alexandra Balbir-Gurman[9], Stanislaw Sierakowski[10], Yannick Allanore[11], Laszlo Czirjak[12], Valeria Riccieri[13], Roberto Giacomelli[14], Armando Gabrielli[15], Gabriela Riemekasten[16], Marco Matucci-Cerinic[17], Dominique Farge[18], Nicolas Hunzelmann[19], Frank H.J. van den Hoogen[20] and Jaap Fransen[21]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Lund University & Skåne University Hopsital, Lund, Sweden, [4]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [5]Second Univ of Napoli, Napoli, Italy, [6]IRCCS Fondazione Policlinico-Mangiagalli-Regina Elena & University of Milan, Milan, Italy, [7]Brescia, Italy, [8]Istanbul University, Istanbul Faculty of Medicine,, Istanbul, Turkey, [9]Rambam Health Care Campus, Haifa, Israel, [10]Department of Rheumatology and Internal Diseases, Medical University of Bialystok, Bialystok, Poland, [11]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [12]Hungary, [13]University of Rome, Medical Clinic and Therapy Department, [14]Rheumatology Unit, University of Aquila, L'Aquila, Italy, [15]Clinica Universitaria Ancona, Ancona, Italy, [16]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [17]University of Florence, Florence, Italy, [18]EBMT, Paris, France, [19]University of Cologne, Cologne, Germany, [20]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [21]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands

Background/Purpose: Systemic sclerosis (SSc) is associated with a significant reduction in life expectancy. The existing clinical prediction model developed in 1999 for 5 year survival in SSc underestimated survival in new patients. Therefore, the objective was to develop and

validate a new clinical prognostic model to predict 5-year survival in early systemic sclerosis (SSc).

Methods: A multi-centre cohort of SSc patients diagnosed before 2002 was established in EUSTAR centers. Patients were eligible if they were followed for five-years or shorter if they died. The sample (N=955) was split in a development sample (2/3 of deaths) and a validation sample (1/3 of deaths). In the development sample, univariate and multivariate logistic regression and a bootstrap procedure were used to develop a prognostic model to predict 5-year survival after diagnosis of SSc. Model performance (discrimination and calibration) was studied in the validation sample.

Results: The development sample consisted of n=700 patients of whom 59 (8.4%) died and the validation sample consisted of n=255 patients of whom 25 (9.8%) died. After univariate logistic regression, 14 clinical variables ($p<0.10$) entered the multivariate logistic regression model. Using a backward selection procedure, a combination of 6 variables ($p<0.20$) remained. The six items were: age >55 at diagnosis (OR 2.16), female gender (OR 1.73), dcSSc (OR 1.93), ECG abnormalities (OR 1.71), low FVC or low DLCO (OR 1.36) and presence of urine protein (OR 2.50). In the validation sample, the 1999 prediction model had an area under the ROC curve of 0.73. The area under the ROC curve of the new model was 0.85 and the predicted probabilities of 5-year survival appropriately ranged from 0.02 to 1.0.

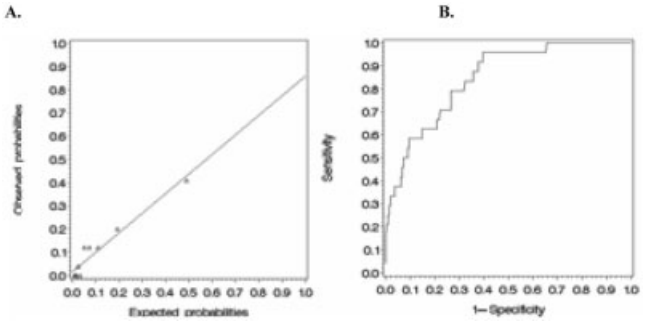

Figure 1. Figure A. Calibrations curves for the prognostic score; **B.** Receiver operating characteristics curve for the new prognostic model.

Conclusion: A new simple prognostic model using 6 disease factors to predict 5 year survival at diagnosis in SSc was developed. It showed good performance regarding calibration and discrimination in the external validation sample.

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Periungueal Capillaroscopy Using Conventional Dermoscopy: Easily Available Method and Simple to Perform During the Regular Office Consult in Patients with Systemic Sclerosis. Nicolle Mazzotti[1], Claiton Brenol[1], Markus Bredemeier[2], João Carlos T. Brenol[1], Ricardo M. Xavier[1] and Tania Cestari[1]. [1]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil

Background/Purpose: Systemic sclerosis (SSc) patients present microvascular dysfunction which can be assessed by nailfold capillaroscopy.The aim of this study was to evaluate the accuracy of capillaroscopy using polarized light noncontact dermoscopy (PLD) and nonpolarized light contact dermoscopy (NPLD) compared to conventional stereomicroscope nailfold capillaroscopy (SNFC) in diagnosing SSc-related alterations.

Methods: Demographics and physical exam of 45 consecutive confirmed SSc patients. Standardized phographs were taken by the same observer, of 4 digits capillaroscopy using the 3 devices: PLD, NPLD and SNFC. Images were randomly analyzed by another blinded observer, considering the parameters: pattern analysis (normal, scleroderma, systemic lupus erythematosus, non specific and traumatic microangiopathy); structure analysis (presence of hemmorrages, ectasia, giant capillaries, bush-shaped and bizarre vessels); morphological variations and degree of devascularization. Statistical analysis to confirm sensitivity, specificity and intra-observer agreement.

Results: Scleroderma pattern was found in 83% of patients (82% women, average age 52yo). PLD and NPLD accuracy were highly sensitive in evaluating deletion (96% and 100%), presence of hemorrhages (96% and 92%) and highly specific for hemorrhage and enlarged loops. The intra-observer Kappa value for diagnosis of SD pattern was moderate to good (0.71, 0.60 and 0.60) for the 3 methods. Presence of hemorrhage showed high Kappa (0.77, 0.90 and 0.95). The average number of capillaries in the central 3 mm presented Pearson's index of 0.94 ($p<0.0$)and the Bland Altman graphic analysis confirmed the good agreement between the used devices.

Conclusion: Both polarized and nonpolarized light dermoscopy are reliable methods with good accuracy to evaluate the nailfold capillaroscopy when compared to the gold standard (stereomicroscopy). These results open a new possibility for conventional dermoscopy that is easily available and simple to perform during the regular office consult.

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Increased Expression of NOX4 in Systemic Sclerosis Dermal Fibroblasts. Regulation by TFG-β, Protein Kinase C Delta and c-Abl Kinase. Sonsoles Piera-Velazquez, Alma Makul and Sergio A. Jimenez. Jefferson Insititute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA

Background/Purpose: Systemic sclerosis (SSc) is characterized by the excessive deposition of collagen and other connective tissue components in skin and multiple internal organs. Although transforming growth factor β (TGF-β) has been shown to play a crucial role in the development of tissue fibrosis in SSc, recently, other factors such as excessive oxidative stress have been implicated in the pathogenesis of the disease. Oxidative stress is caused by cellular overproduction of ROS (reactive oxygen species). One of the main ROS is superoxide anion radical which is generated by NADPH oxidases. NOX4 is one of seven NADPH isoforms which plays a crucial role in the generation of ROS. The purpose of these studies was to examine the role of NOX4 in the pathogenesis of tissue fibrosis in SSc.

Methods: Normal and SSc human dermal fibroblasts were isolated from skin biopsies. Normal dermal fibroblasts were expanded and treated with 10 ng/ml of human recombinant TGF-β in media containing 10% FBS for 24 h with or without previous treatment for 1h with 2.5 and 5 μM of rottlerin, an inhibitor of protein kinase Cδ (PKCδ) or 5 μM of imatinib mesylate an inhibitor of c-Abl kinase. Small interfering RNA (siRNA) was employed to confirm the PKCδ role in normal dermal fibroblasts. RNA and proteins were isolated and examined by Real Time PCR and Western blots using a NOX4 specific antibody.

Results: Immunofluorescence and Western blot analysis showed that NOX4 is constitutively expressed by human dermal fibroblasts and that its expression is upregulated in SSc fibroblasts compared to normal fibroblasts. TGFβ increased the protein and mRNA expression of NOX4 by 3-fold in normal human dermal fibroblasts. Inhibition of PKCδ with rottlerin and a specific PKCδ siRNA or with the c-Abl inhibitor, imatinib mesylate, abrogated the TGF-β-induced stimulation of NOX4.

Conclusion: NOX4 expression and production is constitutively elevated in SSc fibroblasts and its expression is stimulated by TGF-β. PKCδ and the c-Abl kinase are involved in the process. Thus, targeting NOX4 expression may be a novel therapeutic approach for the treatment of SSc and other systemic fibrotic disorders.

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Construct Validity of the Saint George's Respiratory Questionnaire in An Observational Cohort of Patients with Early Diffuse Systemic Sclerosis. Dinesh Khanna[1], James R. Seibold[2], Peter A. Merkel[3], Maureen D. Mayes[4], Kristine Phillips[5], Robert W. Simms[6], Shervin Assassi[7], Philip J. Clements[8] and Daniel E. Furst[9]. [1]University of Michigan, Ann Arbor, MI, [2]Scleroderma Research Consultants LLC, Avon, CT, [3]Boston University School of Medicine, Boston, MA, [4]University of Texas Health Science Center at Houston, Houston, TX, [5]University of Michigan Medical School, Ann Arbor, MI, [6]Boston University School Medical, Boston, MA, [7]Univ of Texas Health Science, Houston, TX, [8]UCLA School of Medicine, Los Angeles, CA, [9]UCLA Medical School, Los Angeles, CA

Background/Purpose: The Saint George's Respiratory Questionnaire (SGRQ) is a self-administered questionnaire for measuring health-related quality of life () in respiratory diseases. It consists of 76 items, producing three sub-scores: Symptoms (SYM), Activity (ACT), and Impacts

(IMPACT), and Total (TOTAL). SYM scale assesses the patients' perception of their respiratory problems; the ACT scale measures he patients' current daily physical activity; the IMPACT scale evaluates the impact of the respiratory problems and the TOTAL scale is a weighted summation of the 3 scales. Scores for each scale can range from 0 (no impairment) to 100 (the worst impairment).

Methods: We recruited patients with early diffuse SSc (< 5 years from 1st non-Raynaud's sign or symptom) at four scleroderma centers in the United States. We hypothesized there would be at least moderate correlations (r>=0.30) between the 4 SGRQ scales vs. FVC% predicted, HAQ-DI, VAS breathing, and 6-minute walk test (6MWT). We also assessed the discriminatory validity to distinguish between i) FVC ≤ 70% vs. > 70% and ii) presence vs. absence of fibrosis as assessed by high-resolution CT.

Results: Of 200 patients, we had data on 177 patients with SGRQ. The mean (SD) age was 51 (12) years, disease duration (from 1st non-Raynaud's sign or symptom) 2.4 (1.6) years, modified Rodnan skin score (MRSS) 21 (10), HAQ-DI 1.1 (0.8), and VAS breathing of 20 (35 on a 0–150mm). The mean (SD) scores for SYM, ACT, IMPACT, and TOTAL scales were 25 (19), 41 (31), 15 (17), and 25 (19), respectively. The table summarizes correlations between SGRQ scores and other outcomes. ACT, IMPACT, and TOTAL scales had significant associations with FVC%, HAQ-DI, VAS breathing, and 6MWT except for SYM scale vs. HAQ-DI and 6 MWT (P> 0.05). Patients with low FVC% (≤ 70%; N=42) had higher (worse) scores for SYM, ACT, IMPACT, and TOTAL scales compared to FVC% >70% (N=135; P< 0.05 for all scales). Patients with evidence of fibrosis on HRCT (N=32) had numerically higher scores for SYM, ACT, IMPACT, and TOTAL scales, although only TOTAL score was statistically significant (p< 0.05).

Conclusion: The SGRQ has acceptable construct validity in early dcSSc. Ongoing longitudinal analysis will define the sensitivity to change and minimally clinically important differences of the SGRQ scales as well as the additive value of SGRQ to other outcome measures for dcSSc.

Table. Correlation coefficients between SGRQ scales and other measures

SGRQ	FVC% Predicted (N = 165)	HAQ-DI (N = 177)	VAS Breathing (N = 175)	6 MWT (N = 54)
SYM	−0.25*	0.12	0.52*	0.16
ACT	−0.36*	0.44*	0.62*	−0.52*
IMAPCT	−0.36*	0.33*	0.79*	−0.45*
TOTAL	−0.38*	0.38*	0.75*	−0.48*

* P value< 0.05

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Progression of Isolated Raynaud's Phenomenon to Systemic Sclerosis: Impact of ANA Subtype and Disease Subset. Pia Moinzadeh[1], Kevin J. Howell[2], Voon Ong[3], Svetlana Nihtyanova[2] and Christopher D. Denton[2]. [1]Royal Free Hospital, Medical School, London, United Kingdom, [2]Royal Free Hospital, Medical School, London, England, [3]UCL Medical School, London, England

Background/Purpose: Raynaud's phenomenon often precedes the diagnosis of systemic sclerosis (SSc) and may be regarded as the first symptom of the disease in many cases. Conversely only a minority of cases of isolated Raynaud's phenomenon (RP) progress to defined connective tissue disease (CTD) including SSc. We have explored the predictive potential of ANA positivity and nailfold capillaroscopy for identifying cases of RP that may progress to CTD and explored the time between onset of RP and SSc-specific ANA pattern in a large patient cohort. This study has significant implications for strategies for earlier diagnosis of SSc that focus on RP.

Methods: To ascertain progression of Raynaud's to CTD patients with isolated RP (n=569) presenting to our centre were evaluated for antinuclear autoantibodies and for scleroderma-typical capillary changes using nailfold capillaroscopy. To explore the duration of isolated RP in cases evolving to SSc patients with definite SSc (n=2150) were evaluated from our clinical database, which was developed to determine and follow the current disease status of SSc patients.

Results: 569 patients with isolated RP were characterized by a mean age of 43 years (+13y), were predominantly female (85%) and had already a mean duration of Raynaud phenomenon features at presentation of 13 years (+13y). Further evaluation revealed that 7% showed antinuclear autoantibodies (ANAs) and 17% showed grade III abnormalities in nailfold capillaroscopy at their first visit. During our follow-up period of 1500 patient years (mean = 4.6 years) only 1.5% (8/569) of cases developed further clinical features of SSc (7/8 had positive capillaries and ANAs at first presentation) and 0.5% (3/569) developed autoantibodies (3/3 had positive capillaries at presentation).

Conversely, for those with definite SSc attending our centre the interval between the onset of the RP and definite SSc onset varied significantly between disease subsets and autoantibodies, being shortest for the dcSSc (2.3+6.5years) variant and longest for the lcSSc (8.4+11.5years) disease variant (p<0.0001) and regarding the antibody status being shortest for patients with anti RNA-Polymerase III (ARA) (1.7+6.4years) and longest for ACA antibodies (10.8+12.5years) (p<0.0001). The duration for other reactivities was 3.6+6.4years for patients with anti-topoisomerase antibodies (ATA), 4.2+6.1years for patients with anti-U1RNP antibodies, 3.9+7.9 years for patients with anti-U3RNP antibodies

Conclusion: Since classification criteria for earlier diagnosis of SSc are being developed the duration of pre-existing RP may be an important determinant of the profile of SSc cases identified through screening. Our analysis revealed that over 95% of patients with isolated Raynaud phenomenon, negative autoimmune serology on more than one visit and normal capillaroscopy score (less than grade 2) showed no progression to CTD. Duration of antecedent RP differs substantially between disease subsets and SSc-specific ANA patters and so a cohort of SSc cases that is selected based upon pre-existing RP may be less likely to include diffuse disease or ARA positive cases.

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Efficacy and Safety of Intravenous Cyclophosphamide In the Treatment of Scleroderma Lung Disease: 7-Year Follow-up. Alexandra Balbir-Gurman[1], Ludmila Guralnik[2], Mordehai Yigla[3], Menahem A. Nahir[1], Alexander P. Rozin[4], Kohava Toledano[1], Doron Markovits[4] and Yolanda Braun-Moscovici[1]. [1]B. Shine Rheumatology Unit, Rambam Health Care Campus, The Bruce Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel, [2]Department of Diagnostic Imaging, Rambam Health Care Campus, The Bruce Rappaport Faculty of Medicine, Technion-Institute of Technology, Israel, [3]Division of Pulmonary Medicine, Rambam Health Care Campus, The Bruce Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel, [4]B. Shine Rheumatology Unit, Rambam Health Care Campus, Haifa, Israel

Background/Purpose: Interstitial lung disease (ILD) is a serious complication in the course of systemic sclerosis (SSc). Various efficacy of cyclophosphamide (CYC) for treatment of SSc-ILD was demonstrated with follow up for 2 years. We analyzed changes in lung function tests (LFTs), pulmonary artery pressure (PAP) estimated by ECHO, and skin changes measured by modified Rodnan skin score (mRSS) at 4 and 7-years after IV CYC monthly treatment of SSc-ILD.

Methods: Active ILD was defined as presence of ground glass and/or fibrosis on chest HRCT and reduction in FVC and/or DLCO for more than 10% during 2 consecutive visits. Patient's data was completed from EUSTAR database at our site. Student paired T-test, Mann-Whitney U-test and Wilcoxon Signed Ranks tests were used for statistical analysis.

Results: Among 170 SSc pts registered at our site 38 pts (21.8%) had active ILD. Data of 28 pts (female 78.6%) started CYC before 2007 and 17 pts started before 2004 were eligible. Age, disease duration, and follow-up period were 50.7 +/− 12.7 yrs, 16.3 +/− 17.9 months, 6.5 +/− 6 yrs. Eight pts (28.6%) died, 2 pts during first 4 yrs. Mean cumulative CYC dose was 8.96 +/− 3.8 G. Changes in FVC and DLCO from baseline and at the end of the first year were: 78.3% and 75.4% (p=NS); 65.6% and 54.7% (p<0.005). More than 20% reduction in FVC, DLCO, and mRSS during 4 and 7 years was registered in 34% vs 7% of pts; 68% vs 24% of pts; 80% vs 7% of pts; more than 20% elevation in PAP was observed in 25% vs 6% respectively. The rate of annual reduction in FVC, DLCO and mRSS different significantly in the first 4 years and next 4–7 years after CYC: 3.2 +/−2.9 and 0.4 +/−1.0 (p<0.004); 4.6 +/−2.9 and 0.9+/−1.6 (p<0.001); 1.8 +/−1.9 and 0.2 +/−0.2 (p<0.002) respectively. Among presenting features (cough, dyspnea, lung crepitus, weight loss, presence of specific antibodies, esophageal widening, CPK level, mRSS) only elevated CPK correlated with FVC, DLCO and PAP changes (p=0.04, p=0.026 and p=0.028 respectively). Reduction in mRSS was significant (p=0.023) at both total CYC doses (6 and 12 G). Adverse events were pneumonia, HBV reactivation, Kaposi sarcoma, premature menopause.

Conclusion: IV CYC stabilized FVC up to one year follow-up but did not prevent further reduction in LFT in the next 4 and 7 yrs. CYC rapidly improved mRSS. CYC doses more than 6G CYC had no additive contribution regarding LFT and mRSS. We suggest that CYC is effective for induction of SSc-ILD remission but should be followed by other less toxic disease-modified drugs for maintenance of LFT stability; more than 24 months of follow-up should be considered in judgment of treatment efficacy in SSc-ILD.

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Preliminary Steps to a Health Index for Systemic Sclerosis Based on the World Health Organization's International Classification of Functioning, Disability and Health: A European League Against Rheumatism Scleroderma Trials and Research Initiative. Lesley Ann Saketkoo[1], Reuben Escorpizo[2], Kevin J. Keen[3] and Oliver Distler[4]. [1]LSU Health Science Center, New Orleans, LA, [2]ICF Research Branch in cooperation with the WHO Collaborating Centre for the Family of International Classifications Department of Health Sciences; and Health Policy, University of Lucerne, Switzerland, [3]University of Northern British Columbia, Prince George, BC, [4]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Systemic Sclerosis (SSc) affects multiple organ systems in varying combinations resulting in many types and degrees of disability in patients. Skin fibrosis, ischemic pain, ulceration, arthritis, contractures, myopathy as well as cardiopulmonary, renal and gastrointestinal manifestitations may carry significant burden on emotional, social and physical functioning.

International Classification of Disability, Health and Functioning (ICF) is a universal framework introduced by the World Health Organization (WHO) to describe and quantify the impact caused by health conditions on functioning which may lead to disability. The ICF uses a standardized alphanumerical language to describe health states in terms of the bio-psycho-social model. The ICF is accepted by national and international health care and policy-making systems to assess the impact of disease on personal, scientific, economic and service levels.

Methods: Comprehensive literature search in PubMed was performed with the following keywords: outcome measures, SSc, rehabilitation, function, quality of life, mental health, sexual health, pain and traditional measures of disease activity to identify 5 validated measures that represent the broadest range of manifestations (OD, LAS). Instruments were deconstructed to meaningful concepts according to ICF linkage rules and linked by 2 health professionals familiar with ICF updated linkage rules (RE, LAS). Inter-linker agreement was analyzed (KK).

Results: The 5 validated measures for this exercise were:
Hand Mobility in Scleroderma Test (HAMIS)
Modified Rodnan Skin Score (mRSS)
Raynaud Condition Score (RCS)
Scleroderma Health Assessment Questionnaire (SHAQ)
Systemic Sclerosis Gastrointestinal Tract Instrument (GIT).

Thirteen ICF Chapters and 65 ICF categories were linked to SSc (Table 1). Overall inter-linker agreement was 66% (95% CI: 57, 75) (Table 2).

Table 1. Linkages from the 5 Pilot Instruments

Domain	Chapter	Title	Number of Categories	Categories Shared Between Instruments	Contributing Instruments
Body Functions	Chapter 1:	Mental	3	0	GIT
	Chapter 2:	Sensory and Pain	4	3	GIT, RCS, SHAQ
	Chapter 4:	Cardiovascular and Respiratory	3	0	SHAQ
	Chapter 5:	Digestive, Metabolic and Endocrine	12	3	GIT, SHAQ
	Chapter 7:	Neuromuscular and Movement	1	0	HAMIS
	Chapter 8:	Skin	2	2	RCS, SHAQ
Body Structures	Chapter 7:	Movement	1	1	RCS
	Chapter 8:	Skin	4	0	mRSS
Activities & Participation	Chapter 4:	Mobility	21	2	GIT, mRSS, RCS, SHAQ
	Chapter 5:	Self-Care	8	0	SHAQ
	Chapter 6:	Domestic Life	3	0	SHAQ
	Chapter 7:	Interpersonal Interactions & Relationships	1	0	GIT
	Chapter 9:	Community, Social & Civic Life	2	0	GIT

Table 2. Instrument Comparison and Inter-Reviewer Agreement

Instrument	Number of Items Linked	Number of Categories Identified	Agreement (%)	Agreement 95% Confidence Interval
HAMIS	11	16	69	(41, 89)
mRSS	16	18	89	(65, 99)
RCS	11	21	52	(30, 74)
SHAQ	14	22	64	(41, 83)
SSc GIT	34	41	63	(47, 78)
(9 Items of the SSc GIT were not included in the agreement analysis.)				
Total	78	118	66	(57,75)

Conclusion: This exercise is the first attempt to establish an ICF language for SSc in terms of functioning, beyond the traditional biomedical aspect of the disease. A preliminary composite of all validated outcome measures in systemic sclerosis will soon be made available using this methodology for ICF engaged health systems and other entities with validation studies to follow. Thus, the global, regional and personal impact of SSc across cultures, age and socioeconomic status may be assessed fairly for use in policy making and provision of services and funding.

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Evaluation of Nutritional Status and Dietary Intake in Women with Systemic Sclerosis. Thais F. Marighela[1], Ligia A. Martini[2], Vera Szejnfeld[1], Marcelo M. Pinheiro[1] and Cristiane Kayser[1]. [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: To evaluate nutritional status, body composition, and dietary intake in systemic sclerosis (SSc) women, as well as to compare these findings according to different disease subsets.

Methods: 61 SSc women (31 with limited and 30 with diffuse cutaneous form) and 67 age-matched healthy women were included in this transversal study. Body composition measurements were performed using dual energy X-ray absorptiometry (DXA) in order to evaluate fat mass, lean mass and appendicular lean mass. Body mass index (BMI) was measured and a validated 3-day food intake questionnaire was used in all patients and controls. Nutrient intakes were assessed using Nutrition Data System for Research software (University of Minnesota, 2007) and their adequacies according DRI's proposed values. Total energy (kcal/day), and total macronutrients and fiber intake were evaluated. In addition, all data were compared among diffuse (dcSSc) and limited cutaneous SSc (lcSSc) patients, and between patients with and without gastrointestinal involvement (oesophageal dysmotility or intestinal abnormalities). $P<0.05$ was set as significant.

Results: Women with SSc had significantly lower BMI, total fat mass, total and appendicular lean mass as compared to healthy controls ($p=0.02$; $p=0.009$; $p=0.04$; $p=0.01$, respectively). Women with lcSSc had no significant changes on body composition when compared to healthy controls. Besides, dcSSc women had significantly lower BMI, total fat mass, and total and appendicular lean mass than healthy women (Table 1). In addition, BMI and appendicular lean mass was also significantly lower in dcSSc in comparison to lcSSc women. There was no significant difference in DXA parameters or BMI values between patients with or without gastrointestinal involvement. The total energy and macronutrients intake was similar between SSc and controls, but there was a lower intake of fibers in SSc patients, with no significant difference between dcSSc and lcSSc patients or between patients with and without gastrointestinal involvement.

	dcSSc	lcSSc	Healthy controls	p
Age (years)	48.5 ± 11.5	53.4 ± 12.1	48.3 ± 14.6	0.12
Body mass index (kg/m$^{2)}$	22.6 ± 6.2***	26.3 ± 5.0**	26.6 ± 4.8*	0.002
Total fat mass (kg)	19.2 ± 11.5*	23.9 ± 10.5	26.3 ± 9.2*	0.007
Total lean mass (kg)	33.0 ± 4.5*	35.4 ± 6.4	36.1 ± 4.9*	0.03
Appendicular lean mass (kg)	13.8 ± 2.7***	15.7 ± 3.4**	16.0 ± 2.6*	0.002

Tukey's test, with $p<0.01$*; $p<0.05$**

Conclusion: An abnormal body composition, probably related to more severe disease, was found in dcSSc women, but not in those with lcSSc. Our data suggest some degree of malnutrition and cachexia in dcSSc patients, regardless dietary intake or previous gastrointestinal involvement. Thus, a more detailed screening, including medical history, nutritional approach and imaging, should be performed for better clinical management in SSc patients.

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Evaluation of the Impact of Recurrent Ischemic Digital Ulcers on Hand Disability in Patients with Systemic Sclerosis (ECLIPSE). Report of the Cohort At the Time of Inclusion. Luc Mouthon[1], Patrick Carpentier[2], Catherine Lok[3], Eve Puzenat[4], Pierre Clerson[5], Virginie Gressin[6] and Marie-Aleth Richard[7]. [1]Hopital Cochin, Paris, France, [2]CHU Grenoble, Grenoble, France, [3]Amiens Hospital, France, [4]Besançon, Besançon, France, [5]Orgametrie, Roubaix, [6]Actelion France, Paris, France, [7]Marseille, Paris, France

Background/Purpose: Ischemic digital ulcers (DU) occur in the course of systemic sclerosis (SSc).

Methods: Prospective, longitudinal, observational study of 24 months evaluating the impact of recurrent DU on hand disability. Patients included fulfilled the American college of Rheumatology and/or Leroy & Medsger diagnosis criteria for SSc, experienced at least one DU during the previous year with or without active DU at the time of inclusion and were candidates to Bosentan therapy. Data were collected on SSc, characteristics of past and active DU, Rodnan skin score, factors influencing hand function and mobility, disability scores (Cochin hand function scale, health assessment questionnaire disability index (HAQ-DI)) and quality of life (SF36).

Results: 178 patients (124 women) were included between September 2009 and December 2010 in 49 centers. Mean age at inclusion and at the time of diagnosis of SSc were 53±15 and 43±14 years, respectively. SSc was diffuse in 44% of the cases, and Raynaud's phenomenon started 14±12 years before inclusion. 11% of patients had pulmonary arterial hypertension, 71% had oesophagus involvement. Mean Rodnan skin score was 14.5±8.9. Time elapsed since the first episode of DU was 8±8 years, 59% of patients had recurrent DU (first non Raynaud's sign for 52%), leading to sequellae including loss of substance (68%), auto-amputation (8%) and surgical amputation (10%). Complications occurred: infection 9%, gangrene 6%, osteitis 2%. 50% of patients had ≥ 1 active DU at the time of inclusion. In these patients, the mean number of DU was 2.4±1.9; 46% had more than one DU, 37% had both hands involved and 2.3±1.7 fingers involved. 23% of cases had ≥ 1 extended DU (>1cm). Concomitant mechanical DU were localized at the dorsal face of fingers (n=22) or bony reliefs (n=13). DU patients complained with more painful hands (visual analog scale 6.07±2.65 vs 2.42±2.5 without DU) and disabling, involving the dominant hand in 68% of the cases. DU increased hand disability (Cochin hand function scale: median 36 in patients with active DU vs 23 without, $p<0.0001$), HAQ-DI and altered the SF36. Other factors were independently participating to the alteration of hand function: diminution of proximal interphalangeal and distal interphalangeal joints mobility on more than one finger (66% and 57% of the cases, respectively), retraction of flexor tendons (46%).

Conclusion: DU represents an early complication of SSc. DU are significantly associated with hand disability in patients with SSc. Prospective follow up at two years will allow to determine the contribution of recurrent episodes to disability in patients with SSc.

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Survival and Causes of Death of 312 Norwegian Patients with Systemic Sclerosis. Anna-Maria Hoffmann-Vold, Oyvind Midtvedt, Oyvind Molberg, Torhild Garen and Jan Tore Gran. Oslo University Hospital, Oslo, Norway

Background/Purpose: The purpose of this study was to determine the survival of systemic sclerosis (SSc) in Norway and to analyse the causes of death in SSc patients.

Methods: Multiple sources of case identification were used to collect all SSc patients in South East Norway with a population of 2 707 021 inhabitants at the time period 1999–2009. All 312 identified patients met either ACR criteria or the modified Medsger and LeRoy criteria for SSc. Vital status at 1 January 2010 was provided for all participants by the national population register. Kaplan-Meyer and Cox proportional hazard models were used to analyse survival in SSc subgroups. The causes of death were based on information obtained from death certificates and chart review.

Results: 43 of 312 patients (14%) died in the study period. Median observation time from disease onset to death, age at onset and age at death for limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) are summarized in table 1. The 5 and 10 years survival rates for lcSSc were estimated to 97.6% and 92.9%, and to 90.6% and 70.3% for dcSSc.

According to the death certificates, 58.1% of deaths were attributed directly to SSc. Among these, 28% to pulmonal arterial hypertension (PAH), 20% to interstitial lung disease (ILD) and 16% were attributed to kidney disease.

Of the non SSc-related deaths, 33.3% were assigned to malignancies, 16.6% to other lung diseases and 16.6% to left heart diseases.

Table 1. Demographic features of 43 patients with SSc

	Male		Female	
Type	lcSSc	dcSSc	lcSSc	dcSSc
Number (% of total)	6 (12)	9 (42.9)	20 (10)	8 (17)
Age at onset, yrs	48 (33–77)	57 (43–74)	55 (20–74)	48.5 (28–74)
Age at death, yrs	56 (45–79)	73 (49–81)	65 (51–87)	59.5 (39–76)
Disease duration	8.5 (2–13)	6 (1–28)	13 (1–33)	4 (1–29)

Conclusion: Survival is decreased in SSc patients in Norway. Outcome is worst among male patients with dcSSc. However, the 5 and 10 year survival rate was better than those reported in earlier studies. The main cause of death was PAH, followed by ILD and kidney affection.

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Characteristics and Impact of Pain in Systemic Sclerosis: Comparison with Rheumatoid Arthritis. Serge Perrot[1], Philippe Dieude[2] and Yannick Allanore[3]. [1]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [2]APHP, Hopital Bichat, Paris, France, [3]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France

Background/Purpose: Pain has a major impact in chronic rheumatic diseases. Pain has been much less studied in systemic sclerosis (SSc) than in rheumatoid arthritis (RA), in which it is systematically assessed and is a major outcome measures both for trials and in routine care. Our objectives were to measure and characterise pain and its management in patients with (SSc), and to compare these aspects between SSc and RA patients.

Methods: A prospective study was carried out over a nine-month period in 3 universitary medical departments: consecutive inpatients with SSc or RA referred for routine assessment of disease activity were examined and asked to complete self-reported pain (MPQ, DN4, BPI), sleep, psychological (PCS, SOPA, Beck, HADs) and quality of life (SF12) questionnaires. Patients referred for severe or end-stage organ involvements were excluded.

Results: We included 159 patients: 82 SSc patients (85% women, 59±12 years of age, 56% with limited cutaneous and 44% with diffuse SSc, relatively severe as reflected by 45% of patients fulfilling Medsger's classes 3–4, SSc-HAQ 1.5±1.0) and 67 RA (68% women, 55±14 years of age, mean DAS 4.3±1.6, HAQ 1.9±1.0). Pain was significantly less frequent (55%) and less intense (VAS 3.9 ± 2.6) in SSc patients than in RA patients (75%, 5.3±2.1, $P<0.001$). Significant differences in type of pain were found between SSc and RA, with pain being more frequently generalised, (26% vs 20%, $p=0.01$), more frequently located in the skin (14% vs 1.3%, $p<0.001$) or muscle (9% vs 2.6, $p=0.03$) in SSc patients. A neuropathic pain component was observed in 40% of SSc vs 32.8% of RA patients ($p<0.01$), and pain related to synovitis and tenosynovitis was found in 25 % of SSc and in 78% of RA patients ($p<0.001$). Pain related to Raynaud's phenomenon was found only in SSc patients (N=25), with mild pain intensity. The MPQ questionnaire subscales demonstrated significant differences between SSc and RA respectively, for both sensory (6.8±6.6 vs 10.8±6.9) and affective dimensions (2.7±3.1 vs 5.4±4.3). Even with adjustment for pain level, pain had a lower impact in SSc than in RA (BPI questionnaire) on general activity ($p<0.001$), mood ($p<0.01$), walking capacity ($p<0.001$), usual work ($p<0.001$), relationships with others ($p<0.001$) and enjoyment of life ($p<0.05$). This was not related to a higher psychological distress since we found similar levels of anxiety and depression in SSc and RA, but was significantly correlated to the presence of joint pain. Pain coping strategies did not found differences in catastrophizing (PCS), but demonstrated higher scores for emotion and medication in RA patients (SOPA). No difference was observed between SSc and RA in analgesic prescriptions, regardless of the type of pain, except for acetaminophen (20% vs 27%, $p=0.02$)

Conclusion: In SSc, pain appears less intense, less frequent and more diffuse than in RA, with a limited impact, and does not represent a major severity symptom, conversely to RA. However, a neuropathic component can be more frequently found in SSc,. Furthermore, in SSc, when there is a joint component, sensory and affective pain dimensions are increased, with high impact and high medication demands, reaching the levels observed in RA patients.

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Esophageal Involvement in Systemic Sclerosis and Rheumatoid Arthritis: Prevalence of Esophagitis and Barrett's Esophagus. Andrey E. Karateev, Mikael M. Movsisyan, Lidiya P. Ananieva and Stefka G. Radenska-Lopovok. Research Institute of Rheumatology RAMS, Moscow, Russia

Background/Purpose: Esophageal involvement is a typical visceral manifestation of systemic sclerosis (SSc). Life threatening complications of esophagitis

in scleroderma such as ulcers and Barrett's esophagus (BE) must be actively monitored and require long-term treatment.

Objectives: To assess prevalence of esophageal involvement in SSc and rheumatoid arthritis (RA) patients, to reveal connection between clinical manifestation and endoscopic findings in patients with scleroderma esophagitis. Also, to assess effectiveness of proton pump inhibitors (PPIs).

Methods: 356 patients with SSc (females 92,6%; males 7,4%, age 47,8 + 19,7 years) and 1018 patients with RA (females 89,0%, males 11,0%, age 44.1 + 16.3 years), among whom glucocorticoids (GC) were administered in 66,7% vs 52,6% of patients, respectively. 1,6% vs 82,9% of patients were treated with NSAIDs, 13,2% vs 0% - D-penicillamine, 15,7% vs 56,5% - cytotoxics, 23,7% vs 8,7% - PPIs. All patients underwent upper gastrointestinal endoscopy.

Results: Subjective symptoms of esophageal pathology were detected in 64,0% vs 33,9% of patients with SSc and RA ($p<0.001$). Dysphagia and substernal ache were revealed in 10,1% and 7,0% of SSc patients, and only in 1,7% of patients with RA. Accoding to endoscopy results musocal hyperemia was seen in 27,4% vs 1,5% of patients, erosive esophagitis in 21,9% vs 2,2%, ulcers of the esophagus in 4 (1,1%) vs 0 ($p=0,000$) patients. Esophageal mucosal biopsy was performed in 92 patients with SSc and we revealed BE (intestinal metaplasia) in 19 patients (20,1%). No cases of BE were detected in RA patients. There was reliable link between symptoms and development of erosive esophagitis ($p=0,001$). At the same time we didn't find correlation between esophagus involvement, age, disease type (limited or systemic) and drugs administration (NSAIDs, GC, cytotoxics). Against the background of regular administration of PPIs (90 SSc patients) erosive esophagitis was detected in 35,0%, BE in 36,8% of patients. All 4 patients with esophageal ulcers were treated with PPIs.

Conclusion: According to our study esophageal involvement was revealed in majority of SSc and only few in RA patients. BE a frequent complication of esophagitis in scleroderma patients, which requires regular endoscopy investigation in all patients with SSc. Erosive esophagitis is often accompanied by clear clinical presentation, however some cases remain asymptomatic. PPIs are not always effective enough, which defines the necessity of administration of these drugs in higher doses or combined treatment regimen usage.

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Ultra Sensitive Troponin in Systemic Sclerosis. Christophe Meune[1], Jérôme Avouac[2], Camille Gobeaux[3], Marine Meunier[2], Andre Kahan[2] and Yannick Allanore[2]. [1]Paris Descartes University, Cardiology department, Cochin Hospital, Paris, France, [2]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [3]Paris Descartes University, Biochemistry A department, Cochin Hospital, Paris, France

Background/Purpose: Microangiopathy is a cardinal feature of SSc that has a critical role in the development of primary myocardial involvement and possibly pulmonary hypertension. Cardiac troponin (cTn) is the recommended biomarker to detect myocardial injury. The recently developed high sensitive assays of cTn (hs-cTn) allow the measurement of concentration 20-fold lower than previously. Numerous studies have reported the high prognostic significance of these new assays; moreover some studies reported that hs-cTnT may be elevated in other condition than acute myocardial infarction, including acute and chronic myocardial ischemia. Our aim was to measure hs-cTn in SSc patients and to examine associated factors with elevated hs-cTn concentrations (99^{th} percentile).

Methods: The plasma HScTnT concentrations were measured using an electrochemiluminescence immunoassay (Roche Diagnostic, Meylan, France) in consecutive stable SSc patients. The 99^{th} percentile, with a CV £10% is achieved for 14 ng/L.

Results: 90 consecutive SSc patients were included (male 19, age 59±13 years, diffuse cutaneous form 30, disease duration 10.3±8.9 years). A single patient had LEVF <55%; reduced LV/RV contractility, as assessed by Tissue-Doppler echocardiography was detected in 18 patients (36.7%). Hs-cTnT concentration ranged between 3ng/l (the limit of detection) and 53ng/l, with 17 patients (19.5%) having elevated hs-cTnT concentration above 14ng/l (99^{th} percentile). Hs-cTnT correlated with NT-proBNP ($r=0.52$, $p<0.001$). By univariate analysis, the following parameters were associated with increased hs-cTnT; age ($p= 0.046$), systolic pulmonary aterial pressure ($p=0.012$), the presence of anti-centromere antibodies ($p=0.03$), c-reactive protein ($p=0.037$), previous treatment with prednisone ($p=0.046$), and untreated hypertension ($p=0.050$). By bivariate analysis, after adjustment for age, the presence of elevated pulmonary artery pressure (sPAP>40mmHg) remained strongly associated with elevated versus normal hs-cTnT concentration ($p=0.031$).

Conclusion: Hs-cTnT, a strong prognosticator, might be elevated in SSc patient. It correlates with NT-proBNP, a marker of global myocardial involvement. The major determinants of SSc elevation were age, sPAP, ACA, and past prednisone treatment which may reflect the severity of the disease. Elevated pulmonary artery pressure remained the main associated factor with elevated versus normal hs-cTnT after adjustment for age. The capacity of hs-cTnT to predict pulmonary hypertension occurrence, as well as its prognostic significance, in the context of SSc remained to be established.

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Hypergammaglobulinemia in Systemic Sclerosis. Nicole Saddic[1], Donna Rose Swistowski[2], Victoria K. Shanmugam[3] and Virginia D. Steen[4]. [1]Georgetown University Hospital, Washington DC, DC, [2]Martinsburg Veterans Affairs Medical Center, Martinsburg, WV, [3]Georgetown University Hospital, Washington, DC, [4]Georgetown Univ Medical Center, Washington, DC

Background/Purpose: Hypergammaglobulinemia (HGGB) is associated with active disease in systemic lupus erythematosus. Sedimentation rates have been shown to be a predictor of survival in systemic sclerosis (SSc), however hypergammaglobulinemia has not been evaluated as a prognostic marker. Altered B-cell homeostasis, HGGB and increased numbers of activated B-cells in SSc suggest that B-cell dysregulation may be important in the pathogenesis of SSc. The purpose of this study was to evaluate the clinical and antibody associations of HGGB in a cohort of SSc patients.

Methods: Using an ICD-9 search of the electronic medical record (Centricity, GE) 249 consecutive SSc patients evaluated in the Georgetown Scleroderma Clinic between June 2008 and June 2009 were identified. Data were collected on demographics, serum protein electorphoresis gammaglobulin levels (GGB), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, creatinine phosphokinase (CPK), albumin and hemoglobin. Antinuclear antibodies (ANA), scleroderma specific autoantibody profiles, and clinical findings were also recorded. Gammaglobulin results were available in 90 patients. Normal gammaglobulin levels (<1.6mg/dL, mean 1.11mg/dL) were found in 51 patients (56.6%) and hypergammaglobulinemia (≥1.6mg/dL mean 2.17 mg/dL) was found in 39 patients (43.3%). Chi-square and t-tests were used to compare the normal gammaglobulin (NGGB) and HGGB groups.

Results: Consistent with our scleroderma population, patients were predominantly female (91%). Of the 90 patients with GGB results, 47.7% were Caucasian and 43.3% African American. However, 60% of the patients with HGGB were African American, compared to only 48% of patients with NGGB ($p=0.0056$). Of the 39 African American patients in the study, 62% had HGGB. Patients with HGGB had significantly higher ESR (mean 39.45 mm/hr +/−5.918 compared to 17.15 mm/hr +/−4.235, $p=0.0032$) and lower hemoglobin (mean 11.52 g/dL +/−0.3163 compared to 12.42 +/−0.2848, $p=0.0391$) than those with NGGB.

SSA antibody was strongly correlated with HGGB ($p=0.0007$) and was positive in 44% (14/32) of African American patients compared to 17% of non-African Americans (5/25). In contrast, we did not find an association between HGGB and anticentromere, Scl-70, U1RNP, SSB antibodies or nucleolar pattern on the ANA. RNA polymerase III (Pol3) antibody (which is clinically associated with absence of myositis and interstitial lung disease) was associated with the NGGB group ($p=0.0271$).

HGGB was not associated with skin score, digital ulcers, tendon rubs, acid reflux, or death, but significant association was seen between HGGB and both pulmonary arterial hypertension ($p=0.038$) and pulmonary fibrosis ($p=0.0084$).

Conclusion: HGGB in SSc is associated with African American race, SSA antibody, ESR, pulmonary hypertension and pulmonary fibrosis. Since African American scleroderma patients often have more severe lung disease and worse outcomes further investigation of gammaglobulin profile as a prognostic indicator and marker of B-cell activation in scleroderma is warranted.

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Mycophenolate Mofetil Is An Effective, Well-Tolerated, Steroid-Sparing Agent for a Diverse Spectrum of Connective Tissue Disease-Associated Interstitial Lung Disease. Aryeh Fischer, Mahalakshmi Krishnamoorthy, Amy L. Olson, Joshua J. Solomon, Evans R. Fernandez-Perez, Tristan J. Huie, Kevin K. Brown and Jeffery J. Swigris. National Jewish Health, Denver, CO

Background/Purpose: Interstitial lung disease (ILD) is a common and often devastating manifestation of connective tissue disease (CTD). Immunosuppressive medications are commonly used for the management of CTD-associated ILD (CTD-ILD). Small series have suggested that mycophenolate mofetil is well tolerated and may be effective for CTD-ILD. The purpose of this study was to describe a single provider's experience with MMF for CTD-ILD at a tertiary referral autoimmune lung center.

Methods: We performed a retrospective assessment of consecutive CTD-ILD patients treated by a rheumatologist (AF) with MMF for whom we had available pulmonary function testing (PFT) at time of MMF initiation and at 12 months from initiation. We also extracted demographic information, dosing of

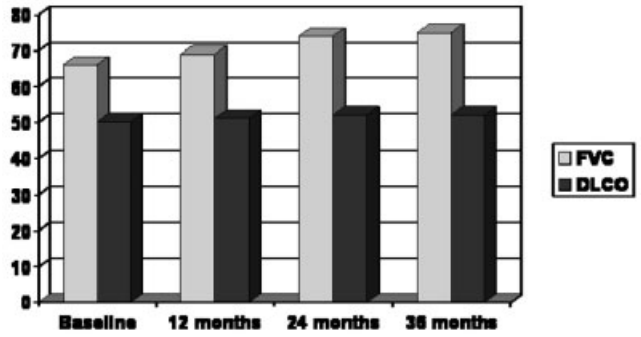
prednisone at baseline and at 12 months from MMF initiation, side effects associated with MMF, rate of discontinuation of MMF, and when available, subsequent PFT results at 24 and 36 months from MMF initiation.

Results: The cohort is comprised of 61 subjects with CTD-ILD; 25 (41%) with systemic sclerosis, 14 (23%) with anti-synthetase syndrome, 9 (15%) with "lung-dominant CTD", 6 (10%) with RA, 3 (5%) with primary Sjögren's syndrome, 2 (3%) with systemic lupus erythematosus, 1 (2%) each with mixed CTD and primary anti-phospholipid syndrome. The duration of MMF therapy was on average 3.5 years (median 4 years [range 1–10 years]), with a dose of 3000 mg/day in 38 (62%), 2000 mg/day in 21 (34%) and 1 each at 2500 mg/day and 1000 mg/day.

Clinical Features of CTD-ILD patients treated with MMF

Age	**55 (21–81)**
Female gender	39 (64%)
Ethnicity	54 (89%) White, 6 (10%) Hispanic, 1 (2%) Black
Past smokers	25 (41%)
Current smokers	0
MMF discontinuation	7 (11%), symptoms of intolerability (3), leukopenia (1) abnormal liver tests (1), lymphoma (1) ILD progression (1)
Prednisone dose @ MMF start	39 patients on prednisone; mean 14 mg / d (+/−16)
Prednisone dose @ 12 months	34 patients on prednisone; mean 4 mg / d (+/−5)
FVC% @ MMF start (n=61)	66 (+/−17)
FVC% @ 12 months (n=61)	69 (+/−16)
FVC% @ 24 months (n=42)	74 (+/−17)
FVC% @ 36 months (n=29)	75 (+/−16)
DLco% @ MMF start (n=61)	50 (+/−17)
DLco% @ 12 months (n=61)	51 (+/−17)
DLco% @ 24 months (n=42)	52 (+/−17)
DLco% @ 36 months (n=29)	52 (+/−16)
Survival @ 36 months	100%

Serial pulmonary function testing in CTD-ILD patients treated with MMF



Conclusion: Among a diverse spectrum of patients with CTD-ILD, MMF treatment appears to be well-tolerated, is associated with few side effects, and has a low rate of discontinuation. Furthermore, MMF treatment for CTD-ILD appears to serve as an effective steroid-sparing agent, and is associated with preservation of lung function. Prospective studies of MMF – such as with the Scleroderma Lung Study II – are indicated to further evaluate the efficacy of MMF in CTD-ILD.

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Scleroderma Digital Ulcers Complicated by Infection with Fecal Pathogens. Dilia Giuggioli[1], Andreina Manfredi[1], Michele Colaci[1], Federica Lumetti[2], Marco Sebastiani[1] and Clodoveo Ferri[3]. [1]University of Modena and Reggio Emilia, Modena, Italy, [2]Universitu of Modena and Reggio Emilia, [3]Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy

Background/Purpose: Digital ulcers represent one of the most frequent complications in the course of systemic sclerosis (SSc); these lesions are very painful, scarcely responsive to treatment, and usually responsible for marked limitations on daily activities. Moreover, infectious complications may severely compromise the outcome of skin lesions in a significant percentage of patients. Therefore, the presence of pain and bandages, frequently used to promote the efficacy of contact medications, may limit the personal hygiene with an increased risk of local infection and difficult ulcer healing. A number of pathogens of different origin may be involved, including bacteria from patients' endogenous flora. We evaluated the possible involvement of faecal pathogens in SSc digital ulcers.

Methods: Among a series of 82 SSc patients with digital ulcers, we retrospectively analyzed 42 subjects with clinical signs of local bacterial infection. All digital ulcers with typical signs of infection (increase of yellow or green exudates, pain, perilesional erythema and swelling, bad odour) have been investigated by swabs.

Results: The table summarizes the main clinico-serological and microbiological features of the 42 SSc patients with digital ulcer infection. Bacterial infection was confirmed in all 42 patients investigated; in particular, Staphylococcus aureus was the most frequently found (50%). Interestingly, 11/42 (26%) patients showed digital ulcers infected by intestinal bacteria; namely, 7 subjects resulted positive for Escherichia coli and 4 for Enterococcus faecalis. A significantly higher percentage of diffuse cutaneous SSc was recorded in the subgroup of 11 patients with digital ulcers infected by faecal pathogens compared to the remaining 31 infected by other bacteria (6/11 vs. 5/31, respectively; Fisher's p=0.011).

Clinico-serological and microbiological data of 42 SSc patients with infected digital ulcers

Male/Female	5/37
Mean age±SD (yrs)	56.3±15.8
Mean disease duration±SD (yrs)	11.1±7.9
L/D	31/11
Scl70/ACA/others	19/15/8
Infections	
E. coli; E. faecalis	11/42 (26%)
P. aeruginosa;	5/42 (12%)
S. aureus	21/42 (50%)
*Others**	5/42 (12%)

L: limited, D: diffuse cutaneous subset;

Scl70: autoantibodies anti-Scl70; ACA: anti-centromere;

* Proteus mirabilis, Streptococcus agalactiae, Citrobacter koseri, Stenotrophomonas maltophilia

Conclusion: A number of effective measures, involving health care personnel and hospital environment, are essential in the management of digital ulcers and prevention of infectious complications. The prevalence of faecal pathogens in a quarter of cases has never been reported previously; it suggests an important role of patient's self-care limitations, generally more frequent in patients with diffuse cutaneous SSc, mainly during intercurrent home medications. Consequently, methodical patients' education on hand hygiene is mandatory to avoid such deleterious complications.

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Lung and Breast Cancer in Systemic Sclerosis: Correlations with the Disease's Features. Michele Colaci, Dilia Giuggioli, Marco Sebastiani, Andreina Manfredi, Caterina Vacchi and Clodoveo Ferri. University of Modena and Reggio Emilia, Modena, Italy

Background/Purpose: Systemic sclerosis (SSc) shows an increased incidence of lung and cancer compared to general population. Chronic interstitial inflammation might have a causative role for lung cancer; while, it is very difficult to explain the breast cancer since mammalian glands are not involved in disease's processes. We aimed to investigate the possible correlations between SSc features and the development of lung or breast cancer in SSc.

Methods: We retrospectively evaluated 312 consecutive SSc patients (30/282 M/F, mean age 60.6 ± 13.7 SD years, mean disease duration 10.1 ± 6.8 SD years). Besides clinical features, individual cumulative radiation dosage (measured in mSv equivalents) for radiological examinations since SSc diagnosis was calculated.

Results: We found 14 cases of lung cancer (4.5%) and 12 cases of breast cancer (3.8%), which appeared 14.3 ± 6.7 SD years and a median period of 5 years (range 1–22) after the diseases onset, respectively. Statistical analysis evidenced significant correlations between pulmonary neoplasia and male sex (p=0.035), disease duration (p=0.019), presence of anti-Scl70 (p=0.001) and

absence of anticentromere ($p<0.0001$) antibodies, lung fibrosis ($p=0.011$), forced vital capacity (FVC) reduction ($p<0.0001$), and cyclophosphamide therapy ($p=0.005$). Logistic regression identified only FVC as significant independent factor (OR 1.08, 95% confidence interval 1.03–1.13; $p=0.02$) for lung cancer. On the contrary, breast cancer did not correlate with any SSc clinical parameters. Finally, cumulative radiation dosage did not affect the appearance of both lung and breast cancer. Interestingly, this latter was inversely related to radiation cumulative dosage ($p=0.022$).

Conclusion: The present findings suggest that a SSc patients' subset with more severe disease might have an increased risk to develop lung cancer. This malignancy mainly affects male patients, as well as subjects with longer disease duration and higher prevalence of lung fibrosis, presence of anti-Scl70 and absence of anticentromere autoantibodies. The correlation with previous cyclophosphamide therapy could be an indirect sign of severe lung involvement. Breast cancer did not show any significant correlations with SSc features; it involved women with significantly lower x-ray exposure, due to the medially shorter time interval between SSc diagnosis and the breast cancer onset, compared to SSc patients without this malignancy.

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Incomplete Thymic Involution in Systemic Sclerosis and Rheumatoid Arthritis. Marine Meunier[1], Ramin Bazeli[2], Jerome Avouac[1], Antoine Feydy[2], jean-Luc Drape[2], Andre Kahan[1] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [2]Paris Descartes University, Radiology B department, Cochin Hospital, Paris, France

Background/Purpose: The thymus is a central lymphatic organ responsible for many immunological functions, including the production of mature functional T cells and the induction of self-tolerance. Several reports have suggested a potential association between thymus alterations and some immune-mediated rheumatic diseases, with radiological thymic alterations, such as incomplete thymic involution, thymic hyperplasia or thymoma., However, data regarding thymus alterations and systemic sclerosis (SSc) or rheumatoid arthritis (RA) are sparse. The aim of this study was to evaluate by chest CT scans the frequency and characteristics of incomplete thymic involution, in patients with SSc and RA, together with a non-autoimmune group of controls.

Methods: We performed a retrospective observational study between 2006 and 2009 including 161 patients who were at least 40 years old. These patients comprised 96 SSc patients (median age 59 years, 80% women) and 65 RA patients (median age 57 years, 88% women). All patients had a systematic chest CT-scan performed during the usual follow-up of their disease. SSc and RA patients were compared with 32 healthy controls (median age 63 years, 62% women) free of autoimmune disease. For the purpose of our study, *complete involution* of the thymus was defined as the absence of a residual thymus or a gland thickness, corresponding to the short axis on the axial slice, of less than 7 mm. We defined *incomplete involution* of the thymus as a residual thymic tissue more than 7 mm thick.

Results: The frequency of incomplete thymus involution was significantly higher in SSc and RA patients (respectively 15% and 14%) than in the control group (0%; $p<0.05$). SSc patients with incomplete thymic involution were younger than SSc patients with complete thymic involution (47 (39–80) years vs. 59 (39–87) years; $p=0.002$) and more likely to have pulmonary fibrosis with restrictive syndrome (24% vs. 0%, $p=0.03$). There was no correlation between incomplete thymic involution and other SSc-related disease characteristics, especially specific autoantibodies. In RA patients, incomplete thymic involution was more frequently associated with treatment with biologics (100% vs. 62%; $p=0.02$) and an absence of antinuclear antibodies (0% vs. 32%, $p=0.05$).

Conclusion: The prevalence of incomplete thymic involution to be higher in SSc and RA patients than in the control group. Our results suggest that incomplete thymic involution is linked to disease severity. Further larger studies are required to confirm this association and clarify the pathological significance of incomplete thymic involution in autoimmune diseases.

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Shock Wave Therapy: A Novel Treatment for Systemic Sclerosis? Laura Belloli[1], Nicola Ughi[1], Maria-Cristina D'Agostino[1], Alberto Tedeschi[2], Marco Massarotti[1], Massimo Cugno[2] and Bianca Marasini[1]. [1]IRCCS Humanitas Clinical Institute, Rozzano (Milan), Italy, [2]Fondazione IRCCS Ca' Granda, University of Milan, Milan, Italy

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular involvement and widespread fibrosis, resulting in significant morbidity and mortality. No single effective treatment exists, and the current therapeutic options target only few aspects of the pathogenetic mechanisms. Since microangiopathy is the key feature of the disease, and extracorporeal shock wave treatment (ESWT) has been suggested to exert a vascular protective action and to enhance nitric oxide availability within the endothelium, we evaluated whether ESWT could reduce SSc endothelial damage and ameliorate skin involvement.

Methods: Eight SSc consecutive females fulfilling SSc validated criteria, aged 66 ± 12 yrs, were included in the study, after informed consent. Four consecutive ESW sessions (Dermagold–MTS Germany defocused lithotripter device, 10,000 shots/session applied at the energy level of 0.06 mJ/mmq) were weekly applied to both hands, including digits, and to one forearm, equally divided on volar and dorsal surfaces. The controlateral forearm served as control. Circulating vascular endothelial growth factor (VEGF), von Willebrand factor (vWf) and tissue plasminogen activator (tPA) were measured before treatment, immediately after the first session and at the end of the cycle. Skin involvement, assessed by Rodnan Skin Score (RSS) and durometer (digits and forearm) and nailfold capillaroscopy were performed at baseline and after the ESWT cycle.

Results: VEGF and vWf significantly decreased after the first session (500.8 ± 227.2 vs 411.0 ± 201.6 pg/ml, $p=0.007$ and 172.3 ± 64.8 vs 152.0 ± 67.6 % of normal, $p=0.004$, respectively), and remained stable at the end of treatment (417.0 ± 129.3 pg/ml and 167.1 ± 70.8 %,VEGF and vWf, respectively, p=ns). tPA did not change (data not shown). At the end of treatment, while total RSS did not change, RSS at fingers appeared significantly reduced (4.9 ± 1.2 vs 3.9 ± 1.7, $p=0.018$). Durometer measurement showed a significant decreased both at forearm (26.9 ± 5.4 vs 23.4 ± 4.3 U.I., $p=0.021$) and at finger-pad: (52.0 ± 9.8 vs 48.8 ± 10.4 U.I., $p<0.0001$). Among capillaroscopic parameters, only haemorrages (score:0–3) were significantly reduced at the end of treatment (-35 ± 15.6%, [mean±SE], $p=0.038$).A significant relationship was observed at baseline between vWf levels and finger RSS ($p=0.016$, $R=0.804$).

Conclusion: Our preliminary data suggest a possible role of ESWT in the therapeutic armamentarium of SSc. However, more studies on a larger series of patients are needed and timing and site of ESWT should better defined.

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Clinical Associations of Elevated Acute Phase Response, Proteinuria and Low Dlco in Early Scleroderma Patients: A Report From the EULAR Scleroderma Trials and ReSearch Group (EUSTAR) Database. Patricia E. Carreira[1], Loreto Carmona[2], Beatriz E. Joven[3], Christopher D. Denton[4], Yannick Allanore[5], Ulrich A. Walker[6], Marco Matucci-Cerinic[7], Ulf Muller-Ladner[8] and EUSTAR coauthors[9]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Fundación Española de Reumatología, Madrid, Spain, [3]HOSPITAL UNIVERSITARIO 12 DE OCTUBRE, MADRID, Spain, [4]Royal Free Hospital, Medical School, London, England, [5]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [6]Dept. of Rheumatology at Basel University, Felix-Platter Spital, Basel, Switzerland, [7]University of Florence, Florence, Italy, [8]Justus-Liebig Universität Gieβen, Kerckhoff-Klinik GmbH, Bad Nauheim, Germany, [9]Florence

Background/Purpose: Elevated ESR, low DLCO and proteinuria are known risk factors for early mortality in systemic sclerosis (SSc). Although these factors are routinely collected by SSc experts, this is not the case in other settings, as general rheumatology clinics. The EUSTAR database allow us to analyze the clinical associations of these mortality risk factors in a large number of early SSc patients, which might help to improve scleroderma care in daily practice. The objective of this study is to identify the clinical associations of elevated ESR, proteinuria and low DLCO in a large group of recently diagnosed SSc patients

Methods: EUSTAR collects prospectively the Minimal Essential Data Set (MEDS), on all sequential SSc patients in participating centres. Patients with disease duration <3 years at the first EUSTAR entry were selected, and baseline data from the first visit were analyzed. Since ESR was not collected in MEDS, we used elevated acute response (ESR > 20 mmHg and/or CRP over normal) as a surrogate. Binary logistic regression, Chi square ant t test were used to analyze differences between groups with or without elevated acute response, proteinuria and low DLCO. Generalized lineal model was used to identify symptoms present in patients with none, one, two or three of these prognostic factors

Results: From 1180 patients (19% men), 482 had diffuse and 590 had limited disease. Mean age was 53 ± 14 years. Mean disease duration was 18 ± 6 months and time between Raynaud onset and first non Raynaud symptom was 3 ± 7 months. By multivariate logistic regression, elevated acute response was associated with older age (OR 1.02; 95%CI 1.009–1.04;

p=0.001), arthritis (OR 2.4; 95%CI 1.6–3.7; p<0.0001), male gender (OR 1.9; 95%CI 1.3–2.8; p=0.003), higher mRSS (OR 1.04; 95%CI 1.02–1.06; p<0.0001), Scl70 (OR 1.6; 95%CI 1.1–2.3; p=0.02), muscular atrophy (OR 1.9; 95%CI 1.1–3.3; p=0.02) and low FVC (OR 1.8; 95%CI 1.3–2.7; p=0.002). Proteinuria was associated with renal crisis (OR 8.1; 95%CI 2.7–24.5; p<0.0001), high blood pressure (OR 2.5; 95%CI 1.2–5.1; p=0.02), intestinal involvement (OR 2.3; 95%CI 1.1–4.8; p=0.02) and pulmonary hypertension (OR 2.5; 95%CI 1.2–5.1; p=0.02). Low DLCO was associated with lung fibrosis (OR 3.7; 95%CI 2.3–5.9; p<0.0001), low FVC (OR 4.5; 95%CI 2.6–7.5; p<0.0001) and pulmonary hypertension (OR 1.7; 95%CI 1–3.2; p=0.05). Generalized lineal model showed that the presence of lung fibrosis (p<0.0001), low FVC (p<0.0001), renal crisis (p<0.004), CK elevation (p=0.04), pulmonary hypertension (p=0.04) and arthritis (p=0.05) were more frequent in patients with increased number of poor prognostic factors

Conclusion: In early SSc patients, elevated acute phase response is associated with severe skin and visceral involvement, proteinuria with renal crisis, and low DLCO with lung disease and pulmonary hypertension. Patients with increased number of these 3 poor prognostic factors present with diffuse disease, renal crisis and lung, articular and muscular involvement. Our results support the importance of a careful evaluation, including acute phase response, DLCO and urine protein, in every SSc patient.

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Correlation Between Exercise Echocardiography and Right Heart Catheterization in Scleroderma Patients At Risk for Pulmonary Hypertension. Ami A. Shah[1], Susan Mayer[1], Reda Girgis[1], James Mudd[2], Laura K. Hummers[1] and Fredrick M. Wigley[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Oregon Health & Science University, Portland, OR

Background/Purpose: Pulmonary hypertension (PH) is a major cause of morbidity and mortality in systemic sclerosis (SSc), and early detection may improve prognosis. Recent studies have utilized exercise provocation during echocardiography as a screening tool to identify patients at high risk for PH, and an increase in estimated right ventricular systolic pressure (RVSP) of 15–20mmHg with exercise has been utilized as a cutoff for a positive test. Among SSc patients who are suspected of PH by clinical or laboratory parameters, we sought to determine whether exercise induced changes in RVSP measured by echocardiography could identify patients with right heart catheterization (RHC) evidence of PH.

Methods: Scleroderma patients with RVSP ≥ 40mmHg and any dyspnea, RVSP ≥45 mmHg regardless of symptoms, isolated decline in diffusing capacity (DLCO) ≥10%, or new onset unexplained dyspnea (Hct>28 and no active ILD, COPD, or LVEF<50%) who underwent supine ergonometric exercise echocardiography (echo) and RHC as part of their routine clinical care were studied. Our outcome of interest was the presence of any PH as defined by a mean pulmonary artery (PA) pressure ≥ 25mmHg at rest or ≥ 30mmHg with peak exercise on right heart catheterization. Three exercise echo cutoffs were compared between patients with and without PH using the Fisher's exact test: 1) increase in RVSP ≥ 15mmHg with exercise, 2) increase in RVSP ≥ 20mmHg with exercise, and 3) peak RVSP ≥ 50mmHg regardless of baseline RVSP.

Results: Twelve SSc subjects met inclusion criteria in this pilot study. The median age was 61 years (range 41.6–77.2 years), 91.7% were female, and 58.3% had limited SSc. At baseline, the median RVSP, forced vital capacity, DLCO and NTproBNP were 40 mmHg (range 27–52 mmHg), 79.7% predicted (range 49.7–99.4%), 59.6% predicted (range 46.3–106.7%), and 207.5 pg/mL (range 20–981 pg/mL), respectively. Eight of 12 subjects (66.7%) met our RHC criteria for any PH. Five of 12 subjects had an increase in RVSP ≥ 15mmHg with exercise, 4 of 12 had an increase in RVSP ≥ 20mmHg with exercise, and 7 of 12 had a peak RVSP ≥ 50mmHg. Only a cutoff peak RVSP ≥ 50mmHg was statistically significantly associated with the presence of any PH on RHC (p=0.01). Neither threshold of increasing RVSP with exercise was statistically associated with the presence of any PH on RHC in this small sample (p=0.08 for 15mmHg cutoff, p=0.21 for 20mmHg cutoff).

Conclusion: Exercise echocardiography may be a useful noninvasive screening tool for the presence of any PH in high-risk SSc patients. These preliminary data suggest a peak RVSP of 50mmHg with exercise may be an important threshold that identifies a patient who needs an invasive hemodynamic assessment by RHC. These preliminary data need to be validated in a large prospective sample of SSc patients to examine the utility of exercise echo as a screening tool for PH and to understand the clinical relevance of abnormal exercise hemodynamics.

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Positive Predictive Value of Anti-Centromere and Anti-Scl-70 Antibody Multiplex Assays in a Rheumatology Practice Setting. Svetlana Meier[1] and Ted R. Mikuls[2]. [1]Univ of Nebraska Med Center, Omaha, NE, [2]Omaha VA and University of Nebraska, Omaha, NE

Background/Purpose: Recent concerns have been raised regarding the sensitivity of multiplex ANA testing compared to 'gold-standard' methods involving Hep2A substrate by immunoflourence (IF). There has been less attention given to the predictive values of antibodies targeting specific nuclear antigens incorporated in the multiplex approach, specifically with regards to anti-centromere and anti-SCL-70 positivity that have had high specificity with conventional assays in the past. The aim of this study was to determine the positive predictive value (PPV) of anti-centromere and anti-SCL-70 antibody multiplex assays in a rheumatology practice setting and to characterize patients with false-positive results using this approach.

Methods: As part of a retrospective medical record review, we identified patients seen in an academic rheumatology practice between January 2008 and January 2010 and with positive test results for either anti-centromere or anti-Scl-70 antibody. As a gold-standard, we categorized patients based on the receipt of a formal connective tissue disease (CTD) diagnosis from a board certified rheumatologist or satisfaction of distinct ACR CTD classification criteria available (with a focus on classification criteria for systemic sclerosis – both limited and diffuse forms). Alternative CTD diagnoses, other health conditions and comorbid illnesses were documented.

Results: There were 73 patients seen over the two-year study period with positive tests for either anti-centromere (n = 47) or anti-SCL-70 (n = 23) (See Table). All patients were examined by a board certified academic rheumatologist. Of the 47 patients who had a positive anti-Scl-70 antibody and were evaluated by a rheumatologist, 2 patients had a diagnosis of diffuse systemic sclerosis and 1 patient had a diagnosis of CREST syndrome, yielding a PPV of only 6.4%. Among patients not meeting criteria for scleroderma and who were anti-SCL-70 positive, 4 were diagnosed with liver cirrhosis or autoimmune hepatitis, 5 had a positive Raynaud's phenomenon without any other CTD manifestations, 6 had SLE complicated by glomerulonephritis, and 2 were diagnosed with RA. Of the 26 patients who were positive for anti-centromere antibodies, 8 patients had a diagnosis of CREST syndrome, yielding a PPV of 30.7%. Additionally, 7 had liver disease, 2 had Raynaud's phenomenon in the absence of other CTD manifestations, 1 had an SLE, and 1 RA.

Test	Diffuse scleroderma	Limited scleroderma (CREST)	Liver disease	Raynaud's phenomenon	SLE	RA
Anti-Scl-70 (+), n = 47	2	1	4	5	6	2
Anti-centromere (+), n = 26	0	8	7	2	1	1

Conclusion: In contrast to prior reports examining the diagnostic characteristics of anti-centromere and anti-SCL-70 using conventional laboratory methods, false positive results are frequently observed using the newer solid-phase multiplex approach. Chronic liver disease, primary Raynaud's phenomenon, SLE, and RA emerged as frequent underlying conditions among rheumatology patients with false-positive results.

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Severe Interstitial Lung Disease within the PHAROS Registry: Baseline Characteristics and Clinical Features. Aryeh Fischer[1], Jerry A. Molitor[2], Laura K. Hummers[3], Vivien M. Hsu[4], Monique E. Hinchcliff[5] and Virginia D. Steen[6]. [1]National Jewish Health, Denver, CO, [2]Univ of MN MMC108, Minneapolis, MN, [3]Johns Hopkins University, Baltimore, MD, [4]RWJ Med Schl Scleroderma Prog, New Brunswick, NJ, [5]Northwestern University, Chicago, IL, [6]Georgetown Univ Medical Center, Washington, DC

Background/Purpose: Pulmonary hypertension (PH) and interstitial lung disease (ILD) are the leading causes of mortality in scleroderma. A significant number of scleroderma patients have both PH and ILD and this combination is associated with a particularly poor prognosis. The multicenter **PHAROS** (**P**ulmonary **H**ypertension **A**ssessment and **R**ecognition of **O**utcomes in **S**cleroderma) registry is comprised of 434 subjects from 21 centers in the USA and Canada and prospectively follows scleroderma subjects at high-risk for, or with incident PH. In this study we sought to determine the prevalence and characteristics of subjects in PHAROS with severe ILD at study entry.

Methods: Pre-PH scleroderma subjects are enrolled if they have a FVC%/DLco% > 1.6, or echo-estimated RVSP > 40 mmHg. Subjects with right-heart

catheterization confirmed incident PH within the previous 6 months are classified into pulmonary arterial hypertension (PAH), pulmonary venous hypertension (PVH) or PH-associated with ILD (PH-ILD). Baseline and biannual demographic, clinical, and laboratory data as well as patient-reported health questionnaires are collected. In this study, we characterize and analyze only those subjects with severe ILD demonstrated by a severe restrictive defect on pulmonary function testing as defined by a FVC% < 60 at enrollment.

Results: Sixty-three (15%) subjects from 17 centers had a FVC% of < 60 at study entry. Gender and scleroderma subtype were more evenly distributed than expected for PAH. Most were Caucasian, the median age was 52 and disease duration from time of diagnosis was 5.8 years. Autoantibodies were recorded in 58 subjects. Positive anti-centromere was noted in 3 (5%), isolated-nucleolar ANA in 13 (22%), anti-Scl-70 in 15 (26%), and other antibody positivity in 17 (29%). Mild dyspnea (NYHA FC II) was noted in 32% and moderate dyspnea (NYHA FC III) in 49%. Median DLco was 28% and most (56%) had a FVC%/DLco > 1.6. Forty-nine (78%) had undergone RHC within 6 months of study entry and 41 (84%) of these had PH (median mPAP 29[17–60]). Among those with PH, 63% had PH-ILD and 27% had PVH.

Baseline characteristics of PHAROS subjects with FVC < 60% at study entry

Age	52.5 (26–81)
Female gender	49 (78%)
Ethnicity	40 W (63%), 15 B (24%), 7 H (11%)
SSc type	27 L (43%), 28 D (44%)
Rodnan skin score	8 (0–43)
UCSD Dyspnea Score	2.04 (0–4.33)
NYHA FC	8-I (13%), 20-II (32%), 31-III (49%), 3-IV (5%)
TLC (range)	55 (32–102)
FVC (range)	50 (27–59)
DLco (range)	28 (10–53)
FVC%/DLco%	1.73 (0.46–5.31)
FVC%/DLco% > 1.6	35 (56%)
Echo RVSP (range)	46 (17–100)
Pericardial Effusion	19 (30%)
Underwent RHC	49 (78%)
mPAP (range)	29 (17–60)
RHC mPAP > 25 mmHg	41 of 49 (84%)
mPCWP (range)	11 (2–35)
RHC mPCWP < 15	37 of 49 (59%)
PH type	31 PH-ILD (63%), 13 PVH (27%)

Conclusion: A sizeable cohort (15%) of PHAROS subjects has severe ILD at study entry. These subjects frequently have a positive anti-Scl-70 or isolated-nucleolar ANA, and are rarely anti-centromere positive. They have a severely reduced DLco, most have a FVC%/DLco% ratio > 1.6 and have PH at study entry. Prospective assessment of this subset within PHAROS will provide valuable information about the natural history of combined PH and ILD in scleroderma.

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Clinical Significance of Antibodies to Ro52/TRIM21 in Systemic Sclerosis. Marie Hudson[1], Janet Pope[2], Solene Tatibouet[1], Russell Steele[1], Murray Baron[3] and Marvin J. Fritzler[4]. [1]McGill University, Montreal, QC, [2]Univ of Western Ontario, London, ON, [3]Jewish General Hospital, Montreal, QC, [4]University of Calgary, Calgary, AB

Background/Purpose: Ro52/TRIM21 antibodies have been identified in 20% of the Canadian Scleroderma Research Group cohort, making it the second most common autoantibody in this group of systemic sclerosis (SSc) patients. Given its high prevalence and the controversy in the literature surrounding its role in autoimmune diseases, we undertook this study to determine whether Ro52/TRIM21 antibodies in SSc are associated with distinct clinical manifestations in SSc.

Methods: Sera from 963 patients with SSc enrolled in a multi-centre cohort study were collected. Antibodies to Ro52/TRIM21 were assayed in a central laboratory by an addressable laser bead immunoassay using a commercially available kit (QUANTAPlex ENA 8, INOVA Diagnostics Inc., San Diego, CA). Associations between Ro52/TRIM21 and clinical and other serological manifestations of SSc were investigated using standard statistical methods.

Results: Mean age of the cohort was 55 (+ 12) years, 87% were female, 85% were White, mean disease duration (since the onset of the first non-Raynaud's disease manifestation) was 11 (+ 9) years, and 59% had limited, 37% had diffuse and 3% had no skin involvement. Ro52/TRIM21 antibodies were present in 194 (20.2%) patients, thus representing the second most common autoantibody in this cohort with anti-centromere, RNA polymerase III and topoisomerase I antibodies present in approximately 35%, 19% and 16% of the patients, respectively. Ro52/TRIM21 overlapped with many other autoantibodies, although the association differed according to antibody. Indeed, whereas 16% of the overall cohort had topoisomerase I antibodies, only 10% of Ro52/TRIM21 positive patients had topoisomerase I antibodies ($p = 0.0129$) and the titres of Ro52/TRIM21 were among the lowest measured (763.28 U/ml) in this subset of patients. On the other hand, whereas 6% of the overall cohort had Ro60 antibodies, 21% of Ro52/TRIM21 positive patients were Ro60 positive ($p < 0.0001$) and the titres of Ro52/TRIM21 were among the highest measured (5530.66 U/ml). Similar strong relationships between Ro52/TRIM21 and Ro60 were noted between Ro52/TRIM21 and U1 RNP ($p = 0.0066$, 2099.45 U/ml), SS-B/La ($p < 0.0001$, 6003.88 U/ml) and Jo-1 ($p = 0.0171$, 4412.83 U/ml), and to a lesser degree between Ro52/TRIM21 and CENP-B ($p = 0.0372$, 1098.86 U/ml) and Sm ($p = 0.0361$, 1482.09 U/ml). In univariate analyses, Ro52/TRIM21 antibodie were associated with interstitial lung disease and polyautoimmunity. In multivariate logistic regression analyses, there was a strong trend towards an association between Ro52/TRIM21 and interstitial lung disease (odds ratio (OR) 1.50; 95% confidence interval (CI): 0.99–2.27; $p = 0.0550$) and to a lesser extent between Ro52/TRIM21 and polyautoimmunity (OR 1.49; 95% CI: 0.89–2.50; $p = 0.1287$).

Conclusion: Ro52/TRIM21 autoantibodies were the second most common autoantibody in this large SSc cohort. In SSc, Ro52/TRIM21 antibodies may be a marker of interstitial lung disease and polyautoimmunity.

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Elevated Pulmonary Vascular Resistance At Rest Is Associated with Exercise Pulmonary Arterial Hypertension in Systemic Sclerosis Patients without Pulmonary Hypertension Hemodynamics At Rest. Jonathan Kushi[1], Mary Ellen Csuka[1], Laura K. Hummers[2], Fredrick M. Wigley[2], Vivien M. Hsu[3], Dinesh Khanna[4], Jerry A. Molitor[5] and Virginia D. Steen[6]. [1]Medical College of Wisconsin, Milwaukee, WI, [2]Johns Hopkins University, Baltimore, MD, [3]RWJ Med Schl Scleroderma Prog, New Brunswick, NJ, [4]University of Michigan, Ann Arbor, MI, [5]Univ of MN MMC108, Minneapolis, MN, [6]Georgetown Univ Medical Center, Washington, DC

Background/Purpose: Pulmonary arterial hypertension occurs in 1 of 7 patients with systemic sclerosis (SSc), but is the leading cause of death. Patients who do not have pulmonary hypertension (PH) at rest have been shown to have elevated mean pulmonary arterial pressure (mPAP) with exercise. This population represents a group that may be at increased risk for PH, which could have implications on prognosis and treatment. This study analyzes the resting and exercise right heart catheterization (RHC) data in the PHAROS (Pulmonary Hypertension Assessment and Recognition of Scleroderma) registry.

Methods: PHAROS is a multicenter cohort of SSc patients designed to determine the outcomes of high risk SSc patients for the development of PH. Of 390 patients within the registry, 87 patients had RHC at rest and with exercise following local protocols. Analysis of the data was performed with focus on the parameters of mPAP, pulmonary capillary wedge pressure (PCWP), and pulmonary vascular resistance (PVR). The following definitions of pulmonary hypertension were used: pulmonary arterial hypertension (PAH) = mPAP ≥ 25mmHg, PCWP ≤ 15mmHg; pulmonary venous hypertension (PVH) = mPAP ≥ 25mmHg, PCWP > 15mmHg; exercise pulmonary arterial hypertension (ePAH) = mPAP with exercise > 30mmHg, PCWP ≤ 18mmHg; exercise pulmonary venous hypertension (ePVH) = mPAP with exercise > 30mmHg, PCWP > 18mmHg.

Results: There were 87 patients within the PHAROS registry that had an exercise RHC. Of these, 52 patients (60%) had no change between resting and exercise RHC, including patients that remained normal with exercise or had pulmonary hypertension with rest and exercise. Thirty-five patients (40%) had discrepant hemodynamic changes with exercise. Within this group of 35, 21 patients (60%) had normal resting RHC with ePAH, 8 patients (23%) had normal resting RHC with ePVH, and 6 patients (17%) had PAH with ePVH. In total, PAH was diagnosed in 22 patients (25%) and ePAH in an additional 21 (24%). Among patients with a normal resting RHC, a PVR >140 dyn·s/cm^5 was associated with ePAH, (positive predictive value 76%, negative predictive value 62%). A PCWP >10mmHg was associated with ePVH, (positive predictive value 62%, negative predictive value 100%).

Conclusion: In patients with SSc, an exercise RHC can reveal underlying pulmonary hypertension despite normal resting hemodynamics. Patients with normal mPAP at rest, but elevated PVR >140 dyn · s/cm^{5}or PCWP >10 mmHg may be at increased risk of ePAH or ePVH respectively. In these patients, pursing an exercise RHC may lead to earlier diagnosis and treatment.

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A Panel of Serum Biomarkers Including Type I Interferon- Related Chemokines Distinguishes Clinical and Autoantibody Status of Patients with Systemic Sclerosis. Emily Baechler Gillespie[1], Jane Hoyt Buckner[2], Joseph C. Wilson[3] and Jerry A. Molitor[3]. [1]University of Minnesota, Minneapolis, MN, [2]Benaroya Research Institute, Seattle, WA, [3]Univ of MN MMC108, Minneapolis, MN

Background/Purpose: Systemic Sclerosis (SSc) is a clinically heterogeneous disorder with inflammatory, fibrotic, and vascular manifestations and a highly variable prognosis and response to therapies. Biomarkers that segregate with disease manifestations and which may predict prognosis or response to therapy are needed. SSc shares a type I interferon (IFN) mRNA signature with Systemic Lupus (SLE). We have previously developed a panel of chemokines which correlate with the IFN signature in SLE, and which predicts SLE disease course. We now report the initial testing of this chemokine panel, and additional potentially relevant biomarkers in SSc patients.

Methods: Serum samples from 57 SSc patients, 5 healthy controls, and 6 autoimmune controls were obtained from the Scleroderma biorepository at the Benaroya Research Institute. Autoantibody status and presence/absence of interstitial lung disease(ILD) was determined by initial chart review at time of sample acquisition. Four IFN-regulated chemokines(IP-10, I-TAC, MCP-1, and MIP-3β) were measured by Searchlight multiplexed immunoassays, and 14 additional cytokines, chemokines, and growth factors were measured by multiplexed bead-based immunoassays (Luminex). Samples were run in duplicate and recombinant proteins were used to generate standard curves. Due to non-normal distribution of analyte values, nonparametric Mann-Whitney tests were used for group comparisons with $p<0.05$ considered significant. Significant variables from the univariate analysis were tested in a stepwise multiple logistic regression model.

Results: In our initial study, IP-10 and MIP-3β were significantly elevated in SSc patients compared to healthy controls. These two chemokines and I-TAC were also significantly elevated in SSc compared to autoimmune controls. A chemokine score (calculated from summed levels of the four chemokines) was significantly higher in SSc compared to both control groups. MCP-1 levels were significantly higher in both anti-topoisomerase (topo) + patients (n=25) and topo-, CENP- patients (n=16) as compared to anti-centromere (CENP) + patients (n=15). Among 14 additional proteins, IL-1ra, VEGF, and Eotaxin were significantly increased in SSc vs. autoimmune controls, but none were found at altered levels in SSc patients compared to healthy controls. IL-1ra, VEGF, and IL-12p70 were elevated in SSc patients with ILD (n=34) compared to patients without ILD (n=18).IL-1ra and VEGF were also lower in CENP+ patients as compared to both Topo+ patients and Topo-, CENP- patients. In multivariate analysis of SSc vs. healthy controls, only IP-10 was retained in the model ($p=0.0047$); the model for SSc vs. autoimmune controls included both IP-10 and IL-1ra ($p=0.0006$). MCP-1 was the only significant variable retained in the model of ILD ($p=0.0004$).

Conclusion: Serum levels of IFN-regulated chemokines and other cytokines associate with specific autoantibodies and with important clinical manifestations of SSc. Further studies are needed to determine whether these putative biomarkers will predict disease course or response to therapy.

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Myocardial Involvement in Systemic Sclerosis As Assessed by Ultrasonography and Scintigraphic Perfusion Imaging. Niki Tsifetaki[1], Charalampos Papagoras[2], Kersten Achenbach[3], Athanasia Georgiou[4], Spyridon Tsiouris[5], Andreas Fotopoulos[6] and Alexandros A. Drosos[7]. [1]Registrar in Rheumatology, Ioannina, Greece, [2]Fellow in Rheumatology, Ioannina, Greece, [3]Cardiologist, Ioannina, Greece, [4]Fellow in Nuclear Medicine, Ioannina, Greece, [5]Registrar of Nuclear Medicine, Greece, [6]Associate Professor of Nuclear Medicine, Greece, [7]Professor of Medicine/Rheumatology, Ioannina, Greece

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease with two cardinal features: vascular involvement with intense vasoconstriction and smooth muscle proliferation, resulting in increased vascular resistance and tissue ischemia, together with excessive extra-cellular collagen deposition resulting in fibrosis. Both features affect multiple organs such as the skin and the lung. However, limited data are available on heart involvement.

Methods: We conducted a cross-sectional study of subclinical heart involvement in patients with SSc followed in a single tertiary rheumatology department. Enrolled patients underwent transthoracic echocardiography (GE Vivid 7 equipment), which assessed left ventricular hypertrophy (LVH) (defined as LV wall thickness >11mm), LV diastolic dysfunction, LV ejection fraction (EF) and pulmonary systolic arterial pressure (PASP). Stress echocardiography with dobutamine was performed in some cases. We also performed stress-rest myocardial perfusion imaging (MPI) scintigraphy by ^{99m}Tc-tetrofosmin single-photon emission computed tomography (SPECT). LV wall was divided in 20 segments to quantify ischemia as follows: mild (1–2), medium (3–4) & significant (≥5).

Results: Thirty-seven patients with SSc were enrolled (33 females, 4 males; median age 56 years, range 30–75). Eighteen of them had limited and 19 diffuse SSc, with median disease duration 15 years (range 2–57). Eleven patients had a history of arterial hypertension (AH), 2 of pulmonary arterial hypertension (PAH), 1 of myocardial infarction and 1 of diabetes mellitus. Two patients were on endothelin receptor antagonists due to PAH, while 14 received bosentan alone or in combination with sildenafil for digital ulcers without PAH. Echocardiography revealed LVH in 9 cases (24.3%); diastolic dysfunction (up to grade 1) was found in 17 (45.9%), though only one had EF<55% (EF median 67%, range 50–80). After excluding patients with a history of AH, LVH was still found in 6 (23.1%) and diastolic dysfunction in 10 (38.5%). PASP>30 mmHg was found in 13 patients (35.1%), 11 of whom had no history of PAH, while 3 were already on bosentan for digital ulcers. Stress echocardiography was performed in 12 patients and was negative in all. MPI by ^{99m}Tc-tetrofosmin SPECT was performed in 35 patients. Twenty-one (60%) exhibited reversible LV perfusion defects consistent with ischemia. Their median age was 54 years (range 30–75); 4 patients were less than 40 years and 8 patients less than 50 years old. In the majority of cases (20) ischemia was graded as mild and in one it was moderate.

Conclusion: Subclinical heart involvement is common in SSc, even in patients in the younger age groups. Diastolic dysfunction without compromised systolic performance, increased PASP and ischemia on MPI SPECT are found in a significant proportion of SSc cases. Although the precise underlying pathology need be elucidated, careful screening of SSc patients for potential heart involvement and consultation by a cardiologist may often be warranted.

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Prevalence of Celiac Antibodies in Patients with Systemic Sclerosis. Lindsy J. Forbess[1], Jessica K. Gordon[1], Kamini Doobay[2], Brian Bosworth[3], Morgana L. Davids[1] and Robert Spiera[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, [3]New York Presbyterian Hospital, Weill Cornell Medical Center, New York, NY

Background/Purpose: Gastrointestinal (GI) manifestations of systemic sclerosis (SSc) are common and symptoms overlap with those of celiac disease. A high prevalence of celiac antibodies has been found in populations with autoimmune conditions. Two prior studies showed celiac antibody prevalence in SSc to be 7% and 10%, which is higher than the general population estimates of 1–2%. These studies were limited by small sample sizes, the lack of correlation of antibody status with symptoms, and the use of traditional celiac screening antibodies, where newer ones with potentially improved sensitivity and specificity have since emerged. We conducted a cross-sectional study to determine the prevalence of celiac antibodies in an SSc population using a registry cohort at a single academic medical center. We used both traditional and newer celiac antibody tests. We also investigated whether the presence of celiac antibodies correlated with GI symptoms in our patients.

Methods: Serum was available on 107 well-characterized SSc patients, and a random number generator was used to select 39 diffuse and 33 limited SSc patients. These 72 patient sera were tested using commercially available enzyme-linked immunosorbent assay kits (INOVA, San Diego, CA) for traditional anti-tissue transglutaminase (anti-TTG) IgA and IgG and newer anti-deamidated gliadin peptide (anti-DGP) IgA and IgG antibodies. If any of the above antibodies were positive, more specific anti-endomysial antibodies were tested on sera using immunofluorescence methods (Quest laboratories, NJ). Clinical data from registry forms was used to determine whether antibody status correlated with GI symptoms. Fischer's exact and Wilcoxon rank-sum tests were used to compare differences.

Results: Of 72 patients tested, 1 patient was positive for anti-TTG IgG and 2 patients were positive for anti-DGP IgA antibodies. Of these 3 patients, none was positive for anti-endomysial antibodies. The prevalence of celiac antibodies in our SSc patient population, therefore, was 3/72 or 4%. No significant differences with respect to GI symptoms, including abdominal pain, early satiety, post-prandial bloating, diarrhea, constipation, vomiting, reflux, or dysphagia, were seen in the celiac antibody positive compared with negative SSc patients. The table below describes baseline characteristics of the 72 patients tested.

Table. Baseline Characteristics of SSc Registry Patients

Characteristic	All patients	Antibody Positive	Antibody Negative	P value
Age, mean ± SD years	51 ± 13.1 (n = 72)	59 ± 9.8 (n = 3)	51 ± 13.2 (n = 69)	0.242
Female (%)	63/72 (87.5)	3/3 (100)	60/69 (87)	1.000
Caucasian (%)	57/72 (79.2)	3/3 (100)	54/69 (78.3)	1.000
Disease duration, mean ± SD years	6.1 ± 6.7 (n = 66)	5.3 ± 4.5 (n = 3)	6.1 ± 6.8 (n = 63)	0.853
Classification				
Diffuse (%)	39/72 (54.2)	2/3 (66.7)	37/69 (53.6)	1.000
Limited (%)	33/72 (45.8)	1/3 (33.3)	32/69 (46.4)	1.000
Modified Rodnan skin score (range 0–51), mean ± SD	13 ± 11.6 (n = 65)	18 ± 9.9 (n = 2)	13 ± 11.8 (n = 63)	0.351
Sicca (%)	30/63 (47.6)	3/3 (100)	27/60 (45)	0.102
Joint involvement (%)	56/67 (83.6)	3/3 (100)	53/64 (82.8)	1.000
Hemoglobin, mean +/− SD	12.4 +/− 1.63 (n = 53)	12.1 +/− 1.7 (n = 3)	12.4 +/− 1.64 (n = 50)	0.658

Conclusion: In the largest study to date, we demonstrate the presence of celiac disease associated antibodies to be 4% in our SSc population, which is lower than previously reported. In our study, there was no difference between celiac antibody positive and negative SSc patients with respect to GI symptoms, likely attributable to the high prevalence of GI involvement in our cohort and the small number of antibody positive patients. Our study does not suggest that concurrent celiac disease is a common cause of GI complaints in patients with SSc.

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Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma: Racial Differences in Systemic Sclerosis-Related Pulmonary Hypertension. Christine Peoples[1], Robyn T. Domsic[1], Thomas A. Medsger Jr.[1], Virginia D. Steen[2] and PHAROS Investigators[3]. [1]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [2]Georgetown Univ Medical Center, Washington, DC, [3]Washington, DC

Background/Purpose: PHAROS is a multi-center, longitudinal study designed to assess risk factors and outcomes in patients with systemic sclerosis (SSc) who have definite pulmonary hypertension (PH) or are at high risk to develop PH (pre-PH). The objective of this study was to examine the racial differences in SSc-related and PH characteristics in the PHAROS population.

Methods: Entry criteria into PHAROS for SSc patients at high risk for PH included a diffusion capacity (DLCO) <55% predicted, a forced vital capacity (FVC) %/DLCO% ratio >1.6, or an estimated pulmonary arterial systolic pressure (PASP) on echocardiogram > 35mmHg. Patients complete questionnaires every 6 months and are seen yearly for physician evaluation. Information collected includes New York Heart Association (NYHA) functional classification, the World Health Organization class of PH, autoantibody profile, pulmonary function test results, and evidence of interstitial lung disease by radiographic imaging. Differences at baseline (first visit) between African American and Caucasian patients were compared by t-test, Wilcoxon, Fisher's exact, and chi-square where appropriate. With correction for multiple comparisons, a p-value of 0.01 was considered significant.

Results: There are 309 Caucasians and 70 African Americans (18%) enrolled in PHAROS. African Americans (mean age 50.5 ± 11.2 years) were significantly younger than Caucasians (59.3 ± 10.5 years, p < 0.0001), although there was no difference in gender (p=0.15).

Table 1. Systemic Sclerosis and Pulmonary Hypertension Characteristics at Time of PHAROS Enrollment in Caucasians and African Americans.

	Caucasians	African-Americans	p-value
SSc Type	–	–	0.01
limited	67%	49%	
diffuse	28%	47%	
unclassified	5%	4%	
Autoantibody Profile	–	–	0.02
anti-centromere	26%	13%	
anti-topoisomerase I	14%	14%	
anti-U1RNP	5%	7%	
nucleolar ANA	14%	30%	
anti-RNA polymerase III	3%	3%	
other antibody	23%	16%	
unidentified/missing	15%	17%	
PH Type	–	–	0.11
pre-PH	58%	67%	
pulmonary arterial hypertension	30%	16%	
pulmonary venous hypertension	5%	7%	
ILD-related PH	7%	10%	
Baseline NYHA Class	–	–	0.76
0	15%	18%	
I, II	58%	58%	
III, IV	27%	24%	

There was no difference in the frequency of pulmonary fibrosis (p=0.90). There was also no difference (p=0.29) between the mean FVC predicted in African Americans (80% ± 19) compared to Caucasians (74% ± 20), but African Americans had a significantly lower DLCO percent predicted (median 39%, IQR 34, 57) compared to Caucasians (44%, IQR 30, 46; p=0.008). There was no difference in the six minute walk distance (p=0.66).

Conclusion: In the PHAROS population of patients with or at high risk for PH, the overall proportion of African Americans is higher than generally seen in published SSc series. African Americans tend to be younger, have a significantly higher proportion of diffuse cutaneous SSc, and a lower DLCO than Caucasians. African Americans less often had anti-centromere antibody, but more frequently had one of the nucleolar ANAs. This suggests that African Americans with a nucleolar ANA should be monitored closely for the development of PH.

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Effects and Safety of Rituximab in Systemic Sclerosis: An Analysis From the European Scleroderma Trial and Research Group. Suzana Jordan[1], Jorg HW Distler[2], Britta Maurer[1], Jacob M. Van Laar[3], Yannick Allanore[4], Oliver Distler[1] and EUSTAR Rituximab Group[5]. [1]University Hospital Zurich, Zurich, Switzerland, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Musculoskeletal Research Group, Newcastle, United Kingdom, [4]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [5]Florence, Italy

Background/Purpose: Preclinical studies and smaller case-series suggest potential effects of Rituximab (RTX) on skin fibrosis, interstitial lung disease and polyarthritis in patients with systemic sclerosis (SSc). Objective of this study was to analyze the effects and safety of RTX in a real-life clinical setting using the EUSTAR cohort.

Methods: Patients treated with RTX were captured from the EUSTAR cohort and centers were asked to provide additional data for this study. Primary outcomes were: modified Rodnan skin score (mRSS) for skin fibrosis, FVC for SSc-ILD, DAS 28 3v for SSc-associated polyarthritis, and CK levels for SSc-associated myositis. Effects on fibrosis were analyzed at the follow up closest to 12 months, and effects on polyarthritis and myositis at the follow up closest to 6 months. Normally distributed data are shown as mean ± SD and were analyzed by paired t-test. Nonparametric data are shown as median and interquartile range and were analyzed by Wilcoxon matched paired signed rank test.

Results: Seventy two SSc patients treated with RTX from 27 EUSTAR centers were available for analysis (52 diffuse SSc/19 limited SSc, disease duration 6 years (3–10 years)). The most frequent application scheme was 2 × 1000mg RTX given 2 weeks apart. Twenty-eight patients had co-treatment with other disease modifying drugs (most frequent methotrexate, n =14).

The mRSS as the primary outcome for skin fibrosis showed a statistically significant reduction compared to baseline (n=47, 18.2+10.9 vs. 14.5+9.9, p=0.0002). This effect became even more evident when the cohort was enriched for patients with extended skin fibrosis (diffuse SSc with mRSS >16 at baseline, n= 26: 26.5+6.8 vs. 20.4+8.9, p<0.0001). This was paralleled by an improvement of the European SSc activity score (n=10; 3.7 (2.6–6.4) vs. 1.7 (0.9–2.5), p=0.01).

There were no effects on FVC in patients with SSc-ILD (n=11, 57.7+9.1 vs. 56.2+16.0 %; p=0.5). Similarly, other lung function parameters including DLCO, TLC, and extent of fibrosis on HRCT did not change after RTX treatment.

In patients with SSc-associated polyarthritis, the DAS 28 score was reduced after RTX treatment (n=8; 4.8 (2.5–7.5) vs. 3.7 (2.6–6.6)), but did not reach statistical significance (p=0.3). Other arthritis outcomes including tender joint count, swollen joint count, VAS articular pain, CRP and ESR showed similar trends.

Levels of CK decreased significantly in patients with SSc-associated myositis after RTX treatment (n=12, 273+177 vs. 184+139, p=0.03). Other measures of myositis such as levels of myoglobin and VAS scores were available only for a limited number of patients and did not change significantly versus baseline.

During RTX treatment, infections occurred in 14 patients, 29 reported fatigue, 9 had nausea and 3 patients developed serum sickness. Four patients died, one of them possibly related to RTX (pneumonia and cardiac failure 1.5 months after RTX infusion).

Conclusion: In this large, observational multicenter EUSTAR study, positive signals for potential efficacy of RTX were obtained for skin fibrosis

and SSc-related myopathy. These results strongly emphasize the need for a randomized controlled trial with RTX in patients with SSc.

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B Cell Depletion Therapy in Systemic Sclerosis: a Follow-up Study of 4 Years on Skin and Lung Involvement in Fourteen Patients. Silvia L. Bosello[1], Antonella Laria[1], Manuela Rucco[1], Mario Bocci[1], Giacomo De Luca[1], Annunziata Capacci[1], Matteo Falcione[2], Francesco Maria Danza[2] and Gianfranco Ferraccioli[1]. [1]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [2]Institute of Radiology, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: Experimental data show that B cells play important roles in fibrogenesis and vascular abnormalities, but discordant results on Rituximab's efficacy in skin and lung involvements in small cohorts of patients have been reported.

The objective of our study was to define the changes in skin score and lung parameters after Rituximab therapy in SSc patients with a long follow-up.

Methods: Fourteen patients with SSc with mean age 44.3±12.2 years were treated with anti-CD20, 1 g at time 0 and after 14 days. All patients presented a diffuse disease. Mean disease duration was 32.9±37.1 months, 8 presented an early disease, defined as a disease duration of less than 24 months. Skin score and presence of digital ulcers were assessed at baseline and at final follow-up. Pulmonary function tests to assess forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) and lung high resolution computed tomography (HR-CT) were performed at baseline and at follow-up. A semiquantitative scores were used to assess the alveolar and interstitial lung involvement. An improvement or a decrease of more than 10% for FVC and 15% for DLCO was considered clinical significant.

Results: A mean follow-up of 41.0±14.8 months was reached. The mean skin score at baseline was 24.9±9.8, while at follow-up it decreased to 12.0±6.7, (p=0,001). All but one of the patients experienced an improvement of skin score higher than 10% with a median decrease of the skin score of 56.0% (range 11.0–85.1%). Six patients presented digital ulcers at baseline and two patients (33%) experienced healing of ulcers and did not present digital ulceration during follow-up.

Considering lung involvement, nine patients (64.3%) presented a stable FVC, 3 (21.4%) showed an improvement and 2 (14.3%) a decrease. None of the patients with an early disease presented a decrease of FVC, while 2 of 6 patients with a long disease showed a decrease of this functional parameter.

The HRCT alveolar score improved or remained stable in 10 patients (71.4%). Only one patient with an early disease presented an increase of alveolar score (12.5%), compared to 3 patients (50%) with a long disease duration.

One (7.2%) patient presented a decrease of interstitial score, 8 patients (57.1%) a stability, while five (35.7%) showed an increase of the interstitial score.

Conclusion: Our data confirm the efficacy of Rituximab on cutaneous involvement as revealed by the significant decrease in the skin score. AntiCD20 therapy seems to preserve the stability of lung involvement as supported by stable or improved FVC and alveolar score, over all in patients with early scleroderma. The long follow-up, considering the rapid progression of lung disease in the first phases of the diffuse scleroderma disease, supports a possible role of CD20 depletion as a disease modifying therapy (DMTSSc) in systemic sclerosis.

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ELF Score: A Validated Serum Test Strongly Predictive of Fibrosis in Systemic Sclerosis. Giuseppina Abignano[1], Giovanna Cuomo[2], Maya H. Buch[1], William M. Rosenberg[3], Gabriele Valentini[4], Paul Emery[5] and Francesco Del Galdo[1]. [1]University of Leeds, Leeds, United Kingdom, [2]Second University of Naples, Naples, Italy, [3]Centre for Hepatology - UCL, London, United Kingdom, [4]Second Univ of Napoli, Napoli, Italy, [5]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom

Background/Purpose: The absence of a serum test predictive of activity or severity in Scleroderma (SSc) is a major burden both for clinical intervention studies and for clinical management. Recently, a large multicenter study has identified an algorithm of three serum biomarkers as predictive of severity and clinical outcome in Chronic Liver Disease.The algorithm,known as Enhanced Liver Fibrosis (ELF), includes the measurement of serum concentrations of hyaluronic acid, TIMP-1 and aminoterminal propeptide of procollagen type III. Objectives: To evaluate the predictive value of ELF test as surrogate outcome measure of fibrosis in SSc.

Methods: 210 patients with SSc, all satisfying the ACR criteria for the classification of the disease, were enrolled in the study. 260 sera were analysed of which 90 were longitudinal samples from 40 patients. All patients were investigated for clinical and serological subset, disease duration, vascular, skin, joint, tendon, muscle, esophago-gastrointestinal, lung, heart and kidney involvement, disease severity, disease activity and HAQ-DI. ELF score was determined blindly by an independent commercial service (iQur, London, UK). Correlations were calculated using Spearman's correlation test and an unpaired two-tailed T-test was used to perform comparison between groups. All the variables found to be correlated in univariate analysis were subsequently assessed by step-wise regression analysis. Data were analysed employing SPSS18 software.

Results: The mean ELF score in SSc patients sera was 8.75±1.05 (normal range < 5.97). ELF score correlated with many clinical and instrumental measures assessing fibrotic involvement including: mRSS ($r = 0.32; p < 0.0001$),DLCO ($r = -0.29; p < 0.0001$), FVC % ($r = -0.21; p = 0.038$), Ejection Fraction ($r = -0.21; p = 0.0009$). The other variables found to be correlated with ELF in univariate analysis were Age, ESR, CRP and FVC. Step-wise regression analysis indicated that the single measures independently associated with ELF score were mRSS, DLCO, EF and age whereas ESR, CRP and FVC were not. When compared to complex clinical indexes ELF score was also found to be correlated with EScSG-Activity Index ($r = 0.20; p = 0.0015$), total Medger's disease severity score ($r=0.35; p<0.0001$) and total HAQ-DI ($r=0.32; p<0.0001$).Most interestingly, in the longitudinal samples ELF test showed a strong sensitivity to change, keeping the correlation with mRSS ($r=0.34$ $p = 0.0009$), DLCO ($r=-0.029; p=0.029$). In the same cohort of longitudinal samples ELF test was again correlated with total Severity ($r=0.49; p< 0.0001$), EScSG-Activity index ($r = 0.21; p=0.046$), and HAQ-DI ($r= 0.42; p<0.0001$).

Conclusion: The ELF test is a simple serum test that strongly correlates with several measures of fibrosis in SSc. It has a clear face validity for measuring the concentration of molecules involved in extracellular matrix turnover and strongly correlates with fibrotic severity and activity in SSc. The profound sensitivity to change with changes in mRSS, severity, activity and lung function indicate a clear discriminant validity of ELF as biomarker in SSc fibrotic involvement. ELF test should be included in the algorithm of activity index in Scleroderma and considered as outcome in clinical trials.

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Optical Coherence Tomography: A New Imaging Technique That Allows Detailed Visualization of Affected Scleroderma Skin. Giuseppina Abignano[1], Sibel Aydin[2], Concepcion Castillo-Gallego Jr.[3], Maya H. Buch[1], Paul Emery[4] and Francesco Del Galdo[1]. [1]University of Leeds, Leeds, United Kingdom, [2]Goztepe Training and Research Hospital, Istanbul, Turkey, [3]Hospital Universitario La Paz, Madrid, Spain, [4]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom

Background/Purpose: Skin involvement in scleroderma is a crucial clinical feature often considered primary outcome in clinical trials and yet orphan of a validated and reliable imaging technique. Optical Coherence Tomography (OCT) is an emerging imaging technology for clinical examination. OCT systems focus a low-intensity infra-red beam in tissue up to 2 mm below the surface. While Ophthalmic OCT has been in development since the early 1990s, advanced laser technology and recent MultiBeam developments have recently enabled the development of high-speed topical OCT providing high-contrast skin mages. The purpose of this study was to describe skin appearances as seen with OCT and to compare these findings clinical assessment of skin in patient affected by Scleroderma.

Methods: Dorsal aspect of fingers, hands and forearm were assessed in this study. A total of 66 skin regions from 22 patients (9 lcSSc, 13 dc-SSC) and 12 healthy controls (HC) were scanned by OCT with topical probe "VivoSight" (Michelson Diagnostics) and optics of Swept-source Fourier-Domain type with a laser wavelength of 1305+/− 15 nm. The investigator was blinded to the clinical details.

Signal changes within epidermis, dermal epidermal junction and

superficial dermis were documented. Clinical skin involvement of the regions examined was determined by an assessor blinded to the OCT findings using the mRSS scoring system.

Results: OCT provided real-time, pain free, video-rated images without any pretreatment or gels applied to the skin. Skin structure was imaged 2mm beneath the surface.showed remarkably high quality images of the skin. Images collected in healthy volunteers showed, consistently with published findings a regular hyperreflective border of the skin surface and a homogeneous hypo-reflective epidermal layer. The papillary dermis consistently showed hyper-reflective properties compared to the adjacent epidermis allowing the visualization of the dermal-epidermal junction. The deeper reticular dermis was imaged as less reflective than the adjacent papillary dermis. Blood and lymphatic vessels could be identified as hypreflective tube-like structures, often with tapering ends and visible both in the papillary and reticular dermis.

Average mRSS on the site of analysis was 2.5 for dcSSc and 1 for lcSSc. (0 for healthy volunteers).

The most striking finding of Scleroderma affected skin was the loss of the hyporeflective epidermal layer and consequently of the visualization of the dermal epidermal junction. Similarly there was no distinction of papillary and reticular dermis. Instead skin was visualized as a homogeneous textured layer. Blood vessels were less numerous than in normal skin or unaffected skin.

Conclusion: This is a proof of concept study determining the potential of OCT as imaging technique of Scleroderma Skin. Here we show that OCT is indeed a powerful harmless technique that allows a finely detailed visualization of the skin. The implementation of a OCT scoring system of the abnormalities we have identified in this initial study is warranted to determined whether OCT could be used as surrogate outcome measure in intervention studies or as predictive of skin involvement in Systemic Sclerosis.

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Decreased Plasma Ghrelin Levels in Patients with Systemic Sclerosis. Yuko OTA, Yasushi Kawaguchi, Kae Takagi, Takahisa Gono, Masanori Hanaoka and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, is a gastric hormone that plays a major role in the regulation of food intake. In 2008, it was reported that rikkunshito, an herbal medicine, had beneficial effects for anorexia in upregulating the secretion of acylated-ghrelin. In addition to energy homeostasis, ghrelin exerts an anti-inflammatory effect and inhibits pro-inflammatory cytokines such as IL-1beta and TNF-alpha. Recently, it was reported that ghrelin attenuated fibrosis progression in hepatocellular injury. The aim of the present study was to investigate the levels of plasma acylated-ghrelin and desacylated-ghrelin in patients with systemic sclerosis (SSc) and to determine the association between ghrelin levels and disease phenotypes. We also explored the effects of skin fibroblasts derived from patients with SSc on collagen production.

Methods: Forty five patients with SSc and 19 healthy controls (HCs) were enrolled in the study; 32 of the patients with SSc were complicated with interstitial lung disease (ILD-SSc). The plasma acylated-ghrelin and desacylated-ghrelin levels were determined by enzyme-linked immunosorbent assay (ELISA). Skin fibroblasts derived from 5 patients with SSc were cultured with various concentrations of recombinant ghrelin. After the skin fibroblasts were cultured for various times, the supernatants were collected and stored at −80°C. Procollagen type I C peptide was then measured using a commercial ELISA kit.

Results: The levels of plasma acylated-ghrelin were 13.2 ± 6.3 fmol/ml in the SSc patients and 21.9 ± 7.9 fmol/ml in the HCs, whereas the levels of plasma desacylated-ghrelin were 66.3 ± 35.1 fmol/ml in the SSc patients and 129.6 ± 50.3 fmol/ml in the HCs. Both the acylated-ghrelin and desacylated-ghrelin concentrations were significantly lower in the patients with SSc than in the HCs ($p < 0.0001$), as shown in Figure 1. In particular, the levels of acylated-ghrelin in patients with ILD-SSc were lower than those in patients with uncomplicated SSc ($p = 0.028$). In the experiments in vitro, procollagen type I C peptide production was suppressed by optimal concentrations of ghrelin in cultured SSc fibroblasts ($p < 0.05$).

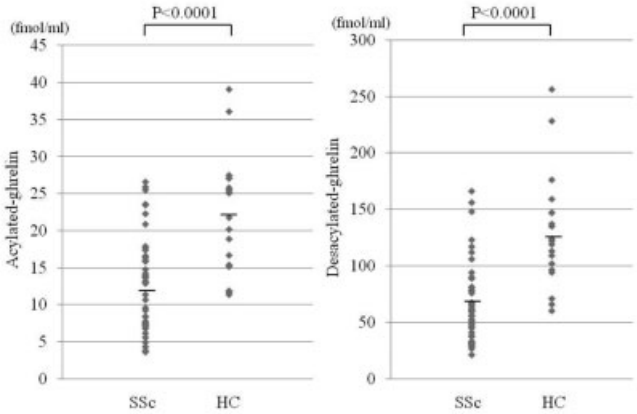

Figure 1. Plasma acylated-ghrelin and desacylated-ghrelin concentrations in patients with SSc and HCs.

Conclusion: The levels of plasma ghrelin were significantly lower in patients with SSc than in the HCs, and the levels of acylated-ghrelin in patients with ILD-SSc were significantly lower than those in patients without ILD. Our results also suggest that ghrelin exerts an anti-fibrotic effect in skin fibrosis, and its use may represent a novel strategy for anti-fibrotic therapy.

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A Pilot Study of Abatacept for the Treatment of Patients with Diffuse Cutaneous Systemic Sclerosis. Eliza F. Chakravarty[1], David Fiorentino[2], Mihoko Bennett[3] and Lorinda Chung[4]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Stanford, Stanford, CA, [3]Stanford University, Palo Alto, CA, [4]Stanford Univ Medical Center, Palo Alto, CA

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by progressive fibrosis of skin and internal organs, vascular damage, and autoantibody production. Several lines of evidence support a role for T-cells in initiating and perpetuating disease. We performed a randomized, double-blinded placebo controlled trial to evaluate the safety and efficacy of intravenous abatacept, an inhibitor of T-cell costimulation, or placebo in patients with diffuse cutaneous systemic sclerosis (dcSSc).

Methods: Adult subjects with dcSSc who had adequate cardiac, pulmonary (FVC>49% predicted, DLCO >39% predicted), and renal function (serum Cr <2.0) were recruited for this study. Prednisone >10 mg daily and other immunosuppressive therapies were not permitted. Subjects with active infection, history of malignancy, or infection with tuberculosis, hepatitis or HIV were also excluded. Subjects were randomized in a 2:1 double-blinded fashion to receive IV abatacept or placebo at weeks 0, 2, 4, and every 4 weeks for a total of 24 weeks. Primary outcomes were safety and the percent change in modified Rodnan Skin Score (mRSS, scale 0–51) from week 24 to baseline. Secondary clinical outcomes included change in Health Assessment Questionnaire-Disability Index (HAQ-DI), patient and physician global assessments by visual analogue scale (VAS), and pulmonary function tests (PFTs).

Results: 12 patients screened for the study: two were not eligible due to lack of peripheral venous access. 10 patients (8 women and 2 men, mean age 42.2 years) enrolled in the study. Mean disease duration from the time of the first non-Raynaud's manifestation was 4.4 (3.8) years. 7 patients were randomized to receive abatacept and 3 received placebo. At baseline, there were no significant differences in mRSS, HAQ-DI, VAS scales and PFTs between the two groups, although subjects randomized to abatacept had shorter disease duration (2.4 vs. 8.8 years, $p=0.004$). Compared with those receiving placebo, subjects treated with abatacept reported greater improvement in HAQ-DI and patient VAS. Numerically, patients receiving abatacept had larger improvements in absolute (−8.6 vs −2.3, $p=0.059$) and mean % change (−33% vs −6.2%, $p=0.31$) in MRSS than the placebo group (**Table**). No deaths or serious adverse events occurred during the study. 14 AEs (7 in each group) were reported in 9 patients: most were mild in nature. One patient, in the placebo arm, terminated the study at week 20 due to infection of a preexisting toe ulcer.

Variable	Abatacept (n = 7)	placebo (n = 3)	p-value
Baseline			
Age (year, SD)	39.8 (11.4)	48.6 (13.9)	0.32
% Male	28.6	0	1
% caucasian	57.1	66.7	1
Duration (raynauds)	3.9 (3.4)	9.2 (3.2)	0.05
Duration (1st non-raynauds)	2.4 (1.6)	8.8 (3.8)	0.0042
mRSS	23.6 (6.6)	30 (3)	0.15
HAQ-DI	0.6 (0.8)	1.5 (1.1)	0.18
Physician Global VAS	37.6 (13.8)	56.3 (5.5)	0.57
Patient Global VAS	53 (35.8)	61.7 (44.8)	0.75
Patient Pain VAS	42.7 (35.3)	53 (47.8)	0.71
FVC	77.3 (19)	73.3 (27.6)	0.79
DLCO	87 (17.5)	80.3 (24)	0.65
Outcomes			
Change in HAQ-DI	−0.04 (0.2)	0.25	0.56
Absolute change in mRSS	−8.6 (7.5)	−2.3 (15.0)	0.059
% change in mRSS	−33 (29.0)	−6.2 (52.3)	0.31
Change in Physician Global	−11.9 (18.1)	−17.3 (23.2)	0.048
Change in Patient Global	−8 (7.6)	−2.7 (6.7)	0.023
Change in Patient Pain	−11.4 (8.3)	−15.0 (25.1)	0.18
Change in FVC	1.3 (8.5)	0.3 (8.5)	0.72
Change in DLCO	2.0 (6.3)	−7.4 (10.7)	0.84
# Adverse events	7	7	

Conclusion: Blockade of T-cell costimulation with abatacept appears to be safe and may be a useful treatment for cutaneous sclerosis in patients with dcSSc. Larger, multi-center placebo-controlled studies limited to patients with early disease are necessary to further evaluate the utility of abatacept in the treatment of patients with dcSSc.

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Clinical Correlates of CENP-A and CENP-B Antibodies in a Large Cohort of Systemic Sclerosis Patients. Marie Hudson[1], Michael Mahler[2], Janet Pope[3], Daniel You[4], Solene Tatibouet[1], Russell Steele[1], Murray Baron[5] and Marvin J. Fritzler[4]. [1]McGill University, Montreal, QC, [2]INOVA Diagnostics, Inc., San Diego, CA, [3]Univ of Western Ontario, London, ON, [4]University of Calgary, Calgary, AB, [5]Jewish General Hospital, Montreal, QC

Background/Purpose: To study the clinical phenotypes of CENP-A and B positive systemic sclerosis (SSc) patients and to compare them to anticentromere antibody (ACA) positive and negative SSc patients.

Methods: Sera from 802 patients with SSc enrolled in the Canadian Scleroderma Research Group multi-centre cohort study were collected. Indirect immunofluorescence was performed on HEp-2 substrate (HEp-2000; ImmunoConcepts, Sacramento, CA, USA) that included fluorescein-conjugated goat antibodies to human IgG (H+L) in Calgary (Mitogen Advanced Diagnostics). CENP-B ELISA (Dr. Fooke Laboratorien GmbH, Neuss, Germany) with recombinant full-length CENP-B expressed in insect cells was used and performed according to the manufacturer's instructions. The CENP-A ELISA (Dr. Fooke Laboratorien GmbH), a CE-certified peptide based assay, was performed according to the manufacturer's AI-Line instructions for use as previously described. Associations with clinical and other serological manifestations of SSc were investigated using standard statistical methods.

Results: CENP-A antibodies were detected in 276 (34%), CENP-B antibodies in 286 (36%) and ACA in 279 (35%) patients. ACA, CENP-A and/or CENP-B patients resembled each other and differed from the remainder of the cohort in many respects: older chronologically and at disease onset; more commonly women; more likely to have limited disease and lower skin scores; less likely to have finger ulcers, digital tuft resorption or finger contractures; more likely to have pulmonary hypertension; less likely to have interstitial lung disease, scleroderma renal crisis, inflammatory arthritis and inflammatory myositis; and lower overall disease severity. CENP-A and/or B status was predictive of the extent of skin involvement over time. Limited patients who were CENP-A *negative* at baseline were more likely to progress to diffuse disease compared to positive patients (odds ratio 2.55, 95% confidence interval 1.37, 4.85, p-value 0.004).

Conclusion: Our study contributes significantly to increase the knowledge concerning the clinical significance of CENP-A and B in SSc. This is the largest and most detailed analysis of the clinical correlates of CENP-A and B in a large SSc cohort with well-defined phenotypes. The clinical phenotypes of CENP-A and/or B patients are generally consistent with that associated with ACA positive patients. The data from this and from previous studies indicate that CENP-A and CENP-B assays can be used a) to identify patients with SSc with high sensitivity and specificity, and b) using optimized cut-off values, to identify the same clinical phenotypes as known for ACA. This data is of considerable clinical importance because clinical immunology labs are increasingly using high throughput ELISA tests to test for CENP antibodies, with or without ACA detected by IIF. Accordingly, it is imperative that clinicians should be informed that the phenotypes that they generally associate with ACA in SSc is similar to that which they should associate with CENP-A and/or B positive antibodies.

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Influenza H1N1 Vaccination in Mixed Connective Tissue Disease: Effectiveness and Safety Independent of Disease or Therapy. Renata Miossi[1], Ricardo Fuller[1], Julio C. B. Moraes[1], Ana Cristina Medeiros[1], Carla G.S. Saad[1], Nadia E. Aikawa[1], Joao Miraglia[2], Maria A. Ishida[3], M.Teresa C. Caleiro[1] and Eloisa Bonfa[1]. [1]University of Sao Paulo, Sao Paulo, Brazil, [2]Fundação Butantan, São Paulo, Brazil, [3]Adolfo Lutz Institute, Sao Paulo, Brazil

Background/Purpose: There are specific recommendations for influenza vaccination in systemic autoimmune diseases and the WHO recently recommended that the 2010–2011 trivalent seasonal flu vaccine must contain the A/California/7/2009 (H1N1) virus. With regard to mixed connective tissue disease (MCTD) there is only one study in the literature from our group focusing solely in vaccine side-effects and the overall immunoresponse in large cohort of rheumatic diseases (Ann Rheum Dis. 70(6): 1068–73, 2011). We therefore evaluated herein the possibility of clinical and laboratorial disease exacerbation as well as the influence of disease manifestations and therapy in antibody response.

Methods: From March 22 to April 02, 2010, 69 subjects diagnosed with MCTD according to Kasukawa's classification criteria and 69 age and gender matched controls were vaccinated with non-adjuvanted influenza A/California/7/2009 (H1N1) virus-like strain. Patients were clinically evaluated and blood samples (inflammatory markers, muscle enzymes) were collected pre- and 21 days post-vaccination. Anti-H1N1 titers were determined by influenza hemagglutination inhibition assay. The percentage of seroprotection (SP), seroconversion (SC) and the factor increase in geometric mean titer (GMT) were calculated.

Results: Mean age (48.6 ±12.6 vs. 48±12, P=0.68) and female gender predominance (95.6%) were alike in patients and controls. The mean disease duration was 12.9±8.9 years. A comparable SP (10.1 vs. 10.1%, P=1), SC (66.7% vs. 65.2%, P=1) and factor increase GMT (10; 95%CI, 7.1–14.1 vs. 8; 95%CI, 6–10.6; P=0.33) was observed in patients and controls. The specific analysis of immunosuppressive therapy influence (prednisone≥7,5mg/day and/or cytotoxic drugs) revealed a similar SC rate in patients with and without these drugs (72.7% vs. 56.0%, P=0.19). Moreover, the SC rate in the only 7 patients with prednisone≥20mg/day were similar to controls (P=0.69). Patients, at entry, with and without current pulmonary disease (P=0.62), pulmonary arterial hypertension (P=0.75) had comparable SC rates. Laboratorial parameters remained stable pre- and post vaccine: CRP (P=0.55), CPK (P=0.31), aldolase (P=0.4). Of note, none of the patients presented deterioration of the clinical disease. No major severe side effects were reported.

Conclusion: The non-adjuvanted influenza A/H1N1 vaccination immunoresponse in MCTD patients is adequate and independent of disease manifestations and therapy. In addition, the observed overall disease clinical and laboratorial safety settles its recommendation.

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How Do Physicians Make a Global Assessment of Raynaud's Phenomenon in a Clinical Trial? Richard W. Martin[1], Andrew J. Head[2], James D. Birmingham[1] and Aaron T. Eggebeen[1]. [1]Michigan State University College of Human Medicine, Grand Rapids, MI, [2]College of Human Medicine, Michigan State University, Grand Rapids, MI

Background/Purpose: To evaluate how physicians in a clinical trial integrate patient historical information to make a judgment of the global activity of Raynauds phenomenon (RP).

Methods: Patients were enrolled in a prospective double blind cross-over clinical trial of topical nitroglycerine for the prevention or treatment of RP. Brief structured interviews were conducted in the clinic weekly where physicians used a standardized template to evaluate and

semi-quantitatively score seven aspects of RP activity experienced by patients over the preceding week. Items assessed number and duration of RP attacks, severity of associated pain (0–5) and numbness (0–5), development of new finger ulcers (yes, no), the impact of RP in restricting activities (0–5) and importance of activity restrictions to patients (0–5). Physicians used the structured interview data to judge the MD global assessment of RP activity (RP MD-GA) (0–9). Physician judgment strategy was represented as a linear regression model, with standardized regression weights describing the relative importance of the 7 historical attributes of RP in determining the physician's global assessment.

Results: Data were analyzed from 100 patient visits of 15 patients. All patients were female, mean age was 38.5 (s =13.1), 91% white, 29% history of scleroderma, 9% had digital ulcers at baseline, 23% were taking concurrent medications to treat RP. Mean number of RP attacks was 2.3 per day (s=.62), mean minutes duration 25.7 (s=14.4). RP MD-GA was significantly correlated with daily # RP =.699 ($p<.001$), RP impact on life =.662 ($p<.001$), RP pain =.625 ($p<.001$), RP importance =.641 ($p<.001$), RP numbness =.436 ($p<.001$), duration RP =.381 ($p<.001$), but not patient age. Due to the exploratory nature of the study, all significantly correlated independent variables plus development of new or worse digital ulcers were included in a stepwise linear regression model with RP MD-GA as the dependent variable.

The most parsimonious model was: MD-GA RP = −1.495 +.472 daily # RP +.308 RP pain +.311 RP impact on life. This model had an overall R=.859 and adjusted R^2=.730. Addition of the other measured variables did not significantly add to the power to predict RP MD-GA.

Conclusion: When 7 RP historical clues were considered, only daily # RP, RP associated pain and RP impact on life significantly influenced physician decision models when they assigned a global assessment of RP. Duration of RP attacks, numbness, patient's view of the importance of the QOL impact, and development of new or worse ulcers did not significantly impact the RP MD-GA. In a RP clinical trial, a physician may only need to ask 3 questions to secure the data needed to assign a global assessment.

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Tendon and Joint Involvement in Diffuse Systemic Sclerosis: An Ultrasound and Magnetic Resonance Imaging Study. Maria S. Stoenoiu[1], Frederic E. Lecouvet[1] and Frédéric. A. Houssiau[2]. [1]Cliniques Universitaires Saint-Luc, Brussels, Belgium, [2]Université catholique de Louvain, Brussels, Belgium

Background/Purpose: Musculoskeletal involvement is present in 40 to 80% of patients suffering from systemic sclerosis (SSc) and impacts their daily activities, thus decreasing their quality of life. Musculoskeletal ultrasonography (MSUS) has emerged as a new imaging modality, which allows detection of synovitis and tenosynovitis. In addition, using power-Doppler (PDUS) techniques, vessels can be detected inside the synovium.

The aim of the present study is (*i*) To report the frequency of tendon and joint involvement at wrists and ankles of patients suffering from diffuse SSc. (*ii*) to describe the morphological substrate of tendon friction rubs (TFR).

Methods: All patients had two MSUS of wrists and ankles performed by a radiologist and a rheumatologist. The first MSUS was performed on the day of the clinical examination. The second was performed on the day of MRI examination, at least 1 week later, in order to look for persistence of synovitis and/or tenosynovitis. MRI was performed at the most affected joint as detected by MSUS. In addition, all sites in which tendon friction rubs (TFR) were present, were imaged by MRI. OMERACT definitions were used to evaluate the presence of synovitis/ tensoynovitis on MSUS-PDUS.

Results: Fifteen consecutive patients suffering from diffuse SSc were included. Synovitis was detected by MSUS in 8/15 patients, tenosynovitis in 4/15 patients and tendon rupture in 2/15 patients. PDUS was positive in the majority of patients. Thickened retinacula were present in 4/15 patients. TFR at ankles were present in 5 patients (9 ankles). Synovitis was similarly distributed in the SSc patients with or without TFR. Tenosynovitis was more frequently observed in ankles in which TFR were present (3/9) than in ankles without TFR (3/21). Juxta-tendinous soft tissue infiltrates were present in all patients with TFR and only one patient without TFR.

Conclusion: Both MSUS/PDUS and MRI are useful to characterize tendon and joint involvement in SSc patients. Tenosynovitis, synovitis and thickened retinacula are not infrequently seen in these patients. Interestingly, our data suggest that juxta-tendinous soft tissue infiltrates are the morphological substrate of tendon friction rubs, which may thus be a misnomer for tissue friction rubs.

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Iloprost Enhances Th17 and Th22 While Decreasing Th1 Cells Expansion in Healthy and Systemic Sclerosis Mononuclear Cells. Marie-Elise Truchetet[1], Yannick Allanore[2], Carlo Chizzolini[1] and Nicolò Costantino Brembilla[1]. [1]University hospital of Geneva, Geneva, Switzerland, [2]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France

Background/Purpose: In systemic sclerosis (SSc) inappropriate T cell responses are thought to participate in initiating events ultimately leading to excessive extracellular matrix deposition and fibrosis. Iloprost, a prostacyclin analog, is currently used as vasodilating agent to treat SSc-related vascular events. However, its immunomodulatory properties in humans remain unclear. Aim of this work was to assess whether Iloprost may influence the polarization and the cytokine-production capacity of T helper cells in healthy donors (HD) and SSc patients and to identify the receptors mediating its effects.

Methods: Peripheral blood mononuclear cells (PBMC) and clinical characteristics were obtained from 30 SSc and 29 age- and sex-matched HD upon informed consent and approval by the ethics committee. None of the patient was under immunosuppressant agents at the time of sampling. Frequencies of interleukin (IL)-17A, IL-22, interferon-gamma (IFN-gamma), and IL-4-producing CD4 T cells were assessed upon 7 days of polyclonal expansion in the presence or absence of Iloprost by multiparametric flow cytometry. The cytokines released in the supernatants were quantified by ELISA. Selective IP and EP receptor antagonists were used to identify the receptors mediating Iloprost effects. Differences between the means were assessed by the Student's t test. P values lower than 0.05 were considered as significant.

Results: Iloprost (Bayer Schering Pharma, Berlin, Germany) enhanced in a dose-dependent manner the CD4+ T cell production of IL-22 and IL-17A while decreasing the production of IFN-gamma. Analysis at single cell level confirmed these results and revealed that Iloprost treatment in vitro slightly but significantly favored the expansion of Th17 ($P<0.0001$) and Th22 cells ($P<0.0001$). Simultaneously, Iloprost induced a quantitatively more important decrease in Th1 cells ($P<0.0001$). No effects of Iloprost were observed on Th2 cells producing IL-4. Of interest, PBMC from SSc and HD responded to the same extent to Iloprost. Finally preliminary experiments indicated that the decreased production of IFN-gamma in the presence of iloprost was specifically reversed by CAY10449 (Cayman Chemical Co, Ann Arbor, MI), a peptide inhibitor specific for IP, while the enhanced production of IL-17A and IL-22 was partially inhibited by CAY10449, AH6809 (antagonist of EP1, EP2, and EP3), and AH23848 (antagonist of EP4) suggesting that the effect of Iloprost on cytokine production by PBMC was cooperatively mediated by several distinct receptors.

Conclusion: Our results show that Iloprost *in vitro* increases IL-17A and IL-22 while decreasing IFN-gamma production by CD4+ T cells, underlying new immunomodulatory proprieties of this compound distinct from its action on endothelial cells and fibroblasts. The capacity of Iloprost to modulate the production of cytokines by T cells should be taken into account in current Iloprost-based therapies and could be exploited for novel therapeutic approaches.

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Evaluation of the Effect of Ambrisentan On Digital Microvascular Flow In Patients with Systemic Sclerosis Using Laser Doppler Perfusion Imaging. Nilanjana Bose[1], James Bena[1], Charles Trunick[1], John Petrich[2], Debora J. Bork[3], Geetha Krishnan[1] and Soumya Chatterjee[1]. [1]Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic, Cleveland, [3]The Cleveland Clinic Found A50, Cleveland, OH

Background/Purpose: Conventional vasodilators such as calcium channel blockers may not be as helpful in Scleroderma (SSc) associated Raynaud's phenomenon (RP), as in primary RP, as they have little effect on the vascular fibro-proliferative changes that lead to chronic digital ischemia in SSc. Ambrisentan (Am) is a selective endothelin receptor type A (ET_A) antagonist FDA approved for the treatment of pulmonary hypertension. Am differs from bosentan in its ability to permit the vasodilatory effect of endothelin through its interaction with the endothelin-B receptor, while inhibiting its vasoconstrictive effect through its interaction with the ET_A receptor. Laser Doppler perfusion imaging (LDPI) is a non-invasive technique that involves perfusion mapping of areas of skin, rather than examination of blood flow at a single point. We hypothesized that Am would increase digital microvascular flow (as measured by LDPI) in patients with SSc-associated digital ischemia.

Methods: In this randomized, double-blinded, placebo controlled trial, we

enrolled 20 patients with limited SSc of duration < 7 years. Smokers and those with pulmonary hypertension or active digital ulcers were excluded. There were 3 visits: week 0 (baseline), week 1 and week 12. At each visit, 3 baseline blood flow readings of fingers of the non-dominant hand were obtained at room temperature (25°C) and after cold challenge (10°C) for 2 minutes. Raynaud's Condition Score (RCS), Scleroderma Health Assessment Questionnaire (S-HAQ) and Pain-Visual Analog Scale (P-VAS) were also completed at each visit. Fifteen patients received Am 5 mg tablets daily for one month and then increased to 10 mg daily for 2 months while 5 patients received placebo throughout. The primary outcome measure was the mean change of blood flow in selected regions of interest (ROI) of the fingers after 1 and 12 weeks of therapy. Secondary outcome measures included changes in RCS, S-HAQ, and P-VAS.

Results: There were 16 females (80%); mean age was 50 years (range: 20 to 70). All but 2 patients completed the study. The Am group showed a 0.11 unit mean increase in perfusion at 1 week and a 0.01 unit mean decrease at 12 weeks. In the placebo group, the corresponding numbers were a mean increase of 0.18 unit and a mean decrease of 0.06 unit. Changes were similar within ROI as well. None of these differences overall or within ROI reached statistical significance. However, patients in the Am group showed significant improvement in RCS ($p = 0.001$) and S-HAQ ($p = 0.005$) with minimal change in P-VAS ($p = 0.14$) scores. No adverse events occurred.

Conclusion: The final analysis for this pilot study did not support increase in digital microvascular blood flow in SSc patients over time; however, there was an improvement in S-HAQ score and RCS over 12 weeks. The study may have been underpowered to detect small differences over a short (3-month) duration of drug exposure. However, if that is not the case, then the results imply that Am does not augment digital blood flow by inducing vasodilation (1 week) and/or reversing remodeling (12 weeks) (as they do in the pulmonary circulation). This difference might be due to intrinsic differences in the vessel wall or in the local micro-environment of the digital arterioles.

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Echo-Doppler Evaluation Does Not Show Abnormal Diastole In Scleroderma Patients with Pulmonary Venous Hypertension. Santhanam Lakshminarayanan[1], Nada Shaban[1], Diane Tran[2], Jason W. Ryan[2], Irina Collins[2], David Hager[1] and Naomi F. Rothfield[1]. [1]University of Connecticut School of Medicine, Farmington, CT, [2]University of Connecticut School of Medicine, Farmington,, CT

Background/Purpose: Systemic sclerosis (SS) is a multisystem disorder which may cause myocardial and pulmonary fibrosis and pulmonary vasculopathy. Pulmonary arterial hypertension (PAH) due to increased pulmonary vascular resistance (PVR) is a major cause of morbidity and mortality in this population. Exercise induced elevation of pulmonary pressures from PAH can identify patients at high risk for chronic PAH. SS patients may also develop elevated pulmonary pressures with exercise in the setting of normal PVR due to diastolic dysfunction and pulmonary venous hypertension (PVH). We report a case series of 19 scleroderma patients with exercise-induced PVH diagnosed with invasive hemodynamic studies. We assessed whether echocardiographic parameters of impaired relaxation could have predicted the presence of PVH.

Methods: The echocardiograms on 19 clinically dyspneic SS patients whose hemodynamic monitoring during exercise showed PVH were retrospectively analyzed for evidence of diastolic dysfunction.

Results: Data on eighteen female patients and one male patient was studied. The mean age was 54 years. Other than hypertension (47%), most did not have medical conditions predisposing to diastolic dysfunction. Hemodynamic testing confirming PVH as shown in Table 1.

Table. RIGHT HEART CATHETERIZATION DATA

MEAN VALUES	REST	EXERCISE
PAP mmHg	18 ± 5	34 ± 7
PCWP mmHg	11 ± 3	26 ± 6
Cardiac Output L/min	5.8 ± 1.4	9.2 ± 3.0
Mean arterial pressure mmHg	94 ± 12	132 ± 9
Systemic vascular resistance dyn·s/cm^5	1306 ± 445	1282 ± 638
PVR dyn·s/cm^5	111 ± 52	81 ± 46
Mixed venous oxygen saturation %	73 ± 6	64 ± 6
Heart rate bpm	79 ± 10	110 ± 18

Mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) increased by an average of 15mmHg with exercise indicating significant PVH. ECHO parameters associated with diastolic dysfunction are listed in Table 2.

Table. ECHO DATA

	Percent
LV Hypertrophy	
Interventricular septum >1.1cm	32
Left Ventricular posterior wall >1.1cm	11
Left ventricular mass index ≥100g/m^2	17
Dilated Left Atrium	
Antero posterior diam ≥4.0cm	32
Left atrial volume ≥28ml/m^2	22
Mitral Inflow Doppler	
Early diastolic mitral inflow velocity/mitral inflow velocity during atrial contraction ≤1	63
Early diastolic mitral inflow velocity/mitral inflow velocity during atrial contraction 1.1–1.4	32
Early diastolic mitral inflow velocity/mitral inflow velocity during atrial contraction ≥1.5	5
Deceleration time ≥200ms	76
Tissue Doppler	
Early diastolic mitral inflow velocity/early diastolic mitral annular tissue velocity ≤8	22
Early diastolic mitral inflow velocity/early diastolic mitral annular tissue velocity 8.1–14.9	61
Early diastolic mitral inflow velocity/early diastolic mitral annular tissue velocity ≥15	17

All patients had preserved ejection fraction. Most patients (>63%) did not have findings associated with diastolic dysfunction when parameters for left ventricular hypertrophy, left atrial (LA) size, mitral doppler inflow, or tissue doppler were analyzed.

Conclusion: Conventional echocardiography may not suggest underlying diastolic dysfunction in the majority of symptomatic SS patients with exercise induced pulmonary venous hypertension.

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Nutrition In Systemic Sclerosis Patients. Maureen Murtaugh[1] and Tracy M. Frech[2]. [1]University of Utah, Salt Lake, [2]University of Utah School of Medicine, SLC, UT

Background/Purpose: The multiple gastrointestinal manifestations in systemic sclerosis (SSc) can potentially affect the nutritional status of patients through several mechanisms. We examine the association of gastrointestinal variables—captured by University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0); weight loss and manifestations of malnutrition—captured by the Subjective Global Assessment (SGA); and possible laboratory markers of gastrointestinal health—albumin, vitamin D, and hematocrit values, with clinical features of SSc.

Methods: Patients were recruited from the University of Utah SSc Clinic and consented during their routine clinic visit (IRB number 00038705). A series of 24 SSc patients were assessed using the SGA and GIT 2.0 questionnaires. Weight was measured in the clinic on the day of study enrollment. Change in weight from a 2 week interval was obtained by patient recall as an increase, no change, or decrease. Change in weight at 6 months and one year was calculated using weights recorded on pulmonary function tests documented in the medical record. A single evaluator (TF) asked the patients questions regarding dietary intake change, gastrointestinal symptoms and functional capacity, and evaluated metabolic demand, physical signs of malnutrition and overall SGA score. Statistical analysis was conducted using SAS version 9.2 (Cary, NC). We used descriptive statistics including mean for continuous variables and frequency for categorical variables to describe the patient population, GIT and nutritional status (SGA). We used Fishers' exact to examine associations between two categorical variables. We used general linear models (PROC GLM) to assess differences in continuous variables across duration of disease or SGA nutritional status category. We assigned significance at $p < 0.05$.

Results: We have identified that although the Medsger severity index did correlate with SGA, no single GI etiology of malnutrition was identified in this study. Nutritional status was not associated with duration of disease and/or presence of reflux, distention/bloating, soilage, and/or constipation, diarrhea, but social and emotional well-being suffered as nutritional status became worse.

Conclusion: Although, malnutrition is important to identify in SSc, its mechanism(s) remains an area that requires further clarification.

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Associations Between the UCLA SCTC GIT 2.0 Vs. Objective Tests of Upper Gastrointestinal Involvement in Systemic Sclerosis. Sangmee Bae[1], Yannick Allanore[2], Daniel E. Furst[3], Vijay Bodukam[4], Baptiste Coustet[5], Olga Morgaceva[6], Paul Maranian[3] and Dinesh Khanna[7]. [1]David Geffen School of Medicine at UCLA, Los Angeles, CA, [2]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [3]UCLA Medical School, Los Angeles, CA, [4]Crozer Chester Medical Center, Upland, PA, [5]Université Paris Descartes, Hopital Cochin, Paris, France, [6]UCLA, Los Angeles, CA, [7]University of Michigan, Ann Arbor, MI

Background/Purpose: UCLA-SCTC-GIT 2.0 is a 34 item instrument designed to assess gastrointestinal (GI) symptoms in systemic sclerosis (SSc). The objective of our study was to assess the associations between the upper GI symptom scales of the instrument (Reflux and Distention/ Bloating (D/B) scales) vs. objective/ laboratory studies of upper GI involvement.

Methods: We enrolled 60 patients at 2 SSc centers (30 from the US, 30 from Europe) with SSc. Each patient filled out the GIT 2.0 and patients had barium swallow with small bowel follow through, gastric emptying study, lactulose breath test, endoscopy, esophageal manometry, HRCT of the chest, and laboratory tests (serum amylase, lipase, iron, 25 hydroxyvitamin D, vasoactive intestinal peptide, gastrin, carotene, methylmalonic acid, and celiac panel). We explored correlations between the Reflux scale scores vs. barium swallow, UGI endoscopic findings, and esophageal manometric abnormalities. We also explored correlations between the D/B scale scores vs. lactulose breath test, gastric emptying study, unplanned weight loss, and laboratory tests. Correlations were assessed using the Spearman's test. We calculated the average scores in patients with positive vs. negative tests and compared them using the T-test and Wilcoxon test.

Results: The mean (SD) age was 53.5 (11.7) yrs and participants were mostly women (90%); 50% had limited SSc. The mean (SD) Reflux score was 0.82 (0.64; moderate) and D/B score was 1.25 (0.85; moderate) The Reflux scale had statistically significant correlations with upper GI objective evaluations and was able to differentiate between patients with EGD proven esophagitis and manometric abnormalities (Table). There were no associations between the Reflux scores vs. HRCT findings for interstitial lung disease. D/B had non-significant associations with the objective tests (Table). Although D/B scores were higher in patients with positive tests, these were non-significant associated with objective measures. There were no significant correlations between laboratory values and GIT 2.0 scales.

Table. ECHO DATA

UCLA SCTC GIT 2.0	Test	Correlations	Positive test	Negative test	p value
Reflux scale	Esophagitis on upper endoscopy (n=32)	0.46*	1.38 (0.54) n=9	0.76 (0.58) n=23	0.01
	Manometry abnormalities (n=29)	0.51*	1.39 (0.70) n=15	0.69 (0.59) n=14	0.01
	Dysmotility on barium swallow (n=22)	0.26	0.93 (0.69) n=16	0.77 (0.46) n=6	0.58
	Presence of fibrosis on HRCT (n=53)	−0.26	0.62 (0.52) n=28	0.96 (0.69) n=25	0.06
	Presence of ground glass on HRCT(n=51)	−0.11	0.62 (0.37) n=16	0.88 (0.71) n=35	0.45
Distention/ Bloating scale	Abnormal lactulose breath test(n=38)	0.07	1.35 (0.94) n=21	1.12 (0.91) n=17	0.67
	Delayed gastric emptying(n=22)	0.13	1.48 (1.15) n=11	1.14 (0.73) n=11	0.55
	Unplanned wt loss (n=53)	0.16	>5% of wt 1.46 (0.71) n=10	<5% of wt 1.22 (0.90) n=43	0.24

*P< 0.05

Conclusion: The GIT 2.0 Reflux scale has significant correlations with esophagitis on the EGD and upper GI dysmotility on barium swallow and was able to differentiate between patients with positive vs. negative tests. Although D/B scale scores were higher in patients with positive vs. negative tests, D/B scale had poor correlations with objective tests. Reflux and D/B scale scores complement the objective tests for assessment of the upper GI involvement.

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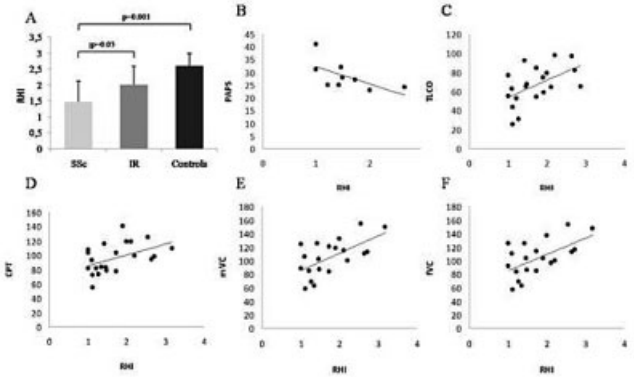
Reactive Hyperemia Index Is Associated with Macroangiopathy and Lung Involvement in Systemic Scleroderma. Alain Meyer[1], Bernard Geny[2], Emmanuel Chatelus[3], Olivier Rouyer[2], Arnaud Theulin[4], Christelle Sordet[4], Rose-Marie Javier[4], Jean Sibilia[5] and Jacques-Eric Gottenberg[6]. [1]Hautepierre Strasbourg university, Strasbourg, France, [2]Medicine faculty, Strasbourg university, Strasbourg, France, [3]Hopital Hautepierre, Strasbourg, France, [4]Hautepierre Strasbourg Hospital University, Strasbourg, France, [5]CHU Hautepierre, Strasbourg, France, [6]Strasbourg University Hospital, Strasbourg, France

Background/Purpose: Both rheumatoid arthritis (RA) and systemic scleroderma (SSc) patients have impaired brachial artery endothelial flow mediated dilatation (FMD) as compared with controls. FMD independently predicts adverse cardiovascular events in different populations and in SSc, it correlates with nailfold microvascular impairment. We compared reactive hyperhemia index (RHI), known to be related to FMD, in inflammatory arthritides (IA) and SSc and searched for correlations with cutaneous, articular, cardiac and pulmonary disease activity in these two groups.

Methods: RHI taken at the estimated maximal vasodilatation (1 min 30 s after release of occlusion) using digital pulse amplitude tonometry was performed on 21 patients with SSc, 14 patients with IR and 15 healthy subjects. In IR and SSc patients, DAS 28, Rodnan score, cardiac echography, spirometry, DLCO and 6 minute walk test were also performed.

The Mann-Withney U test was used to compare RHI values between the 3 groups. The Spearman test was performed to assess correlation between RHI value and the others measured parameters.

Results: *Characteristics of the 3 groups:* Mean age of SSc was 57 years (28–75), sex ratio (SR) was 5/1 and mean disease duration was 4.5 years (0–22). 11 patients had limited form and 7 had diffuse form. The mean Rodnan score in 13 of 18 SSc patients was 10.2 (4–28). IA patients had a mean age of 60 years (38–73) and SR was 6/1. 11 patients had RA, 1 spondylarthropathy, one antisynthetase syndrome and one myositis with SRP antibody. Mean IR duration was 16 years (0–31). Mean DAS 28 in 11 of 14 IR patients was 4.45 (2.03–6.66) and 8 patients were treated with biologic treatments. Controls were 57 years old (53–64) and SR was 6/1. Patients mean weight was comparable: 67 kg (45–106), 67 kg (54–79) and 64 kg (54–91) in SSc, PR and controls respectively. Mean blood pressure was also similar (SSc: 127/73mmHg, PR: 128/76mmHg and controls: 130/75mmHg in SSc). One IR patient suffered of diabetes mellitus and had history of heart infarct.



Results: Median RHI was significantly lower in SSc patients (median 1.45, range 1.00–3.18) compared with IA patients (median 2.01, range 1.35–3.02) ($p=0.03$) and was significantly lower in both SSc and IA patients compared with controls (median 2.60, range 1.40–3.05) ($p=0.001$ and $p=0.049$ respectively). In SSc patient but not in IA patients, RHI value significantly correlated with echocardiograhic PAPs (r:−0.75; $p=0.037$), DLCO (r:0.53; $p=0.017$), total pulmonary capacity (r:0.46; $p=0.032$), functional and maximal vital capacity (r:0.48; $p=0.032$ and r: 0.48; $p=0.033$ respectively).

Conclusion: RHI, an easy and non invasive test, is associated with macroangiopathy and lung involvement in SSc. Further studies are necessary to determine whether RHI may represent disease activity and therapeutic response marker.

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Discovery 2011
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Tofacitinib (CP-690,550), An Oral Janus Kinase Inhibitor, in Combination with Methotrexate, in Patients with Active Rheumatoid Arthritis with An Inadequate Response to Tumor Necrosis Factor-Inhibitors: A 6-Month Phase 3 Study. Gerd-Rüdiger Burmester[1], R. Blanco[2], C. Charles-Schoeman[3], J. Wollenhaupt[4], C A. F. Zerbini[5], B. Benda[6], D. Gruben[7], G. Wallenstein[7], S. Krishnaswami[7], S. H. Zwillich[7], T. Koncz[8], J. D. Bradley[7], C. A. Mebus[7] and the ORAL Step investigators[9]. [1]Charité-University Medicine Berlin, Berlin, Germany, [2]Hospital Universitario Marques De Valdecilla, Santander, Spain, [3]University of California, Los Angeles, CA, [4]Schön Klinik, Hamburg, Germany, [5]Centro Paulista de Investigação Clinica, Sao Paulo, Brazil, [6]Pfizer Inc., Collegeville, PA, [7]Pfizer Inc., Groton, CT, [8]Pfizer Inc., New York, NY, [9]Groton

Background/Purpose: Tofacitinib (CP-690,550) is a novel, oral Janus kinase inhibitor investigated as a targeted immunomodulator for rheumatoid arthritis (RA). This study was designed to compare efficacy and safety of tofacitinib vs placebo (PBO) in pts with active RA with inadequate response to tumor necrosis factor (TNF)-inhibitors.

Methods: In this 6-month (Mo) study (NCT00960440), pts with inadequate response or lack of tolerance to ≥1 TNF inhibitor and on concomitant treatment with a stable (>6 weeks) dose of methotrexate (MTX; 7.5–25 mg/week) were randomized 2:2:1:1 to one of four sequences: tofacitinib 5 mg twice daily (BID); tofacitinib 10 mg BID; PBO advanced to 5 mg BID; PBO advanced to 10 mg BID (at Mo 3 all PBO patients were advanced to tofacitinib 5 or 10 mg according to randomization at baseline; for analyses PBO sequences were combined into one group). Primary endpoints included ACR20 responder rate, change from baseline in HAQ-DI, and rate of pts achieving a DAS28-4(ESR) <2.6, all at Mo 3.

Results: 399 pts were randomized and treated: 5 mg BID (n=133); 10 mg BID (n=134); PBO to 5 mg (n=66); PBO to 10 mg (n=66). Mean baseline values were comparable across treatment sequences: age, 54.3–55.4 years; disease duration, 11.3–13 years; HAQ-DI, 1.50–1.66; DAS28-4(ESR), 6.29–6.64; rheumatoid factor (RF) positive, 60.6–70.8%; anti-CCP positive, 68.5–77.8%; ≥2 prior anti-TNFs, 32.1–36.6%. Both doses of tofacitinib were statistically superior to PBO for all primary efficacy endpoints at Mo 3 and were maintained to Mo 6 (end of study) (Table). Onset of efficacy as measured by significant ACR20 responses vs PBO was seen by Week 2. Key safety endpoints are summarized in the table. Most AEs were mild; most frequently reported were infections and infestations. There was 1 death due to pulmonary emboli in the 10 mg BID dose group. No serious infectious events were reported in Mo 0–3, and 2 (5 mg BID), 2 (10 mg BID), and 1 (PBO to 5 mg) were reported in Mo 3–6. There were no opportunistic infections. Decreases in neutrophils, increases in LDL and HDL, and small increases in serum creatinine were seen with tofacitinib.

Table. Efficacy and safety endpoints

	Tofacitinib 5 mg BID (n=133)	Tofacitinib 10 mg BID (n=134)	PBO (n=132)	PBO to tofacitinib 5 mg BID (n=66)	PBO to tofacitinib 10 mg BID (n=66)
Efficacy					
ACR20[F] (%) [Mo 3[a]]	41.7*	48.1***	24.4	NA	NA
ACR20[F] (%) [Mo 6]	51.5***	54.9***	NA	45.5***	40.0***
ACR50[F] (%) [Mo 3]	26.5***	27.8***	8.4	NA	NA
ACR50[F] (%) [Mo 6]	37.1***	30.1***	NA	28.79***	20.00***
ACR70[F] (%) [Mo 3]	13.6***	10.5***	1.5	NA	NA
ACR70[F] (%) [Mo 6]	15.9***	15.8***	NA	10.6*	9.2*
Mean change HAQ-DI[§] [Mo 3[a]]	-0.43***	-0.46***	-0.18	NA	NA
Mean change HAQ-DI[§] [Mo 6]	-0.51***	-0.50***	NA	-0.54***	-0.38***
DAS28-4(ESR) <2.6[F] (%) [Mo 3[a]]	6.7*	11.2*	1.7	NA	NA
DAS28-4(ESR) <2.6[F] (%) [Mo 6]	10.7*	15.8*	NA	11.1*	3.3
Mean change DAS28-4(ESR) [Mo 3]	-1.9***	-2.1***	-0.9	NA	NA
Mean change DAS28-4(ESR) [Mo 6]	-2.4*	-2.7***	NA	-2.3*	-2.1
Safety, n (%)					
AEs [Mo 0-3]	71 (53.4)	76 (56.7)	75 (56.8)	NA	NA
AEs [Mo 3-6]	57 (42.9)	58 (43.3)	NA	24 (36.4)	28 (42.4)
SAEs [Mo 0-3]	2 (1.5)	2 (1.5)	6 (4.5)	NA	NA
SAEs [Mo 3-6]	5 (3.8)	6 (4.5)	NA	3 (4.5)	2 (3.0)
D/C (AEs) [Mo 0-6]	12 (9.0)	13 (9.7)	7 (5.3)	1 (1.5)	2 (3.0)

Primary endpoints employed a step-down procedure employed to protect Type I error. No protection employed for secondary comparisons
*p< 0.05; ***p< 0.0001 vs PBO (Mo 3) / vs baseline (Mo 6)
[F]Primary endpoints; [a]non-responder imputation; [§]mixed-effect longitudinal linear model
D/C, discontinuation; NA, not available; SAE, serious AE

Conclusion: This was the first Phase 3 study of tofacitinib in combination with MTX in pts with active RA with an inadequate response to TNF-inhibitors. In this treatment refractory patient population, tofacitinib demonstrated rapid, significant, and clinically meaningful improvements in the signs and symptoms of RA, physical function, and disease activity over 6 mo of study treatment. No new safety signals were detected.

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Reduced Cardiovascular Risk with Use of Methotrexate and Tumor Necrosis Factor-α Inhibitors in Patients with Rheumatoid Arthritis. Rasa Bozaite-Gluosniene[1], Xiaoqin Tang[2], H. Lester Kirchner[2], Jana L. Antohe[3], Stephanie J. Morris[4], Mary Chester Wasko[5] and Androniki Bili[1]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Center for Health Research, Danville, PA, [3]Geisinger Health System, Danville, PA, [4]Rose Tree Medical Associates---Riddle Memorial Hos, Danville, PA, [5]West Penn Allegheny Health System, Pittsburgh, PA

Background/Purpose: Methotrexate (MTX) and tumor necrosis factor (TNF)-α inhibitors have been associated with a reduction of incident coronary artery disease (CAD) in rheumatoid arthritis (RA) patients. Here we examine the independent contribution of each medication on risk of CAD.

Methods: Using an inception cohort of 1829 RA patients without preexisting CAD, diagnosed between 1/1/2001–3/31/2008 were identified. Patients were classified as users (n=1119) or nonusers (n=710) of MTX and users (n=588) or nonusers (n=1241) of TNF-α inhibitors (etanercept, adalimumab, infliximab). Medication exposure was analyzed in time-varying fashion using medication start and stop dates, allowing patient

drug exposure status to change over time. Outcome was incident CAD (ICD-9 410. – 419.99 or cardiac revascularization procedure). Cox proportional hazard regression models were used to estimate the associations on developing incident CAD after adjusting for age, gender, hypertension, hyperlipidemia, diabetes, rheumatoid factor, BMI, blood pressure, LDL, ESR, hydroxychloroquine, MTX, corticosteroid and NSAID use. Exposure to MTX, TNF-α inhibitors and all other variables were treated as time-variant in models.

Results: In MTX nonusers and users groups, incidence rate (IR) for CAD was 37.5 vs.17.6 events per 1000 person-years (p-y), respectively. Among MTX users, the hazard for incident CAD was 0.54 (95% confidence interval (CI) 0.37, 0.77; p=0.001) compared to nonusers; among those taking MTX for more than 24 months the hazard was 0.33 (95% CI 0.22, 0.50; p<0.001). In TNF-α inhibitors nonusers and users groups, IR for CAD was 32.1 vs.11.8 events per 1000 p-y, respectively. Among TNF-α inhibitor users the hazard for incident CAD was 0.54 (CI 0.30, 0.95; p=0.03) compared to nonusers; among those taking TNF-α inhibitor for more than 24 months hazard was 0.24 (95% CI 0.12, 0.51; p<0.001).

Conclusion: In this inception RA cohort, the use of MTX or TNF-α inhibitors was independently associated with a 46% reduction in incident CAD compared to nonusers; for MTX or TNF-α inhibitor use for more than 24 months the risk was further decreased by 67% and 76% respectively, raising the possibility that TNF-α inhibitor use offers additional cardioprotective effect in RA patients.

Table. Characteristics of RA patients by methotrexate and TNF-α inhibitors use

		Methotrexate use*			TNF-α inhibitors use*		
	Overall (n = 1829)	Ever (n=1119)	Never (n=710)	p**	Ever (n=588)	Never (n=1241)	p**
N (%)							
Male	526 (28.8%)	297 (26.5%)	229 (32.3%)	.009	170 (28.9%)	356 (28.7%)	.921
White	1732 (94.7%)	1053 (94.1%)	679 (95.6%)	.154	552 (93.9%)	1180 (95.1%)	.282
RF positivity	1013 (77.3%)	630 (77.1%)	383 (77.7%)	.809	342 (80.1%)	671 (76.0%)	.096
Medication use (ever):							
TNF-α inhibitors	588 (32.2%)	447 (40%)	141 (19.9%)	<.0001	na	na	na
MTX	1119	na	na	na	447 (76.1%)	672 (54.2%)	<.0001
HCQ	684 (37.4%)	381 (34.1%)	303 (42.7%)	.0002	230 (39.1%)	454 (36.6%)	.300
Corticosteroids	1547 (84.6%)	1006 (89.9%)	541 (76.2%)	<.0001	546 (92.9%)	1001 (80.1%)	<.0001
NSAIDs	1302 (71.2%)	807 (72.1%)	495 (69.7%)	.270	445 (75.7%)	857 (69.1%)	.004
Statins	544 (29.7%)	332 (29.7%)	212 (29.9%)	.931	169 (28.8%)	375 (30.2%)	.519
Hypertension	847 (46.3%)	521 (46.6%)	326 (45.9%)	.788	262 (44.6%)	585 (47.1%)	.301
Hyperlipidemia	397 (21.7%)	240 (21.5%)	157 (22.1%)	.737	117 (19.9%)	280 (22.5%)	.197
Diabetes	435 (23.8%)	252 (22.5%)	183 (25.8%)	.111	115 (19.6%)	320 (25.8%)	.004
Median (IQR)							
Age at RA diagnosis	58 (47–69)	56 (46–67)	61.5 (50–72)	<.0001	52 (43–60)	61 (51–71)	<.0001
BMI	29.2 (25.3–34.1)	29.5 (25.6–34.9)	28.7 (24.6–32.7)	.0012	30.2 (26.0–35.8)	28.7 (25.0–32.9)	<.0001
Sedimentation rate (max)	33 (18–55)	34 (20–55)	31 (15–60)	.065	35 (21–62)	32 (17–53)	.004
LDL	101 (80, 123)	101 (81–122)	126 (120, 132)	.946	102 (80.8, 122.0)	100 (79, 124)	.833
Systolic BP	72 (69, 78)	72 (70–78)	72 (68–78)	.141	72 (70, 79.5)	71 (68, 78)	<.001
Diastolic BP	126 (120, 133)	126 (120, 132)	126.5 (120, 135)	.083	124 (119, 132)	126 (120, 134)	.020

* Ever Methotrexate or TNF usage prior to CAD diagnosis or censor date.
** P-values obtained either from Chi-square tests (frequencies) or Wilcoxon's test (medians).

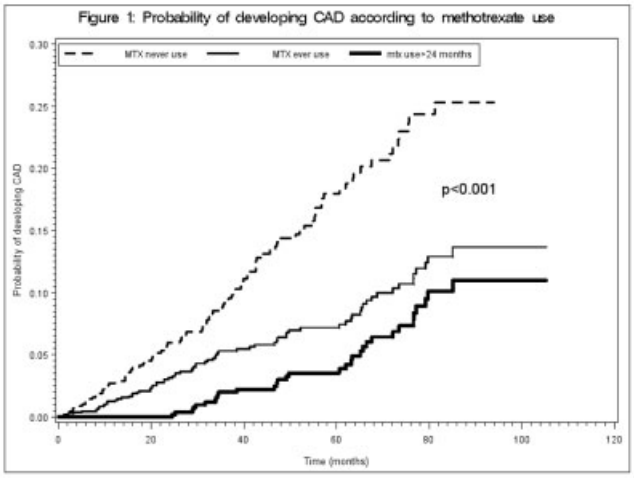

Figure 1.

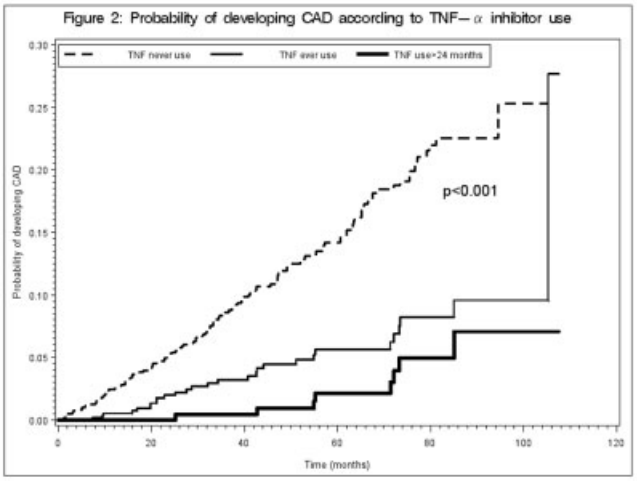

Figure 2.

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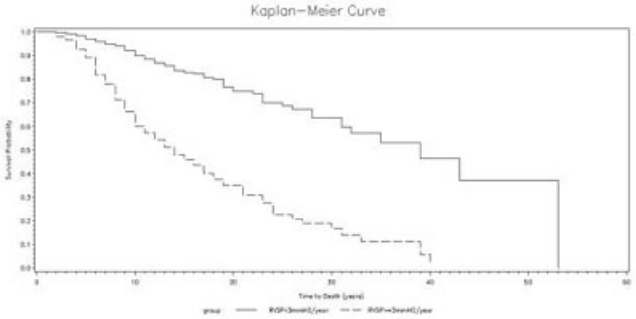
The Value of Periodic Echocardiography Screening to Detect Pulmonary Hypertension and Predict Mortality In Scleroderma. Ami A. Shah, Shang-En Chung, Fredrick M. Wigley and Laura K. Hummers. Johns Hopkins University, Baltimore, MD

Background/Purpose: Pulmonary hypertension (PH) is a leading cause of morbidity and mortality among patients with scleroderma, and early detection of disease may play a critical role in preventing or delaying disease progression. Although data suggest that right ventricular systolic pressure (RVSP) on echocardiography (echo) has a moderate positive correlation with mean pulmonary artery pressure on right heart catheterization (RHC), it is commonly debated whether echo has additional value beyond routine pulmonary function tests (PFTs) and whether serial, annual echo predicts development of PH.

Methods: Subjects in the Johns Hopkins Scleroderma Center database who had at least 3 echos over at least 1 year and had data on the date of SSc onset as defined by the first non-Raynaud's phenomenon symptom were included. The rate of change in RVSP per year was determined by regressing RVSP on years from first non-Raynaud's symptom for each subject. Survival analysis was performed to assess the association between PH and change in RVSP, adjusted for baseline RVSP, FVC%/DLCO% ever $\geq$ 1.4, age, race, gender, scleroderma subtype and smoking status. Similar analysis was performed with mortality as the outcome, and this model included RHC-confirmed PH as an additional explanatory variable. Survival analysis was also performed to identify the minimum rate of change in RVSP that associates with increased risk of death.

Results: 681 scleroderma patients with 3516 echos met inclusion criteria. 140 (20.6%) had RHC-confirmed PH, and 181 (26.7%) were deceased after a median survival of 11 years (mean 13.1; SD 8.32). The mean rate of change in RVSP was 1.82 mmHg/yr (SD 6.45). The hazard ratio for development of PH was 1.07 (95% CI 1.05, 1.08; p<0.0001) per 1mmHg increase in RVSP/yr after adjustment for the other covariates in the model. The hazard ratio for death was 1.06 (95% CI 1.04, 1.08; p<0.0001) per 1mmHg increase in RVSP/yr after adjusting for PH and the other covariates in the model. Relative to patients whose RVSP was stable over time (RVSP change $<$ 1mmHg/yr), the hazard ratio for development of PH was 1.52 (95% CI 0.80, 2.89), 3.22 (95% CI 1.70, 6.11), 4.24 (95% CI 2.14, 8.41), and 6.54 (95% CI 4.10, 10.4) for subjects whose RVSP increased at rates of 1–1.99, 2–2.99, 3–3.99, and 4+ mmHg/yr. Compared to the same reference group, the hazard ratio for death was 0.52 (95% CI 0.27, 0.99), 1.26 (95% CI 0.68, 2.32), 2.00 (95% CI 1.04, 3.84), and 4.27 (95% CI 2.81, 6.48) for subjects whose RVSP increased at rates of 1–1.99, 2–2.99, 3–3.99, and 4+ mmHg/yr. Kaplan-Meier survival curves demonstrate that patients with an increase in RVSP $\geq$ 3 mmHg/yr have a greater mortality risk than subjects with a change in RVSP $<$ 3 mmHg/yr.

Conclusion: Serial echo is an important screening tool for PH and adds additional information beyond that available from routine PFTs. An increase in RVSP $\geq$ 3 mmHg/yr is strongly associated with increased mortality risk.



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Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis. Carol Wallace[1], Edward H. Giannini[2], Steven J. Spalding[3], Philip Hashkes[4], Kathleen M. O'Neil[5], Andrew S. Zeft[6], Ilona S. Szer[7], Sarah Ringold[8], Hermine Brunner[9], Laura E. Schanberg[10], Robert P. Sundel[11], Diana Milojevic[12], Marilynn G. Punaro[13], Peter Chira[14], Beth S. Gottlieb[15], Gloria Higgins[16], Norman T. Ilowite[17], Yukiko Kimura[18], Anne Johnson[19], Stephanie Hamilton[1], Bin Huang[9] and Daniel J. Lovell[9]. [1]Childrens Hosp & Regional Med, Seattle, WA, [2]PRCSG-Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Cleveland Clinic, Cleveland, OH, [4]Shaare Zedek Medical Center, Tel Aviv, Israel, [5]Okla Univ Health Science Ctr, Oklahoma City, OK, [6]University of Utah, Salt Lake City, UT, [7]Rady Childrens Hosp San Diego, San Diego, CA, [8]Children's Hosp Regional Med, Seattle, WA, [9]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [10]Duke University Medical Center, Durham, NC, [11]Childrens Hosp Medical Center, Boston, MA, [12]UCSF, San Francisco, CA, [13]Texas Scottish Rite Hospital, Dallas, TX, [14]Stanford University, Palo Alto, CA, [15]Schneider Children's Hospital, New Hyde Park, NY, [16]PRCSG, Columbus, OH, [17]Children's Hospital Montefiore, Bronx, NY, [18]Hackensack Univ Medical Ctr, Hackensack, NJ, [19]Cincinnati Child Hosp Med Ctr, Cincinnati, OH

Background/Purpose: Early aggressive therapy produces superior outcomes in adults with RA, but evidence for a similar benefit has not been demonstrated in children with JIA.

Methods: The objectives of this study (abbrev TREAT) were to determine if aggressive treatment initiated early in the course of RF (+) or (−) polyarticular JIA (poly JIA) can induce *clinical inactive disease* (CID) within 6 mos (primary endpoint) and *clinical remission on medication* (CRM: CID for 6 continuous mos on medication; exploratory endpoint) within 1 yr of starting therapy. Other endpoints were changes in the ACR pediatric core variables.

TREAT was designed as a multi-center, prospective, double blind, randomized, placebo controlled trial in children aged 2–16 yrs with onset of poly JIA <12 mos in duration. Subjects were randomized 1:1 into 1 of 2 aggressive treatment arms: (Arm 1) MTX 0.5 mg/kg/wk SQ (40 mg max), plus etanercept (ETN) 0.8 mg/kg/wk (50 mg max), plus prednisolone (pred) 0.5 mg/kg/d (60 mg max) tapered to 0 by 17 wks or; (Arm 2) MTX (same dose as Arm 1) plus ETN placebo, plus pred placebo, then followed on protocol for up to 12 mos. After 4 mos on therapy subjects who failed to achieve at least an ACR Pediatric 70 received open label ETN, MTX, and pred in the same doses as Arm 1. At 6 mos, subjects who did not achieve CID received open label medication. Efficacy analyses focused on the intent-to-treat approach. Safety data were recorded for all subjects.

Results: 15 centers enrolled 85 subjects (64 [75%] female; median age 11.1 yrs; disease duration 4.1 mos). 69% were ANA+ and 36% were RF(+). Median values at baseline of ACR pediatric core variables were: physician's global assessment of disease activity 7.5; parent global assessment of well-being 5.5; ESR 33; number of joints with arthritis 19; number of joints with limited motion 11.5, C-HAQ 1.1.

At 4 mos, 30 of 42 (71%) subjects in Arm 1 and 19 of 43 (44%) in Arm 2 achieved an ACR Pediatric 70 ($X^2 = 6.5$; p=0.011). At 6 mos, 17 of 42 (40%) of subjects in Arm 1 achieved CID, compared to 10 of 43 (23%) in Arm 2 ($X^2 = 2.91$; $p = 0.088$). Logistic regression showed the only variable predictive of CID at 6 mos was disease duration at baseline. The odds of CID increased by 1.324 times for each month earlier treatment was started after onset of symptoms (p=0.011). Although all 6 ACR pediatric core variables showed highly significant improvement by 6 mos in both Arms (all p values <0.001), 5 showed statistically greater improvement in Arm 1 vs. Arm 2. By 12 mos, 12 (14%) subjects achieved CRM; 9 (21%) had remained in Arm 1, and 3 (6%) had remained in Arm 2 throughout the study (p=0.053).

There were no significant inter-arm differences in the incidence of Grade 3 or higher adverse events, including infections requiring systemic therapy. There were 3 SAEs: pneumonia (Arm 1), psychosis (open label), and bacteremia with septic arthritis (open label). All resolved without sequelae.

Conclusion: Although this trial did not reach its primary endpoint, early aggressive therapy in this cohort of children with severe JIA and a high rate of RF positivity resulted in substantial proportions of subjects achieving an ACR Pediatric 70 at 4 mos, CID at 6 mos, and CRM within 12 mos of treatment initiation.

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The Intensive Diet and Exercise for Arthritis Trial: 18-Month Clinical Outcomes. Stephen P. Messier[1], Barbara J. Nicklas[2], Claudine Legault[3], Shannon Mihalko[1], Gary D. Miller[1], Paul DeVita[4], Mary Lyles[3], David J. Hunter[5], Felix Eckstein[6], Jeff D. Williamson[3], J. Jeffery Carr[3] and Richard F. Loeser[1]. [1]Wake Forest University, Winston-Salem, NC, [2]Winston-Salem, NC, [3]Wake Forest University School of Medicine, Winston-Salem, NC, [4]East Carolina University, Greenville, NC, [5]Royal North Shore Hospital, Sydney, Australia, [6]Paracelsus Medical University, Salzburg, Austria

Background/Purpose: Obesity is the most prevalent modifiable risk factor, and dietary induced weight loss potentially the best non-pharmacologic treatment for symptomatic knee osteoarthritis (OA) symptoms. We report the clinical outcomes of a long-term study designed to test the hypothesis that intensive weight loss, either with or without exercise, will reduce pain and improve function compared to an exercise only control group in older, overweight and obese adults with symptomatic knee OA.

Methods: The Intensive Diet and Exercise for Arthritis trial (IDEA) was a prospective, single-blind, randomized controlled trial that enrolled 454 overweight and obese (BMI = 27–42 kg/m^2) older (age ≥ 55 yrs) adults with pain and radiographic evidence of tibiofemoral OA (KL = 2–3). Participants were randomized to one of three 18-month interventions: intensive dietary restriction-only (D); intensive dietary restriction-plus-exercise (D+E); or exercise-only control (E). The weight loss goal for the two diet groups was ≥ 10% of baseline body weight, and the exercise intervention consisted of low to moderate intensity walking and resistance training 3 d/wk for 1 hr/d. We used an intention-to-treat analysis to compare changes between groups at 18 month follow-up (FU18) after adjusting for gender, baseline BMI, and baseline values of the dependent variable using repeated measures ANCOVA.

Results: Mean (SD) baseline descriptive characterisitics of the cohort included: age, 65.6 (6.2) yrs.; BMI, 33.6 (3.7) kg/m^2; %female, 72; %white, 81. Bilateral knee OA was evident in 85% of the participants. A total of 399 (88%) participants completed the study (returned for FU18 testing). Mean weight loss was: D+E, 10.6 kg (11.4%); D, 8.9 kg (9.5%); E, 2.0 kg (2.2%). WOMAC pain (baseline, FU 18, %change) was significantly less ($p < 0.0004$) at FU18 in the D+E group (6.7,3.3; 51%) compared to the D (6.6, 4.8; 27%) and E (6.1, 4.4; 29%) groups. Similarly, WOMAC function was significantly ($p = 0.003$) better in the D+E group (24.6,13.0; 47%) relative to the D (24.8,17.3; 30%) and E (23.1,17.5; 24%) groups. Walking speed (m/s), our measure of mobility, was significantly ($p = 0.004$) faster in the D+E group (1.20, 1.34; 12%) than in the D (1.18, 1.30; 10%) and E (1.23, 1.30; 6%) groups. There was no significant difference between the groups on the SF-36 physical or mental health scales.

Conclusion: The IDEA trial shows that intensive weight loss with excellent long-term retention is possible in this population and, when combined with low to moderate intensity exercise, results in an approximate 50% reduction in pain accompanied by significant improvements in function and mobility. These data provide evidence that the best recommendation for long-term symptom reduction in overweight and obese persons with knee OA is intensive weight loss combined with low to moderate intensity exercise.

ACR Concurrent Abstract Session
Antiphospholipid Syndrome
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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Involvement of TLR7 and TLR9 in the Production of Antiphospholipid Antibodies. Renan Aguilar-Valenzuela[1], Kevin Nickerson[2], Zurina Romay-Penabad[1], Mark J. Shlomchik[2], Gracie Vargas[1], Tuya Shilagard[1] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Yale University School of Medicine, New Haven, CT

Background/Purpose: Molecular mimicry and genetic factors have been shown to be involved in the production of antiphospholipid antibodies (aPL)

but a role of innate immunity has not been studied. Our aim was to elucidate the involvement of TLR7, TLR9 and molecular mimicry in aPL production by monitoring the production of pathogenic aPL in lupus mice ($MRL^{lpr/lpr}$) deficient in TLR7 and TLR9 and in autoimmune prone mice (PL/J) immunized with cytomegalovirus (CMV)-derived peptides (TIFI and VITT) in the presence of TLR7 and TLR9 agonists.

Methods: APL (anticardiolipin (aCL) and anti-β_2Glycoprotein I (aβ_2GPI) titers were determined in the sera of $MRL^{lpr/lpr}$ and their congenic *tlr9* and *tlr7* knockout mice (16 weeks old). Additionally, PL/J autoimmune-prone mice were challenged with 150 μg of CMV peptides (TIFI and VITT) in the presence or absence of TLR9 (ODN1585) and TLR7 (CL264) agonists. As negative controls two mouse groups were immunized with Egg Albumin (OVA) (150μg) in the presence or absence of TLR9 agonist (50μg). The aPL titers were followed for 9 weeks using solid phase ELISA. Levels of IL6, IL2, IL10, TNF-α and IL2 were measured using Multiplex Bioassay (Millipore™) and IFN-α was detected by ELISA. At week nine, aPL thrombogenic effects were evaluated using a model of induced thrombosis. Tissue factor (TF) expression in peritoneal macrophages was measured using specific immunostaining and dual photon laser microscopy and nanocrystal bioconjugates.

Results: $MRL^{lpr/lpr}$ mice had significantly higher titers of aCL and aβ_2GPI antibodies when compared to the TLR9 and TLR7 double knockouts ($p<0.05$) and $MRL^{lpr/lpr}$ tlr7 single knockouts had lower IgG or IgM aPL titers compared to $MRL^{lpr/lpr}$. The titers of aPL (aCL and aβ_2GPI) antibodies induced with TIFI and VITT were significantly higher in mice immunized with the TLR9 (ODN1585) or with TLR7 (CL264) agonists at the time of the surgical procedures to examine thrombus formation (Table). No significant titers of aPL were seen in mice receiving only TIFI + VITT. Importantly, increased aPL production correlated with larger thrombi in mice receiving TLR7 and TLR9 agonists, compared with those that did not ($p<0.05$). Increased TF expression was seen in mice treated with CMV peptides and the TLR9 agonist ($p<0.05$).

Treatment	aCL IgG (O.D.)	aCL IgM (O.D.)	aβ_2GPI IgG (O.D.)	aβ_2GPI IgM (O.D.)	Thrombus size (μm^2)
OVA	0.14 (±0.03)	0.2 (±0.05)	0.18 (±0.0007)	0.18 (±0.06)	683 (±88)
OVA+ODN1585	0.2 (±0)	0.3 (±0.17)	0.11 (±0.1)	0.11 (±0.0.6)	674 (±52)
TIFI+VITT	0.13 (±0.047)	0.22 (±0.08)	0.27 (±0.9)	0.27 (±0.04)	605 (±13)
VITT+VITT+ODN1585	0.22 (±0.065)	0.17 (±0.02)	0.79(±0.1)	0.79 (±0.13)	1051.5 (±123)
TIFI+VITT+CL264	0.29 (±0.08)	0.23 (±0.05)	0.91 (±0.28)	0.91 (±0.12)	1280.17 (±166.87)
TIFI+VITT+ ODN1585+CL264	0.3 (±0.06)	0.16 (±0.018)	1.7 (±0.85)	1.7 (±1.2)	1126.56 (±318.1)

Conclusion: Production of pathogenic aPL involves TLR7 in the $MRL^{lpr/lpr}$ mice. In the TIFI/VITT-challenged PL/J mice, the activation of TLR9 and TLR7 lead to the production of pathogenic aPL. Altogether, our data support the involvement of TLR7 and TLR9 in tolerance loss to β_2GPI and raises the possibility of using TLR9 and TLR7 inhibitors to prevent aPL production.

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Endothelial Cell Injury and Activation Promote the Binding of Anti-Phospholipid Antibodies and Thrombus Formation. Patrick Laplante[1], Marc-Antoine Gillis[2], Rebecca Subang[1], David Salem[1], Jerrold S. Levine[3], Yahye Merhi[2] and Joyce Rauch[1]. [1]Research Institute of the McGill University Health Centre, Montreal, QC, [2]Montreal Heart Institute, Montreal, QC, [3]University of Illinois at Chicago, Chicago, IL

Background/Purpose: Anti-phospholipid antibodies (aPL) are found in 20–30% of patients with systemic lupus erythematosus and in all patients with anti-phospholipid syndrome (APS). APS is classified clinically by the combined presence of aPL and a clinical event (e.g., thrombosis and/or pregnancy loss). To date, the mechanisms responsible for both the initiation of aPL production and the development of clinical events are unclear. We propose that aPL alone are insufficient to cause thrombotic events in APS, and that a concomitant trigger of innate immunity (e.g., toll-like receptor [TLR] activation) is required.

Methods: To address this hypothesis, we studied the interactive effects of aPL and TLR ligand by two complementary approaches: (1) *in vitro* endothelial cell (ECs) studies, and (2) an *in vivo* model of thrombosis. aPL were produced by immunizing rabbits with murine β2-glycoprotein I (β2GPI). *In vitro* studies were performed on human umbilical vein (HUVECs) and murine (EOMA cell line) ECs. *In vivo* effects of aPL were evaluated using a ferric chloride ($FeCl_3$)-induced murine model of carotid artery injury; localized induction of thrombosis in this model permits both quantifiable monitoring of thrombus formation and use of the uninjured contralateral carotid artery as a control. Purified rabbit aPL (n=15) or control IgG (n=16) were injected intravenously into naive C57BL/6 mice 48 hours prior to $FeCl_3$-induced carotid artery injury.

Results: *In vitro*, aPL were reactive with murine and human β2GPI, and cardiolipin, and showed dose-dependent binding to HUVECs and EOMA cells by enzyme-linked immunoassay. Stimulation of HUVECs and EOMA cells with TLR4 ligand (lipopolysaccharide [LPS]) resulted in increased expression of E-selectin and von Willebrand factor (vWF), as well as increased binding of aPL to ECs. LPS also induced cultured ECs to produce pro-inflammatory cytokines such as IL-8. *In vivo*, thrombus formation was significantly faster in aPL-treated mice than in control IgG-treated mice ($p<0.05$). For example, aPL-treated mice achieved 50% occlusion of carotid arteries more rapidly than control IgG-treated mice (4.2+/−0.39 minutes versus 7.2+/−0.72 minutes, $p<0.001$), demonstrating that aPL promote thrombus generation in the context of endothelial injury. Furthermore, uninjured contralateral carotid arteries from mice treated with aPL, but not control IgG, showed increased expression of P-selectin and vWF by immunohistochemical staining.

Conclusion: aPL reactive with murine b2GPI bind to ECs *in vitro* and promote thrombus formation in an *in vivo* model of carotid artery injury. TLR4 stimulation of ECs *in vitro* results in enhanced aPL binding, increased E-selectin and vWF expression, and pro-inflammatory cytokine secretion. *In vivo*, aPL promote thrombus formation in injured arteries, and EC activation in uninjured arteries. These data suggest that aPL and TLR4 activation interact to promote thrombogenesis, and may explain why only certain individuals with aPL develop thrombotic events.

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Mitochondrial Dysfunction in Monocytes From Antiphospholipid Syndrome Patients: Implications in the Pathogenesis of the Disease and Effects of Coenzyme Q Treatment. Chary Lopez-Pedrera[1], Carlos Perez-Sanchez[1], Patricia Ruiz-Limon[1], M[a] Angeles Aguirre[1], Rosario M[a] Carretero[1], Nuria Barbarroja[1], Antonio Rodriguez-Ariza[1], Eduardo Collantes-Estevez[1], Jose Antonio Gonzalez-Reyes[2], Jose Manuel Villalba[2], Francisco Velasco[1], Munther A. Khamashta[3], Maria Laura Bertolaccini[3] and M[a] Jose Cuadrado[4]. [1]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [2]University of Cordoba, Cordoba, Spain, [3]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [4]The Rayne Institute, London, United Kingdom

Background/Purpose: Recent studies have evidenced that oxidative stress may play a role in the pathophysiology of APS. However it is still not clear whether oxidative stress is the cause or the effect of the prothrombotic/proinflamatory status of APS. Furthermore, the precise role of mitochondria in the redox imbalance reported in APS remains unknown. Aim: We undertook this study to investigate the role of mitochondrial dysfunction and oxidative stress in aPL-induced prothrombotic status in APS patients, and to test the effects of supplementing cells with coenzyme Q_{10} (CoQ_{10}), a well established mitochondrial cofactor and antioxidant.

Methods: We studied 25 patients and 25 healthy controls. Mitochondrial function in monocytes was analyzed by measuring mitochondrial membrane potential (MMP) with flow cytometry. Oxidative stress was determined by quantifying peroxide and peroxynitrite generation, intracellular glutathione, nitric oxide (NO), and N-Tyr in monocytes and plasma. Various parameters related to thrombosis and inflammation, as well as the intracellular pathways involved were also tested. Mitochondrial function was evaluated through *in vitro* studies in which purified monocytes were preincubated with CoQ_{10}, followed by stimulation with purified IgG from 7 APS patients (aPL-IgG). We also studied mitochondrial dynamics in monocytes treated with aPL-IgG in the presence or in the absence of CoQ_{10}, by measuring cellular levels of proteins controlling mitochondrial fission (Drp-1, Fis1, and Opa-1) or fusion (Mfn-1 and Mfn-2). Mitochondrial alterations were also studied by electron microscopy.

Results: CoQ_{10} decreased significantly the percentage of cells with altered MMP as well as the production of ROS and aPL-IgG-induced production of peroxides. CoQ_{10} treatment also affected significantly the aPL-IgG induced expression of TF, VEGF and Flt1, as well as the intracellular signalling pathways regulating their expression. Treatment of monocytes with aPL-IgG consistently upregulated proteins involved in mitochondrial fission, and these alterations were reversed by pre-treatment with CoQ_{10}. Monocytes treated with aPL-IgG contained rounded mitochondria, and figures evidencing mitochondrial fission were readily observed. Monocytes pretreated with CoQ_{10} contained elongated mitochondria with significantly improved ultrastructure.

Conclusion: The binding of aPL-IgG to monocytes membrane elicites a redox-signalling pathway in which mitochondrial activity is compromised, and dynamics is altered towards enhanced rates of mitochondrial fission. The induced mitochondrial dysfunction, which is prevented by CoQ_{10}, seems to

be directly involved in the aPL-induced monocyte activation. Supported by JA0246/2009, P08CVI04234 and PS09/01809.

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Effects of Fluvastatin on Pro-Inflammatory and Pro-Thrombotic Markers in Antiphospholipid Antibody (aPL)-Positive Patients: Preliminary Results from an Open-Label Prospective Pilot Study. Vijaya L. Murthy[1], Doruk Erkan[2], Praveen Jajoria[1], Rohan Willis[1], JoAnn Vega[2], Giuseppe Barilaro[1], Gurjot Basra[1], Elizabeth Hsu[1], Laura Aline Martinez-Martinez[1], Shraddha Jatwani[1], Elizabeth Papalardo[1], Emilio B. Gonzalez[1], Prashanth R. Sunkureddi[3] and Silvia S. Pierangeli[1]. [1]University of Texas Medical Branch, Galveston, TX, [2]Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, New York, NY, [3]The University of Texas Medical Branch, Nassau Bay, TX

Background/Purpose: Antiphospholipid antibodies (aPL) induce a pro-inflammatory and pro-thrombotic state by upregulating the production of various cytokines, chemokines, and tissue factor (TF). Fluvastatin reduces TF expression and decrease thrombogenic effects of aPL in vitro and in mice. The purpose of this prospective pilot study was to examine the effects of fluvastatin on pro-inflammatory and pro-thrombotic biomarkers in persistently aPL-positive patients.

Methods: Persistently aPL-positive patients received fluvastatin 40 mg daily for 3 months (m). At 3m, patients were instructed to stop fluvastatin and they were followed for another 3m. Persistent aPL positivity was defined as IgG/M aCL $\geq$ 40U, IgG/M aβ_2GPI $\geq$ 20U, and/or positive LA test on $\geq$2 occasions at least 12w apart. Selected exclusion criteria were pregnancy, statin use, prednisone >10 mg/day, and immunosuppressive use (except hydroxychloroquine) at the time of the screening. Serum samples were collected at baseline and monthly thereafter for 6m. IFNα2, IL1β, IL6, IL8, IP10, MCP1, TNFα, VEGF, and sCD40L levels were determined by the MILLIPLEXMAP human cytokine/chemokine assay (Millipore, Billerica, MA). Plasma samples were used to detect soluble tissue factor (sTF) using a chromogenic assay. CRP was evaluated by a nephelometric assay. aCL, aβ_2GPI, soluble ICAM-1, VCAM-1, and E-selectin were evaluated by ELISA. For the purpose of this preliminary analysis of baseline, 1m, 2m, and 3m samples, we: a) compared baseline biomarker levels of patients with serum samples from 30 healthy age/sex-matched controls (Kruskal-Wallis test); and b) analyzed the change in biomarker levels of patients between baseline and 1–3m samples (Spearman test).

Results: When we compared the baseline samples of 41 aPL-positive patients (74% female; mean age: 42 $\pm$ 25; Primary APS: 18; asymptomatic aPL positivity with no SLE:9; APS with SLE: 7; and asymptomatic aPL positivity with SLE:7) with controls, we found that the levels of IL6 (38 vs 0.7 pg/ml), VEGF (225 vs 114 pg/ml), IP10 (584 vs 107 pg/ml); sCD40L (2477 vs 24.7 pg/ml), INFα2 (213 vs 16 pg/ml), IL1β (4.7 vs 0.4 pg/ml), TNFα 30 vs 0.5 pg/ml), and sTF (134 vs 13 pg/ml) were significantly elevated, but not of MCP-1, IL8 or CRP. Based on the analysis of the available follow-up samples, fluvastatin significantly reduced IL6, IL1β, TNFα, sTF, sICAM-1, sVCAM, and sE-sel levels within 30–90 days of treatment (Table). There was no significant change in aCL or aβ_2GPI titers.

Biomarker	# of Patients with Biomarker Levels Above Cut-off Points @ Baseline	# of Patients with Decreased Biomarker Levels with Fluvastatin	% of Maximum Biomarker Level Reduction with Fluvastatin (+/− SD)	Mean Time (Days) to Maximum Biomarker Level Reduction with Fluvastatin
IL8	8/41 (20%)	3/8 (38%)	73.8 ± 31.0	70 ± 34
IL6	17/41 (42%)	14/17 (82%)*	72.9 ± 32.1	51 ± 24
VEGF	17/41 (42%)	6/17 (35%)	59.7 ± 23.4	30 ± 23
IP10	39/41 (95%)	8/39 (21%)	55.4 ± 23.9	45 ± 22
sCD40L	36/41 (88%)	6/36 (17%)	68.0 ± 21.0	30
INFα2	13/41 (32%)	6/13 (46%)	81.0 ± 25.6	30
IL1β	18/41 (44%)	11/18 (61%)*	70.3 ± 30.0	51 ± 28
TNFα	20/41 (49%)	10/20 (50%)*	53.3 ± 30.8	54 ± 28
sTF	39/41 (95%)	22/39 (56%)*	57.0 ± 29.9	56 ± 25
sICAM-1	18/41 (44%)	18/18 (100%)*	55.9 ± 35.9	68 ± 25
sVCAM-1	11/41 (27%)	11/11 (100%)*	49.9 ± 34.6	46 ± 32
E-selectin	11/41 (27%)	11/11 (100%)*	52.9 ± 26.1	33 ± 19

* $p<0.0001$, statistically significant reduction compared to baseline

Conclusion: Based on the preliminary analysis of our ongoing pilot study, fluvastatin 40 mg daily for 3 months significantly reduced the pro-inflammatory and prothrombotic biomarkers in persistently aPL-positive patients with or without SLE. These findings: a) underscore the importance of identifying aPL-related disease biomarkers; and b) provide further support for the potential beneficial effects of statins in aPL-positive patients justifying future controlled clinical studies.

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Rituximab in Antiphospholipid Syndrome (RITAPS)—A Pilot Open-Label Phase II Prospective Trial for Non-Criteria Manifestations of Antiphospholipid Antibodies (aPL). Doruk Erkan[1], JoAnn Vega[2], Glendalee Ramon[2], Elizabeth Kozora[3] and Michael D. Lockshin[2]. [1]Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, New York, NY, [2]Barbara Volcker Center for Women and Rheumatic Diseases: Hospital for Special Surgery, New York, NY, [3]National Jewish Health, Denver, CO

Background/Purpose: Few studies address the treatment of non-criteria aPL manifestations. Given that B cell inhibition can be effective in APS mouse models and rituximab can result in depletion of peripheral B cells, we designed the "RITAPS" trial. The primary objective of this pilot, open-label, Phase II study was to evaluate the safety of rituximab in 20 aPL-positive patients, as assessed by serious and non-serious adverse events (AE) (up to 12 months [m]). The secondary objectives were to evaluate the effect of rituximab on aPL profile (up to 12m) and non-criteria aPL manifestations (up to 6m) as assessed by specific outcome measures (SOM).

Methods: aPL-positive patients (>18yo, no other systemic autoimmune diseases) with persistent thrombocytopenia, autoimmune hemolytic anemia, heart valve disease, skin ulcers, aPL-nephropathy, and/or cognitive dysfunction with/without white matter (WM) changes received two doses of IV rituximab (1000 mg) on Days 1 and 15. aPL-positivity was defined as: positive LA test; aCL IgG/M/A ($\geq$40U); and/or aβ_2GPI IgG/M/A ($\geq$40U), on $\geq$2 occasions including screening, and at least 12 weeks apart. The follow-up aPL profiles and SOMs were analyzed at preset time points only in patients with baseline positivity for that aPL test and SOM. These were categorized as: "complete response (CR)", "partial response (PR)", "no response (NR)", and "recurrence (RC, only for SOM)". Preliminary descriptive results are reported as the study is ongoing.

Results: Of 19 aPL-positive patients enrolled (mean age: 40.5$\pm$13.8), 11 were female and 11 fulfilled APS Criteria. Two patients developed infusion reactions resulting in early termination. There were 59 AEs (12 serious with hospitalizations [all "unlikely" to be related to rituximab]; 7 non-serious within 48h of infusion [all "likely"]; and 40 non-serious [35 "unlikely" and 5 "possibly"]. Table shows the number of patients with positive aPL tests at baseline and the percentage of patients who had follow-up aPL tests with CR (LA test [-] or aPL ELISA<20U), PR (aPL ELISA 20–39U), or NR (LA test [+] or aPL ELISA$\geq$40U) at week 4, 16, 24, and 52. Excluding early termination or pending follow-up, the CR/PR/NR/RC rates at 6m were: 25/25/50/0% for thrombocytopenia (n:4); 0/0/100/0% for heart valve disease (n:2); 60/20/0/20 for skin ulcers (n:5); 0/100/0/0% for aPL-nephropathy (n:1); and 40/20/40/0% for cognitive dysfunction (n:5) (with no improvement in WM changes [n:3]).

Baseline[1]	CR/PR/NR (4w)[2]	CR/PR/NR (16w)[2]	CR/PR/NR (24w)[2]	CR/PR/NR (52w)[2]
LA (n:17)	0/-/100	0/-/100	0/-/100	0/-/100
aCL IgG (n:13)	0/9/91	0/0/100	0/0/100	0/13/87
aCL IgM (n:5)	20/20/60	20/20/60	25/25/50	33/33/33
aCL IgA (n:2)	0/0/100	0/0/100	0/0/100	0/0/100
aβ_2GPI IgG (n:10)	0/0/100	0/29/71	0/33/67	0/33/67
aβ_2GPI IgM (n:5)	0/20/80	0/20/80	25/0/75	66/33/0
aβ_2GPI IgA (n:3)	0/0/100	50/0/50	50/0/50	0/50/50

[1] # of patients with positive aPL.
[2] % of patients with follow up aPL tests excluding early termination or pending follow-up.

Conclusion: Based on the preliminary analysis of our ongoing pilot study of rituximab-receiving aPL-positive patients with non-criteria aPL manifestations: a) safety appears to be consistent with rituximab's known safety profile although 11% of our patients could not complete the treatment protocol due to reactions; b) B cell depletion appears to be effective in controlling some aPL manifestations during 6m of follow-up; and c) no substantial change in aPL profiles was observed in patients who completed 12m of follow-up.

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European Registry of Babies Born to Mothers with Antiphospholipid Syndrome. Arsene Mekinian[1], Priscille loire-Berson[2], Eric Lachassinne[3], Pascale nicaise-Roland[4], Eric Vicaut[5], Jerome Stirnemann[6], Sylvie chollet-Martin[4], Mario Motta[7], Angela Tincani[8], Christine Boinot[9], Olivier Pourrat[10], Tadej Avcin[11], Rapr Tomsik[12], Amelie Benbara[2], Sarah de Carolis[13], Patricia Rovere[14], Lionel Carbillon[2], marie-Helene Aurousseau[15], marie-Claire Boffa[16] and Olivier Fain[6]. [1]Jean Verdier Hospital, Bondy, France, [2]Service de gynécologie-obstétrique, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France, [3]Service de néonatologie et pédiatrie, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France, [4]Unité Fonctionnelles d'Immunologie Autoimmunité et Hypersensibilités, AP-HP, Hôpital Bichat-Claude Bernard, Paris, Paris, France, [5]Paris, France, [6]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France, [7]Obstetric and Gynecology of Brescia, Brescia, Italy, [8]Rheumathology Unit, University of Brescia, Brescia, Italy, Brescia, Italy, [9]Hemostase Poitiers, Poitiers, France, [10]CHU poitiers, Poitiers, France, [11]University Children's Hospital Ljubljana, Ljubljana, Slovenia, [12]University Children's Hospital Ljubljana, Slovenie, Slovenia, [13]Rheumatology, Brescia, Italy, [14]Rheumatology, Milan, Italy, [15]Bondy, France, [16]Service d'hématologie biologique, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France

Background/Purpose: To describe the outcome and the immunological status of children born to mothers with antiphospholipid syndrome (APS), to determine the factors responsibles of children abnormalities, to correlate childrens immunological status to mother's antibodies.

Methods: A prospective follow up of a European multicentric cohort of 130 children born to mothers with APS. Both maternal (clinical features, history, pregnancy features, immunological status) and infant's data at birth were recorded. A clinical, developmental and immunological follow up of infants at 1 to 3, 9 to 12, 24 months and 5 years was performed.

Results: One hundred forty women with APS (Sapporo) (mean age 36±5 years) were included. Eighty one percent of the mothers (n=115) have primary APS and the purely obstetrical APS represents 79% of the cohort (n=111). During pregnancy, treatment with aspirin-low molecular weight heparin was present in 125 cases (90%), steroids in 25 cases (18%), and hydroxychloroquine in 15 cases (11%).

One hundred thirty children born to mothers with APS were analyzed (female sex in 61 cases, birth weight 3000±500 g, height 48±3 cm, cranial perimeter 34±3 cm). Seventeen percent have a premature birth (n=22), and fifteen percent presented birth weight <2500 g (n=19). Thrombopenia was noted in 2 children, without any case of lupus or thrombosis. Four percent of children have lupus anticoagulant and antibeta2GP1 IgG antibodies (n=4), fifteen percent have anticardiolipid IgG antibodies at birth (n=17) (table).

	Cordon (n=40)	First week (n=110)	3 months (n=35)	9 months (n=38)	24 months (n=49)
ACC	0	4 (4%)	1 (3%)	1 (3%)	0
Anticardiolipid IgG	7 (18%)	17 (15%)	3 (9%)	7 (18%)	11 (22%)
Anticardiolipid IgM	0	0	0	0	1 (2%)
AntiB2GP1 IgG	2 (5%)	4 (4%)	5 (14%)	7 (18%)	5 (10%)
AntiB2GP1 IgM	0	0	0	0	1 (2%)

During 5 year follow-up, four children displayed behavioural abnormalities between 3 months and three years of age (psychomotor development delay with axial hypertonia, autism, attention-deficit/hyperactive disorder and language delay, growth failure and language delay (n=1 each)). No thrombosis or lupus was noted during follow-up. Eighteen percent have anticardiolipid IgG and antibeta2GP1 IgG antibodies above 6 months (table). Among children with abnormal psychomotor development, one has persistent anticardiolipid IgG antibodies.

Anticardiolipid Ig G and antibeta2GP1 Ig G antibodies in children, even after 6 months, were correlated with the same antibodies in mother ($p<0.05$).

The presence of maternal lupus with odds ratio 4 [1.2; 15]) and anticardiolipid IgG (odds ratio 6 [1.1; 33]) were predictive of neonates complication, whereas the presence of previous placenta praevia and mother's anticardiolipid IgG antibody were predictive of complications in children at 3 and 9 months.

Conclusion: Despite a high rate of premature birth and persistent antiphospholipid antibodies, the children born to mothers with APS do not have significant abnormalities of psychomotor development, thrombosis or lupus. The significance of persistent antibodies in children is not actually established.

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IL-7 Contributes to Monocyte Migration In Rheumatoid Arthritis. Nathan D. Chamberlain[1], Sarah R. Pickens[1], Richard M. Pope[2], Michael Volin[3] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Northwestern Univ Med School, Chicago, IL, [3]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL

Background/Purpose: The aim of the study was to characterize the expression of IL-7 and IL-7R in rheumatoid arthritis (RA) synovial tissue and to examine their regulation and pathogenic role in RA.

Methods: Expression and regulation of IL-7 and IL-7R was determined in RA and normal (NL) peripheral blood (PB) monocytes and in vitro differentiated macrophages by real-time RT-PCR and/or flow cytometry**.** Next the ability of IL-7 to induce monocyte migration was determined by in vitro chemotaxis.

Results: Since we have previously shown that expression levels of IL-7 and IL-7R were elevated in RA synovial lining and sublining macrophages, we asked whether expression of these factors was increased in RA PB and synovial fluid macrophages compared to NL PB monocytes and macrophages. Expression of IL-7 was elevated 17-fold in RA synovial fluid macrophages and 7-fold in RA PB macrophages compared to their counterpart NL cells by real-time RT-PCR. Levels of IL-7 were 4-fold greater in RA PB monocytes compared to NL monocytes. Further, concentrations of IL-7R were significantly higher in RA synovial fluid (45 fold) and RA PB (10 fold) macrophages compared to NL macrophages employing real-time RT-PCR. Also, RA PB monocytes expressed 8-fold greater levels of IL-7R compared to NL monocytes. Consistent with our mRNA results, flow cytometry experiments demonstrate that IL-7R is significantly elevated in RA monocytes and macrophages compared to NL counterparts. To determine which factors modulate expression of IL-7 and IL-7R in RA PB in vitro differentiated macrophages, cells were either untreated or treated with LPS, IL-1b, TNF-a, IL-17 or RA synovial fluid. Our results demonstrate that both IL-7 and IL-7R expression were greatly induced by LPS, TNF-a and IL-1b activation of RA PB macrophages compared to untreated cells. However only expression levels of IL-7 were upregulated (3.5-fold) by IL-17 stimulation, while RA synovial fluid activation of macrophages resulted in increased IL-7R expression compared to untreated cells. To determine whether IL-7 affects cell trafficking in the RA joint, IL-7-induced monocyte chemotaxis was examined. IL-7 was chemotactic for monocytes beginning at 0.1 ng/ml. Further, neutralization with anti-IL-7R antibody, but not control IgG, suppressed IL-7 mediated chemotaxis. Studies were performed to determine if the IL-7 identified in RA synovial fluid was chemotactic for monocytes. The mean concentration of IL-7 in the 18 RA synovial fluids analyzed was 138 + 19 pg/ml (up to 414 pg/ml), a value that was highly chemotactic. Next, experiments were performed to determine if the monocyte chemotaxis induced by RA synovial fluid was mediated by IL-7. Neutralization of IL-7 with a monoclonal antibody to IL-7, significantly reduced (40%; $p<0.05$) monocyte chemotaxis compared to control IgG-treated RA synovial fluids. Additionally, neutralization of IL-7R on monocytes was also effective in suppressing RA synovial fluid-mediated monocyte migration.

Conclusion: We identify, for the first time, regulators of IL-7 and IL-7R expression in RA PB in vitro differentiated macrophages and we document a novel role of IL-7 in RA monocyte migration.

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CCL21 a Novel Proangiogenic Factor in Rheumatoid Arthritis. Sarah R. Pickens[1], Nathan D. Chamberlain[1], Michael Volin[2], Arthur M. Mandelin II[3] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL, [3]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: This study was performed to determine the role of CCL21 and its corresponding receptor, CCR7, in the pathogenesis of Rheumatoid Arthritis (RA).

Methods: Histological studies were performed to compare the expression of CCR7 in RA with normal (NL) synovial tissues. Next, the role of CCL21 and/or CCR7 in angiogenesis was examined by employing in vitro chemotaxis, tube formation and in vivo matrigel plug assays. Finally the

mechanism by which CCL21 mediates angiogenesis was determined by Western blot analysis, endothelial chemotaxis and tube formation.

Results: In this study, we document that CCR7 expression was significantly increased in RA synovial tissue lining and endothelial cells compared to NL synovial tissue. We next validated that CCR7 is expressed by RA synovial lining macrophages and sublining endothelial cells by co-localizing CCR7 expression on CD68+ and VWF+ cells. Interestingly, the CCR7 expression pattern in RA synovial tissue is similar to what was previously noted for its ligands, CCL19 and CCL21. Since the CCR7, CCL19, and CCL21 are all expressed by RA endothelium, their ability to mediate angiogenesis was examined. For this purpose, chemotaxis was performed in a Boyden chamber with varying concentrations of CCL19 and CCL21, as well as positive (VEGF, 10ng/ml) and negative (PBS) controls. While CCL21 was chemotactic for human microvascular endothelial cells (HMVEC)s at concentrations ranging from 1 to 100 ng/ml ($p<0.05$), CCL19 did not induce HMVEC migration. The mean concentration of CCL21 in the RA synovial fluids ($n=74$) and tissues ($n=11$) analyzed was 519 ± 38 pg/ml (up to 3.4 ng/ml) and 824 ± 104 pg/mg (up to 1.6 ng/mg) respectively, concentrations that were chemotactic for HMVECs. Further, incubation of HMVECs with a neutralizing antibody to CCR7 suppressed CCL21-induced HMVEC migration suggesting that the chemotactic effect was due to CCR7 ligation. We found that CCL21 activates the PI3K, ERK and JNK pathways in HMVECs. While inhibition of ERK and JNK was ineffective in suppressing CCL21-induced HMVEC chemotaxis and tube formation, suppression of PI3K reduced these processes starting at 1 mM by 35–40% ($p<0.05$). Neutralization of either CCL21 in RA synovial fluids or CCR7 on HMVECs significantly reduces the induction of HMVEC migration and/or tube formation by RA synovial fluid. The role of CCL21 on angiogenesis in vivo was assessed by determining its effect on blood vessel formation in matrigel plugs in mice by employing hemoglobin quantification. The hemoglobin content of the CCL21 treated group was 14 times greater ($p<0.05$) than the PBS control. The concentration of CCL21 quantified from day 10 matrigel plugs was 405 pg/ml ± 89 pg/ml which is within the range of CCL21 levels detected in RA synovial fluid and tissue.

Conclusion: These observations identify a novel function for CCL21 as an angiogenic mediator in RA, supporting CCL21/CCR7 as a therapeutic target in RA.

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Evidence for CXCL16 As An Endothelial Progenitor Cell Chemotactic Factor. Jeffrey H. Ruth[1], Takeo Isozaki[1], M. Asif Amin[1], Charles A. Lesch[1], Ali S. Arbab[2] and Alisa E. Koch[3]. [1]University of Michigan, Ann Arbor, MI, [2]Henry Ford Hospital, Detroit, MI, [3]Department of Veteran's Affairs and University of Michigan, Ann Arbor, MI

Background/Purpose: We and others have previously shown that the transmembrane chemokine CXCL16 and its counterpart CXCR6 are important in the pathogenesis of rheumatoid arthritis (RA), predominantly via recruitment and stimulation of monocytes and T-cells. Here, we investigated the possibility that CXCR6 is expressed on human endothelial progenitor cells (EPCs), human dermal microvascular endothelial cells (HMVECs) and mouse lung endothelial cells (ECs). We also examined if CXCL16 recruits EPCs to developing neovasculature in rheumatoid arthritis (RA) synovium *in vivo,* and finally, if CXCR6 deficiency attenuates arthritis development and vascular formation in the K/BxN serum induced arthritis model.

Methods: We utilized the RA synovial tissue (ST) severe combined immunodeficient (SCID) mouse chimera system to examine EPC recruitment into engrafted human synovium injected intragraft with RA synovial fluid (SF) immunodepleted of CXCL16 or sham depleted with non-specific IgG. In addition, CXCR6 deficient ($CXCR6^{-/-}$) and wild-type (Wt) C57BL/6 mice were primed to develop K/BxN serum induced arthritis and evaluated for joint swelling. Joint tissue homogenates from these mice were examined for hemoglobin (Hb) content as a measure of total joint tissue vascularity, whereas OCT embedded joint tissue was examined for vascular formation and leukocyte migration by immunofluorescence histology. Lastly, EC populations including HMVECs, human EPCs from human cord blood and primary mouse ECs from lung tissue were all examined for CXCR6 expression by immunofluorescence.

Results: We show that CXCR6 is prominently expressed on the cell surface of human EPCs. CXCR6 is also expressed on HMVECs and mouse lung ECs and can be upregulated by interleuin-1β (IL-1β) or lipopolysaccharide (LPS) respectively. We also examined the recruitment of human EPCs in the RA ST SCID mouse chimera system and found that SCID mice injected intragraft with RA SF immunodepleted of CXCL16 showed a significant reduction in EPC recruitment compared to mice injected similarly with sham depleted RA SF. Finally, using the K/BxN serum induced inflammatory arthritis model, $CXCR6^{-/-}$ mice showed significantly reduced joint swelling compared to Wt mice at day 5 after serum induction. We measured Hb content in joint tissue homogenates from the K/BxN serum induced mice and discovered profound reductions in Hb levels, that correlated with reductions in monocyte and T-cell recruitment to arthritic joint tissue in $CXCR6^{-/-}$ compared to Wt mice. These findings indicate that CXCR6 deficiency reduces EPC migration to RA synovium, as well as vasculature formation and pro-inflammatory leukocyte recruitment in K/BxN serum induced arthritis.

Conclusion: We show that CXCR6 is expressed on mouse and human ECs and can be upregulated by pro-inflammatory stimuli. We also show that EPCs migrate into RA synovium towards soluble CXCL16 in RA SF. Additionally, K/BxN mice lacking CXCR6 have a reduced arthritic phenotype including reductions in Hb content, vasculature and leukocyte infiltration into inflamed ST. These results indicate that CXCL16 and its receptor CXCR6 may be a central ligand-receptor pair for inducing EPC recruitment and vascular formation in RA synovium.

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Notch Signaling Pathways Mediate Synovial Angiogenesis in Response to Vascular Endothelial Growth Factor and Angiopoietin 2. Wei Gao, Catherine Sweeney, Ceara Walsh, Peadar Rooney, Jennifer McCormick, Douglas J. Veale and Ursula Fearon. Translation Rheumatology Research Group, Dublin, Ireland

Background/Purpose: Angiogenesis plays a crucial role in the formation and maintenance of the pannus in inflammatory arthritis. Endothelial cell (EC) activation and survival signaling pathways preserve synovial blood vessel integrity and facilitates leukocyte infiltration. The Notch signaling pathway is critical for vascular angiogenesis and EC cell fate; however, the mechanisms involved in regulating these processes in the inflamed joint remain to be elucidated. The aim of this study was to examine if Notch signaling pathways mediate Vascular Endothelial Growth Factor (VEGF) and Angiopoietin 2 (Ang2) induced angiogenesis and blood vessel invasion in the inflamed joint.

Methods: Whole tissue synovial explants obtained at arthroscopy and microvascular endothelial cell cultures (HDEC) were utilised. Notch 1IC and 4IC protein expression were measured using western blots, Notch ligand DLL-4 and downstream signaling components Hrt 1 and Hrt 2 were quantified by qRTPCR. Notch signaling was directly blocked by Notch 1 siRNA transfection and DAPT (γ-secretase inhibitor). Measurements of angiogenesis were assessed *in vitro* by matrigel tube formation, invasion assay and pro-MMP-2/9 expression was measured by zymography.

Results: Notch 1IC and 4IC expression were observed in RA and PsA synovial tissue lysates with undetectable levels in OA patients. VEGF and Ang2 alone induced Notch1 IC, and 4IC expression in HDEC and RA synovial explants cultures, with a synergistic increase in Notch 1IC expression in response to VEGF and Ang2 in combination ($p<0.05$). VEGF and Ang2 alone significantly induced Notch 1, its ligand DLL-4 and downstream target genes Hrt 1 and Hrt 2 mRNA expression, with synergistic effects observed when cells were stimulated with VEGF and Ang2 in combination ($p<0.05$). VEGF-induced Notch 1IC expression was completely blocked in the presence of siRNA ($p<0.05$). Furthermore VEGF/Ang2-induced angiogenesis, cell invasion and pro-MMP-2/9 expression, were inhibited in the presence of siRNA or DAPT ($p<0.05$).

Conclusion: These data demonstrate increased expression of Notch 1IC in RA and PsA synovial tissues. VEGF and Ang2 alone and in combination induce Notch1 IC signaling pathways, blockade of which inhibits VEGF/Ang2-induced EC function. Taken together, these results suggest that in the inflamed joint, VEGF/Ang2-induced angiogenesis is in part dependent on the Notch signaling pathways.

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Active Non-Canonical NF-κB Signaling in Blood Vessels of Rheumatoid Arthritis Synovial Tissue May Enhance Inflammation by Stimulating Angiogenesis. Ae-Ri Noort, Katinka P.M. van Zoest, Paul P. Tak and Sander W. Tas. Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam The Netherlands, Amsterdam, Netherlands

Background/Purpose: In rheumatoid arthritis (RA) synovial tissue (ST), (pathological) angiogenesis can be observed already in the earliest phase of disease, and this may be critical in the switch from acute to chronic inflammation. The chemokine CXCL12, which is induced via non-canonical

nuclear factor-KB (NF-KB) signaling, plays an important role in angiogenesis, lymphocyte transendothelial migration, and the homing of endothelial progenitor cells. Therefore, the non-canonical NF-κB pathway, in which NF-κB inducing kinase (NIK) is a key mediator, may play an important role in pathological angiogenesis and the perpetuation of synovial inflammation in RA. Objectives: To study the role of non-canonical NF-κB signaling in pathological angiogenesis in RA.

Methods: ST was obtained via mini-arthroscopy from inflamed joints of RA patients with active disease. Expression of NIK, p52 and CXCL12 was evaluated using immunohistochemistry and immunofluorescence (IF) microscopy. NIK expression was also studied in Grawitz tumor and breast cancer tissues, in combination with vWF or CD31/CD34. The effects of non-canonical NF-κB signaling in endothelial cells (EC) were studied in vitro using angiogenesis/tube formation assays. In addition, VCAM-1 expression was measured by FACS analysis and $\alpha v\beta 5$ integrin levels by PCR.

Results: NIK was highly expressed in vascular structures in RA ST. IF microscopy demonstrated that NIK co-localized with the EC marker vWF in small vessels, but not with lymphatic vessel markers LYVE-1 and podoplanin. p52 and CXCL12 expression was observed in the same vascular structures. Furthermore, NIK was also expressed in EC in Grawitz tumor and breast cancer tissues, whereas normal skin EC did not exhibit increased NIK expression. In vitro, HUVEC treated with stimuli that induce non-canonical NF-KB signaling significantly enhanced tube formation 2,5-fold ($p<0.05$). FACS analysis of stimulated HUVEC showed a 2-fold increased VCAM-1 expression ($p<0.05$) and preliminary data also showed increased $\alpha v\beta 5$ levels.

Conclusion: NIK is preferentially expressed in EC in RA ST, and interestingly also by EC in tumor tissues. CXCL12 and p52 were also expressed in these blood vessels in RA ST, suggesting functional non-canonical NF-KB signaling. In vitro, stimulation of the non-canonical NF-KB pathway resulted in EC activation and enhanced angiogenesis. These findings point towards an important role of the non-canonical NF-KB pathway in (pathological) angiogenesis. This could be exploited for the development of new therapies that could not only be of benefit for RA patients, but also for a wide array of other diseases.

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In Vivo Imaging of T Cell Motility in the Joint Draining Lymph Nodes of Genetically Unmanipulated Mice in a Model of Rheumatoid Arthritis.
Tamas Kobezda, Sheida Ghassemi-Nejad, Colt Egelston, Tibor T. Glant and Katalin Mikecz. Rush University Medical Center, Chicago, IL

Background/Purpose: Development of adaptive immunity relies on the recognition of antigens (Ags) by cognate T cells and subsequent signaling through the T cell receptor (TCR). The threshold of TCR activation is usually high, and co-stimulatory signals are required. Recent in vivo two-photon imaging studies on lymph nodes (LNs) have revealed that T cells exhibit random motility until they encounter an APC that presents cognate Ag and provides co-stimulation, both of which require prolonged cell-cell interaction. Because cognate T cells are thought to be rare, most in vivo imaging experiments employ genetically altered mice expressing a TCR transgene specific for a model Ag. The purpose of our study was to determine if changes in T cell motility (consistent with APC-T cell interaction) can be observed in genetically unmanipulated (wild type, WT) mice in a model of rheumatoid arthritis.

Methods: T cells were isolated from naïve BALB/c mice and from BALB/c mice with cartilage proteoglycan-induced arthritis (PGIA). Naïve T cells were labeled with a green fluorescent cell tracer dye, and Ag-experienced T cells (from PGIA mice) with a red fluorescent dye. The donor cells were then co-transferred (1:1 ratio) into either naïve or arthritic BALB/c recipients. Following cell transfer, proteoglycan (PG, as a cognate Ag) was injected into the ankle joints. The T cell recipient mice were then anesthetized, and the popliteal (ankle joint-draining) LNs were subjected to two-photon microscopy at defined time points between 2 and 72 h after Ag injection.

Results: At the earliest time point (2 h) after intra-articular Ag injection, the co-transferred naïve and Ag-experienced T cells both exhibited high motility ("random walk") in the LNs of naïve recipient mice. However, at 4 h, Ag-experienced, but not naïve, T cells showed significantly reduced motility, which was consistent with their engagement with APCs. At 8 h after Ag injection the Ag-experienced population became highly motile again, suggesting their disengagement from the APCs. When naïve and Ag-experienced T cells were co-transferred into arthritic recipients, both T cell populations exhibited reduced motility in the popliteal LNs 4 h after Ag injection, but naïve T cells disengaged soon afterwards. This prompted us to ask whether the access of naïve T cells to APCs was limited by occupancy of the APCs by Ag-experienced T cells. Indeed, when naïve T cells were transferred alone into arthritic hosts, they exhibited long-lasting interactions with APCs.

Conclusion: It this in vivo study we demonstrate that changes in T cell motility upon Ag presentation occur in genetically unaltered mice. Co-transfer of naïve and Ag-experienced T cells into naïve recipient mice results in preferential interaction of Ag-experienced T cells with APCs in the presence of Ag, as expected. However, naïve T cells also show evidence of cognate interaction with APCs following transfer into arthritic recipients. These results indicate that Ag-experienced T cells from WT mice recapitulate the motility patterns reported in TCR-transgenic mice upon Ag presentation. Our study also suggests that cognate T cells in naïve WT mice are not as rare as previously thought.

ACR Concurrent Abstract Session
Fibromyalgia and Soft Tissue Disorders I
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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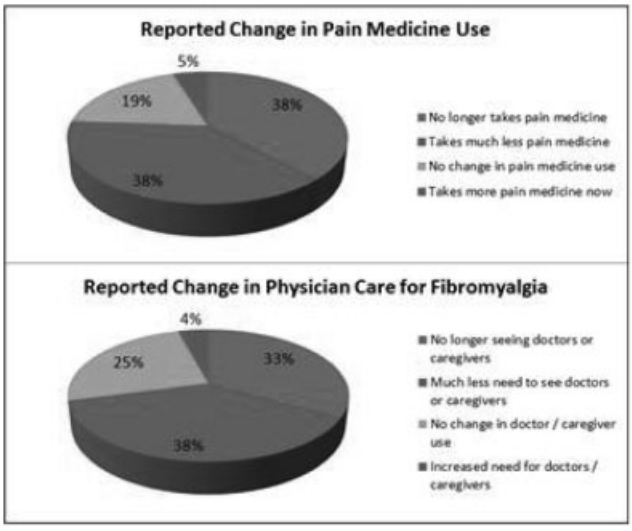
Long-Term Outcomes In Fibromyalgia Patients Treated with Cortical Electrostimulation.
Jeffrey B. Hargrove[1], Robert M. Bennett[2] and Daniel J. Clauw[3]. [1]Kettering University, Flint, MI, [2]Oregon Health & Science Univ, Portland, OR, [3]University of Michigan, Ann Arbor, MI

Background/Purpose: This study evaluated the long-term outcomes of Reduced Impedance Noninvasive Cortical Electrostimulation (RINCE) in fibromyalgia (FM) patients. These FM patients had been treated with RINCE twice weekly over a period of 11-weeks in 2006–2008, in a placebo controlled, double-blind study that targeted areas of the brain considered to be involved in central sensitization (Arthritis Rheum 2010;62(10 Suppl):269–70).

Methods: Under IRB-approval, subjects treated with RINCE were asked to complete an un-blinded follow-up survey that included the Fibromyalgia Impact Questionnaire (FIQ). Thirty-nine subjects were mailed surveys, 25 were returned (64%). In addition to the FIQ, survey responses provided patient self-reports on the duration of symptom improvement, incidence of side effects, and changes in pain medicine use and physician visits.

Results: The average respondent age was 59 years (range 39–71); the average time since completion of therapy was 45 months (range 31–60). The mean total FIQ score was 53 at baseline, 36 at end-of-study (EOS) and 32 at follow-up ($P<0.001$). The change from baseline in FIQ scores at EOS and follow-up were significantly correlated ($R=0.78$, $P<0.001$). Subjects reported symptom improvements lasting at least two-years in pain (68%) sleep (56%) and fatigue (60%). Some 76% of treated subjects reported that they had reduced or completely eliminated medicine use for pain, and 71% indicate reduced or eliminated need to see physicians for FM (see pie charts). No post-treatment side effects were reported.



Conclusion: A high percentage of FM patients, who had been treated with RINCE, continued to experience a worthwhile level of improvement in FM symptoms at a 45-month follow-up. These sustained benefits were

accompanied by significant reductions in pain medicine use and physician visits. Follow-up total FIQ scores demonstrated durability of treatment effect when compared to baseline and EOS. The strong correlation between total FIQ scores at EOS and follow-up suggests that the initial response to RINCE is predictive of a long lasting therapeutic benefit. Cortical electrostimulation is a non-pharmacological modality that shows some promise in the management of FM patients, and has the potential for future development.

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Incidence and Predictors of Fibromyalgia in An Early Arthritis Cohort. Yvonne C. Lee[1], Daniel H. Solomon[1], Bing Lu[1], Gilles Boire[2], Boulos Haraoui[3], Carol A. Hitchon[4], Janet E. Pope[5], J. Carter Thorne[6], Edward Keystone[7], Diane S. Ferland[8] and Vivian Bykerk[9]. [1]Brigham and Women's Hospital, Boston, MA, [2]CHUS-Sherbrooke University, Sherbrooke, QC, [3]Institut de Rhumatologie, Montreal, QC, [4]University of Manitoba, Winnipeg, MB, [5]St. Joseph's Health Care, University of Western Ontario, London, ON, [6]Newmarket, ON, [7]Mount Sinai Hospital, Toronto, ON, [8]LaSalle, QC, [9]Brigham & Women's Hospital, Boston, MA

Background/Purpose: The prevalence of fibromyalgia (FM) is 20% among patients with established rheumatoid arthritis (RA) compared to 3% in the general population. However, little is known about the time course of FM in inflammatory arthritis and whether chronic pain and inflammation due to arthritis impact the risk for FM. We examined the development of FM in an early inflammatory arthritis cohort and assessed the association between baseline clinical variables and future diagnosis of FM.

Methods: Data were analyzed from 1198 patients in the Canadian Early Arthritis Cohort, a prospective, observational, multi-center cohort of early inflammatory arthritis patients. Diagnoses of FM were determined by the participants' rheumatologists. Cumulative incidence rates were calculated, and Cox regression models were used to determine hazard ratios for the development of FM.

Results: The cumulative incidence of FM rose from 0% at baseline (excluding 68 prevalent cases) to 5.9% at 12 months and 11.8% at 60 months (Figure). Female sex (HR 3.66, 95% CI 1.44–9.32), tender joint count (HR 1.06, 95% CI 1.04–1.09), depressed mood (HR 1.81, 95% CI 1.07–3.05) and poor memory (HR 2.05, 95% CI 1.21–3.49) were significantly associated with an increased risk for FM (Table). Swollen joint count (HR 0.96, 0.92–1.00) and erythrocyte sedimentation rate (ESR) (ESR 30–49: HR 0.42, 95% CI 0.20–0.92; ESR ≥ 50: HR 0.28, 95% CI 0.11–0.71) were negatively associated with the development of FM.

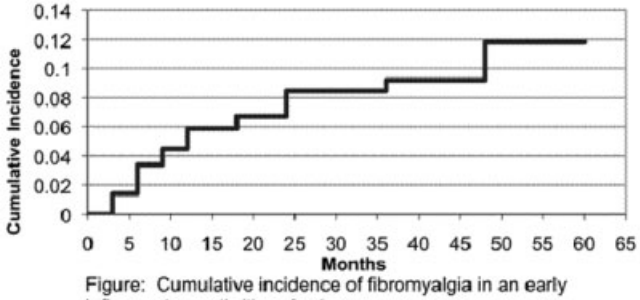

Figure: Cumulative incidence of fibromyalgia in an early inflammatory arthritis cohort.

Table. Multivariable Cox regression models for the development of fibromyalgia in an early inflammatory arthritis cohort (N = 1198).

Baseline Characteristics	Hazard Ratio	95% CI	*P*
Age, per year	1.00	0.98–1.02	0.75
Female	3.66	1.44–9.32	**0.006**
Non-Caucasian	1.38	0.78–2.43	0.27
Current smoker	0.53	0.25–1.14	0.10
68-tender joint count, per joint	1.06	1.04–1.09	**<.0001**
68-swollen joint count, per joint	0.96	0.92–1.00	**0.04**
ESR, per mm/hr	–	–	–
10–19 mm/hr	0.61	0.33–1.14	0.12
20–29 mm/hr	0.50	0.24–1.07	0.07
30–49 mm/hr	0.42	0.20–0.92	**0.03**
≥ 50 mm/hr	0.28	0.11–0.71	**0.008**
Depressed mood	1.81	1.07–3.05	**0.03**
Poor memory	2.05	1.21–3.49	**0.008**

Conclusion: The cumulative incidence of FM increased during the first 60 months after diagnosis of inflammatory arthritis, with the greatest increase occurring over the first 18 months. Although female sex, depression and poor memory were predictive of the development of FM, inflammatory measures were associated with a decreased risk for FM. These results may reflect physician decision-making processes when considering a diagnosis of FM in patients with inflammatory arthritis. Future studies are needed to better define the diagnosis of FM in patients with inflammatory arthritis and understand the role of inflammatory measures as a negative predictor of fibromyalgia.

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Cortical Oscillatory Changes During Mechanical Brushing in Fibromyalgia Syndrome Patients. Nick Fallon, Yee Ho Chiu, Xiaoyun Li, Turo Nurmikko and Andrej Stancak. University of Liverpool, Liverpool, United Kingdom

Background/Purpose: Pain resulting from innocuous mechanical stimuli is common in Fibromyalgia syndrome (FMS) and is likely to be a key pathophsyiological component of FMS symtpomatology. This study aims to investigate the cortical oscillatory changes associated with tactile cutaneous stimuli in FMS patients.

Methods: Nineteen female FMS patients and 18 healthy, age matched, female controls underwent electroencephalographic (EEG) examination during 2 blocks of mechanical brush stimulation of the right arm (right lateral epicondyle). Blocks consisted of 20 cycles, containing 4 seconds of rest and 4 seconds of brushing with a soft bristled paintbrush. After each block participants rated any pain experienced on a 4-point Likert scale ranging from no pain to severe pain. Participants were also required to undergo a clinical manual tender point scale examination and to complete a variety of psychological and clinical questionnaires.

Results: Thirteen patients (no controls) reported discomfort or pain following brushing. A Student's independent t-test indicated a significant difference between the mean total pain score for patients (1.61 ± 1.42) and controls (0.00 ± 0.00); $t(35) = 4.79$, $P < 0.001$.

Surface EEG data was analysed to compare oscillatory changes related to the onset of brushing in each group. FMS patients demonstrated profound amplitude reductions in beta band (16–24Hz) frequencies during brushing (event related desynchronisation, ERD), over bilateral somatosensory areas and limited ERD over much of the scalp. This is indicative of a strong bilateral, widespread activation in response to brushing. Controls demonstrated a more focal ERD, primarily in electrodes over contralateral somatosensory cortex. An independent t-test comparison of beta amplitude changes during brushing revealed three significantly different clusters of electrodes over the medial occipital, ipsilateral prefrontal, and ipsilateral somatosensory cortices. Only the cluster over the ipsilateral primary somatosensory cortex demonstrated a robust unidirectional difference in ERD, patients exhibiting a strong mean ERD (16.87 %) compared to almost no ERD (0.01%) in healthy controls (Students independent T-test, $t(35) = 2.93$, $p = 0.006$).The remaining clusters demonstrated statistically significant amplitude changes due to small but opposing oscillatory alterations, with smaller ERD in the patient group contrasting with slight amplitude increases in the control group. Multiple regression analysis indicated that manual tender point score was a significant predictor of the ERD in the ipsilateral somatosensory cortical area during brushing.

Conclusion: Results point to the presence of cortical activation in the ipsilateral primary somatosensory cortex in FMS patients, but not healthy subjects, during dynamic tactile stimulation. The ipsilateral somatosensory cortex activation during brushing in FMS patients is associated with the manual tender point score suggesting that disinhibition of this area may contribute to clinical pain. Such disinhibition may potentially cause stronger recruitment of thalamic neurons in response to the stream of afferent somatosensory information manifesting in FMS pain.

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Pain Variability Influences Recalled Pain Estimation. Steven E. Harte[1], Robert H. Palmer[2], R. Michael Gendreau[3], Daniel J. Clauw[1] and Richard E. Harris[1]. [1]University of Michigan, Ann Arbor, MI, [2]Forest Research Institute, Jersey City, NJ, [3]Cypress Bioscience, Inc., San Diego, CA

Background/Purpose: Pain variability refers to fluctuations in pain intensity that occur over time. Previous studies indicate that real-time assessment of clinical pain shows significant pain variability both within

and between subjects (Harris et al., Arthritis Rheum 52, 2005). Moreover the degree of variability is associated with analgesic response (Harte et al., Arthritis Rheum 60, S1, 2009). Here we investigated the relationship between pain variability (PVI: pain variability index) and recalled pain in fibromyalgia (FM) patients.

Methods: FM patients (n = 888) were enrolled in a randomized, double-blind, placebo-controlled trial of milnacipran (Mease et al., J Rhem, 2009). Patients entered their current and weekly recalled pain intensity into electronic diaries. Current pain was assessed several times a day by random prompts. Pain intensity was rated on a 0–100 VAS, anchored by "no pain" and "worst possible pain." PVI was calculated as the natural log of the standard deviation in current pain entries over a two-week baseline assessment period conducted before treatment with either milnacipran or placebo. Recall bias was calculated as the difference between average current pain and recalled pain over the same two-week assessment period.

Results: A significant recall bias was observed during the baseline assessment period. Patients reported higher recalled pain as compared to current pain (recalled VAS: 69.89 +/− 11.82 (SD); current VAS: 66.71 +/− 13.59; $p < 0.001$). PVI was significantly associated with pain recall bias ($r = -0.456$; $p < 0.001$) over the same period.

Conclusion: These data indicate that pain recall is influenced by the degree of pain variability experienced during the recall period, with greater variability being associated with greater recall error. These findings have relevance for clinical trials in chronic pain which rely solely on recalled pain.

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Nocebo in Fibromyalgia: Meta-Analysis of Placebo-Controlled Clinical Trials and Implications for Practice. DD Mitsikostas[1], NG Chalarakis[1], LI Mantonakis[1], E. Delicha[2] and PP Sfikakis[2]. [1]Naval Hospital, Athens, Greece, Athens, Greece, [2]First Department of Propaedeutic and Internal Medicine, Laiko, Athens University Medical School, Greece, Athens, Greece

Background/Purpose: Poor medication adherence has long been observed in clinical practice in patients with fibromyalgia. This may result in treatment failure and/or increased total healthcare costs, and can be partly related to nocebo. Nocebo refers to adverse effects generated by patients' fear that medical treatment will likely harm instead of heal and can be assessed in placebo-controlled randomized clinical trials (RCTs). The present meta-analysis examined adverse effects following placebo administration in RCTs for fibromyalgia.

Methods: Following a systematic Medline search for RCTs for fibromyalgia pharmacologic monotherapy treatment published between 2001–2010, we assessed percentages of placebo-treated patients reporting at least one adverse effect or discontinuing due to placebo intolerance and searched for factors influencing nocebo's extent. Percentages were compared to those revealed by similarly performed meta-analyses of placebo-controlled RCT's for multiple sclerosis (Mult Scler, 2010;16:816–828) and primary headaches (Cephalalgia 2011;31:550–61)

Results: Data were extracted from 16 RCTs fulfilling search criteria. Of 2026 placebo-treated patients, 67.2% (95%CI:51.0%–81.5%) reported at least one adverse effect, and 9.5% (95%CI:8.3%–10.9%) discontinued placebo treatment due to intolerance. Adverse effects in placebo arms corresponded quantitatively and qualitatively to those in active drug arms ($\rho > 0.88$, $p < 0.0001$). Younger age and larger placebo arm size were associated with increased dropout rates. Patients with depression were more likely to withdraw from trials. Nocebo dropouts in fibromyalgia trials were 4-fold and 2-fold higher than in RCT's for multiple sclerosis treatment and migraine preventive treatment, respectively.

Conclusion: Nocebo is remarkably prevalent in fibromyalgia patients participating in RCTs probably being a serious confounding factor. Since nocebo contributes to drug intolerance and treatment failure in clinical practice, identification of predisposing factors and efforts to prevent nocebo by educating these patients appropriately seems to be important for fibromyalgia outcome.

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The Performance of American College of Rheumatology 2010 Diagnostic Criteria for Fibromyalgia Among Fibromyalgia Patients Seen in a Rheumatology Clinic and Diagnosed by 1990 Classification Criteria. Muhammad B. Yunus and Jean C. Aldag. University of Illinois College of Medicine at Peoria, Peoria, IL

Background/Purpose: The 2010 American College of Rheumatology (ACR) Diagnostic Criteria for Fibromyalgia (FM) were developed to diagnose FM in the clinic without the need for performing tender point (TP) examination. The predominant purpose of our study was to assess the performance of the above 2010 criteria among FMS patients seen in our clinic. Further, we wished to assess correlations among important variables.

Methods: We selected 473 patients in our data base who fulfilled the 1990 ACR criteria for classification of fibromyalgia (widespread pain plus at least 11 TPs among 18). These patients did not have another condition that would explain the pain. According to the 2010 criteria, widespread pain index (WPI) was calculated by counting sites of pain symptom among 19 sites (possible WPI score 0–19). Symptom severity (SS) scale score was calculated by adding the severity (0–3 categories) of the following symptoms: fatigue, waking unrefreshed and cognitive symptoms, as well as number of total symptoms (0=none, 1= few, 2=moderate and 3= large number). Thus, possible score for SS scale was 0–12. To fulfill the 2010 diagnostic criteria a patient needed to have WPI score of 7 or greater and SS score of 5 or greater, OR WPI score of 3–6 and SS score of 9 or greater.

Results: The mean (SD) age in years was 46.7 (13.2), 95.7% Caucasian, 87.7% female. Mean (SD) duration of symptoms was 9.2 (9.7) years. Mean (SD) number of TPs among 18 sites was 15.7 (2.4). Of the 473 FM patients by 1990 ACR criteria, 408 (86.2%) fulfilled the new 2010 diagnostic criteria. Spearman correlations showed significant correlation of TPs with 19 pain sites (p=.0001), no. of symptoms (p=.0001), no. of subjective swollen sites (p=.0001), no. of subjective numbness sites (p=.003), and AM fatigue (p=.021). No correlation was found between TPs and self-assessed depression or anxiety. Anxiety correlated with depression (p=.0001). Sleep difficulties correlated with AM fatigue (p=.0001), depression (p=.0001), anxiety (p=.001) and AM stiffness (p=.001).

Conclusion: 86.2% of our FM patients diagnosed by 1990 ACR criteria fulfilled the 2010 FM diagnostic criteria. This figure is similar to 88.1% found in the multicenter 2010 criteria study. Since 76% of FM patients diagnosed by a physician in a clinic fulfilled the 1990 ACR criteria in the 2010 study, as many as 33–35% of physician diagnosed FM will be missed by the new 2010 criteria. Given the strong correlation between TPs and number of subjective swollen sites and no. of subjective numbness sites, these symptoms are likely to be part of central sensitization that characterizes FM. Further, TP was not correlated with self-assessed anxiety or depression in our study. However, poor sleep was correlated with both depression and anxiety.

ACR Concurrent Abstract Session
Orthopedics and Low Back Pain
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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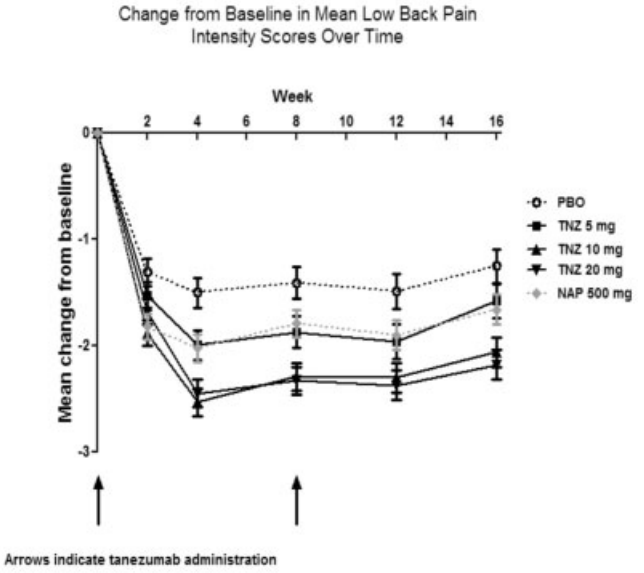
A Study of Tanezumab in Adults with Chronic Low Back Pain (NCT00876187). A. Kivitz[1], Joseph Gimbel[2], Candace Bramson[3], Mary Ann Nemeth[3], David Keller[4], Mark T. Brown[4], Christine R. West[5] and Kenneth M. Verburg[4]. [1]Altoona Center for Clinical Research, Duncansville, PA, [2]Arizona Research Center, Phoenix, AZ, [3]Pfizer, Groton, [4]Pfizer, Groton, CT, [5]Pfizer, Williamston, MI

Background/Purpose: A randomized, double-blind, placebo (PBO)- and active-controlled phase 2 study was conducted to investigate the efficacy and safety of tanezumab (TNZ), a humanized monoclonal antibody that specifically inhibits nerve growth factor vs. naproxen (NAP) and PBO as analgesic treatment for chronic low back pain (LBP).

Methods: Patients with moderate to severe, chronic, non radiculopathic LBP, received TNZ (20, 10, or 5 mg IV every 8 weeks, and oral PBO), NAP (500 mg BID starting at randomization and TNZ vehicle IV), or PBO (TNZ vehicle IV and oral PBO). Patients recorded daily pain scores for average LBP Intensity (aLBPI; an 11-point numeric rating scale). Mean Changes from Baseline (MCB) to Week 16 in the daily aLBPI for TNZ vs. PBO and vs. NAP were primary efficacy endpoints. Key secondary efficacy endpoints were change from Baseline to Week 16 in the Roland Morris Disability Questionnaire (RMDQ; a measure of function used for LBP) and change from Baseline to Week 16 in the Patient Global Assessment (PGA) of LBP. Adverse event (AE) incidence was also assessed.

Results: A total of 1347 patients were randomized and treated. TNZ 20 mg (MCB: −2.18; p<0.001), TNZ 10 mg (MCB: −2.06; p<0.001), and NAP (MCB: −1.66; p=0.037) but not TNZ 5 mg (MCB: −1.58; p=0.113) showed significant improvements in aLBPI versus PBO (MCB: −1.25) at Week 16. Improvements in aLBPI with TNZ 20 mg (p=0.006) and TNZ 10 mg (p=0.035) were also superior to NAP (Figure). Improvements in the RDMQ versus PBO (MCB: −1.75) were observed with TNZ 20 mg (MCB: −2.80; p=0.006) and TNZ 10 mg (MCB: −3.18; p<0.001) but not with TNZ 5 mg (MCB: −2.37; p=0.125) or NAP (MCB: −2.07; p=0.405). Improvements in the PGA versus PBO (MCB: −0.40) were seen with all TNZ treatments (MCB: −0.67, −0.65 and −0.58 by decreasing dose; p≤0.030), but not with NAP (MCB: −0.50; p=0.197). Additionally, both TNZ 20 mg and 10 mg treatment showed significant improvements in efficacy vs. NAP-treatment as measured by the RMDQ (p≤ 0.042) and PGA (p≤0.038).



The overall incidence of AEs was similar among the TNZ treatment groups (range: 58.0–64.4%) but higher than the NAP (48.1%) and PBO (52.2%) treatment groups. The most common AE was paresthesia (TNZ 20 mg, 12.9%; 10 mg, 7.1%; and 5 mg, 4.7%; NAP, 1.7%; and PBO, 2.2%). The incidence of serious AEs was highest in the PBO group and the rate of discontinuation across all treatments was low. There were no reported cases of osteonecrosis or total joint replacement. The AE profile for the TNZ, NAP and PBO treatment groups was comparable to that of previous TNZ studies in patients with osteoarthritis and other conditions of chronic pain.

Conclusion: Treatment with TNZ (20 mg and 10 mg) resulted in superior analgesic efficacy and improvements in pain, function and global assessment as measured by the aLBPI, RDMQ and PGA compared to PBO and NAP treatment. Results indicate that TNZ is efficacious in the treatment of chronic LBP. No new safety signals were identified.

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Time-Course and Extent of Pain and Function Improvements Post-Knee Replacement: The Multicenter Osteoarthritis Study. Tuhina Neogi[1], Jingbo Niu[1], David T. Felson[1], Michael C. Nevitt[2], Yuqing Zhang[1], Laura Frey-Law[3], Jessica L. Maxwell[1] and Jasvinder Singh[4]. [1]Boston University School of Medicine, Boston, MA, [2]University of California-San Francisco, San Francisco, CA, [3]University of Iowa, Iowa City, IA, [4]University of Alabama at Birmingham and Birmingham VA Medical Center, Birmingham, AL

Background/Purpose: Prior studies have reported pain and function improvements post-knee replacement (KR) to be similar between 6 to 24-months post-KR. However, many studies relied on postal surveys, and often had incomplete follow-up. We examined the time-course and extent of pain and function changes post-KR, and whether these differed according to age, sex, and BMI in a comprehensively tracked cohort.

Methods: The Multicenter Osteoarthritis (MOST) Study is a longitudinal NIH-funded cohort of persons with or at high risk of knee OA. Pain and function by WOMAC were assessed at baseline, 30, and 60 months in those who had a KR during follow-up. Data from clinic visits immediately prior to and after the KR were used to evaluate the mean change in and proportion achieving the MCID (Escobar, 2007) for pain (WOMAC ↓ ≥5.6/20) and function (WOMAC ↓ ≥14.2/68), and proportion post-KR with moderate-to-severe pain (≥moderate pain on ≥1 of the 5 WOMAC pain questions) and poor function (≥28/68 (average function in those awaiting TKR)). We plotted the mean change in pain and function for the whole sample using local regression (LOESS). We also stratified changes in pain and function by age, sex, and BMI, additionally adjusting for other potential confounders (depressive symptoms, race/clinic, catastrophizing).

Results: During follow-up, 399 knees from 302 subjects had new KRs with ≥1 study visit post-KR (mean age 67±7.5, BMI 33±7, 72% female), with 97 having bilateral KRs. The median # of months between the pre-KR visit and KR was 16, and between the KR and post-KR visit was 20. Pain and function patterns did not differ by time between pre-KR visit and KR date. The median improvements in pain and function were 4/20 and 10.6/68, respectively. Only 64% and 49% achieved the MCID for pain and function, respectively. Moderate-severe pain in the replaced knee was present in 36% and 16% had poor function post-KR. There were no clinically meaningful differences in mean adjusted pain or function improvements among those age ≤65 vs. >65 (pain: −4.3 vs. −4.5; function: −11.0 vs. −12.0); males vs. females (pain: −4.0 vs. −4.8; function: −10.8 vs. −12.2); and those with BMI <30 vs. ≥30 (pain: −4.2 vs. −4.6; function: −10.8 vs. −12.3). Similar results were seen for VAS pain and performance-based function measures. Pain and function continued to improve between 6–12 months, 12–24 months, and beyond, potentially greater than the minimal perceptible clinical improvement threshold of ~10% (see Figures).

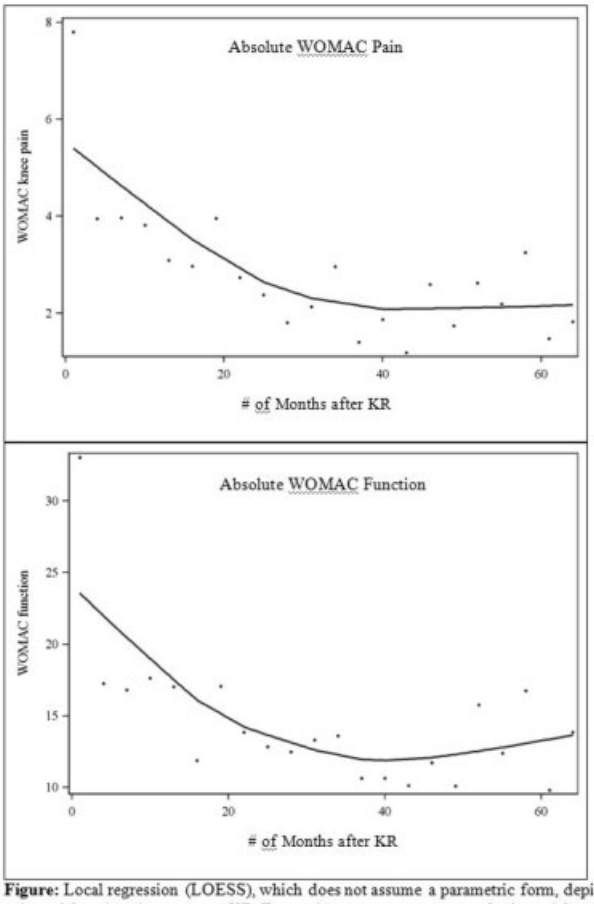

Figure: Local regression (LOESS), which does not assume a parametric form, depicting pain and function changes post-KR. Data points represent average of pain and function over 3-month intervals.

Conclusion: A substantial proportion had poor pain and function outcomes post-KR. In keeping with prior studies, no substantial differences in pain or function changes post-KR were noted based upon age, sex, or BMI. However, in contrast to other studies, pain and function continued to change post-KR between 6 to 24 months and beyond. Further study into factors contributing to poor post-KR outcomes and time-course for improvement is warranted.

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Impact of a Patient Decision Aid with An Interactive Values Component On Decisional Conflict Associated with Total Knee Arthroplasty. Sofia De Achaval[1], Liana Fraenkel[2], Robert Volk[3], Vanessa Cox[3] and Maria E. Suarez-Almazor[4]. [1]U.T. MD Anderson Cancer Center, Houston, TX, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, [3]UT MD Anderson Cancer Center, Houston, TX, [4]University of Texas. M.D Anderson Cancer Center, Houston, TX

Background/Purpose: Decision support tools that include information on risks and benefits, and help patients consider the importance of attributes of competing options, could help patients face difficult medical decisions, such as elective total knee arthroplasty (TKA), by reducing uncertainty. Our objective was to examine the impact of a videobooklet patient decision aid supplemented by an interactive values clarification exercise using adaptive conjoint analysis (ACA) on decisional conflict in patients with knee OA considering TKA.

Methods: 208 patients with knee OA who were considering undergoing TKA participated in the study (mean age 63 years; 68% female; 66% White). Participants were randomized to 1 of 3 groups: (1) Educational booklet about medical and surgical management of OA (control); (2) Videobooklet patient decision aid (DVD) on OA treatment choices; and (3) Videobooklet patient decision aid (DVD) + ACA tool regarding TKA. The ACA tool enables patients to consider competing attributes (i.e. specific risks and benefits) by asking them to rate a series of paired-comparison tasks. The primary outcome was the Decisional Conflict Scale (DCS) which has a possible range of 0 to 100. Differences between groups were analyzed using analysis of variance (ANOVA) and Tukey's honestly significant difference (HSD) post hoc tests.

Results: Overall, decisional conflict decreased significantly in all groups ($p<0.05$). The largest reduction in decision conflict was observed for participants in the DVD decision aid group (21 points). Post hoc analyses indicated statistically significant differences in pre vs. post-intervention DCS total score comparing the DVD decision aid-alone group to the control group (21 vs. 9.5 point reduction; $p<0.001$) and to the DVD + ACA group (21 vs. 14 point reduction; $p<0.001$). The changes in decision conflict for the control compared to the DVD decision aid + ACA group were not significantly different.

Conclusion: Patient decision aids appear to reduce decisional conflict in OA patients, and could be used at point of care to facilitate informed patient decision-making. In our study, an videobooklet patient decision aid (DVD) decreased decisional conflict more than printed material alone and the addition of a more complex computer-based ACA tool requiring more intense cognitive involvement, and explicit value choices.

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Pain Catastrophizing, but Not Widespread Pain, Is Associated with Poor Pain Outcomes After Knee Replacement: An Analysis From the Multicenter Osteoarthritis Study (MOST). Jasvinder A. Singh[1], Cora E. Lewis[2], Ke Wang[3], David T. Felson[4], Michael C. Nevitt[5], James Torner[6], Laurence A. Bradley[7] and Tuhina Neogi[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama, Birmingham City, Birmingham, AL, [3]Boston University, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]University of California-San Francisco, San Francisco, CA, [6]University of Iowa, Iowa City, Iowa City, IA, [7]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: Recent studies have suggested that pre-surgery mental and emotional health impact pain outcomes after knee replacement (KR). Little is known about the associations among pain catastrophizing, widespread pain, and pain outcomes post-KR.

Methods: We used data from the Multicenter Osteoarthritis (MOST) Study, a longitudinal cohort study of persons with or at high risk of knee OA. Western Ontario McMaster Osteoarthritis index (WOMAC) was used to assess pain and function at baseline, 30, and 60 months in entire cohort, including those who had a KR during follow-up. We used data from clinic visits immediately prior to and at least 3 months after KR to assess the proportion of patients with poor pain outcomes: (1) moderate-severe knee pain post-KR (maximal score of at least moderate pain on at least one of the 5 WOMAC pain questions); and (2) poor pain responder (failure to achieve clinically meaningful change in knee pain i.e., decrease of ≥5.6/20 on WOMAC pain in replaced knee after KR). Primary predictor variables of interest were: (1) pain catastrophizing assessed by the Coping Strategies Questionnaire; and (2) widespread pain assessed by a homunculus, categorized as present if there is pain reported above and below the waist, on both sides of the body, and axial pain. Multivariable-adjusted regression analyses adjusted for age, sex, BMI, ethnicity, clinic, contralateral knee OA or KR, comorbidity, lower back pain and pre-KR WOMAC pain.

Results: During follow-up, 297 subjects had 391 new KRs with ≥1 study visit post-KR to ≥3-months after KR. Mean age was 66±8, BMI 33±7, 71% female, median time after KR 20 months with 94 patients having bilateral KRs. 34% patients had moderate-severe knee pain post-KR and 31% patients were poor pain responders. In multivariable-adjusted analyses, pain catastrophizing was associated with significantly higher odds of poor pain outcome with an odds ratio of 2.3 (95% CI, 1.3, 3.9; $p=0.0025$), but widespread pain was not significantly associated, odds ratio of 1.2 (0.7, 2.1; $p=0.49$). Pain catastrophizing was significantly associated with poor pain responder status with odds ratio of 2.8 (95% CI, 1.5, 5.1; $p=0.0008$), but widespread pain was not significantly associated, odds ratio of 1.1 (0.6, 2.0; $p=0.71$).

Conclusion: This is the first evidence in a well-characterized longitudinal osteoarthritis cohort that pain catastrophizing is associated with worse pain outcomes post-KR. It is important to determine the cognitive, behavioral, and neurophysiologic pathways that may mediate this relationship as well as the efficacy of coping skills training prior to KR on catastrophizing and postsurgical outcomes.

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Identifying Comorbid Conditions That Affect the 6 Month Recovery Pattern of Total Knee Arthroplasty. C. Allyson Jones[1], Lauren A. Beaupre[2], Gian S. Jhangri[3] and Maria E. Suarez-Almazor[4]. [1]Departments of Physical Therapy and School of Public Health, University of Alberta, Edmonton, AB, [2]Dept of Physical Therapy, University of Alberta, Edmonton, AB, [3]School of Public Health, University of Alberta, Edmonton, AB, [4]University of Texas. M.D Anderson Cancer Center, Houston, TX

Background/Purpose: Cormorbid conditions can affect the recovery of total knee arthroplasty (TKA), yet aside from counting the number of comorbid conditions, the identification of which conditions have the most impact on pain relief and functional recovery is not clearly understood. We looked at the pattern of recovery for pain and function of TKA to determine what comorbid conditions had the most impact on the recovery following TKA in terms of pain relief and functional improvement.

Methods: Longitudinal prospective inception cohort of 405 patients receiving elective primary TKA were followed within a month prior to surgery, and 1, 3, 6 months after surgery. The outcome measures, knee pain and function were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Comorbid conditions were extracted from the chart and reported by the patient using a list generated from the Charlson Comorbidity Index and National Population Health Survey. The Center for Epidemiologic Studies-Depression (CES-D) was used to screen for depression. Measurements were repeated at each of the follow-up interviews. Linear mixed models were developed for pain and functional recovery to evaluate changes over time while adjusting for covariates.

Results: The mean age was 68 (SD10) yrs; 249(61.5%) were female. Mean pre-operative pain improved from 49.0 (SD 17.0) to 17.9 (SD 17.1) over the 6 months ($p<0.001$). The mean pre-operative function improved from 44.7 (SD 17.3) to 19.8 (SD 16.2) over this time ($p<0.001$). At baseline, mean depression score was 8.7 (SD 8.4), 90 (22%) had chronic respiratory disease, 156 (39%) back pain, 60 (15%) diabetes and 114 (28%) urinary incontinence. After controlling for age, sex, baseline pain and time, depression score (coeff 0.2, $p<0.001$), back pain (2.7, $p<0.01$), chronic respiratory disease (4.1, $p<0.001$), and diabetes (2.8, $p=0.03$) had a deleterious effect on pain relief. For instance, the coefficient of diabetes in this model implies diabetic patients have 2.8 units less pain relief over the 6 months than non-diabetic patients. Depression score (0.2, $p<0.01$), chronic respiratory disease (4.0, $p<0.001$), and urinary incontinence (2.1, $p=0.04$) affected functional improvement. No interactions were found between depression and diabetes, chronic respiratory disease or urinary incontinence.

Conclusion: Patients with higher depression scores or chronic respiratory disease are likely to have slower pain relief and functional improvement over a 6 month recovery. Active pain management and rehabilitation should target these patient subgroups given the slower recovery patterns seen. Managing these conditions before surgery may also help patients attain more favourable outcomes.

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The Role of Pre-Operative Pain Sensitisation in Chronic Pain After Knee Joint Replacement. Vikki Wylde[1], Shea Palmer[2], Ian Learmonth[1] and Paul A. Dieppe[3]. [1]University of Bristol, Bristol, United Kingdom, [2]University of the West of England, Bristol, United Kingdom, [3]University of Exeter, Plymouth, United Kingdom

Background/Purpose: Although total knee replacement (TKR) is a successful intervention for most patients with knee OA, approximately 20% of patients

continue to experience chronic pain in their replaced knee. The reasons for this are unknown. The aim of this study was to use Quantitative Sensory Testing (QST) to explore whether pain sensitisation could be one factor contributing to this phenomenon.

Methods: Pressure pain thresholds (PPTs) were measured in 107 knee OA patients listed for TKR, and a subgroup of 47 of these patients were followed-up for a year after TKR using the WOMAC Pain scale (0–100; worst to best). To provide normative data, PPTs were also measured in 50 age- and gender-matched healthy participants without knee pain. QST was performed on the knee listed for surgery (or the right knee of healthy participants) to identify localised pain sensitisation and the pain-free forearm to identify widespread hyperalgesia. PPTs were measured 3 times at each body site using a digital Algometer, and the mean of the last 2 reading was used as the PPT.

Results: The mean age of the 107 OA patients was 69 years, which was not significantly different from the mean age of 68 years for the healthy participants ($p=0.524$). The gender distribution between the two groups was similar with 52% of OA patients being male, compared to 42% of healthy participants.

Pre-operatively, the 107 OA patients had significant lower median PPTs than healthy participants at the knee ($p<0.001$) and the forearm ($p<0.001$), indicating localised and distant pressure hyperalgesia. Of the 47 patients followed up after surgery, 13 had chronic pain in their replaced knee at 1-year post-operative (defined as WOMAC Pain score ≤ 75 at 3-months and 1-year). There was a trend for approximately twice as many patients with chronic pain after TKR to have had pre-operative localised hyperalgesia (62% vs 29%) or widespread hyperalgesia (38% vs 18%), compared to patients with no chronic pain after TKR. Although this trend did not reach statistical significance for widespread hyperalgesia ($p=0.132$), it was significant for localised hyperalgesia ($p=0.043$).

Conclusion: We found that patients with knee OA have evidence of localised and widespread hyperalgesia to pressure stimuli, suggesting changes in the central nervous system resulting from chronic nociceptive input. This pain sensitisation appears to be associated with the development of chronic pain after TKR. If confirmed in a larger study, this finding suggests that some patients may experience chronic pain after TKR because of abnormal pain processing, and that they could benefit from a pre or post-operative interventions to reduce this pain sensitisation.

ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Clinical Characteristics
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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The Childhood Arthritis & Rheumatology Research Alliance Network Registry: Demographics and Characteristics of the Initial One Year Cohort.

Marc D. Natter[1], Jane R. Winsor[2], Kathleen A. Fox[2], Norman T. Ilowite[3], Kenneth D. Mandl[1], Kelly L. Mieszkalski[4], Christy I. Sandborg[5], John S. Sundy[4], Carol A. Wallace[6], Laura E. Schanberg[4] and CARRAnet Investigators[7]. [1]Children's Hospital Boston, Boston, MA, [2]Duke Clinical Research Institute, Durham, NC, [3]Children's Hospital Montefiore, Bronx, NY, [4]Duke University Medical Center, Durham, NC, [5]Stanford University, Palo Alto, CA, [6]Childrens Hosp & Regional Med, Seattle, WA, [7]Durham, NC

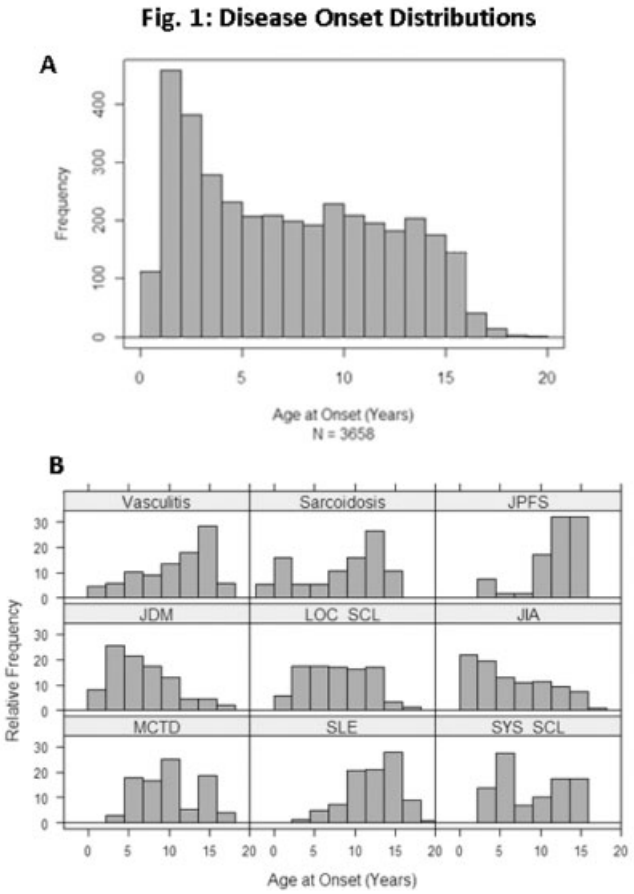
Background/Purpose: In 2009, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) established a longitudinal multicenter, multiple disease U.S. national registry (CARRAnet) for pediatric rheumatology with the intent of providing 60 participating clinical sites a new framework to drive observational clinical research and evidence-based care. CARRAnet seeks to enroll up to 20,000 subjects with childhood-onset rheumatic disease and twice yearly follow-up. We report baseline characteristics of the initial one year enrollment cohort; disease-specific results are reported separately.

Methods: Enrollment commenced 5/29/2010 with data available through 6/10/2011. Inclusion criteria comprised 1 of 8 categories of defined rheumatic disease with pediatric onset (e.g. prior to the 16th birthday) in subjects <=21 years (localized scleroderma, juvenile dermatomyositis, juvenile idiopathic arthritis, juvenile primary fibromyalgia syndrome, SLE or mixed connective tissue disease, sarcoidosis, systemic sclerosis, and vasculitis). A common baseline data set and one disease-specific data set was completed on each participant by interview and chart review. Data cleaning and analysis employed Microsoft Excel and Access (Microsoft Corp), SAS (SAS Institute), and R (R Foundation for Statistical Computing).

Results: The analysis cohort reflected 3860 subjects, predominantly with JIA, enrolled from 51 centers throughout the US; 63 variables were collected for the shared baseline form with summary statistics presented in the table and figures. The population reported overall good to excellent health by patient and physician report: 95% with mean HRQOL good to excellent; physician mean global assessment of disease activity (PGAS) 1.7 on 0–10 scale. PGAS correlated with subject reports (CHAQ, subject global, subject pain scores—Pearson corr. 0.30, 0.40, 0.42 respectively). Medication use was prevalent, including 71% ever on steroids, 40% ever on biologics, and 31% currently on biologics. A wide range, however, was seen on both objective and subjective measures, identifying probable subpopulations with high disease activities.

Table 1. Summary characteristics

Demographic Measures	**N (%)**
Total Participants Studied	3860
Female Gender	2851 (74%)
White/Caucasian	3266 (85%)
Age at onset of symptoms, mean in years	7.3
Age at baseline visit, mean in years	12.1
Black or African American	393 (11%)
Asian	148 (4%)
American Indian or Alaska Native	60 (2%)
Native Hawaiian or Pacific Islander	29 (<1%)
Hispanic Ethnicity	150 (12%)
Primary Rheumatic Diagnosis	
Juvenile Idiopathic Arthritis	2850 (74%)
Juvenile Dermatomyositis	290 (8%)
Systemic Lupus Erythematosus	388 (10%)
Localized Scleroderma	130 (3%)
Mixed Connective Tissue Disease	69 (2%)
Vasculitis	67 (2%)
Systemic Sclerosis	26 (<1%)
Sarcoidosis	19 (<1%)
Juvenile Primary Fibromyalgia Syndrome	41 (1%)
Assessments (scale: best -> worst)	**Mean & (Range)**
Physician Global Assess Disease Activity (0–10)	1.7 (0–10)
Subject Global Assess Disease Activity (0–10)	2.3 (0–10)
Subject Pain Score (0–10)	2.4 (0–10)
CHAQ (0–3)	0.3 (0–3)
HRQOL – Good, Very Good, Excellent (%)	95%
HRQOL – Very Poor, Poor (%)	4%
Family History (First Degree Relative) of	**N (%)**
Psoriasis	246 (6%)
Rheumatoid Arthritis	236 (6%)
Autoimmune Thyroiditis	190 (5%)
Fibromyalgia	154 (4%)
Juvenile Idiopathic Arthritis	136 (4%)
Diabetes Type 1	118 (3%)
Systemic Lupus Erythematosus	88 (2%)
Inflammatory Bowel Disease	82 (2%)
Spondyloarthritis or Ankyl. Spondylitis	56 (1%)
Multiple Sclerosis	35 (1%)
Celiac Disease	28 (<1%)
Uveitis	10 (<1%)
Medication Use	N (%)
Steroids (ever)	2734 (71%)
Steroids (longterm daily, ever)	1862 (48%)
Steroids (IV pulse, ever)	611 (16%)
Steroids (IA, ever)	1301 (34%)
Biologics (ever)	1528 (40%)
Biologics (current)	1184 (31%)
TNF-a Blockers (current)	979 (25%)
DMARDs (ever)	3072 (80%)
DMARDs (current)	2340 (61%)
Methotrexate (current)	1704 (44%)
NSAIDs (current)	1578 (41%)
Opioids (current)	31 (<1%)



Conclusion: The initial CARRAnet cohort reflects predominantly low disease activity with favorable self-reports. This is not a population study and issues of enrollment bias require further investigation. Despite the overall well-being of the population, the high use of steroids, biologics, and DMARDs, along with significant subpopulations concerning for high disease activity, are important areas of future focus.

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Distinct Phenotypical Clusters In Childhood Inflammatory Brain Diseases: Implications for Diagnostic Evaluation. Tania Cellucci, Pascal N. Tyrrell, Marinka Twilt, Gordon S. Soon, Ivanna Yau, Shehla Sheikh and Susanne M. Benseler. The Hospital for Sick Children, Toronto, ON

Background/Purpose: The spectrum of childhood Inflammatory Brain Diseases (IBrainD) is rapidly expanding. Overlapping clinical presentations lead to significant diagnostic uncertainty. However, early diagnosis and treatment are critical to prevent brain damage. The aim of this study was to identify distinct clusters of childhood IBrainD based on clinical, laboratory and imaging features at presentation in order to guide the diagnostic approach.

Methods: A single centre cohort study was performed with consecutive children up to 18 years of age who were diagnosed with an IBrainD from June 1989 to December 2010 and were enrolled in the BrainWorks cohort at The Hospital for Sick Children. Demographic, clinical, laboratory, neuroimaging and histologic data at diagnosis were collected. K-means cluster analysis was performed to identify clusters of patients based on key presenting features. Associations between the clusters and variables including demographic characteristics, diagnostic tests and diagnosis were determined.

Results: A total of 165 children (51% females, median age 8.3 years) with IBrainD were identified: 123 primary angiitis of the CNS (cPACNS), 11 secondary CNS vasculitis, 7 neuronal antibody syndromes, 6 post-infectious IBrainD and 18 other IBrainD (e.g. neurosarcoidosis). Three distinct clusters of children with IBrainD were identified based on key clinical and imaging features at diagnosis. Children in cluster 1 were significantly more likely to present with seizures, behaviour changes and cognitive dysfunction ($p<0.01$), while those in cluster 2 experienced vision abnormalities and ataxia ($p<0.01$). Paresis was the most common presenting feature in cluster 3 ($p<0.01$). Predominant MRI findings in clusters 1 and 2 were bilateral T2/FLAIR lesions ($p<0.01$) and in cluster 3 were unilateral ischemic lesions ($p<0.01$). The clusters were associated with specific diagnoses and diagnostic test results: for example, children in cluster 3 were likely to have positive findings on angiography.

Conclusion: Children with IBrainD presented with distinct phenotypical patterns that are associated with specific diagnoses. This information should inform the development of a diagnostic classification for childhood IBrainD in the future. Based on the identified clusters, specific pathways of diagnostic evaluation are warranted.

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Whole Body Magnetic Resonance Imaging in Juvenile Spondyloarthritis: Will It Provide Vital Information Compared to Clinical Exam Alone? Alisa C. Rachlis[1], Paul S. Babyn[2], Edrise Lobo-Mueller[3], Susanne M. Benseler[1], Jennifer Stimec[4], Michelle Anderson[1], Margaret Reaume[1], Kristi J. Whitney-Mahoney[1], JoAnne Marcuz[1] and Shirley Tse[3]. [1]The Hospital for Sick Children, Toronto, ON, [2]Saskatoon Health Region, Saskatoon, SK, [3]Hospital for Sick Children, Toronto, ON, [4]Hospital For Sick Children, Toronto, ON

Background/Purpose: Juvenile-onset spondyloarthritis (JSpAs), referred to as enthesitis-related arthritis (ERA) sub-type under the International League of Associations for Rheumatology (ILAR) classification are characterized by arthritis and enthesitis largely affecting the lower limbs. Clinical exam can be inconclusive and decisions for therapy become difficult. Whole body MRI (WB-MRI) can assess several body regions within a reasonable scan time. The purpose of this study was to evaluate if WB-MRI identifies areas of inflammation seen with JSpAs and agrees with positive findings on clinical exam.

Methods: Patients diagnosed with ERA (ILAR criteria) followed in the JSpA Clinic at The Hospital for Sick Children (Aug 2008 – Jan 2010) who received a WB-MRI within 3 months of their last clinic visit were included. WB-MRIs consisted of multiple evaluations of 13 regions and were reviewed and scored by consensus of 3 radiologists (PB, ELM, JS). WB-MRIs were correlated to joint and entheseal clinical exam. Arthritis was defined as the presence of synovitis, effusion, or bony erosions (sacroiliac joints (SIs)) and enthesitis as edema in the tendon and bone attachment site. Data were described using means, standard deviations and proportions. MRI results were expressed as detecting more, less or similar findings to clinical exam. Kappa statistics measured agreement.

Results: There were 23 patients (83% male) with a mean age at diagnosis of 12.6 ± 2.1 years. Time between last clinic visit and WB-MRI was 0.87 ± 0.68 months. A total of 42 active joints and 16 entheses were observed on WB-MRI. Bone marrow edema (BME) like signal changes were most common (83%) with the majority in lower extremities. Arthritis was seen in 70% of patients (SIs most common, 48%), bony erosions in 35% (SIs most common, 22%), synovitis in 22% (ankles most common, 17%), and enthesitis in 26% (hip region most common, 17%). Clinical exam revealed 65% of patients had arthritis and 52% had enthesitis. By all joint sites, WB-MRI detected more findings in keeping with enthesitis in 5%, similar results in 82%, and less in 13% in comparison to clinical exam. WB-MRI detected more arthritis in 7%, similar results in 79% and less in 14% by all joint sites in comparison to clinical exam. While 70% of regions on WB-MRI that reported a positive finding had an associated BME like signal change, 40% of BME sites correlated to either clinical arthritis (88%) or enthesitis (39%). Good agreement (Kappa coefficient > 0.4) was demonstrated for knee, ankle and foot arthritis, and hip region enthesitis.

Conclusion: The current study demonstrates that WB-MRI identified characteristic lesions expected in our JSpA population. For arthritis, while there was good agreement for peripheral arthritis, WB-MRI was superior to clinical exam for the hips, SIs and spine. For enthesitis, clinical exam over-estimated disease activity in the periphery making WB-MRI an important tool to evaluate entheseal disease. The results of this study illustrate that WB-MRI may become an objective addition to the diagnostic work-up of JSpAs, allowing for assessment of disease presence and severity, monitoring of treatment outcomes and detection of early and subtle inflammatory changes.

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Decreased Expression of Nicotinamide Phosphoribosyltransferase (NAMPT) in Active Juvenile Idiopathic Arthritis Patients Receiving Methotrexate. E.J. Fox, M. Gibson, L.Q. Zhang, J.S. Leeder, S.Q. Ye and M.L. Becker. Children's Mercy Hospital, Kansas City, MO

Background/Purpose: Nicotinamide phosphoribosyltransferase (NAMPT) also termed Pre-B cell colony-enhancing factor (PBEF) or Visfatin, is an adipocytokine that has been identified as a pro-inflammatory mediator in cardiovascular disease, pulmonary inflammation and sepsis. Most recently, its effects have been studied in rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and ankylosing spondylitis. In RA, NAMPT has been shown to

activate human leukocytes and induce proinflammatory cytokines, including IL-1, IL-6, and TNF-α. However, the role of NAMPT has not been studied in pediatric rheumatic diseases, particularly Juvenile Idiopathic Arthritis (JIA). Our study assesses the variability of NAMPT in a cross sectional JIA cohort and the association with treatment modality, disease severity and subtype.

Methods: This single center cross-sectional study at a tertiary care children's hospital evaluated 115 JIA patients on stable doses of methotrexate (MTX) and 80 JIA patients who were not currently on MTX. After obtaining informed consent, blood was obtained from patients during routine screening labs. Clinical data were collected by chart review. Plasma concentrations of NAMPT were measured using a human NAMPT-specific carboxy-terminal enzyme immunoassay kit, and genotyping was performed for two SNPs (T-1001G and C-1535T) in the NAMPT promoter region using a 5'-nuclease based assay.

Results: A total of 195 JIA patients were included in the analysis. Median (quartile) NAMPT concentrations were 19.8 (15.4, 25.8) ng/ml, (range 7.4– 56.2). Higher concentrations of NAMPT were found in subjects with active arthritis at the time of the visit (p=0.041), specifically in subjects not receiving anti-TNF-α therapies (p=0.026). Lower concentrations of NAMPT were observed in subjects receiving MTX (p=0.018). The use of MTX remained a significant predictor of NAMPT concentrations (p=0.023) in a multivariable linear regression model controlling for the presence of active arthritis and anti-TNF-α use. There was no association between NAMPT concentrations and age, ESR, number of active, swollen, tender, or limited joints, or BMI. There were no statistically significant differences in NAMPT concentrations between JIA subtypes, in subjects receiving anti-TNF-α therapies, or with different genotypes in the SNPs analyzed

Conclusion: NAMPT or PBEF/Visfatin is a pro-inflammatory adipocytokine that inhibits neutrophil apoptosis and has been a new investigational therapeutic target in RA. In our cohort of JIA patients, we have shown higher concentrations of NAMPT in children with active arthritis, specifically in children not being treated with anti-TNF-α therapy. Interestingly, NAMPT concentrations in patients receiving MTX therapy were lower, an effect seen despite controlling for the use of anti-TNF-α therapy. This may suggest additional unknown mechanisms in which MTX affects the innate immune system and complex pathways of cytokine induction. These data also support the potential further study of novel anti-NAMPT therapeutics in children with JIA.

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Brain Morphometric Changes Associated with Childhood-Onset Systemic Lupus Erythematosus and Neurocognitive Deficit. Marisa Klein-Gitelman[1], Adlin Cedeno[1], Aimee Baker[2], Frank Zelko[1], Dean Beebe[2], Blair Dina[1], Anna Carmela P. Sagcal-Gironella[2], Darren Gitelman[3], Hermine Brunner[2], Mark Difrancesco[2] and Travis Beckwith[2]. [1]Children's Memorial Hospital, Chicago, IL, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Northwestern University, Chicago, IL

Background/Purpose: 1) To use structural magnetic resonance imaging (MRI) to characterize gray matter (GM) and white matter (WM) volumetric differences between cSLE patients and matched best-friend controls. 2) To ascertain whether the presence of neurocognitive deficits (NCD), as measured by formal neuropsychological (NP) testing, correlates with these volumetric differences.

Methods: As part of a MRI study protocol, high-resolution (1 mm isotropic), 3-dimensional, T1-weighted structural MRI data were acquired for 44 subjects (F:M=36:8; age 10–17 yrs; 59% African-American, 41% Caucasian; 11% Hispanic), 22 with cSLE and 22 controls matched for age, sex, and race. All subjects underwent NP testing allowing categorization according to NCD status, as defined previously by our group (Arthritis Care Res. 2010; 62: 1029–33). Image data were pre-processed and analyzed in SPM8 (www.fil.ion.ucl.ac.uk/spm) using VBM8, a toolbox for implementing voxel-based morphometry (VBM) analysis (dbm.neuro.uni-jena.de/vbm). Probability density maps for GM and WM tissue types were calculated for each subject and compared according to disease status and NCD status by random effects analysis.

Results: For GM, several regions showed prominent differences in volume between the control and cSLE group (Fig 1). Most notably, a region comprising parts of anterior cingulate cortex, Brodmann area (BA) 32, the frontal eye fields (BA8), and premotor cortex (BA6) had greater volume for controls vs. cSLE. This outcome was also found in left inferior/dorsolateral prefrontal cortex and in right visual association areas (BA19 and BA37). Controls also tended to have greater WM volume than cSLE subjects in the right anterior corona radiate, adjacent to the cingulate regions with GM differences, and in the left superior longitudinal bundle (Fig 1). No WM or GM regions had volume differences with cSLE > controls. ANOVA that considered both disease and NCD status suggested that the anterior cingulate GM volume differences noted above were particularly evident for subjects with neurocognitive dysfunction.

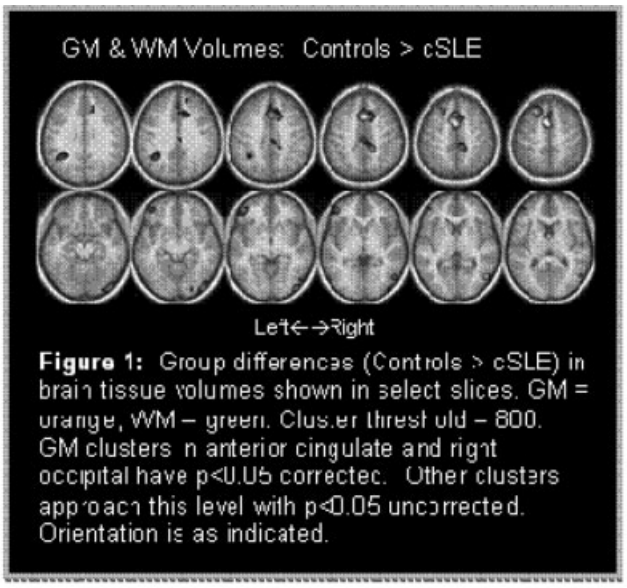

Figure 1: Group differences (Controls > cSLE) in brain tissue volumes shown in select slices. GM = orange, WM = green. Cluster threshold = 800. GM clusters in anterior cingulate and right occipital have p<0.05 corrected. Other clusters approach this level with p<0.05 uncorrected. Orientation is as indicated.

Conclusion: cSLE patients were found to have less GM cortical volume than their best-friend controls in anterior cingulate, prefrontal, and visual association regions that are pertinent to cognitive domains that have been previously shown to have deficits for this disease, including attention, working memory, and visuo-constructional ability. Concordance was observed between volume differences associated with disease state and NCD in the cingulate region. Relationships between these volumetric findings and functional connectivity are also being assessed in pursuit of a comprehensive network-based characterization of cSLE impact on the brain.

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Frequency and Levels of Maternal Antibodies Reactive with Full Length Ro52 and p200 in Umbilical Cord Blood and Risk of Cardiac Neonatal Lupus. Joanne H. Reed, Robert M. Clancy and Jill P. Buyon. New York University School of Medicine, New York, NY

Background/Purpose: Women with anti-SSA/Ro antibodies face a 2% risk of having a child with cardiac manifestations of neonatal lupus (cardiac NL). Serial echocardiograms of all anti-Ro exposed fetuses are generally recommended to detect potentially reversible incomplete blocks. Identification of a more specific marker of cardiac NL would channel intense monitoring to those fetuses at greatest risk of disease. Antibodies against Ro52 amino acids 200–239 (p200) have received international attention with inconsistencies regarding their utility in high risk assessment relative to the pregnancy exposure. Accordingly, evaluation of umbilical cord blood from affected and unaffected pregnancies was used to determine whether p200 antibodies confer added risk of cardiac NL over antibodies to full length Ro52.

Methods: Pregnancies resulting in cardiac or non-cardiac NL were identified from the Research Registry for Neonatal Lupus and the PR Interval and Dexamethasone Evaluation (PRIDE) study. Umbilical cord blood from anti-Ro exposed (mother tested positive for reactivity to native Ro60) neonates with cardiac NL, unaffected siblings, or unaffected neonates without any affected siblings (unaffected non siblings) were evaluated for reactivity with p200 peptide and full length recombinant Ro52 by ELISA. Serum from anti-Ro-positive mothers during the last 6 months of pregnancy was also evaluated. Reactivity (IgG isotype) was expressed as binding units based on a positive calibrator; a positive defined as mean +3 SD > 28 anti-Ro-negative controls.

Results: 122 umbilical cord blood samples were studied, 59 cardiac NL, 35 unaffected siblings, and 28 unaffected non siblings. All were positive for anti-Ro60 and 118 (97%) were positive for full length Ro52 antibodies. The frequency of anti-p200 was equivalent among cardiac NL (81%), unaffected siblings (91%), and unaffected non siblings (79%). Titers of anti-Ro52 were highest in cardiac NL (104.5±11.5) and their unaffected siblings (125.7±17.2) compared to unaffected non siblings (73.4±15.1), p = 0.026 and p=0.007, respectively and independent of gestational age. In contrast, anti-p200 titers were not significantly different among cardiac NL (45.7±3.7), unaffected siblings (59.8±9.3), or unaffected non siblings (50.7±18.1). Serum from 77 pregnant mothers (35 had a child with cardiac NL, 18 with an unaffected child but a prior cardiac NL child, 24 with only unaffected children) were tested. The frequencies and titers of anti-Ro52 and p200 antibodies were not significantly different among

the groups. Serum samples were available from multiple pregnancies in 10 mothers. Titers of anti-Ro52 and p200 antibodies were not significantly different between cardiac NL (Ro52: 69.1±23.5, p200: 49.2±34.1) or unaffected pregnancy (Ro52: 81.1±24.3, p200: 63.9±29.2) in the same mother.

Conclusion: Maternal p200 antibodies do not confer an added risk to fetal conduction defects over full length Ro52 antibodies. Titers of Ro52 or p200 antibodies do not vary over time or between cardiac NL and unaffected pregnancies in the same mother. However, higher titers of full length Ro52 antibodies are associated with neonates with cardiac NL and their unaffected siblings.

ACR Concurrent Abstract Session
Quality Measures and Innovations in Practice Management and Care Delivery I
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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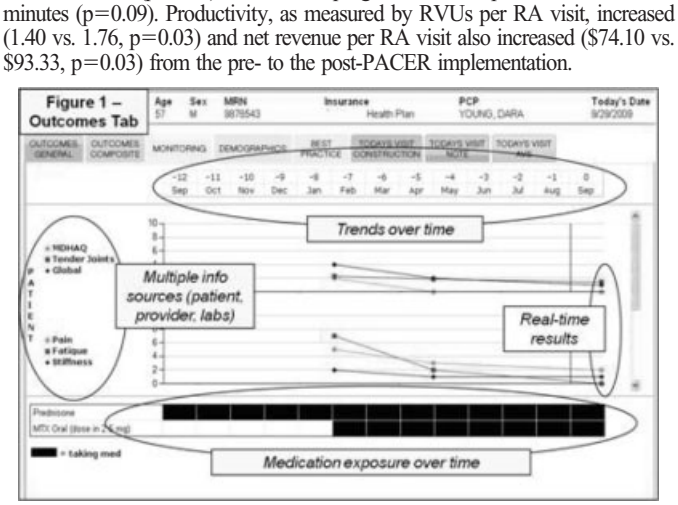
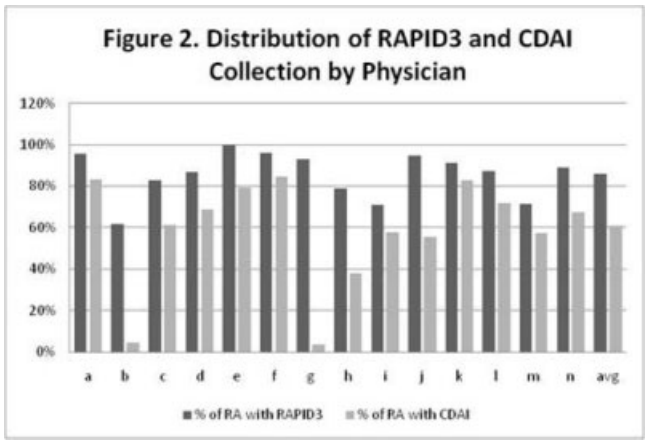
Rheum-PACER—Design, Implementation, and Adoption of Innovative Visual Display Software. Eric D. Newman[1], Virginia Lerch[2], J. B. Jones[2], William T. Ayoub[3], Thomas P. Olenginski[1], Thomas M. Harrington[1], Androniki Bili[1], Brian DelVecchio[1], Alfred E. Denio[1], Brian P. Oppermann[3], Sorina Dancea[1], Jana Antohe[1], Chad Walker[1], Rasa Bozaite-Gluosniene[1] and Walter Stewart[2]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Health System, Danville, PA, [3]Geisinger Medical Group, State College, PA

Background/Purpose: Electronic health records (EHRs) do not provide the information needed for optimal rheumatic disease care. Accordingly, we developed Rheum-PACER (Patient-Centric Electronic Redesign). PACER efficiently collects information from patients (touchscreen questionnaire) and effectively displays information from multiple sources (patient, nurse, physician, EHR) into a series of actionable views.

Methods: PACER is web-based but easily invoked using an EHR hyperlink. Functions include 1) demographics: diagnoses, treatments, social history, rheumatic tests; 2) outcomes: trends over time in simple measures (MDHAQ, pain, fatigue, stiffness, patient and physician global, joint counts—Figure 1) and complex measures (DAS28, CDAI, GAS, RAPID3), in the context of treatment given and in real time; and 3) documentation: auto-generation of a clinic note and patient summary. Implementation involved ownership by key team members, training of staff, and aligning incentives. PDSA (Plan-Do-Study-Act) redesign methodology was used to integrate PACER into 2 Rheumatology Clinics (academic and multispecialty). A pre vs. post-PACER implementation analysis was done for efficiency (physician time for chart review and progress note completion, n=107) and productivity (physician work effort [RVUs], notes reviewed by a certified coder, n=100).

Results: Over a 2 year period, 6,275 return patients completed 19,876 touchscreen questionnaires (TQs). 1,431 unique rheumatoid arthritis (RA) patients completed 6,781 TQs. For disease activity measures, 86% of RA patients had a completed RAPID3 (patient-derived composite measure) and 61% had a completed CDAI (patient and provider derived composite measure). PACER was well adopted by 12/14 physicians (Figure 2). Median chart review time fell from 5 to 4 minutes (p=0.39) and median progress note completion from 7 to 5.5 minutes (p=0.09). Productivity, as measured by RVUs per RA visit, increased (1.40 vs. 1.76, p=0.03) and net revenue per RA visit also increased ($74.10 vs. $93.33, p=0.03) from the pre- to the post-PACER implementation.





Conclusion: Rheum-PACER is innovative software that allows for the collection of objective information vital to optimal patient care delivery in real-time. Adoption of use was seen in 86% of physicians, and productivity improved significantly with no reduction in efficiency. Rheum-PACER has allowed the rapid development of a large objective rheumatic database—next steps include development of quality and task management functions to improve population management of patients with rheumatic diseases.

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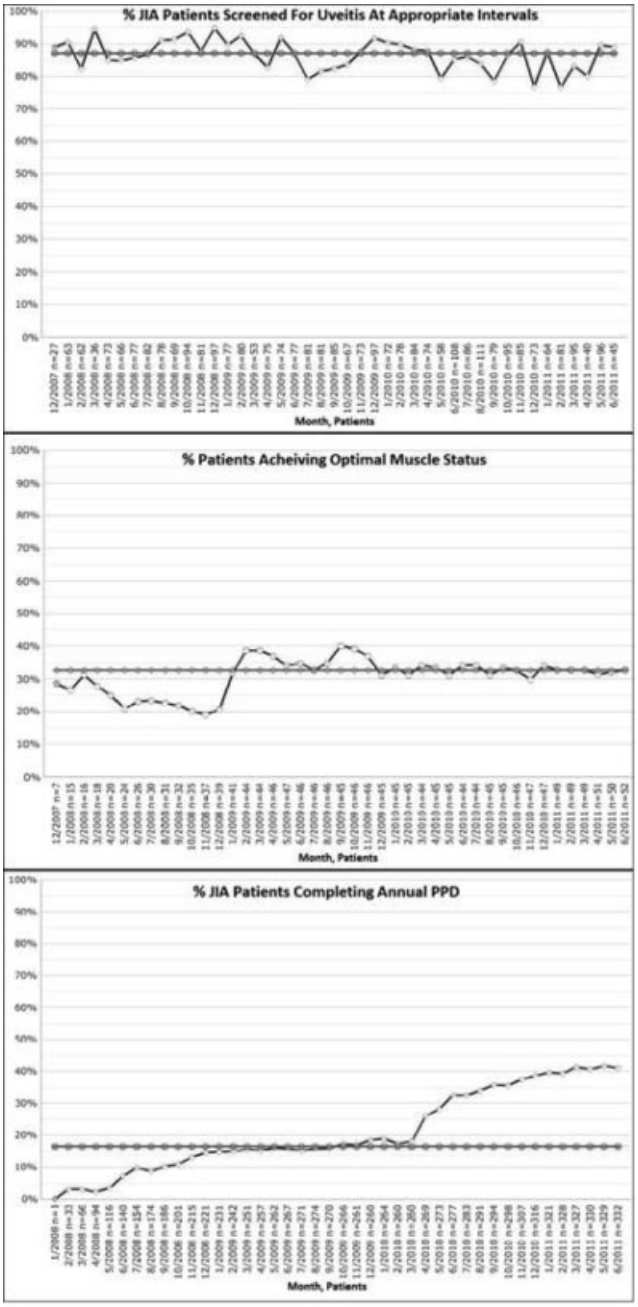
Generating Run Charts for Quality Improvement Using the Electronic Health Record. David W. Moser, Tracy V. Ting, Janalee Taylor, Daniel J. Lovell, Hermine Brunner, Jennifer L. Huggins and Esi M. Morgan DeWitt. Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: The American College of Rheumatology has focused on improving the quality of care. Quality improvement (QI) methodology employs plan-do-study-act cycles as a way of testing change with interventions. Run charts are considered effective analytic tools for studying quality measures over time and are a first step in developing statistical process control charts. The use of run charts allows for: 1) displaying data to make process performance visible; 2) determining if changes tested resulted in improvement; 3) determining if gains are being held; and 4) allowing for a temporal versus static view of data. We discuss how the electronic health record (EHR), specifically Epic, has been leveraged to generate run charts for our QI work.

Methods: An operational definition was created to describe the process being measured. Patients included in the run chart were defined using inclusion and exclusion criteria. Multiple criteria were used for complete ascertainment of the desired population. These data were obtained from problem lists, ICD-9 codes and flowsheets within the EHR. Flowsheets are a structured data capture tool that allow discrete variables to be extracted; free text data in clinic visits is not discrete data and thus not extractable. Data were graphically represented as proportions. The numerator was defined as the number of eligible patients meeting the desired outcome. The denominator was the total number of patients belonging to the process being measured. Data was visualized using a web-based reporting system

Results: We monitor run charts updated at monthly intervals from January 2008 in three rheumatologic conditions. For juvenile idiopathic arthritis we follow the percentage of patients achieving complete clinical remission by Wallace criteria, patients on biologic response modifiers screened for tuberculosis prior to first use and annually, and screening for uveitis at appropriate time intervals. Domains measured in systemic lupus erythematosus include the percentage of patients with controlled disease activity (SLEDAI<5) and hydroxychloroquine prescription rate. For the juvenile dermatomyositis patient population, the percent of patients with optimal muscle strength assessed by the childhood myositis assessment scale is measured. For all conditions we monitor completion of a self-management assessment tool and the percentage of patients with pain scores ≤ 3 (scale 0–10, 0 equals no pain). Examples of disease specific run charts are displayed in the accompanying figure.

Conclusion: The EHR can be designed and specifically modified to readily implement and integrate QI into clinical care. Repurposing clinical data has been a valuable tool in our QI efforts as we can now easily measure our performance in treating multiple diseases.



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Rheumatoid Arthritis Quality Measure Bundle—Development and Implementation. Chad P. Walker[1], Eric D. Newman[1], William T. Ayoub[2], David M. Pugliese[3], Jeffrey M. Barrett[1], Shea Mealia[1] and Androniki Bili[1]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Medical Group, State College, PA, [3]Geisinger Specialty Clinic, Wilkes-Barre, PA

Background/Purpose: Rheumatoid arthritis (RA) is associated with significant morbidity and mortality. The main cause of death is cardiovascular disease (CVD). We developed an RA quality measure bundle to identify care gaps that will allow improvement in population management.

Methods: Using American College of Rheumatology published guidelines, pertinent literature, and team meetings with primary care and Rheumatology, we reached consensus on a core bundle of quality measures for which our Rheumatology group would be attributable. The RA bundle has three areas of focus: disease activity, medication safety and comorbidity measures (Table 1). LDL was chosen as the comorbidity measure due to association of hyperlipidemia with CVD. The US Preventive Services Task Force recommendations for the general population were used (LDL level <130 mg/dl unless indications for lower levels for secondary CVD prevention). Data were extracted from the electronic medical record and specifically developed software that allows routine electronic capture of a composite disease activity measure (CDAI - Clinical Disease Activity Index). CDAI >10 was defined as active and ≤10 as not active RA.

Results: The baseline RA bundle results are displayed in Table 2. As expected, high percentages were noted in RA on DMARD (85%) – even higher when the measure was limited to active RA on DMARD (90%). However, lower scores were seen with % of RA patients with low disease activity–61% in patients where a CDAI was available, and 28% with the most conservative measure (no CDAI available = low disease activity not achieved). Safety measures showed some opportunity (54–73%). Comorbidity measures showed excellent baseline measurement (91% had LDL checked) but opportunity for improvement in the actual measurement goal (76% had LDL within goal).

Table 1. Measure Definitions

Disease Activity Measures	
RA* on DMARD	DMARD on active drug list
Active RA on DMARD	CDAI done and >10, then on DMARD
RA at low disease activity**	CDAI done and ≤ 10
Medication Safety Measures	
PPD if on Biologic	If on biologic, PPD ever done?
Influenza Vaccine per Recommendations	Yearly unless contraindications
Pneumococcal Vaccine per Recommendations	Per 2008 ACR recommendations
Comorbidity Measures	
LDL checked	Checked within 5 years if age > 45
LDL < 130	LDL < 130 within 5 years

RA = Rheumatoid Arthritis, DMARD = Disease Modifying Anti Rheumatic Drug, CDAI = Clinical Disease Activity Index, PPD = Purified Protein Derivative, ACR = American College or Rheumatology, LDL = Low Density Lipoprotein
* RA population defined as 714.0 encounter diagnosis and at least 1 visit to a rheumatology department over the past 12 months
** CDAI ≤ 10

Table 2. Baseline Measure Achievements

	Population (n)	Applicable	% Meeting Metric
Disease Activity Measures			
RA* on DMARD	1409	1663	85
Active RA on DMARD	260	288	90
RA at low disease activity**	460	1663	28
(RA with CDAI measured)		(749)	(61)
Medication Safety Measures			
PPD if on Biologic	414	565	73
Flu Vaccine Yearly	1080	1663	65
Pneumococcal Vaccine if applicable	903	1663	54
Comorbidity Measures* **			
LDL checked	641	705	91
LDL < 130	537	705	76

RA = Rheumatoid Arthritis, DMARD = Disease Modifying Anti Rheumatic Drug, CDAI = Clinical Disease Activity Index, PPD = Purified Protein Derivative, CDC = Center for Disease Control and Prevention, LDL = Low Density Lipoprotein
* RA population defined as 714.0 encounter diagnosis and at least 1 visit to a rheumatology department over the past 12 months
** CDAI ≤ 10
*** Population limited to patients with providers within the health system

Conclusion: This is the first report of a RA quality measure bundle for which a Rheumatology department has agreed to be held accountable. We have developed the ability to capture these measures electronically, including measures which are more difficult to measure and achieve, yet far more important to achieve better outcomes (i.e. % of RA at low disease activity, not just % on DMARD). Opportunities were found to improve data measurement gaps (e.g. greater capture of a CDAI value) and quality

care gaps (e.g. e.g. vaccine rate). Capturing patient and physician data systematically allows identification of care gaps in RA population management. Next steps include internal discussion of the bundle results and focusing on care process redesign to improve these gaps.

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Improving Adherence to Glucocorticoid Induced Osteoporosis Guidelines. Minna J. Kohler[1], Matxalen Amezega[2], James Drozd[3], Susan Crowley[1], Barbara Gulanski[1], Daren Anderson[4] and Liana Fraenkel[5]. [1]Yale University School of Medicine, New Haven, CT, [2]Griffin Hospital, Derby, CT, [3]VA Connecticut Healthcare System, West Haven, CT, [4]Community Health Center, Inc., Middletown, CT, [5]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT

Background/Purpose: ACR guidelines recommend that patients receiving glucocorticoids (GCs) take calcium (Ca) and vitamin D (Vit D) supplements for any duration of GC use. However, adherence to these recommendations is poor. The purpose of this study was to examine whether use of an automated prescription order set increases the number of co-prescriptions for Ca and Vit D for patients on GCs.

Methods: We designed an automated prescription order set such that Ca and Vit D supplements were automatically ordered each time a prednisone electronic prescription was placed for 2 or more weeks. Physicians had the option of not ordering supplements by unchecking a box. The order set was not generated for patients with hypercalcemia. We used a pre-post design to examine the effectiveness of the intervention. A database search was performed for all patients who had one or more orders of GCs. The first GC order was chosen for those with multiple prescriptions. Clinical data were collected over 12 months before (T1) and after (T2) the intervention. We compared the proportion of patients prescribed GCs who were co-prescribed Ca and Vit D supplements or who purchased supplements over the counter. Associations between patient and provider characteristics were examined using logistic regression. Reasons for physician non-adherence were collected after T2.

Results: 1041 patients had a GC prescription of at least 2 weeks duration: 535 during T1 and 506 during T2 respectively. The most frequent prescribers were internal medicine/primary care 480 (46%), rheumatology 179 (17%), and pulmonary 63 (6%) physicians. The percent of co-prescriptions for Ca (37% to 49%) and Vit D (38% to 53%) increased significantly after the new order set was implemented ($p<0.0001$). Patient demographic and clinical characteristics did not differ across time periods. One patient with hypercalcemia was precluded from co-prescription during T1 and 2 were precluded in T2. Older age, female sex, duration on GCs, bisphosphonate use, and being a fellow or resident versus an attending, were also significantly associated with prescription of Ca and Vit D. Bi-and multivariate analyses are presented in the table below. Previous fracture history and physician specialty were not related to ordering supplements. Physicians stated that they were unaware of any evidence supporting the ACR recommendation of Ca and Vit D co-prescription "for any duration of GC use". This reason explained the strong association between duration of GC use and prescribing supplements and the reason many patients did not receive supplements.

Table. Predictors of Ca and Vit D Co-Prescriptions

	Calcium		Vitamin D	
Variable	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Older age	1.26 (0.95–1.66)	1.06 (0.78–1.45)	1.33 (1.01–1.76)	1.20 (0.88–1.63)
White	1.02 (0.71–1.48)	0.97 (0.65–1.46)	0.68 (0.47–0.97)	0.60 (0.40–0.90)
Female	2.62 (1.43–4.78)	2.78 (1.43–5.41)	2.16 (1.19–3.91)	2.22 (1.16–4.26)
GCs for 3 months or more	2.97 (2.29–3.85)	2.92 (2.18–3.00)	2.81 (2.20–3.67)	2.78 (2.09–3.69)
Current bisphosphonate use	5.09 (3.43–7.52)	3.90 (2.50–6.08)	4.04 (2.75–5.94)	3.09 (2.00–4.77)
Diagnosis of osteoporosis	2.60 (1.68–4.04)	1.24 (0.72–2.11)	2.47 (1.59–3.84)	1.30 (0.77–2.20)
Level of provider	0.82 (0.70–0.96)	0.64 (0.54–0.77)	0.84 (0.72–0.98)	0.67 (0.56–0.79)
T2 versus T1	1.68 (1.31–2.15)	1.78 (1.36–2.33)	1.81 (1.42–2.32)	1.90 (1.50–2.48)

Conclusion: Implementation of an automatic prescription for Ca and Vit D supplementation significantly improves adherence to ACR guidelines. Hypercalcemia is not a limiting factor in co-prescription. The lack of data supporting supplements for any duration of GC use is a significant barrier to adherence.

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Use of Quality Improvement Methodology to Improve the Safety of Intravenous Infusions in a Pediatric Rheumatology Practice At a Tertiary Care Children's Hospital. Pai-Yue Lu, Janalee Taylor, Moussa El-hallak, Keith A. Sikora, David W. Moser, Terry M. Moore, Julie V. Ranz, Judy Thomas, Grace McIntyre-Patton, Jennifer L. Huggins and Tracy V. Ting Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: Medication safety remains at the forefront of patient care. The 2006 Institute of Medicine report, "Preventing Medication Errors," urged hospitals to take action to reduce the potential for errors. Regulatory agencies require institutions to identify, evaluate, reduce, respond, and prevent harm related to medical care. Safe administration of intravenous (IV) infusions in pediatric patients is a complex process. The development of new IV biologics for the treatment of pediatric rheumatologic conditions has led to an increase in our hospital administered infusions. The overall aim of this project was to improve the safe delivery of our IV infusions.

Methods: Key members of the pediatric rheumatology division formed a multidisciplinary improvement team led by clinical fellows. First, process flow mapping of the IV infusion system was performed, including scheduling, communication among staff and providers, and order entry. Next, Failure Mode Effect Analysis (FMEA) was conducted, providing the team with a systematic method to identify steps where system failures may occur. Time to an event and order errors were monitored. Lastly, Plan-Do-Study-Act (PDSA) cycles were performed, which focused on 4 areas of change concepts: a) improved work flow, b) improved communication, c) process standardization, and d) building reliability.

Level 1 and Level 2 reliability concepts guided interventions and testing. Level 1 (80–90% reliability) interventions included order training and education. Also, 3 process changes were implemented: delegation of nursing tasks to review upcoming infusions, weekly automated email reminders to providers for sign-off, and weekly order entry by fellows. Level 2 reliability (95% reliability) concepts included standardization of evidence-based order sets and a provider checklist for infusions. Medication errors were categorized using the hospital's coding system of "near miss event", "precursor event", and "serious safety event".

Results: IV infusions are prescribed for 82 patients, with an average of 65 (79%) occurring monthly. Order entry errors occurred 37% of the time. System analysis revealed several problems: 1) discrepancy of prescribed dosages among providers, 2) irregular completion of order entry, 3) untimely provider sign-off on orders, 4) absence of expiration date for electronic orders, and 5) accidental delivery of incorrect medication to a patient, which was our one precursor event – an event that reached the patient but resulted in minimal or temporary harm—that was identified during the process of change.

Conclusion: Quality improvement methods allow for ready identification of problems (order errors, time to event) and solutions for testing and adoption. In performing only a few PDSAs, we were able to implement reliable systems changes, with the goal to prevent future errors. While only one precursor event was identified, this event resulted in institutional policy change for standardizing order expiration. Continued monitoring of the process is important to identify and reduce both unnecessary variability and deviations from clinical guidelines and best practices.

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Improving the Influenza Vaccination Rate in Patients Visiting Pediatric Rheumatology Clinics Using Automatic Best Practice Alert in Electronic Patient Records. Anjali Patwardhan[1], Kelly Kelleher[1], Dennise Cuningham[2] and Charles H. Spencer[1]. [1]Nationwide Childrens Hospital, Columbus, OH, [2]Nationwide Childrens Hospital, Columbus

Background/Purpose: Children with rheumatic disease who are infected with influenza have increased rates of complications. Influenza-related morbidity and mortality can be reduced by improving the flu vaccination rate. We used a single prong best practice alert to increase the influenza vaccination rate in a high risk population of patients with rheumatic diseases.

Methods: Institutional Review Board approval was obtained for retrospective chart review. We examined three yearly cohorts (2007, 2008, and 2009 for baseline status) of rheumatology clinic patients from a large pediatric hospital for evidence of influenza vaccination in the electronic health record. We introduced an electronic health record (EHR) intervention best practice alert reminder in our patients' records from October 2009 until the end of January 2010. We compared claims-based records of receipt over 3 years. Using Clarity Report Write for EPIC, each chart was examined for evidence of influenza vaccination in order to test for vaccination rate difference amongst the cohorts. We revaluated our intervention after the flu season in 2010, through Delphi survey of the stakeholders. Delphi Questionnaire of Stakeholders resulted in the several changes to the EHR intervention. It was reprogrammed to trigger upon initial entry into the EHR and, remained until all questions were answered & the reminder was utilized from 15 Sept 2010 – 15 April 2011. This second EHR best practice alert was made non-negotiable with better blocking power. It was in effect in the flu season for long enough to be able to change a provider's behavior. We re-evaluated the vaccination rate for flu after the flu season in 2011 for improvement. We employed logistic regression equations to control for possible confounders (age, sex, ethnicity, insurance status, distance from clinic and attending physician) using SAS 9.1.3

Results: There was a significant difference in the probability of being vaccinated before and after intervention (p value <0.0001). With the rate increased from 5.9 % in 2007 and 7.8% in 2008 to 25.5 % in 2009. Refinement of the pop-up (2^{nd} intervention) in 2010–2011 resulted in increase of influenza immunization to 43.9%. In all three years, individual attending's contribution and ethnicity of patients had significant effects on vaccination rate

Conclusion: EHR-embedded information in past studies has been only modestly effective in improving care for many chronic conditions. Our automatic best practice alert reminder for flu-vaccine appears to be effective in changing behaviors and improving the vaccination rate in rheumatology clinics

ACR Concurrent Abstract Session
Rheumatoid Arthritis Clinical Aspects: Cardiovascular Disease
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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Differential Predictors of Mixed and Fully Calcified Coronary Plaques in Coronary Artery Disease-Naïve Patients with Rheumatoid Arthritis. George A. Karpouzas[1], Jennifer Malpeso[2], Dong Li[2], Panteja Razaeian[2], Maria V. Peralta[2], Silvia Munoz[1] and Matthew Budoff[2]. [1]Harbor-UCLA, Torrance, CA, [2]Harbor-UCLA Medical Center, Torrance, CA

Background/Purpose: Vulnerable coronary plaques are characterized by a large lipid core, a thin fibrous cap, spotty calcification, and positive remodeling. Multi-detector Computed Tomography Angiography (MDCTA) accurately distinguishes these morphologic features and classifies plaques as Non-Calcified (NCP), Mixed (MP), and fully Calcified (CP). MP commonly combine all the aforementioned vulnerability characteristics, and have been associated with significant risk of future events. By contrast, fully CP are considered more stable plaques with lower such risk. In this report we evaluated potential predictors of MP and CP in coronary artery disease (CAD)- naïve subjects with Rheumatoid Arthritis (RA).

Methods: One hundred and fifty subjects with RA underwent MDCTA for coronary plaque evaluation and assessments of epicardial adipose tissue (EAT) and thoracic adipose tissue (TAT) volumes. The standard 15-segment American Heart Association (AHA) model was used for plaque evaluation, and plaque burden was reported as total plaque segment score for different plaque types as previously described. Disease activity scores (DAS28-3v-CRP), serologic, laboratory, radiographic parameters and treatments were captured. Irreversible articular damage (IAD) defined as subluxation, and/ or fusion, ankylosis, or arthrodesis, as well as joint replacement surgeries were tracked. Determinants of MP and CP were explored in multivariable crude and fully adjusted models for age, gender, hypertension, diabetes, dyslipidemia, smoking, and family history of CAD.

Results: Patients were largely middle aged females, with long standing and robustly seropositive disease. The presence of at least moderate disease activity (DAS28-3v$\geq$3.2), high C- reactive protein (CRP), and the highest quartiles of TAT were significantly associated with a higher adjusted likelihood ratio (LR) of MP prevalence (4.1, 3.9, and 12.7 respectively, all with $p<0.05$- table 1). By contrast, treatment with tumor necrosis factor-a inhibitors (TNFi), even in the absence of good clinical response (DAS28-3v$<$3.2), was associated with a 70% lower risk for MP presence ($p=0.027$). None of the aforementioned parameters predicted the risk for presence of CP; increasing patient age was the only determinant of such plaque (LR=1.1, $p=0.016$).

Conclusion: The presence of high risk mixed plaques was positively predicted by parameters of ongoing inflammation, and TAT, and was inversely related to treatment with TNFi, even in the presence of active disease. Conversely, calcified plaque prevalence was only associated with higher subject age.

Table 1.

	Crude		Adjusted μ	
Mixed Plaque (MP)	***LR (95% CI)***	***p-value***	***LR (95% CI)***	***p-value***
DAS28-3v>3.2	2 (0.8, 5.4)	0.15	4.1 (1.2, 13.3)	*0.0*
Age (yrs)	1.1 (1.0, 1.1)	*0.02*	1.0 (0.98, 1.1)	0.17
RF (+)	0.6 (0.2, 2.1)	0.48	0.5 (0.1, 1.8)	0.23
a-CCP(+)	1.1 (0.3, 4.1)	0.89	0.8 (0.2, 3.5)	0.78
Erosions (+)	1.8 (0.6, 5.2)	0.29	1.5 (0.5, 4.6)	0.52
IAD	1.4 (0.5, 4.5)	0.52	1.2 (0.3, 4.3)	0.82
Joint replacements	0.5 (0.1, 4.1)	0.51	0.1 (0.1, 1.3)	0.08
CRP (mg/dl)	2 (0.8, 5.4)	0.15	3.9 (1.2, 12.5)	*0.02*
DAS28-3v>3.2 on TNFi	0.5 (0.2–1.3)	0.5	0.3 (0.1–0.9)	*0.02*
EAT: Q4 vs. Q1	4.9 (1–25.2)	0.056	5 (0.8–29.6)	0.08
TAT: Q4 vs. Q1	13.7 (1.6–114.8)	*0.015*	12.7 (1.4–118.6)	*0.026*
Calcified Plaque (CP)				
DAS28-3v>3.2	0.8 (0.2, 3.0)	0.73	0.9 (0.2, 4.5)	0.95
Age (yrs)	1.1 (1.0, 1.2)	*0.002*	1.1 (1.0, 1.2)	*0.016*
RF (+)	1.0 (0.2, 4.7)	0.97	1.0 (0.2, 6.2)	0.96
a-CCP(+)	0.6 (0.2, 2.5)	0.51	0.4 (0.1, 2.2)	0.31
Erosions (+)	1.3 (0.4, 4.4)	0.65	0.8 (0.2, 3.3)	0.78
IAD	2.2 (0.6, 8.3)	0.23	1.0 (0.2, 4.7)	0.99
Joint replacements	7.5 (1.7, 32.2)	*0.007*	2.1 (0.3, 14.3)	0.44
CRP (mg/dl)	1.2 (0.8, 1.6)	0.34	1.2 (0.8, 1.7)	0.45
DAS28-3v>3.2 on TNFi	0.8 (0.2, 3.0)	0.73	1.0 (0.2, 4.8)	0.98
EAT: Q4 vs. Q1	2.8 (0.5, 15.3)	0.25	1.0 (0.1, 7.4)	0.97
TAT: Q4 vs. Q1	4.4 (0.5, 41.6)	0.20	3.5 (0.3, 44.3)	0.33

μ adjusted for age, gender, Hypertension, Diabetes, dyslipidemia, smoking, FHx

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Outward Carotid Arterial Wall Remodelling in Rheumatoid Arthritis: A Case-Control Study. Alper M. van Sijl[1], Katja van der Hurk[2], Mike J.L. Peters[3], Vokko P. van Halm[4], Giel Nijpels[2], Coen D.A. Stehouwer[5], Yvo M. Smulders[3], A.E. Voskuyl[6], Jacqueline M. Dekker[2] and Michael T. Nurmohamed[7]. [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]EMGO institute, VU university medical centre, Amsterdam, Netherlands, [3]VU University medical center, Amsterdam, Netherlands, [4]Academic Medical Centre, Amsterdam, Netherlands, [5]Maastricht University, Maastricht, Netherlands, [6]VU Medical Center, Amsterdam, Netherlands, [7]Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased cardiovascular (CV) risk, but mechanisms explaining this increased risk have not been fully elucidated. To maintain circumferential wall stress, arteries react on hemodynamic changes by arterial remodelling. So far arterial remodelling has not been studied in RA.

Methods: 96 RA-patients and 274 healthy controls were investigated in a case-control study. B-mode carotid ultrasonography was used to investigate arterial wall parameters, including intima-media thickness (IMT), inter-adventitial diameter (IAD), lumen diameter (LD), calculated as IAD $-$ (2 $\times$ IMT). Linear regression analyses were used to assess the association between presence of RA and arterial wall parameters.

Results: RA was associated with a significantly greater LD as compared to control subjects: 6.43 mm vs. 6.13 mm.($p=0.02$) IAD was also higher in RA-patients: 8.04 mm vs. 7.79 mm.($p=0.07$) As IMT did not differ between RA patients and control subjects, RA patients had 6.3% ($p=0.02$) greater wall-to-lumen ratio (ratio of IAD to IMT, an indicator of wall thinness or outward remodelling). Associations remained similar after exclusion of patients with prior CV disease and after adjustment for demographic factors and CV risk factors (including mean arterial pressure). Inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, disease activity score of 28 joints and rheumatoid factor positivity) were not associated with arterial wall parameters.

Conclusion: RA is associated with outward remodelling. This is relevant in view of the association between outward remodelling and plaque instability and rupture.

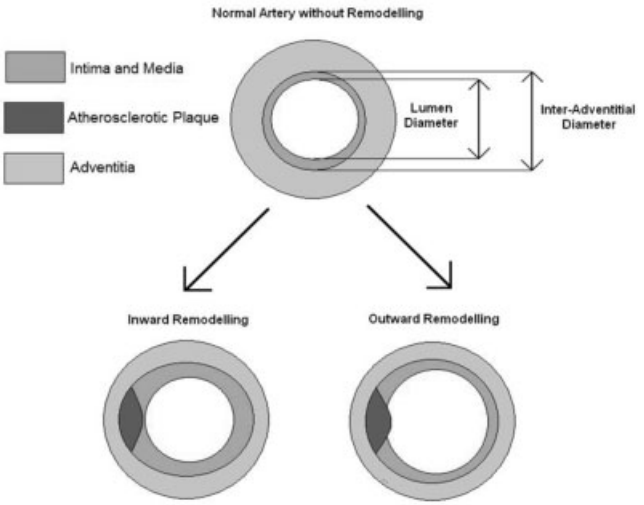

Figure 1. Arterial wall characteristics in compensatory remodelling

Table 1. Baseline characteristics

	Controls (n=274)	Rheumatoid Arthritis (n=96)
Demographics		
Age, years	69 ± 6	63 ± 7*
Sex (% males)	48.5	39.6
Cardiovascular risk factors		
Systolic blood pressure, mmHg	138 ± 21	142 ± 18
Diastolic blood pressure, mmHg	81 ± 11	82 ± 7
Total cholesterol, mmol/L	5.80 ± 1.02	5.69 ± 1.01
HDL-cholesterol, mmol/L	1.51 ± 0.43	1.47 ± 0.48
Prior cardiovascular events, %	41.2	14.6*
Current smoking, %	15.0	31.3*
Arterial wall parameters		
Inter-adventitial diameter, mm	7.79 ± 1.16	8.04 ± 1.01
Lumen diameter, mm	6.13 ± 1.07	6.43 ± 0.95*
Intima media thickness, mm	0.832 ± 0.165	0.805 ± 0.126
Mean arterial pressure, mmHg	95 ± 12	102 ± 10*
Carotid pulse pressure	59 ± 17	62 ± 14
Wall-to-lumen ratio	9.6 ± 2.0	10.2 ± 1.6*
Circumferential wall stress, kPa	452 ± 182	509 ± 152*

* $p < 0.05$. HDL, high-density lipoprotein

Table 2. Carotid artery remodelling in RA-patients as compared to control subjects

Model	Lumen diameter	Intima-media thickness	Inter-adventitial diameter	Wall-to-lumen ratio
1	0.57 (0.34–0.80)*	0.02 (−0.02–0.05)	0.61 (0.37–0.85)*	0.42 (−0.05–0.88)
2	0.37 (0.13–0.60)*	0.01 (−0.03–0.05)	0.38 (0.14–0.63)*	0.25 (−0.25–0.74)
3	0.38 (0.15–0.62)*	0.01 (−0.03–0.05)	0.41 (0.16–0.65)*	0.23 (−0.27–0.72)
4	0.40 (0.16–0.64)*	0.02 (−0.02–0.06)	0.43 (0.19–0.68)*	0.20 (−0.31–0.71)

* $p < 0.05$. Results are presented as regression coefficients (95%-confidence interval)
Model 1: Age + Sex
Model 2: Model 1 + Mean arterial pressure
Model 3: Model 1 + Use of antihypertensives + Use of statins
Model 4: Model 2 + Hypertension + Total cholesterol + Prior CV disease

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Abnormal Concentric Ventricular Remodeling in Rheumatoid Arthritis. John M. Davis III, Veronique L. Roger, Cynthia S. Crowson, Terry M. Therneau, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk for heart failure (HF). Pre-clinical left ventricular (LV) diastolic dysfunction is more frequent in RA patients than the general population, suggesting a distinct pathogenesis of HF in these patients. The purpose of this study was to provide new insights into myocardial disease in RA by evaluating LV geometry in RA and non-RA subjects without HF.

Methods: A cross-sectional, community-based study was conducted among adult subjects (age ≥50 yrs) without HF, 210 with RA and 1446 without RA (non-RA). Participants had an echocardiogram and completed a questionnaire. Data collection included demographics, cardiovascular (CV) risk factors, and RA disease characteristics. Two-dimensional & Doppler echocardiography was performed by a registered diagnostic cardiac sonographer and interpreted by an expert cardiologist. LV geometry was classified into four categories based on relative wall thickness (RWT) and sex-specific cutoffs for LV mass index (LVMI): concentric remodeling, concentric hypertrophy, eccentric hypertrophy, or normal geometry. Sex-specific proportions of subjects with RA vs. non-RA in each category of LV geometry were compared. Logistic regression models were used to identify predictors of abnormal LV geometry (concentric remodeling, concentric hypertrophy, or eccentric hypertrophy) as compared to normal geometry, and separately among patients with abnormal LV geometry, to identify predictors of concentric remodeling as compared to concentric or eccentric hypertrophy. Candidate predictors included RA, disease characteristics, and CV risk factors.

Results: The mean ages of the 210 RA and 1446 non-RA subjects without HF were similar among the females (64.2 ± 10.1 and 65.2 ± 9.5 yrs for RA and non-RA, respectively; p=0.13) whereas male RA subjects were slightly older (67.6 ± 9.3 vs. 64.7 ± 9.4 yrs; p=0.018). Systolic blood pressure was higher in RA women (130 ± 17 vs. 125 ± 20 mm Hg) and RA men (136 ± 19 vs. 127 ± 17 mm Hg) than their non-RA counterparts. LVMI was lower in RA women (80.9 ± 13.9 vs. 87.8 ± 20.0; p=0.001); a trend to lower LVMI was also seen in RA men (94.3 ± 15.7 vs. 99.4 ± 21.6; p=0.26). RWT was higher in both RA females (0.43 ± 0.07 vs. 0.39 ± 0.09; p<0.001) and RA males (0.44 ± 0.07 vs. 0.39 ± 0.06; p<0.001). RA subjects were 26% more likely to have abnormal LV geometry though this was not statistically significant (OR 1.26; 95% CI: 0.89, 1.76; p=0.18). Among those with abnormal LV geometry, RA subjects were 6.5 times more likely to have concentric LV remodeling (OR: 6.5; 95% CI: 3.7, 11.5; p<0.001). After adjusting for age, sex, CV risk factors, and RA characteristics; higher disability (OR: 1.74; 0.97, 3.12; p=0.062) and methotrexate use (OR 2.17; 95% CI 1.11, 4.23; p=0.023) were associated with abnormal LV geometry. RA characteristics were not significantly associated with concentric LV remodeling.

Conclusion: RA is strongly associated with abnormal concentric LV remodeling. These findings suggest that RA disease-related factors promote myocardial injury, remodeling, and ultimately myocardial dysfunction. The biological mechanisms underlying these changes warrant further investigation.

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Expansion of Intra-Thoracic Adipose Tissue Depots Associate with Prevalence and Burden of Mixed (Vulnerable) Plaques in Coronary Artery Disease-Naïve Patients with Rheumatoid Arthritis. George A. Karpouzas[1], Panteja Razaeian[2], Jennifer Malpeso[2], Dong Li[2], Maria V. Peralta[2], Silvia Munoz[1] and Matthew Budoff[2]. [1]Harbor-UCLA, Torrance, CA, [2]Harbor-UCLA Medical Center, Torrance, CA

Background/Purpose: Expansion of intrathoracic adipose tissue (AT) depots were reported to associate with the risk of myocardial infarction and fatal coronary artery disease (CAD) in the general population. Similarly, such AT increase was correlated with higher prevalence and severity of coronary plaque. Multidetector Computed Tomography Angiography (MDCTA) accurately classifies coronary plaque as non-calcified (NCP), mixed (MP), or fully calcified (CP), and readily recognizes features of plaque vulnerability such as a large lipid core, spotty calcification, and positive remodeling, often expressed in MP. In this report we explored the associations of different coronary plaque types with intrathoracic AT volume status, as well as the ability of such volumes to predict the presence of a specific plaque type in CAD-naïve subjects with RA.

Methods: One hundred and fifty patients underwent MDCTA for plaque evaluation and assessment of epicardial adipose tissue (EAT) and thoracic adipose tissue (TAT) volumes. The standard 15-segment American Heart Association (AHA) model was used, and plaque burden was reported as total plaque segment score (TPSS) for different plaque types as previously described. Risk regression analysis models adjusted for age, gender, and all cardiac risk factors were constructed to assess the incremental change of EAT or TAT volumes for different plaque types per standard deviation (SD) of such change in subjects without plaque. Subsequent modeling for evaluation of risk for MP prevalence was attempted by quartile of EAT and TAT.

Results: Subjects with any prevalent coronary plaque (TPSS-all>0) displayed higher EAT and TAT volumes compared to those without (TPSS-all=0- table 1). Of the different plaque types, only the presence of MP was associated with significant expansion of EAT and TAT; for each SD of change in subjects without plaque, there was a 2.5-fold and 3.5-fold change in EAT and TAT in patients with prevalent MP (p<0.05 and <0.01 respectively). The highest TAT quartile was significantly associated with MP prevalence; 29% of patients with TAT in the 4th quartile had MP compared to 2.9% in those with TAT in 1st quartile (p=0.012). In an

adjusted model, patients on the highest TAT quartile had 13-fold higher risk for MP prevalence compared to those in the lowest quartile.

Table 1.

	Plaque (−) TPSS-all=0	Plaque (+) TPSS-all>0	TPSS-NCP>0 & TPSS-MP=0 & TPSS-CP=0	TPSS-MP>0 & TPSS-CP=0	TPSS-CP>0 & TPSS-MP=0 & TPSS-NCP=0
EAT (cc)	100.2±30.2	120.6±45.3	110.1±42.73	130.1±42.1	135±47.1
TAT (cc)	153.9±74.3	193.7±83.8	171.5±78.55	224.7±87.7	214±64.3
Risk Regression analysis (n of SD change/SD change in referent) μ					
EAT	1 (ref)	1.3(0.8,1.9)	1.2(0.7,1.9)	2.5(1.0,5.8)*	2.8(0.4,18.7)
TAT	1 (ref)	1.5(1.0,2.4)*	1.4(0.9,2.3)	3.5(1.4,8.8)**	6.4 (0.6,63.1)

μ adjusted for age, gender, all cardiac risk factors, RA duration, presence of TNF-inhibitors
* p<0.05,**p<0.01

MP prevalence by Quartiles of EAT and TAT

	Quartile 1 N (%)	Quartile 2 N (%)	Quartile 3 N (%)	Quartile 4 N (%)	p-value
EAT					
MP (−)	32(94.1)	28(82.4)	30(85.7)	26(76.5)	0.234
MP (+)	2(5.9)	6(17.6)	5(14.3)	8(23.5)	
TAT					
MP (−)	33(97.1)	31(91.2)	28(80.0)	24(70.6)	*0.012*
MP (+)	1(2.9)	3(8.8)	7(20.0)	10(29.4)	

Association between MP burden and quartiles of EAT and TAT

	Crude			*Adjusted μ*		
	OR	95% CI	p-value	OR	95% CI	p
EAT-Q1	1.0 (Ref)			1.0 (Ref)		
EAT-Q2	3.4	0.6,18.4	0.15	3.7	0.6,23.2	0.17
EAT-Q3	2.7	0.5,14.8	0.26	2.2	0.4,14.3	0.39
EAT-Q4	4.9	1.0,25.2	0.06	4.8	0.8,27.7	0.08
TAT-Q1	1.0 (Ref)			1.0 (Ref)		
TAT-Q2	3.2	0.3,32.4	0.33	3.6	0.3,39.0	0.29
TAT-Q3	8.2	1.0,71.2	0.06	6.5	0.7,61.0	0.10
TAT-Q4	13.7	1.6,114.8	*0.02*	12.9	1.4,121.1	*0.03*

μ adjusted for age, gender, all cardiac risk factors, RA duration, presence of TNF-inhibitors

Conclusion: Coronary plaque presence is associated with a 30% expansion in EAT and 50% expansion in TAT compared to absence of plaque. Of all plaque types, only MP- that commonly harbors vulnerable features-associates with significantly higher EAT and TAT volumes, and highest quartiles of TAT independently predict the presence of MP.

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Oxidation Products of Arachidonic Acid and Linoleic Acid Are Increased in High Density Lipoprotein and Low Density Lipoprotein From Patients with Active Rheumatoid Arthritis. Christina Charles-Schoeman[1], David Meriwether[2], Yuen Yin Lee[2] and Srinivasa T. Reddy[3]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]UCLA, Los Angeles, CA, [3]UCLA, Los Angeles

Background/Purpose: Oxidation products of arachidonic acid and linoleic acid including hydroxyeicosatetraenoic acids (HETES) and hydroxyoctadecadienoic acids (HODES), respectively, play an important role in the pathogenesis of atherosclerosis. These fatty acids contribute to the oxidation of low density lipoprotein (LDL) and their accumulation in high density lipoprotein (HDL) has been proposed to inhibit HDL function, increasing atherosclerotic risk. The current work evaluated the levels of HETES and HODES in HDL and LDL isolated from patients with active rheumatoid arthritis (RA) compared to healthy controls.

Methods: HDL and LDL were isolated from plasma using fast protein liquid chromatography for 10 RA patients and 8 age and sex matched healthy controls. 5-HETE, 12-HETE, 15-HETE, 9-HODE, and 13-HODE levels in HDL and LDL fractions were measured by mass spectrometry as described previously (Imaizumi et al. *Drug Metab Lett.* 2010; 4(3):139–48). HDL's anti-inflammatory function was measured by a cell free assay as described previously (Charles-Schoeman et al. *Arthritis Rheum.* 2009; 60(10):2870–9). Lipoprotein cholesterol levels were determined by standard methods.

Results: 5-HETE, 15-HETE, 9-HODE and 13-HODE levels were significantly increased in both HDL and LDL isolated from patients with active RA compared to healthy controls (see Table). The levels of oxidized fatty acids in HDL correlated significantly with measures of systemic inflammation; ESR and hs-CRP (r values= 0.70–0.80, [ESR]; 0.65–0.74 [hs-CRP]; p values <0.004). Similar correlations were also noted for oxidized fatty acids in LDL (r values= 0.30–0.48, [ESR]; 0.34–0.62 [HSCRP]; p values 0.006–0.25). Moreover, 5-HETE, 15-HETE, 9-HODE and 13-HODE levels in HDL significantly correlated with impaired HDL function as measured by the HDL inflammatory index (HII), r= 0.54–0.58; p values <0.03). No differences in lipoprotein cholesterol levels or traditional cardiovascular risk factors were noted between the two groups.

Conclusions: Oxidation products of arachidonic acid and linoleic acid are increased in HDL and LDL from patients with active rheumatoid arthritis compared to healthy controls, and are strongly correlated with levels of systemic inflammation, particularly in HDL. Elevations of 5-HETE, 15-HETE, 9-HODE and 13-HODE in HDL are also significantly associated with impaired HDL anti-oxidant function. These results suggest a potential mechanism by which active inflammation from RA increases oxidized fatty acids in circulating lipoproteins, promoting LDL oxidation and HDL dysfunction, thereby increasing atherosclerotic risk. Further investigation of therapeutic agents such as apoA-1 mimetic peptides which bind oxidized fatty acids and reduce atherosclerosis in animal models may be warranted in patients with RA.

	Rheumatoid Arthritis (n=10)	Healthy Control (n=8)
Age (years)	49.6 ± 11.8	48.4 ± 15.9
Sex (% female)	80%	75%
Ethnicity (% caucasian)	80%	63%
Total Cholesterol (mg/dL)	178 ± 52	165 ± 22
LDL Cholesterol (mg/dL)	104 ± 35	89 ± 22
HDL Cholesterol (mg/dL)	52 ± 15	56 ± 14
Triglycerides (mg/dL)	116 ± 59	101 ± 84
ESR (mm/hr)	71 ± 24*	6 ± 5
HS-CRP (mg/L)	42.1 ± 40.1*	0.91 ± 1.5
HDL Inflammatory Index (HII)	2.21 ± 0.52*	0.56 ± 0.09
HDL 5-HETE (ng/ml)	72.1 ± 29.1*	29.2 ± 13.2
HDL 12-HETE (ng/ml)	779.4 ± 1693	166.7 ± 40
HDL 15-HETE (ng/ml)	18.9 ± 10.9*	7.0 ± 2.5
HDL 9-HODE (ng/ml)	138.4 ± 74.2*	47.6 ± 28.5
HDL 13-HODE (ng/ml)	190.9 ± 99.5*	68.4 ± 30.7
LDL 5-HETE (ng/ml)	2.9 ± 1.4*	1.1 ± 0.7
LDL 12-HETE (ng/ml)	38.1 ± 47.7	16.9 ± 15.7
LDL 15-HETE (ng/ml)	2.35 ± 0.85*	1.06 ± 0.72
LDL 9-HODE (ng/ml)	26.5 ± 18.0*	8.8 ± 7.2
LDL 13-HODE (ng/ml)	34.0 ± 22.4*	11.3 ± 8.0

All values mean ± standard deviation. *p value ≤ 0.005 compared to controls.

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Cholesterol Efflux by High Density Lipoproteins Is Impaired in Patients with Active Rheumatoid Arthritis. Christina Charles-Schoeman[1], Yuen Yin Lee[2], Victor Grijalva[3], John D. FitzGerald[2], Veena K. Ranganath[4], Mihaela Taylor[2], Maureen A. McMahon[2], Harold E. Paulus[4] and Srinivasa T. Reddy[3]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]UCLA, Los Angeles, CA, [3]UCLA, Los Angeles, [4]University of California, Los Angeles, Los Angeles, CA

Background/Purpose: Reverse cholesterol transport (RCT) and prevention of oxidative stress are two major anti-atherogenic functions of high density lipoprotein (HDL). We previously showed that the anti-oxidant function of HDL in patients with rheumatoid arthritis (RA) is abnormal and associated with high levels of systemic inflammation. Since inflammation has been proposed to impair RCT, in the current work, we evaluated whether the RCT capacity of HDL from RA patients is impaired when compared to healthy controls.

Methods: HDL was isolated from 40 patients with RA and 40 age and sex matched healthy controls. Cholesterol efflux experiments were performed as described previously (Navab et al. Circulation 2004; 109(25):3215–3220). HDL's anti-oxidant function was assessed by cell free assay as described previously (Charles-Schoeman et al. Arthritis Rheum 2009; 60(10):2870–2879), which assesses the ability of patient HDL to inhibit oxidation of a stock LDL. Lipoprotein cholesterol levels were determined by standard methods.

Results: Mean cholesterol efflux capacity of HDL was not significantly different between RA patients (40.2% ± 11.1%) and controls (39.5% ± 8.9%); p=0.75. However, HDL from RA patients with high disease activity measured by a disease activity score using 28 joint count (DAS28 > 5.1), had significantly decreased ability to promote cholesterol efflux compared to HDL from patients with low disease activity (DAS28 < 2.6). In addition, a significant correlation was noted between cholesterol efflux and disease activity measured by the DAS28 (r= −0.39, p=0.01). Higher RA disease activity was associated with decreased efflux by HDL. A similar correlation was observed with ESR, (r= −0.41, p=0.0009), and a trend noted with HS-CRP (r= −0.29, p=0.08). HDL's ability to promote cholesterol efflux

was modestly but significantly correlated with its anti-oxidant function ($r = -0.34$, $p = 0.03$).

Conclusion: Cholesterol efflux capacity of HDL is impaired in RA patients with high disease activity and is correlated with systemic inflammation and HDL's anti-oxidant capacity. Attenuation of HDL function, independent of HDL cholesterol levels, may suggest a mechanism by which active RA contributes to increased CV risk.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Human Etiology and Pathogenesis I: Pathogenesis of the Earliest Stages of Rheumatoid Arthritis
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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Familial Clustering of the Serum Cytokine Profile: Comparison Between the Asymptomatic First-Degree Relatives of Rheumatoid Arthritis Patients and Controls with No Family History of Autoimmune Disease. Hani S. El-Gabalawy[1], David B. Robinson[1], Donna M. Hart[2], Irene Smolik[3], Charles N. Bernstein[1], Marianna M. Newkirk[4] and Marvin J. Fritzler[5]. [1]University of Manitoba, Winnipeg, MB, [2]Health Sciences Centre, Winnipeg, MB, [3]University of Manitoba, Winnipeg, [4]McGill University Health Centr, Montreal, QC, [5]University of Calgary, Calgary, AB

Background/Purpose: Seropositive RA is prevalent in North American Native (NAN) populations, with a high frequency of multi-case families. We studied the first-degree relatives (FDR) of NAN RA probands to evaluate risk factors for disease development. Data from studies of other pre-clinical RA cohorts suggest that many serum cytokines are elevated prior to the onset of clinically detectable disease. We sought to determine whether the serum cytokine profile of the FDR at risk for future disease development differed from that of individuals with no family history of autoimmunity.

Methods: We studied NAN RA patients (n=105), FDR (n=273), healthy NAN (NC) (n=200) and Caucasian controls (CC) (n=150) with no family history of autoimmune disease. Rheumatoid factor (RF) and anti-CCP2 antibodies (CCP) were tested by nephelometry and ELISA, respectively. We used a cytokine/chemokine 42-plex array to test a range of serum cytokines. Confirmation of specific cytokine levels and hsCRP were tested by ELISA. Raw cytokine data were normalized and differences between groups were analyzed by ANOVA. Discriminant analysis was used to classify individuals based on canonical functions generated from transformed cytokine data.

Results: The NAN FDR and NC groups were well matched for age and gender, while the RA and CC groups were older. The prevalence of RF (>50 IU) was RA= 88%, FDR=34%, NC=9% and CC=5%, and CCP (>40 units) was RA= 81%, FDR=9%, NC=4% and CC=0%. Levels of almost all cytokines tested were markedly higher in RA patients compared to the other groups. Of the cytokines tested, 17/40 (43%) were significantly higher in the FDR compared to both NC and CC, in particular IL-1β, IL-6, TNFα, IL-12, IL-8, MCP-1, MIP-1α, and VEGF. Discriminant analysis showed a remarkable distinction between RA, FDR, and controls based on the canonical function centroids, with 85% classification accuracy. Centroids from NC and CC were similar indicating no major ethnic differences in the absence of a family history of RA. Comparison of the FDR and NC groups using a logistic regression model suggested that MCP-1 levels were the strongest single discriminator between these two groups, and results from an MCP-1 ELISA confirmed this finding. There were minimal differences in the cytokine profile of autoantibody positive and negative FDR, indicating that the elevated cytokine levels in the FDR were not explained on the basis of the high prevalence of RF and/or CCP. Moreover, technical effects of RF seropositivity did not appear to impact of the differences in cytokine levels between FDR and NC. Mean hsCRP levels (mg/l) were RA=9.1±5.6, FDR=4.9±4.7, NC=1.6±1.6, CC=4.2±2.2 indicating significantly higher levels in FDR compared to both control groups.

Conclusion: Both pro and anti-inflammatory cytokines are elevated in RA. Surprisingly, levels of these biomarkers, as well as hsCRP, are significantly higher in disease-free FDR of NAN RA patients compared to individuals from families with no autoimmune disease. These data suggest that elevated basal cytokine levels, potentially based on genetic or epigenetic factors, may be part of the risk profile for developing RA in families at risk for this autoimmune disease. Confirmation of these findings in other non-NAN populations is needed.

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***Porphyromonas Gingivalis (P. gingivalis)* is Associated with the Presence of Disease-Specific Autoantibodies in Individuals At Increased Risk for the Future Development of Rheumatoid Arthritis.** Ted R. Mikuls[1], Kevin D. Deane[2], Jeffrey Payne[3], Geoffrey M. Thiele[4], James R. O'Dell[4], Lezlie A. Derber[5], William H. Robinson[6], V. Michael Holers[7] and Jill M. Norris[8]. [1]Omaha VA and University of Nebraska, Omaha, NE, [2]University of Colorado School of Medicine, Aurora, CO, [3]University of Nebraska Medical Center, Lincoln, NE, [4]Univ of Nebraska Med Ctr, Omaha, NE, [5]University of Colorado AMC, Aurora, CO, [6]Stanford University, Stanford, CA, [7]Univ of Colorado School of Med, Aurora, CO, [8]University of Colorado Denver, Aurora, CO

Background/Purpose: *P. gingivalis* (*Pg*) leading to periodontal disease has emerged as a potential environmental risk factor in rheumatoid arthritis (RA). *Pg* is the only prokaryote known to express peptidyl-arginine deiminase (PAD) as a virulence factor, suggesting that this oral pathogen could play a direct role in tolerance loss in RA. Our group has previously shown that patients with established RA are more likely to exhibit antibody to *Pg,* with additional significant correlations between anti-*Pg* and anti-citrullinated protein antibody (ACPA) levels. We sought to examine the relationship of antibody to *Pg* with the presence of RA-related autoantibodies in first-degree relatives (FDRs) of RA probands.

Methods: FDRs (n = 185), none of whom met 1987 ACR criteria for RA, were categorized as being 'high-risk' for developing future classifiable RA (positive anti-CCP or ≥ 2 RF isotypes; n = 38), cases (≥ 1 positive RA-related autoantibody; n = 97), or controls (no positive autoantibody; n = 88). An additional 99 unaffected individuals from an *HLA-DRB1* 'enriched' cohort were included as controls. IgG antibody concentrations (μg/ml) to *Pg* and *P. intermedia* (*Pi;* a common oral pathogen that does not express PAD) were measured using ELISA with bacterial whole cell lysates serving as the coating antigen. Intra-assay coefficients of variation for the ELISAs ranged from 11 to 13%. There were no significant changes in measured anti-bacterial antibody concentrations following RF depletion. Following log-transformation, associations of antibody concentrations with group status (high risk and case vs. control) were examined using logistic regression, adjusting for age, gender, race, educational status, diabetes, ever smoking, and *HLA-DRB1 shared epitope (SE)*.

Results: Log-transformed Anti-*Pg* concentrations were significantly higher in both the high-risk ($p = 0.0043$) and case group ($p = 0.0054$) as compared to the controls. There were no significant group differences for anti-*Pi*. Univariate and multivariable associations of bacterial antibody concentrations with group status are shown:

Bacterial IgG Ab (μg/ml, log-transformed)	Case vs. Control OR (95% CI)		High Risk vs. Control OR (95% CI)	
	Univariate	Multivariable	Univariate	Multivariable
Anti-*Pg*	1.50 (1.12 to 2.00) p = 0.006	1.46 (1.08 to1.98) p = 0.014	1.86 (1.20 to 2.89) p = 0.005	1.99 (1.25 to 3.17) p = 0.004
Anti-*Pi*	1.06 (0.71 to 1.58) p = 0.480	1.11 (0.72 to 1.71) p = 0.631	1.25 (0.68 to 2.30) p = 0.480	1.49 (0.74 to 2.99) p = 0.260

Conclusion: Immunity to *Pg*, but not *Pi*, is significantly associated with the presence of RA-related autoantibodies in FDRs, including those at highest risk for future RA. This association is independent of other factors associated with both RA and PD risk. These results support the hypothesis that infection with Pg may play a central role in the early loss of tolerance to self antigens and may explain prior reported associations of periodontitis with risk for established RA.

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Analysis of Twin Concordance for ACPA Positivity and ACPA fine specificities in a Large Swedish Twin Cohort (TwinGene). Aase Haj Hensvold[1], Patrik KE Magnusson[2], Monika Hansson[1], Lena Israelsson[1], Cecilia Carlens[1], Rikard Holmdahl[3], Per-Johan Jakobsson[1], Johan Askling[4], Vivianne Malmström[1], Lars Klareskog[1] and Anca Irinel Catrina[1]. [1]Rheumatology unit, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [2]Swedish Twin Registry Karolinska Institutet, Stockholm, Sweden, [3]Medical Biochemistry and Biophysics Karolinska Institutet, Stockholm, Sweden, [4]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Both genetic and environmental factors are established risk factors for Anti Citrulline Peptide Antibodies (ACPA) positive rheumatoid arthritis (RA). As ACPA appear before disease onset and are highly specific for RA we aimed to investigate the influence of genetic and environmental factors in ACPA positivity, using a twin study approach.

Methods: We used a subset of the Swedish twin registry, which includes 12 594 monozygotic (MZ) and dizygotic (DZ) twins born 1958 or earlier. All

blood samples were analyzed for ACPA using a commercial ELISA. All available paired samples (n=312 twin pairs) in which at least one twin was ACPA positive were further investigated for presence of ACPA fine specificities against native and citrullinated forms of alpha-enolase (aa5–21; cep1), collagen type II (aa359–369; citC1), fibrinogen (aa566–580; citfib573) and vimentin (aa60–75; citvim60) peptides, using a cut off set at the 98 percentile, based on analysis of sera from healthy controls. RA or other rheumatic joint diseases were verified by, data from register linkage to national care registers or by reviewing medical records.

Concordance for ACPA positivity was estimated by casewise concordance and tetrachoric correlation. Odds ratios (OR) to develop ACPA were calculated according to self-reported smoking status and cumulative dose of smoking estimated by pack years. Twins were defined as smokers (n=6252) if they were or had been smoking regularly or occasionally.

Results: 387 out of 12 594 tested individuals (3.1%) were positive for ACPA. Smokers had an increased risk of developing ACPA as compared with non-smokers (OR 1.33, 95% CI 1.08–1.63) and the risk was highest among those smoking more than 10 pack years (OR 1.49, 95% CI 1.18–1.88).

Among the ACPA positive, 312 twin complete pairs were available, 7 concordant and 305 ACPA discordant pairs. Casewise concordance for ACPA was 6.8% among MZ and 6.2% among DZ twins, with no significant tetrachoric correlation (r MZ twins 0.17, 95% CI −0.10–0.44, and r DZ twins 0.14, 95% CI −0.10–0.36).

Her analysis of ACPA fine specificities was performed in the same subgroup of twins. The most common of the analyzed fine specificities was against Cit-enolase (19% of the 624 tested samples). The casewise concordance rate for Cit-enolase was 19% among MZ and 10% among DZ twins, with no significant tetrachoric correlation (r MZ twins 0.17, 95% CI −0.35–0.69 and r DZ twins −0.32, 95% CI −0.58—0.07). A majority of ACPA positive twins with a RA diagnosis at the time of inclusion, 77%, were positive for one or more of the tested ACPA fine specificities as opposed to ACPA positive twins without any rheumatic joint disease where only 26% were positive for one or more of the tested ACPA fine specificities.

Conclusion: In this large population-based cohort of middle-aged twins, we found a low concordance rate for ACPA in both MZ and DZ twins. Our results indicate that environment, life style and stochastic factors may be more important than genetics in determining which individuals will develop ACPA, whereas genetic factors may have a larger impact in determining which ACPA-positive individuals that will ultimately develop arthritis.

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Prevalence of Periodontitis, Anti-*P. Gingivalis* antibodies, and Rheumatoid Arthritis Autoantibodies in a Community Sample of North American Natives with Prevalent Rheumatoid Arthritis. Isanne Schacter[1], David B. Robinson[1], Donna M. Hart[2], Mary Bertone[1], Christine A. Peschken[1], Irene Smolik[3], Carol A. Hitchon[1] and Hani S. El-Gabalawy[1]. [1]University of Manitoba, Winnipeg, MB, [2]Health Sciences Centre, Winnipeg, MB, [3]University of Manitoba, Winnipeg

Background/Purpose: RA is prevalent and severe in North American Native (NAN) populations. We have studied risk factors for disease development in the Cree-Ojibway population of Central Canada and have previously shown that this population has an excessive burden of genetic risk factors for RA, particularly a high frequency of shared epitope (SE) encoding alleles. Environmental risk factors that have been shown to be associated with RA risk include smoking and the presence of periodontal disease, possibly in association with the oral pathogen *P. gingivalis.* We therefore sought to determine the prevalence of these risk factors in this population, and whether they are associated with the presence of RA autoantibodies and SE alleles.

Methods: We randomly surveyed two isolated NAN communities, Norway House (NH) (n=130) and St Theresa Point (STP) (n=172) Manitoba, for the prevalence of periodontal disease and RA autoantibodies. A dental hygienist performed an examination of the oral cavity in each study subject and quantified the degree of periodontitis using the standardized periodontal screening record (PSR) instrument having a scale ranging from 0 (no periodontitis) to 4 (severe periodontitis). Oral health symptoms, RA-like symptoms, and smoking history were captured using a questionnaire. Serum samples were tested for anti-*P. gingivalis* antibodies, anti-CCP2, and rheumatoid factor (RF). HLA-DRB1 testing was available for 100 study subjects in STP.

Results: The demographic characteristics of the two study populations were comparable age (mean age 35.2 in NH, 34.7 in STP), as well as gender (55.2% female in NH, and 52.9% in STP). The mean PSR score in both communities was comparable (2.94 in NH, and 3.00 in STP, p=NS). Because of this, data from both communities was aggregated. Males had significantly worse PSR scores than females (3.17 versus 2.82, p<0.001). The only self-report symptom that correlated with PSR scores was the presence of bleeding gums (correlation = 0.130, p = 0.026). There was no correlation between the PSR scores and levels of anti-*P. gingivalis* (PSR>2 = 56 vs. PSR<3 = 58 ELISA units, p=NS). Anti-CCP2 and RF were detectable in (2.3% and 4.6%, respectively). Individuals who were anti-CCP2 or RF positive had comparable PSR scores. Although anti-*P. gingivalis* titres were comparable in CCP2+ and CCP2- individuals, RF+ individuals had significantly higher titres than RF negative individuals (66±19 vs 55±19, p=0.02). The prevalence of ever-smokers was very high in all groups (86.6%). PSR scores and anti-*P. gingivalis* titres did not differ between SE+ (91%) and SE- (9%) individuals, but all autoantibody positive individuals were also SE+

Conclusion: In a random sample of two NAN communities known to have a high prevalence of RA we demonstrated a high frequency of the known risk factors for the disease including SE, smoking, and periodontitis. Despite this, the frequency of RA autoantibodies in this community based sample was low, and there was no clear association with the study risk factors, including immune responses to anti-*P. gingivalis*. Thus, the interaction between these risk factors in predisposing to RA does not appear to be preceded by an increased overall frequency of anti-CCP or RF in this population.

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Lung Abnormalities in Subjects with Elevations of Rheumatoid Arthritis-Related Autoantibodies without Arthritis by Examination and Imaging Suggest the Lung Is An Early and Perhaps Initiating Site of Inflammation in Rheumatoid Arthritis. M. Kristen Demoruelle[1], Michael H. Weisman[2], Lezlie A. Derber[3], Jason R. Kolfenbach[4], Chris Striebich[1], Isabel Pedraza[5], Annie Harrington[5], David Lynch[6], Peter Sachs[1], Brian Petersen[1], Colin Strickland[1], Jill Norris[7], V. Michael Holers[4] and Kevin D. Deane[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]Cedars Sinai Med Ctr, Los Angeles, CA, [3]University of Colorado AMC, Aurora, CO, [4]Univ of Colorado School of Med, Aurora, CO, [5]Cedars Sinai Med Ctr, Los Angeles, [6]National Jewish Health, Denver, CO, [7]University of Colorado Denver, Aurora, CO

Background/Purpose: Elevations of serum autoantibodies (Abs) prior to joint symptoms suggest that rheumatoid arthritis (RA) may be initiated outside of the joints. This site is unknown, although several factors suggest that it may be the lungs including the association of inhaled factors such as smoking with RA. Our purpose herein was to evaluate a hypothesis that the lung is a site of initiation of RA-related autoimmunity by comparing lung findings in RA-related Ab+ subjects at risk for future RA but without current inflammatory arthritis (IA) to Ab- controls and patients with established early RA.

Methods: 45 Ab+ cases without IA on 68 joint exam were identified from the Studies of the Etiology of RA (SERA) project, a prospective study of preclinical RA. These cases were positive for Abs >96% specific for future RA: anti-CCP2 (Axis-Shield) or CCP3.1 (INOVA), and/or ≥2 rheumatoid factor (RF) isotypes (IgA, M, G) (INOVA) [N=9 CCP2+; N=25 CCP3.1+; N=11 RFs+ only]. Additionally, 16 Ab- SERA controls (frequency matched to Ab+ cases on age, sex and smoking) and 12 patients with early RF/aCCP2+ RA (<1 year) were selected. All subjects underwent high-resolution computed tomography (HRCT) of the lungs, interpreted in a blinded fashion by 2 chest radiologists according to established criteria (Fleischner Society; Hansell et al 2008). To evaluate for synovitis not detected on joint exam, a subset of Ab+ cases underwent contrasted magnetic resonance imaging (MRI) of the MCPs, wrists and MTPs, scored for synovitis by 2 joint radiologists using the OMERACT/RAMRIS protocols.

Results: 45 Ab+ cases were a mean age of 54, 56% female and 33% smokers (no significant differences from Ab- controls). 77% of Ab+ cases had airways disease on HRCT including bronchial wall thickening, bronchiectasis, centrilobular opacities and air trapping, compared to 31% of Ab- controls (p<0.01). Of the 30 Ab+ cases that were never smokers, 70% had airways disease compared to 3/12 (25%) of never smoking controls (p=0.01). No Ab+ case had evidence of IA on joint exam at time of lung evaluation, and additionally, 15 Ab+ cases with abnormal lungs that underwent joint MRI had no synovitis by imaging. One Ab+ subject with airways disease developed RA by 1987 criteria (Arnett et al 1988) ~13 mos. after lung study. Finally, 9/12 (75%) of early RA subjects (mean age 50, 58% female, 42% smokers) studied in parallel had radiographically indistinguishable airways abnormalities when compared to the Ab+ cases (p>0.5).

Conclusion: Airways abnormalities are present in a high proportion of RA-specific Ab+ cases without IA (examination or MRI), and these lung

abnormalities are similar to those in patients diagnosed with early RA. This suggests that there is a continuum of lung injury during the development of RA, and that lungs are either a site of RA-related autoimmune-mediated injury during the pre-symptomatic phase of disease, or more likely a site of initiation of RA-related autoimmunity perhaps due to external factors beyond smoking that generate local inflammation, especially since the airways interact substantially with the environment. Prospective studies are ongoing to evaluate the generation of RA-specific in the lungs, and to follow the evolution of autoimmunity and IA in these subjects.

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Synovial Inflammation and Expression of Mediators of Pain in Preclinical Rheumatoid Arthritis Subjects with Arthralgia. Maria J. H. de Hair[1], Patrick Leclerc[2], Britt N. Sotthewes[1], Marleen G. H. van de Sande[1], Tamara H. Ramwadhdoebe[1], Christiaan van der Leij[3], Wouter Bos[4], Mario Maas[1], Dirkjan van Schaardenburg[5], Danielle M. Gerlag[1], Marina Korotkova[2], Per Johan Jakobsson[6] and Paul P. Tak[7]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Karolinska Institute, Stockholm, Sweden, [3]Academic Medical Center / University of Amsterdam, [4]Reade, Amsterdam, Netherlands, [5]Jan van Breemen Research Institute / Reade, Amsterdam, Netherlands, [6]Rheumatology Unit, Karolinska Institutet; Karolinska University hospital, Stockholm, Sweden, [7]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam The Netherlands, Amsterdam, Netherlands

Background/Purpose: We have previously shown in a small pilot study that there are no signs of synovial inflammation in preclinical rheumatoid arthritis (RA) subjects with arthralgia when synovial biopsies are obtained at least several months before the development of arthritis. Here, we examined the synovium in a markedly larger group of individuals and evaluated the prostaglandin (PG) pathway, one of the main mechanisms involved in pain perception.

Methods: Forty-nine individuals without any evidence of arthritis upon physical examination who were positive for IgM-rheumatoid factor and/or anti citrullinated protein antibodies were included in the study. All participants underwent MRI and arthroscopic synovial biopsy sampling of a knee joint at inclusion and were prospectively followed to assess arthritis development. Biopsies were analysed by immunohistochemistry for expression of several inflammatory markers and evaluated by semiquantitative analysis. Results were compared with knee MRI and synovial biopsy data of 6 and 7 healthy controls, respectively, and 5 early RA patients. Nineteen individuals were additionally analyzed for the expression of the PGE_2 synthesizing enzymes microsomal prostaglandin E synthase-1 (MPGES-1) and cyclooxygenase (COX) 1 and 2, and its degrading enzyme 15-prostaglandin dehydrogenase (15-PGDH). Four of these individuals did not have joint complaints whereas 15 suffered from arthralgia (arthralgia biopsied knee n=7). Five individuals developed RA after follow up. Stained sections were quantitatively evaluated by digital image analysis.

Results: MRI findings (presence of synovitis, bone marrow edema, erosions and cartilage degeneration) were similar in the autoantibody positive individuals compared to healthy controls. Consistent with these findings, expression of T cells, B cells, intimal macrophages, sublining macrophages, fibroblast-like synoviocytes, plasma cells, and von Willebrand factor was comparable to healthy controls, and significantly low compared to early RA patients. During follow-up of a median of 12 (range 0–47) months, 9 of the 49 individuals (18%) developed RA. In these patients baseline synovium was completely comparable with that of healthy controls and of the individuals who did not develop arthritis. Also, no differences could be observed in the expression of MPGES-1, COX-1 and -2, and 15-PGDH when comparing individuals who did or did not suffer from arthralgia in general or in the biopsied knee joint specifically. Moreover, expression of these enzymes was comparable between individuals who did and who did not develop arthritis over time.

Conclusion: Subclinical inflammation of the synovium does not coincide with the appearance of serum autoantibodies during the preclinical RA stage. Thus, systemic autoimmunity precedes the development of synovitis, suggesting that a 'second hit' is involved. Even though autoantibody positive individuals may suffer from arthralgia, local expression of PGs does not seem to be involved in pain sensation in this preclinical phase. Pain perception in these individuals may be regulated more centrally by PGs or other pain mediators may be involved.

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Preferential Transmission of Genetic Risk Variants of Candidate Loci At 6p21 From Asymptomatic Grandparents to Anti-SSA/Ro Positive Mothers of Children with Neonatal Lupus. Amit Saxena[1], Erin McDonnell[1], Paula S. Ramos[2], Satria Sajuthi[2], Miranda C. Marion[2], Carl D. Langefeld[2], Jill P. Buyon[1] and Robert M. Clancy[1]. [1]New York University School of Medicine, New York, NY, [2]Wake Forest School of Medicine, Winston-Salem, NC

Background/Purpose: Neonatal lupus (NL) occurs in fetuses exposed to maternal anti-SSA/Ro-SSB/La antibodies, and associates with significant morbidity and mortality if manifested by cardiac disease. Although NL mothers may be asymptomatic when the affected child is born, their autoantibodies and susceptibility to having an NL child represent a unique autoimmune phenotype. To evaluate transmission of risk factors for autoantibody aggregation and genetic susceptibility in families, two variant alleles at 6p21 associated with NL in children, rs1800629 (*TNFα-308* promoter) and rs7775397 (*C6orf10*), were evaluated in NL mothers and grandparents.

Methods: 51 mothers of NL children, 48 maternal grandmothers and 35 maternal grandfathers in the Research Registry for Neonatal Lupus (RRNL) were interrogated for clinical symptoms and laboratory assessments including anti-Ro60, Ro52, La48 recombinant proteins and genotype at rs1800629 (*TNFα*-308) and rs7775397 (*C6orf10*). The transmission disequilibrium test (TDT) was computed to evaluate nonrandom transmission from grandparents to the NL mothers.

Results: 92% of the families were Caucasian and 82% had children with cardiac NL. 14 (27%) of the NL mothers had Sjogren's Syndrome (SS), 7 (14%) SLE, 7 (14%) SS and SLE, and 23 (45%) were asymptomatic or had an Undifferentiated Autoimmune Syndrome (UAS). In contrast, only 1 (2%) grandmother had SS, 1 (2%) SLE, 1 (2%) Rheumatoid Arthritis and 1 (2%) Ankylosing Spondylitis, while 44 (92%) were asymptomatic or had UAS. 1 (3%) grandfather had SS and SLE, 1 (3%) SLE, and 33 (94%) were asymptomatic or had UAS. All NL mothers had anti-SSA/Ro antibodies. However, only 2 (5%) of 41 grandmothers had autoantibodies (1 anti-Ro60/Ro52/La48, 1 anti-Ro52) and 1 (4%) of 27 grandfathers had anti-Ro60/Ro52. NL mothers were enriched in variant allelic frequencies at both *TNFα-308* (A allele, 38% vs. 22% in HapMap controls) and *C6orf10* (G allele, 32% vs. 9% in HapMap controls). In contrast, the grandmothers were not enriched in the risk alleles, and their profile was significantly different from NL mothers (21% for *TNFα-308, P=0.02*; 12% for *C6orf10, P*=0.0065). Grandfathers had lower frequencies of risk alleles compared to NL mothers, but were not significantly different (32% for *TNFα-308*, *P*=0.59*;* 23% for *C6orf10, P*=0.35). The TDT analysis showed significant excess transmission of the risk alleles at both *TNFα-308* ($P=3.93\times10^{-4}$, OR=6.67) and *C6orf10* ($P=3.74\times10^{-5}$, OR=35) from maternal grandparents to the NL mothers (see Table).

Table.

Transmission of risk allele (A) for *TNFα-308* promoter SNP (rs1800629) in neonatal lupus (NL) trio cohort (TDT Test)

	Mothers with NL Child			
			Nontransmitted	
	Allele	A	G	
Transmitted	A	3	20	23
	G	3	24	27
		6	44	50

Number of Complete Trios = 25
OR=6.67 CI=(1.98–35.03)
$P_{TDT}=3.93\times10^{-4}$

Transmission of risk allele (G) for *C6orf10* SNP (rs7775397) in neonatal lupus (NL) trio cohort (TDT Test)

	Mothers with NL Child			
			Nontransmitted	
	Allele	G	T	
Transmitted	G	1	17	18
	T	0	34	34
		1	51	52

Number of Complete Trios = 26
OR=35.0 CI=(4.12-infinity)
$P_{TDT}=3.74\times10^{-5}$

Conclusion: Anti-SSA/Ro positive NL mothers are enriched for the *TNFα-308* and *C6orf10* variant alleles, which are preferentially inherited from asymptomatic, serologically silent maternal grandparents with a suggestive skewed pattern from the grandfather. These findings from the largest documented cohort of NL maternal grandparents support the hypothesis that the development of NL and genetic etiology are multigenerational.

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A Point Mutation in the SSA/Ro60 Autoantigen Which Prevents Y RNA Binding Attenuates a Requisite Signal for Cell Surface Expression and TLR-Dependent Inflammation. Joanne H. Reed[1], Soyeong Sim[2], Sandra L. Wolin[2], Jill P. Buyon[1] and Robert M. Clancy[1]. [1]New York University School of Medicine, New York, NY, [2]Yale University School of Medicine, New Haven, CT

Background/Purpose: The Ro/SSA ribonucleoprotein particle is a major autoantigen in Sjögren's syndrome, Systemic Lupus Erythematosus, and asymptomatic mothers of children with heart block. The particle comprises a 60kD Ro protein (Ro60) that binds misfolded RNAs in the nuclei and noncoding RNAs, Y RNAs, in the cytoplasm. During apoptosis, Ro60 translocates to the cell surface where it is available to bind extracellular antibody. Previous studies have demonstrated that the immune complex of RNA and Ro60 bound by anti-Ro60 antibody gains access to the macrophage endosome via FcγR uptake with subsequent ligation of Toll-like receptors (TLR) and secretion of proinflammatory cytokines. This study employed cells expressing novel Ro60 mutants that influence RNA binding to address the dependency of Ro60 associated RNA in translocation of Ro60 during apoptosis and activation of macrophages.

Methods: Murine fibroblast cell lines were obtained in which constitutively transfected constructs of FLAG-tagged forms of mutated Ro60 were introduced into Ro60 knockout cells. Ro60 K170A, R174A (170/4) does not bind misfolded pre5S RNA but binds Y RNA. Ro60 H187S does not bind Y RNA. Evaluations included the capacity of fibroblasts either permeabilized or rendered apoptotic by staurosporine or loss of anchorage signals, to form immune complexes with anti-Ro60 antibody (flow cytometry). Function was assessed by TNFα secretion (ELISA) by macrophages obtained from human peripheral blood mononuclear cells and PMA-differentiated THP-1.

Results: Early apoptotic fibroblasts (Annexin V-positive, PI-negative) transfected with Ro60 170/4 (binds pre5S but not Y RNA) were bound by anti-Ro60, affinity purified from the serum of a mother with a child effected by heart block, but not control IgG (190 ±108 vs 10±9, p=0.027). Cell surface expression of this Ro60 mutant was similar to wild type Ro60 (348±158, p=0.49 vs Ro60 170/4). In contrast, apoptotic fibroblasts transfected with Ro60 H187S (does not bind Y RNA) were not bound by anti-Ro60 (14±8 vs 170/4, p=0.029, vs wild type, p=0.029). Despite differences in cell surface translocation and RNA content, both Ro60 mutants, H187S and 170/4 showed equivalent intracellular binding of anti-Ro60 (1345±738 and 1384±282). The functional consequences of surface bound Ro60-anti-Ro60 complexes were subsequently addressed. Macrophages cultured with Ro60 170/4 apoptotic fibroblasts preincubated with anti-Ro60, secreted significantly higher levels of TNFα compared to macrophages incubated with Ro60 H187S apoptotic fibroblasts also preincubated with anti-Ro60 (146±32 pg/ml vs 46±14 pg/ml respectively, p=0.04). The TNFα secretion induced after macrophages were cultured with Ro60 170/4 apoptotic fibroblasts and anti-Ro60 was inhibited by 45% ± 13% in the presence of the TLR7 inhibitor, IRS661.

Conclusion: These data suggest that an alteration of the Ro60 domain which prevents Y RNA binding attenuates a permissive signal that is required for its participation as an antigen to form immune complexes in apoptotic cells and generate a TLR dependent proinflammatory cascade. Accordingly, the Y RNA moiety of the Ro/SSA ribonucleoprotein imparts a critical role in the pathogenicity of anti-Ro60 autoantibodies.

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Large-Scale, High-Density Genotyping Performed by the Sjögren's Genetics Network Using the ImmunoChip Identifies *PRKRA* as a Novel Sjögren's Syndrome Susceptibility Locus and Confirms Associations with IRF5, BLK and MHC. Christopher J. Lessard[1], Indra Adrianto[1], John A. Ice[1], Jennifer A. Kelly[1], Roland Jonsson[2], Gabor G. Illei[3], Maureen Rischmueller[4], Gunnel Nordmark[5], Xavier Mariette[6], Corinne Miceli-Richard[6], Marie Wahren Herlenius[7], Torsten Witte[8], Michael T. Brennan[9], Roald Omdal[10], Patrick M. Gaffney[11], James A. Lessard[12], Wan-Fai Ng[13], Nelson L. Rhodus[14], Barbara M. Segal[15], R. Hal Scofield[1], Judith A. James[16], Juan-Manuel Anaya[17], John B. Harley[18], Courtney Montgomery[1] and Kathy L. Moser[11]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Bergen, Bergen, Norway, [3]NIDCR/ NIH #10 1N110, Bethesda, MD, [4]Queen Elizabeth Hospital, Adelaide, Australia, [5]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden, [6]Bicêtre University Hospital, Le Kremlin Bicêtre, France, [7]Karolinska Institute, Stockholm, Sweden, [8]Hannover Medical School, Hanover, Germany, [9]Carolinas Medical Center, Charlotte, NC, [10]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway, [11]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [12]Valley Bone & Joint Clinic, Grand Forks, ND, [13]Musculoskeletal Research Group Institute of Cellular Medicine, Newcastle University, Newcastle, England, [14]University of Minnesota, Minneapolis, MN, [15]Hennepin County Medical Center, Minneapolis, MN, [16]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [17]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [18]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH

Background/Purpose: Sjögrens syndrome (SS) is a chronic, inflammatory autoimmune condition characterized by exocrine gland dysfunction and dysregulation of interferon responses. The etiology of SS is largely unknown, but current hypotheses suggest roles for environmental and genetic factors. To date, the identification of SS risk loci has been confined to candidate gene studies. In this study, we sought to evaluate a collection of European-derived SS cases for association with regions previously reported in other related inflammatory conditions (e.g. rheumatoid arthritis, etc).

Methods: We have established the Sjögrens Genetics Network (SGENE) to assemble a sizable cohort for large-scale genetic studies. We used the ImmunoChip, an Illumina iSelect custom array designed with ~196,000 single nucleotide polymorphisms (SNPs) from 12 inflammatory phenotypes. Stringent quality control measures were applied and principal component (PC) analysis was used to determine genetic outliers. After quality control, ~130,000 variants were available to test for association with 1051 SS cases and 1727 controls. Replication was performed in an independent collection of 268 SS cases and 380 controls. SNP-SS association was tested using logistic regression under an additive genetic model in PLINK while adjusting for the first three PCs and gender. Meta-analysis was conducted using weighted Z-scores in METAP.

Results: We identified a novel association unique to SS within the 3′-UTR of the gene protein kinase, interferon-inducible double-stranded RNA-dependent activator (*PRKRA*; $P=6.44\times10\text{E-}24$, OR=0.47, 95%CI=0.40–0.54). This result replicated in the independent case-control cohort ($P=1.04\times10\text{E-}6$ OR=0.43, 95%CI=0.31–0.61) yielding a *Pmeta*=1.3×10E-27. *PRKRA* encodes a double-stranded RNA-activated protein kinase that modulates the interferon cascade upon infection by viruses. Approximately 220 SNPs in the region of interferon regulator factor 5 (*IRF5*) were typed on this array including variants in genes centromeric (*KCP*) and telomeric (*TNPO3*) of this locus. A total of 12 SNPs had $P<5\times10\text{E-}8$, with the most significant SNP resulting in a $P=4.12\times10\text{E-}12$ (OR=1.52, 95%CI=1.35–1.71). *IRF5* encodes a transcription factor involved in the activation of interferon, cell growth and differentiation, apoptosis, and other immunologic-related functions. A SNP in the gene B lymphoid kinase (*BLK*) was found to be significantly associated with SS ($P=4.07\times10\text{E-}8$, OR=1.40, 95%CI=1.24–1.58). *BLK* encodes for a non-receptor protein kinase involved in B cell receptor signaling and B cell development. The strongest overall association identified was within the major histocompatibility complex (MHC) with 1467 SNPs resulting in $P<5\times10\text{E-}8$. Peak association was observed in HLA-DRB1 with $P=1.55\times10\text{E-}52$ (OR=3.675, 95%CI=3.10–4.34).

Conclusion: We have discovered and independently confirmed a novel association unique to SS in *PRKRA*, and report, for the first time, *IRF5* and *BLK* exceeding the genome-wide significance threshold. In addition, we replicate association with the *MHC*. Collectively these genes illustrate the importance of both the innate and adaptive immune responses in the etiology of SS.

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Salivary Gland Epithelial Cells Are Capable to Directly Induce the Differentiation of IL-21-Secreting Follicular Helper CD4 T Cells in Primary Sjögren's Syndrome. Yazhuo Gong[1], Ghada Alsaleh[2], Emmanuel Chatelus[3], Christelle Sordet[4], Jean Sibilia[5], Dominique Wachsmann[1] and Jacques-Eric Gottenberg[2]. [1]EA 44 38, Strasbourg, France, [2]Strasbourg University Hospital, Strasbourg, France, [3]Hopital Hautepierre, Strasbourg, France, [4]Hautepierre Strasbourg Hospital University, Strasbourg, France, [5]CHU Hautepierre, Strasbourg, France

Background/Purpose: Follicular helper CD4 T lymphocytes (Tfh) play a pivotal role in the activation of B lymphocytes, notably through IL-21 secretion. An increase in blood proportion of Tfh was recently reported in primary Sjögren's syndrome (pSS). Salivary gland epithelial cells (SGEC) of patients with pSS express various molecules implicated in innate and acquired immune responses and can act as antigen-presenting cells. We therefore investigated whether SGECs were capable to differentiate naïve T cells into follicular helper T cells.

Methods: Primary culture of salivary epithelial cells was derived from minor salivary gland biopsies isolated from patients with SS or controls (subjects complaining from dry symptoms without any feature of autoimmunity).

Expression of ICOSL by SGECs after stimulation with poly I:C was assessed using qPCR. Naïve T cells were cocultured with SGECs and activated by anti-CD2, anti-CD3 and anti-CD28. Expression of ICOS and CXCR5 was analyzed using flow cytometry. Levels of IL-21, Il-6 and IL-17 were assessed in culture supernatants.

Results: SGECs of patients pSS (n=4) or controls (n=4) both up-regulated the expression of ICOSL when stimulated with poly I:C, but did not secrete IL-21. Coculture between T cells and non stimulated SGECs (1 pSS, 2 SS and 3 controls) induced the increased expression of CXCR5 (MFI 6.5 *versus* 5.2, p=0.09) and ICOS (MFI 41.25±14.8 *versus* 15.75±1.26, p=0.005). 3.76±2.05% on average (n=6) $CXCR5^+ICOS^+$ T cells were differentiated by coculture with SGECs. Secretion of IL-21 was also significantly increased after coculture (671.8±394.6 *versus* 17.8±19.5 pg/ml in CD4 T cells alone and 0 pg/ml in SGECs alone, p=0.0004). Secretion of IL-17, a cytokine that can be secreted by Tfh, was detected in the supernatant of cocultures (57±49.2 pg/ml) but not in the supernatant of SGEC or in T naive alone (p=0.0004). No significant change was observed in ICOS or CXCR5 expression using or not a transwell for cocultures.. However, coculture with a transwell partly inhibited IL-21(198.6±83.3 pg/ml with a transwell *versus* 591.4±308.9 pg/ml without, p=0.0286) and completely inhibited IL-17 secretion.

Conclusion: We demonstrated that SGEC are capable to directly induce the differentiation of IL-21 secreting follicular helper T cells, which might contribute to the marked activation of B lymphocytes in salivary glands. Further analyses are ongoing to determine the pathways implicated in this differentiation, which may involve IL-12. These results emphasize the pivotal role of salivary gland epithelial cells in this autoimmune epithelitis and suggest that follicular helper T cells and IL-21 might represent relevant therapeutic targets in pSS.

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Functional Delivery of EBV-Mir-BART13 by exosomes in Human Salivary Gland Cells Affects Calcium Signaling. Alessia Gallo[1], Mayank Tandon[1], Shyh-Ing Jang[1], Hwei Ling Ong[1], Indu Ambudkar[1], Gabor G. Illei[2] and Ilias Alevizos[1]. [1]NIDCR, Bethesda, MD, [2]NIDCR/NIH #10 1N110, Bethesda, MD

Background/Purpose: Loss of secretory function of salivary glands is one of the most important functional effects of Sjögren's syndrome (SS), a chronic systemic autoimmune disease. We have shown that an EBV microRNA (ebv-mir-BART13) is significantly over-expressed in minor salivary gland biopsies of SS patients, when compared to the healthy volunteers. We have also shown that the over-expression of EBV-mir-BART13 in human salivary gland cell line is responsible of the down regulation of STIM1, an ER-Ca2+ sensor protein regulating store-operated calcium entry. Previous works have also shown that EBV miRNAs can be transferred from B-cells to other cells. Objective of this work is to establish if this mechanism can occur in SS and can explain how EBV-mir-BART13 is delivered into epithelial cells.

Methods: To investigate how the viral microRNA is transferred into epithelial cells from the B we used transwell system where we co-cultured the EBV stably transfected X50-7 B-cell line with a human salivary gland cell line (HSG) or a primary salivary epithelial cells line derived from human minor salivary gland. RT-PCR was performed on HSG cells and primary salivary epithelial cells RNA to assess the uptake of EBV-mir-BART13.

Results: In a transwell system, we co-cultured EBV stably transfected X50-7 B-cell line with a human salivary gland cell line (HSG) or primary salivary epithelial cells line. This system allows the passage of soluble molecules and small microvescicles but not cells. After 7 days of co-culture, we demonstrated by RT-PCR that EBV-miR-BART13 was released from X50-7 B-cell line in the medium and was successfully transferred and taken up by both co-cultured HSG cells and primary salivary epithelial cells. The functional effects EBV-mir-BART13 on these two cell lines was assessed by measuring STIM1 protein level and functional Ca^{2+} assays through thapsigargin-mediated depletion of the endoplasmic reticulum calcium. Cells co-cultured with EBV-miR-BART13 producing B cells showed a decrease in STIM1 expression and a significant delay in the influx of calcium consistent with a functional blockade of STIM1.

Conclusion: Together, these finding suggest that EBV-miR-BART13 can be transferred from the X50-7 B-cell line to human salivary gland cells and primary salivary epithelial cells *via* exosomes. The delivery of this miRNA has also a functional effect by reducing STIM1 expression and affecting the Ca^{2+} signaling. Exosomal delivery of viral microRNAs from lymphocytes to epithelial cells may represent a mechanism by which viruses may contribute to salivary gland dysfunction in Sjogren's syndrome.

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Matriptase Dificency and Primary Sjogren Syndrome Induction: From Patients to Mice. Hongen Yin, Peter Kosa, Xibao Liu, Bill Swaim, Javier Cabrera-Perez, Zhennan Lai, Indu Ambudka, Thomas Bugge and John A. Chiorini NIH/NIDCR, Bethesda, MD

Background/Purpose: The role of epithelial cells in salivary gland function has long been recognized as central to gland activity. However changes in the epithelia of the salivary gland are poorly understood. We previously reported that mice with a ductal cell-specific deletion of the serine protease matriptase display a decrease saliva production following pilocarpine stimulation. This would suggest that matriptase could have a role in the development or maintenance of salivary gland function. The purpose of this study is to determine the role of matriptase in salivary gland function and to investigate its link to salivary gland dysfunction in Sjögren's syndrome.

Methods: Matriptase expression was detected in minor salivary gland biopsy (MSG) of health volunteer (HV) and primary Sjögren's syndrome (pSS) patients by microarray and quantitative PCR (qPCR). The role of matriptase in salivary and lacrimal gland function was studied by using tissue-specific conditional knockout mice ($MMTV\text{-}Cre^{+/0};St14^{LoxP/-}$) mice and salivary gland-specific matriptase knock out [local delivery of adeno-associated virus vector serotype 2 (AAV2) encoding the Cre gene in the submandibular gland (SMG) of $St14^{LoxP/LoxP}$ mice]. SMG and LG from matriptase-ablated and control mice were assessed for inflammation and activity changes by identifying lymphocytic foci (LF) (H&E), pilocarpine stimulated salivary flow rate (SFR) and tear flow rate (TFR) respectively. Autoantibody development was detected by ELISA. Alteration of T cells and cytokine productions were accessed by flow cytometry and multiplex ELISA assay respectively in SMG draining lymph nodes (DLN), spleen and serum. Immunofluorescent staining was used to identify SMG tight junction and ion transport channels. Ductal and acinar cell function was also assayed by regulatory volume decrease (RVD) following hypotonic swelling.

Results: A significant decrease in matriptase expression was found in the MSGs from pSS patients. Furthermore, mice with reduced matriptase expression develop a number of characteristics associated with pSS, including decreased salivary and lacrimal gland function. This decrease in function correlated with a decrease in electrical potential across the epithelial membrane of the gland. In matriptase KO mice, anti-Ro, anti-La and anti-nuclear antibodies (ANA) were detected in serum and a significant increase in LF was detected in LG but not SMG. Altered T cell regulation and cytokines production was found in local and peripheral immune systems. TJ proteins and ion/water channels changes were found in the SMG of matriptase-deficient mice compared to controls. A loss of volume regulation was observed in both ductal and acinar cells after matriptase local depletion in SMG.

Conclusion: Our data suggest that matriptase deficiency is associated with primary Sjögren's syndrome and can induce a pSS-like phenotype in mice. The induction of pSS by matriptase depletion is correlated with a change in epithelial barrier function and subsequent impairment of immune homeostasis in natural and adaptive immunity, resulting in a systemic autoimmune condition similar to pSS.

ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment I
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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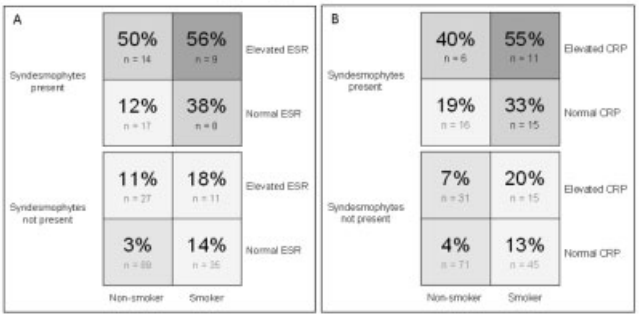
Baseline Radiographic Damage, Elevated Acute Phase Reactants and Cigarette Smoking Status Predict Radiographic Progression in the Spine in Early Axial Spondyloarthritis. Denis Poddubnyy[1], Hildrun Haibel[2], Joachim Listing[3], Elisabeth Märker-Hermann[4], Henning Zeidler[5], Jürgen Braun[6], Joachim Sieper[2] and Martin Rudwaleit[7]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Charité – Campus Benjamin Franklin, Berlin, Germany, [3]German Rheumatism Research Centre, Berlin, Germany, [4]Dr. Horst Schmidt Kliniken, Wiesbaden, Germany, [5]Medizinische Hochschule, Hannover, Germany, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]Ev. Krankenhaus Hagen-Haspe, Hagen, Germany

Background/Purpose: There are some data available on the frequency of structural damage in the spine in patients with ankylosing spondylitis (AS) and about potential risk factors for the development of syndesmophytes, but these data refer exclusively to patients with long-standing AS. Nearly no data exist regarding rates and predictors of radiographic spinal progression in early axial spondyloarthritis (SpA). The objective of the study was to investigate rates and predictors of structural damage development in the spine in patients with early axial SpA (AS with symptoms duration of <10 years and non-radiographic axial SpA (nrSpA) with symptoms duration of <5 years).

Methods: 210 patients with axial SpA (115 with AS according to the modified New York criteria and 95 with nrSpA) from the German Spondyloarthritis Inception Cohort (GESPIC) were selected for this analysis based on availability of radiographs (sacroiliac joints, lumbar and cervical spine lateral views) at baseline and after 2 years of follow-up. Images were centrally collected, digitized, and subsequently scored independently by two trained readers. Spinal radiographs were scored according to the mSASSS scoring system. The readers scored both time points simultaneously but were blinded for the time point and for all clinical data. Significant radiographic spinal progression was defined as a worsening of the mean mSASSS score by ≥ 2 units over two years

Results: Altogether, 14.3% of the patients in the whole SpA group showed spinal radiographic progression according to this definition. This rate was higher in the group of patients with AS (20%) in comparison to non-radiographic axial SpA (7.4%). The following parameters were independently associated with radiographic spinal progression: presence of syndesmophytes at baseline (odds ratio (OR)=6.29, $p<0.001$), elevated markers of systemic inflammation (erythrocyte sedimentation rate: OR=4.04, p=0.001, C-reactive protein: OR=3.81, p=0.001), and cigarette smoking (OR=2.75, p=0.012), that was confirmed in the multivariate logistic regression analysis. No clear association with radiographic spinal progression was found for HLA-B27 status, sex, age, disease duration, BASDAI, BASFI, presence of peripheral arthritis, enthesitis or psoriasis. Based on the obtained data two prediction matrix models were constructed incorporating the following variables: baseline syndesmophytes, smoking status and an elevated acute phase reactant (either ESR or CRP)—figure.

Figure. Matrix model of association of syndesmophytes, elevated acute phase reactants (A - ESR >20 mm/h, B - CRP >6 mg/l at baseline) and smoking (as present at baseline) with spinal radiographic progression over two years in patients with axial SpA (n = 210). Percentages refer to patients with spinal radiographic progression (≥2 mSASSS units over two years), n – number of patients with combination of the respective parameters.



Conclusion: The presence of radiographic damage in the spine (syndesmophytes), elevated acute phase reactants and cigarette smoking status predict spinal radiographic progression in early axial SpA.

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Multivariate Analysis Indicates That Fat Lesions Dominate Over Inflammatory Lesions in Predicting New Bone Formation in the Spine of Patients with Ankylosing Spondylitis. Walter P. Maksymowych, Nathalie Morency, Barbara Conner-Spady and Robert GW Lambert. University of Alberta, Edmonton, AB

Background/Purpose: Recent prospective data indicates that as inflammatory lesions mature, they undergo a process of transformation into fat in the spine of patients with ankylosing spondylitis (AS)[1]. It has been proposed that bone formation becomes uncoupled from inflammation in these complex inflammatory lesions characterized by: 1. Inflammation that has receded from the vertebral corner (VC) on STIR MRI 2.Fat infiltration at the same VC location on T1W MRI. Early inflammatory lesion may resolve completely without sequelae while resolution of complex inflammatory lesion may be accompanied by new bone formation[2]. Consequently, the appearance of fat lesions may indicate an even greater propensity to new bone formation than inflammatory lesions. We tested this hypothesis in this prospective study.

Methods: MRI scans were performed at baseline, 12, and 52 weeks while radiographs were done at baseline and 104 weeks in 76 AS patients randomized to receive either adalimumab (ADA) 40 mg every other week or placebo for 24 weeks in a, double-blind, Phase III study of active AS. After the week 12 assessment, patients were eligible for early escape therapy and after 24 weeks all patients received ADA. The anterior VC of the cervical and lumbar spine were examined for new syndesmophytes and ankylosis (baseline, 104 weeks) on lateral radiographs of the spine. Anonymized MR scans were read independently by 2 readers who recorded the presence/absence of inflammatory and fat lesions at the same anterior VC that were assessed by radiography. We used Generalized Linear Latent and Mixed Models (GLLAMM) multivariate analysis to adjust for within patient dependence in the *total number* of vertebral corners with syndesmophytes/ankylosis at baseline to determine which lesions were independently predictive of new bone.

Results: At the patient level, the mean (SD) number of VC inflammatory or fat lesions was significantly higher on baseline MRI in those who developed new bone compared to those who did not ($p = 0.002$ and 0.0003, respectively). New bone developed significantly more frequently from VC that demonstrated inflammatory lesions (13 of 220 (5.9%)) or fat lesions (20 of 179 (11.2%) on baseline MRI as compared to VC with neither (29 of 1138 (2.5%)) ($p= 0.002$ and <0.0001, respectively). New bone also developed significantly more frequently from VC with ***both*** inflammation and fat (7 of 52 (13.5%)) compared to VC with ***only*** inflammation (6 of 168 (3.6%), $p = 0.015$). GLAMM multivariate analysis that included inflammation, fat, and syndesmophytes/ankylosis showed that fat dominated over inflammation in predicting new bone.

	OR (95%CI)	P value
Inflammation	1.11 (0.48–2.59)	NS
Fat	4.39 (2.08–9.26)	P<0.0001
Syndesmophyte/ankylosis	1.18 (1.10–1.27)	P<0.0001

Conclusion: Our data supports the hypothesis that new bone formation is more likely in complex inflammatory lesions characterized by fat metaplasia where it may be uncoupled from inflammation.

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Anti-Interleukin 17A Monoclonal Antibody Secukinumab Reduces Signs and Symptoms of Psoriatic Arthritis in a 24-Week Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial. I. McInnes[1], J. Sieper[2], J. Braun[3], Paul Emery[4], D. van der Heijde[5], J. Isaacs[6], G. Dahmen[7], J. Wollenhaupt[8], H. Schulze-Koops[9], S. Gsteiger[10], A. Bertolino[11], W. Hueber[11] and P. P. Tak[12]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Charitè Campus Benjamin Franklin, Berlin, Germany, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Newcastle University and the Freeman Hospital, Newcastle-upon-Tyne, United Kingdom, [7]Praxis fuer klinische Studien, Hamburg, Germany, [8]Eilbeck Hospital, Hamburg, Germany, [9]Klinikum Innenstadt der Ludwig-Maximilians-Universität, Munich, Germany, [10]Novartis Pharma AG, Basel, Switzerland, [11]Novartis Institutes for BioMedical Research, Basel, Switzerland, [12]University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Interleukin 17A (IL-17A) is a novel target for the treatment of psoriatic arthritis (PsA). We assessed the safety and preliminary efficacy of secukinumab, an anti-IL-17A monoclonal antibody, in PsA.

Methods: 42 patients with active PsA fulfilling CASPAR criteria were assigned 2:1 to receive two injections with secukinumab (10mg/kg) or placebo, given three weeks apart. The primary efficacy endpoint was the proportion of ACR20 responders at Week 6 in active compared with placebo recipients (one-sided p-value <0.1). As per protocol, no imputation was made for missing data (drop-outs were treated as missing).

Results: 25 (89%) patients on secukinumab and 10 (71%) on placebo completed the study. Five patients (4 secukinumab and 1 placebo) were excluded from the efficacy analysis due to protocol violations. Three (11%) of patients on secukinumab and 4 (29%) on placebo discontinued prematurely for lack of efficacy or withdrawal of consent. Demographics and baseline characteristics were balanced between groups for age, sex and parameters including mean (SD) SJC (secukinumab *vs*. placebo): 8.3 (5.6) *vs*. 9.5 (5.4); TJC 23.5 (19.4) *vs.* 22.6 (11.0); DAS28 4.8 (1.2) *vs.* 4.8 (1.2); MASES 3.0 (4.1) *vs.* 3.4 (2.3). Co-existing psoriasis, prior TNFi exposure and co-medication with DMARDS were present in 23 (98%), 11 (46%) and 21 (88%) patients on secukinumab and in 11 (89%), 5 (38%) and 10 (70%) on placebo, respectively. The ACR20 response rate at week 6 was 39% (9/23) on secukinumab *vs.* 23% (3/13) on placebo (*P = 0.27*). ACR20 response rates were 39% (9/23) *vs*. 15% (2/13) at week 12, and 43% (10/23) *vs*. 18% (2/11) at week 28 with secukinumab *versus* placebo, respectively. ACR50 and ACR70 response rates at week 6 on secukinumab *vs*. placebo were 17% *vs*. 8 % and 9% *vs*. 0%, respectively. CRP reductions at week 6 compared to baseline were observed on secukinumab (median [range] of 5.0 [0.3, 43.0] at baseline *vs*. 3.0 [0.2, 15.2] at week 6, but not on placebo (3.9 [1.3, 39.7] at baseline *vs*. 5.0 [0.8, 29.6] at week 6). Similar reductions were seen for ESR, and reductions in acute phase parameters were maintained up to week 28. The overall rate of adverse events (AEs) was comparable in secukinumab *versus* placebo: 26 (94%) *vs.* 11 (79%). One severe adverse event (cellulitis hand) occurred on secukinumab, and was not suspected by the investigator to be study drug-related. 7 serious AEs were reported in 4 secukinumab patients (tendon rupture/carpal tunnel syndrome/cellulitis, obesity, fall, breast cancer [diagnosed prior to dosing and inclusion constituting a protocol violation]) and 1 with placebo (polyarthritis). Infections were reported in 16 (57%) patients on secukinumab and 7 (50%) patients on placebo.

Conclusion: The safety profile of secukinumab was favorable overall. Although the primary endpoint was not met, a substantial proportion of patients showed rapid and sustained improvements of clinical scores and acute phase parameters up to week 28. Trends towards a beneficial clinical effect support the rationale for larger clinical trials designed to assess clinical effectiveness.

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Oral Apremilast Is Effective with and without Concomitant Methotrexate Therapy in the Treatment of Subjects with Active Psoriatic Arthritis. Georg A. Schett[1], Angela Hu[2] and Randall Stevens[2]. [1]University Erlangen-Nuremberg, Erlangen, Germany, [2]Celgene Corporation, Warren, NJ

Background/Purpose: Phosphodiesterase 4 (PDE4) is expressed in cells mediating immune response. Apremilast (APR) is a novel, orally available small molecule that specifically targets PDE4, thereby increasing cellular cyclic adenosine monophosphate, which modulates multiple pro- and anti-inflammatory mediators. Because a large proportion of psoriatic arthritis (PsA) subjects are treated with methotrexate (MTX), the comparable efficacy and tolerability of APR as monotherapy and in combination with MTX is of interest. *We evaluated the effectiveness of APR for the treatment of* active PsA in subjects taking and not taking concomitant MTX.

Methods: In a phase 2 randomized, double-blind, placebo (PBO)-controlled, multicenter study, subjects with active PsA (joint involvement ≥6 mo; ≥3 tender joints; ≥3 swollen joints) were randomized to PBO, APR 20mg BID (APR20), or APR 40mg QD (APR40) and treated for 12 wks. Stable doses of NSAIDs, corticosteroids, and MTX (≥56 days before screening; dose range 1.5–30mg/wk) were allowed; randomization was stratified by baseline MTX use. Last observation carried forward was used for missing data. The Breslow-Day statistic was used to test the null hypothesis of homogenous odds ratio (OR; APR vs PBO) among subjects treated and not treated with MTX.

Results: Of 204 subjects enrolled (mean PsA duration 7.8 yrs), at baseline 89 subjects were taking MTX (PBO: 29 [42.6%]; APR20: 30 [43.5%]; APR40: 30 [44.8%]) and 115 were not taking MTX (PBO: 39 [57.4%]; APR20: 39 [56.5%]; APR40: 37 [55.2%]). Use of APR20 and APR40 resulted in more subjects achieving an ACR20 vs PBO (OR 3.68–7.58) at wk 12 regardless of concomitant MTX use. No differences were noted in ACR20 in subjects taking MTX vs not taking MTX in any group: PBO, 10.3% vs 12.8%; APR20, 46.7% vs 41.0%; and APR40, 36.7% vs 35.1%. There was no evidence that the APR treatment response (APR vs PBO) differed among subjects treated and not treated with MTX (treatment by MTX interaction: p=0.606 [APR20]; p=0.739 [APR40]). Adverse events (AEs) were reported by 78/89 (87.6%) subjects taking MTX vs 94/115 (81.7%) subjects not taking MTX regardless of randomization assignment. The most commonly reported AEs were diarrhea, headache, nausea, fatigue, and nasopharyngitis. Gastrointestinal AEs, particularly diarrhea and vomiting, tended to occur in more subjects treated with MTX vs without MTX regardless of randomization assignment (Table). Overall, there was no strong evidence for increasing AEs with concomitant APR/MTX treatment vs APR monotherapy.

	Placebo		Apremilast 20 mg BID		Apremilast 40 mg QD		Total	
System Organ Class	**MTX (n=29) n (%)**	**No MTX (n=39) n (%)**	**MTX (n=30) n (%)**	**No MTX (n=39) n (%)**	**MTX (n=30) n (%)**	**No MTX (n=37) n (%)**	**MTX (n=89) n (%)**	**No MTX (n=115) n (%)**
Subjects with ≥1 AE	23 (79.3)	32 (82.1)	26 (86.7)	33 (84.6)	29 (96.7)	29 (78.4)	78 (87.6)	94 (81.7)
GI disorders	12 (41.4)	12 (30.8)	13 (43.3)	18 (46.2)	18 (60.0)	15 (40.5)	43 (48.3)	45 (39.1)
Diarrhea	5 (17.2)	1 (2.6)	7 (23.3)	7 (17.9)	10 (33.3)	8 (21.6)	22 (24.7)	16 (13.9)
Nausea	8 (27.6)	4 (10.3)	6 (20.0)	6 (15.4)	7 (23.3)	8 (21.6)	21 (23.6)	18 (15.7)
Vomiting	3 (10.3)	1 (2.6)	3 (10.0)	1 (2.6)	3 (10.0)	1 (2.7)	9 (10.1)	3 (2.6)
Upper abdominal pain	1 (3.4)	2 (5.1)	5 (16.7)	2 (5.1)	1 (3.3)	3 (8.1)	7 (7.9)	7 (6.1)
Infections and infestations	10 (34.5)	11 (28.2)	6 (20.0)	11 (28.2)	14 (46.7)	10 (27.0)	30 (33.7)	32 (27.8)
Nasopharyngitis	5 (17.2)	7 (17.9)	3 (10.0)	5 (12.8)	4 (13.3)	4 (10.8)	12 (13.5)	16 (13.9)
Gastroenteritis	2 (6.9)	0	1 (3.3)	1 (2.6)	2 (6.7)	0	5 (5.6)	1 (0.9)
Nervous system disorders	6 (20.7)	12 (30.8)	6 (20.0)	16 (41.0)	11 (36.7)	9 (24.3)	23 (25.8)	37 (32.2)
Headache	4 (13.8)	7 (17.9)	1 (3.3)	12 (30.8)	6 (20.0)	9 (24.3)	11 (12.4)	28 (24.3)
Dizziness	1 (3.4)	2 (5.1)	1 (3.3)	2 (5.1)	5 (16.7)	2 (5.4)	7 (7.9)	6 (5.2)
Migraine	0	0	4 (13.3)	2 (5.1)	2 (6.7)	0	6 (6.7)	2 (1.7)
Musculoskeletal and connective tissue disorders	6 (20.7)	11 (28.2)	4 (13.3)	5 (12.8)	6 (20.0)	2 (5.4)	16 (18.0)	18 (15.7)
Psoriatic arthropathy	0	6 (15.4)	2 (6.7)	1 (2.6)	2 (6.7)	0	4 (4.5)	7 (6.1)
General disorders and administration site conditions	4 (13.8)	5 (12.8)	2 (6.7)	6 (15.4)	9 (30.0)	5 (13.5)	15 (16.9)	16 (13.9)
Fatigue	2 (6.9)	4 (10.3)	2 (6.7)	3 (7.7)	7 (23.3)	4 (10.8)	11 (12.4)	11 (9.6)
Respiratory, thoracic, and mediastinal disorders	4 (13.8)	5 (12.8)	3 (10.0)	1 (2.6)	4 (13.3)	1 (2.7)	11 (12.4)	7 (6.1)
Pharyngolaryn-geal pain	3 (10.0)	1 (2.6)	1 (3.3)	0	1 (3.3)	0	5 (5.6)	1 (0.9)

Conclusion: APR was previously shown to be effective in the treatment of active PsA. The current analysis demonstrates the efficacy and safety of APR in PsA subjects with and without concomitant MTX therapy. There was no additional benefit or risk associated with combination APR/MTX therapy. Phase 3 studies are ongoing to further explore APR efficacy for the treatment of PsA and psoriasis.

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The Association Between Human Leukocyte Antigen and Killer-Cell Immunoglobulin-Like Receptor Gene Variants and Progression of Peripheral Joint Damage in Psoriatic Arthritis. Vinod Chandran[1], Arane Thavaneswaran[2], Fawnda Pellett[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Genetic factors may influence peripheral joint damage progression in psoriatic arthritis (PsA). We therefore conducted a case-only study to identify *HLA* and *KIR* polymorphisms associated with progression of peripheral joint damage in PsA.

Methods: Data on the number of clinically damaged joints at each clinic visit 6 months apart was obtained on a cohort of 649 Caucasian subjects with PsA satisfying CASPAR criteria. Peripheral joint damage was defined by the presence of limitation of range of movement of > 20% of the range not related to the presence of joint effusion, the presence of joint deformities, subluxation, flail joints or ankylosis. HLA typing was performed by PCR-SSO, and KIR typing by PCR-SSP with appropriate quality control. The principal outcome was the change in the number of clinically damaged joints between clinic visits. A negative binomial model best fit the distribution of the outcome variable and was used for all analyses. The predictor variables included age at diagnosis, sex and genetic variables (HLA, KIR). To allow for any remaining, unadjusted, within-patient correlation, a generalised estimating equation analysis was used to provide robust estimated standard errors when fitting primary multivariate models.

Results: The 649 subjects [373 (57.5%) males, mean age at diagnosis 36 years, mean age at first visit 43 years, mean duration of PsA 7 years, mean tender joint count 8.6, mean swollen joint count 5.1, mean number of damage joints at first visit 8.7] had a median number of 7 visits during a median follow up of 6 years. Univariate analyses of HLA associations showed that the alleles A*02, C*01, B*27 and B*39 increased risk of joint damage progression whereas the alleles A*11, A*29, C*04, B*35, B*44, B*50, DRB1*13 and DQB1*0604 decreased risk. Multivariate analysis confirmed that HLA- B*39 (OR 1.87, 95% CI 1.38, 2.54, p <0.0001), B*27 (OR 1.51, 95% CI 1.15, 1.97, p =< 0.01) and A*02 (OR 1.30, 95% CI 1.03, 1.63 p = 0.03) independently increase the odds of joint damage progression between clinic visits, whereas HLA DQB1*0604 (OR 0.52, 95% CI 0.35, 0.78 p < 0.01), C*04 (OR 0.69, 95% CI 0.49, 0.97, p = 0.03) and B*50 (OR 0.51, 95% CI 0.27, 0.98, p = 0.04) decreases risk. Of the KIR genes only *KIR3DS1* (OR 1.33, 95% CI 1.07, 1.66, P = 0.01) was associated with joint damage progression. Neither HLA-C C group 1, HLA-C C group 2, HLA-C alleles with high cell-surface expression, HLA-B Bw4, Bw4 80ile, Bw4 80thr or HLA-Bw6 alleles were associated. There was no evidence of an association between KIR genes and joint damage progression in the presence/absence corresponding HLA ligands.

Conclusion: Genetic markers play a role in the progression of clinical joint damage in patients with PsA. HLA alleles HLA-B*39, B*27 and A*02 and the KIR gene *KIR3DS1* are independently associated with increased peripheral joint damage progression between clinic visits in PsA, whereas the alleles DQB1*0604, C*04 and B*50 decreases risk.

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The Impact of Psoriasis Extent On Prevalence of Psoriatic Arthritis. Alexis Ogdie[1], Nicole Seminara[2], Sinead Langan[3] and Joel Gelfand[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania., Philadelphia, PA, [3]London School of Hygiene and Tropical Medicine, United Kingdom

Background/Purpose: Psoriatic arthritis (PsA) is a chronic, inflammatory arthritis associated with psoriasis with prevalence in the general population of approximately 0.25% making it a difficult disease to study from a population-based perspective. The Health Improvement Network (THIN) is a medical record database in the United Kingdom with 7 million patients and an average length of follow up of 7 years that can be used to perform high quality, population-based epidemiology studies. With more than 7,000 patients with at least one code for PsA, this database could be a tremendous resource for the study of PsA. In this study, we aimed to assess the impact of extent of skin psoriasis on the prevalence of PsA.

Methods: 4,900 patients ages 45–65 with a code for psoriasis were randomly selected and a questionnaire was sent to their GP to confirm the diagnosis of psoriasis and disease severity. Among patients with a diagnosis of psoriasis confirmed by the GP, the lifetime prevalence of PsA and prevalence stratified by severity of psoriasis (%BSA) were evaluated. Using logistic regression, we then assessed whether psoriasis severity was an independent predictor for prevalent psoriatic arthritis.

Results: 4,634 surveys have been returned (response rate 95%). Prevalence of psoriasis in THIN is 1.9% overall, consistent with other population based estimates. The psoriasis diagnosis was confirmed in 90% (95%CI: 89–91) of patients. %BSA was obtained for 3,896. Of 4,586 patients with psoriasis between age 45–65, 349 or 8.6% (95%CI: 7.7–9.5) had at least one diagnostic code for psoriatic arthritis. Additionally, patients with more extensive skin psoriasis had a significantly higher prevalence of PsA (Table) which increased in a dose-dependent manner. A multivariable logistic regression model included psoriasis extent (mild, moderate, severe), body mass index category, duration of psoriasis category, age and sex. Age and sex were not significant in the model. Independent predictors of prevalent PsA among psoriasis patients after adjusting for all factors in the model included severe psoriasis or >10% BSA (OR 3.37; 95%CI: 2.39–4.6), BMI (OR 1.80; 95%CI: 1.31–2.4), and duration of psoriasis for 10 or more years (OR 6.36; 95%CI: 3.86–14.25).

	Psoriasis	PsA	% PsA of Total (95%CI)
≤2%	1951	92	4.7 (3.8–5.8)
3–10%	1249	128	10.2 (8.6–12.1)
>10%	370	105	28.4 (23.8–33.3)

Conclusion: The prevalence of PsA among patients with psoriasis is consistent with previous population based estimates in both the US and UK. The prevalence of PsA increases dramatically with increasing severity of skin psoriasis, even after adjusting for BMI, length of disease, age and sex, confirming our findings from a previous US population-based study that was much smaller and relied on patient self-report.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects: Cardiac Disease/Organ Damage
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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The Protective Effect of Antimalarials On Thrombovascular Events In Latin American Systemic Lupus Erythematosus Patients. Guillermo J. Pons-Estel[1], Graciela S. Alarcón[2], Daniel Wojdyla[3], Ana I. Marcos[4], Alejandro J. Alvarellos[5], Antonio A. Iglesias-Gamarra[6], Maria H. Esteva-Spinetti[7], Lilian Costallat[8], Nilzio A. Silva[9], Gloria Vázquez[10], Maria Loreto Massardo[11], Marlene Guibert-Toledano[12], Guillermo F. Huerta-Yáñez[13], Mariano Cucho-Venegas[14] and Bernardo Pons-Estel[15]. [1]Servicio de Enfermedades Autoinmunes, Hospital Clínic Barcelona, Barcelona, Spain, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Universidad Nacional de Rosario, Argentina, Rosario, Argentina, [4]Hospital Interzonal General de Agudos "General San Martin, La Plata, La Plata, Argentina, [5]Hospital Privado, Cordoba, Argentina, [6]Universidad Nacional, Bogota, Colombia, [7]Centro Clinico San Cristobal, San Cristobal, Venezuela, [8]Faculdade de Ciencias Medicas, Universidade Estadual de Campinas, Campinas, Brazil, [9]Faculdade de Medicina, Universidade Federal de Goias, Goiania, Brazil, [10]Universidad de Antioquia, Hospital Universitario "San Vicente de Paul", Medellín, Colombia, [11]Catholic University of Chile, Santiago, Chile, [12]Centro de Investigaciones Médico Quirúrgicas, Habana, La Habana, Cuba, [13]Hospital de Especialidades Miguel Hidalgo, Aguascalientes, Mexico, [14]Almenara Hospital IPSs, Lima, Peru, [15]Hospital Provincial de Rosario, Rosario, Argentina

Background/Purpose: Antimalarials (AMs) have shown to exert a thromboprotective effect in systemic lupus erythematosus (SLE), but studies thus far have been limited to North American and European

patients. This study was conducted to assess whether a similar effect is observed in Latin American patients with SLE.

Methods: SLE patients with a recent diagnosis (≤2 years) recruited and followed longitudinally as part of the GLADEL cohort were examined to establish risk factors for thrombotic events (TEs) and the possible preventive role of AMs. The outcome variable was defined as the presence of an arterial or venous thrombotic event during follow up. AM use was considered present (ever used) or absent (never used). After controlling for possible confounding variables identified in univariable analysis, the use of AM drugs was assessed for its effects on the development of TEs in cohort patients and by Cox proportional hazards regression analyses.

Results: Of the 1,480 patients included in the GLADEL cohort, 1,213 (82%) were considered AMs users. Thrombosis occurred in 87 (5.9%) of the patients during a median follow up time of 64 (range 12–98) months. After adjustment for potential confounders in the Cox proportional hazards regression model, AM use was associated with a 39% reduction in the rate of TEs (hazard ratio 0.61, 95% CI 0.40–0.95). Other variables significantly associated with TEs are depicted in Table 1.

Table 1. Effects of AMs drugs on the development of TEs in SLE patients from the GLADEL cohort by multivariable Cox proportional hazards regression analysis.

Parameter	HR	95% CI		P Value
Antimalarial use	0.612	0.40	0.95	0.0288
Female sex	0.486	0.28	0.84	0.0096
Antiphospholipid antibodies	1.689	1.01	2.82	0.0443
Any Hospitalization	2.200	1.39	3.48	0.0008
Aspirin/Anticoagulant use	2.156	1.14	4.07	0.0181
Thrombosis Previous to SLE Diagnosis	3.688	1.85	7.35	0.0002

Conclusion: After adjusting for possible confounding factors related to AM use, a clear protective effect of AM in the development of TEs in SLE patients from this Latin American cohort was observed.

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Non-Calcified Coronary Plaque in Systemic Lupus Erythematosus Quantitative Analysis. Adnan Kiani[1], Jens Vogel-Claussen[2], Armin Zadeh[2], Margaret Yew[2], Laurence S. Magder[3], Joao Lima[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]University of Maryland, Baltimore, MD

Background/Purpose: Atherosclerosis is accelerated in SLE. Inflammation is a risk factor for both plaque instability and atherosclerosis. New technology (CTA) can measure non-calcified plaque (NCP), which is highly unstable and has a high degree of inflammation compared to calcified plaque. We report on a large quantified study of NCP in SLE.

Methods: 64 (n=106) and 320 (n=41) slice coronary multidetector computed tomography (MDCT) was performed in 147 patients with SLE. The MDCT scans were evaluated quantitatively by a radiologist, using dedicated software.

Results: The 147 SLE pts were 86% female, 70% Caucasian, 27% African-American, 3% other; mean age 51 years. Table 1 shows the mean NCP score, by demographics, traditional cardiovascular risk factors and history of ever positive lupus serologies. Table 2 shows the mean NCP score by current lupus serologies and current medications. Table 3 shows the multivariate regression model.

Table 1. Association of NCP with Demographics and Past History

	Group	Mean Noncalcified Plaque Score	p-value	p-value when age is controlled
Demographics			0.007	–
Age				
	<45 (n=50)	0.14 (0.20)		
	45–55 (n=53)	0.22 (0.31)		
	55+ (n=42)	0.36 (0.33)		
Ethnicity			0.96	0.99
	White (n=102)	0.24 (0.32)		
	Black (n=39)	0.23 (0.23)		
	Other (n=6)	0.21 (0.23)		
Gender			0.11	0.14
	Female (n=126)	0.22 (0.26)		
	Male (n=20)	0.33 (0.43)		
History of Smoking			0.42	0.75
	No (n=95)	0.22 (0.30)		
	Yes (n=51)	0.26 (0.27)		
Menopause[1]			0.060	0.19
	No (n=52)	0.17 (0.22)		
	Yes (n=70)	0.26 (0.29)		
Body Mass Index			0.016[2]	0.031[3]
	<25 (n=34)	0.14 (0.23)		
	25–29 (n=36)	0.26 (0.34)		
	30+ (n=34)	0.31 (0.29)		
History of Hypertension			0.0044	0.041
	No (n=47)	0.13 (0.18)		
	Yes (n=99)	0.28 (0.32		
History of Anti-dsDNA			0.32	0.030
	No (n=46)	0.20 (0.22)		
	Yes (n=100)	0.25 (0.32)		

[1] Only includes women.
[2] P=.020 for trend with BMI as a continuous predictor
[3] P=.011 for trend with BMI as a continuous predictor, controlling for age.

Table 2. Association of NCP with clinical measures from the same day (Current) Visit

	Group	Mean Noncalcified Plaque Score	p-value	p-value when age is controlled
Current C3 <79 mg/dl			0.90	0.53
	No (n=114)	0.23		
	Yes (n=25)	0.22		
Current C4 < 2 mg/dl			0.85	0.32
	No (n=119)	0.24		
	Yes (n=20)	0.23		
Current Lupus anticoagulant (dRVVT)			0.59	0.62
	No (n=107)	0.23		
	Yes (n=23)	0.26		
Current Anticardiolipin IgG >20			0.046	0.026
	No (n=126)	0.22		
	Yes (n=9)	0.42		
Current Prednisone			0.29	0.66
	No (n=98)	0.25		
	Yes (n=48)	0.20		
Current Hydroxychloroquine			0.79	0.99
	No (n=24)	0.22		
	Yes (n=122)	0.25		
Current Aazathioprine			0.53	0.61
	No (n=134)	0.24		
	Yes (n=13)	0.18		
Current Methotrexate			0.0001	0.0001
	No (n=138)	0.21		
	Yes (n=9)	0.59		
Current Mycophenolate			0.097	0.52
	No (n=128)	0.25		
	Yes (n=19)	0.13		
Current NSAIDS			0.45	0.37
	No (n=91)	0.25		
	Yes (n=55)	0.21		

Table 3. Multiple Variable Model to predict mean Noncalcified Plaque

Variable	Effect on mean noncalcified plaque score (95% confidence Interval)	P-value
Age (per 10 years)	0.08 (0.04, 0.12)	<0.0001
Low BMI (vs. normal)	−0.09 (−0.20, 0.02)	0.11
High BMI (vs. normal)	0.03 (−0.08, 0.14)	0.61
Hypertension	0.08 (−0.02, 0.18)	0.12
History of ant-dsDNA	0.12 (0.02, 0.21)	0.019
Male sex	0.08 (−0.04,0.21)	0.20
Methotrexate ever	0.07 (−0.05, 0.19)	0.23
Methotrexate current	0.34 (0.15, 0.53)	0.0005

Conclusion: NCP is a marker of more immediate atherosclerotic risk and contributes to overall atherosclerotic burden. In our univariate analysis, age, weight, methotrexate (MTX) use, anti-dsDNA, hypertension, anticardiolipin IgG and BMI were associated with NCP. It is not explained by homocysteine. In summary, traditional cardiovascular risk factors, anticardiolipin IgG and anti-dsDNA are associated with quantified NCP in SLE. This highlights the multifactorial etiology of accelerated atherosclerosis in SLE, and the potential role of SLE autoantibodies in the process. Confirmation of the harmful association with MTX is necessary before any recommendations can be made on limiting its use.

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Development of Atherosclerotic Vascular Events in Systemic Lupus Erythematosus: How Important Are Race/Ethnicity and Geography?

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Background/Purpose: We have previously demonstrated that there are differences at inception in the atherosclerotic disease related risk factors for the development of AVE in SLE when studied by geographic and race/ethnicity origins. In this study we examined the influences of race/ethnicity and geography on the development of AVEs attributed to atherosclerosis (AS) in patients with SLE followed from inception.

Methods: An international research network comprising 27 centres from 11 countries has followed an inception cohort of SLE patients yearly according to a standardized protocol between 2000 and 2011. Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Vascular events are described and attributed on a specialized form. Events recorded include myocardial infarction (MI), angina, congestive heart failure (CHF), intermittent claudication (PVD), stroke, transient ischemic attack (TIA). Diagnosis of an event was confirmed using standard clinical criteria, relevant laboratory data and imaging where appropriate. Attribution to AS was made on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. Predictor factors for AVE at enrolment included age, sex, SLEDAI-2K, hypercholesterolemia, hypertension, diabetes, metabolic syndrome (MetS), geography, and race/ethnicity. Univariate and multivariate analyses were performed.

Results: 1332 patients have been entered into the inception cohort with at least 1 year followup. Of those 24 had AVEs attributed to AS (angina 10, MI 3, claudication 4, TIA 3, pace maker 2 congestive heart failure 1, stroke 1). In univariate analyses older age at diagnosis, male sex, hypertension, hypercholesterolemia, diabetes, metabolic syndrome at inception were predictive for AVE. Neither individual geographic regions, nor individual race/ethnicities were predictive in univariate analyses. However, AVEs occurred more commonly among Caucasians when compared to other race/ethnicities combined (log rank $p=0.002$). Caucasians were significantly older then non-Caucasians at SLE diagnosis (38.3 ± 14.5 compared to 31.0 ± 11.2, $p<0.0001$) On multivariate regression analysis adjusting for age at diagnosis, sex, SLEDAI-2K, hypercholesterolemia, hypertension and diabetes, only older age at SLE diagnosis (HR = 1.06, 95% CI (1.03, 1.10), $p=0.0002$) and Male Sex (HR=3.58 95% CI (1.40, 9.17), $p=0.008$) remained statistically significantly associated with AVE.

Conclusion: These analyses were unable to establish important influences of geographic region and individual race/ethnicities with respect to AVEs in patients with SLE.

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Vitamin D Insufficiency and Deficiency in Systemic Lupus Erythematosus.

Michelle Petri[1], Kayode J. Bello[1], Hong Fang[1], Caroline D'Souza[1] and Laurence S. Magder[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Vitamin D insufficiency/deficiency is common in SLE patients. The evidence linking various SLE manifestations with vitamin D insufficiency/deficiency is inconclusive. We investigated clinical and laboratory associates of vitamin D insufficiency and deficiency in SLE.

Methods: 922 SLE patients were enrolled in a prospective observational study from 7/2009 to 12/ 2010. Vitamin D status was assessed by measuring serum 25-hydroxyvitamin D levels by chemiluminescence immunoassay. Data were analyzed using univariate, multivariate linear regression and multivariate logistic regression analyses (SAS Institute, Cary, NC, USA). Vitamin D insufficiency was 15–32 ng/mL and deficiency <15 ng/mL.

Results: The 922 SLE patients were 91% female, mean age 44.8 ± 13.0 years, 55% Caucasian, 37% African-American, 8% other ethnicity. The mean 25-OH vitamin D level in Caucasians was 33.0 ± 13.2 ng/mL, African-Americans 24.2 ± 14.6 ng/mL and other ethnicity 32.1 ± 16.0 ng/mL. The mean 25-OH vitamin D level for all 922 patients was 29.7 ± 14.6 ng/mL.

Table 1. Association between various factors and vitamin D deficiency/insufficiency in SLE based on a multivariate logistic regression model

		OR (95% CI) Vit D Deficiency	P-Value	OR (95% CI) Vit D Insufficiency	P-Value
Age	18–30	1.00 (reference)		1.00 (reference)	
	31–49	0.77 (0.45; 1.31)	0.33	1.17 (0.78; 1.75)	0.44
	50+	0.40 (0.22; 0.75)	0.0042	0.59 (0.39; 0.91)	0.018
Ethnicity	Caucasian	1.00 (reference)		1.00 (reference)	
	African-American	6.28 (4.05; 9.74)	<.0001	2.09 (1.53; 2.86)	<.0001
	Other	2.13 (0.93; 4.85)	0.073	1.01 (0.59; 1.73)	0.97
Urine Protein/Cr Ratio	<0.5	1.00 (reference)		1.00 (reference)	
	>=0.5	0.94 (0.53; 1.68)	0.85	1.85 (1.04; 3.30)	0.036
Body Mass Index	<=30	1.00 (reference)		1.00 (reference)	
	>30	2.00 (1.35; 2.95)	0.0005	2.64 (1.91; 3.64)	<.0001
Cholesterol	<=200	1.00 (reference)		1.00 (reference)	
	>200	1.44 (0.95; 2.19)	0.08	1.72 (1.23; 2.40)	0.0015
Systolic BP	No	1.00 (reference)		1.00 (reference)	
	Yes	1.60 (0.99; 2.57)	0.056	1.60 (1.04; 2.45)	0.03
Diabetes Mellitus	No	1.00 (reference)		1.00 (reference)	
	Yes	2.08 (1.21; 3.57)	0.0078	1.53 (0.92; 2.56)	0.10

Table 2. Association between various factors and 25-OH vitamin D levels in SLE based on a multivariate linear regression model

	Effect on Mean Vitamin D (ng/mL)	P-value
Age (per year)	0.11 ± 0.04	0.005
Ethnicity (African-American vs Caucasian)	−6.64 ± 0.97	<0.0001
Systolic BP (per mmHg)	−0.09 ± 0.03	0.0015
Diabetes	−1.92 ± 1.58	0.22
Urine Pr/Cr Ratio	−1.65 ± 0.68	0.015
Body Mass Index	−0.31 ± 0.06	<0.0001
Cholesterol (per mg/dL)	−0.04 ± 0.01	0.0002

Table 3. Percentage of patients with organ damage among those with and without Vitamin D insufficiency

	Percent with Condition			
Condition	Vit D insufficiency (N=381)	Normal Vit D (N=378)	P-value	Adjusted P-value for Race
GFR<50%	5.5	2.4	0.027	0.034
End-stage renal disease	3.9	1.1	0.011	0.0072
Cardiomyopathy	3.9	1.3	0.025	0.047

Conclusion: Younger age, African-American ethnicity, higher systolic blood pressure, higher cholesterol, higher urine protein/creatinine ratio and obesity were associated with low 25-OH vitamin D level in multiple variable models. SLE patients with vitamin D insufficiency were more likely to suffer from renal and cardiovascular damage. Studies of vitamin D supplementation in SLE are clearly indicated, but would have to be long-term to show prevention of organ damage.

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Predictors of Risk for Progression of Subclinical Atherosclerosis in Women with Systemic Lupus Erythematosus.

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Background/Purpose: Women with systemic lupus erythematosus (SLE) have increased rates of subclinical atherosclerosis and cardiovascular events. We sought to determine which cardiovascular (CV) and SLE-related risk factors may be significant in the rate of subclinical atherosclerosis progression in the carotid artery, as measured by the change in intima-media thickness (IMT). We also investigated risk factors for subclinical atherosclerosis progression, as measured by progression in plaque index (PI), coronary artery calcium score (CAC), and aorta calcium score (AS).

Methods: Data were collected on 147 women with SLE including demographics, self-reported and measured traditional CV risk factors. SLE factors collected included the SLE disease activity index (SLEDAI), modified SLICC/ACR-DI Damage Index (SDI) (excluding coronary artery bypass grafting, myocardial infarction, stroke, and angina), disease duration, and corticosteroid and immunosuppressant use. PI and IMT were measured by carotid B-mode ultrasound, and CAC and AS were measured by electron beam or multidimensional computed tomography at baseline and at one follow-up visit in the Study of Lupus Vascular and Bone Long-Term Endpoints (SOLVABLE). An abnormal PI, CAC, and AS was defined as PI≥1, CAC>10 and AS>100. Progression in PI at follow-up was defined as any increase in PI compared to baseline. Progression in CAC at follow-up was defined as a CAC>10 and an increase of >10% compared to baseline. Progression in AS at follow-up was defined as an AS>100 and an increase of >10% compared to baseline. Univariate regression models of PI, CAC, AS, and change in IMT per year with risk factors were examined. These models were further adjusted for follow-up time, age, and body mass index (BMI).

Results: In 147 women with SLE, mean age was 43.6 ± 10.1 yrs, disease duration was 11.8 ± 8.7 yrs, SLEDAI was 3.8 ± 3.5, SDI was 1.6 ± 1.7 (mean ± SD). Imaging data at baseline and follow-up were available on 147 women for IMT and PI, 123 with CAC, and 88 with AS. Mean follow-up time was 3.25 ± 0.36 yrs (mean ± SD).

Change in IMT per year was not significantly associated with any risk factors. PI progression was associated with presence of hypertension, hyperlipidemia, older age, and higher total cholesterol, fasting glucose, low-density lipoprotein, fibrinogen, BMI, waist circumference, disease duration, and SDI. After adjustment for follow-up time, BMI, and age, only higher fasting glucose (p=0.005, OR=3.36, 95% CI 1.55–8.55) and higher SDI (p=0.007, OR=1.40, 95% CI 1.10–1.80) remained significant.

CAC progression was associated with older age, higher fibrinogen, and higher SDI. After adjustment for follow-up time, BMI, and age, only SDI remained significant (p=0.002, OR=1.55, 95% CI 1.18–2.07).

AS progression was associated with older age, increased SDI and disease duration. After adjusting for follow-up time, age, and BMI, only SDI remained a significant factor (p=0.01, OR=1.48, 95% CI 1.10–2.03).

Conclusion: In this group of women with SLE, the progression of PI, CAC, and AS was not significantly associated with most traditional CV risk factors after adjustment for age, BMI, and follow-up time. However, progression in PI, CAC, and AS was associated with higher SLE damage as assessed by the SDI.

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Plasma Tumor Necrosis Factor-Like Weak Inducer of Apoptosis (sTWEAK) Levels Are Associated with Carotid Plaque Progression in Women with SLE. Maureen A. McMahon[1], E. Lorenco[1], Jennifer M. Grossman[1], Lori Sahakian[1], John D. FitzGerald[1], Nagesh Ragavendra[1], Christina Charles-Schoeman[1], Alan H. Gorn[1], Michael H. Weisman[2], Daniel Wallace[3], Bevra H. Hahn[1] and Brian Skaggs[1]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]Cedars Sinai Med Ctr, Los Angeles, CA, [3]Cedars-Sinai/UCLA, Los Angeles, CA

Background/Purpose: Women with SLE have increased risk of coronary artery disease (CAD) that is not adequately explained by traditional risk factors**.** We previously reported that pro-inflammatory HDL (piHDL) and elevated leptin independently confer increased risk for the concurrent presence of carotid artery plaque (ATH). It is unknown, however, whether these or other biomarkers predict future progression of ATH in SLE. Soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) is a cytokine and member of the TNF superfamily. Although sTWEAK levels have been inversely correlated with ATH in the general population, higher levels have been positively associated with acute MI and increased mortality in end stage renal disase patients with high levels of inflammation. In addition, higher sTWEAK levels have been associated with both synovitis in RA and with lupus nephritis, and urinary TWEAK levels have been proposed as a biomarker for lupus nephritis. Here we hypothesize that sTWEAK, piHDL, and other traditional and novel biomarkers in SLE are associated the progression of subclinical ATH in SLE. To determine this, we measured plasma biomarkers and the progression of plaque using carotid ultrasound in a cohort of SLE patients.

Methods: Female SLE and healthy age-and gender- matched subjects not taking statins at baseline were studied. B-mode and Doppler scanning of carotid arteries was performed at baseline and at 24– 36 months. Antioxidant function of HDL was measured as the change in fluorescence intensity caused by oxidation of DCFH by LDL in the presence or absence of test HDL. Fluorescence in the absence of HDL was normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated piHDL. Plasma Leptin and soluble TWEAK levels were measured in the baseline blood samples using ELISA (R&D Biosystems).

Results: Repeat carotid ultrasounds were completed on 200 women with SLE. The mean age of the SLE group was 43.7 ± 12.5 years. Plaque progression (defined as new or increased plaque) was seen in 40 subjects (20%). Mean baseline plasma sTWEAK levels were significantly increased in SLE patients with plaque progression compared to those without: 4093.7 ± 7901.0 vs. 1654.3 ± 3090.1 pg/mL in controls (p<0.02). Similar to factors associated with baseline plaque, piHDL (p<0.001), leptin in the highest quartile (>34ng/mL) (p=0.02), age >48 (p<0.001), diabetes (p=0.001), and plaque on the baseline ultrasound (p<0.001) were also associated with plaque progression. Using logistic regression to control for traditional cardiac risk factors, the factors still significantly associated with plaque progression in SLE included sTWEAK in the highest quartile (>1740 pg/mL) (OR 2.8, p=0.04), piHDL (OR 4.4, p=0.008), age >48 (OR 2.7, p=0.04), and DMII (OR 26.0, p=0.001).

Conclusion: In conclusion, plasma TWEAK and piHDL levels are significantly and independently associated with plaque progression on carotid ultrasound in patients with SLE. A panel of novel and traditional biomarkers may be useful for prediction of which SLE patients are at risk for accelerated progression of ATH in SLE.

ACR Concurrent Abstract Session
Vasculitis I
Sunday, November 6, 2011, 2:30 PM–4:00 PM

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Immunoglobulin Concentrations and Infection Risk Among Patients with ANCA-Associated Vasculitis Treated with Rituximab or Cyclophosphamide. Ulrich Specks[1], Peter A. Merkel[2], Philip Seo[3], Robert F. Spiera[4], Carol A. Langford[5], Gary S. Hoffman[5], Cees G.M. Kallenberg[6], E. William St. Clair[7], Swati Tole[8], Paul Brunetta[9], Shuyi Shen[8], Nadia Tchao[10], Barri J. Fessler[11], Lisa Webber[12], Linna Ding[13], Lourdes P. Sejismundo[14], Kathleen Mieras[1], Deborah J. Phippard[10], Adam Asare[10], Noha Lim[10], David Ikle[15], Brett Jepson[15], Alice Lail[15] and Mark Mueller[16]. [1]Mayo Clinic, Rochester, MN, [2]Boston University School of Medicine, Boston, MA, [3]Johns Hopkins Vasculitis Center, Baltimore, MD, [4]Hospital for Special Surgery, New York, NY, [5]Cleveland Clinic, Cleveland, OH, [6]University Medical Center Groningen, Groningen, Netherlands, [7]Duke University Medical Center, Durham, [8]Genentech, Inc., South San Francisco, CA, [9]Genentech, So San Francisco, CA, [10]Immune Tolerance Network, Bethesda, MD, [11]Univ of Alabama-Birmingham, Birmingham, AL, [12]National Institute of Allergy and Infectious Diseases, [13]NIAID, Bethesda, MD, [14]Johns Hopkins University, Baltimore, MD, [15]Rho, Chapel Hill, NC, [16]Food & Drug Administration, Bethesda, MD

Background/Purpose: Patients (pts) with ANCA-associated vasculitis (AAV) are treated with immunosuppression and are at increased risk of infection. The incidence of low immunoglobulin (Ig) concentrations observed with rituximab (RTX) and cyclophosphamide (CYC) is therefore a potential concern. Limited data exist on the incidence and risk for infection of low Ig concentrations in AAV. We evaluated changes in Ig concentrations among patients (pts) treated with either RTX or CYC followed by azathioprine (CYC/AZA) in the RAVE trial (*NEJM* 2010), and investigated the impact of these changes on infection.

Methods: Post hoc analysis of RAVE, a trial of 197 pts with severe AAV randomized and treated with RTX followed by placebo (n=99) or CYC followed by AZA (n=98). Quantitative assays for IgM, IgG, and IgA were performed at baseline, 6 months (M), and 18M. Proportions of pts with low Ig (<lower limit of normal (LLN)) at each time point and the median changes in Ig at 6M and 18M were assessed, along with the rates of overall and serious infections.

Results: Of the 56 pts who had low Ig of any isotype at baseline, 36 (64%) entered with relapsing disease. Pts in both treatment groups had low Ig at baseline and the proportions with low Ig increased at 6M and 18M (Table 1). Median changes from baseline in Ig concentrations were similar in the RTX and CYC/AZA groups. In the RTX group, pts with low Ig levels at any time had received numerically higher quantities of glucocorticoids (GC) at baseline compared to those who did not have low Ig (IgM: 1.51 g prednisone or equivalent vs 1.03; IgG: 1.31 vs 1.27; IgA 1.73 vs 1.11; p=0.07, 0.45, 0.32, respectively). Rates of overall and serious infections were similar in pts with low Ig at any time compared to those with normal Ig levels (Table 2).

Table 1. Change from Baseline and Proportion of Patients with Low Ig (< LLN[&]) by Visit

	RTX	CYC/AZA
Baseline (n*)	99	94
IgM < LLN	16 (16.2%)	6 (6.4%)
IgG < LLN	18 (18.2%)	20 (21.3%)
IgA < LLN	5 (5.1%)	10 (10.6%)
6M (n*)	83	77
IgM		
Median Change from baseline (mg/dL)	−42.0	−42.5
< LLN	49 (59.0%)	36 (46.8%)
IgG		
Median change from baseline (mg/dL)	−259	−252
< LLN	54 (65.1%)	43 (55.8%)
IgA		
Median change from baseline (mg/dL)	−48	−59
< LLN	25 (30.1%)	24 (31.2%)
18M (n*)	69	60
IgM		
Median Change from baseline (mg/dL)	−38.0	−23.5
< LLN	27 (39.1%)	17 (28.3%)
IgG		
Median Change from baseline (mg/dL)	−185	−131
< LLN	31 (44.9%)	19 (31.7%)
IgA		
Median Change from baseline (mg/dL)	−44	−42
< LLN	19 (27.5%)	16 (26.7%)

[&] LLN: IgM 23 mg/dL (16 – 19 yrs), 40 mg/dL (≥20 yrs); IgG 549 mg/dL, 700 mg/dL; IgA 61 mg/dL, 70 mg/dL
* n indicates number of subjects with available data at the corresponding visits.

Table 2. Rates of overall and serious infectious events (SIE) in patients with low and normal Ig levels

	RTX		CYC/AZA	
	Normal IgM	**IgM < LLN at any time**	**Normal IgM**	**IgM < LLN at any time**
N (pt-year)	45 (51.5)	54 (74.7)	57 (66.5)	39 (51.2)
rate of infection per patient year	1.61	1.28	1.08	1.56
rate of SIE per patient year	0.17	0.08	0.17	0.18
	Normal IgG	**IgG < LLN at anytime**	**Normal IgG**	**IgG < LLN at anytime**
N (pt-year)	36 (37.1)	63 (89.1)	43 (48.4)	53 (69.3)
rate of infection per patient year	1.86	1.23	1.16	1.38
rate of SIE per patient year	0.22	0.08	0.19	0.16
	Normal IgA	**IgA < LLN at anytime**	**Normal IgA**	**IgA < LLN at any time**
N (pt-year)	70 (86.3)	29 (39.9)	66 (77.4)	30 (40.3)
rate of infection per patient year	1.30	1.68	1.24	1.39
rate of SIE per patient year	0.14	0.08	0.18	0.15

Conclusion: A substantial proportion of pts with AAV receiving either RTX or CYC/AZA had low Ig concentrations at baseline, perhaps resulting from immunosuppression prior to trial entry. The proportions of pts with low Ig increased at 6M and 18M in both groups, and median changes in Ig levels were similar in both groups. Low Ig was not associated with increased rates of infections.

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Association of Ferritin Antibodies with GCA/PMR: New Biomarker for Diagnosis. Niklas T. Baerlecken[1], Anna Linnemann[2], Wolfgang L. Gross[3], Frank Moosig[4], T.R. Vazquez-Rodriguez[5], Miguel Gonzalez-Gay[6], Javier Martin[7], Ina Kötter[8], Joerg C. Henes[9], Inga Melchers[10], Peter Vaith[11], Reinhold E. Schmidt[12] and Torsten Witte[13]. [1]MD, Hannover, Germany, [2]Student, Hannover, Germany, [3]Medical University at Lubeck, Lubeck, Germany, [4]Stormarnzing 156, Bad Bramstedt, Germany, [5]MD, Spain, [6]Hospital Marques De Valdecilla, Santander, Spain, [7]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [8]MD, Tübingen, Germany, [9]University Hospital Tuebingen, Tuebingen, Germany, [10]PhD, Freiburg, Germany, [11]Medizinische Uni Klinik, Freiburg, Germany, [12]Hannover Medical School, Hannover, Germany, [13]MD, Hanover, Germany

Background/Purpose: Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are relatively common inflammatory disorders. Establishing the diagnosis however may be difficult, since so far no specific markers of the disorders have been described.

The goal of our study was to find new antibodies as markers of PMR and/or GCA.

Methods: As a screening procedure, we used protein array technology for detection of possible new antigens in GCA and PMR. 6 different GCA sera were screened for the presence of antibodies. In the second step, the results of the protein array were confirmed by an ELISA for the detection of antibodies against human ferritin heavy chain and a second ELISA for the detection of antibodies against N-terminal 27 amino acids of the human ferritin heavy chain. Sera of patients with only GCA (n=85) and only PMR (n=47) and both PMR and GCA (n=31) were collected in Hannover (n=56), Lugo (n=35), Bad Bramstedt (n=22) and Tübingen (n= 14). Sera from patients with SLE (n=40), RA (n=36), *fever above 38.5°C* caused by different infections (n=70) and blood donors (n=180) were obtained in Hannover. The study was approved by our local ethical committee (project number 4928), and the patients provided informed consent.

Results: We could detect antibodies against human ferritin heavy chain in 12/71 (17%) of the sera obtained from patients (treated and untreated patients combined) with both GCA and PMR and in 4/28 (14%) of the patients with isolated GCA and in 8/43 (19%) of the patients with isolated PMR. The presence of IgG antibodies against ferritin was 22% in the 37 patients with GCA and/or PMR, from whom sera were obtained before steroid treatment was initiated. In SLE, the prevalence of autoantibodies against ferritin was 1/32 (3%). 0/36 (0%) patients with RA were positive. In the further control groups, the prevalence of autoantibodies against ferritin was 4/34 (12%) in fever above 38.5°C and 0/50 (0%) in blood donors.

In the ELISA for antibodies against N-terminal 27 amino acids of the human ferritin heavy chain 64/117 (55%) of the sera obtained from all patients (treated and untreated patients combined) with isolated GCA, isolated PMR and combined GCA and PMR were positive. The prevalence of IgG antibodies against the ferritin peptide was 92% in the 36 GCA and/or PMR patients, from whom sera were obtained before steroid treatment was initiated. In the sera of GCA and PMR patients drawn in remission, the prevalence of antibodies was only 13%. 22/32 (69%) of the patients with disease flares of GCA and PMR had antibodies. In other autoimmune disorders, the prevalence was 11/38 (29%) in active SLE and 1/36 (3%) in RA. In *blood donors*, the prevalence was 1/100 (1%).

Conclusion: In conclusion, antibodies against the human ferritin peptide were present in up to 92% of untreated GCA and PMR patients at disease onset. They can be useful as a diagnostic and activity marker of PMR and GCA.

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Immunological Signature Discriminates Active and Inactive Patients with Takayasu Arteritis. David Saadoun[1], Benjamin Terrier[2], Guillaume Geri[3], Wahiba Chaara[4], Michelle Rosenzwajg[5], Nathalie Costedoat-Chalumeau[3], Pierre Fourret[6], Lucile Musset[3], Adrien Six[4], David Klatzmann[5] and Patrice Cacoub[3]. [1]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]Pitié-Salpêtrière Hospital, Paris, France, [3]CHU Pitié-Salpêtrière, Paris, France, [4]Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Paris, France, [5]Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Paris, France, [6]Anatomopathology, Groupe Hospitalier Pitié-Salpetrière, Paris, France

Background/Purpose: Takayasu arteritis (TA) is a large-vessel vasculitis of unknown origin. Data on predictive criteria of TA activity are lacking. Objective: To identify an immunological signature that help to discriminate active and inactive patients with TA.

Methods: Thirty TA patients (11 active untreated [aTA] and 19 treated and inactive [iTA]) fulfilling the American College of Rheumatology criteria and 20 healthy donors (HD) were included. We measured levels of 26 cytokines in culture supernatants using Luminex and ELISA. We used a multivariate analysis in order to identify a signature that discriminate active and inactive TA patients. Flow cytometric analysis of peripheral blood mononuclear cells was performed for cell surface markers, intracellular production of cytokines and FoxP3 expression. Artery biopsies from 3 TA patients and 3 controls were tested by immunohistochemistry.

Results: Multivariate analysis identified a cytokine signature discriminating active and inactive TA patients with positive and negative predictive values of 100% and 95%, respectively. Using FACS analysis, we observed the expansion of Th17 cells in peripheral blood of aTA compared with iTA and HD (3.0 vs. 1.3

and 0.6 %, P=0.0005 and P<0.0001, respectively), as well as Th1 cells (24.2 vs. 10.7 and 18.3 %, P<0.0001 and P=0.02, respectively) and IFN-g producing CD8+ T cells (51.0 vs. 36.9 and 36.0 %, P=0.02 and P=0.01, respectively). Immunohistochemical analysis revealed an expression of IL-17A, IFN-g, IL-6, CCL20 and TLR5 within large-vessel inflammatory infiltrates of TA patients,

Expansion of IL-21-producing CD4+ T cells was also observed in peripheral blood of aTA compared with iTA and HD (7.9 vs. 4.1 and 1.7%, P=0.001 and P<0.0001, respectively), that correlated with Th17cells (r=0.68; P<0.0001) and Th1 cells (r=0.56; P=0.002) expansion. Stimulation of purified CD4+ T cells from TA patients with human recombinant IL-21 increased Th17 cells and decreased FoxP3 expression. In contrast, the blockade of IL-21 using IL-21R/Fc chimera markedly decreased production of IL-17A and increased FoxP3 expression.

Conclusion: We identified an immunological signature that discriminate active and inactive Takayasu arteritis patients with high sensitivity and specificity. Cytokine measurement, FACS and immunochemistry analyses suggest the major role of Th1, Th17 and IL-21 in the pathogenesis of TA. IL-21 exerts a critical role in modulating Th1 and Th17 responses and regulatory T cells in TA, and might represent a potential target for novel therapy.

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Serum Proteins Reflecting Inflammation, Injury, and Repair As Biomarkers of Disease Activity in ANCA-Associated Vasculitis. Paul A. Monach[1], Roscoe L. Warner[2], Gunnar Tomasson[3], Ulrich Specks[4], John H. Stone[5], Linna Ding[6], Fernando Fervenza[4], Barri J. Fessler[7], Gary S. Hoffman[8], David Ikle[9], Cees GM Kallenberg[10], Jeffrey Krischer[11], Carol A. Langford[12], Mark Mueller[13], Philip Seo[14], E. William St Clair[15], Robert Spiera[16], Nadia Tchao[17], Steven R. Ytterberg[4], Kent J. Johnson[2] and Peter A. Merkel[3]. [1]Boston University, Boston, MA, [2]University of Michigan, Ann Arbor, MI, [3]Boston University School of Medicine, Boston, MA, [4]Mayo Clinic, Rochester, MN, [5]Massachusetts General Hospital, Boston, MA, [6]NIAID, Bethesda, MD, [7]Univ of Alabama-Birmingham, Birmingham, AL, [8]Cleveland Clinic Found A50, Cleveland, OH, [9]Rho, Chapel Hill, NC, [10]University Medical Center Groningen, Groningen, Netherlands, [11]University of South Florida, Tampa, FL, [12]Cleveland Clinic, Cleveland, OH, [13]Food & Drug Administration, Bethesda, MD, [14]Johns Hopkins Vasculitis Center, Baltimore, MD, [15]Duke University Medical Center, Durham, NC, [16]Hospital for Special Surgery, New York, NY, [17]Immune Tolerance Network, Bethesda, MD

Background/Purpose: To identify biomarkers that distinguish between active ANCA-associated vasculitis (AAV) and remission.

Methods: Twenty-eight serum markers representing diverse aspects of the biology of AAV were measured before and 6 months after treatment in a large clinical trial in AAV. 186 subjects enrolled in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial were studied. ESR and CRP levels were available for comparison. The primary outcome was the ability of markers to distinguish severe AAV (BVAS/WG ≥ 3 at screening) from remission (BVAS/WG = 0 at month 6) in the same patients (n=137), using areas under receiver operating characteristic (ROC) curves (AUC). Secondary outcomes included distinction of severe AAV (n=186) from healthy controls (n=68), and distinction of mild AAV (n=25) from remission (n=137) at month 6.

Results: All subjects had severe active vasculitis (median BVAS/WG score 8) at screening. Among 137 subjects in remission at month 6, 24 of 28 markers showed significant declines (see **Table**). ROC analysis indicated that levels of CXCL13 (BCA-1), MMP3, and TIMP-1 best discriminated between active AAV and remission, with AUC > 0.8 (P < 0.05 vs. AUC = 0.76 for ESR, see **Figure**). Comparing active AAV to remission: CXCL13 > 70 pg/ml was 77% sensitive and 85% specific; MMP3 > 38 ng/ml was 82% sensitive and 88% specific; and TIMP-1 > 270 ng/ml was 78% sensitive and 82% specific. These three markers were also among the best (AUC > 0.9) in distinguishing active AAV from healthy controls. Multivariable modeling showed that a combination of 5 markers (ACE, GM-CSF, MMP3, TIMP-1, and ESR) distinguished severe AAV from remission quite well (AUC 0.96), but had only modest ability to distinguish mild AAV (median BVAS/WG score 1) from remission (AUC 0.78).

Table. Marker levels in severe active AAV (screening) and in remission 6 months later, in the same patients.

Marker*	Units	Screening Median (25%; 75%) N = 137	Month 6 Remission Median (25%; 75%) N = 137
Cytokines			
G-CSF	pg/ml	20.4 (8.01;45.9)*	10.5 (5.63,23.7)
GM-CSF	pg/ml	27.6 (2.28;269)*	1.17 (<0.98,4.99)
IFNg	pg/ml	<0.49 (<0.49;2.01)*	<0.49 (<0.49,<0.49)
IL-6	pg/ml	2.14 (<0.69;19.8)*	<0.49 (<0.49,0.77)
IL-15	pg/ml	21.6 (7.65;109)*	5.69 (2.60,13.5)
IL-18	pg/ml	57.4 (37.2;101)‡	51.9 (31.0,85.8)
Osteopontin	ng/ml	65.0 (38.8;101)‡	54.4 (37.8,80.9)
Chemokines			
BCA-1/CXCL13	pg/ml	170 (74.2;489)*	32.0 (18.2,55.6)
IL-8/CXCL8	pg/ml	19.5 (7.33;51.2)*	7.09 (3.59,15.3)
IP-10/CXCL10	pg/ml	11.1 (6.01;23.7)	13.2 (7.68,25.0)
RANTES/CCL5	ng/ml	60.3 (33.4;107)	52.3 (30.8,90.0)
TARC/CCL17	pg/ml	520 (234;1535)‡	655 (347,>2500)
Soluble Receptors			
IL-18BP	pg/ml	116 (21.6;768)*	14.6 (<6.11,55.1)
sIL-2R	pg/ml	<2.44 (<2.44;1530)*	<2.44 (<2.44,<2.44)
sIL-6R	ng/ml	27.4 (21.1;43.1)†	21.9 (15.4,33.0)
sTNF-RII	pg/ml	2671 (1306;4855)	2417 (1350,5808)
Tissue Damage and Repair			
ACE	ng/ml	105 (73.8;144)*	178 (130,252)
bFGF	pg/ml	3.05 (<0.98;34.4)*	<0.98 (<0.98,9.77)
KIM-1	pg/ml	242 (73.4;744)*	45.6 (17.2,127)
MMP3	ng/ml	96.6 (46.6;148)*	15.6 (11.8,29.1)
NGFb	pg/ml	9.11 (3.15;37.0)*	2.48 (1.25,4.32)
PDGF-AB	pg/ml	4298 (1573;6585)†	3260 (879,5374)
TIMP-1	ng/ml	477 (302;862)*	166 (125,233)
Inflammation and Vascular Injury			
Clusterin	mg/ml	77.1 (65.3;89.3)‡	73.0 (59.4,85.9)
CRP	mg/dl	1.2 (0.5;4.0)*	0.5 (0.3,1.2)
ESR	mm/hr	37 (16;60)*	14 (7,22)
ICAM-1	ng/ml	463 (307;933)‡	537 (345,882)
NGAL	ng/ml	271 (176;399)*	172 (129,237)
PAI-1	pg/ml	1491 (<977;5650)	1202 (<977,4719)
VCAM-1	ng/ml	133 (95.4;174)‡	148 (108,224)

* P<0.0001 by Signed Rank test. † P=0.0001–0.001. ‡ P=0.001–0.05.

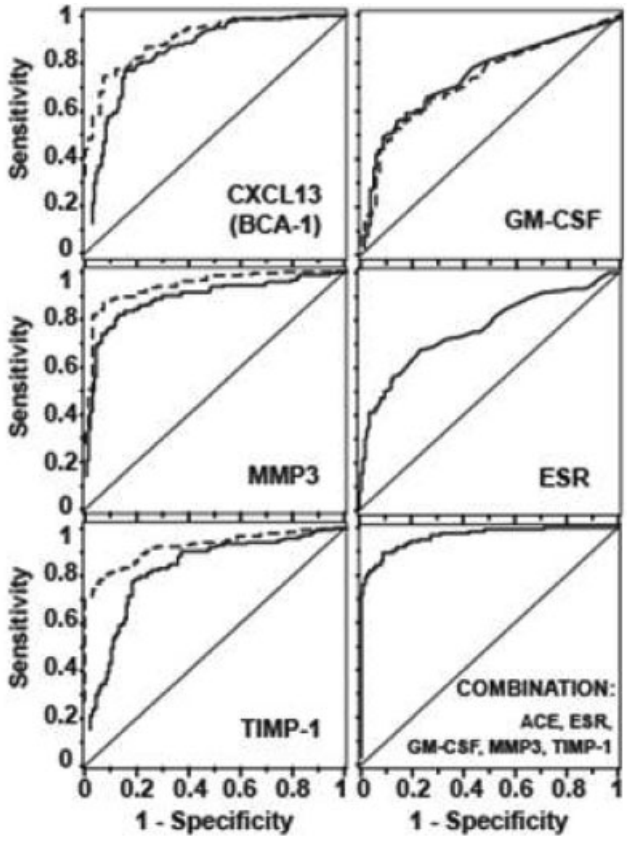

Figure. Receiver operating characteristic (ROC) curves for 5 individual markers and for a combination of 5 markers, comparing active vasculitis to remission (solid curves) or to healthy controls (dashed curves, not done for ESR or the combination of markers).

Conclusion: Many markers are elevated in severe active AAV and decline with treatment, but CXCL13, MMP3, and TIMP-1 distinguish between active AAV and either remission or healthy controls better than the other markers studied, and ACE, GM-CSF, and ESR provide additional information. These markers have potential clinical utility for measuring disease activity in AAV. Finally, the finding that levels of CXCL13—a chemokine specific for B cells—correlate well with disease activity may provide insight into the pathophysiology of AAV.

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In Situ Immune Complex (MPO-anti MPO antibody) and Complement 3 cause Glomerular Capillary Injury in Human MPO-ANCA Associated Glomerulonephritis. Soko Kawashima, Yoshihiro Arimura, Yoshinori Komagata, Shinya Kaname and Akira Yamada. Kyorin University School of Medicine, Tokyo, Japan

Background/Purpose: Pauci-immune necrotizing glomerulonephritis(NCGN) is often seen in a patient of myeloperoxidase anti-neutrophil

cytoplasmic antibody (MPO-ANCA) associated vasculitis. MPO-ANCA has been thought to be involved in the activation of neutrophils in the pathogenesis of NCGN. Recent studies suggest that immunoglobulins precipitated on the glomerular capillaries might play some role in the pathogenesis of MPO-ANCA associated GN. Here, we investigated a possible role of MPO, IgG, complements and MPO-positive cells in the pathogenesis of MPO-ANCA associated GN.

Methods: Renal specimen including 317 glomeruli obtained from 20 patients with MPO-ANCA associated GN were analyzed. Glomerular infiltration of MPO-positive cells, deposition of extracellular MPO and endothelial cell injury were analyzed and the number of infiltrating MPO-positive cells was scored in each glomerulus, especially in early stage of the disease. Colocalization of MPO, IgG, C3 and CD34 deposition was analyzed. Immunofluorescence staining for triple staining (MPO, IgG and CD34) were performed for samples of renal biopsies.

Results: All of 20 patients showed a weak but significant staining for IgG (pauci-immune GN), which was often accompanied by MPO deposition along the glomerular capillary walls. Double positive (MPO & IgG) deposition was detected in 45 glomeruli (14%) mainly with low activity and chronicity. Double positive (MPO & C3) deposition was detected in 41glomeruli (13%) mainly with low activity and chronicity. Triple positive (MPO, IgG & C3) deposition was detected in 15 glomeruli (5%) mainly with low activity and chronicity. CD34 staining was lost around the area where MPO and IgG were detected, suggesting the endothelial injury may be induced by MPO- and IgG-associated pathogenic mechanism. Deposition of MPO, IgG and C3 was observed along the glomerular capillary walls predominantly in the early stage of MPO-ANCA associated GN.

Conclusion: These results indicate that not only the activation of neutrophils, but also MPO and the immune complexes composed of MPO-anti MPO antibody may play some direct roles in the pathogenesis of glomerular capillary injury in the early phase of human MPO-ANCA associated GN.

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Increased Frequency of Circulating Follicular Helper T-Cells (T_{FH}) in Patients with Granulomatosis with Polyangiitis. Wayel H. Abdulahad[1], Nikola Lepse[1], Henko Tadema[1], Minke G. Huitema[1], Berber Doornbos-van der Meer[1], Coen Stegeman[1], Pieter C. Limburg[1], Peter Heeringa[2] and Cees GM Kallenberg[1]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]University Medical Center Groningen, Netherlands

Background/Purpose: Follicular helper T cells (T_{FH}) are a newly distinguishable subset of Th *cells* characterized by IL-21 production that influences B-cell differentiation and antibody production. Recent studies support the concept that T_{FH} cells are an important player in antibody-mediated *autoimmune* diseases. In the present study, we aimed to explore a possible role for T_{FH} cells in the immunopathogenesis of granulomatosis with polyangiitis *(GPA).*

Methods: Peripheral blood from 33 GPA-patients in remission and 22 age-matched healthy controls (HCs) were stimulated in vitro with Phorbol-Myristate-Acetate and Calcium-Ionophore in the presence of Brefeldin-A. Intracellular IL-21 was used as a marker for T_{FH} cells. Since Th-17 cells produce a low level of IL-21, IL-17 was also included in the analysis to discriminate between T_{FH} cells ($IL\text{-}17^{-}IL\text{-}21^{+}$) and Th-17 cells ($IL\text{-}17^{+}IL\text{-}21^{+/-}$). The frequencies of T_{FH} cells were determined by 4-color cytometric detection of CD4 (negatively gated as $CD3^{+}CD8^{-}$ cells), and intracellular cytokine expression of IL-21 and IL-17. The mRNA expression level of transcription factors Bcl-6 (for T_{FH}) and RoRgc (for Th17) were evaluated in lysed cell from GPA-patients and HCs. To investigate the effect of IL-21 on antibody-production, PBMCs from GPA-patients were stimulated in vitro with BAFF/IL-21 for 12 days and total IgG was measured in supernatants by ELISA. In addition, the expression level of IL-21-receptor on B-cells was analyzed in GPA-patients and HCs.

Results: Percentages of circulating T_{FH} cells were significantly elevated in GPA-patients compared to HCs ($P = 0.001$). The expression level of Bcl-6 was significantly higher in GPA-patients, whereas no difference was found in RoRgc between GPA-patients and HCs. The hallmark cytokine for T_{FH}, IL-21, enhance the production of IgG *in vitro* in stimulated PBMCs from GPA-patients. Moreover, frequencies of T_{FH} cells were significantly increased in ANCA-positive patients (n=21) in comparison to HCs (P= 0.0009), whereas no such difference was found between ANCA-negative patients (n=12) and HCs.

Conclusion: Increased frequencies of circulating T_{FH} cells producing IL-21 suggest a role for these cells in the immunopathogenesis of GPA. Blockade of IL-21 could constitute a new therapeutic strategy for GPA.

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Musculoskeletal Conditions Are the Most Common Causes of Work Limitation in U.S. Adults. Kristina A. Theis[1], Charles G. Helmick[1] and Jennifer M. Hootman[2]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]Centers for Disease Control and Prevention, Kennesaw, GA

Background/Purpose: People with work limitations are less likely to be employed, contribute to payroll taxes, or add to national productivity than those without work limitations, and chronic diseases are among the major causes of work limitation. However, there are existing interventions that can decrease, delay, or mitigate work limitations that may be especially effective if targeted to appropriate populations. We estimated the most common causes of work limitation among U.S. adults overall and among those with 7 common chronic diseases.

Methods: The data source was the 2009 National Health Interview Survey, an annual survey designed to be nationally representative of civilian, non-institutionalized U.S. adults (age ≥18 years) conducted by in-person interview (n = 27,731; response rate = 65%). Work limitation was identified by self-report of being "unable to work" or "limited in work." Respondents with limitations were shown a flashcard of 18 health conditions plus an "other" category and asked to identify all health problems causing their difficulties. All respondents were separately asked about the presence of 7 chronic conditions. Arthritis was identified by "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" The same question wording was used for hypertension, stroke, asthma, cancer, diabetes, and heart conditions (coronary heart disease, angina, heart attack, and any other kind of heart condition or disease). Diagnoses were not mutually exclusive. Weighted proportions and 95% confidence intervals (CI) were calculated, accounting for the complex sample design (SAS 9.2).

Results: Overall, 28.4 million (12.5%, 95% CI = 12.0–13.1) U.S. adults reported work limitation. The most commonly reported causes of work limitation were back/neck problems (25.8%, 95% CI = 24.0–27.6) and arthritis/rheumatism (19.4%, 95% CI = 17.7–21.2), followed by depression/anxiety/emotional problems (15.1%, 95% CI = 13.6–16.6), heart problems (14.6%, 95% CI = 13.2–16.0), and musculoskeletal/connective tissue problems (13.1%, 95% CI = 11.6–14.7). Among those with 7 common chronic diseases and work limitation, arthritis/rheumatism and/or back/neck problems were among the top 3 causes for each (Table).

Table. Most Common Causes of Work Limitation by Chronic Condition, weighted prevalence estimates and proportions with 95% confidence intervals (CI), NHIS, 2009

Chronic condition	Causes of work limitation	Prevalence (in 1,000s)	Proportion in % (95% CI)
Hypertension	Back/neck problems	4,077	26.4 (24.0–28.7)
	Arthritis/rheumatism	3,892	25.2 (22.7–27.7)
	Hypertension	3,295	21.3 (19.0–23.6)
Stroke	Stroke	1,146	39.3 (34.6–44.0)
	Heart problems	742	25.4 (22.3–28.5)
	Arthritis/rheumatism	690	23.7 (19.9–27.4)
Asthma	Lung/breath problems	2,130	33.5 (29.9–37.0)
	Back/neck problems	1,753	27.6 (24.0–31.1)
	Arthritis/rheumatism	1,398	22.0 (18.9–25.0)
Cancer	Cancer	1,193	26.5 (23.1–29.8)
	Back/neck problems	1,108	24.6 (21.1–28.1)
	Arthritis/rheumatism	1,099	24.4 (20.7–28.0)
Diabetes	Diabetes	3,446	51.8 (48.0–55.6)
	Arthritis/rheumatism	1,745	26.2 (22.6–29.9)
	Back/neck problems	1,653	24.9 (21.3–28.4)
Heart conditions	Heart problems	184	41.9 (38.8–45.1)
	Arthritis/rheumatism	2,171	23.5 (20.7–26.3)
	Back/neck problems	2,152	23.3 (20.5–26.1)
Arthritis	Arthritis/rheumatism	5,175	33.5 (30.7–36.3)
	Back/neck problems	4,997	32.4 (29.8–34.9)
	Musculoskeletal/ connective tissue problems	2,300	19.4 (17.3–21.6)

Conclusion: In addition to being the most common causes of work limitation overall, arthritis/rheumatism and/or back/neck problems were among the top 3 causes of work limitation regardless of chronic condition, suggesting that addressing work limitation caused by musculoskeletal conditions is important no matter what other chronic conditions are present.

Evidence-based public health interventions (e.g., the Chronic Disease Self-Management Program) and vocational rehabilitation may delay or reverse disability among adults with chronic conditions experiencing work limitations.

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A Population-Based Approach to Establishing the National Burden of Severe Hip and Knee Osteoarthritis In Australia. Ilana N. Ackerman[1] and Richard H. Osborne[2]. [1]The University of Melbourne, Melbourne, Australia, [2]Deakin University, Melbourne, Australia

Background/Purpose: Severe hip and knee osteoarthritis (OA) is an ongoing public health problem in Australia, as evidenced by the growing demand for joint replacement surgery. However, the burden of these conditions has not been evaluated using a national, population-based approach. Rising rates of obesity are also of great concern, similar to many developed countries. This study aimed to investigate the prevalence and impact of severe hip and knee OA in Australia and examine the relationship between obesity and wellbeing in OA.

Methods: Five thousand Australians were randomly selected from the federal government electoral roll and invited to participate. Participants completed a questionnaire to identify doctor-diagnosed hip and knee OA and evaluate the severity and burden of these conditions. Pain, stiffness and function were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (range 0–100; scored best-worst). Total WOMAC score was used to classify OA severity (<7 = asymptomatic, 7–38 = mild-moderate, ≥39 = severe). Health-Related Quality of Life (HRQoL) was assessed using the Assessment of Quality of Life (AQoL) instrument (range −0.04–1.00; scored worst to best; minimal important difference 0.06 AQoL units). Body Mass Index (BMI) was used to classify underweight/normal weight (BMI ≤24.99 kg/m^2), overweight (BMI 25–29.99) and obesity (BMI ≥30). Analysis of covariance was used to determine the effect of OA severity on HRQoL and the effect of obesity on HRQoL, pain, stiffness and function, after adjusting for age and gender.

Results: Data for analysis were available from 1153 participants (23%). The prevalence of hip OA was 4.9% (n=56) and prevalence of knee OA was 8.2% (n=95). The specific prevalence of severe hip and knee OA was 2.3% (n=27) and 3.2% (n=37), respectively. Reduced HRQoL was seen with increasing OA severity ($F=59.02$, $p<0.01$ for hip OA; $F=67.40$, $p<0.01$ for knee OA); participants with severe OA had extremely low HRQoL (mean AQoL 0.34 for hip OA, 0.39 for knee OA), compared to those with mild-moderate OA (mean AQoL 0.75 for hip OA, 0.72 for knee OA), those who were asymptomatic (mean AQoL 0.77 for hip OA, 0.81 for knee OA) and those without OA (mean AQoL 0.82 without hip OA, 0.83 without knee OA).

Obesity was strongly associated with poorer wellbeing in OA, even after adjusting for age and gender. Of those with hip OA, participants who were obese had the highest pain (mean WOMAC pain 50.3 vs 24.4 for underweight/normal weight; $F=3.69$, $p=0.03$) and lowest HRQoL (mean AQoL 0.33 vs 0.59 for underweight/normal weight; $F=3.88$, $p=0.03$). In knee OA, those who were obese had the highest pain (mean WOMAC pain 40.0 vs 27.4 for underweight/normal weight; $F=3.99$, $p=0.02$), greatest stiffness (mean WOMAC stiffness 44.3 vs 29.9 for underweight/normal weight; $F=3.86$, $p=0.03$) and poorest function (mean WOMAC function 40.6 vs 23.7 for underweight/normal weight; $F=5.07$, $p=0.01$).

Conclusion: This study provides the first Australian data on the prevalence of severe hip and knee OA and clearly shows that severe OA is associated with markedly reduced HRQoL. The relationship between obesity and poorer wellbeing in OA highlights the importance of targeted interventions for this patient group.

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Does Physical Performance Mediate the Effect of Knee Osteoarthritis and Risk of Indoor and Outdoor Falls in Older Men and Women? Uyen Sa D. Nguyen[1], Yuqing Zhang[1], Tyler J. VanderWeele[2], Jingbo Niu[1], Robert H. Shmerling[3], Douglas P. Kiel[4], Suzanne G. Leveille[5], Carol A. Oatis[6] and Marian T. Hannan[7]. [1]Boston University School of Medicine, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Beth Israel Deaconess Med Ctr, Boston, MA, [4]Hebrew Senior Life/Harvard Medical School, Boston, MA, [5]University of Massachusetts-Boston, Boston, MA, [6]Arcadia University, Glenside, PA, [7]Hebrew SeniorLife & Harvard Med Sch, Boston, MA

Background/Purpose: Knee osteoarthritis (OA) and falls are common in older adults and limit mobility. Research has shown that having knee OA increases the risk of indoor falls for men and outdoor falls for women. It is possible that men and women with OA differ in physical performance (PP) ability, which could potentially explain the differences in the effect of knee OA on the risk of indoor and outdoor falls by gender. We explored to what extent the effect of knee OA on the risk of indoor and outdoor falls may possibly be mediated by PP and whether such a mediating effect varied by gender.

Methods: This study included 764 participants from the MOBILIZE Boston Study, a population-based cohort of older adults. Knee OA was assessed at baseline using the ACR clinical criteria. Falls data were prospectively collected using monthly calendars, with phone follow-up to assess location of falls. PP was measured at baseline using the Short Physical Performance Battery (SPPB, range 0–12, with a higher score indicating better performance). Using negative binomial regression, we examined the sex-specific association of knee OA with the risk of indoor falls and with outdoor falls adjusting for confounders. We assessed the extent such associations were mediated by SPPB using linear and negative binomial regressions, and a counterfactual approach of mediation analysis to estimate the direct and indirect effect, controlling for potential confounders.

Results: Of 764 participants (486 women and 278 men, mean age: 78 years, mean BMI: 27.3), 25% had ACR-defined clinical knee OA. Over an average of 2.2 years, 60% of participants had ≥ 1 fall, 318 (42%) had ≥ 1 indoor fall, and 300 (39%) had ≥ 1 outdoor fall. Mean SPPB (SD) scores for people with and without knee OA were 9.1 (2.6) and 9.7 (2.3) in men, and 8.6 (2.8) and 9.3 (2.5) in women. Having a higher SPPB *decreased* the risk of *indoor* falls in men and *increased* the risk of *outdoor* falls in women. Also, men and women with knee OA had lower SPPB scores than their counterparts without OA (Table 1). In men, the rate ratio (RR) for the total effect of knee OA compared with no OA (Table 2) on risk of *indoor* falls in men was 1.6 (95%CI: 1.0, 2.5). Adjusting for SPPB decreased the RR for the direct effect of knee OA on risk of indoor falls in men by 16%. For women, the RR for the total effect of OA on risk of *outdoor* falls in women was 1.7 (95%CI: 1.2, 2.4). Adjusting for SPPB increased the RR for the direct effect of OA on risk of outdoor falls by 13%.

Table 1. Associations among Knee OA, SPPB, and Risk of Indoor and Outdoor Falls in Men and Women: The MOBILIZE Boston Study

		Each 1 Unit Increase in SPPB and Risk of Falls[1]		SPPB Scores in OA vs. No OA[2]	
	Falls	RR (95% CI)	P-Value	Mean Difference	P-Value
Men	Indoor	0.91 (0.83, 1.01)	0.07	−0.67	0.025
Women	Outdoor	1.11 (1.03, 1.21)	0.01	−0.50	0.03

[1]From negative binomial regression model with falls as outcome and SPPB, knee OA, age, BMI, use of medications (anti-depressants, anti-psychotics, anti-hypertensives, and sedatives), no. of co-morbidities (high blood pressure, stroke, heart disease, diabetes, ulcer/stomach disease, kidney disease, anemia, cancer/skin cancer, rheumatoid arthritis), and history of falls as predictors.
[2]From linear regression with baseline SPPB as outcome and knee OA, age, BMI, use of medications (anti-depressants, anti-psychotics, anti-hypertensives, and sedatives), no. of co-morbidities (high blood pressure, stroke, heart disease, diabetes, ulcer/stomach disease, kidney disease, anemia, cancer/skin cancer, rheumatoid arthritis), and history of falls as predictors, irrespective of falls.

Table 2. Rate Ratio for the Association between Knee OA and Rate of Indoor and Outdoor Falls

		Rate Ratio (95% CI)					
				Adjusted[2] with SPPB			
	Falls	Unadjusted	Adjusted[1] w/o SPPB	Direct Effect	Indirect Effect	Total Effect	Δ in RR
Men	Indoor	1.39 (0.83, 2.32)	1.58 (0.99, 2.52)	1.48 (0.93, 2.37)	1.06 (0.98, 1.16)	1.58 (0.99, 2.52)	16%
Women	Outdoor	1.64 (1.15, 2.34)	1.70 (1.21, 2.40)	1.81 (1.28, 2.55)	0.95 (0.89, 1.01)	1.71 (1.22, 2.42)	−13%

[1]Adjusted for age, BMI, use of medications (anti-depressants, anti-psychotics, anti-hypertensives, and sedatives), no. of co-morbidities (high blood pressure, stroke, heart disease, diabetes, ulcer/stomach disease, kidney disease, anemia, cancer/skin cancer, rheumatoid arthritis), and history of falls.
[2]Adjusted for above covariates and SPPB: (a) Direct Effect (DE) is the effect of knee OA on risk of falls adjusting for covariates including SPPB; (b) Indirect Effect (IE) is the effect of OA mediated by SPPB on risk of falls; (c) Total Effect (TE) is the product of the estimates for Direct and Indirect effect, e.g., RR(DE)*RR(IE); (d) Δ in RR is % change in estimates before and after adjusting for SPPB, e.g., [RR(TE)-RR(DE)]/[RR(TE)-1].

Conclusion: Among older individuals with knee OA, the increased risk of indoor falls in men and outdoor falls in women may be partially explained by differences in physical performance, but in opposite directions. It is possible that women with higher SPPB may be more mobile when outdoors, thus may be more likely to fall. Future studies should examine specific mechanisms why physical performance affect risk of indoor and outdoor falls differently for men and women.

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Trajectory of Weight Associated with Arthritis: A Population-Based Longitudinal Cohort Analysis. Orit Schieir[1], S. Hogg-Johnson[2] and E. M. Badley[3]. [1]University of Toronto, Toronto, ON, [2]Institute for Work and Health, and Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [3]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background/Purpose: While it is known that both overweight and obesity are more prevalent in arthritis populations, the potential role of arthritis on trajectories of weight change has not been explored. The objective was to estimate associations between arthritis with and without activity limitation, on trajectories of weight in the adult Canadian general population over a 16-year period.

Methods: The present study was a longitudinal analysis of 8 cycles of the longitudinal Canadian National Population Health Survey (NPHS - 1994/95 to 2008/09). Every 2 years, NPHS participants completed a standardized questionnaire including self-reported diagnosed chronic conditions present for at least 6 months, socio-demographic variables and lifestyle/health behaviours, administered by trained interviewers. Descriptive statistics and time-lagged linear multi-level regression models were used to estimate the association between arthritis and the trajectory of weight over time, adjusting for both time-invariant (sex, baseline physical activity, activity limitation, and weight) and time-varying (age, income, smoking, alcohol) covariates. Time-varying joint effects of arthritis and activity limitation were examined with interaction terms.

Results: The NPHS included 14 117 participants aged 18+ years that were eligible for analysis. The mean age of the sample was 45 years, 54% were female, and 18% reported having arthritis at baseline. Results of linear multi-level regression analysis with time (measured as NPHS cycle) as the only predictor showed that overall, weight increased over time in the Canadian population with an average rate of change of 1.12 lbs (95% CI: −4.57, 6.82 lbs) every 2 years. The covariance between initial weight status and rate of change in weight was negative indicating that individuals with higher initial weights changed less over time (and vice versa). Results from analyses that included arthritis and interactions for arthritis with time as predictors, showed that persons with arthritis had a higher average starting weight (+3.61 lbs, 95% CI: 2.95 – 4.26 lbs) and a smaller but still positive rate of change of 0.4 lbs every 2 years relative to Canadians without arthritis. Analyses that included interactions for arthritis with activity limitation and with time, showed that persons with arthritis but without activity limitation, and persons with arthritis and activity limitation, had higher average starting weights (+3.24, and +4.34 lbs, respectively) and smaller but still positive rates of change relative to Canadians without arthritis and no activity limitation. Results were unchanged after adjusting for time-invariant and time-varying predictors.

Conclusion: Persons with arthritis, and persons with arthritis and activity limitation in particular, had higher average starting weights and, lower but nevertheless positive increases in weight over time suggesting that primary prevention initiatives providing reinforcement about the benefits of weight control for persons with arthritis is warranted.

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Identifying Obesity in Rheumatoid Arthritis: Current BMI Definition of Obesity Does Not Accurately Reflect Body Composition. Patricia P. Katz[1], Mary E. Margaretten[2], Steven Gregorich[3], Sandi Kaplan[4], Holly Wing[4], Edward Yelin[5] and Lindsey A. Criswell[5]. [1]Univercity of California San Francisco, San Francisco, CA, [2]UCSF, San Francisco, CA, [3]University of California, San Francisco, San Francisco, CA, [4]University of California, San Francisco, CA, [5]University of California San Francisco, San Francisco, CA

Background/Purpose: There is evidence that body mass index (BMI), the most commonly used measure of body composition or obesity, is not an accurate reflection of body composition among individuals with rheumatoid arthritis (RA). The purpose of these analyses was to determine the prevalence of obesity and evaluate how accurately the standard BMI definition identified obesity in RA.

Methods: Data were collected from an in-person visit conducted at the Clinical and Translational Science Institute's Clinical Research Center (CRC). Subjects (n=141, 85 women 56 men) were drawn from participants in a longitudinal cohort study of RA, who lived in proximity to the clinical site. Body composition was measured with dual-energy x-ray absorptiometry (DXA), and obesity defined using % body fat criteria based on age, sex, and race/ethnicity. Height and weight were also collected to calculate body mass index (BMI; obesity defined as BMI ≥30 kg/m^2). Correspondence between obesity measures was assessed with Cohen's kappa. Receiver operating characteristic (ROC) curves determined optimal cut-points for BMI, relative to DXA.

Results: Overall, 58% were classified as obese by DXA, and 27% by BMI. A greater proportion of men were obese according to DXA (80% of men, 44% of women); sex differences in the prevalence of obesity defined by BMI were small (29% men, 26% women). Correspondence between anthropometric and DEXA-based measures was weak to moderate (total: kappa=0.39, 67% correctly classified; men: kappa=0.16, 54% correctly classified; women: kappa=0.49, 77% correctly classified). Individuals misclassified by anthropometric measures had significantly more truncal fat and significantly less appendicular fat mass; men also had significantly less appendicular lean mass. Cut-points were identified for BMI that better approximated obesity estimated from DXA-obtained percent body fat: ≥24.7 kg/m^2 for men, and ≥ 25.7 for women. With the revised cut-points, 73% of men and 80% of women were correctly classified as obese by BMI.

Conclusion: A large percentage of this sample with RA was obese, but substantial portions were misclassified by BMI. DXA-defined obesity was more common in men than women, and fewer women than men were misclassified by BMI. Misclassification may be at least partially attributable to appendicular muscle wasting. Revised cut-points permit better estimation of obesity with BMI, although the utility of these new cut-points in terms of health outcomes remains to be investigated.

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Does Hallux Valgus and Foot Pain Affect Self-Reported Lower Extremity Limitations in Men and Women? the Framingham Study. Alyssa B. Dufour[1], Virginia A. Casey[2], Patricia P. Katz[3], Robert R. McLean[4] and Marian T. Hannan[4]. [1]Hebrew SeniorLife & Boston Univ, Boston, MA, [2]Hebrew Senior Life, Boston, MA, [3]Univercity of California San Francisco, San Francisco, CA, [4]Hebrew SeniorLife & Harvard Med Sch, Boston, MA

Background/Purpose: Hallux valgus (HV) may affect the base of support in older adults, and thus could affect lower extremity physical abilities. It is unknown whether foot pain contributes to lower extremity physical limitation along with, or separately from, HV. This study investigated HV and foot pain and their relations with self-reported lower extremity physical limitation in community-dwelling older adults.

Methods: This cross-sectional study included 2208 ambulatory adults, contributing 4414 feet, from the population-based Framingham Study. We used a validated foot exam done by trained examiners with criteria to assess HV and foot pain. HV was present if the angle of the hallux toward the lesser toes was observed to be >15°. Foot pain (y/n) was queried: "On most days, do you have pain, aching or stiffness in either foot?" Each foot was categorized into four groups based on foot pain and HV status: 1) foot pain and no HV, 2) no foot pain and HV, 3) foot pain and HV, and 4) no foot pain, no HV. Lower extremity physical limitation was assessed using the subject's ability to climb stairs and to stand for 15 minutes. Self-reported difficulty, inability, or instruction from a physician to avoid was considered to be a limitation (y/n). Age, sex, and body mass index (BMI, kg/m^2) were also collected. Sex-specific generalized estimation equations, to account for within-person correlation of feet, adjusting for age and BMI, were performed to determine the odds ratios (and 95% confidence intervals) for limitations in climbing stairs and standing for 15 minutes among feet with 1) foot pain and no HV, 2) no foot pain and HV, and 3) foot pain and HV, versus feet with neither foot pain nor HV.

Results: 956 men and 1252 women had mean age of 66 ± 11.4 y (range 36–100 y). 7%, 9% and 2% of men had foot pain, HV, or both. In women, 8%, 14% and 6% had foot pain, HV, or both. Limitation in standing was seen in 17% of men and 19% of women. Limitation in walking up and down stairs was present in 13% of men and 19% of women. Among men, although foot pain only was not associated with limitation, those with HV only had 20–40% increased risk of limitation (see Table). Furthermore, men with foot pain and HV had almost 30% increased risk of limitation in standing, and 70% increased risk of being limited in climbing stairs. In women, while foot pain only and foot pain and HV were associated with limitations in both stairs and standing, those with HV only were not at increased risk of being limited in either outcome.

Conclusion: The combination of foot pain and HV had consistently

higher risks of physical limitation in climbing stairs in both men and women. Additionally, the risk of lower extremity limitation was only elevated in women with foot pain (and no HV), whereas in men, the risk was elevated in those with HV (and no foot pain). This study suggests that foot pain is important in evaluating the relation between structural foot disorders and lower extremity physical limitations in older adults and is different for men and women.

Table. Odds ratios and 95% confidence intervals for the association between lower extremity physical limitation and foot pain and hallux valgus.

	Men		Women	
	% limited	OR (95% CI)	% limited	OR (95% CI)
Up and down stairs				
Neither (referent)	6.4	1.00	6.8	1.00
Foot pain only	2.8	0.90 (0.45, 1.77)	4.4	1.73 (1.28, 2.35)
Hallux valgus only	2.2	1.38 (1.07, 1.77)	4.7	1.19 (0.90, 1.57)
Foot pain and hallux valgus	1.4	1.69 (1.07, 2.66)	3.0	1.83 (1.27, 2.64)
Standing 15 minutes				
Neither (referent)	9.2	1.00	6.0	1.00
Foot pain only	3.6	0.92 (0.53, 1.62)	5.2	1.74 (1.28, 2.36)
Hallux valgus only	2.8	1.21 (0.88, 1.65)	4.6	1.06 (0.78, 1.42)
Foot pain and hallux valgus	1.1	1.26 (0.61, 2.58)	3.2	1.26 (0.95, 1.69)

ACR Concurrent Abstract Session
Epidemiology and Health Services Research V: Drugs
Sunday, November 6, 2011, 4:30 PM–6:00 PM

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Initiation of Biologic DMARDs and the Risk of Hospitalization for Infection in Patients with Autoimmune Diseases. Carlos Grijalva[1], Lang Chen[2], Elizabeth S. Delzell[2], John Baddley[2], Timothy Beukelman[3], Kevin L. Winthrop[4], Marie Griffin[5], Lisa Herrinton[6], Liyan Liu[6], Parivash Nourjah[7], Nivedita M. Patkar[3], Daniel H. Solomon[8], James Lewis[9], Fenglong Xie[2], Kenneth G. Saag[2] and Jeffrey R. Curtis[2]. [1]Vanderbilt University, Nashville, TN, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Univ of Alabama-Birmingham, Birmingham, AL, [4]Oregon Health Science Univ, Portland, OR, [5]Vanderbilt, [6]Oakland, CA, [7]Rockville, MD, [8]Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [9]University of Pennsylvania

Background/Purpose: Although TNF-alpha(α) antagonists are increasingly used in place of other non-biologic disease modifying antirheumatic drugs (DMARDs), their safety profile remains debatable. The objective of this study was to determine whether initiation of TNF-α antagonists increases the risk of serious infections compared with non-biologic DMARDs in patients with autoimmune diseases.

Methods: We combined data from Kaiser Permanente Northern California, Pharmaceutical Assistance Contract for the Elderly, Tennessee Medicaid and National Medicaid/Medicare, in a retrospective cohort (1998–2007). We identified patients with rheumatoid arthritis (RA); inflammatory bowel disease (IBD); and psoriasis (PsO), psoriatic arthritis (PsA) or ankylosing spondylitis (PsO-PsA-AS). The incidence of hospitalizations for serious infections was compared between initiators of TNF-α antagonists and alternate non-biologic DMARD regimens in disease specific-propensity score (PS) - matched cohorts using Cox regression models with non-biologics as reference. Baseline glucocorticoid use was categorized according to the estimated average daily dose of prednisone equivalents (none, >0-<5 (low dose), 5–10 (medium dose) and >10 mg (high dose)), and evaluated as a separate covariate.

Results: Among RA, IBD and PsO-PsA-AS patients, we identified 10602, 3219 and 1323 PS-matched pairs of episodes of TNF-α antagonist and alternate regimen use, respectively. Among RA patients, hospitalization rates of serious infections were 8.17 and 7.66 per 100 person-years, respectively (adjusted hazard ratio [aHR]: 1.09 (95% CI: 0.94–1.25)). Among IBD patients, the respective rates were 10.91 and 9.49 per 100 person-years (aHR: 1.14, (0.86–1.52)) whereas among PsO-PsA-AS patients, the respective rates were 5.41 and 5.19 per 100 person-years (aHR: 1.10, (0.80–1.53)). Among RA patients, infliximab was associated with a significant increase in the risk of serious infections compared with etanercept and adalimumab (aHRs: 1.26 (1.08–1.49) and 1.23 (1.02–1.48), respectively). For RA and PsO-PsA-AS, baseline glucocorticoid use was associated with a dose-dependent increase in risk of infections compared with no glucocorticoid use (for RA, aHRs: 1.39, 1.76 and 2.73; and for PsO-PsA-AS, aHRs: 1.36, 2.24 and 2.28 for low, medium and high doses, respectively).

Conclusion: In this large study consisting predominantly of older and low income patients with autoimmune diseases, initiation of TNF-α antagonists (as a group) was not associated with a significant increase in the risk of hospitalization for infections compared with alternate non-biologic regimens. Glucocorticoid use was associated with a dose-dependent increase in risk.

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Short Periods of Glucocorticoid Use Are Associated with a Prolonged Risk of Osteonecrosis. Steven C. Vlad[1], Donald R. Miller[2], Yuqing Zhang[1] and David T. Felson[1]. [1]Boston University School of Medicine, Boston, MA, [2]Edith Nourse Rogers Memorial VA Hospital, Bedford, MA

Background/Purpose: Chronic glucocorticoid (GC) use has long been known to be a risk factor for osteonecrosis (ON). What is less clear is whether short periods of GC use instill an elevated risk of ON, and how long the risk persists.

Methods: We conducted a case-control study using national Veterans Affairs healthcare data, including linked outpatient/inpatient administrative and outpatient pharmacy records. Based on a published case-finding algorithm (Vlad, 2009) we found 6206 potential ON cases from fiscal years 1999 through 2006. These persons were free of GC use and ON in the first year of their enrollment and had never received inpatient GCs. Of these, we randomly reviewed 1112 medical records to confirm the ON diagnosis. Confirmed cases had ON (X-ray, MRI, CT, or bone scan by the criteria of Sugano, et al. (1999)) according to radiology reports, and had symptom onset within 1 year of the first ON code according to clinical notes. Each case was matched by sex, race, age (10 year windows from 20 to 90), year of 1st VA visit, VA location, and VA priority rating (a combined measure of need and service related disability) to up to 10 randomly selected controls by risk-set sampling. We defined GC exposure (oral and IV, ignoring inhaled and topical) relative to an index date one year prior to the 1st ON code as 1) current, or last used 1–90, 91–180, 181–365, 366–730, or > 730 days previously; and 2) cumulative number of days used (1–30, 31–90, 91–180, 181–365, > 365). We also looked at cumulative dose in those who last used GCs > 365 days before the index date (remote users). No use was the for reference all analyses. We used conditional logistic regression adjusted for (ever) bisphosphonate use, heavy alcohol use, and osteoporosis; fracture within the prior year; and new cancer diagnosis within the 2 prior years to calculate odds ratios for ON.

Results: We identified 172 ON cases (164 men) and 1581 controls (1553 men). Mean age was 60.3 years (std 10.7). 43 cases (25.0%) and 82 controls (5.2%) had at least one GC prescription. Compared to no GC use, the risk of ON was elevated in all strata regardless of recency of use (though there were few current users). Compared to no GC use, the risk of ON was elevated for all categories of cumulative use, even for those using =< 30 days (OR 3.8, 95% CI 2.1–6.8). Even in remote GC users, =< 30 days use carried an elevated risk for ON (OR 3.4, 95% CI 1.7–6.8).

Conclusion: We found that even a short period of GC use (=< 30 days) puts patients at risk for ON, even after 1 year of drug discontinuation. Potential limitations of this study include small numbers of GC users in some strata (generating wide CIs), not taking GC dosing into account, and residual confounding, e.g. by indication.

Table. Association of glucocorticoid use with osteonecrosis

Glucocorticoid use	Cases N (%) (N = 172)	Controls N (%) (N = 1581)	OR	(95% CI)
Never used (reference)	129 (75.0)	1499 (94.8)	1	–
Recency of use (prior to an index date one year prior to 1st ON code)				
Use at index date	1 (0.6)	1 (0.1)	13.3	(0.8, 220.1)
1–90 days prior	4 (2.3)	9 (0.6)	5.8	(1.6, 21.2)
91–180 days prior	4 (2.3)	6 (0.4)	9.7	(2.5, 38.4)
181–365 days prior	5 (2.9)	8 (0.5)	8.9	(2.5, 32.5)
366–730 days prior	13 (7.6)	23 (1.5)	5.6	(2.5, 12.4)
>730 days prior	16 (9.3)	35 (2.2)	4.3	(2.0, 9.0)
Cumulative duration of use				
1–30 days	22 (12.8)	68 (4.3)	3.8	(2.1, 6.8)
31–90 days	6 (3.5)	8 (0.5)	11.5	(3.5, 38.1)
90–180 days	6 (3.5)	3 (0.2)	12.8	(2.7, 60.1)
181–365 days	2 (1.2)	2 (0.1)	12.6	(1.1, 150.0)
>365 days	7 (4.1)	1 (0.1)	212.2	(8.9, >999.9)
Duration of use in remote users (>365 days prior to index date)				
1–30 days	16 (9.3)	45 (2.9)	3.4	(1.7, 6.8)
31–90 days	4 (2.3)	8 (0.5)	9.3	(2.5, 34.9)
90–180 days	2 (1.2)	2 (0.1)	4.1	(0.4, 47.9)
181–365 days	1 (0.6)	2 (0.1)	3.0	(0.2, 60.7)
>365 days	6 (3.5)	1 (0.6)	165.4	(7.0, >999.9)

Odds ratios (ORs) adjusted for bisphosphonate use, heavy alcohol use, fracture within prior year, osteoporosis, and recent cancer diagnosis. Duration of use in remote users also adjusted for recent use.

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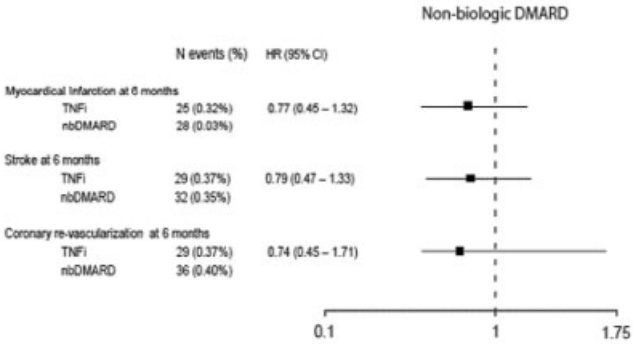
Cardiovascular Risk Reduction Associated with TNF Blockade: Results From a Large Multi-Site Observational Study. Daniel H. Solomon[1], Leslie R. Harrold[2], Jeremy Rassen[1], Huichuan Lii[3], Lang Chen[4], David Graham[5], Marie Griffin[6], Mary Kowal[3], Bindee Kuriya[7], James Lewis[8], Liyan Liu[9], Kenneth G. Saag[10] and Jeffrey R. Curtis[10]. [1]Brigham & Womens Hospital, Boston, MA, [2]UMass Medical School, Worcester, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Food and Drug Administration, [6]Vanderbilt, [7]University of Toronto, Toronto, ON, [8]University of Pennsylvania, [9]Kaiser Permanente, [10]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: The risk of cardiovascular disease (CVD) is increased in rheumatoid arthritis (RA) and is a major source of morbidity and mortality. Inflammation mediated by TNF may increase CV risk. Prior studies suggest that TNF blockade (TNFi) may reduce the risk of ischemic CV events. However, little is known about the timing, pattern and patient populations at risk, or the specific types of CV events.

Methods: Administrative data from 1998–2007 for patients with ≥ 2 RA diagnoses who had previously used methotrexate (MTX) were aggregated across a large US health maintenance organization, Medicare and Medicaid. Follow-up began when another non-biologic disease modifying antirheumatic drug (nbDMARD) or a TNFi was added to or substituted for MTX, creating two groups of new users. We matched these groups (n:1) based on a propensity score (PS) that included cardiovascular risk factors, relevant medications, sociodemographic variables, and health care utilization data. Cox proportional hazard regression models were fit, with a composite CV endpoint including MI, stroke and coronary revascularization. One analysis used an "intention to treat" approach carrying the first exposure forward and another used an "as-treated" approach, censoring individuals 30 days after exposure ended.

Results: From a total source population of 139,611 we found 22,907 potentially eligible individuals with RA using MTX. Among this group, 9,034 new users of a nbDMARD were PS-matched with 7,780 new users of a TNFi. The baseline covariates were well matched. Incidence rates per 100 person-years for the composite CV endpoint were 2.99 (95% CI 2.41–3.71) for nbDMARDs and 2.26 (95% CI 1.78–2.87) for TNFi. The glucocorticoid adjusted PS-matched hazard ratio (HR) for the intention to treat result at 6 months was 0.79 (95% CI 0.60–1.04), while the as-treated analysis at 6 months was 0.72 (95% CI 0.62–0.99). At 12 months in the as-treated analysis, the HR was 0.86 (95% CI 0.66–1.13). In as-treated analyses at 6 months, similar effects were seen across MI, stroke, and coronary re-vascularization (see **Figure**). The potential cardiovascular benefits of TNFi were only seen among persons ≥ 65 years of age (HR 0.51, 95% CI 0.33– 0.78) versus < 65 (HR 1.20, 95% CI 0.72–2.01).



Conclusion: In this large observational study of RA, we found a trend towards reduced CV risk among new users of TNFi compared with nbDMARDs, but this effect seems to wane after the first six months. The effect of TNFi on CV risk in the first 6 months includes all types of CV events and may be most pronounced in older adults. Randomized controlled trials would help clarify these relationships.

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Use of Bisphosphonates for the Prevention of Glucocorticoid-Induced Osteoporosis in Rheumatoid Arthritis—a Population Based Study. Diane Lacaille[1], Mushfiqur Rahman[1] and John Esdaile[2]. [1]Arthritis Research Centre; University of British Columbia, Vancouver, BC, [2]University of Calgary, Calgary, AB

Background/Purpose: Osteoporosis is a common co-morbidity in rheumatoid arthritis (RA). The increased osteoporosis in RA is felt to be due to the inflammatory process itself, decreased mobility from physical impairment, as well as treatment with glucocorticoids (GC). Glucocorticoid-induced osteoporosis (GIOP) is a preventable cause of osteoporosis in RA, since bisphosphonates (BPPs) have been shown to prevent bone loss associated with GC and to reduce fracture risk. American and Canadian guidelines recommend BPPs as primary prevention in all cases starting prednisone at a dose >5 mg/d and >7.5 mg/d, respectively, for an expected duration > 3 mos. The purpose of this study was to evaluate the compliance with these guidelines in a population-based cohort of RA and to determine if compliance has improved over time.

Methods: Using administrative billing data from the Ministry of Health, we have assembled a population-based cohort of all RA cases who received care by a physician for RA between 01/1996 and 03/2006. Previously published RA criteria included: at least 2 MD visits, at least 2 mos apart, where ICD-9 code for RA was used for reimbursement of MD visits. Cases were excluded if they had at least 2 subsequent visits for another type of inflammatory arthritis, if assessment by a rheumatologist did not confirm the diagnosis of RA made by another physician, or if no subsequent RA visits occurred over > 5 years. Our population-based cohort includes 37,151 RA cases, yielding an RA prevalence of 0.82%. For this study, all RA cases in the population-based cohort who were prescribed GC at doses >5 mg/d (prednisone equivalent) for >= 3 months were included (N = 10,153). Data on all medications were obtained for all RA cases. The use of BPP during courses of GC was evaluated and compared before and after the year 2000.

Results: Of our population-based cohort, 10,153 RA cases (27%) received GC for >3 mos at a mean daily dose > 5mg, with a total number of GC courses of 21,547. BPP were prescribed for 8,692 of the GC courses (8,692/21,547 or 40.3%) in 4,669 RA cases (4,669/10,153 or 46%). In 4,215 GC courses (2,473 RA cases) the BPP preceded the GC; in 1673 GC courses (1,499 RA cases) BPP and GC were started simultaneously, and in 2,804 GC courses (2,448 RA cases) the BPP were started after the GC, with a median delay of 4.3 months (IQR = 2.3;9.3 mos). Of the 8,692 GC courses with BPP prophylaxis, BPP were used for 55% (95% CI:54%;56%) of the time of the duration of the GC courses. The use of BPP prophylaxis for GIOP prevention improved after the year 2000. BPP were used in 33.0% of GC courses before 2000 vs 46.7% after 2000, and were used for 46% (95% CI: 44%;48%) vs 63% (95% CI:62%;64%) of the duration of the GC courses.

Conclusion: Despite the burden of osteoporosis in RA and the evidence supporting the use of BPP as prophylaxis to prevent GIOP, concomitant use of BPP during courses of glucocorticoids was infrequent in our population-based study. Although use of BPP improved after the year 2000, it still remains suboptimal both in terms of frequency and duration of its use.

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Switching From Oral Bisphosphonates to Intravenous Zoledronic Acid Is Associated with A Reduction In the Incidence Rates of Morphometric Vertebral Fractures Among Patients with Postmenopausal Osteoporosis?—A Real-World Time-Series Study. Peter Sun[1], Jean Lian[2], Chris Recknor[3] and Julie Recknor[3]. [1]Kailo Research Group, Indianapolis, IN, [2]Novartis Pharmaceuticals Corp., East Hanover, NJ, [3]United Osteoporosis Centers, Gainesville, GA

Background/Purpose: Once-yearly intravenous zoledronic acid is a potent third-generation amino-bisphosphonate approved by Food and Drug Administration (FDA) for postmenopausal osteoporosis in 2007. This real-world study examines the impact of switching from oral bisphosphonates to intravenous zoledronic acid (with assured annual compliance) on the incidence rates of morphometric vertebral fractures among patients with postmenopausal osteoporosis in a clinical practice setting.

Methods: We used a retrospective time-series study design, and electronic medical records databases from a large US osteoporosis treatment center, where a systematic clinical protocol change to convert oral bisphosphonate patients to zoledronic acid occurred in 2007. Patients with postmenopausal osteoporosis and a switch from oral bisphosphonates to once-yearly intravenous zoledronic acid after the protocol change met the criteria for the study if they had 24 months of oral bisphosphonates prescriptions before the switch and 24 months of zoledronic acid treatment after the switch, and were continuously observed by the center throughout the 48-month study period. Based on electronic medical records, the monthly incidence rates of morphometric vertebral fractures were calculated. Eight interrupted time-series analysis models were developed to examine whether the switch was associated with any changes in the monthly incidence rates of morphometric vertebral fractures. To ensure the robustness of these interrupted time-series

models, both conditional least square method and maximum likelihood method were used.

Results: We identified 897 patients who received once-yearly intravenous zoledronic acid, had once-yearly spine X-rays and frequent fracture history inquiry during the study period. Of these 897 patients, 144 patients met our selection criteria. These patients had a mean age of 70 years at switch, were 99% white. The average incidence rates of morphometric vertebral fractures were 7.13 per 1,000 patients per month in the last two pre-switch years, and 1.93 per 1,000 patients per month in the first 2 post-switch years. The eight interrupted time-series models suggested that the switch was associated with a reduction in morphometric vertebral fracture rates by 5.15~5.25 per 1,000 patients per month in the first 2 post-switch years (all $p<0.05$).

Conclusion: In a large osteoporosis treatment center, switching from oral bisphosphonates to once-yearly intravenous zoledronic acid therapy was associated with a significant reduction in the monthly incidence rates of morphometric vertebral fractures.

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Safety of Zoster Vaccine in Individuals with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Inflammatory Bowel Disease. Jie Zhang[1], Fenglong Xie[1], Elizabeth S. Delzell[1], Lang Chen[1], Kenneth G. Saag[1], Kevin L. Winthrop[2] and Jeffrey R. Curtis[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Oregon Health Science Univ, Portland, OR, [3]Univ of Alabama-Birmingham, Birmingham, AL

Background/Purpose: The live zoster vaccine is approved in the US for individuals ages 50 and older to reduce risk and severity of Herpes zoster infection, also known as shingles. Based upon limited data, the vaccine is currently considered to be contraindicated in individuals taking biologics. The objective of the study is to examine whether the administration of zoster vaccine is associated with an increased risk of Herpes zoster shortly following vaccination among persons treated with biologics for autoimmune and inflammatory diseases.

Methods: From 2006 through 2009, we identified from the 100% Medicare fee for service population individuals who were 60 years of age or older; had rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease; and received zoster vaccine. We classified these individuals according to their concomitant medications (biologics; non-biologic DMARDs, including methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine; oral glucocorticoids) within 60 days prior to or after vaccination. The cumulative incidence of Herpes zoster infection within 42 days following vaccination (the typically-used risk window in zoster vaccine trials) was calculated according to drug exposure.

Results: A total of 6793 subjects were vaccinated; among these, 76 had ankylosing spondylitis, 1,260 had inflammatory bowel disease, 161 had psoriatic arthritis, 1,745 had psoriasis, 3,246 had rheumatoid arthritis, and 305 had two or more diseases; 580 were on biologics, 1825 on non-biologic DMARRDs, and 1432 were on glucocorticoids at the time of or immediately prior (+- 60 days) to vaccination. The mean ± standard deviation (SD) age of vaccinated patients was 74.5 ± 6.3, 72% were women, and 96% were Caucasians.

Within 42 days following vaccination, the overall cumulative incidence of Herpes zoster infection was 2.2 per 1,000 persons. The cumulative incidence of zoster infection was not significantly different between those who were using biologics (1.7 per 1,000) or only non-biologic DMARDs (2.7 per 1,000). Irrespective of biologic or DMARD use, the short term risk of zoster infection was higher for patients receiving oral glucocorticoids compared to those not ($p = 0.07$) (Table).

Drug Exposure Within 60 days of Vaccination	Number of patients vaccinated	Cumulative Incidence of Zoster within 42 days, per 1000 persons (95% CI)
Biologics with oral glucocorticoids	193	5.2 (0.0–15.3)
Biologics without oral glucocorticoids	387	0.0 (0.0–9.5)
DMARDs with oral glucocorticoids	550	5.5 (0.0–11.6)
DMARDs without oral glucocorticoids	1275	1.6 (0.0–3.7)

Conclusion: Zoster vaccine in current biologic users does not appear to be associated with a short term risk of Herpes zoster infection following vaccination compared to those using only non-biologic DMARDs. In addition, the risks were not different than the rates observed in the general population participating in a large zoster vaccine trial of 38,546 individuals in which the cumulative incidence of Herpes zoster infection within 42 days 1.2 per 1,000 among those who receiving placebo. Vaccination with the live zoster vaccine may be reasonable to consider for patients currently using biologics.

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Can Ultrasound (PDUS) Easily Detect Erosions? Evaluation of Physiological and Abnormal Cortical Breaks of Small Joints in Healthy Individuals (HI) and Rheumatoid Arthritis (RA) Patients by PDUS Comparison with Micro Computed Tomography (μCT) Scan. Stephanie Finzel[1], Philippe Aegerter[2], Georg Schett[1], Maria-Antonietta D'Agostino[2] and OMERACT Ultrasound Task Force[3]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Versailles-Saint Quentin en Yvelines University- APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, Paris, France, Paris, France, [3]Paris, France

Background/Purpose: The correct detection of bone erosions in RA by ultrasound is sometimes delicate due to the presence of pitfalls such as physiological vessel channels, grooves, sesamoids and osteophytes. Thus, ultrasound needs further standardization. Objective: To evaluate by PDUS the size and location of physiological and abnormal cortical breaks in HI and RA patients by using μCT as gold standard.

Methods: Metacarpophalangeal joints (MCPJ) of both hands of 43 HI (without history of inflammatory joint disease) and 40 RA patients (disease duration > 6 months; fulfilling the new ACR/EULAR classification criteria) were examined by PDUS using a palmar, dorsal and, where possible, a lateral approach. All accessible joint facets were assessed in longitudinal and transversal planes. PDUS was performed by using an ESAOTE MyLab 70 (Genoa Italy) both in B- (linear array probe of 18 MHz) and PD-mode (10.2 MHz; PRF of 500). Cortical break was defined as a break in cortical lining detectable in two perpendicular planes. For each plane the width and the depth were recorded. Physiological and abnormal breaks were defined according to the opinion of ultrasonographer. Additionally, a μCT scan of MCPJ (2 to 5) was performed at a resolution of $82\times82\times82$ μm voxel size of the clinically more affected hands of 26 RA patients and of the dominant hands of 17 HI. The prevalence, sensitivity and specificity of breaks as determined by PDUS and μCT were recorded and compared.

Results: A total of 430 and 390 MCPJ were scanned by PDUS in HI and RA respectively. 48 and 81 MCPJ were additionally evaluated by μCT in HI and RA respectively. In HI, among the 1118 performed scans 226 breaks (20%) were recorded, 222 (98%) physiological (61% in the palmar side) and 4 (2%) pathological (3 in the lateral side). In RA patients 255 breaks were detected out of 1014 scans performed (25%). 143 (14%) were considered physiological (64% in the palmar side) and 112 (11%) as abnormal – erosions (51% in the lateral side). All physiological breaks were considered as vessel channels, despite the absence of PD signal. Overall there was an excellent agreement between PDUS and μCT regarding the specificity of detection of physiological and abnormal breaks in HI and RA (Sp of 1 for HI and 0.95 for RA) except for the dorsal side of MCP 2 (κ values of 0 for HI and 0.1 for RA). Sensitivity was difficult to assess due to low sample size in both groups. Table 1 shows the mean (mm) cortical physiological and abnormal breaks by PDUS and μCT in HI and RA.

Table 1.

	PDUS (mean in mm)				μCT (mean in mm)			
	longitudinal		transversal		longitudinal		transversal	
	Width	Depth	Width	Depth	Width	Depth	Width	Depth
HI (physiological breaks)	1.85	2.2	1.77	2.18	0.66	1.41	0.61	1.51
RA (physiological breaks)	0.48	0.63	0.66	0.8	1.03	1.24	1.02	1.27
HI (abnomal breaks)	2.5	3.2	1.8	2.3	0.67	1.74	0.84	1.59
RA (abnormal breaks)	1.43	1.35	1.53	1.43	1.83	1.79	1.79	1.79

Conclusion: Ultrasound is a valuable method for the detection of and the discrimination between abnormal (i.e. erosions) and physiological breaks in cortical bone. Predilection sides for nutritive vessels could be identified in both ultrasound and μCT. This study could work as a map for the correct detection of bone erosions in rheumatoid arthritis allowing for the discrimination between pathological and physiological breaks.

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Imaging As An Outcome Measure in Early Inflammatory Arthritis: Monitoring Disease Activity and Patients' Response to Therapy Using Ultrasonography. Yasser M. El Miedany[1], Maha El Gaafary[2], Deborah Palmer[1] and Sally Youssef[2]. [1]Darent Valley Hospital, Dartford, United Kingdom, [2]Ain Shams University, Cairo, Egypt

Background/Purpose: 1. To compare grey scale (GS) and PD US with clinical and biological findings in early arthritis patients treated with DMARDs/Biologic therapy and fulfill clinical remission criteria. 2. To assess US imaging as an outcome measure in monitoring the RA patients' response to therapy and its impact on the patients' management. 3. To identify which joints should be US scanned in the standard clinical practice.

Methods: Inclusion criteria: (1) Inflammatory arthritis diagnosed according to ACR/EULAR criteria (2) clinical remission (DAS28 <2.6) (3) no flares of disease in past 6 months. Each patient completed a copy of the PROMs including patients self-reportded joint tenderness. Clinical examination of tender and swollen joints was recorded and US assessment was carried out for every patient for: Hands: 1–5th MCP and 2–5 PIP joints, both wrists, both knee joints, feet: 1–5 MTP and 2–5 PIP joints in addition to any other painful/tender or swollen joint. Individual joints were scored for GS synovial hypertrophy and PD using a validated semi-quantitative method (0–3). Correlation between the clinical findings and US activity score was carried out. Patients who had active synovitis as proved by US were treated aiming at achieving US remission. Post-treatment correlation with clinical outcome measures was assessed.

Results: 121 patients receiving either DMARDs (n=65) or anti-TNF (n=56) were included. Over 1-year period of 3 monthly monitoring, 38/484 (7.9%) US scans showed active inflammatory arthritis. In comparison to clinical examination, US showed significantly more joints with effusion (mean 14.2) and synovitis (mean 16.1) than clinical examination (mean 10.2, $p < 0.05$). A significant correlation was found between patient self-reported joint tenderness and both US-PD as well as total US scores ($p< 0.0001$). US findings correlated significantly with pain score and CRP ($p< 0.01$), ESR ($p< 0.05$) whereas it did not correlated with patient global assessment, nor functional disability score. US findings had an impact on the patients' management where following: 16/38 (42.1%) scans the DMARDs dose was increased, 16/38 (42.1%) scans the DMARDs agent was changed, 12/38 (31.6%) scans the biologic therapy frequency was increased whereas an intra-articular injection was given following 20/38 (52.6%) scans. In the follow up visits, US was sensitive to change as improvement in US and PD scores were associated with clinical and laboratory changes ($p< 0.01$) in response to treatment. Therapeutic intervention based on US findings maintained the DAS-28 score at the same range (< 2.6) over the 1-year follow up period.

Conclusion: The combination of GS US and PD joint assessment is a sensitive and reliable outcome measure that should be a component of RA remission criteria. Despite DAS-28 score < 2.6, US imaging-detected subclinical active joint inflammation that warranted change of the current patient's management. In the standard clinical practice, patient self-reported joint tenderness is the best marker to identify joints need to be US scanned. Therapeutic intervention based on US findings has helped to achieve disease remission state that is of importance for subsequent clinical and radiographic progression.

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Ultrasonography Is a Potent Tool for Prediction of Ongoing Joint Destruction During Clinical Remission of Rheumatoid Arthritis. Ryusuke Yoshimi, Kaoru Takase, Maasa Hama, Daiga Kishimoto, Kayo Terauchi, Reikou Watanabe, Takeaki Uehara, Darisuren Tsolmon, Sei Samukawa, Atsushi Ihata, Atsuhisa Ueda, Mitsuhiro Takeno and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan

Background/Purpose: Although "clinical remission" has been a realistic goal of treatment in rheumatoid arthritis (RA), there is evidence that subclinical synovitis is associated with progression of structural damage even after achieving clinical remission. Here we assessed whether ultrasonography (US) can predict progressive joint destruction in RA patients who are evaluated as clinical remission.

Methods: Twenty-seven RA patients who were in clinical remission (DAS28-ESR < 2.6 or DAS28-CRP < 2.3) were recruited. Bilateral wrists, and all of MCPs and PIPs were examined by power Doppler (PD) US. Gray scale (GS) and PD signals were scored in each joint from 0 to 3, respectively. Total PD score and total GS score were calculated by summing up the score of individual joints. Hand X-ray was performed at the entry and at 2 years. Patients were defined as radiographically progressing cases when the change of the van der Heijde-modified total Sharp score exceeded 0.5 units per year and the others were as non-progressing cases. In principle, therapy was not modified during the study, unless the patients had clinical flare-up.

Results: Twenty-two patients maintained clinical remission during the 2-year follow-up, while 5 patients had clinical flare-up. The remission-maintaining group was further divided into 7 progressing cases (32%) and 15 non-progressing cases (68%) based on radiographic findings. There was no significant difference in age (51.4 ± 7.74 years vs 59.2 ± 12.1 years, $p = 0.15$) and disease duration (7.3 ± 3.9 years vs 6.7 ± 3.7 years, $p = 0.74$) at the entry between the two groups. Progressive radiographic destruction was strongly associated with total PD score at the entry, but not with total GS score (*Table 1*). Progressive radiological destruction in any joints was found in 7 of 11 patients (64%) having more than 2 of total PD score in US at the entry, but none of the other 11 patients having PD score, one or zero. There was no significant association of particular therapeutic agents with progressing cases or non-progressing cases.

Table 1. Correlation between radiographic change and baseline variables during clinical remission

Baseline variable	No radiographic progression ($n = 15$)	Radiographic progression ($n = 7$)	p
Total PD score	0.87 ± 1.15	6.00 ± 6.44	0.0099**
Total GS score	8.80 ± 5.78	12.6 ± 12.4	0.36
Swollen joint count	0.33 ± 0.79	1.29 ± 0.70	0.017*
Tender joint count	0.13 ± 0.34	0.57 ± 0.49	0.032*
Global VAS (mm)	9.40 ± 9.58	12.7 ± 4.40	0.41
ESR (mm/h)	10.2 ± 5.94	18.6 ± 16.2	0.11
CRP (mg/dl)	0.12 ± 0.15	0.08 ± 0.12	0.60
MMP-3 (ng/ml)	96.8 ± 110	62.1 ± 19.7	0.44
RF (U/ml)	73.8 ± 89.5	86.8 ± 68.1	0.77

* $p < 0.05$,** $p < 0.01$

Conclusion: PDUS detects latent synovitis which causes joint destruction even in the clinical remission of RA patients, irrespective of therapeutic agents. Thus, imaging remission in US is essential to reach "true remission" of RA.

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Does Rheumatoid Synovitis Activity Vary During the Day? A Sonographic and Doppler Evaluation. Agnes Lhoste, Bruno Pereira, Marion Couderc Sr. and Martin Soubrier. CHU Clermont-Ferrand, Clermont-Ferrand, France

Background/Purpose: Rheumatoid arthritis (RA) is an inflammatory disease, and patients' symptoms often decrease during the day. Sonography and Doppler have been shown to reliably depict activity of the synovitis, but may possibly decrease as well. The aim of this study is to determine whether Doppler activity of rheumatoid synovitis is the same in the morning and in the afternoon.

Methods: 27 patients (23 women and 4 men) with definite (1987 ACR criteria) and active RA (DAS28 4.66 ± 1.32) were included in the study.

Sonographic evaluation with B-mode and Color Doppler was performed twice for each patient, before 9 am and at 4 pm on the same day, using the same unit, with the same transducer and settings, by a single experienced radiologist (ALT). 22 synovial areas were scanned on each wrist, hand and forefoot, including 15 joints and 7 tendon sheaths. "Synovitis" was noted as defined by the OMERACT group as abnormal hypoechoic synovial hypertrophy. Synovial was considered as "normal" if thin and hardly visible. Synovial vascularization was visualized by color Doppler and scored as follow: "inactive synovitis" = S0 if no flow; "mild active synovitis" = S1 if color flow was detected in less than 1/3 of the hypertrophic synovial area; "moderate active synovitis" = S2 if flow was detected in more than 1/3 but less than 2/3 of the hypertrophic synovial area; "marked active synovitis" = S3 if flow was detected in more than 2/3 of the hypertrophic synovial area.

Results: 1) Number of detected synovitis: of the 1188 imaged joints and sheaths, 328 showed synovitis in the morning, 381 in the afternoon

(p = 0.05). This number increased in 20 patients, was the same in 6, and decreased in one. Statistical analysis of each localisation showed that right forth PIP modified significatively (p = 0.02), and right second MCP had a tendency to modify (p = 0.08), whether tenosynovitis did not modify (p = 1).

2) Activity of synovitis modified in 26 patients. this change concerned several joints in 21 patients, and only one in five. Activity significantly increased in left second MCP (p = 0.02) and right fifth MCP (p = 0.04) and had a tendency to increase in the third and forth right PIP and in the left radio-carpal joint (p = 0.08). Some inactive or mild synovitis (S0 and S1) may turn to moderate or marked (S2 or S3): This was significant in the second right MCP (p = 0.013) and in the combination of all explored hand and wrist joints of the right side (p = 0.002) and of the left side (p = 0.026)

Conclusion: These data suggest that synovitis activity changes during the day, surprisingly more often increasing than decreasing, and not uniformly in each patient. Only mild changes seem to be linked to the subjective scoring method. Daily physical activity may also be considered, as suggested by more significant variations on several dominant hand joints of these patients. Further data are needed to confirm with a larger cohort including patients in clinical remission, evaluating the risk of underestimating disease activity in this population. Our results, if confirmed, may have a direct impact on the patients' follow-up, as ultrasound performed for remission evaluation should not concern dominant side only, and should be repeated if necessary at the same hour of the day: but when?

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Sonoelastography Detects Rigidity of Salivary Glands in Primary Sjögren's Syndrome. Christian Dejaco[1], Tobias DeZordo[2], Daniel Heber[1], Rainer Lipp[1], Andre Lutfi[1], Marton Magyar[1], Saelde Baumgartner[1], Dorothea Zauner[1], Winfried B. Graninger[1] and Josef Hermann[1]. [1]Medical University Graz, Graz, Austria, [2]Innsbruck Medical University, Innsbruck, Austria

Background/Purpose: To investigate the value of sonoelastography (SElasto) in patients with primary Sjögren's syndrome (pSS).

Methods: Prospective study on 38 pSS patients fulfilling the American-European consensus group criteria [mean age 58 years; 92% female; median duration of sicca symptoms 6 years, 65% histological sialadenitis] and 11 healthy controls. B-mode sonography and SElasto of parotid and submandibular glands was performed using a GE Logiq E9 ultrasound device. Parenchymal homogenicity, echogenicity, hypoechogenic areals, hyperechoic reflections and clearness of glandular borders were semiquantitatively scored (total score ranging from 0–48) [Hocevar A et al, 2005]. SElasto was used to examine the elasticity of glandular parenchyma and a semiquantitative rating was performed with 0=no, 1=up to 25%, 2=up to 50%, 3=up to 75% and 4=more than 75% hardened areas within the salivary gland. The total score ranged from 0 to 16. Clinical assessments were performed at the same day of sonographic evaluation and included: Saxon test, Schirmer test, Xerostomia inventory (XI), and the Ocular Surface Disease Index (OSDI). Statistical analysis was performed using SPSS program (v18.0) and the Mann-Whitney-U and Spearman rank correlation test were performed as appropriate. Interobserver variability of sonography was tested in 30% of pSS patients by intraclass correlation coefficient (ICC).

Results: pSS patients had higher B-mode scores [median 25 (range 2.0–44.0) vs. 2.0 (0–8.0), p<0.001] and SElasto scores [6.0 (2.0–12.0) vs. 3.0 (1.0–4.0), p<0.001] than healthy controls.

pSS patients showed a median salivary flow rate of 1.69 g/2min (range 0.31–3.79), a median moisture on the filter paper (Schirmer test) of 4.0mm/5min (0–50.0), a median XI of 27.5 (8.0–43.9) and an median OSDI of 43.8 (0–77.1). In pSS patients, an inverse correlation was found between the result of the Saxon test and SElasto score ($corr_{coeff}$ −0.426, p=0.009), whereas B-mode ultrasound results were not associated with saliva production. No correlation was found between SElasto scores and Schirmer test as well as subjective ratings of dryness according to the XI and OSDI. In addition, neither disease duration nor duration of sicca symptoms influenced ultrasound results.

A good reproducibility of B-mode and SElasto results was found as indicated by an ICC of 0.926 (95%CI 0.565–0.983) and 0.934 (0.787–0.981), respectively.

Conclusion: Increased rigidity of major salivary glands as demonstrated by sonoelastography in patients with pSS correlates with the impairment of saliva secretion.

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Vertebral Fracture Assessment (VFA): A Valid Tool to Detect Vertebral Fractures in Community-Dwelling Older Individuals. Diogo S. Domiciano[1], Jaqueline B. Lopes[1], Liliam Takayama[2], Camille Figueiredo[1], Valéria Caparbo[1], Eloisa Bonfa[3] and Rosa M.R. Pereira[4]. [1]University of São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]University of Sao Paulo, Sao Paulo, Brazil, [4]Disciplina de Reumatologia da FMUSP, Sao Paulo, Brazil

Background/Purpose: Vertebral fractures (VFx) are associated with higher morbidity and mortality in the general population. Since 70% of the VFx are clinically silent, radiologic image of spine has to be acquired for the diagnosis. Vertebral Fracture Assessment (VFA) has emerged as possible alternative for the gold standard radiographic image to detect prevalent VFx. Previous studies evaluating this method are hampered by the limited sample size, selection of women with specific indication for spine X-ray and inclusion of patients under 70 years. Thus, the aim of this study was to compare the performance of VFA with X-ray to identify VFx in healthy community-dwelling older men and women.

Methods: 429 non-institutionalized subjects (60% women), aged over 65 years, from community, were enrolled in this cohort. VFA by DXA measurements was evaluated by two expert rheumatologists by consensus and spine X-ray (T4 to L4) were analyzed according to semiquantitative method (Genant HK, 1993) by an expert radiologist. The correlation between VFA and spine X-ray to identify VFx was analyzed by kappa (k) scores. P<0.05 was set as significant.

Results: The average age of subjects was 73.1 ± 5.1 years. The prevalences of VFx in VFA and X-ray were 30.1 and 28.6% in women (P=0.68), and 28.2 and 30.6% in men (P=0.78), respectively. The frequency of unavailable vertebrae was significantly lower in spine X-ray than VFA (1% and 5.5%, respectively, P<0.001), particularly along with T4-T6. According to VFA, 5013 (96%) vertebrae were identified as normal, 144 (2.7%) had grade 1 fractures, 58 (1.1%) grade 2 fractures and 12 (0.2) grade 3 fractures. The sensitivity of VFA was 73% and the specificity was 99.1% to identify VFx. The sensitivity increased to 93% and specificity to 99.6% excluding deformities grade 1. A good correlation between VFA and X-ray (k=0.74) was observed and the exclusion of grade 1 resulted in an even better agreement (k=0.84). The correlation vertebrae by vertebrae between VFA and spine X-ray was lower for T5-T7 (k=0.60). Correlations between the two methods were comparable in both gender (k=0.72 in men, k=0.75 in women).

Conclusion: In elderly community, VFA and X-ray had comparable performances to identify VFx, particularly if mild deformities are excluded. Thus, this methodology is an easy and feasible promising alternative to improve the identification and management of patients with high risk of osteoporotic fractures.

ACR Concurrent Abstract Session
Innate Immunity and Rheumatic Disease
Sunday, November 6, 2011, 4:30 PM–6:00 PM

813 WITHDRAWN

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Circulating Mitochondrial DNA Copy Numbers As a Disease and Activity Marker in ANCA-Associated Vasculitis. Ulrich A. Walker[1], Nora M. Effelsberg[2], Nils Venhoff[3], Chingching Foocharoen[1], Jens Thiel[3], Paul Hasler[4] and Dirk Lebrecht[3]. [1]University of Basel, Basel, Switzerland, [2]Dept. of Rheumatology and Centre of Chronic Immunodeficiency, University of Freiburg, Freiburg, Germany, Freiburg, Germany, [3]Dpt. of Rheumatology and Center of Chronic Immunodeficiency, University of Freiburg, Freiburg, Germany, Freiburg, Germany, [4]Dept. of Rheumatology, Kantonsspital Aarau, Aarau, Switzerland, Aarau, Switzerland

Background/Purpose: Polymorphonuclear neutrophils and eosinophils may play an important role in the pathogenesis of ANCA-associated vasculitis (AAV) by releasing DNA in the process of extracellular trap generation after priming by endothelial cells, anti-proteinase 3 (PR3) autoantibodies, or S. aureus. Extracellular traps may contain mitochondrial DNA (mtDNA), which by binding to toll-like receptor 9, contributes to systemic inflammation and organ damage. The purpose of this study was to determine the characteristics of circulating cell free mtDNA in AAV and to examine if mtDNA quantification could be useful in the diagnosis and monitoring of AAV.

Methods: 54 consecutive subjects with AAV and 31 controls (healthy volunteers, and persons hospitalized for osteoarthritis or herniated intervertebral disks) were included in this crossectional study. mtDNA and nuclear DNA (nDNA) copy numbers were measured by quantitative PCR in plasma. AAV activity was measured with the Birmingham Vasculitis Activity Score (BVAS vs. 3). Anti-PR3 autoantibody titers, S. aureus nasal carriage and routine lab parameters were determined simultaneously.

Results: The intra-run coefficient of variation of the assay was 2.8% for the mtDNA and 5.3% for the nDNA amplicon. The inter-run coefficient of variation was 5.4 for both assays.

In control plasma, the median mtDNA copy number was 15,400/ml (interquartile range, IQR 10,992–31,233) and 449,683/ml (IQR 257,500–1,120,000) in AAV. On multivariate analysis, only BVAS ($p<0.001$) and CRP ($p=0.001$) remained predictive for circulating mtDNA-levels. CRP however contributed only little to the goodness of fit, indicating that BVAS is the major predictor of mtDNA plasma levels.

Conversely BVAS was only predicted by circulating mtDNA copy numbers ($p<0.001$) and neutrophil counts ($p=0.03$), generating an adjusted R^2 value of 0.635. Notably PR3-ANCA levels, and CRP levels were not predictive of BVAS. Cell free nDNA copies in control plasma were low (median 5,747 copies/ml), similar in AAV patients (5,125 copies/ml, $p=0.93$), and not correlated with BVAS.

In our patient population, the receiver operating characteristic curve determined an area under the curve of 0.968 with a cut-off of 178,000 mtDNA copies/ml plasma. The same cut-off would result in a sensitivity of 87.5%, a specificity of 100%, and a positive likelihood ratio of 27.1.

Conclusion: Circulating mtDNA, unlike nDNA, is markedly increased in patients with AAV compared to non-inflammatory controls. Elevated cell free mtDNA-levels distinguish most patients with AAV from healthy persons irrespective of disease activity. Within AAV subjects, circulating mtDNA copy numbers may contribute to systemic inflammation and are valid predictors of disease activity.

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Soluble CD14 in Synovial Fluid From Patients with Early-Stage Osteoarthritis Augments Synoviocyte Responses to TLR-2 and TLR-4 Ligands. Anjali Nair[1], Veero Kanda[1], Charles Bush-Joseph[1], Nikhil Verma[1], Susanna Chubinskaya[1], Katalin Mikecz[1], Tibor T. Glant[1], Anne-Marie Malfait[1], Mary K. Crow[2], Greg Spear[1], Alison Finnegan[1] and Carla R. Scanzello[1]. [1]Rush University Medical Center, Chicago, IL, [2]Hospital for Special Surgery, New York, NY

Background/Purpose: Low-grade synovitis is a variable feature of osteoarthritis (OA) that is associated with symptoms and is detectable even at early stages of disease. This inflammation is hypothesized to be triggered in part via stimulation of Toll-like receptors (TLRs) by products released from cartilage matrix degradation, we tested whether a TLR-2 or TLR-4 stimulating factor in synovial fluid (SF) from these early-stage knee OA patients with meniscal injury could lead to inflammatory activation of synoviocytes.

Methods: SF was obtained from patients undergoing arthroscopic meniscal procedures. Given the well described association between meniscal lesions and OA, these patients serve as a model population of patients with early-stage knee OA cartilage lesions. Cartilage damage was confirmed by intra-operative inspection and the extent graded according to the Outerbridge scoring system. X-rays were also evaluated using the Kellgren-Lawrence scoring system. Synovial tissue specimens for establishment of fibroblast-like synoviocyte (FLS) lines were obtained from asymptomatic organ donors with no documented history of joint disease via IRB approved protocols. SF from the patients was used to stimulate primary FLS, as well as HEK-293 cell lines transfected with TLR-2 or TLR-4. SF was used alone and in combination with a known TLR-2 stimulus (Pam_3Cysk_4) or TLR-4 stimulus (LPS). Stimulation was measured by IL-6 and IL-8 release into the culture media measured by ELISA, and by real-time quantitative PCR measurement of IL-6 and IL-8 mRNA expression levels in stimulated cell lysates. Levels of soluble CD14 were measured in SF by ELISA. A monoclonal anti-CD14 antibody was used to block the effects of CD14 in the stimulation assays.

Results: SF from these patients did not in general stimulate IL-8 release from the TLR transfectants. However, compared with SF on its own, SF (0.09–25%) in combination with TLR-2 or TLR-4 ligands resulted in significant augmentation of IL-8 release from the transfectants (greater than 100-fold), and significantly augmented release of both IL-8 and IL-6 from the primary FLS ($p<0.01$ to $p<0.001$ compared with SF or ligands alone). Augmentation of IL-6 and IL-8 mRNA expression was also demonstrated by real-time PCR. Soluble CD14 (sCD14), a co-receptor for TLRs, was measured in early OA SF at levels comparable to advanced OA and rheumatoid arthritis (RA) but significantly higher than in asymptomatic organ donors. Blockade with anti-CD14 antibody abolished the ability of SF to augment IL-8 production in response to LPS, and diminished Pam_3CysK_4 responses.

Conclusion: SF from patient with early stage OA augments FLS IL-6 and IL-8 production in response to TLR-2 and TLR-4 ligands. This effect appeared to be largely due to sCD14 in the fluid specimens. Our results demonstrate that sCD14 in the setting of OA and meniscal injury can sensitize FLS to respond more robustly to inflammatory stimuli such as TLR ligands. It suggests similarities between RA and OA at the level of innate immune activation in the joint. As synoviocytes are expected to be in contact with SF *in vivo*, we speculate that this priming of FLS inflammatory responses may have relevance to symptomatic "flares" seen clinically in OA patients.

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Abatacept (CTLA-4Ig) Treatment Reduces Adhesion and Migratory Capacity of Monocytes in Patients with Rheumatoid Arthritis (RA). Michael Bonelli[1], Elisabeth Ferner[1], Anastasiya Hladik[1], Lisa Goeschl[1], Thomas Karonitsch[1], Hans Peter Kiener[1], Stefan Bluemel[1], Carl-Walter Steiner[1], Michael Bergmann[1], Josef Smolen[2] and Clemens Scheinecker[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Abatacept (CTLA-4Ig) inhibits the binding of CD28 to the B7 ligands CD80/CD86 and thereby effector T cell activation. In addition, binding of CTLA-4Ig and reverse signalling via CD80/CD86 potentially exerts effects on antigen presenting cells (APC) and might therefore contribute to the therapeutic effect. In order to further elucidate the mechanism of CTLA-4Ig we performed phenotypic and functional analysis of APC in rheumatoid arthritis (RA) patients before and after the initiation of CTLA-4Ig therapy.

Methods: Peripheral blood mononuclear cells (PBMC) from RA patients (n=12) were analyzed before and 2 and 4 weeks after the initiation of CTLA-4Ig therapy. Proportions of $CD14^+$ monocytes, $CD19^+$ B cells, $CD1c^+$ myeloid dendritic cells (DC) and $CD303^+$ plasmacytoid DC were determined by flow cytometry. Monocytes were further analyzed for the expression of costimulatory and adhesion molecules and for their transendothelial migratory capacity in vitro. Further, $CD14^+$ cells from healthy controls (HC) were isolated by fluorescence activated cell sorting (FACS) and magnetic cell sorting (MACS), incubated with CTLA-4Ig and analyzed for their migratory and spreading capacity.

Results: Proportions of $CD14^+$ monocytes were significantly increased in RA patients treated with CTLA-4Ig. Phenotypic analysis revealed no significant differences in the expression of costimulatory molecules whereas the expression of several adhesion molecules was found to be significantly diminished. In addition isolated monocytes displayed a significant reduction in their adhesion and transendothelial migratory capacity upon treatment with CTLA-4Ig. Likewise, isolated monocytes from HC displayed a significant reduction in their migratory capacity after pre-incubation with CTLA-4Ig in a dose dependent manner. In line with these findings, spreading assays also revealed a profound impact of CTLA-4Ig on actin cytoskeletal and focal adhesion reorganization in $CD14^+$ monocytes.

Conclusion: Our data suggest that CTLA-4Ig directly affects phenotypic and functional characteristics of monocytes, which might decrease monocyte migration to the synovium. These findings represent an additional mechanism of CTLA-4Ig therapy in RA.

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A Novel Autoinflammatory Syndrome Presenting with Chronic Atypical Neutrophilic Dermatitis, Lipodystrophy and Elevated Temperatures (CANDLE syndrome) Caused by Mutation in the Immunoproteasome. Yin Liu[1], Yongqing Chen[1], Yuval Ramot[2], Damaris Garcia[1], Antonio Torrelo[3], Afzal Sheikh[4], Amy Paller[5], Adam Reinhardt[6], Deborah Stone[1], Massimo Gadina[7], Plass1 Plass[1], Dawn Chapelle[1], Zlotogorski Zlotogorski[2] and Raphaela T. Goldbach-Mansky[8]. [1]Translational Autoinflammatory Disease Section, Office of the Clinical Director NIAMS, Bethesda, MD, [2]Department of Dermatology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel., Jerusalem, Israel, [3]Departments of Pediatric Dermatology, Hospital Niño Jesús, Madrid, Spain, Madrid, Spain, [4]Medical Genetics Branch, NHGRI, Bethesda, MD, [5]Departments of Dermatology and Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA;, Chicago, IL, [6]Faculty of Physicians of the University of Nebraska Medical Center, College of Medicine, Nebraska, [7]NIAMS, Bethesda, MD, [8]NIH Building 10 Room 6D47B, Bethesda, MD

Background/Purpose: Chronic atypical neutrophilic dermatitis, lipodystrophy and elevated temperature (CANDLE) syndrome is a novel autoinflammatory syndrome in the pediatric population. We investigated the clinical phenotype, the genetic cause and characterize the immune-dysregulation in 9 clinically defined CANDLE syndrome patients. PSMB8 is a critical subunit of the immunoproteasome, a multi-protein complex which degrades poly-ubiquitinated proteins in the cells.

Methods: Homozygosity analysis and genomic DNA sequencing were performed. Bio-rad multiplex cytokine assay was used to analyze the cytokine profile in patient serum or supernatant from stimulated PBMC. Blood microarray profile (n=4) and stat-1 phosphorylation were assessed and skin biopsies were evaluated immunohistochemically.

Results: Genomic DNA sequencing showed that one patient was homozygous for a nonsense mutation in *PSMB8* (c.405C>A encoding p. C135Z) leading to a protein trunctation, 5 patients were homozygous and 2 were heterozygous for a missense mutation (c.224C>T encoding p.T75M) recently reported to cause joint contractures, muscle atrophy, and panniculitis-induced lipodystrophy (JMP) syndrome in adults; 1 patient was mutation negative. Analysis of skin biopsy showed heavy infiltration of myeloperoxidase and leder stain positive immature granulocytes and activated, macrophages positive for CD68/CD163 and Myeloperoxidase staining. *PSMB8* mutation positive and negative patients expressed high serum levels of the IFN induced cytokine IP-10. Other elevated cytokines included MCP-1, IL-6, and IL-1Ra. Whole blood microarray analysis on four patients showed a strong IFN signaling signature that distinguishes it from other autoinflammatory syndromes. IFN stimulated stat-1 phsophorylation in patient monocytes was stronger than in healthy controls. Both STAT1 phosphorylation and IP-10 production in patients can be blocked by a JAK kinase inhibitor, as in healthy controls.

Conclusion: CANDLE is caused by mutations in *PSMB8,* a gene encoding a component of the immunoproteasome. Our data extend the clinical and pathogenic description of this novel autoinflammatory syndrome and suggest a novel mechanism of immunedysregulation involving IFN. The prominent IFN signature raises questions of pathways linking proteasome dysfunction to the interferon signaling and IFN signaling may be a key mediator of the inflammatory response that can be targeted therapeutically in patients with *PSMB8* associated disorders

ACR Concurrent Abstract Session
Muscle Biology, Myositis and Myopathies: Insights into the Pathogenesis of Myositis
Sunday, November 6, 2011, 4:30 PM–6:00 PM

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Micrornas Mir-15b and Mir-206 Are Key Factors in the Regulation of Impaired Angiogenesis in Muscle of Children with Untreated Juvenile Dermatomyositis. Simone Treiger Sredni[1], Peter Hendrickson[2], Erin Kim[3], Gabrielle Morgan[3], Sheela Shrestha[3], Yi-Wen Chen[4], Chiang-Ching Huang[5] and Lauren M. Pachman[1]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Children's Memorial Research Center, Chicago, IL, [3]Children's Memorial Hospital, Chicago, IL, [4]George Washington University, Washington, [5]Northwestern Univ Med School, Chicago, IL

Background/Purpose: Juvenile dermatomyositis (JDM), the most common pediatric inflammatory myopathy, is an autoimmune vasculopathy. The hallmark of JDM, damaged small blood vessels, is associated with local hypoxia and tissue apoptosis. MicroRNAs are non-coding RNAs that regulate several messenger RNAs simultaneously by mechanisms such as translational repression or cleavage of target messages, offering a new prototype for therapeutic intervention.

Objectives: To compare the microRNA expression profile in muscle from untreated children with active symptoms of JDM and healthy pediatric controls in order to investigate the pathophysiology of JDM.

Methods: All diagnostic muscle biopsies were MRI directed, and approved consent was obtained from JDM and controls (IRB# 2008–13457, IRB# 2001–11715 respectively). For microRNA expression, 6 children with definite/probable JDM (Bohan and Peter criteria) and two age/gender-matched orthopedic control muscles were profiled. MicroRNA array experiments were conducted in triplicate on Exiqon's miRCURY LNA microRNA Array, v.11.0. For gene expression, 25 JDM and 4 healthy age-matched orthopedic control muscles were profiled using Affymetrix U133A arrays. After normalization, fold change and t-tests assessed the mean difference of GE and microRNA expression between JDM and controls. MicroRNAs and protein-coding genes with FC $\geq$1.5 or FC$\leq$ $-$1.5 and p-value $\leq$0.05 were evaluated. Selected protein-coding genes and miRNAs were validated by qRT-PCR.

Results: A total of 19 microRNAs were differentially expressed in JDM: Seven were up regulated and 12 were down regulated. MicroRNAs miR-15b (FC= 1.92, p-value=0.028) and miR-206 (FC=2.57, p-value=0.03) were among the top miRNAs that were up regulated. Both of these microRNAs target the angiogenesis regulator, EGFR, down regulated (FC=$-$1.8, p-value=0.008) in the JDM samples. Besides regulating EGFR, miR-15b targets the Bcl2 gene (FC=$-$2, p$<$0.0003) that together with EGFR, controls expression of NF-kB2 (FC=$-$1.6, p-value=0.02). NF-kB and EGFR regulate MAPK1 (FC=$-$2, p-value 0.03) that contributes to angiogenesis by controlling VEGF (VEGFA FC=$-$2, p-value= 0.009 and VEGFB FC=$-$1.6, p-value=0.01) through JUN (FC=$-$3.2, p-value=0.008). These results suggest that the down regulation of a network of pro-angiogenic genes by miR-15b and miR-206 does not allow recovery of the impaired vascular network, thus sustaining the hypoxic conditions at a tissue level. Thus, miRNA activity in JDM muscle impairs recovery of angiogenesis, contributing to disease chronicity. In addition, an inhibitor of angiogenesis, TIMP-1, is up-regulated (FC=3.5, p-value=0.004), compounding this inhibitory process. No association with duration of untreated disease was observed.

Conclusion: The data suggest that neoangiogenesis, normally stimulated by tissue hypoxia, is impaired in untreated JDM muscle, and that this impairment is regulated by the microRNAs—miR-15b and miR-206. These findings add to the current knowledge of JDM pathophysiology and might potentially lead to new forms of therapeutic intervention.

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Type I Interferon-Related Biomarkers Predict Clinical Disease Activity in Inflammatory Myositis. Ann M. Reed[1], Cynthia S. Crowson[1], Hatice Bilgic[2], Emily Baechler Gillespie[2], Molly Hein[1], Steven R. Ytterberg[1], Shreyasee Amin[1] and Erik J. Peterson[2]. [1]Mayo Clinic, Rochester, MN, [2]University of Minnesota, Minneapolis, MN

Background/Purpose: Biomarkers are needed that are sensitive to disease activity during treatment for juvenile and adult dermatomyositis (DM). DM subjects carry distinct immune Type I interferon (IFN)-inducible gene and chemokine signatures in peripheral blood, which are correlated cross-sectionally with disease activity. We evaluated whether changes in peripheral blood IFN-inducible gene and chemokine scores may serve as novel biomarkers for treatment-independent change in DM disease activity.

Methods: We followed 51 patients with juvenile (mean age 8 yrs; n=21) and adult (mean age 45 yrs; n=30) DM prospectively for 2 study visits separated by 3–6 months. At each visit, peripheral blood was collected, and clinical data were recorded regarding medication use and disease activity (global, muscle, and extra-muscular) each assessed using a 10 cm visual analog scale (VAS). The whole-blood Type I IFN gene score was defined by expression levels of 3 IFN-regulated genes (IFIT1, G1P2, IRF7) measured by quantitative real-time RT-PCR. Multiplexed immunoassays were used to quantify serum levels of pro-inflammatory cytokines including IL-6, and of Type I IFN-regulated chemokines (I-TAC, IP-10, MCP-1; together yielding a derived IFN chemokine score). Spearman partial correlation methods were used to correlate changes in disease activity with changes in analytes adjusting for medication use.

Results: The median global disease activity for the total DM cohort at visit 1 was 26 (range 0–80) and median change in global disease activity (visit 2-visit 1) was −13 (range −69, 45). We found strong positive correlations between change in global and muscle disease activity and change in Type 1 IFN chemokine scores (see Table). These measures were correlated both before and after adjustment for medication use. Furthermore, decreasing levels of cytokines and chemokines were highly correlated with a decrease in disease activity, even after medication adjustment ($p<0.001$–0.009). No differences in results were seen between juvenile and adult DM subgroups.

Cytokine or Chemokine	N	Spearman Partial Correlation Coefficient After Adjustment for Medication Use (p-value) Global VAS	Muscle VAS	Extra-muscular VAS
IL-6	51	**0.39 (0.009)**	**0.49 (0.001)**	**0.31 (0.049)**
IP-10	51	**0.48 (0.001)**	**0.45 (0.003)**	**0.48 (0.002)**
ITAC	51	**0.42 (0.004)**	**0.53 (<0.001)**	**0.45 (0.003)**
MCP-1	51	**0.32 (0.032)**	**0.46 (0.002)**	**0.33 (0.036)**
IFNγ	50	−0.11 (0.48)	−0.26 (0.10)	−0.06 (0.72)
IL-1β	50	−0.22 (0.16)	−0.12 (0.47)	−0.14 (0.38)
IL-8	50	**0.37 (0.016)**	**0.50 (<0.001)**	0.31 (0.055)
TNFα	50	**0.32 (0.040)**	**0.48 (0.001)**	0.28 (0.085)
MCP-2	41	0.29 (0.095)	**0.51 (0.002)**	0.16 (0.39)
IFN gene score	49	0.26 (0.096)	**0.41 (0.007)**	0.19 (0.25)
IFN chemokine Score*	51	**0.50 (<0.001)**	**0.55 (<0.001)**	**0.52 (<0.001)**

* IFN chemokine score contains: IP-10, I-TAC and MCP-1.

Conclusion: Changes in whole blood Type I IFN gene and chemokine signatures, as well as in levels of T-cell cytokines IL-6, IL-8 and TNFa, are highly correlated with changing DM disease activity irrespective of medication use.

821

Pandemic Unadjuvanted Influenza A 2009 Vaccine in Adult Dermatomyositis and Polymyositis: Immunogenicity Independent of Therapy and No Harmful Effect in Disease. Samuel K. Shinjo[1], Maurício Levy Neto[1], Clovis A. Silva[1], Julio C. B. Moraes[1], Ana C. M. Ribeiro[1], Carla G.S. Saad[1], Nadia E. Aikawa[1], Alexander R. Precioso[2], Maria C.S. Timenetsky[3] and Eloisa Bonfa[1]. [1]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil, [2]Butantan Institute, Sao Paulo, Brazil, [3]Instituto Adolfo Lutz, São Paulo, Brazil

Background/Purpose: There are specific recommendations for influenza vaccination in systemic autoimmune diseases and the WHO recently recommended that the 2010–2011 trivalent seasonal flu vaccine must contain the A/California/7/2009 (H1N1) virus. The vaccine potential deleterious effect in adult dermatomyosisits (DM) and polymyositis (PM) and the influence of therapy in antibody response in these diseases has not been explored in our previous report (*Ann Rheum Dis*, 2011).

Methods: Fifty-eight patients (37 DM and 21 PM - Bohan and Peter's criteria, 1975) were gender and age-matched to 116 healthy controls. All subjects were vaccinated with a unadjuvanted influenza A/California/7/2009 (H1N1) strain and evaluated pre- and 21 days post-vaccination. Patients with fever, egg allergy, and autoimmune neurological diseases were not included. Antibody titers were evaluated by hemagglutination inhibition (HAI) assay. Percentage of seroprotection (titer ≥1:40) before and after immunization, and seroconversion (pre-vaccination titer <1:10 and a post vaccination HIA titer ≥1:40 or pre-vaccination titers ≥1:10 and a ≥ 4-fold rise post-vaccination) were calculated. Adverse events of vaccination were also analyzed. DM/PM muscle enzyme and scores (patient's visual analog scale (VAS), physician's VAS and MMT-8 (manual muscle strength score)) were evaluated before and after vaccination.

Results: Mean age (43.1±9.9 *vs*. 43.8±8.4 years, $P=0.607$) and frequency of female gender ($P=1.000$) were comparable in patients and controls with a mean DM/PM duration of 7.3±3.0 years. Seroprotection (72.4% *vs*. 84.5%, $P=0.058$) and seroconversion rates (72.4% *vs*. 78.5%, $P=0.377$) were similar in both groups. Of note, patients under glucocorticoids and/or immunosupressors (72.4%) also reached an adequate seroconversion rate (69.8% *vs*. 78.5%, $P=0.254$), including those 9 patients under prednisone ≥0.5mg/kg/day (88.9% *vs*. 78.5%, $P=0.254$). Disease activity and muscle parameters remained stable during the protocol (pre and post-vaccination): CK 224.1±209.0 *vs*. 242.1±256.9U/L, aldolase 5.8±5.9 *vs*. 5.8±5.4U/L, MMT-8 77.7±5.3 *vs*. 77.8±5.2, patient's VAS 9.5±0.9 *vs*. 9.5±0.9, physician's VAS 9.3±0.8 *vs*. 9.6±0.7 (all $P>0.05$) and seroconversion rate was similar to controls in eight patients with active disease (75.0 *vs*. 78.5%, $P=0.819$). The frequencies of minor local reactions (8.6 *vs*. 11.2%, $P=0.597$) and of mild systemic reactions (15.5 vs. 25.7%, $P=0.123$) were alike in patients and controls, without any report of severe side effects.

Conclusion: This prospective study of pandemic influenza A H1N1/2009 vaccination in DM/PM patients emphasizes its recommendation supported by novel evidence of its adequate immunogenicity in spite of therapy with no short-term harmful effect in disease itself (ClinicalTrials.gov number, NCT01151644).

822

CD28null T Cells From Myositis Patients Are Cytotoxic to Autologous Muscle Cells in Vitro. Paulius Venalis, Jayesh Pandya, Vanessa Stache, Gustavo Nader, Vivianne Malmström, Ingrid E. Lundberg and Andreas Fasth. Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) are chronic, rheumatic disorders characterized by muscle weakness, leading to disability. T cells have been implicated in the disease pathogenesis, but precise phenotype, function and specificity of these cells remain unclear. We have previously demonstrated that CD28null T cells dominate both in the affected muscle and peripheral blood of patients with myositis. These cells are apoptosis resistant, pro-inflammatory and potentially cytolytic. Here we have investigated whether CD28null T cells are directly cytotoxic to autologous muscle cells.

Methods: An autologous co-culture system was developed with peripheral blood cells and myotubes derived from three patients with definite DM or PM and with >10% of $CD4^+$ $CD28^{null}$ T cells in peripheral blood. Biopsy specimens were obtained from tibialis anterior muscle. Enzymatic digestion was performed for myoblast collection. Myoblasts cultures, showing 90% N-CAM positivity, were further differentiated into myotubes. PBMC were isolated by ficoll separation, and further into $CD4^+CD28^{null}$, $CD4^+CD28^+$, $CD8^+CD28^{null}$ and $CD8^+CD28^+$ T cell populations by flow cytometry. Before co culturing, myotubes were labeled with calcein and the autologous T cell subsets were stimulated with PHA. Co cultures were set at varying effector-target ratios. Supernatants were harvested after 24 hours, and calcein release was measured. The results are expressed as percentage of maximal lysis and were confirmed by morphological changes.

Results: We have assessed the potential of autologous CD28null T cells from both the CD4+ and CD8+ lineage to kill myotubes by cell mediated cytotoxicity. We have previously demonstrated that CD4+CD28null T cells from myositis patients contain perforin. Here, we investigated whether such T cells had direct cytolytic capability. Indeed CD4+28null showed 30.5±3.5% myocytotoxicity (in 2 out of 3 tested patients) in autologous 24h coculture (at effector-target ratio 10:1), whereas no significant cytotoxicity was observed in CD4+CD28+ population. We have also shown that CD8+CD28null T cells contain more perforin than CD8+CD28+ T cells and here we compared the

cytolytic capability of these populations. Myocytotoxicity was higher in CD8+CD28null than in CD8+CD28+ T cells, 15±5.3% versus 0.1±1.6% respectively (at 5:1 effector-target ratio, n=3). When increasing the effector-target ratio to 15:1 and 30:1 in CD8+CD28null compartment, the myocytotoxicity was further increased to 37% and 60% respectively.

Conclusion: Although we need to analyze more patients, we could demonstrate that CD28null T cells of both the CD4 and CD8 lineage can make use of their cytolytic granules and kill autologous myotubes derived from muscle biopsies of myositis patients. These T cells may contribute to loss of muscle fiber and as they are apoptosis resistant they may contribute to the chronicity of PM/DM disease.

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Role of MyD88-Dependent Toll-Like Receptor Signaling in a Murine Model of Histidyl-tRNA Synthetase-Induced Myositis. Lisa Harlow[1], Irina Fernandez[1], Yunjuan Zang[1], Makoto Soejima[2], Eric L. Greidinger[3] and Dana P. Ascherman[3]. [1]University of Miami Miller School of Medicine, Miami, FL, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Miami, Miami, FL

Background/Purpose: In previous work, we have demonstrated that IM immunization with Jo-1 induces exuberant muscle inflammation in multiple strains of mice. This phenotype does not require Jo-1-specific TCR recognition and can also occur in the absence of functional TLR4 signaling, suggesting the contribution of other non-TLR4-mediated signaling pathways of the innate immune system.

Objectives: To determine the contribution of toll-like receptor signaling in a murine model of myositis induced by intramuscular immunization with histidyl-tRNA synthetase (Jo-1)

Methods: To examine the potential role of innate signaling pathways beyond TLR4, we immunized B6.MyD88$^{-/-}$ and B6.TLR2$^{-/-}$ mice with a recombinant amino terminal fragment of murine Jo-1 fused to maltose binding protein (MA/MBP=amino acids 1–151 of murine Jo-1 linked to maltose binding protein) in the absence of exogenous adjuvant. At Day 17, we obtained quadriceps and hamstring muscle from euthanized mice for subsequent analysis of lymphocytic infiltrates in hematoxylin/eosin stained specimens. As a complement to this in vivo modeling, we assessed the capacity of our recombinant murine Jo-1 fragment and appropriate control proteins to activate TLR2 and TLR4 signaling through in vitro stimulation of TLR2 transfected 293 cells and Limulus Amebocyte Lysate testing, respectively.

Results: MA/MBP immunization of B6.MyD88$^{-/-}$ mice (n=7) failed to replicate the muscle inflammation previously demonstrated in parental C57BL/6 mice, implicating MyD88-dependent TLR signaling in this model system of Jo-1-induced myositis. In vitro assessment of Limulus Amebocyte Lysate activation demonstrated that recombinant Jo-1 proteins/fragments possess endotoxin-like activity (log order greater activity than MBP or the control autoantigen, 70 kDa RNP) capable of activating TLR4. At the same time, in vitro stimulation of TLR2 transfected 293 cells with different versions of recombinant Jo-1 revealed antigen-specific induction of IL-8 secretion relative to MBP and other recombinant autoantigens, supporting a potential role for this alternative MyD88-dependent signaling pathway in modulating the muscle inflammation detectable in the setting of functional TLR4 deficiency. Strikingly, however, IM immunization of B6.TLR2$^{-/-}$ mice (n=10) with MA/MBP yielded robust lymphocytic infiltration of muscle tissue relative to that generated in C57BL/6 WT mice—findings that paralleled the relationship between muscle inflammation induced in TLR4-deficient C3H/HeJ and WT C3H/HeOuJ mice.

Conclusion: Collectively, these results demonstrate that our model of Jo-1-induced myositis requires the TLR adaptor molecule MyD88, but is not absolutely dependent on either TLR2- or TLR4-mediated signaling cascades. Future assessment of TLR2$^{-/-}$/TLR4$^{-/-}$ double knockout mice will further clarify the apparent functional redundancy of these TLR systems (suggested by in vitro stimulation assays) and allow us to rule out the involvement of other, less likely MyD88-dependent TLR signaling pathways.

824

Clinical and Autoantibody Associations in Myositis Patients with Anti p155/140kDa Autoantibodies—a Multicenter European Study. Herman F. Mann[1], Lenka Plestilova[2], Hector Chinoy[3], Robert G. Cooper[4], Lara Dani[5], Ingrid E. Lundberg[5], Zoe Betteridge[6], Neil J. McHugh[7] and Jiri Vencovsky[2]. [1]Institute of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague 2, Czech Republic, [2]Institute of Rheumatology, Prague 2, Czech Republic, [3]The University of Manchester, Manchester, United Kingdom, [4]Hope Hospital, Salford, United Kingdom, [5]Karolinska Institutet, Stockholm, Sweden, [6]Royal National Hospital, Bath, United Kingdom, [7]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom

Background/Purpose: Malignancy is common among patients with dermatomyositis (DM). A novel myositis specific autoantibody (autoAb) directed against a 155/140 kDa (p155/140) protein has been reported in association with cancer associated DM. This study investigated anti-p155/140 antibodies in patients with idiopathic inflammatory myopathies from 3 European centers and the association with malignancy types and with the presence of other concurrent autoantibodies.

Methods: A multi-center cross sectional study of adult patients with IIM was performed as a part of ongoing collaboration within the EuMyoNet project. All patients fulfilled probable/definite criteria for IIM diagnosis according to the Bohan & Peter criteria. Six hundred and forty seven sera were tested for presence of various myositis specific and myositis associated autoAbs by immunoprecipitation using ^{35}S methionine labeled extracts from K562 leukemia cell line in a single facility (Bath, UK). Clinical data regarding IIM and malignancies were collected by treating physicians at the 3 participating sites (UK, S, CZ). Cancer associated myositis (CAM) was defined as cancer occurring in IIM patients within 3 years of disease onset.

Results: 40 patients (6.2%) (37 DM, 2 polymyositis and 1 with IIM/CTD□overlap syndrome) tested positive for p155/140. Patients were predominantly Caucasian (39) and mostly women (32/40). 17/40 p155/140 positive patients (all DM) developed cancer (6 breast, 3 ovarian, 2 bladder, 2 lymphatic tissue, 1 each in esophagus, gallbladder, uterus and unknown primary localization) within 3 years of IIM onset (4 prior, 8 after and 5 concurrent with IIM). In addition one patient had a history of colon cancer 10 years prior to first IIM symptoms. The subgroup of p155/140 positive CAM patients were compared to 16 p155/140 negative CAM patients (4PM, 12DM) from 2 participating sites (S, CZ). There was no difference in mean age at the onset of IIM (56.8±9.8 and 54.9±10.8 years, p=0.6), diagnosis of cancer (57.1±9.7 and 56.1±10.6 years; p=0.78) or sex (76% vs. 73% women) between p155/140 positive and negative groups. The type of malignancies did not differ between the two cancer groups.

Seventy-five percent of the p155/140 negative CAM patients had another myositis specific or associated autoAb (SAE 3x, Mi-2 2x, Jo-1 2x, p140 2x, SRP 1x, U1 RNP 1x, Ro 2x) whereas only 17.5 % of the p155/140 had another autoantibody (Ro 4x, U1RNP 2x, KS 1x, SRP 1x).

Conclusion: Prevalence of CAM in our p155/140 cohort (43%) was similar to that reported previously. Presence of the p155/140 autoantibody is not restricted to DM patients only, but the increased risk of cancer associated with p155/140 seems to be confined to the DM population. We were not able to identify any difference in terms of age of IIM or clinical presentations between p155/140 positive and negative CAM patients. In addition the p155/140 autoAb is not exclusive as some patients may have other, even myositis specific autoAb, at the same time.

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ACR Concurrent Abstract Session
Osteoarthritis - Clinical Aspects I
Sunday, November 6, 2011, 4:30 PM–6:00 PM

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Heritability and Linkage of Radiographic Progression of Hip and Knee Osteoarthritis: Results From the Longitudinal Component of the Genetics of Generalized Osteoarthritis Study. Michelle S. Yau[1], Laura Yerges-Armstrong[1], Michael Doherty[2], Marc Hochberg[1], Joanne M. Jordan[3], Virginia Byers Kraus[4], Braxton Mitchell[1], A. G. Wilson[5] and GOGO Investigators[6]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]City Hospital, Nottingham, United Kingdom, [3]UNC Thurston ARC, Chapel Hill, NC, [4]Duke University Medical Center, Durham, NC, [5]Sheffield Uni /Medical School, Sheffield, United Kingdom, [6]Durham

Background/Purpose: Understanding the role of genetics in the progression of osteoarthritis (OA) may help identify biological mechanisms, potential treatments, and individuals at risk for rapid progression of OA. Using data from the Genetics of Generalized Osteoarthritis (GOGO) study, we 1) assessed heritability of radiographic progression of OA and 2) used genome-wide linkage analysis to identify susceptibility loci for progression of OA.

Methods: OA of the hip and knee were analyzed separately for progression. Progression was defined as an increase in Kellgren-Lawrence

(KL) grade, osteophyte score or joint space narrowing (JSN) score, or decline in minimum joint space width (mJSW) >= 0.1 mm/year. We assessed heritability of baseline mJSW and rate of change in mJSW (mm/year) in the lateral and medial compartments of the left and right knees, and left and right hip, using a variance components approach as implemented in SOLAR. Age, gender, and their interaction were included as covariates in the models. We used MERLIN for the non-parametric linkage analysis of hip and knee OA progression based on 1115 microsatellite markers. Prior to linkage analysis, Mendelian inconsistencies and unlikely recombinations were detected and corrected using PedCheck and MERLIN.

Results: A total of 1374 and 1381 individuals with a mean follow-up of 3 years were included in the hip and knee OA progression analyses, respectively. There was significant heritability ($P < 0.01$) of baseline mJSW at the hip (40–42%) and medial knee compartment (27–31%), but not the lateral knee compartment. Heritability of the rate of change in mJSW was significant at the hip (25–26%) but not in either knee compartment. There was significant evidence for linkage to progression of hip and knee OA on the X chromosome (hip: peak LOD=2.71 at 92cM; knee: peak LOD=5.52 at 110cM). Potential candidate genes in this region include *DIAPH2*, which may play a role in the development and function of ovaries; *IL1RAPL2*, an interleukin-1 signaling accessory receptor; *CHRDL1*, an antagonist of bone morphogenic protein 4; *PAK3*, which may be involved in focal adhesion and T cell receptor signaling pathways; *CAPN6*, which may regulate microtubule dynamics and cytoskeletal organization; *AMOT*, which may play a role in tight junction maintenance via a complex formed with ARHGAP1; *PGRMC1*, a putative membrane-associated progesterone steroid receptor; *IL13RA1* and *IL13RA2*, interleukin-13 receptors that may mediate activation of JAK1, STAT3, and STAT6; *NKAP*, an NF$\kappa\beta$ activating protein; *NKRF*, an NF$\kappa\beta$ repressing factor; and *SLC6A14*, an amino acid carrier that may be associated with X-linked obesity.

Conclusion: Heritability analyses show that mJSW at both the hip and knee and change in mJSW at the hip have a genetic component. However, hip mJSW and its rate of change are more heritable than knee mJSW, suggesting that progression of knee OA may be more susceptible to environmental factors than hip OA. Linkage analyses revealed several susceptibility loci present on chromosome X, suggesting involvement of bone morphology, sex hormones, inflammation and obesity in OA progression. Further work will interrogate susceptibility regions and determine how various pathways may interact to cause OA progression.

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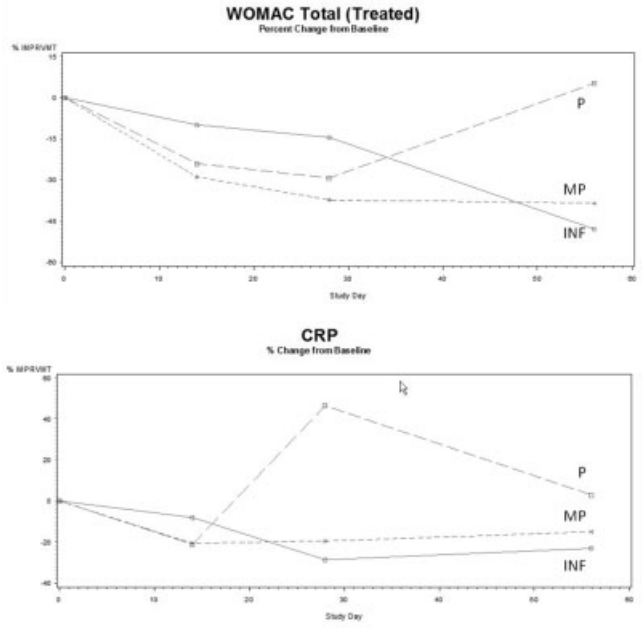
Treatment of Knee Osteoarthritis with Intraarticular Infliximab May Improve Knee Function and Reduce Synovial Infiltration by Macrophages. Jeremy R. Schue[1], Ossama Tawfik[1], Donald D. Smith[1], Gary Hinson, Rebecca Bolce[3], Jo A. Wick and Herbert B. Lindsley[1]. [1]Kansas University Med Ctr, Kansas City, KS, [2]Janssen Services, LLC, Horsham, PA

Background/Purpose: Synovial tissue from patients with early osteoarthritis (OA) demonstrated higher levels of inflammation than from late OA (Benito et al. Ann Rheum Dis 2005). We hypothesized that a single intraarticular (IA) injection of an anti-TNF drug would result in decreased inflammatory cell infiltration and ultimately reduce articular injury.

Methods: This study was single center, 2:1:1 [INF:MP:P] randomization, double-blind, placebo-controlled treatment of knee OA with IA treatments of infliximab (INF) 100 mg, methylprednisolone (MP) 80 mg or saline (P) on Day 0. Subjects (n=16) had to have knee pain and show minimal to moderate osteoarthritic change on plain radiographs. Closed needle synovial biopsies (Bx) were taken from the suprapatellar pouch on Days 0 and 28 and assessed for reduction in inflammation. Changes in categorical variables (scored 0 to 3) were calculated and the proportions of observed decreases were compared between groups using Fisher's Exact tests. Differences in continuous measures between groups were assessed using Wilcoxon tests.

Results: The median Total WOMAC score improved between Day 0 and 28 in all three groups and then declined in the P group (Fig 1). The INF and MP groups trended better than the P group, with MP showing more improvement initially and INF delayed benefit. The median CRP (Fig 2; baseline values = 0.57–1.21 mg/dl) for MP and P declined by Day 14; MP reached a plateau Days 14– 56, whereas Group P exceeded baseline (Days 28, 56). INF reached a plateau by Day 28. Of the 3 groups INF had the greatest % improvement at Day 56 for WOMAC and CRP. Synovial tissue showed reduction in two markers: CD68 macrophages (3 of 7 Bx INF) and CD54 ICAM-1 (2 of 4 Bx MP). Otherwise there was no reduction in inflammation for the remaining markers in any group; these included fibrosis, TNFα, IL-1β, IL-6, IL-17, CD56, CD68, CD3, and CD25. Flow cytometric studies of PBMCs at Days 0 and 28 showed reduced numbers of INF subjects with TNF-expressing CD20 B cells and high-MFI CD14 monocytes; likewise total low-MFI monocytes were reduced (p=0.07) in INF.



Conclusion: In this pilot study the Total WOMAC score showed early persisting improvement in MP and delayed improvement in INF, compared to transient improvement seen in P. The two anti-inflammatory treatments reduced CRP levels mildly. There was no statistical difference between baseline and post-treatment values in WOMAC, CRP or synovial tissue scoring. However, both INF and MP showed a trend in improvement both in knee function (WOMAC) and in CRP reduction.

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Prolonged Improvement of Clinical Status and Structural Cartilage Tissue Repair by Joint Distraction in Treatment of End-Stage Knee Osteoarthritis; The 2 Years Follow-up Data. Karen Wiegant[1], Femke Intema[1], Peter van Roermund[1], Anne C. A. Marijnissen[2], Sebastian Cotofana[3], Felix Eckstein[3], SC Mastbergen[2] and Floris Lafeber[1]. [1]University Medical Centre Utrecht, Utrecht, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]Paracelsus Medical University, Salzburg, Austria

Background/Purpose: Knee joint distraction (KJD) is a new treatment for end-stage osteoarthritis (OA) of the knee that temporarily unloads the femorotibial cartilage and subchondral bone. This technique was previously shown to be clinically effective at 1 year follow-up. Clinical improvement coincided with the significant increase of joint space width. The current study provides 2 year follow-up results on the effect of KJD.

Methods: The open, uncontrolled study included 20 patients (age 49±6 years; 11 females) with knee OA, considered for total knee replacement. Patients were treated with KJD for 2 months. The study was approved by the medical ethical committee (METC) of the University of Utrecht and all patients gave written informed consent. Two monotubes with internal coil springs were placed parallel, bridging the knee joint, creating a distance between both cartilage surfaces of 5 mm, confirmed by X-ray. Patients were encouraged to load the knee during distraction, in order to attain intermittent intra-articular fluid pressures.

The primary clinical outcome parameter was pain and function by use of the 'Western Ontario McMasters University Index' (WOMAC) questionnaire, with a visual analoge pain score (VAS) as secondary outcome. The primary structural outcome was minimal joint space width (JSW) on semi-flexed, anterior-posterior, weight bearing radiographs analyzed by digital interactive computer analysis (KIDA). Secondary structural outcomes were quantitative MRI parameters of cartilage morphology, analyzed by Chondrometrics Gmbh (Ainring, Germany). Additionally, biomarkers for

synthesis (sPIIANP) and breakdown (uCTXII) of collagen type II were evaluated.

Results: Total WOMAC score increased from 45%±3.6 at baseline to 78%±4.8 ($p<0.000$) and the VAS pain score decreased from 73±2.1 at baseline to 28±6.0 mm ($p<0.000$). The clinical improvement coincided with structural tissue changes: the minimum JSW increased from 1.0±0.3 to 1.8±0.3 mm ($p<0.03$) and quantitative MRI analysis showed an increase in cartilage thickness over total subchondral bone area (ThCtAB) of the most affected compartment (from 2.4±0.1 at baseline to 2.8±0.1 mm; $p<0.05$) and a decrease of the percentage of subchondral bone area that was denuded (dABp: change from 22±5 at baseline to 8±2%; $p<0.004$). MRI and X-ray changes were moderately correlated ($r=0.67$ $p<0.000$). Biomarker analysis shows that from 6 months post-treatment to 2 years follow-up, the average change in the ratio of PIIANP / CTXII changed in favor of collagen type II synthesis ($p<0.003$).

Conclusion: Joint distraction results in significant improvement in the clinical (pain, already 1 month after treatment) and structural (cartilage) status in end-stage knee OA which is sustained for at least 2 years. MRIs suggest an increase in cartilage thickness and covering of denuded areas in comparison with baseline values. The mechanical competence of the formed tissue is suggested by increased JSW of weight-bearing X-ray, and the hyaline nature by collagen type II biomarker analysis. At present, distraction therapy appears to be the first treatment that can reverse cartilage damage in end-stage knee osteoarthritis accompanied by significant clinical improvement.

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Efficacy of Tanezumab Compared with Non-Steroidal Anti-Inflammatory Drugs in Patients with Knee or Hip Osteoarthritis (NCT00809354). Yusuf Yazici[1], Evan F. Ekman[2], H. Scott Greenberg[3], Michael D. Smith[3], Mark T. Brown[3], Christine R. West[4] and Kenneth M. Verburg[3]. [1]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY, [2]Southern Orthopaedic Sports Medicine, Columbia, SC, [3]Pfizer, Groton, CT, [4]Pfizer, Williamston, MI

Background/Purpose: A phase III study evaluated efficacy & reported on safety events of intravenous (IV) tanezumab (Tzb), a monoclonal antibody that inhibits nerve growth factor & reduces osteoarthritis (OA) pain, alone or combined with non-steroidal anti-inflammatory drugs (NSAID) versus NSAID alone.

Methods: Patients with moderate to severe knee or hip OA experiencing only partial symptomatic relief with NSAID received oral naproxen 500 mg BID, oral celecoxib 100 mg BID, Tzb (5 or 10 mg, IV every 8 weeks), or Tzb (5 or 10 mg, IV every 8 weeks) combined with naproxen 500 mg BID or celecoxib 100 mg BID. Co-primary efficacy endpoints (Western Ontario & McMaster Universities OA Index [WOMAC] Pain subscale, WOMAC Physical Function subscale, & Patient Global Assessment [PGA] of OA) were assessed at Week 16 versus naproxen or celecoxib. Long-term safety of Tzb alone & in combination with NSAID was evaluated up to Week 56.

Results: Tzb alone or with NSAID provided significantly greater improvement in WOMAC Pain & Physical Function subscales than naproxen & celecoxib alone ($p\leq0.015$; Table). For PGA, Tzb 10mg + naproxen, Tzb 10mg + celecoxib & Tzb 5mg + celecoxib provided significantly greater improvement versus NSAID alone, but improvements with Tzb alone & Tzb 5mg + naproxen were not statistically significant. The general safety profile was similar to previous Tzb trials, although incidence of adverse events (AEs) was higher likely due to longer treatment. Overall incidence of AEs & withdrawals due to AEs were higher with Tzb alone (ranges 74–75% & 12–16%, respectively) or Tzb with NSAID (ranges 73–74% & 14–18%) than NSAID alone (68% & 9%). Overall incidence of serious AEs was higher in Tzb + NSAID (range 10–12%) than either Tzb (8–9%) or NSAID alone (9%), which had similar rates. Differences in crude incidence of reported osteonecrosis or all-cause total joint replacement were not statistically significant for Tzb groups versus NSAID. Statistically significant risk increases for rapidly progressive OA were observed with Tzb (Tzb alone: 0.94–1.69/100 patient-years; Tzb + NSAID: 2.13–3.12/100 patient-years) versus NSAID alone (0.24/100 patient-years). Mean reduction in medial joint space was greater with Tzb versus NSAID alone; differences vs. NSAID alone were statistically significant for Tzb alone in knee patients and for Tzb 5 mg + NSAID for hip patients. A higher proportion of Tzb-treated patients reported AEs of abnormal peripheral sensation than with NSAID alone, but the majority of patients had no new or worsened abnormalities at final neurologic examination.

Table

	Naproxen cohort					Celecoxib cohort				
	Tzb 5 mg (n=265)	Tzb 10 mg (n=268)	Tzb 5 mg + naproxen 500 mg BID (n=280)	Tzb 10 mg + naproxen 500 mg BID (n=288)	Naproxen 500 mg BID (n=263)	Tzb 5 mg (n=256)	Tzb 10 mg (n=254)	Tzb 5 mg + celecoxib 100 mg BID (n=256)	Tzb 10 mg + celecoxib 100 mg BID (n=254)	Celecoxib 100 mg BID (n=256)
WOMAC Pain*										
Baseline, mean ± SD	6.39±1.61	6.50±1.57	6.52±1.65	6.33±1.65	6.32±1.64	6.48±1.55	6.44±1.53	6.41±1.66	6.27±1.64	6.29±1.60
Week 16 LS Mean Change ± SE	-1.88±0.14	-2.02±0.14	-2.13±0.14	-2.36±0.14	-1.44±0.14	-2.02±0.16	-2.05±0.16	-2.22±0.16	-2.41±0.16	-1.47±0.15
Difference vs NSAID (95% CI)	-0.45 (-0.81, -0.09)	-0.58 (-0.94, -0.23)	-0.70 (-1.06, -0.33)	-0.92 (-1.28, -0.57)		-0.55 (-0.95, -0.15)	-0.58 (-0.98, -0.18)	-0.75 (-1.15, -0.35)	-0.94 (-1.34, -0.54)	
P-value	0.015	0.001	<0.001	< 0.001		0.007	0.004	<0.001	< 0.001	
WOMAC Physical Function*										
Baseline, mean ± SD	6.46±1.72	6.47±1.61	6.57±1.67	6.39±1.62	6.32±1.62	6.67±1.66	6.58±1.58	6.57±1.72	6.39±1.62	6.47±1.59
Week 16 LS Mean Change ± SE	-1.86±0.13	-1.90±0.13	-2.16±0.14	-2.26±0.13	-1.38±0.13	-2.05±0.15	-2.04±0.15	-2.22±0.15	-2.42±0.15	-1.42±0.15
Difference vs NSAID (95% CI)	-0.48 (-0.83, -0.13)	-0.52 (0.87, -0.17)	-0.78 (-1.13, -0.43)	-0.88 (-1.23, -0.53)		-0.63 (-1.02, -0.24)	-0.63 (-1.02, -0.24)	-0.81 (-1.20, -0.42)	-1.01 (-1.40, -0.62)	
P-value	0.007	0.003	<0.001	< 0.001		0.002	0.002	< 0.001	<0.001	
PGA*										
Baseline, mean ± SD	3.39±0.63	3.41±0.62	3.39±0.63	3.39±0.63	3.39±0.63	3.44±0.65	3.48±0.63	3.45±0.67	3.81±0.64	3.37±0.59
Week 16 LS Mean Change ± SE	-0.54±0.05	-0.61±0.05	-0.62±0.05	-0.72±0.05	-0.54±0.05	-0.67±0.05	-0.59±0.05	-0.74±0.05	-0.75±0.05	-0.54±0.05
Difference vs NSAID (95% CI)	-0.00 (-0.14, 0.13)	-0.06 (-0.22, 0.06)	-0.08 (-0.22, 0.06)	-0.18 (-0.32, -0.05)		-0.13 (-0.27, 0.00)	-0.06 (-0.20, 0.08)	-0.20 (-0.34, -0.06)	-0.21 (-0.35, -0.08)	
P-value	0.961	0.251	0.251	0.006		0.057	0.414	0.004	0.002	

LS Mean, least squares mean; PGA, Patient Global Assessment; SD, standard deviation; SE, standard error; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; *WOMAC subscales were assessed on a 0-10 numerical rating scale & PGA was assessed on a 5-point Likert scale; baseline observation carried forward imputation was used for missing data.

Conclusion: Tzb alone or combined with NSAID resulted in greater improvement in pain & physical function than NSAID alone. An increased risk of rapidly progressive OA, particularly for Tzb combined with NSAIDs was noted. No other new safety signals emerged when Tzb was combined with naproxen or celecoxib; however a false negative result cannot be ruled out.

829

Osteoarthritis Is Related to An Increased Risk of Falls and Fractures: A Prospective Multinational Cohort Study (the GLOW study). Daniel Prieto-Alhambra[1], Xavier Nogués[2], M. Kassim Javaid[3], Nigel K. Arden[3], Cyrus Cooper[4], Allison Wyman[5], Adolfo Díez-Pérez[6] and GLOW Investigators. [1]URFOA-IMIM, Parc de Salut Mar; Idiap Jordi Gol i Gurina-Institut Català de la Salut; Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK, Barcelona, Spain, [2]Hospital del Mar-IMIM, Universitat Autònoma de Barcelona, Barcelona; and RETICEF, ISCIII Madrid; Spain, Barcelona, United Kingdom, [3]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK, Oxford, United Kingdom, [4]Southampton General Hospital, Southampton, United Kingdom, [5]Center for Outcomes Research, UMass Medical School, Worcester, MA, [6]Hospital del Mar-IMIM, Universitat Autònoma de Barcelona, Barcelona; and RETICEF, ISCIII Madrid; Spain, Barcelona, Spain

Background/Purpose: Although patients with osteoarthritis (OA) have increased bone mass, no corresponding decrease in fractures has been observed. We therefore studied the association between OA and incident falls and fractures in postmenopausal women.

Methods: The Global Longitudinal Study of Osteoporosis in Women (GLOW) is a prospective, multinational, observational cohort study. Practices that were typical of each region were identified through primary care networks organized for administrative, research, or educational purposes. Non-institutionalized women aged ≥55 years who visited a practice within the previous 2 years were eligible. A total of 60,393 women agreed to participate. Participants were mailed a self-administered questionnaire at baseline; follow-up questionnaires were sent at 12-month intervals for 3 years. Patients were classified as having OA or not according to their answer to the following question in the baseline survey: "Has a doctor or other health provider ever said that you had osteoarthritis or degenerative joint disease?" Information on incident falls and fractures, and potential confounders were self-reported by participants. For this analysis, women with missing baseline OA or fracture information, as well as those with celiac disease or rheumatoid arthritis, were excluded. The cumulative fracture incidence was calculated by the Kaplan-Meier method. Unadjusted and multivariable Cox models for incident fractures and falls were used to compute hazard ratios (HRs) according to baseline OA status. A Kaplan-Meier curve was computed on the subset of women with complete follow-up data.

Results: Of 51,386 women who were followed up for a median time of 1072 days (interquartile range 772 to 1095 days), 20,409 (39.7%) were classified as having OA. The unadjusted HR for fracture among OA patients was 1.40 (95% CI 1.32–1.48; $p<0.0001$), and this remained significant after multivariable adjustment (HR 1.21; 95% CI 1.13–1.30; $p<0.0001$; Figure). Falls were also more likely in women with OA (adjusted HR 1.27; 95% CI 1.23–1.30; $p<0.0001$). The association between OA and fracture remained significant even after adjusting for baseline falls (HR 1.16; 95% CI 1.08–1.25; $p<0.0001$).

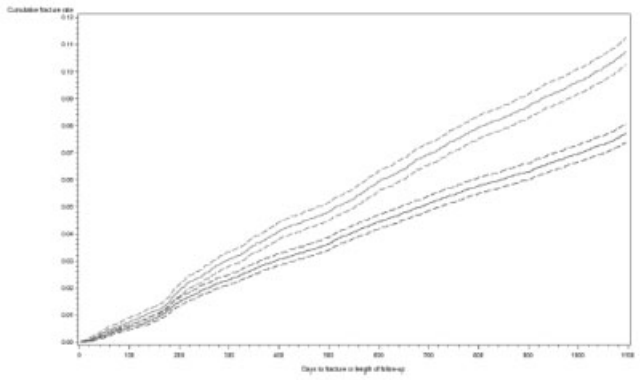

Figure 1. Kaplan-Meier curve predicting fracture by year 3, by baseline OA status, with 95% CIs (women with all 4 years of survey data only, n = 40132).

Conclusion: Postmenopausal women with OA have a 20% higher risk of fracture and experience almost 30% more falls than those without OA. Although incident falls may partially explain the increased risk of fracture observed in women with OA, our data suggest that the association between OA and fracture is independent of the number of falls.

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Association of Candidate Single Nucleotide Polymorphisms with Radiographic Knee Osteoarthritis in African-Americans: Data From the Genetic Components of Knee Osteoarthritis Study. Rebecca Jackson[1], Changwan (Larry) Lu[2], Laura Yerges-Armstrong[2], David Duggen[3], Marc Hochberg[2], Braxton Mitchell[2] and OAI Investigators[4]. [1]Ohio State University, Columbus, OH, [2]University of Maryland School of Medicine, Baltimore, MD, [3]TGen, Pheonix, AZ, [4]San Francisco

Background/Purpose: Most genetic epidemiology studies in osteoarthritis (OA) have been conducted in either Asian or Caucasian populations. To our knowledge, no data from extension of these genetic association studies to African-American populations have been published. We used data from the African American subjects enrolled in the Genetic Components of Knee Osteoarthritis (GeCKO) Study to examine associations between radiographic knee OA (RKOA) and 13 single nucleotide polymorphisms (SNPs) previously reported to be associated with RKOA with odds ratios (OR) ranging from 1.15 to 6.6 (see Valdes AM, Spector TD: Nat Rev Rheumatol 2011;7:23–32).

Methods: 666 African American participants from the GeCKO Study, a genome wide association study (GWAS) using biospecimens from participants enrolled in the Osteoarthritis Initiative (OAI), with complete genotype and phenotype information were included in this analysis. Cases (n=446) had at least one knee with definite RKOA, defined as the presence of definite osteophytes (OARSI grade $\geq$1) regardless of the presence of joint space narrowing. Controls (n=220) were free of RKOA in both knees (i.e., both osteophyte and joint space narrowing grade = 0). Genotyping was completed on the Illumina 2.5M platform as part of the larger GWAS of OAI participants. Nine of the 13 previously reported SNPs were available on this platform for extension analysis. Association results for these individual SNPs were calculated using logistic regression with adjustment for age and sex; results were considered nominally significant with a p-value $<$ 0.05.

Results: Cases were slightly older (mean age 60.4 vs. 56.9 years) and more often female (69.9% vs. 64.5% women) than controls. Assuming a nominal α of 0.05, we estimated that our sample had 80% power to detect an OR of at least 1.22 for a SNP with a minor allele frequency (MAF) of 40% or an OR of at least 1.46 for a SNP with a MAF of 5%. Of the nine previously reported SNPs available for extension analyses, only one SNP, rs419598, was nominally associated with RKOA (P = 0.02). This is a synonymous coding variant in the Interleukin 1 Receptor Antagonist (*IL1RN*) gene that has been reported previously as associated with RKOA severity in Caucasian populations. The OR for association with RKOA in African Americans in the GeCKO study was 0.59 compared to an observed OR of 0.22 for severe knee OA, defined as KL grade 3–4, in 130 Caucasian individuals (Attur M, et al: Ann Rheum Dis 2010;69:856–61).

Conclusion: This preliminary extension study in African American subjects participating in the OAI GWAS provides evidence of genetic association of RKOA in the IL1RN gene region, but was unable to replicate many other previously reported genetic associations. The lack of association with many previously reported SNPs may be due to low power or to differences in allele frequency and/or linkage disequilibrium structure between African Americans and Asians/Caucasians. Future work in larger, ethnically diverse populations to extend previous findings and refine association signals is still needed, as is study of novel association patterns detectable only in African Americans.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Animal Models I
Sunday, November 6, 2011, 4:30 PM–6:00 PM

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Nanoparticle Encapsulated STAT1 siRNAs Induce Regression of Established Collagen Arthritis In Mice. Robert I. Scheinman, Ruchit Trivedi and Uday Kompella. University of Colorado Denver, Aurora, CO

Background/Purpose: Disease progression in Rheumatoid Arthritis (RA) is driven by a network of cytokines promoting the interactions between synovial cells and infiltrating immune cells. Macrophages represent a key cell type within the arthritic joint space, against which, no therapeutic has specifically been targeted. This cell is attractive in that it serves as a major source of cytokines such as TNFα and also functions as a source of antigen for the activation of lymphocytes. Nano-carrier systems such as functionalized polymeric nanoparticles are being explored for the targeted delivery of therapeutics to specific tissues. Here we attempted to design a functionalized nanoparticle with increased uptake properties in diseased joints. Hypothesizing that these nanoparticles would be preferentially taken up by phagocytic cells, we loaded them with an siRNA pool targeting STAT1 and explored the consequences of administration of this therapeutic to mice with developing or established disease. Knockdown of STAT1 in macrophages would be predicted to decrease IFNγ mediated events such as priming.

Methods: The FDA approved polymer; poly(lactic-co-glycolytic acid) (PLGA) was used to encapsulate either a pool of STAT1 targeted siRNAs, a non-targeting siRNA, or one of several tracking molecules using the water/oil/water emulsion method. Nanoparticles were functionalized by conjugating some of the polymers to a peptide containing an RGD domain which binds to $\alpha_v b_3$ integrins. Mice were made arthritic by either the Collagen Induced Arthritis (CIA) protocol or the Collagen Antibody Induced Arthritis (CAIA) protocol. Nanoparticles were introduced by weekly tail vein injections. Mice were assessed for disease. Upon sacrifice, tissues were obtained and assessed for nanoparticle uptake, disease measures, flow cytometry, and mRNA levels.

Results: Nanoparticles containing siRNA or Nile Red were 100 – 200 nm in diameter as measured by transmission electron microscopy. The RGD peptide was present at the surface of the nanoparticles as measured by changes in the zeta (surface) potential. Inclusion of the RGD integrin binding domain increased uptake in arthritic paw tissues by 10 – 20 fold. Nanoparticles were taken up by macrophages as measured by flow cytometry and by immunohistochemistry. STAT1 siRNA containing nanoparticles were effective in decreasing disease while empty nanoparticles and non-targeting siRNA loaded nanoparticles had no effect on disease progression. Remarkably, even when administered after disease was well established, STAT1 siRNAs effected a regression of swelling and redness. Analysis of mRNA levels demonstrated a reduction in STAT1 mRNA in tissues and suggested an increase in IL-10 signaling.

Conclusion: We have successfully delivered siRNAs to arthritic joint tissue using functionalized nanoparticles. Knock down of STAT1 stops disease progression and in some instances promotes disease regression. The data suggests that the mechanism is via the modulation of the activation state of macrophages, and possibly, dendritic cells.

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Identification of Microrna-221, −222 and −323-3p Association with Rheumatoid Arthritis Via Predictions Using the Human TNF Transgenic Mouse Model. Ioannis Pandis[1], Caroline Ospelt[2], Niki Karagianni[3], Maria C. Denis[4], Martin Reczko[5], Artemis Hatzigeorgiou[5], Jiannis Ragoussis[6], Steffen Gay[2] and George Kollias[1]. [1]Institute of Immunology, Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece, [2]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [3]Institute of Immunology, Biomedical Sciences Research Center 'Alexander Fleming' and Biomedcode Hellas SA, Vari, Greece, [4]Biomed-Code Hellas SA, Vari, Greece, [5]Institute of Molecular Oncology, Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece, [6]Institute of Molecular Biology & Genetics, Biomedical Sciences Research Center 'Alexander Fleming' and Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom

Background/Purpose: Molecular alignment of animal models to their corresponding human disease is essential for basic understanding of biological mechanisms, the identification and validation of novel pathogenic pathways and the evaluation of diagnostic and therapeutic agents. MicroRNAs (miRs) have been found dysregulated and functionally involved in many inflammatory diseases, including rheumatoid arthritis (RA). In this study we sought to discover novel miRs associated with RA pathogenesis exploiting the predictive value of the human TNF transgenic (TghuTNF, Tg197) mouse model.

Methods: Mouse synovial fibroblasts (SFs) were isolated from fully diseased 8-week-old TghuTNF and wild type (WT) littermate mice and human SFs from RA and osteoarthritis (OA) patients. Total SF RNA was isolated using the mirVana™ miR Isolation Kit (Ambion). TghuTNF SF miR expression was determined via small RNA sequencing using an Illumina platform. Individual microRNA quantitation in human and mouse SFs was achieved via qRT-PCR based TaqMan microRNA assays.

Results: miR sequencing showed that TghuTNF SFs, a key cell type mediating RA pathogenesis, exhibit a significantly distinct miR expression profile with 12 upregulated and 16 downregulated miRs, compared to WT SFs. miRs 223, 146a, 221, 222, 155 and 323-3p were upregulated and miRs 322 and 335 downregulated in TghuTNF SFs in qRT-PCR validation assays. These results showed a high degree of correlation with sequence-based measurements ($R^2=0.954$, $p<0.0001$), indicating that the profile is highly quantitative. Several miRs have been reported in the literature to be dysregulated in human RA patient SFs, namely miR-124 (downregulated) and miRs 203, 155, 146a (upregulated) compared to OA SFs. miRs 155 and 146a have also been found to be induced by TNF in human RA SFs. Markedly, both TNF induced miRs 146a and 155 are also found upregulated in the TghuTNF mouse, suggesting that TghuTNF SFs align well with human RA SFs. Most notably, of the remaining validated miRs of the mouse profile, miR-221, miR-222 and miR-323-3p were also found to be significantly upregulated in RA SFs vs OA SFs, indicating that the TghuTNF model can be used effectively to predict previously unidentified miR dysregulations in human RA SFs.

Conclusion: Our comparative analysis of the TghuTNF miR profile with human patient data identified three novel miRs (miR-221, miR-222 and miR-323-3p) to be associated with human RA. Moreover, our results confirm that the TghuTNF model is a valuable predictive tool to study TNF-driven biology in RA SFs and propose novel modifiers and biomarkers with relevance to human disease.

833

Why p38 Inhibitors Are Ineffective in Rheumatoid Arthritis (RA): Increased Pro-Inflammatory Macrophage Function. Monica Guma, Deepa Hammaker, Meghan Edgar, Katharyn Topolewski, Mary Corr and Gary S. Firestein. UCSD School of Medicine, La Jolla, CA

Background/Purpose: p38 inhibitors have limited benefit in RA. One explanationfor this unexpected observation could be related to anti-inflammatory functionsof p38a in macrophages. For example, p38a inhibitors suppressexpression of IL-10 and the phosphatase DUSP1. Low DUSP1 expression couldprolong activation of other MAP kinases. Therefore, we determined if selective deletionof p38a in macrophages affectsseverity of arthritis in the passive K/BxN mouse model of arthritis. Wealso determined whether blocking upstream kinases in the p38 pathway mightavoid the limitations of traditional p38a inhibitors.

Methods: Wildtype (WT) and mice with selective deletion of p38ain macrophages ($p38a^{dM}$; p38adeletion using Cre/lysozyme M promoter) were injected with K/BxN sera once orweekly to induce acute or chronic arthritis, respectively. Joint extracts wereevaluated by ELISA, qPCR, and Western blot (WB). WT, MKK3, and MKK6-deficientbone marrow derived macrophages (BMDM) were stimulated with LPS and evaluatedby ELISA, qPCR, and WB.

Results: $p38a^{dM}$ mice had higher clinical scores and a delay inarthritis resolution compared with WT mice. In the acute model, day 8 scoreswere 6.8 ± 1.2 and 9.75 ± 0.1 andday 14 scores were 1.1 ± 0.3 and 3 ± 0.3($p=0.01$) for WT and $p38a^{dM}$ mice, respectively. In the chronic model (Fig 1), scores were persistently higher in $p38a^{dM}$mice (day 28 5.2 ± 1.6 and 10.2 ± 1.1,$p=0.05$, for WT and $p38a^{dM}$ mice, respectively). On day 5, DUSP1 mRNAexpression was lower and ERK phosphorylation was higher in inflamed $p38a^{dM}$ joints. On day 28 in the chronicmodel, IL-1b protein levels were 1.5 fold higherin inflamed $p38a^{dM}$ joints compared with WT joints ($p=0.02$). For in vitro experiments,LPS-stimulated IL-10 and IL-6 expression in p38inhibitor (SB203580)-treated BMDM was decreased by 80% and 50%, respectively.DUSP1 expression was also decreased by 50%, which was accompanied by persistentJNK and ERK phosphorylation. LPS stimulated MKK6 and MKK3-deficient BMDMalso had suppressed IL-6 expression but surprisingly, had normal IL-10production, DUSP1 expression, and JNK and ERKphosphorylation. In contrast to $p38a^{dM}$ mice, WTchimeric mice with either MKK6 or MKK3-deficient bone marrow had markedlydecreased severity of passive K/BxN arthritis.

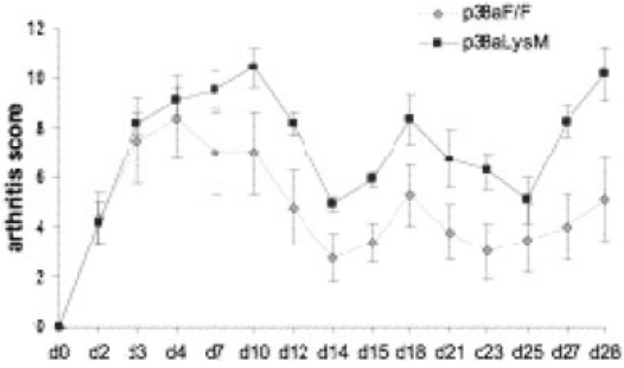

Figure 1. Chronicpassive K/BxN model in WT (p38aF/F)and $p38a^{dM}$mice

Conclusion: Selective deletion of p38a in macrophages increases inflammatory arthritis in mice bysuppressing anti-inflammatory feedback loops like IL-10 and DUSP1 expression.Targeting p38 in a disease like RA dominated by macrophage cytokines couldparadoxically interfere with anti-inflammatory pathways and lead to increaseddisease severity. Alternatively, targeting an upstream kinase that regulatesp38 could be more effective by suppressing pro-inflammatory cytokineswhile sparing IL-10 expression and preventing increased ERK/JNK activation.

834

Superior Efficacy of Ozoralizumab, An Anti-Human TNF Nanobody in a Transgenic Mouse Model of Polyarthritis. Martin Hegen[1], Els Beirnaert[2], Guy Hermans[2], Peter Casteels[2], Marina Shen[1], Julie Lee[1], Lori Fitz[1], Nilufer Seth[1], Yulia Vugmeyster[1], Christopher Wrocklage[1], Kyri Dunussi-Joannopoulos[1], Cheryl L. Nickerson-Nutter[1] and Mary Collins[1]. [1]Pfizer, Cambridge, MA, [2]Ablynx nv, Zwijnaarde, Belgium

Background/Purpose: Tumor necrosis factor (TNF) is expressed as a trimeric transmembrane protein that can be proteolytically cleaved by TNF converting enzyme to release its soluble form. Both forms of TNF interact with TNF receptor (TNFR) 1 and TNFR 2. Inhibition of TNF has been shown

to be an effective treatment of Rheumatoid Arthritis (RA). Nanobodies are antibody-derived single domain antigen binding therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies derived from camelids. They have a high degree of sequence and structural homology to human immunoglobulin variant heavy chain domains. The aim was to develop a new protein-based TNF therapeutic using novel protein moieties that has the potential to maximize efficacy while optimizing the product for ease of delivery.

Methods: Nanobodies that were high affinity binders of human TNF were selected. The strategy was to humanize and optimize a lead molecule for potency and *in vivo* half-life extension. Binding kinetics to human and rhesus monkey TNF and to human and rhesus monkey albumin were determined using surface plasmon resonance. Potent neutralizers of human TNF were identified in an *in vitro* bioassay and the *in vivo* efficacy of the lead molecule was subsequently evaluated in a human TNF transgenic mouse model of RA.

Results: Ozoralizumab (ATN-103) is a humanized, trivalent, bispecific Nanobody containing two human TNF-binding domains linked to a human serum albumin-binding domain. Human and rhesus monkey TNF had very similar on and off-rates, resulting in nearly identical equilibrium dissociation constants. In addition, Ozoralizumab demonstrated identical equilibrium dissociation constants based on binding to human and rhesus monkey albumin. In an *in vitro* bioassay, Ozoralizumab was as potent or more potent than currently marketed TNF inhibitor agents, as measured by the ability to neutralize the *in vitro* cell cytotoxicity of human and rhesus monkey TNF. Ozoralizumab does not have an antibody Fc region and is therefore unable to mediate any antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. Pharmacokinetic analysis in mice and in non-human primates confirmed the long *in vivo* half-life of Ozoralizumab, adopting the half-life of serum albumin. Ozoralizumab further demonstrated efficacy by inhibiting infiltration of neutrophils induced by human TNF in a mouse air pouch model. In comparison with Infliximab, Ozoralizumab demonstrated superior efficacy in a therapeutic treatment protocol in a TNF transgenic mouse model of RA. Ozoralizumab was able to decrease the clinical scores and reverse the pathology.

Conclusion: The data presented show that Ozoralizumab combines high potency with long *in vivo* half-life. Ozoralizumab is considered to be a more effective anti-TNF therapeutic with less frequent and more convenient dosing for RA.

835

CXCL5 An Important IL-17 Mediated Proangiogenic Factor in Rheumatoid Arthritis and Experimental Arthritis Model. Nathan D. Chamberlain[1], Michael Volin[2] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL

Background/Purpose: These studies were performed to identify IL-17 down stream proangiogenic mediators in rheumatoid arthritis (RA) and IL-17-induced arthritis.

Methods: IL-17-induced proangiogenic factors were determined in RA synovial tissue explants and IL-17-induced arthritis joints employing ELISA. Next, the mechanism of proangiogenic factor induction by IL-17 was examined in macrophages and RA fibroblasts using ELISA. To determine whether angiogenesis is differentially modulated by the identified proangiogenic factors compared to IL-17, signaling pathways contributing to *in vitro* endothelial migration were determined.

Results: To determine IL-17 mediated proangiogenic factors in RA explants, tissues were activated with IL-17 or PBS and results were demonstrated as fold increase above the PBS value. We found that IL-17 significantly increases levels of CXCL1 (8 fold), CXCL5 (12 fold) and FGF2 (3 fold) compared to control, however VEGF levels were not affected in this process. To examine proangiogenic mediators in the IL-17-induced arthritis model, C57BL/6 mice were injected intra-articularly with 10^7 PFU adenoviral (Ad)-IL-17 or Ad-control. Ankles were harvested on day 10 post injection, and joint proangiogenic factors were quantified. We found that similar to RA synovial tissue explants, local expression of IL-17 significantly upregulates production of CXCL1 (40 fold), CXCL5 (10 fold) and FGF2 (2 fold) without affecting VEGF levels compared to control treatment. As CXCL1 and CXCL5 were the most prominent proangiogenic factors their mechanism of production was examined in macrophages and RA fibroblasts. To determine the mechanism by which IL-17 induces CXCL1 and CXCL5 production, signaling pathways were suppressed in IL-17-activated cells. Inhibition of PI3K or ERK pathways suppress production of CXCL1 in macrophages and CXCL5 in both cell types, however, in RA fibroblasts only inhibition of PI3K was capable of reducing IL-17-mediated CXCL1 levels. Our earlier studies demonstrate that IL-17-mediated arthritis severity and vascularization was significantly reduced in the anti-CXCL5 treatment group whereas, anti-CXCL1 treatment had no effect on these processes. To address the different efficacy of blocking CXCL1 and CXCL5 in IL-17 arthritis model we examined the mechanism by which these chemokines induce endothelial migration. We found that in HMVECs CXCL1 signals through PI3K and ERK, however this chemokine was unable to activate NF-kB or p38 signaling pathways. CXCL5 stimulation of HMVECs results in activation of the NF-kB pathway only. To demonstrate the mechanism by which CXCL1 and CXCL5 mediate HMVEC migration, inhibitors to these pathways were employed in *in vitro* chemotaxis. In agreement with our signaling results, inhibition of PI3K suppresses CXCL1-induced HMVEC migration, while chemotaxis mediated by CXCL5 was reduced through NF-kB inhibition.

Conclusion: Our results demonstrate that inhibition of CXCL1 is ineffective in reducing joint inflammation because IL-17 is present in the mouse ankles and can induce angiogenesis through PI3K pathway whereas CXCL5 mediates angiogenesis through a non-overlapping IL-17 mechanism.

836

Novel Small Molecule Inhibitors of Interleukin-1 Receptor Associated Kinase-4 Are Effective in a Preclinical Model of Arthritis. Eric G. Vajda, Tsung H. Lin, Bojing Wang, Koc-Kan Ho, Arjan van Oeveren, Brian McGuinness, Jeffrey Letourneau, Yong-Hee Lee, Deepa Rungta, Lin Zhi and Keith B. Marschke. Ligand Pharmaceuticals, La Jolla, CA

Background/Purpose: Interleukin-1 Receptor Associated Kinase-4 (IRAK4) is a serine/threonine protein kinase that activates NF-kappaB in both the toll-like receptor (TLR) and interleukin-1 (IL-1) signaling pathways. IRAK4 plays a critical role in innate immunity and recent evidence suggests it may play an important role in multiple autoimmune conditions including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and gout. We have discovered potent small molecule inhibitors of IRAK4 which may provide a novel therapeutic approach for the treatment of a range of inflammatory conditions.

Methods: Kinase inhibition was measured by IMAP technology or radioisotope filtration binding assays. Cell-based activity was determined in human and mouse cell lines, as well as human PBMCs. Cells were stimulated with either IL-1β or LPS and IL-6 secretion was measured by ELISA. Pathway selectivity was determined by flow cytometry measurements of NF-kappaB or STAT1 phosphorylation after stimulation with TNF or interferon-γ, respectively. Acute measurements of IL-1 pathway suppression *in vivo* were determined in mice orally administered IRAK4 inhibitors and injected i.p. with IL-1β. Serum IL-6 and TNF levels were determined by ELISA. Chronic assessment of IRAK4 suppression was determined in the mouse collagen induced arthritis (CIA) model.

Results: We have identified a lead series of compounds that bind to the ATP pocket of IRAK4 and inhibit kinase activity with potencies <10 nM. Compounds are selective inhibitors of IRAK4, with reduced inhibition versus a panel of off-target kinases. IL-1β-induced IL-6 secretion was inhibited in cell based assays with potencies <100 nM. In primary human PBMCs, both IL-1β and LPS induced IL-6 secretion were inhibited, indicating suppression of both IL-1 receptor and TLR-4 receptor signaling activity. Compounds had minimal activity in the TNF or interferon-γ pathways. The lead compound, LG0224912, inhibited IL-1 cytokine signaling after oral administration to mice. Suppression of TNF and IL-6 in mice tracked closely with exposure levels, demonstrating a clear pharmacodynamic-pharmacokinetic relationship. Oral administration of LG0224912 to mice with established CIA resulted in significant suppression of inflammation comparable to etanercept, and is the first demonstration of efficacy of an IRAK4 inhibitor in a disease model.

Conclusion: We have identified novel IRAK4 inhibitors that suppress both IL-1 receptor and TLR-4 receptor signaling. The compounds are active in an animal model of arthritis and have the potential to treat a range of inflammatory conditions including RA, SLE, IBD, and gout.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Biomarkers

Sunday, November 6, 2011, 4:30 PM–6:00 PM

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A Plasmablast Molecular Biomarker for Reduced Clinical Benefit From Anti-CD20 Therapy in Rheumatoid Arthritis. Kasia Owczarczyk[1], Preeti Lal[2], Alexander R. Abbas[1], Kristen Wolslegel[1], Cecile TJ Holweg[1], Wolfgang Dummer[2], Ariella Kelman[2], Paul Brunetta[2], Nicholas Lewin-Koh[2], Marco Sorani[1], Diane Leong[2], Paul Fielder[1], David E. Yocum[2], Carole Ho[2], Ward Ortmann[2], Michael J. Townsend[1] and Timothy W. Behrens[2]. [1]Genentech Research and Early Development, South San Francisco, CA, [2]Genentech, South San Francisco, CA

Background/Purpose: An important goal for personalized health care is the identification of biomarkers that predict the likelihood of treatment responses. Here, we tested the hypothesis that quantitative mRNA assays for B lineage cells in blood could serve as baseline predictors of therapeutic response to anti CD20-mediated B cell depletion therapy in subjects with rheumatoid arthritis (RA).

Methods: A reverse transcription-quantitative PCR panel comprising B cell-specific genes was developed to establish levels of B lineage cells using messenger RNA from whole blood of patients. *IgJ* gene expression was established as a marker of plasmablasts and plasma cells, while a B cell-specific splice variant of *FcRL5 (IRTA2c)* was established as a marker of mature B cells. Whole blood RNA samples from 3 large placebo-controlled trials of rituximab as well as a large placebo-controlled trial of ocrelizumab in RA patients were assessed for association of baseline B cell lineage status with clinical outcome. P values and confidence intervals for odds ratios were calculated using two-tailed Fisher's exact test.

Results: In samples from the REFLEX trial of rituximab in anti-TNF inadequate responders (118 rituximab, 23 placebo), a 25% subgroup of treated subjects with elevated baseline mRNA levels of *IgJ*, a marker for antibody-secreting plasmablasts, showed reduced clinical response rates (9% ACR50 response in IgJ^{hi}, 31% ACR50 in IgJ^{lo}). There were no significant efficacy differences in the placebo arm subjects stratified by this marker. Prospective testing of the *IgJ* biomarker in the DANCER and SERENE rituximab clinical trial cohorts (total n=200 rituximab, 93 placebo) and the SCRIPT ocrelizumab cohort (275 ocrelizumab, 137 placebo) confirmed the utility of this marker to predict lesser clinical benefit to anti-CD20 therapy ($P_{REPLICATION}$=0.006; OR = 2.4, 95% c.i. (1.2, 5.0). A combination mRNA biomarker, $IgJ^{hi}FCRL5^{lo}$, showed improved test performance over IgJ^{hi} alone by removing all ACR50 responders in the REFLEX trial. Prospective testing of the $IgJ^{hi}FCRL5^{lo}$ profile, representing a 17% subgroup in the replication cohorts, confirmed its utility ($P_{REPLICATION}$=0.008; OR = 2.7, 95% c.i. (1.3, 6.3).

Conclusion: This study demonstrates that baseline blood levels of molecular markers for late B lineage stage plasmablasts identify a ~20% subgroup of active RA subjects who are unlikely to gain significant clinical benefit from anti-CD20 B cell depletion therapy compared with placebo. Additional investigation into alternate dosing regimens and monitoring of plasmablast biomarkers may be warranted for these patients.

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Development of a Multi-Biomarker Structural Damage Score in Rheumatoid Arthritis to Predict Radiographic Progression in the Leiden Early Arthritis Cohort. Annette H.M. van der Helm-van Mil[1], Rachel Knevel[1], William C. Manning[2], Lyndal K. Hesterberg[2], Guy Cavet[2], T.W.J. Huizinga[3] and Yijing Shen[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Crescendo Bioscience, Inc., South San Francisco, CA, [3]Leiden University Medical Centre, Leiden, Netherlands

Background/Purpose: The ability to predict progressive structural damage has the potential to improve disease management in rheumatoid arthritis (RA) patients. We aimed to develop a Multi-Biomarker Structural Damage (MBSD) score to predict the risk and quantity of joint damage in an individual patient over 12 months.

Methods: 28 serum biomarkers representing diverse biological pathways were previously selected from 93 candidates in a series of studies based on their performance at predicting joint damage. Biomarker concentrations were determined in 307 serum samples from 187 patients followed in the Leiden Early Arthritis Cohort. The concentrations of individual biomarkers were assessed for their association with change in total van der Heijde Sharp Scores (SHS) over 12 month intervals by Spearman correlation.. Multivariate statistical models were built using linear regression to predict both the rate of change in SHS (ΔSHS) and risk of progression (RP) using combinations of biomarkers and conventional variables. Independent contributions of variables to modeling were assessed in ordinary least squares (OLS) regression. Model performance for ΔSHS was evaluated in Leave One Out cross-validation by the area under the receiver operating characteristic curve (AUROC). Model performance for RP models was evaluated by specificity, sensitivity, total classification error and AUROC for classifying ≤ 0 versus > 0 ΔSHS.

Results: At False Discovery Rate (FDR) < 0.05, 15 biomarkers were correlated with ΔSHS. Prototype MBSD models using serum markers had the highest observed performance among clinical measures with an AUROC of 0.73.The performance values of clinical measures that were significantly correlated with ΔSHS were: initial erosion score (AUROC=0.70), initial SHS (AUROC=0.67), ESR (AUROC=0.62), initial joint space narrowing score (AUROC=0.6), SJC44 (AUROC=0.58), CRP (AUROC=0.59) and DAS44 (AUROC=0.57). MBSD had higher observed performance than a combination of clinically available variables (CRP, ESR, SJC44, CCP, Presence of Erosions, Ritchie Articular Index (RAI), Patient Global (PG) and RF; AUROC=0.64). The combination of serum biomarkers and initial erosion score gave slightly higher performance than either alone (AUROC=0.74). RF and CCP titers, PG, age, and RAI were not significantly correlated with ΔSHS. In OLS multivariate regression (with JSN and erosion scores included separately), only two measures were significant independent predictors of ΔSHS: initial erosion score ($p<0.001$) and MBSD ($p=0.002$). The sensitivity, specificity and total classification error of MBSD for risk of progression were 0.63, 0.73 and 0.32, respectively.

Conclusion: Combinations of serum biomarkers had independent predictive value and higher observed performance than conventional clinical measures at predicting progressive structural damage in RA. An MBSD score generated by serum biomarkers has the potential to improve prediction of radiographic change in clinical practice.

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New Assay Generation for Antibodies Against Modified and Citrullinated Peptides Predicts Poor Response to TNF Inhibitor Therapy. Lotta Ljung[1], Karl Egerer[2], Holger Bang[3], Eugen Feist[4], Gerd R. Burmester[5] and Solbritt Rantapää Dahlqvist[1]. [1]Umeå University Hospital, Umeå, Sweden, [2]Labor Berlin - Charité Vivantes GmbH, Berlin, Germany, [3]Orgentec Diagnostika GmbH, Mainz, Germany, [4]Charité Medical School, Berlin, Germany, [5]Charité - Universitätsmedizin Berlin, Berlin, Germany

Background/Purpose: Current perception of the therapy for rheumatoid arthritis (RA) suggests that response to treatment is only partially predictable by autoantibodies against citrullinated proteins (ACPAs). These antibodies precede the debut of RA and are associated with a more aggressive course of the disease. Our aim in this study was to analyse several new ACPAs against antigens with additional post-translational modifications and to evaluate their predictive value for response to therapy using tumour necrosis factor (TNF) inhibitors.

Methods: The study included 118 patients (mean age at inclusion 52.9±12.6 years) with polyarthritis, who started on treatment with their first TNF-inhibitor (etanercept n=23, 19.5%, adalimumab n=6, 5.1%, infliximab n=89, 75.4%). Of these patients (pts), 109 (92.4%) fulfilled the ACR 1987 RA criteria, 4 (3.4%) had undifferentiated polyarthritis, 4 (3.4%) juvenile idiopathic arthritis and one (0.8%) psoriatic polyarthritis. Disease activity score for 28 joint count (DAS28) was evaluated at start of treatment and after three months. The mean DAS28 at start of therapy was 5.64±1.24, without significant difference between smokers (n=22, 18.6%) and non-smokers. Poor response was defined as a DAS28 ≥3.2 at three months. Blood samples for analyses of ACPAs were drawn before treatment started. Antibodies (abs) against cyclic citrullinated peptid (a-CCP) and mutated citrullinated vimentin (a-MCV) were analysed by commercial assays; modified MCV (a-modMCV), sialinized MCV (a-sialMCV) and anti-modified vimentin (a-modvim) were analysed by research assays. Cut-off for all research assays was 20 U/ml. Test for anti-vimentin (a-vim) abs was used as negative control. Odds ratios for poor response were calculated by logistic regression analyses using SPSS 19.0.

Results: Positivity for a-CCP abs was found in 100 pts (84.7%), for a-MCV abs in 99 pts (83.9%), for a-modMCV abs in 65 pts (55.1%) and for

a-modvim abs in 37 pts (31.4%). All pts except one had a-sialMCV ab concentrations above cut-off level (n=117, 99.2%) and none had a-vim abs above cut-off. The mean DAS28 after 3 months of treatment was 3.68±1.23, with 78 pts (66.1%) not achieving remission or low disease activity. In simple logistic regression models, poor response to therapy was significantly associated with smoking (OR 4.0, 95%CI 1.1–14.4) and a positive test for a-modMCV abs (OR 3.0, 1.4–6.6), but not with positivity for the other ACPAs, age, sex or disease duration. The combination of smoking and positivity for abs against a-modMCV or a-MCV, significantly predicted poor response to the TNF-inhibitor (OR 14.7, 1.8–120.0 and OR 7.0, 1.5–32.0, respectively) compared with not having these factors. Similar patterns, although not significant, were also seen for a-CCP abs and a-modvim abs in combination with smoking.

Conclusion: Antibodies against modified MCV, or smoking in combination with a-MCV abs or a-modMCV abs, respectively, significantly predicted a poor response to TNF inhibitor after 3 months of therapy. Thus, the individual ACPA status could represent a negative predictive factor for response to TNF inhibitors, particularly in conjunction with smoking habits.

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Protein Array Screening Reveals Autoantigenicity Patterns Predicting Anti-TNF Alpha Therapy Response in Rheumatoid Arthritis Patients. Zoltan Konthur[1], Katja Köpke[2], Hans Lehrach[1], Gerd R. Burmester[2] and Karl Skriner[2]. [1]Max Planck Institute for Molecular Genetics, Berlin, Germany, [2]Charité - Universitätsmedizin Berlin, Berlin, Germany

Background/Purpose: One third of rheumatoid arthritis patients treated with biologicals targeting TNFα are therapy non-responders. We investigated the differences in seroreactivity of patients responding and not responding toanti-TNF alpha therapies prior and after therapy to deduce diagnostically applicable autoantigenicity patterns

Methods: Screening with patient sera were conducted on protein macroarrays consisting of 37.830 unique putative expression clones. Response patterns of different immunoglobulin classes were recorded and bioinformatically evaluated enabling us to deduce a set of proteins, which allow to distinguish between therapy responders and non-responders. Next, selected candidates were expressed recombinantly in *E. coli*, purified and further stratified with larger patient cohort in ELISA.

Results: Comparative analysis of macroarray results with sera from responders and non-responders to anti TNF drug revealed a more than 30-fold higher number of autoantigens targeted by high titers of IgA autoantibodies in non-responders compared to responders (221 versus 6).More detailed analyses suggest that with 5 autoantigens found to be common in all individual non-responders to anti-TNFα treatment, a reduced number of antigens might be sufficient to predict non-responsiveness. Pretreatment sera from patients with diagnosis of RA based on the ACR classification criteria who were initiated on therapy with TNF inhibitors were analyzed with three markers from the biomarker set of highest priority (RAB11B, PPP2R1A, KPNB1) using an ELISAs assay. In total, analyses of 69 patients were carried out, of which 13 were clearly defined as responder and 8 were clearly defined as non-responder. Of these, already 5 (62,5%) Non-responders could clearly be identified with already three markers from biomarker set of highest priority (RAB11B, PPP2R1A, KPNB1). None of the Responder or Intermediate Responder gave any signal on said markers on IgA-level. The remaining 48 patient samples are derived prior treatment with anti-TNFalpha inhibitors and were blinded. According to published studies, 20–25% of RA patients treated with TNFalpha inhibitors are Non-responders: Hence we expect ~10 patients to be non-responder. Within this set, 5 patients (50%) showed clear IgA response to three markers from biomarker set of highest priority (RAB11B, PPP2R1A, KPNB1).

Conclusion: These data suggest that non-response to anti-TNFα biologicals might be predicted based on frequency and magnitude of autoantibodies of the IgA class. Furthermore, 5 IgA autoantigens common in all individual non-responders may be sufficient to predict non-responsiveness.

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Gene-Gene Interactions in Folate Pathway Contribute to Methotrexate Adverse Events in Rheumatoid Arthritis. Thierry Dervieux[1], Judith Wessels[2], J. M. Kremer[3], Tom W.J. Huizinga[2] and Henk-Jan Guchelaar[2]. [1]Exagen Diagnostics, Albuquerque, NM, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: To determine whether gene-gene interactions (epistasis) in folate, purine and pyrimidine gene pathways contribute to adverse events following methotrexate (MTX) therapy in rheumatoid arthritis (RA).

Methods: The discovery cohort consisted of 186 patients (93% Caucasians) with early RA enrolled in the monotherapy arm of the BeSt study. MTX therapy was started at 7.5 mg/week and increased to 25 mg/week to control disease activity. MTX related adverse events were evaluated after 6-months therapy. A total of 12 SNPs in folate (RFC-1, MTHFR, MTHFD1, MS, GGH, SHMT1), purine (ATIC, AMPD1, ITPA) and pyrimidine (TYMS) pathways were measured using standard molecular methods. Haplotypes in Methylenetetrahydrofolate Reductase (MTHFR 677C/T-1298A/C) were inferred using expectation-maximization algorithms. Data analysis consisted of multifactor dimensionality reduction technique (MDR). MDR detects non-linear gene-gene interactions by combining predisposing genotypes of adverse events (predisposing genetic attribute) into two separate groups depending on whether they are more common in patients presenting with adverse events or not. The robustness and significance of the model was tested through internal cross validation consistency (CVC, 10-fold) and 1000-fold permutation testing. The predictive value of the predisposing genetic attribute of adverse events was further tested independently in a validation cohort consisting of 47 RA patients from the United States (92% Caucasians) starting MTX (7.5 mg/week) with adverse events evaluated after 4-months MTX therapy.

Results: After 6-months MTX therapy, the incidence of MTX related adverse events was 29% in patients enrolled in the BeSt study (median MTX dose received was 25 mg/week). MDR analysis revealed a non linear pattern of interactions between MTHFR 677C/T-1298A/C haplotypes and variants in GGH [C16T] and MTHFD1 [G1958A] (Table I). The stepwise addition of the three genetic components increased the testing accuracy from 0.49 to 0.64. The constructed predisposing genetic attribute pooling higher and lower likelihood of adverse events in two separate groups revealed a 6.1 fold (CI 95%: 2.9–12.9, $p<0.001$) greater likelihood of adverse events in carriers (50%) versus non carriers ($p<0.001$). Sensitivity was 79.6% and specificity was 60.1%. In the validation cohort, the incidence of MTX adverse event was 51% after 4 months therapy (median MTX dose received was 15 mg/week). A total 66% patients carried the genetic attribute predisposing to MTX adverse events. These patients were 5.4 fold (CI 95%: 1.4–21.3, $p<0.001$) more likely to develop adverse events than those without the predisposing genetic attribute. Sensitivity was 83% and specificity was 52%.

Table. Multifactor dimensionality reduction analysis

Model	Training accuracy	Testing accuracy	CVC	P value
GGH C16T	0.553	0.490	6/10	0.838
GGH C16T + MTHFR 677C/T-1298A/C haplotype	0.621	0.610	10/10	0.081
GGH C16T + MTHFR 677C/T-1298A/C haplotype + MTHFD1 G1958A	0.706	0.639	10/10	0.016

CVC: cross validation consistency; GGH: Gamma-glutamyl-Hydrolase; MTHFD1: Methylene tetrahydrofolate dehydrogenase.

Conclusion: These hypothesis generating data indicate that gene-gene interactions contribute to MTX-induced adverse events in RA.

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Patterns of Interaction Between Genetic and Non-Genetic Attributes and Methotrexate Efficacy in Rheumatoid Arthritis. Thierry Dervieux[1], Judith Wessels[2], J. M. Kremer[3], Leonid Padyukov[4], Maria Seddighzadeh[4], Saedis Saevarsdottir[4], R.F. van Vollenhoven[4], Lars Klareskog[4], T. Huizinga[2] and Henk-Jan Guchelaar[2]. [1]Exagen Diagnostics, Albuquerque, NM, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Albany Medical College and The Center for Rheumatology, Albany, NY, [4]Karolinska Institutet, Stockholm, Sweden

Background/Purpose: The contribution of low-penetrance single nucleotide polymorphisms to methotrexate (MTX) efficacy in rheumatoid arthritis (RA) is inconsistent between studies. We sought to elucidate an architecture of MTX response in three cohorts of RA patients treated with MTX.

Methods: SNP frequencies in genes from folate, purine and pyrimi-

dine pathways were measured to develop a model of gene-gene interactions (epistasis). The cohorts consisted of 439 patients who received MTX in the United States (n=255) and The Netherlands (n=184). A third cohort of 530 RA patients from Sweden was used to replicate the findings. MTX efficacy was assessed using the European League Against Rheumatism criteria in the majority of patients. Gene-gene interactions were detected and a predisposing genetic attribute of response was constructed using multifactor dimensionality technique (MDR). Meta-analysis was conducted and Cochran's Q test was used to detect heterogeneity.

Results: Non-linear patterns of gene-gene interactions between variants in Amino-Imidazole Carboxamide Ribonucleotide Transformylase (C347G), Reduced Folate Carrier (G80A) and Inosine Triphosphate Pyrophosphatase (C94A) revealed a predisposing genetic attribute significantly associated with MTX response in the US and Dutch cohorts (OR=2.9, CI95%:1.9–4.2; p<0.001), a finding that did not replicate in the Swedish cohort (OR=0.9; CI95%: 0.64–1.37; p=0.74). A meta-analysis combining the three cohorts revealed significant heterogeneity (Q=15.3; p=0.005) with random effects odd ratio of 1.8 (OR=1.79 CI95%: 0.80–4.02). We reasoned that difference in population structure and, hence, heterogeneity may explain the lack of replication in the Swedish cohort. Therefore, we conducted an additional MDR analysis by superimposing patient age, gender and anti-citrullinated peptide antibodies (ACPA) status on the constructed predisposing genetic attribute. MDR revealed that the stepwise addition of these genetic and non genetic components increased the testing accuracy from 0.518 (genetic attribute only) to 0.585 (genetic attribute with gender, age and ACPA status). This new attribute resulted into a 2.2-fold (OR=2.2, CI95%: 1.6–2.9; p<0.01) higher likelihood of response and significance was achieved in the three cohorts. The selective advantage toward response in the presence of the predisposing genetic attribute was not observed in females and ACPA positive patients, while older and male ACPA negative patients tended to exhibit a greater likelihood of response in the absence of the predisposing genetic attribute. No significant heterogeneity was detected (Q=3.67; p=0.160) and random effects OR was 2.3 (OR=2.31 CI95%: 1.53–3.49).

Conclusion: Gene-gene interactions together with non-genetic attributes may contribute to MTX efficacy in RA. Apparent inconsistencies between studies on MTX responsiveness were reconciled using MDR, by demonstrating that complex gene-gene interactions together with non-genetic attributes predict MTX efficacy in RA.

ACR Concurrent Abstract Session
Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics I
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Survival and Predictors of Mortality In Australian Patients with Connective Tissue Disease-Associated Pulmonary Arterial Hypertension. Gene-Siew Ngian[1], Wendy Stevens[2], Jill Byron[2], Ai Tran[3], Janet E. Roddy[3], Robert Minson[4], Catherine L. Hill[5], Ken Chow[6], Joanne Sahhar[7], Susanna Proudman[6] and Mandana Nikpour[1]. [1]The University of Melbourne, Melbourne, Australia, [2]St Vincent's Hospital, Melbourne, Australia, [3]Royal Perth Hospital, Perth, Australia, [4]Flinders Medical Centre, Adelaide, Australia, [5]The Queen Elizabeth Hospital, Woodville, Australia, [6]Royal Adelaide Hospital, Adelaide, Australia, [7]Monash Medical Centre, Melbourne, Australia

Background/Purpose: We sought to determine predictors of mortality in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH).

Methods: This was a retrospective cohort study of patients with CTD-PAH recruited from six tertiary hospitals. In addition to data prospectively collected as part of the Australian Scleroderma Cohort Study, physician records were reviewed. PAH was defined on right heart catheterization. All patients had systemic sclerosis (SSc) or another underlying CTD. Records were censored at 31/12/09. Survival was determined using Kaplan-Meier estimates. Univariate and multivariable predictors of survival were determined using log-rank / Wilcoxon tests, and proportional hazards regression modelling.

Results: Amongst 117 patients (105 female) there were 32 deaths. Mean age at PAH diagnosis was 61.5 ± 11.4 years. SSc was the most common underlying CTD, accounting for 104 patients (88.9%). Forty-eight patients (41.0%) had coexistent interstitial lung disease (ILD). At baseline, mean six-minute walk distance was 325 ± 127 m and 88 patients (75.2%) were in WHO functional class III. Average duration of follow-up from PAH diagnosis was 2.6 ± 1.8 years. Seventy patients (59.8%) received monotherapy, 12 (10.3%) sequential monotherapy and 34 (29.0%) combination pulmonary vasodilator therapy. Bosentan was the most commonly prescribed medication, used in 102 patients (87.2%). Sildenafil was the next most common, followed by inhaled iloprost and sitaxentan. One-, two- and three-year survival was 94%, 89% and 73%, respectively (see Figure 1). On univariate analysis, predictors of mortality were WHO functional class IV at baseline, male sex, ILD, right ventricular dysfunction, pericardial effusion, absence of warfarin therapy, absence of combination therapy and higher mean right atrial pressure (mRAP) at PAH diagnosis. On multiple regression analysis, WHO functional class IV at baseline, higher mRAP at PAH diagnosis, coexistent ILD and absence of warfarin therapy remained independent predictors of mortality (see Table 1).

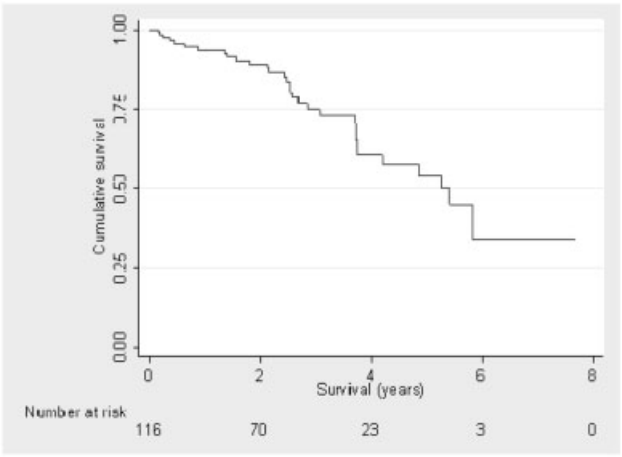

Figure 1. Survival from PAH diagnosis.

Table 1. Predictors of mortality on multivariable analysis

Variable	Adjusted HR (95% CI)	*p* value
Male sex	8.23 (0.59–114.98)	0.117
WHO class at baseline	7.45 (1.18–47.13)	0.033
Warfarin therapy ever	0.07 (0.01–0.88)	0.040
ILD	9.81 (1.07–89.92)	0.043
Pericardial effusion	3.83 (0.67–21.79)	0.130
mRAP	1.19 (1.01–1.40)	0.037
Baseline 6-minute walk distance	0.995 (0.987–1.003)	0.199
Combination therapy	0.43 (0.14–1.33)	0.145

Conclusion: Among patients in this study, three-year survival is 73%; this is better than that reported in several studies of CTD-PAH in the current treatment era. Predictors of survival include lower WHO functional class at baseline, lower mRAP at PAH diagnosis and warfarin therapy, suggesting that earlier diagnosis of PAH and treatment with warfarin in addition to advanced pulmonary vasodilator therapy may improve survival in these patients.

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Prognostic and Diagnostic Significance of Autoantibodies to Citrullinated Proteins (ACPA) in Patients with a Scleroderma-Rheumatoid Arthritis (SSc-RA) Overlap Syndrome. Makoto Soejima[1], Zhou Zhijie[2], Donald M. Jones[1], Danielle Goudeau[1], Christine L. Amity[1], Lynne M. Frydrych[1], Robyn T. Domsic[1], Aarat M. Patel[1], Larry W. Moreland[3], David M. Lee[4], Thomas A. Medsger[1] and Marc C. Levesque[1]. [1]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [2]Aurora Health Care Oshkosh, Oshkosh, WI, [3]University of Pittsburgh, Pittsburgh, PA, [4]Brigham and Womens Hospital, Boston, MA

Background/Purpose: In clinical practice, the anti-CCP test is used to detect ACPA and is used as a diagnostic test for RA. However, approximately 3–5% of patients with SSc are anti-CCP positive. It is uncertain whether anti-CCP tests are only positive in patients with SSc-RA overlap syndromes or are also positive in patients with SSc only. It is also not clear whether the ACPA antigens recognized by anti-CCP antibodies from anti-CCP positive SSc patients differ from those of RA patients.

Methods: We performed a chart review of new sequential patients with a

diagnosis of SSc enrolled in a University of Pittsburgh Medical Center (UPMC) SSc registry in the calendar years from 2004 to 2007 (N = 300). We also reviewed the records of 16 other SSc patients seen prior to 2004 who had symptoms suggestive of both SSc and RA. Finally, we reviewed the records of 143 patients from the UPMC RA Comparative Effectiveness Research (RACER) registry. We used the 1987 and 2010 ACR/EULAR RA criteria to determine the number of patients in each group with RA only, with a SSc-RA overlap syndrome or with SSc only. We determined the frequency of interstitial lung disease (ILD) and other clinical features in each group of subjects. Serum samples were analyzed for anti-CCP by ELISA (anti-CCP2; Axis-Shield, UK). A panel of linear and cyclic citrullinated and non-citrullinated peptides derived from fibrinogen, vimentin, enolase and filaggrin were examined by ELISA for reactivity with the same serum samples.

Results: Among the 300 sequential SSc patients seen initially between 2004 and 2007, we identified 8 (2.7%) subjects with RA. The 16 SSc patients seen prior to 2004 also met criteria for a diagnosis of RA. Among the SSc only subjects, 1 was anti-CCP positive and among the SSc-RA overlap subjects, 14 of 24 were anti-CCP positive ($p < 0.0001$; Fisher's exact test; 99% specificity; 58% sensitivity). 116 of 143 (81%) RA only subjects were anti-CCP positive. Among the anti-CCP positive subjects, the pattern of ACPA peptide reactivity was essentially identical in the SSc-RA overlap subjects as compared to the RA only subjects. There was an increased frequency of ILD, but not other clinical features, among SSc-RA subjects as compared to SSc only subjects (63% vs. 29%, respectively; $p=0.0008$, Fisher's exact test). Among SSc-RA patients, 63% of anti-CCP positive patients had ILD, while 63% of anti-CCP negative SSc-RA patients had ILD ($p=1.0000$), suggesting that anti-CCP positivity is not specifically associated with ILD in SSc-RA.

Conclusion: These studies indicate that among patients with SSc, a positive anti-CCP test is highly specific for a SSc-RA overlap syndrome. Furthermore, the ACPA peptide reactivity pattern by ELISA in SSc-RA patients suggests that these patients have RA that is indistinguishable from RA patients without SSc. SSc-RA overlap patients have a higher frequency of ILD suggesting that an overlap of these disorders may promote development of ILD. Taken together, these studies provide a better understanding of the test characteristics of the anti-CCP ELISA and a better understanding of rheumatic overlap syndromes.

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Detection of Autoantibodies to RNA-Protein Complex in Scleroderma by Quantitative-PCR of RNA Components of the Antigens. Angela Ceribelli, Minoru Satoh and Edward K.L. Chan. University of Florida, Gainesville, FL

Background/Purpose: Autoantibody tests in scleroderma (SSc) are useful to help diagnosis, predict organ involvement, and prognosis. SSc autoantibodies recognizing RNA-protein complex, anti-Th/To (7-2RNA, 8-2RNA-protein complex) and anti-fibrillarin/U3-snoRNP (U3RNA-protein complex), have been known for over 20 years. However, they are usually detected by immunoprecipitation (IP) and validated commercial assays are not available. Quantitative PCR (qPCR) has become a standard technique to quantify mRNA levels of specific genes in cells or tissues, but qPCR of the RNA component of autoantigens has not been applied to identify autoantibodies. Our aim is to establish a novel method for anti-Th/To and U3-snoRNP antibodies, using qPCR to detect the RNA component of the autoantigens.

Methods: Standard IP was performed using K562 cell extract. cDNA was made from RNA extracted from immunoprecipitate, and qPCR was performed using primers for the 7-2 RNA (Th) and U3 RNA. Ct (cycle threshold) values were compared in a titration experiment, serially diluting the cell lysate, RNA and cDNA up to 1:4096, to test the efficacy and sensitivity of the assay. Evaluation was based on 22 anti-Th/To (+), 12 anti-U3 (+) sera and 39 controls (normal controls and SSc with other autoantibodies).

Results: When cell extract was serially diluted for IP, linear dose response curves showed that with every 1:8 dilution, Ct value changed by ~3, which reflects the 8 fold difference as expected. Difference of Ct between antibody positive and negative samples was 8–10 and it was similar throughout the dilutions. Similar results were obtained when serial dilutions were made at the level of RNA purified after IP or cDNA after RT, indicating that reliable range of Ct numbers can be obtained even with very small amount of cell extract, RNA and cDNA. In the screening of anti-Th and anti-U3 samples using cell extract from one million cells, the mean Ct value is 15.28 (SD 0.7) for anti-Th/To (+) and 20.37 (SD 1.83) for anti-U3 (+). These values were significantly lower compared with the control group, with a difference of 8 Ct values for anti-Th/To (+) and 5 Ct values for anti-U3 ($p<0.05$).Sensitivity of our method is 100% for anti-Th/To and 92% for anti-U3 antibodies, while specificity is 97% and 94%, respectively, compared with IP followed by urea-PAGE/silver staining of the RNAs.

Conclusion: This new method offers highly reliable identification of antibodies to Th/To and U3 compared with the gold standard IP assay. Making tests for these autoantibodies widely available to clinicians should be helpful in the diagnosis and follow-up of SSc patients.

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The Significance of Tendon Friction Rubs in Early Diffuse Systemic Sclerosis Patients. Adam Doré[1], Thomas A. Medsger Jr.[2], Mary Lucas[3], Dana Ivanco[3] and Robyn T. Domsic[2]. [1]UPMC Presbyterian Shadyside Hospital, Pittsburgh, PA, [2]University of Pittsburgh Med Ctr, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Palpable tendon friction rubs (TFR) in systemic sclerosis (SSc) have been associated with diffuse cutaneous (dc) skin disease and increased disability index scores, but little information on patient outcomes has been published. The objective of this study was to determine the relationship of TFR in early dcSSc to the development of new internal organ system involvement and survival.

Methods: From our prospectively enrolled institutional scleroderma databank we identified a group of early dcSSc patients (disease duration < 2 years from the first symptom attributable to SSc) who were first evaluated during 1980–2005 and found to have one or more palpable TFRs on exam. The next consecutive early dcSSc patient seen without TFR was matched (1:1) as the control. All cases and controls had at least two clinic visits and five years of follow-up from the time of their first visit. Survival was obtained through the Social Security Death Index. Cases and controls not seen in the last year were contacted via mail questionnaire. Testing results were located in those who responded and organ system involvement determined. Descriptive statistics were used for baseline data, and conditional logistic regression to assess risk of new internal organ involvement. Cox proportional hazards was used to identify factors associated with survival.

Results: 287 early dcSSc patients with TFRs were matched to 287 early dcSSc controls. There was no difference in age or gender between the groups. Patients with TFR had a higher median modified Rodnan skin thickness score, compared to controls (26 vs 21, $p <.0001$). Patients with TFRs had a shorter median disease duration (0.83 years, IQR 0.61, 1.13) compared to controls (1.03 years, IQR 0.70,1.48, $p < 0.0001$). The TFR group had a higher proportion of Caucasians (94%) compared to controls (89%, $p=0.02$)

The five year cumulative survival rate in TFR patients was 32% compared to 19% in controls ($p=0.006$). After adjustment for age and gender, patients with TFR were 83% more likely to die within five years after their initial evaluation (OR 1.83, 95% CI 1.25 – 2.67, $p=0.002$).

Patients with TFRs were significantly more likely to later develop new renal crisis or cardiac involvement, as displayed in Table 1. There was no increased risk in patients with TFR to develop new pulmonary or gastrointestinal involvement.

Table 1. Risk of new internal organ involvement in early dcSSc patients with tendon friction rubs

	Odds Ratio	95% Confidence Interval	p-value
Renal Crisis	4.00	2.00 – 8.00	<.0001
Cardiac	3.72	1.96 – 7.05	<.0001
Interstitial Lung Disease	1.32	0.88 – 1.97	0.18
Gastrointestinal	1.16	0.78 – 1.73	0.46
Pulmonary Hypertension	2.33	0.60 – 9.02	0.22

Conclusion: Early dcSSc patients with a TFR on exam are at increased risk for five year mortality compared to early dcSSc patients without a TFR. Patients with TFR have a four-fold increased risk of later developing renal crisis, and a 3.7-fold risk of later developing cardiac system involvement. The TFR is an important prognostic physical exam finding in early dcSSc patients.

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Long-Term Follow-up of Limited Cutaneous Systemic Sclerosis Patients with Anti-Th/to Antibody. Erin Snell[1], Mary Lucas[1], Dana Ivanco[1], Thomas A. Medsger[2] and Robyn T. Domsic[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh, Pittsburgh, PA

Background/Purpose: Anti-Th/To antibody occurs in 5–10% of limited cutaneous Systemic Sclerosis (lcSSc) patients. Anti-Th/To testing is not commercially available, thus only small case series have been described. The objective of this study was to assess the clinical features and long-term outcomes of lcSSc patients with anti-Th/To.

Methods: From our prospectively enrolled scleroderma databank we identified lcSSc patients first seen from 1980 – 2005 who were anti-Th/To positive. 3:1 matched controls were the next three consecutive lcSSc patients seen after each case. Survival and death cause were obtained from the National Death Index. Cases and controls not seen in the last year were contacted via mail questionnaire. Testing results were located in responders and organ system involvement determined. Descriptive statistics were used for baseline data and conditional logistic regression to assess risk of internal organ involvement. Cox proportional hazards was used to identify factors associated with survival.

Results: 175 anti-Th/To positive lcSSc patients were matched to 525 lcSSc controls. The mean ages were 52.2 and 53.5 years, respectively (p=0.29). There was no significant difference in female gender (82% cases, 84% controls; p=0.49) or Caucasian race (94% cases, 92% controls; p=0.43). Median duration of follow-up after first visit was 8.0 years in both groups (p=0.57). Five year cumulative survival was 66% in cases and 71% in controls (p= 0.98), with no difference in risk after adjustment for age and gender.

Patients with anti-Th/To were 47% more likely to develop interstitial lung disease (ILD), although 37% less likely to have esophageal involvement (Table 1). Anti-Th/To patients were 65% more likely to have pulmonary hypertension (PH), either primary or secondary, when verified by clinical data. This difference persisted when we included those with PH listed as the cause of death without available medical record confirmation. Anti-Th/To patients with ILD were twice as likely (OR 2.09, 95% CI 1.03–4.22, p=0.04) to also have PH compared to controls with ILD, with no difference in risk of associated PH in those without ILD (p=0.63). Overall 32% of anti-Th/To patients and 25% of controls had PH when using cause of death or verified clinical information. Thus long-term follow-up identifies a greater proportion of lcSSc patients ultimately developing PH than previously reported.

Table 1. Risk of patients with anti-Th/To having internal organ complications

	Odds Ratio	95% Confidence Interval	p-value
Interstital Lung Disease (ILD)	1.47	1.04 – 2.10	0.03
Pulmonary Hypertension (PH)	1.65	1.11 – 2.44	0.01
Esophageal Involvement	0.63	0.44 – 0.91	0.01
Cardiac Involvement	1.48	0.98 – 2.25	0.06
Renal Crisis	1.30	0.49 – 3.44	0.60
Muscle Involvement	0.41	0.14 – 1.17	0.09

Conclusion: This is the first and largest cohort of anti-Th/To positive SSc patients for whom there is long-term follow-up. Anti-Th/To patients with lcSSc are more likely to have ILD and PH than other patients with lcSSc, with significantly increased risk of having both PH and ILD. Anti-Th/To patients are less likely to develop esophageal involvement. Patients with anti-Th/To should be carefully screened for ILD and PH as part of their initial and follow-up evaluations.

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A Prospective Observational Study of Mycophenolate Mofetil Treatment in Rapidly Progressive Diffuse Cutaneous Systemic Sclerosis of Recent Onset. Fabian A. Mendoza[1], Sarah J. Nagle[2], Jason B. Lee[3] and Sergio A. Jimenez[4]. [1]Jefferson Institute of Molecular Medicine and Scleroderma Center, Rheumatology Division, Department of Medicine, Thomas Jefferson University, Philadelphia, PA, [2]Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, [3]Dermopathology Division, Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA, [4]Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA

Background/Purpose: The introduction of target organ specific therapies has substantially decreased Systemic Sclerosis (SSc) morbidity and mortality. In contrast, most studies of potential disease-modifying agents have shown negative results and currently there is no generally accepted SSc disease modifying therapy. The purpose of this study was to perform a prospective observational study to examine the effects of mycophenolate mofetil (MMF) treatment on skin and pulmonary involvement in patients with rapidly progressive diffuse cutaneous systemic sclerosis (SSc) of recent onset. The clinical observations were validated by skin histopathology and assessment of fibrosis-related gene expression.

Methods: Twenty five consecutive patients with early (<24 months) rapidly progressive diffuse cutaneous systemic sclerosis who had not received immunosuppressive or anti-fibrotic treatment received MMF as the only disease-modifying therapy. A modified Rodnan skin score (mRSS), assessment of affected body surface area (BSA), and a modified SSc severity scale were compared from initiation of MMF to the end of study. Histopathology and real time PCR assessment of fibrosis-related gene expression were performed before and after treatment in skin biopsies from 3 patients.

Results: At a mean+/−SD of 18.2 ± 8.73 months duration of MMF therapy and at a median dose of 2000 mg per day the mRSS decreased significantly from 24.56 ± 8.62 to 14.52± 10.9 (p=0.0004) and the BSA improved from 36 ±16% to 14 ±13.3% (p=0.00001). MMF therapy also prevented pulmonary function deterioration as total lung capacity and diffusion capacity remained stable without statistically significant differences between the pre- and post-treatment values. Histopathology showed a remarkable reduction in fibrotic tissue accumulation. Real time PCR showed a marked decrease in the expression of fibrosis-related genes. Adverse events were mild and most of the patients tolerated well the medication. One patient had a fatal outcome from dilated cardiomyopathy of unknown origin but not likely related to MMF treatment.

Conclusion: Treatment of previously untreated patients with diffuse cutaneous SSc of recent onset and rapid progression with MMF as the only disease modifying therapy resulted in marked clinical improvement in the extent and severity of skin involvement and caused an improvement of skin histopathological abnormalities and decreased expression of fibrosis-related genes. MMF also prevented pulmonary function deterioration in these patients.

ACR Concurrent Abstract Session

T-cell Biology and Targets in Autoimmune Disease: Lymphocyte Biology and Targets in Autoimmune Disease

Sunday, November 6, 2011, 4:30 PM–6:00 PM

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Therapeutic Effects of TGF-β-Induced Regulatory T Cells on the Established Autoimmune Diseases. Song G. Zheng[1], Qin Lan[2], Julie Wang[2], David Brand[3], David A. Horwitz[4], Zhong-Min Liu[5] and Hejian Zou[6]. [1]USC Keck School of Medicine, Los Angeles, CA, [2]University of Southern California, Los Angeles, CA, [3]VA Medical Center, Memphis, TN, [4]USC School of Medicine, Los Angeles, CA, [5]Shanghai East Hospital, Tonji University, Shanghai, China, [6]Huashan Hospital, Shanghai, China

Background/Purpose: While it has been well recognized that both natural Foxp3+ regulatory T (nTreg) cells and TGF-β-induced Treg (iTreg) cells can prevent autoimmune diseases in animal models, recent studies reveled that injection of nTregs has less therapeutic effects on established autoimmune diseases. It is less clear if iTregs can treat the established autoimmune diseases. We now provide evidence that unlike nTregs, injection of iTreg cells can markedly ameliorate the established autoimmune arthritis and lupus.

Methods: iTregs induction was developed as previously described. Collagen-induced arthritis (CIA) was induced in DBA/1J mice after immunized with CII/CFA. 80×10^6 DBA/2 spleens were transferred into D2B6F1 mice to induce chronic GVHD with a typical lupus syndrome. Cytokine levels were examined by FACS and ELISA. Bone erosion was determined by micro-CT and osteoclast differentiation was analyzed by TRAP staining.

Results: Both antigen-specific and polyclonally induced iTregs suppressed the established CIA although antigen-specific iTregs had a superior therapeutic effect. CIA mice given iTregs have a significantly lower incidence of disease and lower clinic scores than mice given nTregs, Teff cells or no cells. We found while nTregs were converted into Th1/Th17 cells *in vitro* and *in vivo* in the inflammatory milieu, iTregs were resistant to T effector cell conversion in the similar condition. Injection of iTregs to naïve mice and

immune deficient mice displayed similar levels of Foxp3 stability as comparing with nTregs. Of note, the stability of Foxp3 expression was only found in iTreg cells during established CIA. iTregs suppressed Th17 cell and osteoclast differentiation that paralleled with improved clinical scores, CII-specific IgG production and bone erosion. Injection of iTregs to the established lupus mice significantly decreased the levels of anti-dsDNA and proteinuria, and markedly prolonged the survival of lupus. Blocking of TGF-β/TGF-βR pathway using anti-TGF-β antibody or TGF-βRI (ALK5) inhibitor, or anti-IL-10R antibody almost completely abolished the therapeutic effects of iTregs on lupus, suggesting that TGF-β and/or IL-10 secreted by iTregs play a crucial role in the cell therapy. We further observed that DC isolated from lupus mice received iTregs but not control cells expressed lower levels of CD80 and CD86 and adoptive transfer of these DCs to another lupus mouse can suppress the disease development. Interestingly, blockade of TGF-β but not IL-10 signal abolished the suppressive effects of tolerogenic DC on the lupus in mice.

Conclusion: We therefore suggest that iTregs are stable and able to target DC in the inflammatory milieu, these DC then have become tolerogenic DC and further suppress disease progression through its direct or indirect effect (inducing new iTregs) in autoimmune disease settings. Manipulation of iTregs might have a therapeutic value in patients with RA and SLE.

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p53 Regulates Th17-Mediated Autoimmune Arthritis. Jin-Sil Park[1], Mi-La Cho[1], Mi-Ae Lim[1], Young-Mee Moon[1], Hye-Jwa Oh[1], Joo-Yeon Jhun[1], Jun-Geol Ryu[1], Jae-Kyeong Byun[1], Eun-Joo Jeon[1], Hye-Rin Jeong[1], Sang-Heon Lee[2] and Ho-Youn Kim[1]. [1]Catholic University of Korea, Seoul, South Korea, [2]Konkuk University School of Medicine, Seoul, South Korea

Background/Purpose: A great deal of effort has focused on the role of the p53 tumor suppressor in cancer. Recently, previous observations indicated that p53 can play a protective role in several immune and inflammatory diseases. To identify the role of p53 in autoimmune disorders, we examined whether p53 could regulate the *in vivo* effects of rheumatoid arthritis (RA).

Methods: Arthritis severity of wild type or p53 knockout (KO) mice with CIA was assessed by clinical and histologic scoring. p53 agonist or antagonist was administered via intraperitoneal injection in C57BL/6 mice and the *in vivo* effects were determined by assessing joint swelling, histological changes. The proliferation was determined by [^{3}H] thymidine incorporation and concentrations of CII-specific IgG2a, IL-17, and TNF-α were determined by ELISA. The expression of Th17 and Treg cells was analyzed by flow cytometry. Adoptive transfer of CD4+ T cells from WT or p53KO mice, respectively, to IL-17KO mice was performed. In human, CD4+ T cells from human peripheral blood mononuclear cells were differentiated into Th17 cells with p53 agonist and proportion of Th17/Treg was determined by flow cytometry.

Results: p53 inhibits Th17 differentiation of CD4+ T cells, while p53 promotes expression of Foxp3 *in vitro*. We observed that p53 mediated the suppression of Th17 differentiation by physically interacting with STAT3 or STAT5, which is major transcription factor for Th17 and Treg, respectively. p53 deficiency in mice exacerbated disease in collagen-induced arthritis (CIA) model, whereas p53 activation ameliorated the severity of arthritis through regulation of the balance between Th17 and Treg cells. Adoptive transfers of CD4+ T cells from p53 KO mice with CIA into IL-17 KO with CIA, which is resistant to CIA, induced severe autoimmune arthritis. p53 could regulate the differentiation of Th17 more effectively in patients with RA, when compare to healthy controls.

Conclusion: These results demonstrated that p53 serves as a novel regulator of Th17-Treg mediated autoimmunity and could be a new therapeutic target for rheumatoid arthritis.

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Citrullinated Fibrinogen-Specific CD4$^+$ T Cells Display Memory and Regulatory Phenotypes. Laura Su and Mark M. Davis. Stanford University School of Medicine, Stanford, CA

Background/Purpose: Rheumatoid arthritis (RA) is a common, highly debilitating systemic inflammatory condition. To date, little is known about which autoantigens are involved in RA and how T cells which recognize self-proteins may become pathogenic in disease. Fibrinogen is a common target of autoantibodies in RA patients, and a putative T cell autoantigen involved in disease development. The goal of this study is to identify and characterize fibrinogen-specific CD4$^+$ T cells.

Methods: Autoantigen-specific T cells were identified directly *ex vivo* using peptide-MHC tetramers. To identify individuals carrying the HLA-DRB1*0401 (DR4) allele, HLA typing was performed on healthy blood donors and RA patients using sequence-specific primer PCR. To identify antigen-specific T cells, tetramer staining was performed at room temperature for 1 hour using tetramers loaded with peptides from hemagglutinin (HA), citrullinated fibrinogen (cit-Fib), melanosomal matrix protein gp100, or the human immunodeficiency virus (HIV). Memory phenotyping was performed using antibodies against CD45RO and CCR7. Regulatory T cells (Tregs) were identified by Foxp3, CD25, and CTLA4 staining. Tetramer tagged cells were magnetically enriched and analyzed by flow cytometry.

Results: We demonstrated that the frequency of cit-Fib-specific CD4$^+$ T cells ranges from 0.5 to 22 per million CD4$^+$ T cells in healthy individuals. Surprisingly though, on average, 66% of cells display an antigen-experienced phenotype. This finding suggests prior TCR stimulation by cit- Fib or cross-reactive ligand(s) and brings up the question of why these fibrinogen-specific T cells do not cause autoimmunity in healthy individuals. Cell lineage analysis demonstrated that many cit-Fib-specific lymphocytes are Tregs that express Foxp3. Compared to other antigen-specific populations, the frequency of Tregs among cit-Fib-specific T cells is similar to that of another self-antigen specific population which recognizes gp100. Cit-Fib-specific Treg frequency is also similar to cells that recognize naïve epitopes from HIV. In contrast, Tregs are nearly undetectable among highly expanded populations of influenza-specific T cells. These results indicate that a significant response to foreign antigens correlates with a smaller, to nearly absent Treg population in the peripheral blood, and suggests that this may be a precondition for a robust T cell response against microbial challenges. Preliminary analysis using peripheral blood from RA patients demonstrates that cit-Fib-specific T cells can be identified and are present at higher frequency in comparison to healthy people. Further investigation is current ongoing to evaluate whether these cells are deficient in Foxp3 expression. A deficiency in cit-Fib-specific Tregs may contribute to exaggerated effector activity against citrullinated fibrinogen in RA patients.

Conclusion: T cells that recognize citrullinated fibrinogen can be detected in the peripheral blood of healthy individuals. These Cit-fib-specific populations contain large numbers of antigen-experienced T cells, many of which exhibit a Treg phenotype.

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Characterization of the Expanded Populations of TH17 and T Follicular Helper Cells in New Zealand Black (NZB) Chromosome 1 Congenic Mice. Nafiseh Talaei[1], Carolina Landolt-Marticorena[2], Babak Noamani[1], Evelyn Pau[1], Nan-Hua Chang[3] and Joan E. Wither[1]. [1]Toronto Western Research Institute, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Toronto Western Research Institute, University Health Network, Toronto, ON

Background/Purpose: We have previously shown that B6 mice with an introgressed homozygous NZB chromosome (c) 1 interval (70 to 100 cM) develop high titres of antinuclear antibodies and severe renal disease, with approximately 40% of the mice dying by 8 months age. Using subcongenic mice with shorter intervals in this region we found that expansion of T follicular helper (T_{FH}) and IL-17-producing T (T_H17) populations was closely associated with the severity of renal disease. In this report, we have characterized the nature and origin of these two cell populations.

Methods: To assess the cytokine profile of T_{FH} and T_H17 cells, splenocytes from c1(70–100), c1(88–100), c1(96–100), and B6 four month old mice were stimulated with PMA/Ionomycin for 4h in presence of GolgiStop, and analyzed by flow cytometry after cell surface (anti -CD3, -CD4, -PD1, and –CXCR5) and intracellular staining for IL-4, IL-17, IL-21 and IFN-g. Naïve T cells were differentiated in-vitro by stimulation with a-CD3 and -CD28 under T_H0 (a-IFN-g, a-IL-4), T_H17 (rIL-6, rIL-23 and rTGF-b and a-IFN-g, a-IL-4) and T_{FH} (rIL-6 and a-IFN-g, a-IL-4) cell conditions for 5 days before measuring intracellular cytokine production by flow cytometry.

Results: A significant proportion of the T_{FH} ($CD3^+CD4^+PD1^{hi}CXCR5^{hi}$) cells in c1 congenic mice secreted IL-21 alone or together with IFN-g. Very few T_{FH} cells secreted IL-17 and the proportion of these cells was not increased in c1 congenic mice. An increased proportion of IL-21-secreting cells was also seen in the conventional (T_{CON}, gated as non-T_{FH}) T cell subset. In contrast, the majority of IL-17 secreting cells were seen in the T_{CON} population and, consistent with previous reports, low levels of IL-21 but not IFN-g were also secreted by these cells. c1(88–100) and c1(70–100) mice demonstrated an equivalent enhanced tendency to differentiate towards T_H17 cells in-vitro as compared to B6 and c1(96–100) mice. However, differentiation of naive T cells to T_H0 and T_{FH} cells

was similar for all strains. We have previously shown that T cells from pre-autoimmune 8 wk old c1 congenic mice demonstrate enhanced differentiation to T_{FH} and T_H17 cells following immunization with an exogenous antigen stimulus (OVA/CFA i.p.). Preliminary adoptive transfer experiments where OVA-specific T cells, obtained from B6 or c1(70–100) OT-II TCR transgenic mice, were injected into B6 or c1(70–100) mice and subsequently immunized with OVA/CFA, confirmed that the enhanced T_H17 but not T_{FH} differentiation arises in part from an intrinsic T cell defect.

Conclusion: The findings suggest that a genetic polymorphism on NZB c1, located in the 88–96 cM interval, is associated with an intrinsic T cell functional defect that leads to enhanced differentiation of auto-reactive and antigen-primed T cells to IL-17 producing cells and that this polymorphism is associated with increased renal disease.

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Contribution of a Kidney-Infiltrating CD4$^+$ T Cell Clone to Nephritis in Lupus-Prone Mice. Akiko Okamoto[1], Keishi Fujio[1] and Kazuhiko Yamamoto[2]. [1]Graduate school of Medicine, The University of Tokyo, Tokyo, Japan, [2]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Background/Purpose: In systemic lupus erythematosus (SLE), CD4$^+$ T cells play key roles in the initiation and promotion of autoantigen-specific humoral immunity.Although autoantibody-associated T cells are supposed to exacerbate lupus-nephritis by enhancing autoantibody production, whether organ-infiltrating T cells directly contribute to kidney inflammation is unclear because it is difficult to directly analyze organ infiltrating T cells. In this study, we attempted to examine the pathogenic roles of autoreactive cytokine-expressing CD4$^+$ T cells from the kidney of early nephritic MRL/lpr mice. We focused on IFN-γ as a pathogenic cytokine because previous studies demonstrated the role of IFN-γ in the pathogenesis of lupus nephritis. And we hypothesized that the autoreactive T cells that responded to self-antigens in the early inflamed kidney would exhibit increased CD5 expression levels, because previous reports of TCR transgenic mice revealed that high CD5 and TCR expression are reflective of high avidity interactions with self-peptide:MHC complex and can be used to predict the survival/homeostatic expansion capacity of CD4$^+$ T cells.

Methods: We examined surface CD5 expression and cytokine secretion of CD4$^+$ T cells with flow cytometry. We performed single-cell analyses of CD5^{high}TCR^{high}CD4$^+$ T cells in the kidneys of early nephritic mice. We have retrovirally reconstituted TCR α/β genes of IFN-γ expressing cells in CD4$^+$ T cells.

Results: In the early nephritic MRL/lpr mice, the kidney CD4$^+$ T cells exhibited increased CD5 levels. We observed that IFN-γ secreting cells were enriched among CD5^{high}CD4$^+$ T cells from early inflamed kidney. Using single cell analyses of the TCR^{high}CD5^{high}CD4$^+$ T cells from the kidney of early nephritic MRL/lpr mice, two IFN-γ-expressing CD4$^+$ T cell clones, MLK2 and MLK3, were identified. TCR genes from MLK2- and MLK3-transduced CD4$^+$ T cells respond to splenic dendritic cells in an MHC class II dependent manner, but not to B cells or macrophages. MLK3-transduced CD4$^+$ T cells proliferated in the spleens of pre-nephritic mice and promoted nephritis progression upon adoptive transfer. Interestingly, MLK3-transduced CD4$^+$ T cells enhanced the deposition of C3 without promoting anti-dsDNA antibody production.

Conclusion: Our results suggest that CD4$^+$ T cells in the inflamed kidney of MRL/lpr mice contribute to nephritis progression without enhancing production of anti-dsDNA antibody. Although it is difficult to isolate and culture cytokine expressing clones that have infiltrated a parenchymatous organ, a combination of single cell sorting and TCR reconstitution enabled us to verify the pathological role of kidney infiltrating CD4$^+$ T cells in lupus-prone mice.

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Deficient Ubiquitin Ligase Casitas B-Lineage Lymphoma b Expression and Abnormal Peripheral Tolerance in CD4$^+$ T Cells From Systemic Lupus Erythematosus Patients. Diana Gomez-Martin, Maria J., Ibarra-Sanchez, Jose Cruz-Ruiz, Jorge Romo-Tena, Jose Esparza-Lopez, Mariana Diaz-Zamudio and Jorge Alcocer-Varela. Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico city, Mexico

Background/Purpose: A resistant to anergy phenotype has been evidenced in T cells from SLE patients. This might be related to intrinsic defects associated to abnormalities in the anergy induced genetic program, particularly ubiquitin ligases such as Casitas B-lineage lymphoma b (Cbl-b), which have not been fully addressed in SLE. The aim of this study was to analyze the expression of Cbl-b in CD4$^+$ T cells from SLE patients upon anergy induction and the associated proliferative and effector response.

Methods: Twenty patients with SLE (11 in clinical remission and 9 with active untreated disease) and 20 healthy controls were included. PBMC were isolated and CD4$^+$ T cells were negatively selected. Four experimental conditions were defined as followed: ex vivo, activation (anti-CD3 +anti-CD28), anergy (ionomycin) and rest. Cellular proliferation was addressed by CFSE dilution method. Cbl-b expression was assessed by real time PCR and western blot. Cytokine production was measured in the supernatants from cell cultures by luminometry. Surface expression of activation and costimulatory molecules were analyzed by flow cytometry. Mean and standard deviation or median and interquartilar range were used for descriptive statistics. Comparison between groups was made by means of Student's T test and Mann Whitney test.

Results: Upon anergy induction, Cbl-b normalized mRNA (0.21 vs 0.47, $p=0.015$) and protein expression (0.73 vs 0.90, $p=0.038$) in CD4$^+$ cells from SLE patients was decreased in comparison to controls. No differences were found between active and remission patients. CD4$^+$ cells from SLE patients shown multiple abnormalities regarding the proliferative response, particularly, resistance to anergy was evidenced by a decreased anergy index in patients vs controls (237 vs 558, $p<0.05$), as well as higher IL-2 production (43.4 vs 17.1 pg/mL) after ionomycin treatment. Moreover, the proliferative response to activation protocol was lower for SLE patients vs controls. Among SLE patients, after anergy induction, the synthesis of pro-inflammatory cytokines was diminished in comparison to activation protocol, being this difference significant only for IFN-' (130.30 pg/mL vs 23.72 pg/mL, $p<0.05$).After ionomycin treatment, a dichotomy between suppressive cytokines was displayed, as IL-4 production was increased and IL-10 was decreased in SLE patients vs controls (IL-4: 33 vs 24.2 pg/mL; IL-10: 159.5 vs 1166.7 pg/mL). In terms of activation surface markers, after anergy induction, increased expression of CD69 (20.1 vs 2.1, $p<0.001$), CD83 (30.7 vs 10.1, $p=0.001$) and CD40L (33.6 vs 15.1, $p<0.001$) was found in SLE patients vs healthy controls.

Conclusion: CD4$^+$ T cells from SLE patients display a vast array of abnormalities regarding proliferative and effector responses to activation and anergy induction. Our data suggest that resistance to anergy in CD4$^+$ cells from SLE patients, without regarding disease activity, is related to decreased Cbl-b expression as well as overexpression of activation and costimulatory molecules. These might be related to persistent proliferation of autoreactive T cells even under the absence of appropriate costimulation.

ACR Concurrent Abstract Session
Vasculitis II

Sunday, November 6, 2011, 4:30 PM–6:00 PM

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Prednisone Versus Tamoxifen for Idiopathic Retroperitoneal Fibrosis. Augusto Vaglio[1], Alessandra Palmisano[1], Stefania Ferretti[1], Rocco Cobelli[1], Luigi Boiardi[2], Carlo Buzio[1] and Carlo Salvarani[2]. [1]University of Parma, Parma, Italy, [2]Arcispedale S Maria Nuova, Reggio Emilia, Italy

Background/Purpose: Glucocorticoids are the mainstay of therapy for idiopathic retroperitoneal fibrosis (IRF), but they often have considerable toxicity. Several reports have suggested that tamoxifen may be a valid alternative to glucocorticoids. In this open-label, randomised controlled trial, we compared the efficacy of prednisone and tamoxifen in patients with IRF.

Methods: Forty patients with newly diagnosed IRF received induction therapy with 1 mg/kg/day of prednisone for 1 month, at the end of which those who achieved remission were randomly assigned to receive tapering prednisone (initial dose, 0.5 mg/kg/day) for 8 months or tamoxifen (fixed dose, 0.5 mg/kg/day) for 8 months. After the end of treatment, the patients were followed up for an additional 18 months (overall, 26 months). The primary end-point was the relapse rate by the end of treatment (month 8). Secondary end-points included 8-month change in IRF size and renal function. This trial is registered with ClinicalTrials.gov, number NCT00440349.

Results: Thirty-six of the 40 enrolled patients achieved remission following induction therapy and were randomised to receive prednisone or tamoxifen (18 per group). One patient (6%) in the prednisone group and seven patients (39%) in the tamoxifen group developed relapses by the end of treatment (difference −33% [95% confidence interval −58% to −8%, P=0.04]). The difference in relapse rates between the groups was sustained after the additional 18-month follow-up (26-month estimated cumulative relapse probability 17% with prednisone and 50% with

tamoxifen, P=0.04). Prednisone also induced a greater reduction in size of IRF (P=0.03), whereas no differences were found in renal function improvement.

Conclusion: Prednisone is more effective than tamoxifen in preventing relapses in IRF patients, and induces a greater shrinkage of the retroperitoneal mass.

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The Relationship Between Systemic Vasculitis and Retinal Vasculitis. James T. Rosenbaum[1], Jennifer Ku[2], Amro Ali[2], Dongseok Choi[2] and Eric B. Suhler[2]. [1]Oregon Health & Science University, Portland, OR, [2]Oregon Health & Science Univ, Portland, OR

Background/Purpose: Systemic vasculitis is often assumed to be a common cause of retinal vasculitis. We sought to determine the relationship between retinal vasculitis and systemic vasculitis as diagnosed in a tertiary referral clinic for patients with uveitis.

Methods: A selected review was performed on 1390 charts of patients attending the uveitis clinic at the Oregon Health & Science University, Casey Eye Institute, between 1985 and 2010. Included in the review were all patients with diagnoses commonly associated with retinal vasculitis and all patients who were diagnosed with a systemic vasculitis. Retinal vasculitis was identified by perivascular exudates, intraretinal hemorrhage, or cotton wool spots as seen on clinical examination or by vascular occlusion or leakage as identified by fluorescein angiogram.

Results: Of the 1390 charts reviewed, 207 or 14.9% had retinal vasculitis as a component of the intraocular inflammation. Thirty-five patients had retinal vasculitis which was primary, i.e. not associated with a systemic disease, and the dominant manifestation of the uveitis. Fourteen of the patients with retinal vasculitis had Behcet's disease. Only 11 of the 1390 patients with uveitis had a systemic vasculitis, 3 with granulomatosis with polyangiitis (formerly Wegener's granulomatosis), 4 with primary central nervous system vasculitis, 2 with Churg-Strauss syndrome, 1 with leukocytoclastic vasculitis, and one with pulmonary vasculitis. Of these 11, four had retinal vasculitis including one secondary to a CMV retinitis. Thus, systemic vasculitis was directly responsible for 1.4% or 3 of 207 cases of retinal vasculitis. In comparison to systemic vasculitides, non-vasculitic systemic diseases such as sarcoidosis (n=13), immune-mediated syndromes confined to the eye such as birdshot retinochoroidopathy (n=9) or pars planitis (n=36), and intraocular infections (n=29) were far more common causes of retinal vasculitis.

Conclusion: Retinal vasculitis is not defined by vessel wall destruction, a hallmark of systemic vasculitis. Retinal vasculitis is a relatively common feature of uveitis, but it is an extremely uncommon manifestation of the classical systemic vasculitides.

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Efficacy and Tolerance of Treatments in Patients with Non-Infectious Mixed Cryoglobulinemia Vasculitis: Results From the French Nationwide CryoVas Survey. Benjamin Terrier[1], Evguenia Krastinova[2], Isabelle Marie[3], Adeline Lacraz[4], David Launay[5], Emmanuelle Plaisier[6], Luc de Saint-Martin[7], Fabrice Bonnet[8], Pauline Belenotti[9], Jean-Emmanuel Kahn[10], Olivier Hinschberger[11], Patricia Rullier[12] and Patrice Cacoub[13]. [1]Pitié-Salpêtrière Hospital, Paris, France, [2]INSERM U707, Paris, France, [3]Service de médecine interne, CHU de Rouen, Rouen, France., Rouen, France, [4]Nephrology, CHU Bordeaux, Bordeaux, France, [5]Internal Medicine, CHRU Claude Huriez, Lille, France, [6]Nephrology, Tenon Hospital, Paris, France, [7]Internal Medicine, CHU Brest, Brest, France, [8]Internal Medicine, CHU Bordeaux, Bordeaux, France, [9]Internal Medicine, CHU Marseille, Marseille, France, [10]Internal Medicine, Foch Hospital, Suresnes, France, [11]Internal Medicine, CH Mulhouse, Mulhouse, France, [12]Internal Medicine, CHU Montpellier, Montpellier, France, [13]CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: Data on efficacy and tolerance of treatments in non-infectious mixed cryoglobulinemia vasculitis (CryoVas) in the era of hepatitis C virus screening are lacking. The CryoVas survey was set up to describe presentation and evaluate efficacy and tolerance of treatments in patients with non-infectious CryoVas, in the absence of large series and therapeutic guidelines. Objective: To analyze the efficacy and the tolerance of treatments in patients with non-infectious mixed CryoVas.

Methods: Eighty-one French centers from Universitary and general hospitals have included 242 patients with non-infectious mixed CryoVas diagnosed between January, 1995 and July, 2010. We compared the efficacy and tolerance of corticosteroids alone versus corticosteroids plus immunosuppressive agents. In order to analyze the impact of treatments in the presence of time-dependent confounders, we used Cox Marginal Structural Models (Cox-MSM). We created a pseudo-population using the inverse probability of treatment weighting. Baseline covariates (age, gender, GFR, cause of CryoVas) and time-dependant covariates (i.e., clinical manifestations of vasculitis) were included in the model.

Results: Data on 209 patients (86%) who received therapy and had at least 6 months of follow-up were analyzed for efficacy and tolerance. Treatments used during follow-up were: corticosteroids (n=209 patients), alkylating agents (n=95), rituximab (n=80), plasmapheresis (n=43), azathioprine/mycophenolate mofetil (n=31).

Regarding efficacy, rituximab plus corticosteroids was more effective than corticosteroids alone for achieving a complete clinical response (HR 3.7, P=0.01), a prednisone dosage <10 mg/d at month 6 (HR 2.5, P<0.0001), a renal response (HR 31.6, P=0.03) and an immunological response (HR 33.8, P=0.001). In contrast, alkylating agents plus corticosteroids was more effective than corticosteroids alone only for achieving a prednisone dosage < 10 mg/d at month 6 (HR 1.5, P=0.004) and an immunological response (HR 5.7, P=0.001).

Regarding tolerance, rituximab plus corticosteroids was more frequently associated with serious infections than corticosteroids alone (HR 9.0, P<0.0001), while death rates did not differ between therapy groups. Among patients who received rituximab, a daily dose of corticosteroids >50 mg/d was more frequent in those who experienced a serious infection (71% vs. 39%, P=0.008). In contrast, alkylating agents plus corticosteroids was less frequently associated with serious infections than corticosteroids alone (HR 0.2, P=0.002), while death rates did not differ between therapy groups.

Conclusion: Data from this large survey show that in patients with non-infectious mixed cryoglobulinemia vasculitis, rituximab plus corticosteroids showed the greater efficacy. This regimen was also associated with serious infections, particularly when higher dose of corticosteroids were used. The place of each therapeutic strategies remains to be defined in well-designed randomized controlled trials.

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Churg–Strauss Syndrome: Description and Long-Term Follow-up of the 383 Patients Enrolled In the FVSG Cohort. Christian Pagnoux[1], Chloe Comarmond[2], Mehdi Khellaf[3], Jean-Francois Cordier[4], Mohamed Hamidou[5], Jean-Francois Viallard[6], Francois Maurier[7], Philippe Delaval[8], Boris Bienvenu[9], Xavier Puechal[10], Olivier Aumaître[11], Marc Ruivard[12], Alain Le Quellec[13], Ramiro Cevallos[14], Olivier Fain[15], Bertrand Godeau[3]. Raphaèle Seror[2], Alfred Mahr[16], Pascal Cohen[17], Luc Mouthon[18], Loic Guillevin[19] and French Vasculitis Study Group (FVSG)*, [1]University of Toronto, Toronto, ON, [2]Referral Center for Necrotizing Vasculitides, Hôpital Cochin, AP–HP, Université Paris–Descartes, Paris, France, [3]Service de médecine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, Creteil, France, [4]Division of Pneumology, Hôpital Louis-Pradel, Hospices Civils de Lyon, Lyon 1, Lyon, France, [5]Service de médecine interne, Hôpital Universitaire de Nantes, Nantes, France, Nantes, France, [6]Division of internal Medicine, Hôpital Haut-Lévêque, Université Victor Segalen – Bordeaux 2, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, Bordeaux, France, [7]Division of internal Medicine, CHR Metz, Metz, Metz, France, [8]Division of Pneumology, Centre Hospitalier Régional Universitaire de Rennes, Rennes, Rennes, France, [9]Division of Internal Medicine, Centre Hospitalier Régional Universitaire de Caen, Côte de Nacre, Caen, Caen, France, [10]Le Mans General Hospital, Le Mans, France, [11]Division of internal Medicine, Centre Hospitalier Universitaire, Hôpital Gabriel Montpied, Clermont–Ferrand, Clermont–Ferrand, France, [12]Medicine, Centre Hospitalier Universitaire, Hôpital Gabriel Montpied, Clermont–Ferrand, Clermont–Ferrand, France, [13]Division of internal Medicine, Hôpital Saint-Eloi, Centre Hospitalier Universitaire de Montpellier, Montpellier, Montpellier, France, [14]CH Compiegne, Compiegne, France, [15]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France, [16]Hospital Saint-Louis, Paris, France, [17]Service de médecine interne, Centre de Références des Vascularites, Université Paris Descartes, APHP, Hôpital Cochin, 75005 Paris, France., Paris, France, [18]Hopital Cochim, Paris, France, [19]Cochin University Hospital, Paris, France

Background/Purpose: Earlier studies on Churg–Strauss syndrome (CSS, recently renamed eosinophilic granulomatosis with polyangiitis/EGPA), including each less than 120 patients, demonstrated that ANCA+ and ANCA– patients differed clinically at diagnosis but not in their outcomes. However, their mean follow-up durations were limited (< 3 years). Our aims were to describe the main characteristics of a larger cohort of patients and their

long-term outcomes and to determine potential predictors of death and relapse.

Methods: We conducted a retrospective study of the patients diagnosed with CSS, satisfying the American College of Rheumatology and/or Chapel Hill criteria, entered in the FVSG database since its creation in 1983. Their characteristics and outcomes were compared according to their ANCA status at diagnosis and year of diagnosis (≤ or >1996, when the FFS was devised). ANCA were tested either on fresh or, for those patients diagnosed before ANCA testing became routinely available, on stored frozen serum samples, when available. Vasculitis relapse was defined as the recurrence or worsening of a clinical manifestation of CSS, following a period of remission of ≥3 months. Isolated asthma flares, which might have required transient increase of corticosteroid dose, sinusitis (or rhinitis) and/or increases in eosinophil count without any other clinical CSS manifestations were recorded, but not considered as vasculitis relapse per se, and were analyzed separately.

Results: We identified 383 patients diagnosed with CSS between 1957 and June 2009 (128 (33.4%) ≤ 1996) and followed for 66.8 ± 62.5 months. At diagnosis, their mean age was 50.3 ± 15.7 years and 91.1% had asthma (since 9.3 ± 10.8 years). Main disease manifestations were peripheral neuropathy (51.4%), ENT manifestations (48.0%), skin lesions (39.7%), lung infiltrate (38.6%), gastrointestinal signs (23.2%), renal disease (21.7%) and/or cardiomyopathy (16.5%). Among the 348 patients tested for ANCA, 108 were positive (31.0%) and had significantly ($P < 0.05$) more frequent ENT manifestations (59.3% vs. 44.2%), peripheral neuropathy (63.0% vs. 44.2%) or renal involvement (26.9% vs. 16.3%), but less frequent clinical cardiomyopathy (19.2% vs. 8.3%) than ANCA– patients. Vasculitis relapses occurred in 35.2% of ANCA+ vs 22.5% of ANCA– patients ($P = 0.01$) and deaths in 5.6% vs 12.5%, respectively ($P < 0.05$). Relapse-free survival at 5 years was 58.1% [95% CI; 45.6–68.6] for ANCA+ and 67.8% [95% CI; 59.8–74.5] for ANCA– patients ($P = 0.35$). Both original and revised FFS were predictive of mortality. Multivariable analysis on individual parameters identified cardiomyopathy, older age and a diagnosis ≤1996 as risk factors for death. The sole independent predictors of relapse were a lower eosinophil count at diagnosis (< 7,065/mm3) and, if excluding eosinophil count from the model, ANCA positivity.

Conclusion: CSS patients differ according to their ANCA status, in their clinical presentation at diagnosis but also in their long-term outcomes. Even though CSS mortality has declined over the past decades, at least since 1996, relapses remain frequent, especially in the ANCA+ patients.

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Surgery Versus Endovascular Repair in Takayasu Arteritis: A Multicenter Study of 166 Procedures. David Saadoun[1], Marc Lambert[2], Tristan Mirault[3], Yoland Shoindre[1], Zahir Amoura[4], Mathieu Resche Rigon[1], Pierre yves Hatron[5], Joseph Emmerich[3] and Patrice P. Cacoub[6]. [1]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]Service de médecine interne, Hôpital Claude Huriez, Université Lille II, Lille, France, Lille, France, [3]Service de Médecine Vasculaire HEGP, Paris, France, [4]CHU Pitié-Salpêtrière, Paris, France, [5]Service de médecine interne, Hôpital Claude Huriez, Université Lille II, Lille, France, Paris, France, [6]Hopital La Pitie, Paris, France

Background/Purpose: With recent advances in endovascular treatment, percutaneous endoluminal angioplasty (PTA) has become particularly attractive for arterial lesions of Takayasu arteritis (TA). However, data provided from cases reports or small series and the long term outcome has not been reported. The incidence of potential vascular complications after surgery or endovascular treatment is still to be determined.

Methods: Retrospective multicenter study comparing the results and outcome of 79 consecutive patients with TA [median (IQR) age 39 (25–50) years, with 63 (79.7%) females)] who underwent 166 vascular procedures [104 (62.7%) surgery and 62 (37.3%) PTA] for the management of arterial complications.

Results: After a time of follow-up of 6.5 (2.2–11.5) years, 74 complications were observed including restenosis (n=42), thrombosis (n=7), renal insufficiency (n=7), bleeding (n=6), sepsis (n=4), stroke (n=4) and hypertension (n=4). The 5- and 10-years arterial complication free survival rates were 60% and 57% versus 49% and 29% ($P<0.05$) in the surgery group versus PTA group, respectively. In multivariate analysis, PTA [OR (95%CI) 3.61 (1.3–10.3); $P=0.021$] was independently associated with the occurence of arterial complications. Patients who experienced complications had higher erythrocyte sedimentation rate ($P<0.001$), C-reactive protein ($P<0.001$) and fibrinogen ($P<0.005$) serum levels compared to those without complications.

Conclusion: Our study is the first to show in TA that PTA increase by 4 times the likelihood of complications compared to surgery. Biological inflammation at the time of revascularisation is associated with an increase odds of arterial complications.

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Causes and Prognostic Factors of Mortality in Patients with Non-Infectious Mixed Cryoglobulinemia Vasculitis: Results From the French Nationwide CryoVas Survey. Benjamin Terrier[1], Evguenia Krastinova[2], Isabelle Marie[3], Adeline Lacraz[4], David Launay[5], Emmanuelle Plaisier[6], Luc de Saint-Martin[7], Fabrice Bonnet[8], Pauline Belenotti[9], Jean-Emmanuel Kahn[10], Olivier Hinschberger[11], Patricia Rullier[12] and Patrice Cacoub[13]. [1]Pitié-Salpêtrière Hospital, Paris, France, [2]INSERM U707, Paris, France, [3]Service de médecine interne, CHU de Rouen, Rouen, France., Rouen, France, [4]Nephrology, CHU Bordeaux, Bordeaux, France, [5]Internal Medicine, CHRU Claude Huriez, Lille, France, [6]Nephrology, Tenon Hospital, Paris, France, [7]Internal Medicine, CHU Brest, Brest, France, [8]Internal Medicine, CHU Bordeaux, Bordeaux, France, [9]Internal Medicine, CHU Marseille, Marseille, France, [10]Internal Medicine, Foch Hospital, Suresnes, France, [11]Internal Medicine, CH Mulhouse, Mulhouse, France, [12]Internal Medicine, CHU Montpellier, Montpellier, France, [13]CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: Data on prognosis in non-infectious mixed cryoglobulinemia vasculitis (CryoVas) in the era of hepatitis C virus screening are lacking. Objective: To analyze causes of death and prognostic factors in patients with non-infectious mixed CryoVas.

Methods: Eighty-one French centers of Internal Medicine, Nephrology, Rheumatology, Hematology, Dermatology and Neurology from Universitary and general hospitals have included 242 patients with non-infectious mixed CryoVas diagnosed between January, 1995 and July, 2010. Causes of death and prognostic factors were assessed. We included all variables with p value >0.2 in the univariate anlysis in a multivariate Cox proportional hazard ratio model.

Results: 166 women and 76 men (sex ratio W/M 2,2), mean age 62.6±14.5 years, were included. Baseline manifestations were: purpura (75%), peripheral neuropathy (52%), arthralgia (44%), glomerulonephritis (35%), Raynaud phenomenon (26%), cutaneous ulcers (16%), necrosis (14%), myalgia (10%), gastrointestinal involvement (5%), central nervous system (2%) and pulmonary (2%) involvement.

After a median follow-up of 54 months (IQR 9–77), 42 patients (17%) died. Causes of death were: infections (n=21), vasculitis (n=8), cardiovascular disease (n=5), deterioration of the general health status (n=2), unknown (n=7). One-year, 2-year, 5-year and 10-year overall survival were 91, 89, 79 and 65%, respectively.

In multivariate analysis, factors significantly associated with death were: age > 65 years [Hazard Ratio (HR) 1.04 (95% IC 1.02–1.08); P=0.001], gastrointestinal involvement [HR 2.29 (0.99–5.31); P=0.05], male gender [HR 2.13 (1.01–4.11); P=0.02] and a glomerular filtration rate < 60 mL/min [HR 1.90 (1.01–3.56); P=0.04].

A prognostic score (CryoVas score, CVS) including these factors was significantly associated with survival (P<0.0001, with HR for death of 1, 8.2 and 26.8 for a score of 0, 1 and ≥ 2, respectively). The Five Factor Score 2009 (FFS) was also significantly associated with survival (P<0,0001, with HR for death of 1, 3.8 and 10.2 for a score of 0, 1 and ≥ 2, respectively). Comparison between CVS and FFS showed a better but not significant performance of the CVS.

Conclusion: In patients with non-infectious mixed cryoglobulinemia vasculitis, main prognostic factors are age >65 years, gastrointestinal involvement, male gender and renal failure. A score including these variables is significantly associated with survival.

ACR Combined Session

ACR/ARHP Combined Pediatrics Abstract Session

Sunday, November 6, 2011, 4:30 PM–6:00 PM

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The Development of a New Service for the Management of Non-Inflammatory Musculoskeletal Pain. Susan Maillard, Swati Bhagat, Charmaine Bernie, Alice Morgan, David Adkins, Ellie Haggart and Clarissa Pilkington. Great Ormond Street Hospital, London, United Kingdom

Background/Purpose: Great Ormond Street Hospital Rheumatology Department recognised that 50% of the referrals that were received were for

young people with non-inflammatory musculoskeletal pain (NIMP) but that the service was not able to provide adequate treatment after diagnosis. A business plan was proposed to the hospital management board and a new service was developed and subsequently reviewed.

Methods: The business plan was developed by senior multidisciplinary members of the Rheumatology team. The new service was set up and then specific outcome measures were followed after 1 year to monitor the success and effectiveness of the treatments and service.

Results: The service was funded to employ a full time Physiotherapist (PT), Occupational Therapist (OT), Psychologist (Psych) and administrator. Out-patient appointments were established and patients were placed into the new service. The initial appointment was in a new-patient clinic and they were assessed by a Consultant paediatric Rheumatologist and a specialist physiotherapist. This initial assessment ensured that there was no other diagnosis other than a non-inflammatory condition such as hypermobility syndrome; the patient was then referred to PT, OT and Psych as appropriate. The treatments included individualised home muscle strength training programmes, life style advice, group patient and parent education programmes and individualised pain management interventions. Specific Outcome measures (OCM) were used to monitor the success of the treatments provided. The most significant OCM's were:

School attendance which increased from 75% missing at least 1 day a week due to pain to only 7%.

Loss of muscle strength was present in 98% of children and this was resolved in 100% of those who completed the programme given.

Participation in PE increased from only 25% participating to 75% joining in sport at school.

The cost of providing the staff and facilities was less than 50% of the revenue the service brought into the hospital and so the service made a significant profit.

Conclusion: The establishment of a dedicated service to the management of NIMPS has been shown to be both clinically and cost effective and has worked extremely well as an AHP led service enabling the medical staff to focus upon inflammatory diseases.

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Development of a Questionnaire for Early Detection of Factors Associated to the Adherence to Treatment of Children and Adolescents with Chronic Rheumatic Diseases—"the Pediatric Rheumatology Adherence Questionnaire (PRAQ)". Vanessa M. Bugni[1], Karine Y. K. Okamoto[1], Luciana S. Ozaki[1], Fernanda M. Teles[1], Juliana Molina[1], Vanessa C. Bueno[1], Maria Odete E. Hilário[1], Claudio A. Len[1] and Maria Teresa Terreri[2]. [1]Universidade Federal de São Paulo/UNIFESP, São Paulo, Brazil, [2]Universidade Federal de São Paulo/UNIFESP, Sao Paulo, Brazil

Background/Purpose: Over the last three decades the interest in studying adherence to treatment in children and adolescents with chronic rheumatic diseases has substantially increased. This is of particular importance since harmful and irreversible effects may arise due to poor treatment adherence. Our objective is to develop a questionnaire that would allow an early identification of factors related to the adherence to medical and non-medical treatments of children and adolescents with chronic rheumatic diseases.

Methods: First step: a preliminary questionnaire composed of 46 questions directed at parents was created by a group of experts in the treatment of children with chronic rheumatic diseases (4 pediatric rheumatologists, 2 physical therapists, 1 psychologist) and by a group of 3 parents from our patient population. 2nd step: a panel of 4 pediatric rheumatologists prepared a questionnaire with the following parameters: socioeconomic status, relationship with the health care team and system, diagnoses, therapy and relationship between patient and caregiver. 3rd step: the questionnaire was tested in a group of parents of low socioeconomic status, who accompanied their children to the Pediatric Rheumatology Outpatient clinic at the beginning of their treatment. After six months, a different questionnaire was administered to identify good or poor adherence to treatment. Poor adherence was defined as adherence to less than 80% or more than 120% of the medical treatments and/or appointments and exams. We applied the Cronbach's alpha coefficient for reliability evaluation, the Kappa coefficient for agreement between the questions in each block and Spearman correlation to test the correlation between the parameters and the percentages of adherence.

Results: Thirty three patient's parents answered the questionnaires. The average age in the initial evaluation was 10.3 years. Thirteen patients presented idiopathic juvenile arthritis, 10 had systemic lupus erythematosus, 7 had juvenile dermatomyositis and 3 had localized scleroderma. We observed poor adherence to the medical and/or non-medical treatment in 25% of the patients. After statistical analysis to evaluate for internal consistency, 27/46 questions were retained and included in the PRAQ. We observed a tendency for correlation within the socioeconomic block (distance to the hospital, type of transportation, number of children and parent's work) and poor adherence to the medical treatment ($p=0.087$). No significant correlations among the other parameters and adherence to the medical treatment and/or appointments and exams were observed.

Conclusion: The development of tools which identify indicators for poor treatment adherence is important in order to make better therapeutic decisions and better monitoring of patients with chronic rheumatic diseases. The administration of the PRAQ must be conducted in a larger number of patients in order to reach the proposed objectives.

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Characterization of Active Joint Count Trajectories in Juvenile Idiopathic Arthritis. Roberta A. Berard[1], George A. Tomlinson[2], Xiuying Li[3], Kiem Oen[4], Alan M. Rosenberg[5], Brian M. Feldman[6], Rae SM Yeung[7] and Claire Bombardier[8]. [1]Children's Hospital of Western Ontario, London, ON, [2]University of Toronto, Toronto, ON, [3]University Health Network, Toronto, ON, [4]University of Manitoba, Winnipeg, MB, [5]Royal University Hospital, Saskatoon, SK, [6]The Hospital for Sick Children, Toronto, ON, [7]Hospital for Sick Children, Toronto, ON, [8]Institute for Work & Health, Toronto, ON

Background/Purpose: To describe the patterns of longitudinal disease activity (active joint count (tender and swollen joints) in juvenile idiopathic arthritis (JIA) and to examine the association of clinical and laboratory characteristics with these patterns.

Methods: A retrospective cohort study at two Canadian centres was performed. The longitudinal patterns of active joint counts were described using latent curve growth analysis. This method is ideally suited to a population whereby the underlying hypothesis is that the population is comprised of (unobserved) subpopulations. Latent curve growth analysis aims to classify individuals into statistically distinct groups based on individual response patterns so that individuals within a group are more similar than individuals between groups. The trajectory classes are each defined by a longitudinal growth curve. The association of baseline characteristics with class membership was performed by conducting a test of mean difference across classes for continuous variables and by comparing proportions for categorical variables.

Results: Data were analyzed on 659 children diagnosed with JIA between 1990/03–2009/09. The median age at diagnosis was 10.00 (IQR 3.67–13.39), 61% (402/659) were female and 45% (286/629) were ANA positive. The distribution of the ILAR diagnoses were as follows: systemic (7%), oligoarthritis (36%), polyarthritis (RF negative) (13%), polyarthritis (RF positive) (4%), psoriatic arthritis (8%), enthesitis-related arthritis (20%) and undifferentiated (12%). A maximum of 10 years of follow-up data was included in the longitudinal analysis. The 659 patients were classified into 5 statistically different patterns of longitudinal active joint count (AJC) profiles using a latent curve growth analysis. 44% of patients were in group 1 characterized by a low initial AJC (mean 0.9) following by a decrease in joint count, 18% in group 2—minimal to no active joint disease throughout course (mean 0.3), 19% in group 3—moderate persistent AJC (mean 3.8), 10% in group 4—initial mean AJC 4.9 followed by an increase in AJC at 5 years (mean 9.7) and finally 10% in group 5 characterized by an initial polyarthritis (mean 14) followed by a decline in AJC. The baseline characteristics of participants stratified by trajectory were statistically significantly different for all variables considered (age, sex, diagnostic delay, ANA positive, HLA-B27 positive, systemic fever, lumbosacral back pain, family history of HLA-B27 associated disease).

Conclusion: This study was a successful application of a novel approach to longitudinal growth curve modeling to identify distinct trajectories of disease activity in JIA. The trajectories identified were statistically and clinically distinct from the ILAR subtypes. Identification of patterns of disease course is important in working towards the development of an outcome-based classification system in JIA.

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Predictors of Health-Related Quality of Life in Children and Adolescents with Juvenile Idiopathic Arthritis: Results From a Web-Based Survey.
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Background/Purpose: Children with Juvenile Idiopathic Arthritis (JIA) experience functional impairment due to joint manifestations of the disease. Based on previous studies, children with JIA have lower Health Related Quality Of Life (HRQoL) scores compared to their healthy peers. However, comparison between studies is hampered because of e.g. heterogeneity of age cohorts and recruitment protocols. The aim of our present study was to assess Health Related Quality of Life (HRQoL) by the use of Patient Reported Outcomes (PROs) and its predictors in a group of children and adolescents with JIA.

Methods: This study is part of the 'KLIK study', which assesses the effect of identifying and discussing HRQOL problems using PROs. The study sample includes all JIA patients (6–18 years) visiting four pediatric rheumatology outpatient clinics in Amsterdam in the period February 2009 until March 2010. Patients or parents (of children 6–7 years) are invited to complete questionnaires online before visiting the rheumatologist. The outcome (PROfile) is presented to the paediatricians to help identify and discuss HRQoL issues. HRQoL is measured using the Pediatric Quality of Life Inventory 4.0 (Pedsql 4.0). Functional ability is measured using the Child Health Assessment Questionnaire (CHAQ). Data concerning disease characteristics, disease activity parameters, joint counts and medication use were collected at consultation. The study sample was compared to healthy peers and to peers with other chronic illnesses using a two sample t-test. The proportion of children with JIA with an impaired HRQoL was evaluated and multivariate regression analyses were performed to predict HRQoL outcome. Effect sizes (d) were calculated.

Results: Approximately 70% of the eligible JIA patients participated (n=157). Data of 14 children aged 6–7 years (M=7.22), 63 children aged 8–12 years (M=11.20) and 78 adolescents aged 13–18 years (M=15.95) were available for analysis. At consultation, 40% of the patients had inactive, 38% mild and 22% moderate to severe disease activity; the mean CHAQ score was 0.79; 90% of the patients used DMARDS including biologicals. Children and adolescents with JIA differed on almost all domains significantly with healthy controls and a chronic health condition. Effect sizes were moderate to large, with the exception of emotional functioning (table 1). Approximately half of the children with JIA have an impaired HRQoL. The main predictors of HRQoL were physical functioning, subjective burden of medication use and school absence.

	Children with JIA			Norm population				Chronic illnesses			
Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	***d***	**N**	**Mean**	**SD**	***d***
Group 6–7 (proxy report)											
Total score	14	70.26*	23.02	61	86.07	8.29	*1.9*	11	80.33	9.39	*1.1*
Psychosocial health		72.98*	18.75		84.59	9.23	*1.3*		79.24	10.99	*1.7*
Physical health		65.18*	32.22		88.83	9.43	*2.5*		82.39	11.38	*1.5*
Emotional functioning		69.29	22.09		78.44	12.77	*0.7*		74.09	12.61	*0.4*
Social functioning		76.79*	20.06		89.02	11.21	*1.1*		84.09	10.68	*0.7*
School functioning		72.86*	19.88		86.31	10.80	*1.3*		79.55	16.65	*0.4*
Group 8–12 (self report)											
Total score	63	71.67***^^	14.06	192	82.31	8.83	*1.2*	26	80.64	9.32	*1.0*
Psychosocial health		71.90***^	13.90		80.75	10.34	*0.9*		79.81	10.43	*0.8*
Physical health		71.23***^^	20.48		85.25	8.85	*1.6*		82.21	12.14	*0.9*
Emotional functioning		69.84*^	20.32		76.85	13.76	*0.5*		78.85	13.21	*0.7*
Social functioning		76.98***	15.07		86.51	12.24	*0.8*		83.27	12.80	*0.5*
School functioning		68.89***^	17.04		78.88	11.90	*0.8*		77.31	13.13	*0.6*
Group 13–18 (self report)											
Total score	75	71.91***	17.36	148	83.14	8.99	*1.3*	25	77.09	9.40	*0.6*
Psychosocial health		74.38**	15.99		81.21	10.22	*0.7*		75.0	9.56	*0.1*
Physical health		67.29***^^^	23.92		86.76	9.21	*2.1*		81.0	12.00	*1.1*
Emotional functioning		72.6	23.07		77.53	15.01	*0.3*		71.4	16.62	*0.1*
Social functioning		83.27***	13.89		90.14	11.37	*0.6*		83.4	12.97	*0.0*
School functioning		67.27**	20.46		75.95	12.68	*0.7*		70.2	15.17	*0.2*

*1. *p<.05, **p<.01, ***p<.001 versus Dutch norm population*
2. ^p<.05, ^^p<.01, ^^^p<.001 versus children with a chronic health condition
3. Higher scores represent a better HRQoL
4. p values at two sample t-test: JIA versus norm and JIA versus chronic health condition

Conclusion: HRQOL is severely affected in children and adolescents with JIA. Children with JIA report significant impairments in physical health, emotional, social and school functioning. These findings underline the need to systematically pay attention to HRQOL in clinical daily practice and to investigate the effectiveness of HRQOL feedback to the pediatric rheumatologist.

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Glucocorticoid: Major Factor for Reduced Immunogenicity of 2009 Influenza A (H1N1) Vaccine in Juvenile Autoimmune Rheumatic Diseases Patients.
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Background/Purpose: In 2010 the Advisory Committee on Immunization Practices from the Center for Disease Control and Prevention recommended that all children and adolescents should receive the trivalent seasonal influenza vaccine containing the A/California/7/2009(H1N1)-like virus. There are, however, no data evaluating the immunogenicity and safety of the non-adjuvanted influenza A H1N1/2009 vaccine in a large cohort of juvenile autoimmune rheumatic diseases (ARD) patients.

Methods: 237 juvenile ARD patients [juvenile systemic lupus erythematosus (JSLE), juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM), juvenile scleroderma and primary vasculitis] and 91 age-matched healthy controls were vaccinated with a non-adjuvanted preparation of influenza A/California/7/2009 (H1N1) virus-like vaccine. Subjects were ≥ 9 and ≤ 21 years old. All participants were evaluated pre- and 21 days post-vaccination and serology for anti-H1N1 antibody was performed by hemagglutination inhibition (HI) assay. Seroprotection (percentage of subjects with HI antibody titer ≥ 1:40), seroconversion (percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer > 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer) rates, geometric mean titres (GMT) and factor increase (FI) in GMT (ratio of the GMT after vaccination to the GMT before vaccination) were calculated. Adverse events were also evaluated.

Results: Age was comparable in juvenile ARD patients and controls (14.8 ± 3.0 vs. 14.6 ± 3.7 years, p=0.47). Three weeks after immunization, seroprotection rates (81.4 vs. 95.6%; p=0.0007), seroconversion rates (74.3 vs. 95.6%; p<0.0001) and the factor increase in GMT (12.9 vs. 20.3; p=0.012) were significantly lower in juvenile ARD patients *versus* controls. Subgroup analysis comparing with controls revealed reduced seroconversion rates in JSLE (p<0.0001), JIA (p=0.008), JDM (p=0.025) and primary vasculitis (p=0.017). Additionally, seroprotection (p<0.0001) and GMT (p<0.0001) were decreased solely in JSLE. Glucocorticoid use and lymphopenia were associated with lower seroconversion rate (60.4 vs. 82.9%, p=0.0001 and 55.6 vs. 77.2%, p=0.012), compared to patients without these conditions. Multivariate logistic regression including each disease (JSLE, JIA, JDM, primary vasculitis), lymphopenia, glucocorticoid and immunosuppressants use revealed that only glucocorticoid use remained significant (OR 0.20, 95%CI 0.06–0.70, p=0.012).

Conclusion: This is the largest study to demonstrate a reduced immune response to 2009 influenza A (H1N1) vaccine in juvenile ARD patients and it identified current glucocorticoid use as the major factor for this deleterious effect. The short-term safety supports its routine recommendation for juvenile ARD patients and the indication of a second boost in patients under this therapy. (ClinicalTrials.gov, #NCT01151644)

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Silent Arthritis Progression in Children with Juvenile Idiopathic Arthritis Detected by Magnetic Resonance Imaging.
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Background/Purpose: The aim of the study was to detect silent (subclinical) arthritis (SA) progression in patients with juvenile idiopathic arthritis (JIA) and inactive disease using MRI.

Methods: Patients with JIA according to Durban criteria presenting

with inactive disease according to the Wallace criteria underwent clinical examination (active joints, joints with limited range of motion) and laboratory tests (CRP, ESR). CHAQ, physician global assessment (PGA) and patient's visual analogue scale (VAS) for pain were recorded. Minimally swollen joints were not considered inactive. A standardized MRI-protocol was applied to examine the same target joint in the same patient during disease course. The protocol included: coronal/axial T1 weighted images [T1WI], coronal fluid sensitive images (STIR) and coronal/axial fat saturated Gadolinium enhanced T1WI. Target joints were: wrists, knees, ankles. MRI criteria for inflammation were: effusion, synovitis, synovial hypertrophy, bone marrow edema (BME), osteitis, erosions, tenosynovitis. SA was defined as isolated pain on end grade of motion with VAS pain < 2 (no other symptoms), limited range of motion $< 5°$ (no other symptoms), normal lab results, normal CHAQ (0,00). Silent progression was considered if bone marrow edema/osteitis and or erosions occurred.

Results: 21 consecutive patients with JIA on medication (methotrexate, NSAIDs, TNF α antagonists) with a median age at inclusion of 10.2 years (7.0 – 16.8) were evaluated in the study. JIA subtype distribution was: 5 oligo persistent, 4 oligo extended, 6 polyarthritis, 5 psoriatic arthritis, 1 undifferentiated arthritis. Median follow up time was 2.5 years (1.2 – 5.6). All patients had at all MRI examinations synovitis and synovial hypertrophy. Seven of the patients progressed silently developing BME/osteitis and erosions. One patient developed BME/osteitis without having erosions. One patient developed erosions without preceding BME/osteitis. Tenosynovitis was a frequent finding.

Conclusion: Despite clinically inactive disease patients with JIA may have a silent progressive course leading to joint destruction. Gadolinium enhanced MRI is capable in detecting early changes (BME/osteitis) which precede the development of erosions. MRI appears to be an indispensable tool for monitoring disease activity and drug treatment in order to prevent from joint damage.

ARHP Concurrent Abstract Session
ARHP Clinical Practice/Patient Care I
Sunday, November 6, 2011, 4:30 PM–6:00 PM

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Factors That Influence Appointment Compliance Rates In a Multi-Disciplinary Specialized Lupus Clinic. Pretima G. Persad[1], Su Jin Kim[2], Kyriakos A. Kirou[1] and Doruk Erkan[1]. [1]Mary Kirkland Center for Lupus Care- Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY

Background/Purpose: Missed patient appointments can interfere with treatment adherence and lead to poor health outcomes. The primary objective of this two-phase study was to analyze the demographic and clinical characteristics of a select cohort of "low-income" lupus patients in our clinic who missed a significant number of appointments over one year. The secondary objective was to determine the effectiveness of a "telephone intervention" on appointment compliance.

Methods: *During phase one*, "low income" patients receiving public health insurance benefits (Medicaid and Medicare) who had appointments scheduled between October 2009 and October 2010 were identified from our lupus clinic database. Patient demographics, lupus manifestations (based on the American College of Rheumatology Criteria), and appointment compliance rates (1%–30% [poor compliance], 31%–70% [average compliance], 71–100% [good compliance]) were retrospectively analyzed. Clinic patients who had never scheduled a follow-up appointment within the year's time were designated as having zero compliance and were excluded from the analysis. *During phase two* (January 2011 to June 2011), a "telephone intervention" was implemented. This consisted of: a) reminder phone calls for all patients one day before their appointments; and b) follow-up phone calls either the same or following day for patients who missed their appointments (for re-scheduling and identifying reasons for their missed appointments). A Chi-square test was used to compare categorical variables.

Results: *During phase one*, we identified 143 patients with an average compliance rate of 67%. Patients with poor, average, and good compliance rates were 7 (4%), 66 (46%), and 70 (50%), respectively. The seven patients with poor compliance were excluded from the analysis due to small sample size. When patients with average compliance (n: 66; 89% female; mean age: 38.5 +/− 13.9; number of total appointments: 6.2 +/− 3.3, and number of missed appointments: 3.1 +/− 2.0) and good compliance (n: 70; 83% female; mean age: 40.9 +/− 15.7; number of total appointments: 5.0 +/− 3.5, and number of missed appointments: 0.7 +/− 0.9) were compared, there were no statistical differences in demographics or cumulative lupus manifestations. *During phase two*, the overall compliance rate was 69%. Based on the missed appointment follow-up phone survey, the top three reasons patients missed their appointments were: transportation problems (44%) (e.g., ambulette cancelling or not picking patients up on time, patients not having funds for public transportation); no child care available (19%); and job-related conflicts (12%). Only 5% of the patients missed their appointments due to forgetfulness.

Conclusion: In a multi-disciplinary specialized lupus clinic serving patients who receive public health insurance benefits, we found that appointment compliance is more likely related to socioeconomic factors rather than to demographics, lupus manifestations, or appointment confirmations. Our data suggests that improving transportation services and providing access to temporary childcare for medical appointments may aid in increasing appointment compliance rates.

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Identifying Predictors of Medication Adherence In Patients with Rheumatoid Arthritis. Elizabeth G. Salt and Susan K. Frazier. University of Kentucky, Lexington, KY

Background/Purpose: Despite the many effective disease modifying anti-rheumatic drugs (DMARDs) available to treat rheumatoid arthritis (RA), medication adherence is a significant problem. Inconsistencies in reported research have resulted in a lack of predictors of medication adherence in patients with RA. The purpose of this study was to: 1) describe self-reported medication adherence to DMARDs; 2) compare demographic (age, residence, marital status, employment status, years of education, and race) and clinical (duration of disease and number of medications) factors of adherent and nonadherent individuals; and 3) determine the predictive power of demographic and clinical factors for DMARD adherence.

Methods: This study will use a cross-sectional descriptive, predictive design in a sample of 108 patients with RA. A validated, self-report scale using various cut-points (used in prior research, mean, and median) will be used to determine medication adherence. Logistic regression modeling, independent samples t-tests, and Chi square analyses were used to analyze these data.

Results: Ninety percent of the individuals (mean age 52 ± 13 years, 76% female) reported adherence with their prescribed DMARD prescriptions using a cut-point of 39 for the Medication Adherence Report Scale (Horne and Weinman, 2002). Race was the only demographic or clinical difference between the adherent and nonadherent group ($p=0.04$); white individuals reported significantly more adherence with their prescribed DMARDs when compared to non-white individuals (Table 1). Similarly, race (OR= 3.34–10.1; $p< 0.05$) and the number of medications taken (OR=1.7; $p< 0.05$) were predictors of medication nonadherence using logistic regression models with 3 cut-points (Table 2).

Table 1. Characteristics of Participants.

Variable	Total sample (n = 108)	Adherent group (n = 98)	Nonadherent group (n = 10)	p value
Age in years	52 ± 13	52 ± 14	53 ± 9	0.77
Gender female	82 (76%)	75 (76%)	6 (68%)	0.69
Ethnicity	89 (83%)	84 (86%)	5 (56%)	
Caucasian	14 (13%)	11 (11%)	3 (33%)	
African American/Other	4 (4%)	3 (3%)	1 (11%)	0.04
Education in years	13 ± 3	13 ± 3	12 ± 3	0.81
Marital status				
Married/cohabit	62 (58%)	56 (57%)	6 (67%)	0.74
Widowed	7 (7%)	7 (7%)	0	
Divorced/Separated	20 (19%)	19 (19%)	1 (11%)	
Single/ Never Married	18 (17%)	16 (16%)	2 (22%)	
Employment				
Employed full-time	27 (26%)	25 (26%)	2 (22%)	0.72
Employed part-time	7 (7%)	7 (7%)	1 (11%)	
Unemployed	10 (9%)	10 (10%)	0	
Sick leave/disability	35 (33%)	33 (34%)	2 (22%)	
Homemaker	7 (7%)	6 (6%)	1 (11%)	
Retired	20 (19%)	17 (17%)	3 (33%)	

Residence location				
Urban	55 (51%)	48 (53%)	7 (78%)	0.18
Rural	45 (42%)	43 (47%)	2 (22%)	
Years since diagnosis	10 ± 10	10 ± 10	11 ± 8	0.73
Total number of RA medications	2 ± 1	2 ± 1	3 ± 2	0.43

Values are mean + SD or frequency (%), May not total to 100% due to some missing data points
Variables compared with independent t tests or Chi square analyses based on level of measurement
For those variables with no cases in a cell, categories were collapsed to ensure the assumptions of Chi square were met prior to analysis

Table 2. Predictors of Adherence to DMARDs.

Using the cut point from a prior research study

Factor	Odds Ratio	Significance	95% Confidence Interval	
			lower	upper
Race (white versus nonwhite)	10.10	0.01	1.66	61.40
Residence (rural versus urban)	7.52	0.10	83.33	0.70
Duration of disease	1.00	0.83	1.01	1.00
Years of education	1.09	0.61	1.50	0.79
Total number of medications taken for RA	1.26	0.51	2.53	0.63
Marital status (married versus not married)	1.44	0.75	0.151	13.68
Employment (full time versus not full-time)	2.19	0.52	21.3	0.21
Age	1.01	0.80	0.94	1.08

Using the median cut point

Factor	Odds Ratio	Significance	95% Confidence Interval	
			lower	upper
Race (white versus nonwhite)	2.67	0.12	0.78	9.17
Residence (rural versus urban)	1.54	0.38	0.58	4.08
Duration of disease	1.00	0.18	1.01	0.99
Years of education	1.03	0.73	0.89	1.19
Total number of medications taken for RA	1.69	0.02	2.63	1.09
Marital status (married versus not married)	2.76	0.17	11.63	0.66
Employment (full time versus not full-time)	2.71	0.20	0.59	12.40
Age	0.99	0.71	1.04	0.97

Using the mean cut point

Factor	Odds Ratio	Significance	95% Confidence Interval	
			lower	upper
Race (white versus nonwhite)	3.34	0.05	1.02	10.95
Residence (rural versus urban)	1.87	0.22	0.70	5.05
Duration of disease	1.00	0.11	1.01	0.99
Years of education	1.04	0.59	1.21	0.89
Total number of medications taken for RA	1.37	0.16	2.11	0.89
Marital status (married versus not married)	2.11	0.30	8.62	0.51
Employment (full time versus not full-time)	2.62	0.21	0.58	11.79
Age	1.00	0.88	1.04	0.97

Conclusion: Race and taking an increased number of medications for RA were independent predictors of medication adherence in this sample of patients with RA. These findings further define a health disparity. Future research is needed to develop a full understanding of this problem and thus, to improve patient outcomes.

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Clinical Decision Support System Improves Bone Mineral Density Screening Rates in 65 Year Old Women. Kori A. Dewing[1], Basia Belza[2], Brenda Zierler[2] and Andrea LaCroix[3]. [1]Virginia Mason Medical Center, Seattle, WA, [2]University of Washington, Seattle, WA, [3]Fred Hutchinson Cancer Research Center, Seattle, WA

Background/Purpose: Clinical decision support systems can improve efficiency and standardization in patient care by flagging electronic medical records of patients due for recommended health maintenance screening. Bone mineral density testing is an important tool in identifying who is at risk for osteoporotic fracture. Despite the staggering numbers of people affected by osteoporosis and the economic and medical consequences of suffering a preventable osteoporotic fracture, rates of screening by bone mineral density testing by dual-emission x-ray absorptiometry (DXA) remain low.

The purpose of this quality improvement project was to evaluate the effectiveness of a clinical decision support tool (health maintenance module or HMM) in improving rates of bone mineral density testing in women age 65 within the Virginia Mason Medical Center health system.

Methods: The implementation date for the HMM was September 30, 2008. The study periods chosen for data analysis were October 1, 2006 to September 30, 2007 (pre HMM), October 1, 2007 to September 30, 2008 (pre HMM), October 1, 2008 to September 30, 2009 (post HMM), and October 1, 2009 to September 30, 2010 (post HMM). The population cohort included women turning 65 in the year prior to each study period, who were seen twice by primary care during the study period. There was no subject overlap between study periods. Subjects who died or were in hospice care were excluded. Information on BMD testing, and diagnosis of osteoporosis was collected using administrative data. A systematic review using the electronic medical records was performed on the remaining subjects to determine DXA results, documentation of previous DXA in chart notes, diagnosis of osteoporosis, or documentation of bisphosphonate use during the study period.

Percent rate differences were calculated by comparing each post-HMM study period to the mean of the two pre-HMM study periods. The odds ratios were also calculated by comparing each post-HMM study period to the mean of the two pre-HMM study periods.

Results: Rates of bone mineral density testing by DXA increased significantly from 84.3% and 81.2% in the two years prior to implementation of the HMM to 97.3% (OR 7.7, 14.5% rate increase) in the first year post-implementation of the HMM, and 99.6% (OR 70.5, 16.8% rate increase) in the second year post-implementation of the HMM. See Table 1 below.

Table 1. Performance of HMM in improving rates of BMD testing in 65 year old women

Study Period	Number of women screened/number of women eligible for screening	% of eligible women screened		Odds Ratio	% Rate Difference	95% Confidence Interval
10/1/06–9/30/07	364/432	84.3	Mean 82.8			
10/1/07–9/30/08	302/372	81.2				
10/1/08–9/30/09	360/370	97.3		7.7	+14.5	13.5–15.1
10/1/09–9/30/10	330/331	99.6		70.5	+16.8	15.8–17.8

Conclusion: In conclusion, this quality improvement project found an improvement in bone mineral density testing rates in 65 year old women in the two years following implementation of a clinical decision support system. The clinical decision support tool (HMM) provided standardization of health maintenance screening and helped to better identify those patients at risk of osteoporotic fracture.

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Assessment and Treatment of Osteoporosis After Hip-Fracture: An Observational Study. Maria Antonelli, Douglas Einstadter and Marina N. Magrey. Case Western Reserve University/MetroHealth Medical Center, Cleveland, OH

Background/Purpose: Most patients with osteoporosis (OP) are untreated and remain so even after hip fracture. Outcomes following osteoporotic hip fractures are worse among men and non-Caucasians compared to Caucasian women. We hypothesized that screening and treatment of OP after hip fracture remains low in men and non-Caucasian women.

Methods: We identified all patients aged ≥ 65 years old with a primary diagnosis of hip fracture (ICD9-DM code 820.xx) discharged form an urban public hospital between Jan 1, 2000 and Dec. 31, 2010. Patients with active malignancy (one year before or after the fracture), and Paget's disease were excluded. Also, patients were excluded if they had less than two encounters for post-event care at the hospital. Patient charts were reviewed to obtain information on demographics, post- fracture osteoporosis screening status (Dual-energy x-ray absorptiometry (DXA) ordered or resulted), osteoporosis treatment status (prescription for oral bisphosphonates, raloxifene, zoledronic acid, calcitonin or teriparatide), and referral to rheumatology clinic. Data were captured using Research Electronic Data Capture (REDCap). Differences in frequency of patients who had been evaluated by DXA and/or prescribed anti-osteoporotic therapy after hip fractures overall and stratified by sex and race were evaluated using Chi-square tests. The study was approved by our hospital IRB.

Results: There were a total of 597 patients discharged with a primary diagnosis of hip fracture during the study period. After exclusions, 420 patients

remained and were included in the analyses. The median age was 80 years (range 65– 95), 113 (27%) were men, and 243 were White women (57.9%). Overall, 13.8% of patients were ordered DXA after their hospital discharge, 8.9% of men and 15.6% of women (p = 0.43). A total of 19% received treatment for osteoporosis, and women were nearly 3 times more likely to receive treatment than men (23.1% vs. 8%, p = 0.004). Less than 1% of patients were referred to a Rheumatologist. The rates of DXA, treatment and referral to Rheumatology did not differ by race.

Conclusion: The frequency of osteoporosis screening using DXA scan, and the initiation of osteoporosis treatment was low in all patients after fragility fractures of hip. Women were more likely than men to receive DXA and significantly more likely to receive osteoporosis treatment. While representative of only one hospital, these data suggest that more attention should be paid to possible osteoporosis among elderly patients hospitalized for hip fracture, and especially among men.

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The Association of Symptomatic Osteoarthritis At Multiple Time Points with Functional Limitation Over 5 Years: The Multicenter Osteoarthritis Study. Daniel K. White[1], Yuqing Zhang[1], Jingbo Niu[1], Michael C. Nevitt[2], C.E. Lewis[3], James Torner[4] and Tuhina Neogi[5]. [1]Boston University School of Medicine, Boston, MA, [2]University of California-San Francisco, San Francisco, CA, [3]University of Alabama, Birmingham City, AL, [4]University of Iowa, Iowa City, Iowa City, IA, [5]Boston University, Boston, MA

Background/Purpose: Knee pain associated with knee osteoarthritis (OA) is a complex phenomenon that can come and go over time. While pain over the short-term is associated with functional limitation, it is not known if pain over the long-term confers greater risk for functional limitation, with few studies examining this association beyond 3 years. It may be that people learn to cope with their pain over time, and therefore have sufficient adaptation as to lessen the impact on functional limitation. Thus, we examined the association of the presence of symptomatic OA at different time points during the course of 5 years of follow-up with the incidence of functional limitation, as well as with decreased recovery from functional limitation.

Methods: The Multicenter Osteoarthritis Study (MOST) is an NIH funded longitudinal study of people who have or are at high risk for knee OA. We included people who had symptomatic radiographic knee OA at the baseline visit, with symptomatic defined as reporting pain at two time points: a telephone screen and a clinic visit occurring approximately one month later. We classified the presence of symptomatic OA at different time points as follows: i) at baseline only; ii) baseline and 30 months; iii) baseline and 60 months; and iv) baseline, 30 and 60 months. We examined the incidence of functional limitation with self report and performance outcomes at 60 months using WOMAC physical function ≥ 28/68 (risk factor for total joint replacement) and gait speed <1.22 m/s (minimal speed needed to walk in the community) among subjects without these outcomes at baseline using logistic regression adjusting for potential confounders. We also examined recovery at 60 months among subjects with functional limitation at baseline.

Results: Of the 797 subjects (Age 64 ± 8 yrs, BMI 33 ± 7 kg/m^2, female 64%), 12% had symptomatic knee OA at baseline only, 20% at baseline and 30 mo, 13% at baseline and 60 mo, and 45% at baseline, 30, and 60 mo. Of those without functional limitation at baseline, 20% of 348 and 36% of 192 subjects developed functional limitation at 60 mo by self-report and performance, respectively. We found an increasing odds of functional limitation for the presence of symptomatic OA at more time points (adj OR 1.2–8.1). Of those with functional limitation at baseline, 68% of 327 and 8% of 547 subjects recovered from poor function at 60 mo by self-report and performance, respectively. We found a deceasing odds of recovery from functional limitation for presence of symptomatic OA at more time points (adj OR 0.1–0.9).

Conclusion: The presence of symptomatic OA over multiple time points during the course of 5 years contributed to greater risk of functional limitation and less recovery from functional limitation. It therefore seems unlikely that adaptation to pain related to knee OA limits pain's impact on functioning.

Table.

	Incidence of Functional Limitation*	
SxOA	**(%) n/N**	**Adjusted** OR [95% CI]**
Self Report (WOMAC Physical Function)		
0m only	7.7 (5/64)	1.0 [Reference]
0m and 30 m	16 (8/49)	2.0 [0.6, 6.8]
0m and 60 m	18 (8/45)	3.0 [0.9, 10.3]
0m, 30 m, and 60 m	37.9 (44/116)	8.1 [2.9, 22.9]
Performance (Walking Speed)		
0m only	25.0 (10/40)	1.0 [Reference]
0m and 30 m	34.6 (9/26)	1.2 [0.4, 3.9]
0m and 60 m	37.5 (9/24)	1.5 [0.5, 5.0]
0m, 30 m, and 60 m	45.8 (33/72)	3.0 [1.1, 7.8]
Recovery from Functional Limitation***		
SxOA	**(%) n/N**	**Adjusted** OR [95% CI]**
Self Report (WOMAC Physical Function)		
0m only	80.0 (24/30)	1.0 [Reference]
0m and 30 m	70.6 (24/34)	0.6 [0.2, 1.9]
0m and 60 m	40.0 (6/15)	0.2 [0.1, 0.9]
0m, 30 m, and 60 m	32.6 (30/92)	0.1 [0.0, 0.3]
Performance (Walking Speed)		
0m only	19.9 (11/58)	1.0 [Reference]
0m and 30 m	14.0 (9/64)	0.6 [0.2, 1.5]
0m and 60 m	23.7 (9/38)	0.9 [0.3, 2.7]
0m, 30 m, and 60 m	5.7 (8/140)	0.2 [0.1, 0.5]

*Functional Limitation incidence was defined as developing a score of ≥28/68 for the WOMAC physical function or developing a walking speed <1.22 m/s at the 60 month visit. Higher OR indicate a higher odds of developing functional limitation at 60 months.
**Adjusted for age, sex, BMI, knee pain severity, and disease severity (KL grade) at baseline.
***Functional Limitation recovery was defined as recovering from a score of ≥28/68 at baseline to <28/68 at the 60 month visit for the WOMAC physical function or walking <1.22 m/s at baseline and ≥1.22 m/s at the 60 month visit. Lower OR indicate a lower odds of recovery from functional limitation at 60 months.

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Continued Tocilizumab Infusion for Rheumatoid Arthritis Is Well Tolerated and Safe At An Accelerated Infusion Rate.. Gunhild Bukh, Michael Sejer Hansen, Sussi Larsen and Susse Skalsted Rasmussen. Gentofte Hospital, Hellerup, Denmark

Background/Purpose: Rheumatoid arthritis (RA) is a chronic systemic disease related to progressive disability and an increased mortality compared to the general population. New therapies are needed and one promising candidate is Tocilizumab ® that binds specifically to the IL-6 receptor. This treatment is given every four week over one hour, and is quit time-consuming over time. No serious infusion-reactions have been reported after the 5th infusion. The purpose of our study was to evaluate if an accelerated infusion-rate of Tocilizumab after the 5th infusion would be as safe and tolerable for RA patients as the conventional infusion regiment. The reduced infusion-time is comparable with the reduced time used for infliximab ® infusion at our department after the 10th infusion.

Methods: The present study was conducted consecutively for RA patients allocated to treatment with Tocilizumab. Fifty RA patients have received Tocilizumab-infusion at our Department since 2005.

21 have stopped Tocilizumab treatment. 9 due to lack of efficacy, 5 patients due to adverse events, 4 due to remission and 3 lost to follow-up. Twenty-nine patients are still successfully treated with Tocilizumab; 4 with the recommending Tocilizumab-infusion procedure (1 hour/infusion) and 3 patients in a RCT (ActRay) study. The study population is thereafter comprised of 22 patients and was treated with Tocilizumab at an accelerated infusion rate (30 minutes/infusion). These patients are characterized as: 17 F/ 5 M, median age 55 years (range 27–77), disease duration 11 years (2–45), positive IgM-RF or anti-CCP: 18 (85%), DAS28CRP 5.5 (2.7–7.2), HAQ-score 1.5 (0.0–2.375), number of previous DMARDs 2.3 (0–8), number of previous biologics 2.3 (0–5). 18 patients were on concomitant DMARDs (15 Methotrexate, 2 Azathioprine) and 1 Sulfasalazin. Tocilizumab was given at a dose of 8 mg/kg/100 ml isot NaCl during one hour for infusion number 1 – 5, and from infusion 6 and thereafter at the same dosage during 30 minutes.

During the infusion period, the patients were monitored with blood pressure, pulse, temperature, respiration and registration of any kind of side effects according to the CTC grading system.

Results: 321 Tocilizumab infusions at an accelerated infusion rate of 30 minutes/infusion were given to 22 patients (median 5 (range 1–27) infusions/ patient) with only a small number of side-effects. One patient had had a serious adverse event after the 23rd ½-hour infusion and has been treated for septicaemia. Result unresolved. One patient got dizzy and nausea after the 31st ½-hour infusion. This side effect was resolved by increasing the infusion time to one hour. No long term side effects were found for any of the treatment regimens.

Conclusion: The patients with RA were satisfied and comfortable with an accelerated time-sparing infusion regimen as well as the health professionals. No unexpected adverse events were recorded. These results have led to a change in our routine management of Tocilizumab infusions.

873 WITHDRAWN

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Osteoarthritis Severity Is Associated with Increased Risk for Diabetes and Heart Disease. Gillian A. Hawker, Andrew Warner and Taryn Simms. Women's College Hospital, Toronto, ON

Background/Purpose: Prior studies have documented increased rates of diabetes and heart disease in individuals with osteoarthritis (OA). However, there is a paucity of research that has examined if OA severity contributes independently to these relationships. Our study aim was to evaluate the relationship between OA severity and prevalence of heart disease and diabetes and the extent to which these relationships, if found, were explained by common risk factors.

Methods: In a population cohort with hip and knee OA, sociodemographics, OA severity (WOMAC subscale and summary scores), body mass index (BMI) general health status (SF36) and comorbidity (list of 13 non-musculoskeletal, MSK, conditions) were assessed. Diabetes and heart disease were defined as present if the participant reported having 'ever' received a diagnosis or received treatment in the past year. Logistic regression was used to examine the association of OA severity with each of diabetes and heart disease, first unadjusted, then controlling for potential confounders (age, sex, education, income, BMI and diabetes). We assessed for potential interactions between OA severity and age, sex, education, and income, and between OA severity and diabetes on heart disease. Statistical significance was considered at a 2-tailed level of 0.05.

Results: Mean age of the 2225 participants was 70.7 years, 72.0% were female and 96.1% Caucasian; 81.1% reported ≤ high school education and 63.9% reported an annual income < $20,000. WOMAC scores indicated moderate to severe OA pain and disability. Mean BMI was 27.9 kg/m^2; 38.8% were overweight and 30.9% were obese. Three-quarters (73.1%) reported receiving treatment for at least one other non-MSK chronic condition; 22.5% reported 3 or more comorbid conditions; 30.4% reported heart disease and 16.8% reported diabetes. Unadjusted for other factors, a 10-point increase in WOMAC summary scores was associated with a 10% increase in the odds of self-reporting diabetes (odds ratio 1.10; 95% confidence interval 1.04–1.16). This relationship was attenuated, becoming non-significant, after controlling for BMI. Unadjusted for other factors, a 10-point increase in WOMAC summary scores was associated with a 12% increase in the odds of reporting heart disease (odds ratio 1.12; 95% confidence interval 1.06–1.17). In adjusted analyses, self-reported heart disease was significantly and independently associated with male sex, lower income, and interactions between OA severity and each of age ($p = 0.015$) and self-reported diabetes ($p = 0.02$); the effect of a 10-point increase in WOMAC summary scores on the odds of self-reporting heart disease decreased with increasing age, but was significantly greater at all ages among those with comorbid diabetes.

Conclusion: In a population cohort with moderately severe hip and knee OA, the prevalence of comorbid diabetes and heart disease was substantial and positively linked to increasing symptomatic OA severity. For diabetes, this relationship was explained by a common risk factor, obesity. For heart disease, this relationship remained significant even after controlling for common risk factors, and was stronger among those with comorbid DM.

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Serum 25 Hydroxy Vitamin D (25OHD) and Incident or Worsening Knee Pain In Older Adults: A Five Year Longitudinal Study. Laura Laslett[1], Chang-Hai Ding[2], Stephen Quinn[3], John Burgess[4], Venkat Parameswaran[4], Tania Winzenberg[1] and Graeme Jones[1]. [1]University of Tasmania, Hobart, Australia, [2]University of Tasmania & Monash University, Hobart, Australia, [3]Flinders University, Australia, [4]Royal Hobart Hospital, Hobart, Australia

Background/Purpose: Vitamin D is important for bone, cartilage and muscle function. However, there is little data on its association with pain. The aim of this study was to describe the association between serum 250HD and change in knee pain over five years.

Methods: Longitudinal population-based study of randomly selected older adults (n=766). Serum 25OHD was assessed by radioimmunoassay and knee pain using the WOMAC questionnaire at baseline and again after five years. We used linear regression with adjustment for season, age, sex and BMI. We also examined potential structural mechanisms for any effect by additionally adjusting for radiographic osteoarthritis, bone marrow lesions, chondral defects and muscle strength.

Results: Participants were aged 50–80 years (mean 62 years), 50% were male with a mean WOMAC score of 3.2 (range 0–39). Mean serum vitamin D was 53.8 nmol/l (range 13–166 nmol/l), with 4.2% of participants having moderate deficiency (<25 nmol/l). Knee pain (total WOMAC score) was stable in participants with vitamin D 25–50 and ≥50 nmol/l but worsened over five years in persons with vitamin D <25 nmol/l (b −1.02, p=0.002), with consistent results within each of the pain subscales. This association persisted after adjustment for covariates. When vitamin D was analysed as a continuous measure, there were no associations between vitamin D and change in WOMAC score (b −0.12, p=0.2). This effect was largely independent of structural factors.

Conclusion: Serum vitamin D level in the osteomalacic range (<25 nmol/l) is an independent predictor of worsening or incident knee pain over five years suggesting a lag time between the development of low levels and pain. This suggests supplementing levels below this will prevent worsening knee pain.

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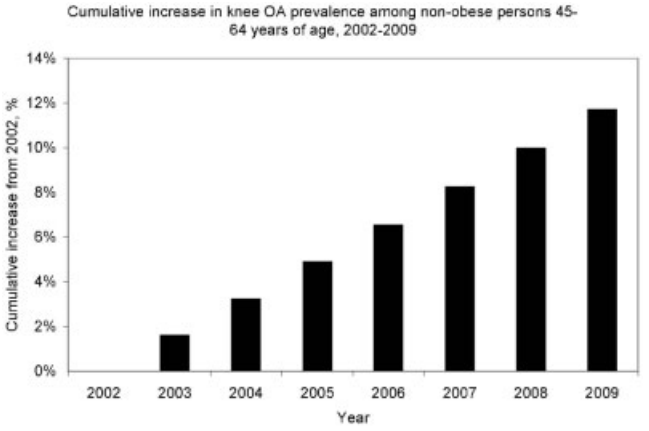
Trends in the Prevalence of Symptomatic Knee Osteoarthritis From 2002 to 2009. William M. Reichmann[1], Jeffrey N. Katz[2], Sara A. Burbine[3], Meghan E. Daigle[3], Benjamin N. Rome[3], Alexander M. Weinstein[3] and Elena Losina[3]. [1]Brigham and Womens Hospital, Boston, MA, [2]Brigham & Womens Hospital, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA

Background/Purpose: A growing body of evidence suggests that the prevalence of symptomatic knee OA has increased over time from the 1980s to early 2000s. The goal of this study is to describe temporal trends in the prevalence of symptomatic knee OA from 2002 through 2009 and to determine whether increases in knee OA prevalence occur across all age groups and for obese and non-obese persons.

Methods: We used data from the National Health Interview Survey (NHIS) from 2002 to 2009. The NHIS is an annual survey of the non-institutionalized United States population with approximately 30,000 respondents during each year. We defined persons with symptomatic knee OA as those who stated that a physician diagnosed arthritis and that they had right or left knee pain, aching, or stiffness in the last 30 days. We used logistic regression to obtain prevalence estimates by obesity status for the overall population and by age groups (25–44, 45–64, and 65+) adjusting for sex and age within the age group. We defined obesity as BMI 30+. To assess the temporal trends in the prevalence of symptomatic knee OA, we included survey year in the model as a continuous variable. We accounted for the complex multi-stage sampling design of NHIS to derive prevalence estimates that were representative of the US.

Results: In the overall population we did not find evidence of increased prevalence of symptomatic knee OA between 2002 and 2009, adjusting for age and sex among obese and non-obese persons. Among obese persons, the age- and sex-adjusted prevalence of knee OA was 15.2%, vs. 6.6% among non-obese. When we further stratified by age group, we found the prevalence of symptomatic knee OA ranged from 2.8% in non-obese persons aged 25–44 to 34.8% among obese aged 65+. We found a statistically significant increase in prevalence of symptomatic knee OA over time for those that were non-obese and in the 45–64 age group (p for linear trend = 0.04; Figure). We estimated that the prevalence of symptomatic knee OA increased from 9.2% in 2002 to 10.3% in 2009 in these persons.



Conclusion: From 2002 to 2009, we found a consistent increase in prevalence of symptomatic knee OA in non-obese persons ages 45–64. One possible explanation for the increase among non-obese persons ages 45–64 is that an increase in knee injuries has led to an increase in symptomatic knee OA. These data are helpful in understanding the burden of symptomatic knee OA in US.

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Impact of Psychosocial Determinants on Total Knee Replacement Costs: Results From the Patient Expectations about Knee Surgery Cohort. Christian A. Waimann[1], Rodrigo J. Fernandez-Mazarambroz[1], Scott B. Cantor[1], Maria Lopez-Olivo[1], Hong Zhang[1], Glenn C. Landon[2], Sherwin J. Siff[2] and Maria E. Suarez-Almazor[1]. [1]University of Texas, M.D Anderson Cancer Center, Houston, TX, [2]St. Luke's Episcopal Health System, Houston, TX

Background/Purpose: Psychosocial factors have been associated with clinical outcomes after total knee replacement (TKR) in patients with osteoarthritis (OA). We hypothesized that poor baseline psychosocial determinants and skills would increase TKR-related costs during the initial 6 months of follow up.

Methods: PEAKS is a prospective cohort of patients with OA who underwent TKR. Patients were followed for 6 months after surgery, and we collected sociodemographic data, TKR-related costs, clinical outcomes (Western Ontario McMaster (WOMAC) pain and function) and psychosocial determinants (Medical Outcomes Study Social Support Scale (MOS-SSS); Health Locus of Control (MHLC); Brief COPE Inventory; Depression, Anxiety, and Stress Scale (DASS); Arthritis Self-Efficacy Scale (ASES); and Life Orientation Test-Revised (LOT-R)). The economic analysis was conducted using a societal perspective based on 2007 US dollars. Direct medical costs were estimated using the Medicare Reimbursement Prospective Payment System and hospital billing was adjusted by cost-to-charge ratios reported to Medicare. Average wholesale price was used for drugs costs. Productivity losses (patient and relatives) were calculated using time lost multiplied by estimated wage per occupation reported by the Bureau Labor of Statistics for Texas. We also estimated each patient's OA-related costs in the 2 months prior to surgery. Bivariate analysis and stepwise multiple regression were performed to identify the impact of psychosocial outcomes on total TKR-related costs adjusted by gender, age, body mass index, ethnicity, baseline WOMAC and patient OA-related costs prior to surgery.

Results: 218 patients were included; 65% were female, 69% were white, mean age was 65±9 years. Baseline WOMAC pain was 55±19 and function was 54±20. Mean total costs were ≈$24,000±10,000 USD. Bivariate analysis showed that younger patients and those with less social support (emotional, tangible, positive), more anxiety, more depression, stronger belief that their health is related to events given by chance and less optimism, were more likely to have higher TKR-related costs. Stepwise regression analyses (Figure 1) indicated that more anxiety, lower stress, and less emotional/information support were significantly associated with higher TKR-related costs (R^2=0.35).

Stepwise regression using TKR-related total costs as dependent variable

Baseline variables	b	SE	B	p
Intercept	21457	5508.2	0	<0.01
Age	−53.8	52.7	−0.06	>0.20
Female	−1603.3	1012.6	−0.10	0.12
Non-white race	2892.1	975.7	0.18	<0.01
Body mass index	311.5	72.1	0.29	<0.01
WOMAC function	−14.6	24.2	−0.04	>0.20
Patient usual expenses prior to surgery	0.3	0.2	0.11	0.07
DASS anxiety subscale	483.6	119.0	0.34	<0.01
DASS stress subscale	−160.0	82.7	−0.16	0.05
MOS emotionalscale	−1777.3	550.2	−0.19	<0.01
MHLC powerful to others subscale	142.8	80.1	0.11	0.08

Score direction: WOMAC, higher scores indicating greater discomfort; MOS-SSS, higher scores indicate more support; DASS, higher scores indicating worse emotional states; MHLC, higher scores indicating stronger beliefs that others persons are the determinants of his health.

Conclusion: Patients' level of stress, anxiety and emotional support are associated with total costs following TKR. A perioperative psychosocial evaluation and intervention may reduce TKR-related costs.

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Incidence of Hip Symptoms and Radiographic and Symptomatic Hip Osteoarthritis in African Americans and Caucasians: The Johnston County Osteoarthritis Project. Barbara T. Do[1], Louise Murphy[1], Charles G. Helmick[1], Kamil E. Barbour[1], Yiling J. Cheng[1] and Joanne M. Jordan[2]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]UNC Thurston Arthritis Center, Chapel Hill, NC

Background/Purpose: Estimate the population-based incidence of 4 hip osteoarthritis (hOA)-related outcomes.

Methods: We analyzed baseline (1991–1997) and first follow up (1999–2005) data from Johnston County Osteoarthritis Project participants (n=1,423; aged > 45 years). The 4 outcomes were: 1) hip symptoms (pain, aching, and/or stiffness on most days in their hip and/or groin); 2 & 3) radiographic and severe radiographic hOA (Kellgren-Lawrence [K-L] radiographic grade of >2 and >3, respectively); and 4) symptomatic hOA (K-L radiographic grade of >2 and hip symptoms in the radiographically affected hip). Incidence rates were calculated overall and stratified (age; sex; race; highest education attainment; body mass index [BMI] at age 18 and at baseline; and history of hip injury in affected hip) for each outcome among those who did not have the outcome at baseline.

Results: The overall incidence rates (people per 100 person-years) were 5.5 for hip symptoms, 2.2 for radiographic hOA, 1.7 for symptomatic hOA, and 0.3 for severe radiographic hOA. The subgroup analysis indicated that incidence rates generally rose with increasing age, self-reported BMI at age 18, and clinically measured BMI at baseline and were higher among women and those with a history of hip injury. The largest absolute difference in incidence for any characteristic was for hip symptoms among those with and without a history of hip injury (9.2 and 5.3, respectively). Across all subgroups, incidence was generally higher among African Americans than Caucasians.

Conclusion: The incidence of 4 hip OA-related outcomes in this >45 year old population ranged from 0.3 to 5.5% each year. For each outcome, older age, being female, and having a history of hip injury were all predictors of increased incidence. Our findings indicate that greater intervention efforts (self-management education, physical activity, weight management, joint injury prevention) may reduce the onset and effects of these outcomes.

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Back Pain. Gary J. Macfarlane[1], Marcus Beasley[1], Elizabeth A. Jones[1], Karina Lovell[2], Gordon J. Prescott[1], Philip Keeley[2], John McBeth[2], Gareth T. Jones[1] and MUSICIAN study team[1]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]University of Manchester, Manchester, United Kingdom

Background/Purpose: Relatively little is known about back pain at older ages although it has been claimed to be under-assessed and managed in this age group. The aim of the current study was to determine: the prevalence of back pain and associated disability across the whole adult

age range; the frequency of consultations to general practice; whether there are differences in management by age of the person consulting with back pain.

Methods: We conducted a cross-sectional population-based study in Aberdeen city and Cheshire county, UK. Participants were 15,272 persons aged 25 years and older, randomly selected from participating GP registers and who returned a completed postal questionnaire. The outcomes of interest were the reporting of back pain on a body manikin (with or without disability as measured by the Chronic Pain Grade); consultation to general practice amongst persons with back pain; the management recommended as a result of consultation, by patient self-report.

Results: The one-month period prevalence of low back pain was 28.5 %. It peaked at age 41– 50 years and decreased thereafter, but at ages over 80 years 1 in 4 persons still reported back pain. However the impact of pain is greater at older ages: the prevalence of more severe pain (Chronic Pain Grade III/IV) continued to increase with age and low back pain in the elderly leads to a greater likelihood of consultation. Management by GPs differed by age of the patient. Older persons (over 70 years v. 40 years or less) were significantly more likely to only have only been prescribed painkillers (Odds ratio (OR) 1.74 95% Confidence Interval (CI) (1.28,2.35)) or only pain killers with other medications (OR 1.45 95% CI (1.07, 1.98)). They were significantly less likely to receive a prescription for physiotherapy or exercise (OR 0.63, 95% CI (0.46, 0.85), or to be referred to a specialist (OR 0.77, 95% CI 0.57, 1.04). Older persons were more likely to have previously received exercise therapy for pain, they were less likely to be enthusiastic about receiving it ($p < 0.0001$)and if they were to receive it they were less likely to think it would result in improved symptoms ($p < 0.0001$).

Conclusion: In order to achieve optimal outcome from episodes of back pain it is important that older persons, who have the highest prevalence of back pain with disability and are most likely to consult, are receiving both pharmacological and non-pharmacological management. Future studies should investigate why pharmacological management predominates and is likely to have to address patient attitudes and beliefs as well as ensuring that GPs are using the full range of treatment shown to be efficacious.

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Association of Lumbar Spine Individual Radiographic Features with Serum C-Propeptide (sCPII) and Serum Collagen Neoepitope (sC2C) of Type II Collagen: The Johnston County Osteoarthritis Project. Adam P. Goode[1], Virginia B. Kraus[1], Yvonne M. Golightly[2], Stephen W. Marshall[3], Debra E. Irwin[3] and Joanne M. Jordan[2]. [1]Duke University Medical Center, Durham, NC, [2]University of North Carolina Thurston Arthritis Center, Chapel Hill, NC, [3]University of North Carolina, Chapel Hill, NC

Background/Purpose: Serum levels of C-propeptide (sCPII), a biomarker of type II collagen synthesis, and serum collagen neoepitope (sC2C), a biomarker of type II collagen degradation, have been associated with radiographic knee osteoarthritis (OA). Whether these biomarkers are associated with joint metabolism changes in the lumbar spine has not been reported previously. We sought to: 1) determine if elevated levels of sCPII and sC2C reflect the presence and severity of the lumbar spine individual radiographic features (IRF) of disc space narrowing (DSN) and vertebral osteophytes (OST), controlling for the presence of knee OA, and 2) determine if these associations differ significantly by gender or race.

Methods: Of the 1,015 participants enrolled in the Johnston County OA Project from 2003–2004, lumbar spine IRF (DSN and OST) were available for 547 participants with complete sCPII and sC2C data (mean age 62.3 (SD 9.9), 61.8% female, 37.8% African American, mean [body mass index (BMI) 30.1 (SD 6.2)], 29.2% knee OA). Both sC2C and sCPII were natural log transformed to meet model assumptions due to a right skewed distribution. Each lumbar spine level was graded in a semi-quantitative fashion (0–3) according to the Burnett Atlas. A summary score was developed, separately for each IRF (DSN and OST), by adding the severity grade from each participant's five lumbar levels. Analysis of variance was used to determine differences in geometric mean levels of sCPII and sC2C across severity of both DSN and OST. Proportional odds models were used to determine associations of DSN and OST severity with sCPII and sC2C. All analyses were adjusted for age, gender, race, BMI and concomitant radiographic knee OA (defined as Kellgren-Lawrence score of 2–4). Interactions were tested with likelihood ratio tests to determine if associations differed significantly ($p<0.10$) by gender or race.

Results: No significant differences in mean levels of sCPII across severity of DSN ($p=0.074$) or OST ($p=0.863$) were observed. After adjustment, a one-unit change in sCPII was associated with 64% higher odds of DSN [adjusted odds ratio (aOR) = 1.64 (95% CI 1.07, 2.40)], but there was no association between sCPII and OST severity (aOR = 1.03 (95% CI 0.67, 1.60).

In contrast, significant differences in mean levels of sC2C were found across severity of DSN ($p=0.007$), but not for OST ($p=0.503$). After adjustment, a one unit change in sC2C was associated with an 89% higher odds of DSN (aOR=1.89 (95% CI 1.04, 3.46). The association with OST was moderate but not statistically significant (aOR=1.32 (95% CI 0.73, 2.39).

No significant interactions were found across gender or race.

Conclusion: Moderate to strong significant associations were found for sC2C and sCPII separately with DSN, above and beyond associations of each biomarker with radiographic knee OA, whereas no significant associations were found with OST. These findings suggest active collagen turnover in the lumbar spine intervertebral disc and underscore the importance of analyzing IRF separately for revealing biological insights through OA biomarker studies.

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To What Degree Is the Rise in US Total Knee Replacement Rates Attributable to Aging of the Population? Louise Murphy[1], Gillian A. Hawker[2], Erica Odom[1] and Charles G. Helmick[1]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]Women's College Hospital, Toronto, ON

Background/Purpose: In the past decade, total knee replacement (TKR) rates have increased resulting from multiple factors including the aging of the US population, rising prevalence of obesity and increased access to and demand for TKRs. To quantify the degree to which aging accounts for the observed increase in TKRs, we examined TKR rates, annual percent change (APC) and standardized incidence ratio (SIR) over 13 years among US adults aged ≥18 years.

Methods: Using 1997–2009 US Nationwide Inpatient Sample data – hospital discharge data for 44 states comprising 95% of all US hospital discharges -- we estimated overall and age-specific (18–44, 45–64, 65–84, and ≥85 years) annual hospital discharge rates, and APC for TKRs (ICD-9-CM procedure=81.54 [excludes revisions]). Also, we calculated overall and age-specific SIRs with 1997 and 2009 data to examine whether the rise in TKR rates from 1997 to 2009 was attributable solely to changes in the age distribution of the US population. Expected 2009 values, based on estimated 1997 TKR rates (# of TKR in 2007/# of people in 2000 US Census Population) were applied to population estimates from the 2010 US Census. SIRs were the ratio of observed to expected number of TKRs in 2009.

Results: Among all US adults aged ≥ 18 years, approximately 1 and 3 per 1000 people had a TKR discharge in 1997 and 2009 respectively. TKR rates (per 1000 people) in 2009 were higher than 1997 for all age groups: 18–44=0.04 and 0.1; 45–64=1.1 and 3.1; 65–84=5.9 and 9.7; and ≥85 years=2.2 and 3.1. The APC was 10% among all US adults (from 264,331[1997] to 620,192 [2009]); across age groups the largest APC was among those 45–64 years (21%) (18–44=11%; 65–84=7%; ≥85=6%). The overall SIR was 2.1; age-specific SIRs were 2.4, 2.9, 1.6 and 1.4 for adults aged 18–44, 45–64, 65–84, and ≥85 years respectively.

Conclusion: From 1997 to 2009, overall TKR rates tripled representing an APC of 10%. Although TKR rates rose most rapidly among people aged 45–64 years (APC=21%), observed rates in both 1997 and 2009 were highest among those aged 65–84 years (5.9 and 9.7). SIRs indicated that rates were between approximately 1.5 to 3 times higher than would be expected if the rise was attributable to aging alone. In this analysis, we were unable to quantify the effect of increased prevalence of obesity, a major risk factor for knee osteoarthritis and subsequent TKRs, and increased access to and demand for TKRs on this increase but it is likely substantial.

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Patterns of Population Use of Total Joint Arthroplasty: Focus on Outcomes Following a *Single* primary TJA Is Too Narrow. Ruth Croxford[1] and Gillian A. Hawker[2]. [1]Institute for Clinical and Evaluative Science, Toronto, ON, [2]Women's College Hospital, Toronto, ON

Background/Purpose: Many studies have evaluated outcomes following total joint arthroplasty (TJA) for hip and knee osteoarthritis (OA) and, on average, outcomes are good to excellent. However, these studies have focused on

recipients of a single hip or knee replacement procedure, excluding those with bilateral or consecutive TJAs. The extent to which this reduces the generalizability of these studies to all patients receiving TJA is unknown. To address this gap, we evaluated patterns of use of TJA following an index primary TJA over an 8-year period.

Methods: Primary and revision TJA procedures performed on Ontario, Canada, residents aged 55+ years between April 2002 (baseline) and March 2010 were identified from hospital discharge abstracts using specific ICD-10-CA/CCI procedure and diagnosis codes. The records of individuals who underwent TJA prior to April 1, 2002 (i.e. pre-baseline) or before age 55 years were excluded as were non-elective TJAs and those performed for cancer, fractures or trauma. We examined the proportions with repeat hospitalizations for TJA, and the associated TJA type (elective versus non-elective, hip versus knee, primary versus revision).

Results: Excluding those with a pre-baseline TJA, 164,330 index TJA procedures were identified. Of these, 129,937 were eligible for inclusion (90.4% of TJAs performed in people aged 55+ years). Bilateral knee replacements in the same hospitalization were more frequent (n=4,460, 3.44%) than were bilateral hip replacements (n=228, 0.18%). Further, knee replacements as the first TJA were almost twice as common as hip replacements (65.85% vs. 34.15%). A total of 33,474 (25.76%) second TJA hospitalizations occurred. Of 85,565 index primary knee replacements (4,460 bilateral), 23,984 (28.03%) experienced a second TJA hospitalization, with a median duration (IQR) from the index procedure of 1.37 years (0.63–2.93 years). Of these, 83.68% were for primary TJA of the contra-lateral knee, 1,802 (7.51%) were single or bilateral primary hip replacements, and 2,087 (8.7%) were for revision of one or both index knees. Of 44,372 index primary hip replacements (228 bilateral), 9,490 (21.39%) experienced a second TJA hospitalization with a median duration of 1.21 years (0.64–2.58 years) from the index procedure. Of these, 69.52% were for primary TJA of the contra-lateral hip, 2,193 (23.11%) were single or bilateral primary knee replacements, and 700 (7.38%) were for revision or one or both index hips. Of those who experienced a second TJA hospitalization, 2,561 (1.97% of the cohort) went on to receive a third within a median duration of 2.8 years (IQR 1.1–4.1 years) from the index procedure; the majority (89.54%) of these were elective TJAs.

Conclusion: In a population cohort undergoing primary hip or knee TJA, repeat TJA hospitalizations are frequent; approximately one-quarter experienced a second TJA hospitalization, which was most often for primary TJA of the contra-lateral hip or knee. Most repeat hospitalizations occurred within 3 years of the index TJA. Together, these data suggest that exclusion of such individuals from TJA cohort studies reduces the generalizability of results to all patients undergoing primary TJA.

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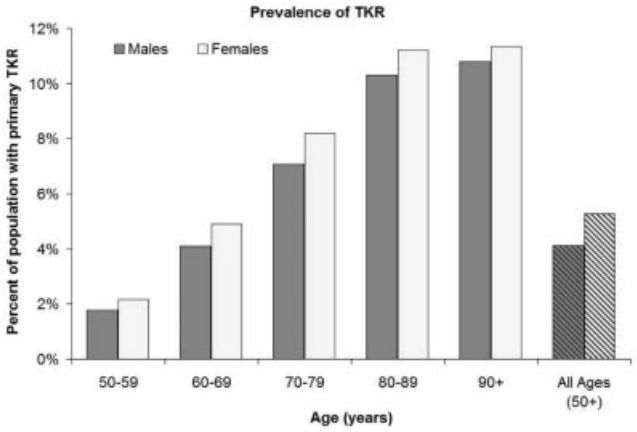
How Many Americans Are Currently Living with Total Knee Replacement?

Alexander M. Weinstein, Benjamin N. Rome, William M. Reichmann, Jamie E. Collins, Sara A. Burbine, Thomas S. Thornhill, John Wright, Jeffrey N. Katz and Elena Losina. Brigham and Women's Hospital, Boston, MA

Background/Purpose: In the last decade, the number of total knee replacements (TKRs) performed in the US doubled, exceeding 600,000 in 2009. The vast majority are done for osteoarthritis (OA). The growth in TKR use has been greatest among younger individuals, and as a result the average age at which patients receive TKR has decreased over time. The rapid growth in TKR utilization among younger individuals, coupled with increased life expectancy, may lead to increased health care costs due to periprosthetic fractures, prosthetic infections, and symptomatic loosening, with the need for revision TKR. While changes in annual rates of TKR over time have been described, estimates of the number of persons in the US living with knee implants have not been reported.

Methods: We used the OAPol Model, a state-transition, computer-simulation model, to estimate the prevalence of primary TKR stratified by age and sex. We combined these prevalence estimates with 2009 US Census data to calculate the number of Americans currently living with an intact primary TKR. The incidence and prevalence of symptomatic knee OA were derived using data from the National Health Interview Survey. The annual incidence of TKR among persons with advanced knee OA (Kellgren-Lawrence grade 3 or 4) was derived using the data from two national longitudinal studies of persons with knee OA (Multicenter Osteoarthritis Study and Osteoarthritis Initiative). Input parameters related to mortality, obesity, comorbidities, non-surgical OA treatments, and prosthesis failure were obtained from national survey data and published literature.

Results: Over 4.5 million Americans currently have an intact primary TKR, representing 4.7% of the population aged 50 years or older. The prevalence of TKR is higher in females (5.3%) than males (4.1%). Among persons 60–69 years of age, 4.1% of men and 4.9% of women have had at least one knee replaced. Among those 70–79 years of age, 7.1% of men and 8.2% of women have had at least one knee replaced. Approximately 10% of those older than 80 years have had at least one knee replaced. (Figure).



Conclusion: Five percent (5%) of females and 4% of males older than 50 years are living with TKR. Among persons older than 50 years of age, TKR has become considerably more prevalent than rheumatoid arthritis or congestive heart failure. Knowledge of TKR prevalence is useful in planning health services specific to the population living with TKR. This includes the prevention and management of periprosthetic fractures and infections, as well as planning for adequate capacity for revision TKR.

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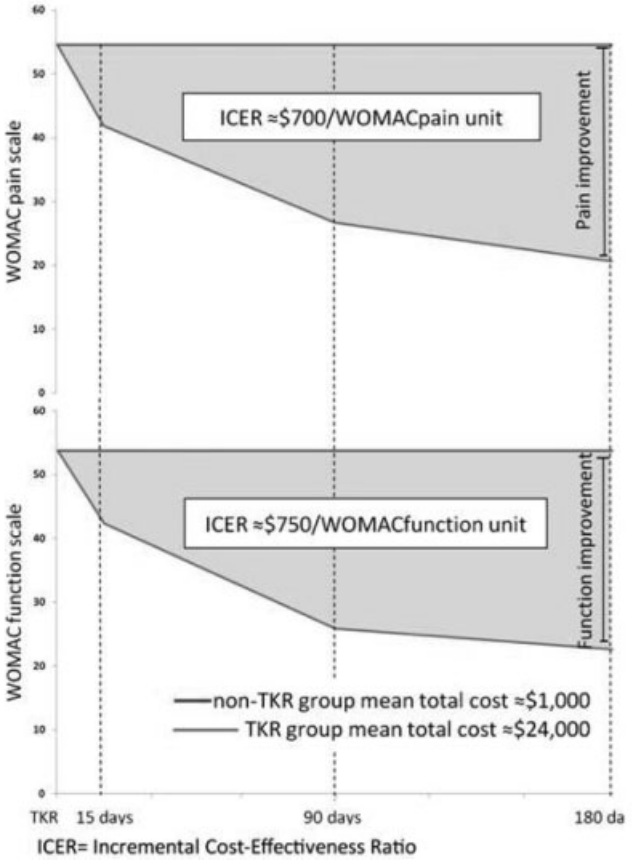
Impact of Slow Recovery and Poor Functional Outcomes on Direct and Indirect Costs After Total Knee Replacement in Osteoarthritis Patients.

Christian A. Waimann[1], Rodrigo J. Fernandez-Mazarambroz[1], Scott B. Cantor[1], Maria Lopez-Olivo[1], Hong Zhang[1], Glenn C. Landon[2], Sherwin J. Siff[2] and Maria E. Suarez-Almazor[1]. [1]University of Texas. M.D Anderson Cancer Center, Houston, TX, [2]St. Luke's Episcopal Health System, Houston, TX

Background/Purpose: About 15–30% of patients with osteoarthritis (OA) who undergo total knee replacement (TKR) have little or no improvement after the surgery. The aim of our study is to determine the impact of slow recovery and poor functional outcomes on TKR-related costs.

Methods: PEAKS (Patient Expectations About Knee Surgery Study) is a prospective cohort of patients with OA who underwent TKR. We followed patients for 6 months after surgery, and collected sociodemographic data, TKR-related costs, and clinical outcomes (the Western Ontario McMaster (WOMAC) pain and function scale). The economic analysis was conducted using a societal perspective based on 2007 US dollars. Direct medical costs were estimated using the Medicare Reimbursement Prospective Payment System; hospital bills were adjusted by cost-to-charge ratios reported to Medicare. Average wholesale price was used for drugs costs. Productivity losses (patients and relatives) were calculated using time lost from work multiplied by estimated wage per occupation reported by the Bureau Labor of Statistics for Texas. We defined improvement as either absolute (minimal clinically important difference (MCID), 20-point change), or relative (20%, 50% or 70% improvement in WOMAC (WOMAC20, 50 and 70)). Incremental cost-effectiveness ratios (ICERs) for each level were calculated, assuming a hypothetical non-TKR cohort where WOMAC scales and OA-related costs prior to surgery remained stable. We stratified WOMAC in four severity levels: none-to-mild (0 to ≤25), mild-to-moderate (>25 to ≤50), moderate-to-severe (>50 to ≤75), and severe-to-extreme (>75 to ≤100). TKR-related costs were calculated for each level at 3 and 6 months post-surgery.

Results: 218 patients were included; 65% were female, 69% were white, mean age was 65±9 years. Mean total costs were ≈$24,000±10,000. At 6 months 91% of patients improved, 61% showed a MCID and 80% WOMAC20 response. Figure 1 shows ICERs for WOMAC at 6 months. The ICERs for MCID, WOMAC20, WOMAC50, WOMAC70 were ≈$39000, ≈$30000, ≈$41000 and ≈$67000, respectively. TKR-related costs were higher in patients with poor function and worse pain (moderate-to-extreme level, WOMAC score >50 points) at 3 and 6 months, in comparison to better levels of function and pain.



Conclusion: TKR remains a cost-effective intervention at low and high levels of improvement. Patients with worse pain and function outcomes had higher TKR-related costs, suggesting that peri-operative interventions that can lead to a fast recovery and improve TKR outcomes might be cost-effective by decreasing subsequent costs.

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Predictors of Suboptimal Patient Outcome Following Total Joint Arthroplasty. Gillian A. Hawker[1], Ruth Croxford[2], A. M. Davis[3], Sheila Dunn[1], Joy G. Elkayam[1], Melissa R. French[1], M. A. Gignac[4], Susan B. Jaglal[5] and Joanna Sale[5]. [1]Women's College Hospital, Toronto, ON, [2]Institute for Clinical and Evaluative Science, Toronto, ON, [3]Health Care and Outcomes Research, Toronto Western Research Institute; Departments of Rehabilitation Science and Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, [4]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [5]University of Toronto, Toronto, ON

Background/Purpose: Total Joint Arthroplasty (TJA) on average shows good to excellent outcomes for patients that have failed medical management, but significant variability has been observed. The determinants of suboptimal TJA outcome have not been well studied; thus our aim was to evaluate the determinants of suboptimal TJA outcome at a patient level.

Methods: Participants were members of a population cohort with hip/knee arthritis, recruited from 1996–98 through screening 100% aged 55+ years in two regions, one rural and one urban (n=2,411). Annual interviews assessed socio-demographics, arthritis type (OA versus inflammatory arthritis, IA); arthritis severity (WOMAC), other MSK complaints (presence of other troublesome hips/knees, low back pain), joint replaced (hip versus knee), health status (SF36 mental health and general health scores) and comorbidity (0, 1, 2, 3+ conditions). Survey data were linked with health administrative databases to examine receipt of primary, elective TJA from 1988 to 2008. Suboptimal outcome was defined as a pre-post change in WOMAC summary score less than a Minimal Important Difference (MID) (MID = 0.5 SD change of the mean difference in scores). Pre- and post-surgery WOMAC scores were those obtained at the interview closest in date and prior to the index TJA date, and closest in date to the end of the 6 month post-operative period, respectively. Logistic regression was used to model predictors of sub-optimal outcome. Akaike's Information Criterion (AIC) was used to determine the size of the best predictive model, and then all possible subset regression was used to identify the final model of the selected size.

Results: 166 cohort members received a TJA following their baseline interview and completed a post-TJA assessment. Mean age at TJA was 71 years; most recipients were female and had a knee replaced. Almost half the TJA recipients (48.7%) met the criterion for sub-optimal outcome (reduction in WOMAC score of < 9/100 points; 49.5% knees versus 42.4% hips, p=0.42). In univariate analyses, only pre-surgery WOMAC score distinguished those with versus without a suboptimal outcome, with a lower (better) score associated with suboptimal outcome. The multivariable predictive model found that the probability of a suboptimal outcome following TJA increased with lower pre-surgery pain and disability (WOMAC summary score) and poorer pre-surgery mental health, and increased if the patient had another troublesome hip/knee and/or a diagnosis of IA (Table 1) (c-statistic 0.79).

Predictor variables	Odds Ratio	Confidence Interval	p-value
Pre-surgery WOMAC score, per 10-point increase*	0.43	0.32 to 0.58	<0.0001
Pre-surgery SF-36 mental health score, per 10-point increase†	0.79	0.64 to 0.98	0.031
Presence of 1+ other troublesome hip/knee at surgery	3.06	1.02 to 9.17	0.046
Inflammatory arthritis	8.47	1.70 to 41.7	0.009

*Increasing values indicate increasing pain and disability
† Increasing SF36 values indicate improved health

Conclusion: Suboptimal outcome, observed in almost half of participants, was associated with lower levels of arthritis severity, poor mental health status, and the presence of other troublesome hips/knees or IA diagnosis pre-surgery. These results may help prospective patients and their health care providers make an informed cost-benefit decision on the expected outcomes of TJA.

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Alcohol Intake Is Associated with Incident Gout Among Black and White, Men and Women in the Atherosclerosis Risk in Communities Study. Mara McAdams DeMarco[1], Janet W. Maynard[2], Alan N. Baer[2] and Josef Coresh[1]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD

Background/Purpose: Alcohol increases gout risk in white men. We sought to quantify the association of alcohol intake and incident gout in a biracial population-based cohort.

Methods: The Atherosclerosis Risk in Communities study (ARIC) is a prospective cohort study of 15,792 individuals from 4 US communities, consisting of 4 visits administered 3 years apart. At visit 4, participants reported their gout status. We excluded those who did not attend visit 4 or had gout prior to visit 1. The % daily calories from alcohol intake was categorized into quintiles (≤1.5, 1.5–3.1, 3.1–5.3, 5.3–9.8, >9.8) as well as no alcohol intake. We tested the association of categorical alcohol intake and incident gout using a Cox Proportional Hazards model with age as the time scale (adjusted for sex, race, BMI, diuretics, eGFR, hypertension, calories, and intake of specific foods). We adjusted for serum urate and tested for sex, race, BMI and serum urate level interactions.

Results: This study contains 10,799 participants; 6,495 (60%) abstained from alcohol and 275 (2.5%) developed gout. The study population was 57% female and 22% African American. Results are presented in the table. Compared with no alcohol intake (reference), the adjusted hazard ratio (HR) and 95% CI for quintiles of alcohol intake were 1.00 (0.60, 1.70); 0.93 (0.54, 1.63); 0.92 (0.53, 1.61); 2.26 (1.54, 2.29); 2.31 (1.57, 3.40), respectively (p-value for trend <0.001). The increased HR for gout in the higher quintiles of alcohol intake was not changed significantly when adjusted for serum urate level. There was no interaction of alcohol intake with sex (p-value=0.8), race (p-value=0.2) or BMI (p-value=0.3). However, there was a statistical interaction between baseline serum urate level and alcohol intake (p-value=0.029).

Hazard rate ratio (HR) of incident gout by categorical baseline alcohol intake in the ARIC cohort (n=10,799)

Model	No alcohol intake	Quintile 1 (≤1.5%)	Quintile 2 (1.5%–3.1%)	Quintile 3 (3.1%–5.3%)	Quintile 4 (5.3%–9.8%)	Quintile 5 (>9.8%)	p-value for the trend
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Sex adjusted	–	0.76 (0.46, 1.28)	0.64 (0.37, 1.11)	0.64 (0.37, 1.01)	1.64 (1.15, 2.36)	1.53 (1.06, 2.21)	0.02
Model 1	–	0.98 (0.58, 1.65)	0.88 (0.51, 1.54)	0.86 (0.50, 1.51)	2.16 (1.48, 3.14)	2.26 (1.54, 3.30)	<0.0001
Model 2	–	1.00 (0.60, 1.70)	0.93 (0.54, 1.63)	0.92 (0.53, 1.61)	2.26 (1.54, 2.29)	2.31 (1.57, 3.40)	<0.0001
Model 3	–	0.85 (0.50, 1.43)	0.91 (0.52, 1.59)	0.84 (0.48, 1.46)	1.71 (1.17, 2.48)	1.81 (1.29, 2.66)	0.001

Model 1: Adjusted for sex, race, and baseline BMI, diuretic use, categorical eGFR, hypertension, and total calories.
Model 2: Model 1 additionally adjusted for fructose intake, caffeine intake, and vitamin c intake.
Model 3: Model 2 additionally adjusted for serum urate at baseline
Age was used as the time-scale.

Conclusion: Participants in the 2 highest quintiles of alcohol intake had more than a 2-fold risk of gout, independent of confounders. Additionally, this is the first study to detect an interaction of serum urate level and alcohol intake such that patients with higher serum urate levels and high alcohol intake are at the highest risk of developing gout.

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Gout Treatment Gaps and Factors Associated with Incident Patients Having Uric Acid Goal Attainment: A Retrospective Cohort Study in An Integrated Healthcare System. Nazia Rashid[1], T. Craig Cheetham[1], Jeffery R. Curtis[2], Gerald D. Levy[3], Kenneth G. Saag[2] and Ted R. Mikuls[4]. [1]Kaiser Permanente Pharmacy Analytic Services, Downey, CA, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Southern California Permanente Medical Group, Downey, CA, [4]Omaha VA and University of Nebraska, Omaha, NE

Background/Purpose: Gout affects approximately 1 to 2% of the US population and is the most common form of inflammatory arthritis in men. Urate lowering therapy is effective; however is often characterized by inadequate dose adjustment to achieve goal-directed urate lowering. This study was undertaken to characterize the gaps in gout care leading to suboptimal outcomes in an integrated healthcare delivery system.

Methods: This was a retrospective cohort study of gout patients in Kaiser Permanente Southern California. Patients aged 18 years and older with a diagnosis of gout (ICD9 274.xx) and allopurinol prescription from January 1, 2007 to June 31, 2010 were included. Incident allopurinol users were defined as patients that had no allopurinol prescription within 12 months prior of the 1st gout diagnosis. Patients were followed from the 1st gout diagnosis until disenrollment or end of study period.

Primary outcome of interest was attainment of serum uric acid (sUA) level <6mg/dl, and secondary outcome of interest was sUA monitoring. Descriptive statistics were calculated comparing incident patients at sUA goal or not at sUA goal (>=6mg/dl) at the end of observation (at least 12 months after treatment initiation). Logistic regression was used to evaluate characteristics such as age, gender, race, co-morbid conditions, concomitant medications, adherence, care by a rheumatologist, and allopurinol dose adjustment associated with sUA goal attainment.

Results: 15,596 patients were identified as incident gout patients (mean age 60 years, men 81%). Overall, all patients had at least one comorbid condition: hypertension (73%), chronic kidney disease (30%), and diabetes (25%) being the most common; hydrochlorothiazide (20%) and furosemide (15%) were the most commonly utilized concomitant medications. Only 9,287 patients (60%) had follow up uric acid lab levels after the 1st allopurinol prescription. At the end of observation, 2,917 patients (30%) were at sUA goal (mean age 63 years, men 71%) versus 6,538 patients not at goal (mean age 59 years, men 81%). Patients whom saw a Rheumatologist within 6 months of their 1st allopurinol prescription and preceding their 1st sUA level were more likely at goal (Odds Ratio [OR] = 1.21, 95% CI 1.02 – 1.43). Older patients (OR = 1.02, 95% CI 1.01–1.02) and those who were at least 80% adherent (OR = 2.82, 95% CI 2.56–3.11) were more likely to achieve goal sUA. Overall, male patients were 37% less likely to be at goal. CHF and CKD were significantly associated with not achieving target sUA.

Conclusion: A total of 40% of incident allopurinol users did not have a follow up sUA level after their 1st prescription of allopurinol. Factors such as age, care by a rheumatologist, and adherence were key factors associated with achieving goal serum urate levels.

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Evaluation of Healthcare Costs for Patients with Gout by Serum Uric Acid. Karen Rascati[1], Karim Prasla[2], Haesuk Park[1] and Tyrone McBayne[3]. [1]University of Texas at Austin College of Pharmacy, Austin, TX, [2]Scott and White Health Plan, Temple, TX, [3]Takeda Pharmaceuticals America, Inc., Deerfield, IL

Background/Purpose: The objective of this study was to assess the costs and utilization patterns of medical and pharmacy services, categorized into 3 cohorts based on serum uric acid (sUA) levels.

Methods: Retrospective analysis was conducted using lab, pharmacy, and medical service claims data (January 1, 2005-June 30, 2010) for patients 18 years and older enrolled in a regional staff model health plan. Inclusion criteria were at least 2 sUA levels and at least 1 primary gout diagnosis (ICD-9: 274.xx), and at least 1 prescription for one of the following gout-specific medications: allopurinol, colchicine, probenecid, probenecid/colchicine, or febuxostat. Costs, healthcare resource utilization, and medication utilization patterns were assessed for 1 year post-index and summarized for the 3 cohorts based on sUA: 1) <6 mg/dL; 2) 6–8.99 mg/dL; and 3) ≥9 mg/dL. Costs were defined as total allowed amount, including allowable plan costs plus patient costs. Cost components were compared using either a generalized linear model (GLM) or a 2-part model that controlled for baseline clinical and demographic parameters. Medication adherence, including medication possession ratio and proportion of days covered, persistence, and treatment patterns were measured for 1 year post-index.

Results: 352 patients met inclusion criteria: Cohort 1 (sUA <6 mg/dL) n=38, mean age 59 yrs, 71% male; Cohort 2 (sUA 6–8.99 mg/dL) n=231, mean age 61 yrs, 77% male; Cohort 3 (sUA ≥ 9 mg/dL) n=83, mean age 62 yrs, 61% male. Mean adjusted gout-related healthcare costs were $332, $353, and $663, respectively ($P<0.05$); mean adjusted all-cause healthcare costs were $11,365, $11,551, and $14,474, respectively, for the 3 cohorts ($P<0.05$). The difference in the mean number of all-cause hospitalizations claims and all-cause emergency department (ER) visits was statistically significant. The mean number of all-cause hospitalizations claims were 0.84, 0.94, and 1.67, respectively ($P=0.019$); mean number of all-cause emergency department visits were 0.39, 0.51, and 0.86, respectively, for the 3 cohorts ($P=0.026$). Gout medication adherence and persistence were significantly associated with sUA levels. Significantly more patients with sUA <6 mg/dL (56.0%) achieved adherence rates of 80% or better relative to patients with sUA between 6 and 8.99 mg/dL (28.5%) or patients with sUA ≥9 mg/dL (30.5%) ($P<0.05$). Patients with sUA <6.0 mg/dL had a longer mean duration of continuous treatment before 60-day discontinuation (255 days) than the other 2 cohorts (164 days for patients with sUA 6–8.99 mg/dL and 178 days for patients with sUA ≥9.0 mg/dL, respectively: $P<0.05$).

Conclusion: Patients with higher sUA levels have higher gout-related and all-cause healthcare costs, increased all-cause medical, hospital, and ER utilization, while also exhibiting poorer adherence and persistence.

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Total Health-Care Costs Among Gout Patients On Allopurinol or Febuxostat. Brett W. Pinsky[1], Bhavik J. Pandya[2], Gabriel Gomez Rey[3] and Jasvinder A. Singh[4]. [1]Innovus, O'Fallon, MO, [2]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [3]Innovus, Eden Prairie, MN, [4]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: The goal of the study was to identify the total health-care (HC) costs for gout patients receiving allopurinol (ALLO) or febuxostat (FEB).

Methods: This retrospective study in adult patients (pts) used 2009–10 medical and pharmacy claims linked with laboratory data from a large US managed-care population. All pts had at least 1 fill for ALLO or FEB; any pt prescribed FEB was placed in the FEB cohort. The ALLO cohort included only pts with no FEB use. The index date was the date of first fill during the study period. Pts were required to have at least 1 serum uric acid (sUA) measurement ≥14 days post index date. Pts had 6 months of continuous enrollment prior to their index date (baseline period) and were followed for ≥90 days post treatment start (follow-up). Total HC costs were calculated as per member per month (PMPM) to adjust for variable follow-up. The change in cost (baseline vs follow-up) was examined. HC costs were also divided into subcategories: pharmacy and total medical (all non-pharmacy) costs; medical costs were further broken down into inpatient, ER, and office/outpatient costs. A multivariate log-linked regression using a gamma distribution was conducted to further examine HC costs.

Results: The study sample included 451 FEB pts and 5,880 ALLO pts. Prior to starting therapy, FEB pts had a higher Quan-Charlson score (1.4 vs 1.0; $p<0.01$). Baseline PMPM total HC costs were higher for FEB pts vs ALLO pts ($p=0.02$) (Table). Following initiation of index medication, total PMPM HC costs decreased $97 ($p=0.65$) from the baseline period in FEB pts, compared to an increase of $204 ($p<0.01$) in ALLO pts. The change was mainly due to medical costs. Medical costs decreased 18% in the FEB pts and

increased 23% in ALLO pts. After controlling for comorbidities (hypertension, peripheral artery disease, heart failure, rheumatoid arthritis, osteoarthritis, hyperlipidemia, kidney failure); presence of tophi; baseline sUA; baseline utilization (ER visits, inpatient, and office/outpatient visits); geographic region; gender; age; and insurance type, pharmacy costs were higher in FEB patients ($p<0.01$); however, no difference in follow-up total HC costs was observed between ALLO and FEB pts ($p=0.89$).

Table. Total Health-Care Costs in the Baseline and Follow-Up Periods

PMPM HC costs (SUS)	Baseline			Unadjusted Follow-up			Adjusted Follow-up		
	FEB†	ALLO‡	p-value	FEB	ALLO	p-value	FEB	ALLO	p-value*
Total Healthcare	1,294	817	**0.02**	1,196	1,022	0.14	1,074	1,096	0.89
Medical	1,040	634	**0.04**	857	818	0.72	762	884	0.42
Inpatient	483	241	0.16	381	385	0.95	409	524	0.55
ER	21	18	0.32	28	19	0.08	29	21	**0.04**
Office/outpatient	447	326	**0.04**	379	356	0.51	341	362	0.57
Pharmacy	255	182	0.05	339	204	**<0.01**	331	205	**<0.01**

† 451 FEB patients
‡ 5,880 ALLO patients
* Adjusted p-value based on the regression model parameter estimate.
Note: p-values in boldface are significant ($p<0.05$).

Conclusion: At baseline, total HC costs for FEB pts were higher compared to pts on ALLO; however, the follow-up total HC costs of the 2 cohorts were similar. Total HC costs increased between baseline and follow-up for ALLO-treated patients, while there was a decreased trend for FEB-treated patients during the same time period.

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Serum Urate−Lowering Effectiveness of Febuxostat Compared with Allopurinol and Switching to Febuxostat From Allopurinol In the Real-World Setting. Bhavik J. Pandya[1], Brett W. Pinsky[2], Gabriel Gomez Rey[3] and Jasvinder A. Singh[4]. [1]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [2]Innovus, O'Fallon, MO, [3]Innovus, Eden Prairie, MN, [4]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: The study goal was to examine the changes in serum uric acid (sUA) level for gout patients (pts) new to sUA-lowering medication vs patients with prior allopurinol (ALLO) use, who did or did not switch to febuxostat (FEB).

Methods: This retrospective study in adult pts used 2009–10 medical and pharmacy claims linked with laboratory data from a large US managed-care population. All pts had at least 1 fill for ALLO or FEB. The ALLO cohorts included only pts with no FEB use. The index date was the date of first fill during the study period. Pts were categorized into 4 cohorts based on their index medication and prior ALLO use. Pts were required to have at least 1 sUA measurement ≥14 days post index date. Pts had 6 months of continuous enrollment prior to their index date (baseline period) and were followed for ≥90 days post treatment start (follow-up). Follow-up sUA and change in sUA was examined using a t-test and linear regression; likelihood to attain sUA goal was examined using logistic regression.

Results: The study sample included 264 new FEB pts without prior ALLO (FEB-N), 187 FEB switch pts (FEB-S; switched from ALLO to FEB), 2,552 new ALLO pts (ALLO-N), and 3,328 ALLO continuation pts (ALLO-C). Prior to starting therapy, FEB-S pts had the highest Quan-Charlson score (1.8 vs 1.2 [FEB-N], 1.1 [ALLO-N], and 1.0 [ALLO-C]; $p<0.01$). Baseline sUA was higher for FEB-N (9.1 mg/dL pts vs FEB-S (8.2 mg/dL; $p<0.01$) and ALLO-C pts (6.6; $p<0.01$) (Table). There was no difference in baseline sUA value between ALLO-N and FEB-N patients. FEB-N pts had the highest average decrease in sUA of 2.5 mg/dL (t-test; $p<0.01$ compared with FEB-S, ALLO-N and ALLO-C). Over 80% of both FEB-N and FEB-S pts received an index dose of 40 mg. and over33% of ALLO-N and ALLO-C pts had an index dose <300mg. Over 45% of ALLO-N and ALLO-C pts had an index dose of 300mg. After controlling for comorbidities (hypertension, peripheral artery disease, heart failure, rheumatoid arthritis, osteoarthritis, hyperlipidemia, kidney failure), presence of tophi, baseline sUA, geographic region, gender, age, and insurance type, FEB-N pts had 93% higher odds ratio of attaining sUA goal at ≤6 mg/dL ($p<0.01$) and 168% higher odds of attaining sUA of ≤5 mg/dL (OR 2.68; $p<0.01$) compared with ALLO-N. FEB-S pts had 60% higher odds ratio of attaining sUA goal at ≤6 mg/dL ($p<0.01$) and 74% higher odds ratio of attaining sUA of ≤5 mg/dL (OR 1.74; $p<0.01$) compared with ALLO-C. The mean dose at time of goal attainment was slightly higher in pts achieving an sUA goal of <5 mg/dL(FEB-N=52.9 mg; FEB-S=59.1mg; ALLO-N=305.7mg; ALLO-C=309. mg) than <6 mg/dL (FEB-N=54.0mg; FEB-S=54.9mg; ALLO-N=280mg; ALLO-C=292mg).

Table. Unadjusted sUA Values and sUA Goal Attainment

Parameter	Baseline sUA*	Follow-up sUA	Change in sUA*	% of Patients Attaining Goal (<6.0 mg/dL)	% of Patients Attaining Goal (<5.0 mg/dL)
FEB-N Pts	9.1	6.4	2.5	53.8%	32.2%
FEB-S Pts	8.2	6.5	1.6	59.4%	33.2%
ALLO-N Pts	9.0	6.9	2.0	38.7%	16.0%
ALLO-C Pts	6.6	6.1	0.3	55.9%	28.2%
p-value FEB-N vs FEB-S	<0.01	0.90	<0.01	0.24	0.83
p-value FEB-N vs ALLO-N	0.37	<0.01	<0.01	<0.01	<0.01
p-value FEB-S vs ALLO-C	<0.01	0.06	<0.01	0.35	0.15

* Baseline sUA and Change in sUA only available for subset of the population: FEB-N=176, FEB-S=136, ALLO-N=1,284, and ALLO-C=1,161.

Conclusion: Pts newly started on urate-lowering therapy had the largest decrease in sUA. FEB-N pts had the largest drop in sUA, while ALLO-C pts had the smallest drop. ALLO-N pts were the least likely to attain sUA goal, and FEB-S pts were the most likely to attain sUA goal.

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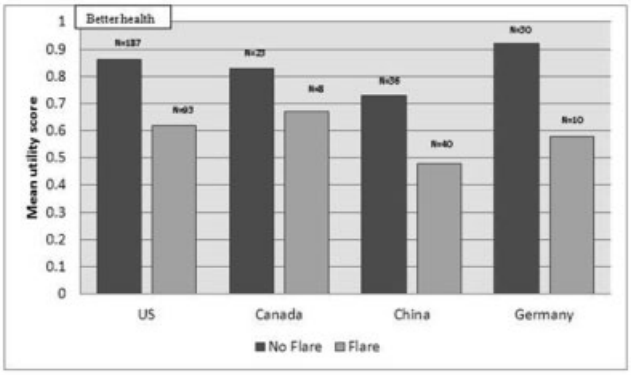
Multinational, Prospective, Observational Study to Characterize and Assess the Burden of Refractory Gouty Arthritis on Patients Over One Year: Global Baseline Results. Pascal Lecomte[1], Louis Bessette[2], Alberto Ferreira[1], Hans-Peter Goertz[1], Paula Jones[3] and Jasvinder A. Singh[4]. [1]Novartis Pharma AG, Basel, Switzerland, [2]CHUL, Quebec, [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [4]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Gouty arthritis (GA) is the most prevalent form of inflammatory arthritis. Refractory (or difficult to treat) GA occurs when therapies are ineffective, not tolerated, or contraindicated, leading to frequent attacks. The objective of this study is to characterize the humanistic and economic burden of refractory GA on patients in selected countries.

Methods: The MOTION study is an ongoing multinational, non-interventional, prospective, observational study of patients with GA who experienced at least 3 gout attacks in the previous year. Enrolled patients were refractory to at least one anti-inflammatory therapy (NSAIDs, colchicine or corticosteroids) or to urate lowering therapies. The study is being conducted in six countries (Canada; China; France; Germany; Spain; US). The primary objective of this study is to assess patient health utility during a GA attack and the intercritical period (between attacks), using the EuroQol Health Status Questionnaire 5D (EQ-5D). This instrument consists of the EQ-5D descriptive system which enables calculation of a utility score (ranging from 0.0 (dead) to 1.0 (perfect health)) and the EQ-5D visual analog scale (VAS) (ranging from 0 (worst imaginable health state) to 100 (best imaginable health state)). Secondary objectives are to evaluate patient quality of life; patient and physician satisfaction with treatment and quantify health care resource utilization; assess lost work productivity; and characterize pain during GA attack and the intercritical period. Data are being collected monthly over 12 months. We report baseline characteristics of all enrolled patients.

Results: Among the 454 patients enrolled in 57 sites, most were men (86%), and the mean age was 56 years. Nearly all (84%) suffered from polyarticular gout with 51% of patients having 4 or more joints affected in an acute GA attack. The mean disease duration was 11 years with a mean number of attacks of 6.9 in the year prior to enrollment. Tophi were documented in 30% of the patients and those that presented with tophi had a mean of 5.4 tophi. More than 80% of patients suffered from at least one comorbidity. During the baseline GA attack,

mean EQ-5D utility score was 0.57 and VAS score 60. During the baseline intercritical period, mean EQ-5D utility score was 0.85 and VAS score 76.



Conclusion: MOTION study population consisted mostly of men, frequently flaring, who suffered from polyarticular gout and comorbidities. Impact of GA attack on patient health utility as assessed with the EQ-5D, was marked. Among countries participating, the smallest mean drop in utility due to GA attack was 0.16. Monthly assessments of health utility in the MOTION study will help to better quantify the impact of GA attacks on patients.

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Frequency of Gouty Arthritis Attacks and Presence of Comorbid Conditions Have An Impact on Gout-Related Healthcare Resource Utilization and Costs. Joseph J. Saseen[1], Neetu Agashivala[2], Richard R. Allen[3], Vahram Ghushchyan[1] and Kavita V. Nair[1]. [1]University of Colorado, Aurora, CO, [2]Novartis Pharmaceutical Corporation, East Hanover, NJ, [3]Peakstat Statistical Services, Evergreen, CO

Background/Purpose: Gouty arthritis attacks cause significant pain and inflammation, and typically require medical intervention and pharmacotherapy for proper resolution. Although prior retrospective analyses have estimated health care costs associated with gouty arthritis attacks, predictors of patients with higher healthcare costs and the effect of comorbidities have not been completely assessed. We examined the impact of the cumulative number of attacks and comorbidities on healthcare expenditures.

Methods: We used the MarketScan database to identify patients > 18 years and above with an ICD9 code for gout (274.xx) or at least 1 prescription claim for specific gout-related medication (allopurinol, febuxostat, probenecid or colchicine) between July 1, 2005–June 30, 2010. The date of the first diagnosis or prescription claim was the index date. Patients were required to have a minimum of 12 months pre and post enrollment data from the index date. Patients were categorized as having frequent gouty arthritis (≥3 attacks in the 1-year post index period) using a claims-based algorithm and were compared to patients with infrequent gouty arthritis (<3 attacks) who were matched in a 1:2 ratio on age, sex and geographic region. All costs were inflation adjusted to 2011 dollars.

Results: A total of 5,222 patients with ≥3 (frequent) and 10,444 patients <3 (infrequent) gouty arthritis attacks were identified. The mean age was 58 years and 77.3% were men. Patients with frequent gouty arthritis had a higher prevalence of comorbid conditions: chronic kidney disease, 12.2% vs. 7.2%; hypertension, 59.1% vs. 50.8%; heart failure, 10.1% vs. 6.8%; rheumatoid arthritis, 8.8% vs. 3.2% and osteoarthritis, 32.3% vs. 17.5% (all $p<0.001$). Mean number of all-cause and gout-related outpatient visits were 23.9 and 5.4 for patients with frequent gouty arthritis versus 17.3 and 1.2 for patients with infrequent gouty arthritis (between groups, both $p<0.001$). Mean gout-related medical costs and total costs expressed in 2011 dollars were $834 and $889 for patients with frequent gouty arthritis versus $176 and $210 for infrequent gouty arthritis (between groups, both $p<0.001$). Mean all-cause outpatient visits in patients with comorbid conditions compared with patients with only gouty arthritis were 25.8 vs. 11.8 in the frequent gouty arthritis group, and 19.8 vs. 8.5 in the infrequent gouty arthritis group (between groups, both $p<0.001$). Mean number of gout-related outpatient visits were higher in patients with comorbid conditions in the frequent gouty arthritis group (5.5 vs. 4.9, $p<0.001$), and in patient with infrequent gouty arthritis (1.2 vs. 1.1, $p<0.001$). However, mean gout related medical costs were higher in the frequent gouty arthritis group in patients with comorbid conditions ($886 vs. $513, $p=0.03$), but was similar in the infrequent gouty arthritis group in patients with comorbid conditions ($180 vs. $156, $p=0.25$).

Conclusion: Frequency of gouty arthritis attacks and presence of comorbid conditions are associated with higher health care costs. Severity of gouty arthritis and other health conditions should be considered when projecting health care costs in this population.

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Multinational, Prospective, Observational Study to Characterize and Assess the Burden of Refractory Gouty Arthritis on Patients Over One Year: US Baseline Results. Pascal Lecomte[1], Louis Bessette[2], Alberto Ferreira[1], Hans-Peter Goertz[1], Paula Jones[3] and Jasvinder Singh[4]. [1]Novartis Pharma AG, Basel, Switzerland, [2]CHUL, Quebec, [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [4]University of Alabama and VA Medical Center, Birmingham, AL

Background/Purpose: Gouty arthritis (GA) is the most prevalent form of inflammatory arthritis. Refractory (or difficult to treat) GA occurs when therapies are ineffective, not tolerated, or contraindicated, leading to frequent attacks. The objective of this study is to characterize the humanistic and economic burden of refractory GA on patients in selected countries.

Methods: The MOTION study is an ongoing multinational, non-interventional, prospective, observational study of patients with GA who experienced at least 3 gout attacks in the previous year. Enrolled patients were refractory to at least one anti-inflammatory therapy (NSAIDs, colchicine or corticosteroids) or to urate lowering therapies. The study is being conducted in six countries (Canada; China; France; Germany; Spain; US). The primary objective of this study is to assess patient health utility during a GA attack and the intercritical period (between attacks), using the EuroQol Health Status Questionnaire 5D (EQ-5D). This instrument consists of the EQ-5D descriptive system which enables calculation of a utility score and the EQ-5D visual analog scale (VAS). For each item, a higher value indicates better health. Secondary objectives are to evaluate patient quality of life; patient and physician satisfaction with treatment; quantify health care resource utilization; assess lost work productivity; and characterize pain during GA attack and the intercritical period. Data are being collected monthly over 12 months. We report baseline characteristics of the subgroup of US patients.

Results: In total, 284 US patients were enrolled from 35 sites. Patients were predominately male (82%); mean age was 57 years; 50% were employed; mean BMI was 34 Kg/m^2. Polyarticular gout was reported in 84% of patients; mean disease duration was 11 years; mean number of attacks in the year prior to enrollment was 6.6. Tophi were documented in 23% of patients. More than 85% of patients suffered from at least one comorbidity: 69% from cardiovascular disease or hypertension; 42% from lipid disorder; 25% from diabetes; 19% from gastrointestinal disorders; and 6% from chronic kidney disease. At baseline, mean EQ-5D utility score for patients during a GA attack and during the intercritical period was 0.62 and 0.86, respectively. In the last month, 5% of patients had visited the emergency unit; 2% had been admitted to the hospital; 40% visited a physician; and 22% required help at home due to GA.

Table. Patients contra-indicated or intolerant or with lack of efficacy to the following treatments

	N=284	% Overall
MONOTHERAPY		
NSAIDs	242	85.2%
Colchicine	122	43.0%
Corticosteroids	64	22.5%
DUALTHERAPY		
NSAIDs and colchicine	98	34.5%
NSAIDs and corticosteroids	50	17.6%
Colchicine and corticosteroids	30	10.6%
TRIPLETHERAPY		
NSAIDs and colchicine and corticosteroids	27	9.5%

Conclusion: Refractory GA patients suffer from many comorbidities and are frequently flaring, which yields to additional, and sometimes very costly, health care utilization. Contra-indication, intolerance, lack of efficacy to current treatments leave a lot of patients without options. Patients experiencing a GA attack show a sharp decrease in their health utility as assessed with the EQ-5D.

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Gout Characteristics, Health-Related Quality of Life and Health Care Utilization: Caucasians Vs. Non-Caucasians In An Observational Cohort of Patients with Gout. Puja Khanna[1], Jan Hirsch[2], Susan J. Lee[3], Robert Terkeltaub[4], Jasvinder Singh[5], Arthur F. Kavanaugh[6], Andrew Sarkin[7] and Dinesh Khanna[1]. [1]University of Michigan, Ann Arbor, MI, [2]Skaggs School of Pharmacy & Pharmaceutical Sciences, University of California San Diego, San Diego, CA, [3]Univ of California San Diego, La Jolla, CA, [4]VA Medical Ctr, San Diego, CA, [5]University of Alabama and VA Medical Center, Birmingham, AL, [6]University of California San Diego, San Diego, CA, [7]Health Services Research, University of California San Diego, San Diego, CA

Background/Purpose: Ethnic differences are well documented in patients with arthritis; however, there are no such studies in patients with gout. We sought to compare gout characteristics, health-related quality of life (HRQOL), and health care utilization (HCU) between Caucasian (Cau) and Non-Caucasian (Non-Cau) patients with gout in a cross-sectional US observational study.

Methods: Data were obtained from patients who participated in a cross-sectional validation study of a gout-specific HRQOL instrument. Patients completed the SF-36 v2 and the Gout Impact Scale (GIS), which assesses impact of gout during an attack and overall (each scale 0 to 100 [greater gout impact]), and reported gout characteristics, comorbidities, demographics, and gout-related HCU over past year. Differences were evaluated using Student t-test and chi-square analyses.

Results: Of the 308 patients, 220 (71%) were Caucasian, 37 (12%) were African American, 16 (5%) were Asian, 17 (6%) indicated Other, and 18 (6%) did not specify. The Cau vs. Non-Cau sample was older (63 vs.58, $p=0.01$), and had a greater proportion of males (92% vs. 83%, $p=0.02$) and longer duration of gout (15 vs. 11 years, $p=0.05$). Non-Cau appeared to have poorer gout control—higher sUA level, greater percentage of subjects experiencing attack in past 3 months, and higher pain rating for worst attack (all $p<0.05$). No significant difference in SF-36 or HCU was observed. However, non-Cau had significantly higher (worse, $p<0.05$) scores for 3 of the 5 GIS scales.

Variable [mean(SD) unless noted]	Caucasian (n=220)	Non-Caucasian (n=70)
GOUT CHARACTERISTICS		
Physician has prescribed medication (prevention &/or acute), %	94	88
Latest sUA, mg/dl	6.9 (1.9)	7.6 (1.7)*
Presence of tophi, %	24	29
Gout attack in the last 3 months, %	53.3	69.6*
Pain during (0–100 VAS)		
typical attack	64.9 (26.5)	71.1 (23.4)
worst attack	75.5 (25.4)	86.3 (16.7)*
HRQOL		
SF-36 PCS†	38.8 (8.5)	40.3 (7.7)
SF-36 MCS†	44.1 (7.2)	42.9 (6.5)
GIS: Gout concern	58.9 (28.2)	75.8 (22.6)*
GIS Medication side effects	45.4 (24.7)	57.9 (26.6)*
GAQ Unmet treatment need	37.2 (22.0)	41.4 (19.3)
GAQ Well-being during attack	54.6 (26.2)	60.9 (25.1)
GAQ Concern during attack	47.7 (23.1)	57.2 (26.2)*
HEALTH CARE UTILIZATION		
Physician or Nurse	2.2 (3.9)	3.2 (3.9)
Rheumatologist	1.6 (4.6)	2.5 (3.7)
ER or Urgent Care	0.7 (1.7)	1.2 (2.5)

* $p<0.05$, † US Normal population score mean = 50 and SD = 10. VAS=visual analogue scale. PCS=physical component summary. MCS=mental component summary. GAQ=gout assessment questionnaire.
For GAQ: higher scores denotes poor HRQOL; for SF-36: higher score denotes better HRQOL.

Conclusion: In this cohort, Non-Cau appeared to have poorer gout control and experienced greater impact of gout on their HRQOL. Future studies should explore possible ethnic differences and explanatory factors.

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Ambulatory Resource Utilization for Gouty Arthritis and Gouty Arthritis Attacks. Chenghui Li[1], Bradley C. Martin[1], Dosha F. Cummins[1], L.M. Andrews[2], Feride Frech-Tamas[2] and Anthony Yadao[2]. [1]University of Arkansas for Medical Sciences College of Pharmacy, Little Rock, AR, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ

Background/Purpose: Gouty arthritis (GA) is increasingly prevalent worldwide and is associated with significant economic burden. The objectives of this study are: 1) to describe ambulatory medical care resource utilization and prescribing patterns for patients with GA and GA attacks as well as the associated costs; and 2) to determine the patient characteristics associated with visits for GA and GA attacks.

Methods: Data from the 2002–2008 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey were used to provide national estimates of office-based visits, hospital outpatient department (OPD) visits, and emergency department (ED) visits in the U.S. Visits associated with GA and GA attacks were identified based on physician diagnosis codes, reason for visit codes, and supplemented with medication mentions for antigout and antihyperuricemic agents during the visits. Rates of visits per 1,000 persons per year in the U.S. population stratified by age, gender, race, ethnicity, and geographic region were estimated using U.S. census data. Unit costs for visits and drug prescribing obtained from a commercial administrative claims database were used to estimate U.S. costs expressed in 2009 dollars. Logistic regression was used to examine patient characteristics associated with ambulatory visits for GA or GA attacks. Data were analyzed using STATA 9.2, accounting for complex survey design, and weights were applied to generate national estimates.

Results: An estimated 7 million ambulatory visits annually were associated with GA, with 2 million (28%) of them attributable to GA attacks. Eighty-nine percent of GA-related visits and 80% of visits for GA attacks occurred in physician offices; 5% and 13% occurred in the EDs, with the remainder in OPDs. The rates were 23.81 and 6.68 visits per 1000 persons per year for GA and GA attacks, respectively, and more than doubled from 2002 to 2008. The rates increased with age and were higher in males (33.85 vs. 13.46 visits per 1000 persons per year in females). Among patients who had an ambulatory visit, the likelihood of GA-related visits increased with the diagnosis of renal disease (OR: 5.38; 95% CI: 3.80–7.63), hypertension (OR: 2.23; 95% CI: 1.79–2.77), diabetes (OR: 1.46; 95% CI: 1.15–1.85), heart failure (OR: 1.81; 95% CI: 1.21–2.69), and non-GA arthritis (OR: 1.54; 95% CI: 1.02–2.33). Allopurinol (63%), NSAIDS (20%), and colchicine (17%) were the most frequently recorded drugs during GA-related visits. For visits associated with GA attacks, NSAIDS (44%), colchicine (28%), and allopurinol (26%) were most frequently recorded. The total ambulatory care costs associated with GA were estimated at $923 million per year, with 32% of the costs attributed to GA attacks. Drug costs accounted for 61% of the total costs.

Conclusion: The annual ambulatory care costs associated with GA were near $1 billion with 32% of the costs attributed to GA attacks. Drug expenditures accounted for 61% of the total costs during the period 2002–2008. Annual rates of GA and GA attack-related ambulatory visits more than doubled from 2002 to 2008 and varied across demographic groups and by patient comorbid conditions.

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Health Care Resource Utilization Is Associated with Attack Frequency in Patients with Gouty Arthritis. Prakash Navaratnam[1], Carl deMoor[1], Michael Shaffer[2], Paula Chakravarti[3], L.M. Andrews[3] and Anthony Yadao[3]. [1]DataMed Solutions LLC, Hilliard, OH, [2]BioTrends Research Group LLC, Exton, PA, [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ

Background/Purpose: The objective of this analysis was to evaluate the extent to which frequency of gouty arthritis attacks is associated with disease progression and health care resource utilization.

Methods: 226 primary care physicians and rheumatologists who treated ≥50 gouty arthritis patients in the last year were asked to complete a cross-sectional, retrospective chart review for patients with gouty arthritis. Patients were stratified by number of gouty arthritis attacks in the last year (<3 and ≥3). Multivariate regression analysis was conducted to assess health-related outcomes during a 12-month observation period, to

evaluate demographic and clinical characteristics, as well as to identify factors associated with attacks that resulted in an ER visit, urgent care utilization, or hospitalization. Variables included gouty arthritis severity, serum uric acid (sUA) level, prescription use, age, gender, duration of disease, presence of tophi, organ/joint damage, and comorbidities. SAS version 9.1 was used to conduct analyses.

Results: 1,039 gouty arthritis patients were identified for the analysis. 39.1% of patients were 50–64 yrs of age and 81.9% were male. Time since diagnosis was 52.5±67.0 (mean±SD) months. The most frequently reported comorbidities were hypertension (51.2%), hyperlipidemia (37.9%), obesity (26.4%), osteoarthritis (22.9%), and diabetes (20.1%). 19.8% of patients had cardiovascular disease, while 16.9% of patients had chronic kidney disease. 14% of the patient population had organ/joint damage, and 17% had tophi at the most recent visit. Nearly 74% of patients were prescribed uric acid lowering therapy at the time of the survey. NSAIDs (46.0%), steroids (44.4%), and colchicine (32.1%) were therapies most commonly used for treatment of attacks. Patients in the ≥3 attacks group (n = 195) were more likely to have physician-reported alcohol use (21% vs 10.8%, p<0.001), chronic kidney disease (25.6% vs 14.5%, p<0.001), obesity (32.3% vs 25%, p=0.040), and organ/joint damage (18.5% vs. 13%, p=0.056) compared to the <3 attacks group (n=844). sUA levels were 8.4±2.4 mg/dL in the ≥3 attacks group and 7.0±2.1 mg/dL in the <3 attacks group. Patients with ≥3 attacks were more likely to be seen primarily by rheumatologists (58% vs. 47.9%, p=0.011) and be reported as having severe gouty arthritis (24.1% vs. 12.0%, p<0.0001). These patients were also nearly twice as likely to use narcotics for treatment of gouty arthritis attacks compared with patients who had <3 attacks (22.6% vs. 12.3%, p=0.001). In the multivariate regression analysis, gouty arthritis attack frequency was the strongest predictor of having an ER visit (OR=4.00, 95% CI 2.56–6.25), urgent care visit (OR=5.59, 95% CI 2.37–13.19), or hospitalization (OR=2.59, 95% CI 1.80–3.72), p<0.05 in all cases.

Conclusion: Patients with ≥3 gouty arthritis attacks were more likely to have attacks result in ER visits, urgent care center visits, and overnight hospitalizations, compared with the <3 attacks group. Greater attack frequency was also associated with alcohol use, CKD, obesity, organ/joint damage, increased gouty arthritis severity, higher prevalence of tophi, and use of narcotics.

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Hypertension, but Not Pre-Hypertension, Is Associated with Incident Gout in White and Black, Men and Women From the Atherosclerosis Risk in Communities Study. Mara McAdams DeMarco[1], Janet W. Maynard[2], Alan N. Baer[2] and Josef Coresh[1]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD

Background/Purpose: Hypertension as a known risk factor for gout. The role of hypertension on the development of gout in a population of African American and white, men and women as well as the association of pre-hypertension and gout has never been quantified.

Methods: Atherosclerosis Risk in Communities Study (ARIC) is a prospective population-based cohort recruited in 1987–1989 from 4 US communities, consisting of 4 visits over 9-years. Participants were included in this analysis if they answered the gout query and were free of gout at baseline. Incident gout was defined as self-reported onset after baseline. Using a time-dependent Cox Proportional Hazards model, we estimated the hazard rate ratio (HR) of incident gout by time-varying hypertension (self-report of medication to treat hypertension, or a measured blood pressure ≥ 140/90 mmHg) and time-varying pre-hypertension (no hypertension treatment and blood pressure ≥ 120/80 but < 140/90 mmHg) adjusted for confounders, and tested for mediation by serum urate level.

Results: There were 10,872 participants among whom 45% had pre-hypertension and 44% had hypertension at baseline or during follow-up. Over 9 years of follow-up, 274 participants developed gout; 1.8% of women and 3.5% of men. The results are presented in the table. The unadjusted HR of incident gout was 3 times (95% CI: 2.20, 3.97) greater for those with hypertension compared to those without hypertension. Adjusting for confounders resulted in an attenuated but still significant association between hypertension and the development of gout (HR= 1.92; 95% CI: 1.41, 2.62). Serum urate level mediated the association between hypertension and incident gout (HR=1.19, 95% CI: 0.86, 1.64). Pre-hypertension was not associated with the development of gout except in the adjusted models, where a weak protective effect was noted (HR=0.65, 95% CI: 0.43, 0.98) after accounting for serum urate level. There was no evidence of effect modification of the association of hypertension and gout by sex (p-value=0.39), race (p-value=0.89) or obesity at baseline (p-value=0.90). Results were similar when the study was limited to those without diuretic use.

Hazard rate ratio and 95% confidence intervals of incident gout by time-varying hypertension and pre-hypertension status in ARIC (N=10,872)

	Hypertension	Pre-hypertension
Unadjusted	2.95 (2.20, 3.97)	0.94 (0.63, 1.41)
Sex and race adjusted	2.47 (1.82, 3.34)	0.86 (0.57, 1.28)
Confounder adjusted	1.92 (1.41, 2.62)	0.75 (0.50, 1.12)
Confounder and serum urate adjusted	1.19 (0.86, 1.64)	0.65 (0.43, 0.98)

Confounders: Sex, race, BMI, estimated glomerular filtration rate and alcohol intake.

Conclusion: In a cohort of men and women of both African American and white race, participants with hypertension had a two-fold increased risk of gout; this is the first study to show that the association was mediated by hyperuricemia. Participants with pre-hypertension did not have an elevated risk. These results confirmed that hypertension is a risk factor for gout. This is the first study to suggest that the risk of gout may not increase until a patient transitions from having pre-hypertension to the development of hypertension.

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Prevalence and Risk Factors of Sarcopenia Among Community-Dwelling Older Women with High Frequency of Overweight/Obesity. Diogo S. Domiciano[1], Camille Figueiredo[1], Jaqueline B. Lopes[1], Valéria Caparbo[1], Liliam Takayama[2], Eloisa Bonfa[3] and Rosa M.R. Pereira[4]. [1]University of São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil, [4]Disciplina de Reumatologia da FMUSP, Sao Paulo, Brazil

Background/Purpose: Sarcopenia is a syndrome characterized by progressive loss of skeletal muscle mass, which results in decreased muscle strength, impairment of physical and functional capacity and increased risk of death. The most widely used criteria for sarcopenia (Baumgartner *et al*.) has the disadvantage to underestimate the prevalence in overweight/obese people, whereas the Newman *et al*. definition considers appendicular muscle mass adjusted to total fat mass. Since prevalence of overweight/obesity is a growing public health issue in the world population, including older people, the aim of this study was to evaluate the prevalence and risk factors associated with sarcopenia, according to these two criteria in older women.

Methods: A total of 611 community-dwelling women, aged over 65 years, were included. Anthropometric data, lifestyle and medical history were assessed by a specific questionnaire. Body composition and bone mineral density were evaluated by DXA measurements (Hologic QDR 4500A). Laboratory tests were also performed (25-hydroxyvitamin D, intact parathormone, calcium, phosphorus, creatinine, glucose and lipid profile). Logistic regression models were used to identify risk factors related to sarcopenia in each criteria used.

Results: The prevalence of overweight/obesity (BMI > 24.9 kg/ m^2) in this community-dwelling older women was high (74.3%). The frequency of sarcopenia was significantly lower (3.7%) using Baumgartner than Newman's (19.9%) criteria (P<0.0001). Of note, less than 5% (1/23) of those classified as sarcopenic by Baumgartner's criteria had overweight/obesity, whereas 60% (74/122) of sarcopenic women by Newman's definition had this complication. Risk factors, after adjustments for age, were identified to be distinct in these two groups of individuals. Using Baumgartner's definition, the only risk factor observed in logistic regression models was T-score on femoral neck (OR=0.45; IC95% 0.27–0.76; *P*=0.003). In contrast, we have identified that creatinine (OR=0.24; IC95% 0.08–0.71; *P*=0.01) and ethnicity (non-Caucasian race: OR=0.48; IC95% 0.30–0.77; *P*=0.003) had a significant association with sarcopenia in the group defined by Newman's criteria.

Conclusion: In women with overweight/obesity, Newman′s definition seems to be more appropriate for sarcopenia diagnosis. This finding has relevant public health implications taking into consideration the distinct risk

factors identified herein and the high prevalence of overweight/obesity in older women.

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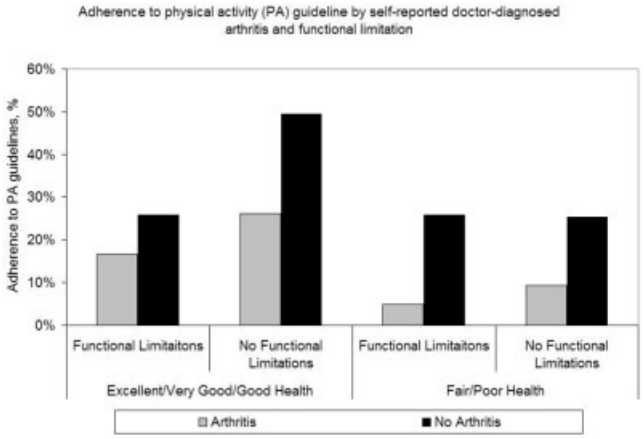
Adherence to Physical Activity Guidelines and Its Relationship with Self-Rated Health Among Persons with Doctor-Diagnosed Arthritis. William M. Reichmann[1], Jeffrey N. Katz[2], Sara A. Burbine[3], Meghan E. Daigle[3], Benjamin N. Rome[3], Alexander M. Weinstein[3] and Elena Losina[3]. [1]Brigham and Womens Hospital, Boston, MA, [2]Brigham & Womens Hospital, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA

Background/Purpose: Adherence to physical activity (PA) guidelines set forth by the US Department of Health and Human Services has been linked to higher quality of life for persons with and without arthritis. The goal of this study is to describe the degree of adherence to PA guidelines in the US among persons with and without arthritis.

Methods: We used data from two cycles (2003–2004 and 2005–2006) of the National Health and Nutrition Examination Survey (NHANES). PA was assessed using an accelerometer, which counted the amount of PA the subject engaged in every minute for seven consecutive days. We defined adherence to PA guidelines as having at least 150 minutes of moderate/vigorous activity during the week. We also considered data on self-rated health (SRH), doctor-diagnosed arthritis, age, sex, race/ethnicity, body mass index (BMI), comorbidities, and functional limitation. SRH was defined as fair/poor (FP) versus excellent/very good/good (EVGG). Obesity was defined by BMI = 30. We used logistic regression models to estimate the level of adherence to PA guidelines for those with and without arthritis by SRH and functional limitation, adjusting for age, sex, race/ethnicity, obesity and comorbidities. All analyses accounted for the sampling design and used sampling weights to obtain estimates representative of the US population.

Results: 5,938 participants aged 25+ were included in the analysis. No groups had >50% adherence to PA guidelines. Among those with arthritis, the adherence to PA guidelines ranged from 4% among those with functional limitations and FP health to 27% among those without functional limitations and in EVGG health (Figure). Older age and female sex were associated with lower adherence to PA guidelines for all combinations of SRH, arthritis diagnosis and functional limitations.



Conclusion: Despite growing evidence that PA promotes good health among those with arthritis, adherence to PA guidelines is poor, especially among persons with arthritis who are in worse health, older, female, and obese. Further efforts to promote adherence to PA are urgently needed.

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Do Climatological Changes Affect Arthritic Pain Severity in Patients with Rheumatic Diseases? K. Deftereou[1], B. Haidich[2], A. Benos[2], M. Trachana[3] and A. Garyfallos[1]. [1]4th Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece, [2]Department of Hygiene, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece, [3]1st Department of Paediatrics, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background/Purpose: Literature reports and clinical practice evidence support that patients with rheumatic diseases demonstrate exacerbation of arthritic pain in relation with changes in weather conditions. The aim of the study was to assess the effect of day by day weather condition changes on the frequency and severity of incidents of increased arthritic pain in patients with Rheumatoid Arthritis (RA), Osteoarthritis (OA) and Juvenile Rheumatoid Arthritis (JRA).

Methods: All participants (118 in total, 40 with RA, 26 with OA, 25 with JRA and 27 healthy volunteers) were asked to record all incidents of increased arthritic pain and mark their severity according to the Visual Analogue Scale (VAS) within an 11 weeks period of time. ESR and CPR were measured to exclude possible disease flare. Weather data [mean temperature (T), relative humidity (RH) and atmospheric pressure (AP)] on the day of the incidence and five days before and after were retrieved from the official archives of the National Institute of Meteorology of Greece.

Results: At least one incident of increased arthritic pain was reported by 58% of the RA patients, 100% of the OA and 44% of the JRA patients (280 incidents in total). No increase in ESR or CRP was found. No incidents were reported in the control group. VAS scores were higher in RA and OA groups than in the JRA group ($P<0.001$ and $P=0.003$ respectively) whereas there was no difference between the RA and OA groups ($P=0.776$). Incidents were also more frequent in the OA group than in the JRA group ($P<0.001$), whereas there was no difference between the RA and JRA groups ($P=0.328$). Women with RA demonstrated higher frequency of incidents ($P=0.011$) and higher VAS score ($P=0.002$) than men. Women with JRA demonstrated higher frequency of incidents ($P<0.001$) but no difference in VAS score ($P=0.455$) whereas within the OA group there was no difference in frequency ($P=0.05$) or VAS score ($P=0.250$) between women and men. In the RA group it was found that higher VAS scores were associated with changes in RH ($\beta=-0.265$ $P=0.014$) and T ($\beta=-1.778$ $P=0.026$) 24h before the incident and with changes in AP 48h before ($\beta=-0.280$ $P=0.045$) and 24h after ($\beta=0.485$ $P=0.041$) the incident. In the JRA group, pain severity was found to correlate with RH ($r=0.397$ $P=0.022$) and AP ($r=0.361$ $P=0.039$). Higher AP was associated with higher VAS scores ($\beta=0.075$ $P=0.017$). In the OA group pain severity was found to correlate with RH ($r=0.218$ $P=0.01$), T ($r=-0.190$ $P=0.024$) and RH change 24h ($r=0.208$ $P=0.014$) and 48h ($r=0.189$ $P=0.03$) before the incident. Higher RH ($\beta=0.213$ $P=0.004$) and lower T ($\beta=-0.409$ $P=0.012$) the day of incidence and RH raise 24h before ($\beta=0.173$ $P=0.011$) were associated with higher VAS scores.

Conclusion: Weather conditions and their changes are associated with severity and frequency of arthritic pain in patients with rheumatic diseases in a way that is not related to disease activity. This association does not seem to be uniform across different disease groups and sexes, a fact that reflects the perplexity of the condition and possible different mechanisms.

902

Economic Burden of Fibromyalgia: A Systematic Review and Meta-Analysis. John B. Wong, Marcia P. Griffith and Chenchen Wang. Tufts Medical Center, Boston, MA

Background/Purpose: Despite the 2% prevalence of fibromyalgia and its associated morbidity, the economic costs of fibromyalgia remains understudied, and to date, no systematic quantification of its financial consequences exists, so our aim was to determine the economic costs associated with fibromyalgia.

Methods: A systematic review of Medline from inception to 2011 for economic studies regarding fibromyalgia resulted in 483 titles when using recommended search terms for identifying health economic studies. Of these 483 titles, 19 studies contributed to the base case analysis. We calculated annual direct medical care costs. Using the United States (US) Consumer Price Index (CPI) for medical care services, we inflated annual cost data to 2010 US dollars, and we used World Health Organization (WHO) purchasing power parity data from 2005 to convert foreign currencies to US dollars. Data were pooled using the DerSimonian and Laird random effects model with weighting by the inverse variance.

Results: Based on 19 studies from 1996–2010, annual direct medical care costs were $3700 (95% CI $3682–3718). Sensitivity analysis considering 4 additional studies without reported standard deviations did not alter the results. Among 4 studies estimating the ratio of indirect to direct medical care costs, 3 of them yielded ratios of 1.7 to 2.2 and a fourth outlier estimated a ratio of 0.4. Based on 5 studies, patients with fibromyalgia had annual costs that were 1.7 to 2.9 times population controls. Not surprisingly, pain medication costs were higher in patients diagnosed with fibromyalgia versus controls. One study found that the co-existence of fibromyalgia and depression raised annual cost by 2.3 fold versus fibromyalgia alone and 1.5 fold

versus depression alone. Another study showed that annual fibromyalgia costs were about 0.75 times that for patients with osteoarthritis. Data were conflicting with regard to the effect of the diagnosis of fibromyalgia on costs with 3 studies suggesting annual savings post- versus pre-diagnosis of $146-$1711 and 2 studies suggesting increased annual costs of $2577-$6276 following fibromyalgia diagnosis. One study identified a non-statistically significant increase in annual costs for 2 higher Fibromyalgia Impact Questionnaire (FIQ) categories versus the lowest one.

Conclusion: Fibromyalgia is associated with substantial annual direct medical costs and indirect costs, exceeding that for population controls and approximating those for patients with osteoarthritis. Effective interventions may reduce fibromyalgia costs, and cost-effectiveness analyses of these interventions are needed.

903

Bone Mineral Density Across Age and Gender in Navajo People Compared to the National Health and Nutrition Examination Surveys III: the Education and Research Toward Health Study. Karla L. Miller, Tracy M. Frech, Tom Greene, Khe-ni Ma, Molly McFadden, Lillian Tom-Orme, Laurie J. Moyer-Mileur, Martha Slattery and Maureen Murtaugh. University of Utah School of Medicine, SLC, UT

Background/Purpose: To compare bone mineral density (BMD) as defined by bone mineral content (BMC) and measured bone area (BA) by age and gender in an adult Navajo population to those reported in other ethnicities by the National Health and Nutrition Examination Surveys (NHANES) III.

Methods: Study participants (N=1100) were randomly selected from the Education and Research Toward Health (EARTH) study to fill age and gender groups between November 2007 and January 2010. Dual energy x-ray absorptiometry (DXA) measurements of bone mineral density (BMD) were obtained at the left femoral neck, total hip, and lumbar spine (L1–4) by a certified DXA technician using standard protocol on a Hologic Discovery W machine. SAS version 9.2 (SAS Institute, Carey, NC) was utilized for data analysis. NHANES III data were analyzed using weights for design effects of clustering (SDPPSU6), stratification (SDPSTR6), and exam (WTPFEX6) for the unequal probability of sampling and non-response. Age and gender specific (6853 men and 7207 women) means from NHANES III data were created using proc survey means which adjusts for the unequal probability of sampling and non-response. Comparison of the age and gender specific means for large independent samples with normal approximation was used to assess difference.

Results: In general, BMD and BMC in Navajo men were similar to that of Non-Hispanic white (NH-white) and Mexican American men. BMD and BMC were lower among Navajo men compared to Non-Hispanic black (NH-black) men in all age groups. BA in Navajo men was lower than in NH-white and NH-black men, but similar to that of Mexican American men. BMD and BMC in Navajo women over 30 were higher than in NH-white women of similar age. BMD and BMC in Navajo women were lower than in NH-black women, and similar to Mexican American women in all age groups. BA in Navajo women over the age of 30 was lower than in NH-white women, and similar to NH-black women. BA in Navajo women was similar to Mexican American women between the ages of 40 and 70, but higher among those at the extremes of age. These differences were statistically significant.

Conclusion: In Navajo men compared to NH-black men, differences in BMD may be accounted for by lower BMC. Differences in BMD in Navajo women compared to NH-white women may be accounted for by higher BMC in the former, and higher BA in the latter. In general, BMD was similar in Navajo men and women compared to Mexican American men and women. Few data exist that address BMD among Native American populations, especially in men. Future studies are needed to determine the clinical implications posed by differences in BMC and BA among ethnicities, and the significance of our findings with respect to fragility fracture risk.

904

Prevalence of Anti-Osteoporotic Medication Use in a Cohort of Older Women with Both Rheumatoid Arthritis and Postmenopausal Osteoporosis. Gregory Cherkowski, Cynthia O'Malley and Primal P. Kaur. Amgen, Inc., Thousand Oaks, CA

Background/Purpose: With the known increased risk of fracture among women with RA (Gabrile, *Arthritis Rheum* 2009), the treatment of postmenopausal osteoporosis (PMO) should be considered in the management of RA. We examined overlapping use of pharmacologic osteoporosis therapy in a population of older women with both RA and PMO, across a selection of pharmacologic RA therapies.

Methods: Using administrative claims data from the 2005–2009 MarketScan Database, we identified a cohort of women aged ≥55 with both RA and PMO. RA and PMO were identified through ICD-9 diagnosis codes. The cohort was restricted to those treated with an anti-tumor necrosis factor alpha (anti-TNF-α) (etanercept, infliximab, and adalimumab), or a disease-modifying antirheumatic drug (DMARD) (hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine). Medication exposure was identified through procedure J codes, HCPCS codes and outpatient prescription drug claims. Given that subjects are treated with overlapping combinations of therapy classes, we distributed subjects as follows: those who received DMARD and no anti-TNF-α were entered into the DMARD treatment group, and those who received anti-TNF-α, with or without DMARD, were assigned into the anti-TNF-α treatment group. Stratified by RA treatment groups, frequencies describing subject demographics, co-morbidities and osteoporosis medication use during the study period were collected.

Results: We identified 3,719 women aged ≥55 with RA, PMO, and the specified RA treatment. Among the study cohort, 2,287 (61.5%) received DMARD but no anti-TNF-α and 1,432 (38.5%) women were treated with anti-TNF-α. Anti-TNF users were slightly younger than nonusers. Both treatment arms received similar administration of PMO medication: 1,773 (77.5%) of the DMARD only group and 1,080 (75.4%) of the anti-TNF-α users received at least one class of PMO medication. Oral bisphosphonate use was highest across both treatment groups compared to all other PMO treatments. IV bisphosphonate and teriparatide use was lower in the DMARD group.

Demographic, co-morbidity and medication use characteristics of women aged ≥55 with both postmenopausal osteoporosis (PMO) and rheumatoid arthritis (RA), stratified by RA treatment in the MarketScan Database

	DMARD† n=2,287		Anti-TNF-α‡ n=1,432		Total n=3,719	
	No.	%	No.	%	No.	%
Demographics						
Age**						
55–64	734	32.1	667	46.6	1,401	37.7
65+	1,553	67.9	765	53.4	2,318	62.3
Mean age** (std dev)	71.0 (9.2)	67.4 (9.7)	69.6 (9.7)			
Region*						
Northeast	213	9.3	125	8.7	338	9.1
North Central	772	33.8	431	30.1	1,203	32.3
South	874	38.2	618	43.2	1,492	40.1
West	422	18.4	255	17.8	677	18.2
Unknown	6	0.3	3	0.2	9	0.2
Metropolitan statistical area$^{\mu}$						
Yes	1,901	83.1	1,156	80.7	3,057	82.2
RA medication						
Anti-TNF-α**	0.0	0.0	1,432	100	1,432	38.5
DMARD**	2,287	100	1,041	72.7	3,328	89.5
PMO medication						
Any PMO medication	1,773	77.5	1,080	75.4	2,853	76.7
PMO medication by class**						
Oral bisphosphonate	1,509	66.0	911	63.6	2,420	65.1
IV bisphosphonate	135	5.9	104	7.3	239	6.4
Raloxifene	177	7.7	99	6.9	276	7.4
Teriparatide	193	8.4	154	10.7	347	9.3
Calcitonin	192	8.4	71	5.0	263	7.1

† Treated with hydroxychloroquine, leflunomide, methotrexate, or sulfasalazine with no TNF-α inhibitor use
‡ Treated with etanercept, infliximab, or adalimumab
μ Metropolitan statistical area measured by zip code
*p <0.05
**p <0.01

Conclusion: Data indicate that over 75% of older women with RA and PMO receiving RA pharmacotherapy are also receiving pharmacologic osteoporosis therapies. DMARD use was greater than anti-TNF-α use; anti-PMO medication use was similar among DMARD and anti-TNF-α user groups.

905

Prevalence of Low Bone Mass and Osteoporosis in Navajo People Older Than 50 Across Age, Gender, and Body Mass Index. Karla L. Miller, Tracy M. Frech, Tom Greene, Khe-ni Ma, Molly McFadden, Lillian Tom-Orme, Laurie J. Moyer-Mileur, Martha Slattery and Maureen Murtaugh. University of Utah School of Medicine, SLC, UT

Background/Purpose: To describe the prevalence of low bone mass (osteopenia) and osteoporosis in in Navajo men and women over the age

of 50 as defined by the World Health Organization (WHO) classification criteria for densitometric diagnosis.

Methods: Study participants were randomly selected from the Education and Research Toward Health (EARTH) study to fill age and gender groups between November 2007 and January 2010. Dual energy x-ray absorptiometry (DXA) measurements of bone mineral density (BMD) were obtained at the left femoral neck, total hip, and lumbar spine (L1–4) by a certified DXA technician using standard protocol on a Hologic Discovery W machine. WHO classification criteria were applied to BMD measurements for densitometric diagnosis of low bone mass (T-score between −1 and −2.5) and osteoporosis (T-score ≤ −2.5). Health history was assessed by the Health, Lifestyle, and Physical Activity questionnaire. Dietary intake was assessed by questionnaire adapted from the CARDIA diet history to include foods common to the diet of the select population. SAS version 9.1 (SAS Institute, Carey, NC) was utilized for data analysis. A Chi-square test p value of less than 0.05 was used to note statistically significant differences. Age and body mass index (BMI) were assessed categorically. Femoral neck BMD was adjusted for age, hormone use, and education in women, and for age and education in men.

Results: Prevalence of low bone mass by femoral neck T-scores in men over 50 was 42.5%, and osteoporosis was 1.5%. Prevalence of low bone mass by femoral neck T-scores in women over the age of 50 was 47.9% and osteoporosis was 6%. There were no significant differences in the prevalence of low bone mass and osteoporosis by femoral neck T-score when compared to the overall prevalence reported in NHANES III for women over the age of 50. Prevalence of low bone mass and osteoporosis in men and women over the age of 50 increased significantly using BMD measurements obtained at the lumbar spine (L1–4) with osteoporosis and low bone mass diagnosed in 14% and 41% of women, respectively, and 4.5% and 22% of men, respectively. Bone mineral density measurements increased significantly among both men and women across BMI groups.

Conclusion: Overall prevalence of low bone mass and osteoporosis by bone densitometry in this Navajo population was low, but increased among men and women over the age of 50. Prevalence of low bone mass and osteoporosis by T-score in women over the age of 50 is similar to that reported by NHANES III. This is the first report to our knowledge describing prevalence of low bone mass and osteoporosis in an American Indian male population. Previously reported increases in BMD across BMI have been reported in American Indian and other populations. This observation was substantiated by this study.

906

Health-Related Quality of Life Among Patients with Osteoporotic Fractures In Mexico. Patricia Clark[1], Fernando Carlos[2], Gabriela Chico[1], Oskar Ström[3], Ingrid Lekander[3] and Fredrik Borgström[3]. [1]Hospital Infantil de México Federico Gómez, Mexico City, Mexico, [2]RAC Salud Consultores, S.A. de C.V., Mexico, Mexico, [3]Innovus, Sweden

Background/Purpose: To evaluate the change in health-related quality of life (HRQoL) among patients with osteoporotic fractures in Mexico.

Methods: A cohort of 261 patients 50 years and over, both sexes, that had sustained a low energy fracture, was recruited as part of the ICUROS study in three different centers in Mexico City. Patients were interviewed about their health status at three different times: before fracture (recollected), within 14 days after fracture, and 4 months after the fracture. HRQoL was assessedby using the EQ-5D instrument (including VAS scale) and a time-trade-off (TTO) questionnaire with a maximum of ten years life horizon. The UK algorithm was used to transform each EQ-5D profile to an EQ-5D utility value, censored to zero. Differences in means were calculated with a one-way Kruskal-Wallis analysis of variances.

Results: Mean age was 71.43±1.61 years and 85.8% were women. Hip fractures (61.7%) were the most frequent type of fracture, followed by ankle (14.2%), wrist (9.2%), humeral (8.0%) and vertebral (3.4%).

Baseline mean (±SD) scores of EQ-5D utility, EQ-5D VAS and TTO were 0.64±0.31, 0.79±0.19 and 0.78±0.26 respectively.

After sustaining an osteoporotic fracture, HRQoL decreased dramatically. Mean differences between HRQoL immediately after fracture and the HRQoL prior the fracture were: −0.58 (95%CI: −0.54 to −0.62; p<0.001) for EQ-5D; −25.8 (95%CI: −0.22 to −0.30; p<0.001) for EQ-5D VAS and −0.13 (95%CI: −0.10 to −0.16; p<0.001) for TTO.

Four months after the patients had sustained an osteoporotic fracture, their HRQoL was better than it was immediately after the fracture had occurred, but significant lower in comparison with pre-fracture health state using EQ-5D utility index. Mean gain from immediately after the fracture were: 0.44 (95%CI: 0.38–0.49; p<0.001) for EQ-5D index; 0.22 (95%CI: 0.16–0.27; p<0.001) for EQ-5D VAS and 0.22 (95%CI: 0.13–0.30; p<0.001) for TTO.

32 patients were withdrawn of the study, almost half of them (n=14) died during the 4 months period after fracture, and all of them had a hip fracture.

Conclusion: HRQoL decreases in all osteoporosis-related fractures immediately after fracture but has increased significantly after a period of 4 months.

907

Disparities in the Prevention/Treatment of Glucocorticoid-Induced Osteoporosis. Florina M. Constantinescu[1], Primal Bhatia[2], Lenore M. Buckley[3], Paul Falzer[4] and Liana Fraenkel[5]. [1]Washington Hospital Ctr/Georgetown University, Washington, DC, [2]Washington Hospital Center, Washington, DC, [3]VCU School of Medicine, Richmond, VA, [4]VA Connecticut Healthcare System, New Haven, CT, [5]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT

Background/Purpose: Significant efforts have been made to improve the quality of care delivered to women on glucocorticoids to prevent/treat glucocorticoid (GC)-induced osteoporosis (GIOP). The objectives of this study were 1) to examine current trends in the quality of care of women on at least 90 days of consecutive GCs under the care of a rheumatologist, and 2) to determine if differences in care exist between specific sociodemographic groups.

Methods: Women identifying themselves as either African American (AA) or White, with at least 90-days exposure to prednisone, and able to read and write English, completed a survey after their appointments in outpatient rheumatology clinics. Women were classified into 3 groups: 1) AA women with annual household income levels less than $20,000, 2) AA women with annual household income levels of $20,000 or more, and 3) White women. We examined the relationship between group membership and: 1) the likelihood of having had a bone densitometry exam, 2) the likelihood of having had a physician recommend that they take treatment to prevent GIOP or fractures, and 3) the likelihood of currently taking both calcium and vitamin D. Multivariate logistic regression was used to adjust for age, fracture history and previous bone densitometry results. The same analyses were repeated for 3 groups classified based on race and education level: 1) AA women with no college education, 2) AA women with at least some college education, and 3) White.

Results: 186 women were interviewed: mean age (SD) = 49 (16); 60% were AA; 26% reported incomes less than $20,000; 32% did not have any college education; 28% of the subjects had not undergone bone densitometry. The relationship between sociodemographic group (based on race and income as well as race and education level) and care for GIOP is provided in the Table. In each case, White women are treated as the referent group.

Conclusion: Despite the presence of well-established risk factors for osteoporosis, the likelihood of reporting 1) having undergone a bone densitometry, 2) receiving a doctor recommendation to initiate treatment for prevention/treatment of GIOP, and 3) currently using daily calcium and vitamin D was significantly less among AA women with low income and less education than White women. In contrast, no significant differences were found between AA with higher incomes and education levels compared to White women. These results have important clinical implications and indicate that further efforts are warranted to improve GIOP-related care among AA disadvantaged women.

Table. Associations between Sociodemographic Group and Care to Prevent/Treat GIOP

	Odds Ratio (95% CI): Having Undergone Bone Densitometry		Odds Ratio (95% CI): Reporting a Physician Recommendation		Odds Ratio (95% CI): Current Use of Calcium and Vitamin D	
Group (%)	Unadjusted	Adjusted*	Unadjusted	Adjusted**	Unadjusted	Adjusted**
AA + income less than $20,000 (23)	0.23 (0.09,0.55)	**0.33 (0.13,0.82)**	0.14 (0.06,0.33)	**0.23 (0.08,0.60)**	0.26 (0.11,0.57)	**0.38 (0.16,0.93)**
AA + income at least $20,000 (35)	0.48 (0.21,1.10)	0.63 (0.26,1.50)	0.44 (0.21,0.88)	0.56 (0.24,1.28)	0.41 (0.2,0.82)	0.49 (0.23,1.06)
White (41)	Reference	Reference	Reference	Reference	Reference	Reference
AA + no college (26)	0.19 (0.08,0.45)	**0.25 (0.11,0.59)**	0.21 (0.10,0.47)	**0.33 (0.13,0.82)**	0.23 (0.11,0.49)	**0.34 (0.15,0.79)**
AA + at least some college (33)	0.63 (0.27,1.45)	0.96 (0.39,2.34)	0.43 (0.17,0.71)	0.48 (0.21,1.09)	0.45 (0.22,0.91)	0.57 (0.26,1.23)
White (41)	Reference	Reference	Reference	Reference	Reference	Reference

*Adjusted for age and fracture history.
** Adjusted for age, fracture history, and densitometry results (never had, normal, osteopenia/osteoporosis).
Adjusted significant associations are bolded.

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Obesity Increases the Risk of Adhesive Capsulitis. Yuqing Zhang[1], Christine Peloquin[1], Daniel K. White[1], Yanyan Zhu[1], Young Hee Rho[2] and Hyon K. Choi[1]. [1]Boston University School of Medicine, Boston, MA, [2]Vanderbilt Medical Center, Nashville, TN

Background/Purpose: Adhesive capsulitis (AC) is a painful and disabling shoulder disorder, with an incidence rate of 3 per 1000 person-years among individuals >=40 years. Previous studies have shown that AC occurs more frequently among individuals with diabetes and cardiovascular diseases; however, to date, no study has examined the relation of obesity, a strong risk factor for diabetes and cardiovascular diseases, to the risk of AC.

Methods: We conducted a case-control study to examine the association between obesity and the risk of AC using The Health Improvement Network (THIN), an electronic medical record database of 7.3 million patients from general practices across the United Kingdom from 1990 to 2010. An incident case of AC was defined as a first diagnosis of AC by a general practitioner in a subject aged >=40 years, following at least four years of enrollment in the database. For each AC case, we identified a control who did not have AC at the time of case diagnosis (i.e., index date), matched by sex, age, and year of enrollment in THIN. Body Mass Index (BMI, kg/m^2) prior to the index date was divided into 4 categories: < 25, 25-<30, 30-<35, and >=35. Potential confounders, including diabetes, cardiovascular disease, hypertension, and hypothyroidism, were all assessed prior to BMI assessment. We examined the association between BMI categories and risk of AC using the conditional logistic regression, adjusted for confounders. Finally, we evaluated the effect of obesity on the risk of AC across strata of age (<65 vs. >=65) and sex and assessed whether the effect of obesity on the risk of AC was modified by each of these factors.

Results: We identified 21,303 cases of AC (mean age: 63 years, 39% male). Higher BMI was associated with a higher risk of AC. Compared with those with BMI < 25, the odds ratios were 1.06, 1.27, and 1.31 for individuals with BMIs of 25-<30, 30-<35, and >=35, respectively (p for trend < 0.001). The association was consistent across age categories but was stronger in women than in men (Table).

		Adhesive Capsulitis			
Variable	BMI (kg/m^2)	Cases	Controls	OR (95% CI)	P for interaction
Men	<25	2117	2220	1.0	0.007
	25-<30	3615	3797	0.99 (0.91, 1.06)	
	>30	2568	2283	1.15 (1.06, 1.25)	
Women	<25	4133	4752	1.0	
	25-<30	4422	4568	1.11 (1.04, 1.18)	
	>30	4448	3683	1.36 (1.28, 1.45)	
<65 years	<25	3813	3418	1.0	0.98
	25-<30	4576	4344	1.05 (0.98, 1.11)	
	>30	3695	4322	1.25 (1.17, 1.34)	
>=65 years	<25	3159	2832	1.0	
	25-<30	3789	3693	1.09 (1.01, 1.16)	
	>30	2271	2694	1.32 (1.22, 1.43)	

Conclusion: This general population study provides the first epidemiologic evidence that obesity is associated with an increased risk of AC. Future studies to understand the biological mechanisms linking obesity to the risk of AC are warranted.

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Prevalence and Impact of Extreme Obesity (Class III) Among US Adults with Arthritis. Jennifer M. Hootman[1], Charles G. Helmick[2] and Casey Hannan[2]. [1]Centers for Disease Control and Prevention, Kennesaw, GA, [2]Centers for Disease Control and Prevention, Atlanta, GA

Background/Purpose: Obesity is highly prevalent among adults with arthritis. Extreme obesity (Class III) is specifically associated with poor quality-of-life, worse WOMAC pain scores, intra-operative difficulties and post-surgical complications after total joint replacement surgery. The purpose of this study was to assess the prevalence and personal impact of extreme obesity among adults with arthritis.

Methods: Data were from the 2009 Behavioral Risk Factor Surveillance System, an annual telephone health survey conducted in all 50 states and the District of Columbia (n = 424,592 adults). Arthritis was defined as a 'yes' response to "Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?". Body mass index (BMI = weight kg/ height m^2) was calculated from self-reported height and weight. BMI was categorized as underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), obese class I (30.0 – 34.9), obese class II (35.0–39.9), and extreme obese class III (>40.0). Seven impact measures included three arthritis-related and general health measures [arthritis-attributable activity limitation, severe pain (>7 on a 0–10 scale), and fair/poor self-rated health] and four unhealthy days measures (14+ days in the past 30) [frequent mental distress, frequent physical distress, frequent activity limitation days, and frequent sleep insufficiency]. Prevalence (percent), odds ratios (OR) and 95% confidence intervals (CI) were calculated using statistical weights to account for the complex sample design. BMI categorical distributions were compared between adults with and without arthritis using Wald Chi Square tests ($p < 0.05$). Among adults with arthritis, logistic regression was used to estimate the association between extreme obesity (referent = normal weight) and the 7 impact measures adjusting for age, sex, and race/ethnicity.

Results: The prevalence of obesity was significantly higher among adults with arthritis compared with adults without arthritis (Class I: 20.4% vs. 15.2%; Class II: 8.5% vs. 5.3%; Extreme Class III: 6.2% vs. 2.9%). Adults with arthritis were 2.2 (CI 2.2 – 2.3) times more likely to be extremely obese than adults without arthritis. Compared to normal weight adults with arthritis and adjusting for age, sex, and race/ethnicity, extremely obese adults with arthritis were significantly more likely to report activity limitation (OR 3.3, CI 3.1–3.4), severe pain (OR 3.0, CI 2.8–3.2), fair/poor self-rated health (OR 3.8, CI 3.6–4.0), frequent mental distress (OR 1.8, CI 1.7–2.0), frequent physical distress (OR 2.5, CI 2.4–2.7), frequent activity limitation days (OR 2.6, CI 2.4–2.7), and frequent sleep insufficiency (OR 1.7, CI 1.6–1.8). Results for analyses using Class I obesity as the referent group were similar, all associations were statistically significant but smaller in magnitude.

Conclusion: Extreme obesity is relatively common [6%, 3.4 million] among adults with arthritis and severely affects all seven personal impact measures. Aggressively screening, counseling, and treating obese patients with arthritis may improve these outcomes.

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A Patient Reported Frailty Index That Can Predict Mortality Outcomes Among Patients with Arthritis. Eswar Krishnan[1], James F. Fries[2] and Bharathi Lingala[3]. [1]Stanford University, Stanford, CA, [2]Stanford Univ Medical Center, Palo Alto, CA, [3]Stanford

Background/Purpose: Physical Frailty, conceptually defined as loss of functional reserves at organ and organism level, is increasingly recognized as a state that is distinct from functional disability and contributes to adverse patient outcomes. There have been few studies that have examined the predictive power of Frailty in patients with arthritis.

Methods: Utilizing the domain framework of physical Frailty from published literature, we constructed a simple five-item Patient reported (PRO)-Frailty Index using the following components- fatigue, poor balance, grip strength, anorexia and memory loss. Using Cox regressions, we analyzed the utility of this Index to predict all-cause mortality in a cohort of 3,185 (78% women, mean age 64 years) patients with rheumatoid arthritis and osteoarthritis followed for a mean 4.3 years. Receiver Operating Curve (ROC) analyses were performed to identify the optimal cutoff that can be used to dichotomize the Frailty Index.

Results: The PRO-Frailty Index (range 0–5) had a near-normal distribution in the population studied with a mean (SD) of 1.3(1.1) overall. The PRO-Frailty Index predicted mortality in age-sex adjusted analyses with a hazard ratio of 1.15 (1.01–1.31) for each unit increase in PRO-frailty index. In multivariable analyses where the effect of age, gender, disease duration and education level were accounted for, each unit increase in PRO-Frailty Index was associated with 17% increased mor-

tality risk (1.17; 1.02–1.34). ROC analyses suggested that dichotomizing the index at 0 and >0 offered the best model fit. The frailty-mortality association was observed in both the arthritis categories although the confidence interval was too wide for statistical significance individually.

Conclusion: PRO-Frailty Index can predict mortality among patients with arthritis.

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Unintended Consequences; Increased Prescription of Narcotic Analgesics for Osteoarthritis in the Elderly Is Associated with Increased Falls and Fractures in the Post-Vioxx Era. Lydia Rolita[1], Adele Spegman[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]Geisinger Health System, Danville, PA, [3]New York Univ Medical Center, New York, NY

Background/Purpose: Narcotic analgesics (NA) have long been used to treat pain although a number of alternatives have been developed, including selective COX-2 inhibitors. In 2004 Merck withdrew Rofecoxib from the market due to cardiovascular events and subsequent guidelines for treating chronic pain by the AHA and AGS recommend short-term narcotic analgesic use as the first step in managing chronic pain. Falls in the elderly are common and because NA contribute to falls in the elderly we determined whether prescriptions for NA for elderly patients were increased after COX-2 inhibitors were taken off the market and whether the incidence of falls/fractures changed in these patients.

Methods: Records of all patients >65yo with a diagnosis of OA (>10,000 patients) over the years 2001–2009 were identified in the Geisinger EMR data warehouse for analysis. Diagnoses of falls and fractures were identified by ICD 9 codes. Three analgesic prescription groups were identified: NA with or without other analgesics, COX-2 alone or with other analgesics, and NSAIDS, others and none. Other factors analyzed were age, gender, and Charlson Index Score of comorbidities (CI).

Results: From 2001–2004, patients receiving only NA prescriptions increased from 8% to 20% of the population and doubled again to 40% by 2009. COX-2 usage was low in this population (8%). The incidence of falls/fractures increased from less than 1% of all patients in 2001 to 4% in 2009 (Fig 2) and appears to be associated with the increased use of narcotic analgesics (Figure 1). Across all groups, patients with falls were older (78.1±6.6 v 73.8±6.3), yet in the NA group only, patients with falls had higher CI. The influence of age and comorbidities on falls were examined using conditional logistic regression; *no fall patients* were matched 3:1 to *fall patients* according to age and CI at time of fall. Falls risk increased with NA use in both study periods. In 2005–2009 when compared with: COX-2, NA use was associated with a 3.7 OR (2.6, 5.4; p <.001) and with NSAID a 4.4 OR for falls (3.9, 4.9; p <.001).

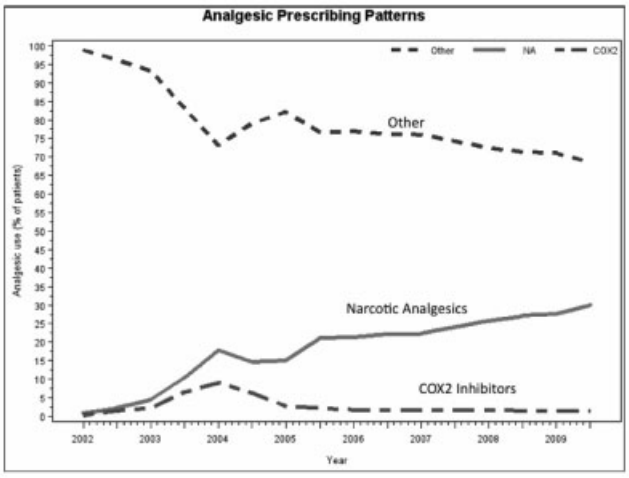

Figure 1.

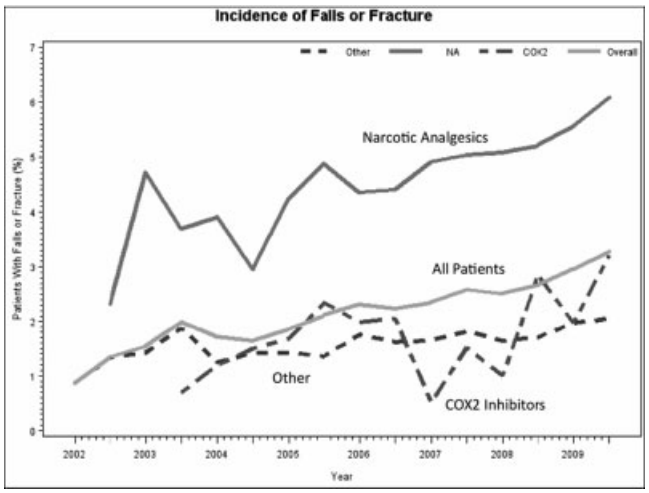

Figure 2.

Conclusion: After Vioxx was taken off the market there was a marked increase in the prescription of narcotic analgesics. Falls and fractures in this elderly population with OA increased markedly and all of the increase in falls were in patients prescribed narcotic analgesics. These findings strongly indicate that recommendations for the treatment of chronic pain be re-evaluated.

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The Impact of Biologics for the Treatment of Rheumatoid Arthritis: The Case of Total Hip and Knee Replacement Surgery. Neeta Tandon[1], Guy David[2], Arthur Kavanaugh[3] and Candace Gunnarsson[4]. [1]Janssen Services, LLC, Horsham, PA, [2]University of Pennsylvania Wharton School of Business, Philadelphia, PA, [3]University of California San Diego, San Diego, CA, [4]S2 Statistical Solutions, Inc, Cincinnati, OH

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, progressive systemic inflammatory disease that can be associated with severe long-term disability caused by joint destruction. Important sequelae of joint damage include joint replacement (e.g. total knee replacement [TKR] and total hip replacement [THR]). While effective, such surgeries are expensive and can pose risks for patients. A notable proportion of patients with uncontrolled RA may require TKR and/or THR. Since the late 1990's, the availability of highly effective biologic therapies has helped change the treatment paradigm in RA, and led to improved outcomes. One way of studying the impact of biologics is by examining RA patients' need for procedures due to RA-related damage, such as TKR and THR.

Methods: We performed a retrospective analysis of patient hospital discharges data between 1993 and 2008 in the United States from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP). We used a coding algorithm to identify all 1,742,935 patients having THR or TKR procedures, 58,036 of which had a diagnosis of RA. Difference-in-differences methodology was utilized to examine the potential effect of the introduction of biologic agents on the likelihood that RA is the primary reason for receiving THR or TKR by comparing RA patients after the time these drugs were introduced with RA patients before their introduction, and to patients' without a diagnosis of RA in order to capture general trends for THR and TKR. All models controlled for patient demographics and co-morbidities.

Results: The number of annual THR procedures more than doubled between 1993 and 2008 (25,987 to 56,478), and the number of annual TKR procedures more than tripled over this period (38,136 to 125,881). However, patients with RA (as a primary or secondary diagnosis), had a statistically significant (p<.01) 28% decrease in the likelihood of RA being the primary reason for receiving THR or TKR after the time that biologic agents (In particular the TNF inhibitors etanercept, infliximab and then adalimumab) were introduced.

Conclusion: Since the time of the introduction of biologics for the treatment of RA, there has been a reduction in THR and TKR surgeries among patients with a primary diagnosis of RA. This consistent and significant finding suggests that the availability of biologic agents, as well as other changes in the therapeutic approach to RA, may confer long term benefits to both RA patients and health care systems.

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Costs and Absences Associated with Rheumatoid Arthritis On Work Productivity: A Comparison Between Employees with and without Rheumatoid Arthritis In a United States Population. Nathan L. Kleinman[1], Richard A. Brook[2], Stephanie E. Kirbach[3] and Mary A. Cifaldi[3]. [1]HCMS Group, Cheyenne, WY, [2]The JeSTARx Group, Newfoundland, NJ, [3]Abbott Laboratories, Abbott Park, IL

Background/Purpose: Rheumatoid Arthritis (RA) was recently reported to have societal costs in the US of $19.3 billion and $39.2 billion (in 2005 dollars) without and with intangible costs, respectively. (Birnbaum 2010) However, most indirect components were subjectively imputed. This research was designed to use objective data to quantify the incremental work absence and indirect costs associated with RA in an employed population and compare these absences and costs to controls.

Methods: Employee records from multiple large employers in the US providing data about demographic, job-related information, and health care use in the HCMS database were assessed from 1/1/01 to 6/30/10. Patients with RA were identified by claims with primary, secondary, or tertiary ICD-9 codes of 714.xx, and the date of the first claim was considered the index date. Controls were employees without claims for RA, and their index date was defined as the average index date (by employer) among RA patients. All subjects were required tohave 12 months continuous health plan enrollment. Absences and indirect costs were measured for the 12 months following each employee's index date. All costs were adjusted to June 2010 US$. Regression modeling was used to separately compare days absent and indirect costs using two-part models controlling for demographics, job-related variables, location, and modified Charlson Comorbidity Index.

Results: Out of more than 800,000 employees in the HCMS database, 2705 (0.79% of employees) had RA and 338,035 were controls (Table 1).

Table 1. Descriptive Statistics for Employees with and without RA

Variable	Employees with RA (N=2,705) Mean (Standard Error) or %	Employees without RA (N=338,035) Mean (Standard Error) or %	P-Value
Age, at index date (N, controls=338,017)	45.13 (0.19)	40.37 (0.02)	<0.0001
Female	61.4%	40.9%	<0.0001
Married	42.5%	45.1%	0.0065
Not Married	31.1%	32.9%	0.0436
Missing Marital Status	26.4%	22.0%	<0.0001
White	44.1%	41.3%	0.0036
Black	8.6%	11.6%	<0.0001
Hispanic	10.8%	6.6%	<0.0001
Other Race	2.4%	3.6%	0.0007
Missing Race	34.1%	36.8%	0.0036
Annual Salary (N, RA=2686; N, controls=332,333)	$53,499 ($771)	$53,655 ($300)	0.9629
Tenure, at index date	9.60 (0.17)	8.92 (0.01)	<0.0001
Exempt	31.3%	33.0%	0.0614
Full Time	94.6%	89.7%	<0.0001
Modified Charlson Index	0.477 (0.021)	0.129 (0.001)	<0.0001

The incremental indirect costs (RA minus controls, Table 2) were: Sick Leave $145; Short-term Disability $249; Long-term Disability $41 (P=0.0505); Workers' Compensation $90; and Total $525. Incremental absence days (Table 2) were: Sick Leave 1.2; Short-term Disability 1.91; Long-term Disability 0.47 (P>0.05); Workers' Compensation −0.01 (P>0.05), and Total 3.58. All comparisons P<0.01 except where noted.

Table 2. Annual Indirect Costs and Absences for Employees with and without RA (†Adjusted Mean, ‡difference due to rounding)

Component	Employees with RA			Employees without RA			P-Value	
	N	Cost†	Days†	N	Cost†	Days†	Cost†	Days†
Sick Leave	1,106	$470	3.25	145,354	$325	2.05	**<0.0001**	**<0.0001**
Short-term Disability	1,562	$466	3.74	188,103	$218	1.83	**<0.0001**	**<0.0001**
Long-term Disability	2,153	$55	0.74	247,497	$14	0.26	0.0505	0.1136
Workers' Compensation	2,440	$271	0.18	312,226	$181	0.19	**0.0093**	0.8715
Total (sum above)		$1,262	7.92		‡$737	4.34		

Conclusion: Employees with RA incur 71% more indirect costs than those without RA and utilize 82% more lost time.

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A Simple Model That Suggests Possible Cost Savings When Modified-Release Prednisone 5mg/Day Is Added to Current Treatment In Patients with Active Rheumatoid Arthritis. Maarten Boers[1] and Frank Buttgereit[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Charité University Medicine, Berlin, Germany

Background/Purpose: The prognosis of rheumatoid arthritis (RA) has improved through the application of early treat-to-target strategies with innovative combinations of traditional antirheumatic drugs and rapid switch to biological agents. However, the high cost of biologic agents is straining health care budgets; consequently reimbursement is restricted.

Increasing evidence suggests glucocorticoids have a good benefit/harm ratio when used at low doses. Recently, a modified-release prednisone preparation has become available (MR-pred) that promises an even better benefit/harm ratio.

Methods: We used data from a 12-week placebo-controlled study to model the economical benefits of starting MR-pred in patients that have a reimbursable indication for biologic treatment. In the Netherlands, this indication is persistent disease activity (Disease Activity Score threshold, DAS28 > 3.2) despite treatment with at least two antirheumatic drugs. In Belgium and UK the threshold is DAS28 > 3.7 and > 5.1, respectively.

Results: The CAPRA-2 study randomized 350 RA patients with active disease (mean DAS28: 5.2; SD 0.8) despite disease-modifying antirheumatic therapy to MR-pred 5mg/day (n=231) or placebo (n=119). After 12 weeks DAS28 was reduced by mean 1.2 in the MR-pred group compared to 0.6 in the placebo group. Analysis according to last observation carried forward suggests that 28% of patients in the MR-pred group and 15% in the placebo group had a DAS28 ≤ 3.2 at the end of the study, a difference of 13% (95% CI: 4–21%; Mundipharma: CAPRA-2 study report; submitted for publication). Thus, starting MR-pred would have delayed initiation of biologics by at least 3 months in 28% of these patients: a net effect of 13% against the wait-and-see policy (or placebo), increasing to 28% when biologics are started immediately.

For Belgium and UK 97 resp. 55% of patients had an indication for reimbursement. The Table shows that the effect of MR-pred is similar at different thresholds (difference between treatment groups: 13% resp. 11%).

Without any further extrapolation beyond 3 months the conservative net estimate of 13% results in 3.25% (i.e., 13/4) less biologics prescriptions on a yearly basis. Assuming € 15,000 as mean drug cost of one year of biologics treatment and € 1.- as daily cost for MR-pred, net drug cost savings can be calculated to be € 396, i.e.: Costs savings in biologics: €487,50 (=3,25% * 15.000); minus Costs of 3 months MR-pred: € 91,25.

Table. Proportion of patients dropping below reimbursement thresholds of disease activity during the trial.

% of patients at or below threshold	*DAS28 threshold for reimbursement* *UK: 5.1* MR pred	Plac	*Belgium: 3.7* MR pred	Plac	*NL: 3.2* MR pred	Plac
Baseline	45	45	3	3	0	0
12 weeks	79	68	42	29	28	15
Improvement	*34*	*23*	*39*	*26*	*28*	*15*
Difference (MR pred–placebo)	**11**		**13**		**13**	

Conclusion: Despite a considerably higher cost price than conventional prednisone, MR-pred is a cost-effective option for patients not on glucocorticoids that are eligible for therapy with biologic agents.

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Costs of Tumor Necrosis Factor Blockers Per Treated Rheumatoid Arthritis Patient Using Real-World Drug Data in US Commercially-Insured Population. Vernon F. Schabert[1], Shravanthi R. Gandra[2], Crystal Watson[2], Jason Yeaw[1], Seth Goodman[1], Kathy M. Fox[3], Sandra Milev[4] and David J. Harrison[2]. [1]IMS Consulting Group, Alexandria, VA, [2]Amgen Inc, Thousand Oaks, CA, [3]Strategic Healthcare Solutions, LLC, Monkton, MD, [4]IMS Brogan, Ottawa, ON

Background/Purpose: Etanercept (ETN), adalimumab (ADA), and infliximab (INF) are FDA-approved tumor necrosis factor (TNF)-blocker treatments for moderate to severe rheumatoid arthritis (RA). However, they

differ in their mode of administration, dosing ranges and dosing frequency. These differences can lead to cost fluctuations that can be captured using real world data. This study describes the annual costs of ETN, ADA and INF per treated RA patient using real-world drug data in a US commercially-insured population.

Methods: IMS LifeLink™ Health Plan Claims database was used to identify adult patients (≥18y) with ≥1 claim for ETN, ADA or INF between January 1, 2005 and March 31, 2009 (first claim in study period is index claim); including patients new to TNF-blocker treatment (i.e., with no claims for a TNF blocker during the 180 days prior to index claim) and those continuing TNF-blocker treatment. Patients had to have 360 days continuous plan enrollment following index claim (follow-up) and 180 days prior to index claim (pre-index period).

In the pre-index period, patients had to have a RA diagnosis, but were excluded if they had a diagnosis of psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis or juvenile idiopathic arthritis. Patients were followed for 1-year or until end of study period (March 31, 2010).

Mean monthly dose was computed for patients on therapy; 2011 wholesale acquisition costs were applied to mean monthly dose and 2011 Medicare Physician Fee Schedule was applied to related drug administrations. Costs from restarting index TNF blocker therapy after discontinuation and costs from switching to a different TNF blocker were included and attributed to patients' index TNF-blocker therapy.

Results: Overall, 18,094 patients with RA (8,840 ETN, 4,578 ADA, 4,676 INF) were identified. Mean age was 50 years old, with 76% female. The 1-year mean TNF-blocker cost per treated patient for all RA patients was lowest for patients on ETN, $13,482, followed by ADA, $17,652 then INF, $19,824. For biologic-naïve patients, mean TNF-blocker cost per treated patient was $12,863 for ETN, $16,402 ADA, and $17,276 INF. For patients continuing biologic therapy, TNF-blocker cost per treated patient was $13,939 ETN, $18,920 ADA, and $21,217 INF.

Conclusion: When evaluating the TNF-blocker cost per treated RA patient across commonly used TNF-blockers with different modes of administration and dosing frequencies, patients on ETN had the lowest annual TNF-blocker cost for RA patients using real-world drug utilization data from US commercially-insured population.

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Direct Costs in Newly Diagnosed and Established Rheumatoid Arthritis Patients, and Comparison with Non-Rheumatoid Arthritis Controls in An Insurance Claims Database. Martin M. Crane[1], Stephanie Manson[2], Maneesh Juneja[3], Jeffery Allen[1], Regina H. Kurrasch[4], Myron E. Chu[5], Emilia Quattrocchi[2] and David J. Chang[5]. [1]GlaxoSmithKline, Research Triangle, NC, [2]London, United Kingdom, [3]GlaxoSmithKline, Stockley Park, United Kingdom, [4]Medicines Development, GlaxoSmithKline, King of Prussia, PA, [5]Medicines Development GlaxoSmithKline, King of Prussia, PA

Background/Purpose: Although DMARDs (disease modifying antirheumatic drugs) remain a mainstay of rheumatoid arthritis (RA) therapy, the cost structure of treating these patients has significantly changed, often with higher direct medical costs, since introduction of biologics. We sought to quantify these costs in different RA populations.

Methods: An incident (newly diagnosed in 2006) and a prevalent RA (end of 2005) cohort based on two Outpatient(OP)/Inpatient (IP) visits >30 days apart were identified by ICD9 codes from the Pharmetrics Choice administrative claims database and followed through 9/2008. An "aggressive" subset of incident patients was defined based on >8 OP/IP visits in the first 12 months. Annualized direct costs per patient were determined for medication, OP (includes laboratory and imaging), and IP (includes ER), based on actual amounts reimbursed to providers; co-pays were also available. Costs are presented as mean (SD), adjusted for inflation. A non-RA cohort, matched by age, gender and duration in the database was selected for comparison.

Results: There were 2,136 incident (265 in the aggressive subset) and 19,805 established patients (incidence 0.07%; prevalence 0.65%). Between years 1 and 2, total annualized costs per incident patient increased from $4,703 ($8,339) to $5,137 ($9,273). Medications, OP and IP costs comprised 66%, 24% and 10% respectively of the total in Year 1 and 78%, 14% and 8% in Year 2. For the aggressive subgroup, the total cost per patient in Year 1 was $8,804 ($9,268) and $10,803 ($12,557) inYear 2 due more rapid and extensive uptake of biologics (50% by end of Year 2 vs 22% in the non-aggressive group); co-pays in the aggressive patients averaged $1,200/year vs $600 in the non-aggressive patients. During the total study period (median follow-up 2.3 yrs), 71.5% of incident patients were not prescribed an anti-TNF and the total cost over follow-up was $1,573 ($3,389); of those who were prescribed an anti-TNF, 66.7% continued with the original prescription, 21.0% switched to a second, and 4.9% switched to a third with total costs of $13,224 ($9,066), $17,059 ($10,891), and $18,691 ($9,330), respectively. In established patients,total annualized costs increased with duration of documented RA up to four years after first known date of diagnosis: in 2006, costs increased from $5,508 ($9,299) in patients with duration up to one year to $8,653 ($14,423) for patients with duration up to four years. Prevalent RA patients compared to the non-RA group had higher rates of cardiovascular disease (20% vs 14%), anemia (29% vs 15%) and infections (91% vs 84%) and greater total medical costs from 2005-Sept/2008 ($15,276 ($18,683) vs $5,753 ($10,642)); costs in all categories (medications, OP, IP, ER, lab, imaging) were greater in the RA cohort, especially medication [$7,128 ($9,633) vs $1,499 ($3,299)].

Conclusion: Medications accounted for the highest proportion of direct costs in incident RA patients and costs for those prescribed biologics were an order of magnitude higher than those receiving conventional DMARDs. Total direct costs increased with duration of disease in established RA patients up to at least four years post-diagnosis. RA is an expensive disease due, in large part, to medication costs.

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Healthcare Utilization of Patients with Systemic Lupus Erythematosus In a U.S. Medicaid Population. Xue Song[1], Hong Kan[2], Barbara H. Johnson[3], Benno Bechtel[4], Donna O'Sullivan[3] and Charles T. Molta[5]. [1]Thomson Reuters, Cambridge, MA, [2]GlaxoSmithKline, Research Triangle Park, NC, [3]Thomson Reuters, Washington, DC, [4]GlaxoSmithKline, Munich, Germany, [5]GlaxoSmithKline, Philadelphia, PA

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that requires extensive medical treatment and healthcare utilization. This study examines healthcare utilization associated with SLE in a Medicaid population in the U.S.

Methods: Patients ≥18 years old who had ≥1 inpatient or ≥2 outpatient diagnostic codes for SLE (ICD-9-CM 710.0x) ≥30 days apart but within 2 years were extracted from the Thomson Reuters MarketScan® Medicaid Multi-State Database 2002–2009. Proportion of Medicaid enrollees with SLE diagnosis in 2005 was estimated. For the healthcare utilization analysis, index date was the date of the first SLE diagnosis. Patients without SLE were matched to patients with SLE separately in each Medicaid state using demographic (age, gender, race, Medicare dual eligibility, Medicaid basis of eligiblity, health plan type, index year) and clinical chracteristics (Charlson comorbidity index, comorbidities) as matching factors. All patients had at least 6-month continuous enrollment prior to (baseline) and 12-month continuous enrollment post (follow up period) the index date. Patients were followed from index date to inpatient death, end of continuous enrollment, or end of study period (12/31/2009), whichever came first. Annualized healthcare utilization was assessed during the follow up period. Logistic and generalized linear models (GLM) were used to adjust for any remaining inbalances on patient demographic and clinical characteristics between the matched SLE and non-SLE cohorts to estimate incremental healthcare utilization associated with SLE.

Results: In 2005, 251 per 100,000 Medicaid enrollees had SLE diagnosis, with the highest rates in women aged 35–64 and African Americans. For the healthcare utilization analysis, a total of 14,777 SLE patients met the study criteria, and 14,262 were matched to non-SLE patients, with a mean age of 45 years, 92.6% women and 36.1% African Americans. Compared with matched controls, SLE patients were more likely to have inpatient admissions (59.3% vs. 39.6%) and emergency room (ER) visits (78.5% vs. 67.5%), had more physician office visits (9.8 vs. 6.4), more hospital outpatient visits (3.3 vs. 2.2), and more outpatient other services (69.7 vs. 56.8) per year ($p<0.001$ in all cases). Logistic regressions estimated an odds ratio of 2.6 for having at least one inpatient admission and 2.0 for having at least one ER visit per year for SLE patients relative to their controls. After GLM model adjustment, SLE patients had 0.3 more inpatient admissions, 0.7 more ER visits, 3.5 more physician office visits, 1.2 more hospital outpatient visits, and 15.9 more outpatient other services per year than their matched controls ($p<0.001$ in all cases). Multivariate adjusted healthcare utiliza-

tion varied significantly across the different Medicaid states included in the database.

Conclusion: This study estimated that SLE patients had significantly higher healthcare resource utilization than their matched non-SLE controls. Further research is needed to understand the potential impact of SLE treatment on healthcare resource use in the Medicaid population.

918 WITHDRAWN

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Economic Burden of Psoriatic Arthritis and Diabetes in Patients with Psoriatic Arthritis in the United States. Annie Guerin[1], Genevieve Gauthier[1], Robert Day[2], Zeba Khan[2] and Frank Zhang[2]. [1]Analysis Group, Inc., Montreal, QC, [2]Celgene Corporation, Summit, NJ

Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy characterized by arthritis and psoriasis. Recently, PsA was reported has a disease with a high prevalence of diabetes. This retrospective study aimed to estimate the incremental costs of having both PsA and diabetes.

Methods: Adult patients with PsA (i.e., ≥2 claims with a diagnosis for PsA ICD-9 codes: 696.0) were selected from a US administrative claims database (2004–2008). PsA-free controls (i.e., no PsA or psoriasis (ICD-9 code 696.1) during the observation period) were matched to each PsA patient by age and gender in a 1:1 ratio. To capture patients at all stages of PsA, the index date was selected from all the dates of health services coded with a diagnosis of PsA in the database. Claims histories were followed for one year after the index date to assess healthcare resource utilization and to estimate associated costs (USD 2010) from a third-party payer perspective. Annual incidence rate (IR) differences and incremental total direct costs associated with both PsA and diabetes (ICD-9 codes 250.xx) versus each condition individually were estimated using multivariate Poisson regression models and generalized linear models, respectively.

Results: A total of 21,332 matched pairs were studied. Among PsA patients, 19% had diabetes compared to 13% of the PsA-free controls ($p<.01$). Among PsA patients, diabetic patients had on average 32 more urgent care visits (i.e., hospitalization and emergency room visits) per 100 patient-years than patients without diabetes (unadjusted IR: 78 vs. 40; $p<.01$). Among PsA-free patients, diabetic patients had on average 25 more urgent care visits per 100 patient-years than non-diabetic patients (unadjusted IR: 56 vs. 26; $p<.01$). Thus, patients with both PsA and diabetes had on average 7 more urgent care visits per 100 patient-years (unadjusted IR: 32 vs. 25; $p<.04$) when compared to patients with diabetes only. Among PsA patients, diabetes presented a $8,118 adjusted incremental cost when compared to the non-diabetic patients ($28,137 vs. $18,309; $p<.01$). Among PsA-free patients, diabetes presented a $6,441 adjusted incremental cost when compared to the non-diabetic patients ($13,350 vs. $5,280; $p<.01$). Thus, having both PsA and diabetes resulted in a higher $1,677 adjusted incremental cost ($8,118 vs. $6,441; $p<.03$) compared to diabetes only.

Conclusion: The incremental economic burden of patients having both PsA and diabetes is significantly higher than each condition individually. This could potentially be explained by the complexity of managing both conditions at the same time, however further investigations are warranted to confirm this assumption.

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Economic Burden of Psoriatic Arthritis and Obesity in Patients with Psoriatic Arthritis in the United States. Frank Zhang[1], Annie Guerin[2], Dominick Latremouille-Viau[2], Robert Day[1] and Zeba Khan[1]. [1]Celgene Corporation, Summit,, NJ, [2]Analysis Group, Inc., Montreal, QC

Background/Purpose: Psoriatic arthritis (PsA), a chronic inflammatory arthropathy characterized by arthritis and psoriasis, has been associated with a high prevalence of obesity. This retrospective study aimed to estimate the incremental costs of having both PsA and obesity versus each condition individually.

Methods: Adult patients with PsA (i.e., ≥2 claims with a diagnosis for PsA ICD-9 codes: 696.0) were identified in a large US administrative claims database (2004–2008). One PsA-free control (i.e., no claims with a diagnosis of PsA or psoriasis (ICD-9 code 696.1) from 2004 to 2008) was matched to each PsA patient on the basis of age and gender. Obesity was defined based on patients' reported body mass index (BMI≥30). To capture patients at all stages of PsA, the index date was selected from all the dates of health services coded with a diagnosis of PsA in the database Claims histories were followed for one year after the index date to assess their healthcare costs (USD 2010), measured from a third-party payer perspective. Annual incremental total direct costs associated with both psoriasis and obesity versus each condition individually were estimated using multivariate generalized linear models (GLM) with random effect to account for matched pairs.

Results: A total of 426 matched pairs with reported BMI were studied. Among PsA patients, 41% were obese compared to 29% of the PsA-free controls ($p<0.01$). Among obese patients, PsA presented a $15,891 adjusted

incremental cost when compared to the PsA-free patients ($22,772 vs. $6,660; p<0.01). In the group of non-obese patients, PsA presented a $12,883 adjusted incremental cost when compared to the non-diabetic patients ($17,784 vs. $4,403; p<0.01). Among PsA patients, obesity was associated with a $4,361 adjusted incremental cost when compared to the non-obese patients ($22,772 vs. $17,784; p<0.02). In the group of PsA-free patients, obesity was associated with a $1,353 adjusted incremental cost when compared to the non-obese patients ($6,660 vs. $4,403; p<0.01). The difference associated with having both PsA and obesity versus each condition individually ($15,891 vs. $12,883 and $4,361 vs. $1,353; p=0.17) was not statistically significant.

Conclusion: PsA patients have a higher prevalence of obesity when compared to PsA-free patients. Both PsA and obesity were associated with significant incremental healthcare costs. Consequently, there may be some benefits of closely managing patients with both PsA and obesity.

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Musculoskeletal Corticosteroid and Local Anesthetic Injections; A Survey of Practice Patterns Among Members of the American College of Rheumatology. Leah Alon[1], Nina Ramessar[1], Jenny Cabas-Vargas[2], Dimitre Stefanov[1] and Deana M. Lazaro[3]. [1]SUNY Downstate Medical Center, Brooklyn, NY, [2]SUNY Downstate, Brooklyn, NY, [3]Brooklyn VA, Brooklyn, NY

Background/Purpose: Corticosteroid and lidocaine injections into joints, bursae, tendon sheaths and trigger points are performed by rheumatologists and other practitioners. There is little evidence-based medicine for guidance on techniques, choice of injectable medications and on possible adverse effects. Most practice is based upon local standards of care. We undertook a descriptive study on the current practice patterns among members of the American College of Rheumatology (ACR). We hypothesized that corticosteroid and local anesthetic injection techniques will depend upon experience of the physician and type of practice.

Methods: We conducted an email survey of members of the ACR regarding corticosteroid and local anesthetic injection techniques. An email list was compiled from the 2010 ACR Directory. All members were included and all names in the first five pages of each alphabetical letter from the directory were chosen for the survey. Surveys were sent to 2616 members of the ACR with 275 responses (10.5% response rate). Respondents were asked about consent, frequency of injections, types and amounts of medication used, and complications experienced.

Results: Physicians who answered the survey included 64% males, 46% in private practice, and 41% in academic medicine. Forty-five percent indicated that they perform 2–15 injections per month, and 46% perform >15 injections monthly. The most common indications for the injections were rheumatoid arthritis, osteoarthritis, bursitis, tendonitis, gout, pseudogout and trigger finger. Most respondents use aseptic technique to prepare the area of injection. Written consent rate was 22% higher in academic/government practice group when compared to private practice (p<.001). Fifty-two percent perform a time out procedure and this was also more common in academic practice (p=.03). The most commonly used corticosteroid medications were methylprednisolone (47%), triamcinolone acetonide (26%) and triamcinolone hexacetonide (23%). Most respondents reported that they use an equivalent of 40mg prednisone to inject large joints, 20mg prednisone equivalent dose for intermediate structures, and 10mg for smaller structures. When injection technique was analyzed by years in practice (<5 years of practice, 5–20 years, >20 years) more experienced clinicians tend to use lower doses of corticosteroids for shoulder injections (p=0.003) and knee injections (p=0.02). Most respondents indicated that they wait 2–4 months before repeating an injection to the same anatomic structure, with a frequency of 3–4 injections per year for large joints and 1–2 injections per year for smaller structures. The most common adverse effects, reported in 1–10% of cases, were painful injection (45%) and elevated serum glucose (37%). In <1% of cases, fat atrophy (58% reported), skin discoloration (57%), bruising (43%), and infection (19%) were noted.

Conclusion: Corticosteroid injections were considered safe and well-tolerated by the physicians we surveyed. Although there are no official guidelines for corticosteroid injection, we found good agreement on the dose of steroid used and frequency of injections. There are some differences in practice based upon experience and practice type.

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Cost Per Placebo Adjusted Response of Golimumab, Adalimumab, and Etanercept in Patients with Active Ankylosing Spondylitis. Atul Deodhar[1], J. Braun[2], R. D. Inman[3], Désirée van der Heijde[4], Benjamin Hsu[5], Neeta Tandon[6] and Chenglong Han[7]. [1]Oregon Health & Science University, Portland, OR, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]The Arthritis Program, Toronto Western Hospital and Division of Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON, [4]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Centocor R&D, a division of J&J Pharmaceutical R& D, LLC/Univ. of Pennsylvania, Malvern/Philadelphia, PA, [6]Janssen Services, LLC, Horsham, PA, [7]Janssen Services, LLC, Malvern, PA

Background/Purpose: Golimumab (GLM) is a once monthly subcutaneous (SC) human anti-tumor necrosis factor treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). This study compares cost-per-placebo adjusted response of 3 SC anti-TNF biologic therapies: GLM, adalimumab (ADA), and etanercept (ETN) in pts with active AS.

Methods: Proportion of pts achieving at least 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria (ASAS20) were obtained from pivotal phase III clinical trials for GLM[1], ADA[2] and ETN[3]. The pt populations were similar at baseline in these clinical studies in terms of inclusion criteria, disease severity and treatment histories. Wk24 was the common time point for all three trials. In addition, efficacy at wk12 in studies of ADA and ETN, and at wk14 in the GLM study were used for the wk14 cost-efficacy analysis. Dosing was assumed to be per labeled indication in AS (GLM 50mg, monthly; ADA 40mg every other week and ETN 50mg weekly). US wholesale acquisition cost (WAC) as of May 2011 was used for calculating drug costs.

Results: At wk12–14, the placebo adjusted ASAS20 response rate (active treatment minus placebo) was 38%, 37% and 31% for GLM, ADA and ETN, respectively. The cost-per-placebo adjusted ASAS20 responder for 14-wks of therapy was $15,442, $16,958 and $19,295, for GLM, ADA and ETN, respectively. At wk24, the placebo adjusted ASAS20 response rate was 33%, 32% and 35%, and the cost-per-placebo adjusted ASAS20 responder for 24-wks therapy was $30,484, $33,613 and $29,296 for GLM, ADA and ETN, respectively.

Conclusion: The cost-per-placebo adjusted response analysis from 3 SC anti-TNF biologics for AS across three different trials demonstrated similar results. This must be interpreted given the limitations of cross-study comparisons and of potential inter-study differences. The cost-effectiveness in clinical practice will depend on the actual dose used, and actual effectiveness achieved; which may also depend on other factors such as compliance persistency, convenience, dose intervals and tolerability.

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The "Table-1 p Value" Issue; Baseline Group Comparison Is Inappropriately Omitted in Non-Randomized Studies. Koray Tascilar, Emine Atac, Fehim Esen and Hasan Yazici. Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

Background/Purpose: Guidelines on reporting randomized controlled trials advise against performing baseline comparison in randomized groups (1). Such comparison is considered futile as any difference will be by chance by definition (2). In non-randomized studies, on the contrary, the baseline characteristics of the study groups should be compared because the differences may have direct implications on the results. The aim of this study was to determine the frequency of inappropriate commission or omission of baseline comparisons in randomized and non-randomized studies, respectively.

Methods: A PubMed search was conducted to identify clinical studies among human, designed to test the effect of a treatment or an observation

in more than one group Annals of the Rheumatic Diseases, Arthritis and Rheumatism and Rheumatology (Oxford) from January 2010 to June 2011 were searched. Studies were grouped as either randomized or non-randomized. We evaluated each study as to how the baseline characteristics were presented. Also the frequencies of inappropriate commission or omission of statistical comparisons were tabulated.

Results: 205 studies were found, 107 were included. There were 60 randomized trials and 47 non-randomized studies. Among the randomized studies, 6/60 (10%) reported inappropriate baseline statistical comparisons. On the other hand among the non-randomized studies, 27/47 (57%) omitted baseline statistical comparison. In 10 of these 27 studies, there was no table presenting the characteristics of the groups subject to comparison. 17 studies on the other hand presented baseline groups in a table 1 but did no statistical comparisons although necessary.

Conclusion: The CONSORT statement seems to be better adhered to when reporting randomized controlled trials. On the other hand there is common and inappropriate omission of the necessary statistical comparisons at baseline in non-randomized studies. In this line there's an obvious need to improve adherence to the TREND statement (3).

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Seasonal Variation in Mortality of Six Rheumatic Diseases in Hong Kong, China: An Analysis of 2772 Deaths. Chi Hung To, Ka Lung Yu and Chi Chiu Mok. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: To examine the seasonal variation in the mortality of 6 groups of patients with different rheumatic diseases in Hong Kong and its relationship with weather parameters.

Methods: All patients with a diagnosis of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic vasculitis (SV), or systemic sclerosis (SSc) who died between 2000 and 2008 in public hospitals in Hong Kong were studied. The date of death was retrieved by using the Clinical Data Analysis and Reporting System (CDARS) in public hospitals. The monthly death rates in each calendar month from 2000 to 2008 were calculated for patients with each of these rheumatic diseases by using the total number of patients registered in the CDARS with the corresponding rheumatic disease in each calendar year, inclusive of those who attended our out-patient clinics and all hospital admissions. The monthly death rates of all and individual rheumatic disease were correlated by Pearson's correlation method with a number of weather parameters which included mean maximum temperature, relative humidity, rainfall, duration of sunshine and mean ultraviolet light intensity index in the corresponding month (data retrieved from the web page of the Royal Observatory of Hong Kong).

Results: Between 2000 and 2008, a total of 2772 deaths (493 SLE, 1620 RA, 186 AS, 50 PsA, 314 SV, 109 SSc) were recorded in our system. For all these deaths with different rheumatic diseases, the mean monthly mortality rates varied between 9.88 ± 4.3 and 15.61 ± 6.1 per 1000 patient-month from January to December. The monthly mortality rate was higher in winter and spring seasons (ranged from 13.28 ± 5.1 to 15.61 ± 6.1 per 1000 patient-month from November to April) compared to summer and autumn seasons (ranged from 9.88 ± 4.3 to 12.87 ± 2.8 per 1000 patient-month from May to October), and the difference was statistically significant when the death rate of October was compared to March and November ($p=0.035$ and $p=0.034$ respectively). There was a significant negative correlation between the monthly death rates of patients with all these rheumatic diseases and the mean monthly temperature ($r=-0.022$, $p=0.02$) but no significant correlation could be found with other weather parameters. In the analysis of individual rheumatic disease, only the mortality rate of RA had a significant correlation to weather parameters, but not the other rheumatic diseases (SLE, AS, PsA, SV, SSc). The monthly death rate of RA was negatively correlated to the mean monthly maximum temperature ($r=-0.25$, $p=0.01$), total monthly rainfall ($r=-0.21$, $p=0.33$), and mean ultraviolet light intensity index ($r=-0.19$, $p=0.04$) but not correlated to the mean monthly relative humidity ($r=-0.06$, $p=0.51$) and total duration of sunshine ($r=-0.108$, $p=0.26$).

Conclusion: Seasonal variation of mortality of the 6 rheumatic diseases exists. Deaths were more common in the seasons of winter and spring compared to summer and autumn. Particularly for patients with RA, an increase in infection and cardiovascular diseases might have been contributed to increased mortality in winter months but which remains to be confirmed in further studies.

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Milnacipran Improves Health Outcomes in Fibromyalgia Patients Who Have Had An Inadequate Response to Duloxetine Treatment As Measured by PROMIS Computer Adaptive Testing. Steven I. Blum, Stavros Tourkodimitris and Allan Spera. Forest Research Institute, Jersey City, NJ

Background/Purpose: This study sought to evaluate whether fibromyalgia (FM) patients who failed to achieve adequate treatment response to duloxetine (DLX) for FM would show improvement in health outcomes following a direct switch to milnacipran (MLN) treatment. Outcomes were measured using four different PROMIS® computer adaptive testing (CAT) instruments. PROMIS is a National Institutes of Health (NIH) funded initiative to develop new self-reported health measures using modern measurement tools like item response theory, item banking and CAT. PROMIS instruments can be used across a wide variety of chronic diseases/conditions and in the general population.

Methods: Patients with FM were eligible for this study if they were currently receiving a stable dosage of DLX (60 mg/d) for ≥4 weeks prior to screening. Following 2 additional weeks of open-label treatment with DLX 60 mg/d, patients that were not fully satisfied with DLX and had a 1-week recall VAS pain score ≥40 (range, 0–100 mm) were randomized 4:1 to receive double-blind MLN 100 mg/d (n=86) or placebo (PBO, n=21) treatment for 10 weeks. The purpose of the small PBO group was to minimize expectation bias rather than provide a comparator arm, since patients would be discontinuing a treatment that may have been partially efficacious. PROMIS CAT assessments, based on version 1.0 Item Banks (www.nihpromis.org) for Fatigue (F), Physical Function (PF), Satisfaction with Discretionary Social Activity (DSA), and Wake Disturbance (WD) were administered via Assessment Center™, an online system developed by PROMIS. The PROMIS CAT T-Score metric has a population norm of 50 and each 10 points in either direction represents 1 standard deviation (SD). Higher scores for F and WD and lower scores for PF and DSA indicate greater impairment. Mean change (using LOCF) from baseline in each domain T-Score was evaluated by a one-sample two-sided t-test comparing the difference to zero.

Results: For patients who were switched from DLX to MLN, baseline PROMIS CAT mean T-Scores were more than 1 SD from the population norm for F (mean=65.5; SD=5.8; range=[46.0,77.7]), PF (36.5 ± 4.7; [23.5,54.3]) and WD (63.6 ± 7.1; [37.2,76.0]), and within 1 SD for DSA (41.3 ± 7.6; [26.8,68.9]), despite at least 6 weeks of DLX treatment. Following a direct switch from DLX to MLN, patients demonstrated improvements at week 10 in each PROMIS CAT domain. MLN patients had significant reductions in F (-3.2 ± 9.8, $p=0.0067$) and WD (-2.8 ± 9.2, $p=0.0106$) and nonsignificant gains in PF (1.2 ± 6.2) and DSA (1.0 ± 10.8). Patients who discontinued active treatment with DLX and switched to PBO, had nonsignificant reductions in F (-0.4 ± 9.0), PF (-0.1 ± 4.7) and DSA (-1.5 ± 6.8), and increases in WD (0.5 ± 6.3).

Conclusion: Among patients who received an inadequate response to DLX treatment for FM, switching to MLN may improve health outcomes as measured by PROMIS CAT. Patients switched to MLN experienced improvements in each PROMIS domain (fatigue, physical function, social satisfaction, and sleep-related impairment) measured. To our knowledge, this is one of the first clinical trials to have used PROMIS CAT in assessing drug efficacy. Additional research is needed to further validate the use of PROMIS CAT and assess the clinical relevance of these results.

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The Frequency of Fibromyalgia Syndrome and the Quality of Life in Patients with Periton Dialysis. Muyesser Okumus, Hulya Parpucu, Seher Kocaoglu, Esma Ceceli, Pinar Borman and Murat Duranay. Ministry of Health Ankara Education and Training Hospital, Ankara, Turkey

Background/Purpose: Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain, fatigue, and sleep disturbances. As musculoskeletal pain is regarded as the most prevalent form of chronic pain in chronic kidney diseases, a differential diagnosis of FMS should be considered in that group of patients. The aim of this study was to determine the frequency of FMS in patients on periton dialysis (PD) and to investigate its impact on the quality of life of that population.

Methods: A hundred and twenty four patients with end stage renal disease who had undergone PD 4 or 5 times daily, and a control group of 54 age and sex-matched healthy volunteers were included to the study. Demographic characteristics of the subjects including age, sex, disease and dialysis durations were recorded. The associated symptoms including fatigue, morning stiffness, headache, irritable bowel syndrome, sleep disturbance, depression, anxiety, raynaud phenomen, restless leg syndrome, and paraesthesia of subjects were evaluated. Fibromyalgia Impact Questionnaire (FIQ) was used to measure the components of health status of the PD patients and controls. The quality of life of all subjects was assessed by Nottingham Health Profile (NHP).

Results: The mean age of the patients (68 female, 56 male) and control subjects (36 female 18 male) were 43.5±13.4 and 41.2±9.2 years respectively. The mean duration of PD was 34.3±29.8 months. The prevalence of FMS in the PD patients and controls were determined as 9.7% (12 patients) and 11.1% (6 controls) respectively and were found to be similar ($p=0.983$). The frequency of restless leg syndrome, anxiety and paraesthesia were found to be more common in PD patients with FMS, than in the control group with FMS. The mean FIQ and social subgroup of NHP scores in the PD group with FMS were significantly higher than, in the control group with FMS ($p<0.000$ and $p=0.043$ respectively). Except the social subgroup of NHP, the scores of all the subgroups and the mean FIQ levels were significantly higher than in PD patients with FMS than those without FMS. FMS related clinical features such as fatigue, morning stiffness, headache and restless leg syndrome were found to be significantly more common in the PD patients with FMS than in those without FMS.

Conclusion: In conclusion although the prevalence of FMS appears to be similar in PD patients and control subjects, the frequencies of associated symptoms are higher in PD patients. The functional disability is common and quality of life is worse in PD patients with FM than in patients without FMS. Fibromyalgia symptoms are suggested to be evaluated in patients receiving dialysis, in order to increase the quality of life of the patients suffering from this chronic condition.

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Correlates of Word Finding Deficits in Fibromyalgia. Robert S. Katz and Frank Leavitt. Rush University Medical Center, Chicago, IL

Background/Purpose: Fibromyalgia (FMS) is associated with deficits in three different language retrieval skills; word finding ability, word naming speed, and letter-cued word generation proficiency. The purpose of this study is to determine if difficulty retrieving the appropriate words to convey the intended message in a natural manner is related to language retrieval skills involving word naming speed and letter-cued word generation.

Methods: A word naming speed measure (Stroop Color and Word Test) and a letter-cued word generation measure (Controlled Oral Word Association Test) were administered to 120 patients with fibromyalgia, 80 with word finding problems and 40 without. The FMS patients were female, met ACR criteria for FMS and had memory problems for a duration of at least six months.

Results: The fibromyalgia samples with and without word finding difficulty did not differ in age (46.3±11.6 versus 47.7±11.5), education (14.6 ±2.2 versus 14.8±2.4), vocabulary subscale score (11.1±2.5 versus 10.9±2.4) or Beck Depression score (16.2±8.1 versus 16.0 ± 7.4). Naming speed was significantly slower in the FMS group reporting word finding difficulty. The word finding sample read 86.5 words in 45 seconds or 520 milliseconds per word. The FMS sample without word finding difficulty read 97.2 words in 45 seconds or 463 milliseconds. The word finding sample was 57 milliseconds slower. Letter cued word generation did not differ for the two groups (word finding: 35.9±11.3 versus 38.0±11.1 for letters F, A and S over 180 seconds).

Conclusion: The findings support a role for naming speed deficiency in discourse fluency, but not for letter fluency. People with word finding difficulty name words at a slower speed than those without word finding difficulty. Slow naming speed likely reflects time delays in accessing the mental lexicon. Lags in speed in the magnitude of 57 milliseconds may disrupt the normal flow of information along connecting routes of the language retrieval network.

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Carpal Tunnel Syndrome in Fibromyalgia: Evidence of a Subclinical Neuropathy? Robert S. Katz[1] and Bhagwan Shahani[2]. [1]Rush University Medical Center, Chicago, IL, [2]University of Chicago Hospital, Chicago

Background/Purpose: Fibromyalgia may be associated with central pain processing abnormalities, including central sensitization. However, peripheral mechanisms in muscles and nerves have not been excluded as possible sources of pain in fibromyalgia. We describe 22 patients who on EMG testing were found to have unilateral or bilateral carpal tunnel syndrome.

Methods: Sixty-seven patients with fibromyalgia who complained of paresthesias, as well as widespread pain, were assessed by EMG testing for peripheral neuropathy, entrapment neuropathy, and radiculopathy. Detailed electrphysiological studies including motor and sensory nerve conduction as well as late response studies were performed using a TECA EMG machine.

Results: 67 fibromyalgia syndrome patients had an EMG because of pain and paresthesias. 22 patients with fibromyalgia were found to have carpal tunnel syndrome. 13 had bilateral carpal tunnel and 9 had unilateral carpal tunnel syndrome based on electrophysiological studies.

Conclusion: Almost one third of the fibromyalgia patients tested were found to have carpal tunnel syndrome. Frequently, carpal tunnel syndrome was bilateral in these patients. Carpal tunnel syndrome in patients with fibromyalgia could represent a subclinical peripheral neuropathy, thereby possibly implicating peripheral nerves in addition to central pain processing as causes for the pain and paresthesias in patients with the fibromyalgia syndrome.

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Designing a Fibromyalgia Screening Questionnaire for Primary Care Settings. Robert S. Katz[1], Alexandra Small[2], Lauren Kwan[3], Patricia Kuenzi[1] and Jessica L. Polyak[3]. [1]Rush University Medical Center, Chicago, IL, [2]University of Illinois Medical School, [3]Rheumatology Associates, Chicago, IL

Background/Purpose: The diagnosis of fibromyalgia can be complicated for non-rheumatologists.The purpose of this study is to develop a screening tool that can be employed in the primary care setting.

Methods: 125 patients with various rheumatic diseases answered a rheumatology office questionnaire that included questions about pain location, pain words, and a human-figure diagram. Pain words, based on the McGill Pain Questionnaire, were divided into those that were thought to be more likely associated with FMS, and included stabbing, exhausting, unbearable, squeezing, gnawing, numb, shooting, pricking, burning, penetrating, miserable, and radiating. Words associated with arthritis, but not with FMS, were thought to be aching and dull. Words that might be associated with either condition were sharp, nagging, throbbing, tender, tiring, cramping, and deep. An assumption was made that patients circling wide areas on a pain diagram or checking both many peripheral joints and spine locations on a list of pain regions were more likely to have FMS. An attempt was made to determine whether pain words alone, pain location alone, the pain diagram, or a combination of these, was most helpful in the diagnosis of FMS.

Results: A rheumatology health care professional was able to diagnosis FMS correctly in 118 of 125 (94%) patients using pain words, pain location, and the human diagram together. 52 of 61 (85%) fibromyalgia patients could be identified correctly using only fibromyalgia pain words. The diagnosis of FMS was made in 47 of 61 (77%) patients evaluating the human-figure diagram alone...A non-rheumatology health care professionals was able to correctly identify 52 of 61 (85%) of FMS patients when using all three components of this screening tool. Using only using pain words, they were able to diagnosis 45 of 61 (74%) FMS patients correctly.

The most effective method for the diagnosis of FMS was combining these three assessments: pain location from a checklist, pain word descriptors, and a human diagram.

Conclusion: A screening questionnaire can be devised using specific pain words, pain locations and a human figure diagram that could be used in population studies and screening in primary care offices and also in schools, health fairs, pharmacies and other locations to identify patients who need further evaluation for possible FMS.

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The Effectiveness of Long-Term and Short-Term Interdisciplinary Treatment Approaches in Female Patients with Fibromyalgia. Ilknur Saral[1], Dilsad Sindel[1], Ozlem S. Berk[2] and Sina Esmaeilzadeh[1]. [1]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Istanbul University, Faculty of Letters, Istanbul, Turkey

Background/Purpose: The aim of this study is to determine the effectiveness of long-term and short-term interdisciplinary treatment approaches on reducing the symptoms, improving the quality of life and physical functioning in patients with Fibromyalgia (FM) in comparison to control

group, as well as to evaluate the advantage of each interdisciplinary treatment over another.

Methods: We conducted a prospective, randomized and controlled trial involving 66 female patients with FM and randomized to long-term interdisciplinary treatment group (UDG, n=22) which consisted of ten sessions of cognitive-behavioral treatment (CBT) and all-day of exercise and educational programs, short-term interdisciplinary treatment group (KDG, n=19) which consisted of educational, exercise and CBT programs in two days and control group (KG, n=19). Patients were evaluated by the Visual Analogue Scale (pain, fatigue and sleep), Fibromyalgia Impact Questionnaire, Beck Depression Inventory, Short Form-36 Questionnaire, total tender point score and a pressure algometer at baseline, 3 and 6-month follow up after the treatment. Statistical tests were conducted at the 0.05 significance level for all outcome measures.

Results: The mean age of the patients was 41.66±10.25 years. We found that the long-term and short-term treatments were effective on reducing the severity of pain and the number of tender points, increasing the level of pain threshold ($p<0.001$) and improving the physical functioning ($p<0.05$). There was no evidence that the approaches have efficacy on decreasing the level of depression, reducing the fatigue and improving the quality of sleep and quality of life ($p>0.05$). When the efficacy of the long-term and short-term interdisciplinary treatments was compared to each other, there was no significant difference between two groups.

Conclusion: The long-term and short-term interdisciplinary treatments were determined to be effective on reducing the severity of symptoms and activity of disease in patients with FM. Further research should include studies with more participants, longer follow up durations and interventions that intend to decrease the level of depression and improve the quality of sleep.

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Continuing Efficacy of Milnacipran Demonstrated After Long-Term Treatment of Fibromyalgia. Daniel J. Clauw[1], Philip J. Mease[2], Yimin Ma[3], Arlene Baldecchi[3], Robert H. Palmer[3] and Joel M. Trugman[3]. [1]University of Michigan, Ann Arbor, MI, [2]Seattle Rheumatology Associates and Swedish Medical Center, Seattle, WA, [3]Forest Research Institute, Jersey City, NJ

Background/Purpose: The efficacy of milnacipran for the management of pain, fatigue, and other fibromyalgia (FM) symptoms has been demonstrated in several 3- to 6-month double-blind (DB), placebo-controlled trials and in 6- to 9-month DB dose-controlled extension studies. Patients from these studies who were enrolled in a long-term open-label (OL) study of milnacipran (up to 3.25 years) were eligible for participation in this 17-week, multicenter, DB, placebo-controlled discontinuation study. This study was designed to evaluate the effect of discontinuation of long-term milnacipran treatment on the symptoms of FM.

Methods: Patients were enrolled and treated with OL milnacipran (up to 200 mg/day) for 4 weeks at the same dose as in the prior OL study. At the end of this 4 week period, patients taking milnacipran ≥100 mg/day and achieving a ≥50% reduction in visual analog scale (VAS) pain score from pre-milnacipran exposure to current status were randomized 2:1 to DB treatment with milnacipran (ie, milnacipran continued) or placebo (ie, milnacipran withdrawn) for 12 weeks. The primary efficacy parameter was the time to loss of therapeutic response (LTR), defined as an increase in VAS pain score to <30% reduction from pre-milnacipran exposure or a worsening of FM requiring an alternative treatment. Time to LTR was analyzed using Kaplan-Meier estimates and the log-rank test. Additional efficacy parameters included changes from baseline (randomization visit) in VAS pain and Brief Pain Inventory (BPI) scores.

Results: Time to LTR was significantly shorter for patients treated with placebo (ie, milnacipran withdrawn, n=50) than with milnacipran (ie, milnacipran continued, n=100, $P=.0004$). The median time to LTR was 56 days (95% CI, 28–85) for patients in whom milnacipran was withdrawn and not calculable for patients in whom milnacipran was continued, since half of these patients had not lost therapeutic response by study end. At the end of DB treatment, 64% of patients in whom milnacipran was withdrawn met LTR criteria vs 35% of patients in whom milnacipran was continued. Mean changes from baseline in VAS pain and BPI average pain scores indicated significant worsening at each postbaseline visit ($P<.05$) in patients in whom milnacipran was withdrawn as compared with patients in whom milnacipran was continued. Discontinuation due to treatment-emergent adverse events occurred in 2 milnacipran-treated patients (2.0%) and no placebo-treated patients.

Conclusion: In patients treated with milnacipran for up to 3.25 years, the loss of therapeutic response upon discontinuation of long-term treatment provides evidence of the continuing efficacy of milnacipran as a treatment for FM.

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The Care Gap in Management of Fibromyalgia: A Needs Assessment Prompting the Development of Clinically Relevant Guidelines for the Diagnosis, Management and Follow-up of Patients. Peter A. Ste-Marie[1], Mary-Ann Fitzcharles[2], Pantelis Panopalis[2], John Pereira[3] and Yoram Shir[2]. [1]University of Montreal, Montreal, QC, [2]McGill University, Montreal, QC, [3]University of Calgary, Calgary, AB

Background/Purpose: Clinicians remain challenged regarding the clinical care of fibromyalgia (FM) patients. Uncertainty may even have been fuelled by publication of the 2010 diagnostic criteria recognizing symptoms beyond pain. The elimination of the tender point examination, a physical finding previously entrenched in this clinical concept, but with uncertain value, the absence of a positive diagnostic test and lack of an ideal treatment further nurtures insecurity. There is understandably a clear need for direction in the diagnosis and care of FM patients. Our objective was to perform a needs assessment for healthcare professionals regarding challenges in the management of these patients, formulate these needs into a battery of questions that could drive a literature search as the first step towards development of clinically useful and applicable guidelines.

Methods: 139 healthcare professionals treating patients with FM from various disciplines including physicians (rheumatologists, family physicians, pain specialists, neurologists, psychiatrists and physiatrists), pharmacists, nurses, and psychologists convened in workshop settings in eight regions of Canada. Following a formal presentation of current concepts in FM, open discussion followed with recording of commentary. Following review of all recorded discussions, a needs assessment was formulated as a series of questions and is presented as a descriptive analysis.

Results: The 4 major domains of clinical challenge were identified: 1. Diagnosis; 2. Knowledge gap; 3. Treatment; 4. Outcome. Highlights of discussions within each group are presented. 1. There is insecurity in making and confirming a diagnosis, often with need for confirmation by a specialist, which might be patient or payer driven. Concerns exist regarding misdiagnosis with resulting excessive investigation. 2. There is generally a poor understanding of pain mechanisms and a perception of a considerable knowledge gap especially for the primary care physician. 3. Treatment choices are confusing in the context of multiple symptoms, and with the perception that pharmacologic treatment recommendations may be largely industry driven. The large volume of often anecdotal literature of treatments options further adds to uncertainty. Non-pharmacologic treatments, although recommended, are often poorly accessible and costly, with limited direction regarding treatment combinations. 4. Ideal follow-up is unknown without guidance regarding monitoring of symptoms, ideal outcome measures and frequency of follow-up visits. Physician biases are emphasized with the perception that FM patients are "difficult", requiring prolonged clinical time, and often demonstrating suboptimal treatment responses.

Conclusion: There exists considerable uncertainty and an important care gap in the understanding, diagnosis and management of FM. Updated clinically applicable and comprehensive guidelines that address these issues are required in order to provide better care for patients with FM.

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Supporting Evidence for the Clinical Utility of the Pain Subscale of the American College of Rheumatology 2010 Preliminary Diagnostic Criteria for Fibromyalgia. Peter A. Ste-Marie[1], Marc-Olivier Martel[2], Mary-Ann Fitzcharles[2] and Yoram Shir[2]. [1]University of Montreal, Montreal, QC, [2]McGill University, Montreal, QC

Background/Purpose: Understanding and recording the patient's experience of chronic pain is challenging, with no single measurement accepted as the standard. The clinical evaluation of pain may be by narrative report, measurement by pain scales or completion of pain drawings. As persons understand pain differently, specific measures may be subject to variable interpretation and may evaluate different components of pain such as location, intensity or emotional value. Our objective was to examine the agreement between the pain subscale of the ACR 2010

preliminary diagnostic criteria for fibromyalgia (FM), the Widespread Pain Index (WPI), completed as a checkbox, and the Body Map (BM), a drawn report of pain on a manikin, in FM patients. The WPI was also correlated with other measures of pain.

Methods: FM patients currently in a cohort study at a tertiary care multidisciplinary pain centre completed the WPI (total score 19), the BM (total score 50) and other measures of pain including: pain intensity Visual Analog Scale (VAS), McGill Pain Questionnaire (MPQ), Pain Disability Index (PDI) and Pain Catastrophizing Scale (PCS). The manikin was rescored to correspond to the 19 regions used in the WPI. Correlations between the WPI and the newly scored manikin, termed manikin WPI (manWPI), were calculated. Comparisons were made for the total scores as well as for each of the 19 individual regions for the WPI and the manWPI, and both the WPI and manWPI were compared to other pain instruments using Pearson's correlation coefficient.

Results: One hundred and three patients, 97 (94%) females, with a mean age 50±10 yrs and mean Fibromyalgia Impact Questionnaire 60±21 completed all pain instruments at a single routine clinic visit. The correlation coefficients for the WPI vs BM, WPI vs manWPI and manWPI vs. BM were.73,.72 and.90 respectively ($p<0.001$ for all values). Correlation coefficients for each of the 19 individual areas ranged between 0.27 and 0.60, showing overall moderate correlations, with strongest for low back pain and weakest for jaw pain. Other measures of pain similarly showed good correlation with both the WPI and manWPI, with lowest values recorded for PCS (Table 1).

Table 1. Correlation coefficients between the WPI and other pain measures

	WPI	manWPI
Pain VAS	.54**	.46**
MPQ	.50**	.46*
PDI	.57**	.52*
PCS	.36**	.23*

P<0.05*, P<0.001**

Conclusion: The WPI component of the ACR 2010 preliminary diagnostic criteria for FM correlates well with a visual representation of pain as portrayed in a manikin drawing, irrespective of the scoring method, as well as with other measures of pain. In view of this good correlation and taking into account the simplicity of the checkbox format, the WPI can be recommended as a reliable pain measurement for FM.

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Fibromyalgia Syndrome in the General Population of Israel: A Prevalence Study. Jacob N. Ablin[1], Anat Oren[2], Sarit Cohen[3], Valerie Aloush[1], Ori Elkayam[4], Yonatan Wolman[1] and Mark Berman[1]. [1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Tel Aviv University, Tel Aviv, Israel, [3]Carmel Medical Center, Haifa, Israel, [4]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Background/Purpose: Fibromyalgia (FMS), a condition traditionally defined by the presence of chronic widespread pain and tenderness, represents the tip of the iceberg of chronic pain in the general population. Estimating the prevalence of FMS is challenging, as many cases go undiagnosed.

We have attempted to estimate the prevalence of FMS in the Israeli population, using the London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ), an instrument previously utilized in several European countries.

Methods: The London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ) is an epidemiological tool recently implemented in a number of European countries for evaluating the prevalence of FMS. The questionnaire includes two components, the LFESSQ-4, screening for widespread pain, and the LFESSQ-6, which screens for both widespread pain and chronic fatigue. The pain criteria include 4 questions regarding musculo – skeletal pain in the upper or lower limbs or in the spine. The LFESSQ-6 adds two fatigue criteria (fatigue and limitation of activity due to fatigue).

The LFESSQ was administered via telephone to a representative sample of 1019 individuals selected by the quota method. A positive screen was defined as: (1) meeting the 4-pain criteria alone (LFESSQ-4), or (2) meeting both the 4-pain and 2-fatigue criteria (LFESSQ-6). To estimate the positive predictive value (PPV) of LFESSQ-4 and LFESSQ-6, this questionnaire was submitted to a sample of consecutive rheumatology outpatients (n=64, 17 males), who were then examined to confirm the diagnosis of FMS according to the 1990 ACR criteria. The prevalence of FMS in the general population was estimated by applying the PPV to eligible community subjects (i.e. positive screens).

Results: In the community survey 5.1% and 3.92% screened positive for LFESSQ-4 and LFESSQ-6, respectively. Among males interviewed, 3.0% and 2.2% screened positive for the LFESSQ-4 and LFESSQ-6, respectively, while among females 7.1% and 5.6% screened positive for the LFESSQ-4 and LFESSQ-6, respectively.

Among rheumatology outpatients, 41.5% screened positive for LFESSQ-4 and 33.8% for LFESSQ-6, whereas 21.5% were confirmed FMS cases. Based on positive screens for LFESSQ-4, the prevalence of FMS was estimated at 2.64% in the Israeli general population. The corresponding figure was 2.49 % if positive screens for LFESSQ-6 were considered. Among males, the prevalence of FMS based on the LFESSQ-4 was 1.55%; based on the LFESSQ-6 the prevalence was 1.4%.

Among females the prevalence based on the LFESSQ-4 was 3.68% and based on the LFESSQ-6 it was 3.56%.

Conclusion: The prevalence of FMS in the Israeli population is considerable, as estimated by the use of the LFESSQ, and constitutes a significant health care issue. The prevalence is similar to that observed in other western populations.

Using the LFESSQ-4 and the LFESSQ-6 yields similar results, but the LEFSSQ-6 appears more accurate, having a higher PPV for an individual meeting ACR criteria for FMS. The LEFSSQ-6 also addresses fatigue, recognized as a central clinical feature of FMS. Based on this tool, over 25% of FMS cases appear to be males, a proportion higher than generally appreciated.

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Concordance Between Subjective Dry Eye Symptoms and Objective Findings in Fibromyalgia Patients. Marco Antivalle, Michele Battellino, Alberto Batticciotto, Maria Chiara Ditto, Alessandra Mutti. Gabriella Santalena, Valentina Varisco and Piercarlo Sarzi-Puttini, L. Sacco University Hospital, Milano, Italy

Background/Purpose: Dry eye symptoms and signs have been frequently reported in fibromyalgia patients (1,2). However, no study so far has addressed the concordance between subjective symptoms and objective findings in this population. Aim of this study was to assess the concordance between subjective symptoms of dry eye and objective findings in fibromyalgia.

Methods: 52 patients were studied, 23 with fibromyalgia (FM: 20 F, 3 M, mean age 41.57 years, range 20–57) and 29 control subjects affected by miscellaneous rheumatic diseases (Controls: 26 F, 3 M, mean age 42.17 years, range 18–59). All patients completed the questionnaire used in the diagnosis of Sjögren's syndrome (3), and the McMonnies dry eye questionnaire, a 14-item validated questionnaire (4). In all patients Schirmer's I test (ST) was performed, and a result < 5 mm after 5 minutes was defined as positive. The impact of FM was assessed by the Widespread Pain Index (WPI), and by the Symptom Severity score (SS) (5). Statistical methods included chi-square statistic, and non-parametric ANOVA. The relatioship of selected variables on dry eye symptoms was assessed by binary logistic regression.

Results: Antinuclear antibodies (ANA) were positive in 15/52 (28.8%) patients (1 FM, 14 Controls). Schirmer's test was positive in 7/52 (13.5%) patients (FM 2/23 (8.7%); Controls 5/29 (17.2%)). 30/52 (57.7%) patients answered affirmatively to at least one of the three questions related to dry eye of the Sjögren's questionnaire (FM 18/23 (78.3%); Controls 12/29 (41.4%)), including 28 (53.8%) patients with negative ST (FM 16/21 (76.2%); Controls 12/24 (50.0%)) (fig 1). By McMonnies questionnaire, 32/52 (61.5%) patients (FM: 18/23 (78.3%); Controls 14/29 (48.3%)) were classified as having dry eye, including 27 with negative ST (FM 16/21 (76.2%); Controls 11/24 (45.8%)). Logistic regression results showed that for both the Sjogren's questionnaire and the McMonnies questionnaire, dry eye symptoms were correlated to age ($p = 0.003$) and to the presence of FM ($p = 0.004$ and $p = 0.040$ respectively), but not to age, to actual ST result, nor to ANA-positivity. Among FM patients, dry eye symptoms were correlated to higher SS scores (fig 2).

Fig. 1 - Number of affirmative answers to dry eye questionnaire

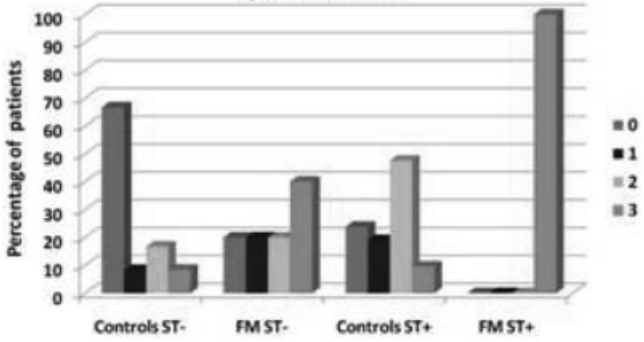
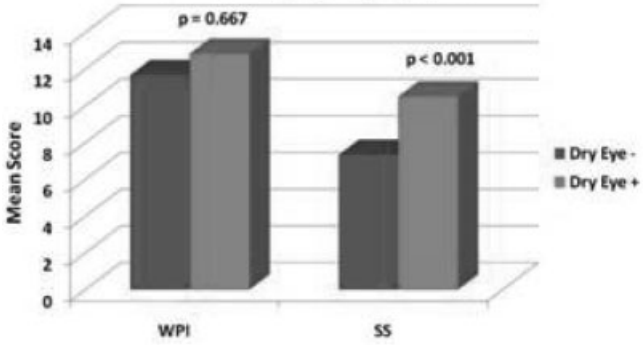


Fig. 2 - Mean WPI and SS score in patients with and without dry eye symptoms



Conclusion: To our knowledge, this is the first study addressing the concordance between subjective symptoms and objective findings in the assessment of dry eye in fibromyalgia. Our results show that in this population, dry eye symptoms are extremely frequent, but are related to the severity of FM symptoms rather than to the results of Schirmer's test.

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High Prevalence of Fibromyalgia Symptoms Among Healthy Full Term Pregnant. Sharon Saad, Ariel Many, Giris Jacob and Jacob N. Ablin. Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background/Purpose: Fibromyalgia (FMS), a syndrome characterized by centrally mediated pain, tenderness and fatigue, is more prevalent among females compared with males. The impact of fibromyalgia on the course of pregnancy is not clearly defined. In the current stud we have evaluated the frequency of FMS symptoms among full term healthy pregnant women and the impact of such symptoms on the course of delivery.

Methods: After signing informed consent, participants (N=57) were interviewed and filled out questionnaires. The 2011 modification of the ACR 2010 criteria for the diagnosis of fibromyalgia was used. In addition, participants filled out the Fibromyalgia Impact Questionnaire (FIQ) and the SF-36 and the AIMS questionnaires. Manual dolorimetry was performed using a standard manual dolorimeter, in order to document the 1990 ACR criteria. After delivery, data was collected from the obstetric files relating to the course of the delivery. This data Included documenting the implementation of induction, the length (In minutes) of stage 1,2 and 3 of delivery, the implementation of epidural anesthesia, the need for artificial rupture of membranes (AROM), instrumental delivery and cesarean section. A VAS scale recording pain intensity during delivery was also documented. The study was conducted as an open label, observational research. The setting of the study was the Obstetric clinic of the Tel Aviv Sourasky medical center. Participants were pregnant women attending the obstetric clinic for routine evaluation before birth. This evaluation is generally conducted at week 38 of pregnancy. High risk pregnancies were excluded.

Results: Out of 57 women recruited, 14 (24.6%) fulfilled Modified FMS criteria. This result did not correlate with the 1990 criteria, since none of these individuals fulfilled ACR 1990 criteria. The mean FIQ was 38.5 (SD- 14.5) and the men SF-36 (general health) was 82.3 (SD- 14.2). The mean SF-36 pain was 63.2 (SD- 22.8). A significant negative correlation was observed between the length of stage 3 of delivery and the SF-36 for social functioning (Pearson correlation −0.36, $p<0.05$). The VAS scale of pain during delivery was significantly positively correlated with the SF-36 pain recorded on the examination before delivery (Pearson correlation 0.482, $p=0.05$). Among women not fulfilling FMS criteria, 69.8% required epidural anesthesia. The corresponding figure among individuals fulfilling FMS criteria was 100%.

Conclusion: FMS symptoms were found to be highly prevalent among healthy pregnant women at term. The presence of such symptoms on evaluation before delivery correlated with the severity of pain during delivery and may have an impact on the course of delivery and the need for anesthesia. Evaluating for features of centrally mediated pain may be of clinical relevance for physicians involved in the treatment of pregnant women as well as for obstetricians.

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Fibromyalgia: Can Online Cognitive Behavioral Therapy Help? Gwendoline Menga[1], Bobby J. Dupre[2], Carl Gauthier[3], William E. Davis[4], Tamika A. Webb-Detiege[5], Eve Scopelitis[3], Jerald M. Zakem[4] and Robert Quinet[6]. [1]Ochsner Clinic Center, New Orleans, LA, [2]Ochsner Health System, Baton Rouge, LA, [3]Ochsner Clinic Foundation, New Orleans, LA, [4]Ochsner Clinic, New Orleans, LA, [5]Ochsner Medical Ctr, New Orleans, LA, [6]Ochsner Medical Center - New Orleans, New Orleans, LA

Background/Purpose: Cognitive behavioral therapy (CBT) has proven useful in the treatment of fibromyalgia, depression, and anxiety. Access to such therapy, though, can be limited. Computerized delivery of cognitive behavioral therapy allows for increased access in a comfortable, worry free environment. The purpose of this study was to assess the effect of Internet- based online CBT on fibromyalgia impact questionnaire composite (FIQ) score and tender point (TP) assessment.

Methods: We conducted a 12 week randomized controlled trial including patients, 18 years of age or older, with ACR criteria for fibromyalgia and mild to moderate depression and anxiety. A total of 56 subjects were randomized into either a 6-week Internet-based CBT program (MoodGYM), or control group (usual care). Patients in both groups were evaluated at baseline and 6 and 12 week follow-up. The primary outcome measure was change in Fibromyalgia Impact Questionnaire composite (FIQ) score. A secondary outcome measure was change in tender point (TP) assessment.

Results: The mean age of study participants was 55 years, 88% female. There were no significant changes in the serial FIQ scores across the 3 time points in either group. However, mean FIQ scores were significantly lower in the MoodGYM group compared to the control. ($p<0.05$ for group differences at 6 and 12 weeks respectively). Mean TP scores were also significantly lower in the MoodGYM group ($p<0.0001$ for group differences at 6 and 12 weeks respectively).

Conclusion: Patients in the Internet-based MoodGYM CBT program had lower FIQ and TP scores at 6 and 12 week follow-ups. Internet-based CBT could be beneficial therapy in the treatment of mild to moderate symptoms of depression and anxiety in patients with fibromyalgia, by allowing for increased access to CBT.

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The 2010 American College of Rheumatology Fibromyalgia Survey Diagnostic Criteria and Symptom Severity Scale Is Valid and Reliable in a French Speaking Fibromyalgia Cohort. Peter A. Ste-Marie[1], Pantelis Panopalis[2], Mary-Ann Fitzcharles[2], Henri A. Menard[3], Yoram Shir[2] and Frederick Wolfe[4]. [1]University of Montreal, Montreal, QC, [2]McGill University, Montreal, QC, [3]Montreal General Hospital, Montreal, QC, [4]National Data Bank for Rheumatic Diseases, Wichita, KS

Background/Purpose: There is currently no consensus regarding the ideal measurement to assess symptom severity in fibromyalgia (FM), or to follow patients regarding change in symptoms or outcome. The Fibromyalgia Survey Diagnostic Criteria and Severity Scale (FSDC) is a patient administered questionnaire that assesses both the diagnosis of FM as well as symptom

severity (Wolfe, Clauw et al. 2011). The FSDC assesses the locations of body pain measured by the Widespread Pain Index (WPI), and associated symptom severity (SS) of fatigue, unrefreshed sleep, cognitive complaints and somatic symptoms. The sum of WPI and SS provides a score (0–31), a composite measurement of symptoms termed the fibromyalgianess scale. We have evaluated the reliability and validity of the translated French version of the FSDC in patients with an established diagnosis of fibromyalgia in a tertiary care setting.

Methods: After translation of the FSDC into French, the questionnaire was administered on two occasions within a 1 week period to persons with FM, and the FSDC was correlated with the following commonly used measures of symptom status to test construct validity: the Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ), McGill Pain Questionnaire (MPQ), and a visual analogue scale (VAS) for global severity and pain. Test-retest reliability was assessed with Pearson's correlation coefficients and internal consistency was evaluated using Cronbach's alpha coefficient. Construct validity was evaluated using the Spearman correlation coefficient.

Results: The study sample consisted of 73 patients, mean age 52±9 years, 67(92%) female, and mean disease duration 12±12 years. Test-retest reliability was between .600 and .888 for the 31 single items of the FSDC, and .912 for the total FSDC, with all correlations significant ($p<0.0001$). Cronbach's alpha was .846 for FSDC assessment 1, and .867 for FSDC assessment 2 indicating good internal consistency. Construct validity showed significant correlations between the FSDC and the FIQ 0.670, HAQ 0.413, MPQ 0.562, global VAS 0.591 and pain VAS 0.663 ($p<0.001$).

Conclusion: The French FSDC is a valid instrument for measuring symptom severity in French patients with FM and showed reliability as well as construct validity with other measures of symptom status in FM. This new scoring questionnaire, which is easily completed by patients and simple to score, has the potential to become the standard for measurement of symptom severity in FM.

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The Michigan Body Map and Its Use in Assessing the American College of Rheumatology Survey Criteria for Fibromyalgia. Chad M. Brummett[1], Afton L. Hassett[2], Katherine A. Brummett[1], Daniel J. Clauw[3] and David A. Williams[4]. [1]University of Michigan Health System, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI, [4]Univ of MI Hlth System-Lobby M, Ann Arbor, MI

Background/Purpose: Body maps have been used for many years to assess the locations of pain complaints; however, quantifying and analyzing these data have been challenging. The ACR Survey Criteria for Fibromyalgia (FM) includes the assessment of pain in 19 selected body areas associated with rheumatologic complaints. To facilitate collection of the survey-based pain data, we created the Michigan Body Map (MBM). The MBM contains the 19 areas from the Widespread Pain Index (WPI) used to evaluate the FM clinical criteria, plus 16 additional areas for more general use. We present preliminary data using the MBM in combination with the ACR Symptom Severity (SS) scale to create a fibromyalgianess score. The MBM was also correlated with other measures of pain, mood and function and scored either with all 35 sites or those from the WPI.

Methods: 497 new patients presenting to the pain clinic were prospectively phenotyped using validated self-report measures, including the Brief Pain Inventory (BPI), PainDETECT, Hospital Anxiety and Depression Scale (HADS), PROMIS Physical Function Short Form (PROMIS SF1), and SS scale from the ACR Survey Criteria for FM. In addition, patients completed the MBM, which asks patients to check all of the 35 potential body areas in which they have experienced persistent or recurrent pain for 3 months or more on a one sided body image. Included in the MBM are the body regions included in WPI from the ACR FM survey criteria. Data were entered into the APOLO Electronic Data Capture system and analyzed using PASW 18.

Results: Correlations between the ACR Survey Criteria for FM, MBM and WPI are noted in Table 1. Fibromyalgianess correlated well with pain severity, pain interference, neuropathic pain descriptors, depression, and anxiety. It also showed an inverse correlation with positive affect and physical function. Fibromyalgianess was more highly correlated for all measurements when compared with a measure of widespread body pain alone using either the MBM or the WPI from the ACR FM Survey Criteria. The 35-item MBM demonstrated similar or stronger relationships in all measures, except for pain intensity, when compared with the WPI from the ACR FM Survey Criteria.

Table 1.

	ACR Survey Criteria for FM ("Fibromyalgianess")	Michigan Body Map (MBM)	WPI from ACR FM Criteria
BPI Pain Severity	0.363	0.216	0.272
BPI Pain Interference	0.477	0.309	0.283
PainDETECT	0.472	0.417	0.388
HADS Depression	0.436	0.274	0.241
HADS Anxiety	0.510	0.329	0.325
HADS Positive Affect	−0.442	−0.277	−0.248
PROMIS SF1	−0.356	−0.288	−0.256

Pearson Correlation. $p < 0.0001$ for all noted correlations in Table 1.

Conclusion: The MBM allows patients to note areas of chronic pain on a body map in a quantifiable manner. The selection of the body areas noted in the ACR Survey Criteria for FM along with the SS scale can be used to calculate a fibromyalgianess score. Future studies will determine the impact of the additional body areas in the MBM when combined with a symptom assessment.

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Longitudinal Assessment of Fibromyalgia in Young Adults Previously Diagnosed with Juvenile Fibromyalgia. Tracy V. Ting[1], Daniel Strotman[1], Emily Verkamp[1], Anjali Desai[1], Anne Lynch-Jordan[1], Lesley M. Arnold[2] and Susmita Kashikar-Zuck[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]University of Cincinnati College of Medicine, Cincinnati, OH

Background/Purpose: At present, little is known about the prognosis for children and adolescents diagnosed with Juvenile Fibromyalgia (JFM). As part of a longitudinal assessment of outcomes in adolescents with JFM compared with healthy controls, we are collecting data about fibromyalgia (FM) symptoms as they transition into the young adult years. The objective of this study was to determine how many of the JFM patients and controls meet criteria for FM over time using 3 approaches to the diagnosis of FM: the 1990 American College of Rheumatology (ACR) criteria [Wolfe F et al. *Arthritis Rheum* 1990], the 2010 ACR criteria [Wolfe F et al. *Arthritis Rheum* 2010], and a questionnaire for FM developed by Pope and Hudson [Pope HG, Hudson JI. *Int J Psychiatry* Med 1991]. Another goal was to assess the sensitivity and specificity of the 2010 ACR criteria and the Pope-Hudson questionnaire in this population using the 1990 ACR criteria as the gold standard.

Methods: Participants were recruited approximately 4 years from initial participation and asked to complete a survey that contained the 2010 ACR criteria self-report questionnaire and the Pope-Hudson questionnaire. The 1990 ACR criteria were determined by an in-person evaluation by a trained research staff member. Demographic information, chi-square analysis and sensitivity and specificity calculations were performed.

Results: Forty-two young adults with a previous diagnosis of JFM and 20 healthy controls were recruited. The group included 98.4% females, average age = 22.6 years, 87.1% Caucasian. The JFM group was more likely to have FM based on all 3 criteria. FM was identified in 69% (N=29), 71.4% (N=30), and 88.1% (N=37) of the JFM group according to the 2010 ACR, Pope-Hudson and 1990 ACR criteria respectively. Only the Pope-Hudson questionnaire revealed FM among 20% (N=4) of controls, while neither the 2010 nor 1990 ACR criteria identified FM among controls. Using the 1990 ACR Criteria as the gold standard for the diagnosis of FM, the sensitivity and specificity of the 2010 ACR criteria was 76% and 96% respectively and Pope-Hudson questionnaire was 76% for both.

Conclusion: This study reports ongoing findings from the first controlled longitudinal study to explore the persistence of FM symptoms in a cohort of JFM patients and their healthy counterparts. The results indicate that a substantial number of JFM patients have persistence of FM through the transitional young adult years; therefore continued close follow-up and treatment may be warranted. In addition, both the 2010 ACR criteria and the Pope-Hudson questionnaire demonstrated good sensitivity and specificity in identifying FM using the 1990 ACR criteria as the gold standard, with greater specificity using the 2010 ACR criteria.

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Prevalence of Physician-Diagnosed Fibromyalgia and Fibromyalgia-Related Fatigue in Olmsted County. Ann Vincent[1], Debra L. Barton[2], Daniel J. Clauw[3], Mary Whipple[1], Brian Lahr[4], Eric Hawkins[1], Terry H. Oh[2], Connie Luedtke[1] and Jennifer St.Sauver[4]. [1]Mayo Clinic, Rochester, MN, Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]University of Michigan, Ann Arbor, MI, [4]Mayo Clinic, Rochester

Background/Purpose: Our primary objective was to estimate the prevalence of physician-diagnosed fibromyalgia (FM) in Olmsted County, MN in 2009. In addition, we sought to: a) determine the percentage of patients in this group who met the ACR 2010 criteria for FM, b) determine the percentage of patients in this group who reported any fatigue and c) describe the distribution of fatigue severity in this group.

Methods: Patients who carried an ICD-9 code for FM (729.1) in Olmsted County were identified using the Rochester Epidemiology Project. In doing so, we identified 3685 potential cases. We then conducted a medical record review to confirm that each potential case carried a diagnosis of FM (ACR 1990 criteria). Only 1509 (40.9%) of the 3685 patients were confirmed as having a physician diagnosis of FM, of whom 947 were prevalence cases between the ages of 18 to 70. All 1509 patients were sent a survey that included the 2010 ACR criteria for FM, along with the first three questions of the Multidimensional Assessment of Fatigue (MAF) questionnaire. Non-responders received a second survey at 4 weeks. The prevalence of physician-diagnosed FM in Olmsted County was estimated assuming the entire population with an age between 18–70 years was at risk.

Results: The overall prevalence of FM was 1.03% (0.13% in males and 1.88% in females). Additional follow-up of all 1509 patients by mailed questionnaire yielded a 42.1% response rate. Among responders, 516 (81.3%) met the ACR 2010 criteria for fibromyalgia and 616 (97.0%) reported fatigue. On the ACR fatigue question, 99 respondents (15.7%) reported slight or mild fatigue, 354 (56.1%) reported moderate fatigue, and 163 (25.8%) reported severe fatigue. Similarly, on the fatigue severity question on the MAF, 96 patients (15.3%) reported no fatigue to mild fatigue (score 0–4), 260 (41.5%) reported moderate fatigue (score 5–7), and 270 (43.1%) severe fatigue (score 8+). Correlation of fatigue severity between the ACR 2010 fatigue question and the MAF fatigue severity question demonstrated good correlation (Spearman correlation coefficient=0.72, P <0.0001).

Conclusion: The prevalence of physician-diagnosed FM in Olmsted County is 1.03%, much lower than known FM prevalence rates of 4%. This may be related to poor recognition and under diagnosis of FM among health care providers. Our study also demonstrates that moderate to severe fatigue is a significant problem in a vast majority of patients with FM.

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What Does Affect the Sexual Behaviour in Fibromyalgic Patients? Laura Bazzichi[1], Alessandra Rossi[2], Ciro Conversano[2], Camillo Giacomelli[2], Claudia Ferrari[1], Francesca De Feo[2], Francesca Sernissi[2], Marica Doveri[2], Linda Carli[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]University of Pisa, Pisa, Italy

Background/Purpose: Sexuality is an important aspect of life. The prevalence of sexual difficulties in patients with chronic pain is high (Ambler et al., 2001). The aim of our study was to compare the sexual behavior of patients with fibromyalgia (FM) with patients affected by rheumatoid arthritis (RA).

FM is a chronic disease characterized by widespread pain and symptoms associated with several neurovegetative disorders. RA is a chronic, systemic and inflammatory condition characterized by pain, disability and joint deformations. Both FM and RA affect all domains of life, with a severe impairment in terms of quality, involving also the sexual behavior.

Methods: We enrolled 100 patients with FM, 20 patients with RA and 25 healthy subjects (all females of comparable age).

All subjects were administered the questionnaires "Index of Sexual Satisfaction" (ISS) and "Female Sexual Function Index" (FSFI). The ISS assesses, using 25 items, sexual functioning as a natural part of a relationship; the patients with an overall score higher than 30 points (cut-off point) were considered to have sexual dysfunction.

The FSFI assesses sexual satisfaction and includes the domain of sexual desire, arousal, lubrication, orgasm, satisfaction, and pain during sexual intercourse. The maximum score for total FSFI is 36, a good sexual function is associated with higher scores, the total score of less than 22.7 is indicative of sexual dysfunction.

Results: The mean age of FM patients was 47 years (± 8), the mean number of TP was 16.95 (± 2.80), VAS pain 6.3 (± 2.6) and FIQ total score 59.7 (± 18.7). The mean age of RA patients was 48.6 years (± 9), the mean HAQ values was 0.65 ± 045, DAS28 was 3.80 ± 1.91 and VAS 5 ± 2.7. The mean age of the healthy controls was 40.5 (± 10). The percentage of postmenopausal patients was 41% in FM and in RA and 23% in healthy controls.

The mean ISS score is significantly greater in FM patients (34.25 ± 9.58) than that for healthy controls (24.39 ± 14.00), and did not differ between FM and RA (28.87 ± 16.70) and between RA and controls. Fifty-seven % of patients with FM had ISS> 30, indicative of sexual dysfunction versus 36% of healthy controls (p=0.005). No differences were found between ISS values of healthy controls vs RA patients (42%) and between RA vs FM patients.

The mean total FSFI score did not differ between the 3 groups of subjects (FM=21.33±8.04, RA=22.52±6.66, controls=23.84±4.84).

When the subscores of each domain were evaluated, the most common sexual problem was diminished arousal, lubrication, satisfaction in FM patients and diminished pain during intercourse and orgasm in RA patients.

The percentage of patients with FSFI<22.7, indicative of sexual dysfunction, is significantly greater in FM and RA patients compared with controls (48%, 39%, 10.5%, p = 0.0001).

Conclusion: The sexual behavior of both FM and RA patients is affected by rheumatic disease, but probably in different ways; the couple's relationship of FM patients (as indicated by greater ISS values) appears to have considerable weight with respect to sexual dysfunction, suggesting that in FM patients emotions may play a crucial role in sexual behavior, perhaps deeper than that played by pain and physical disability.

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Functional MRI (fMRI) in Patients with Cognitive Dysfunction Related to Fibromyalgia (Fibrofog). Robert S. Katz[1], Vy T. Dinh[1], Glen Stebbins[2] and Frank Leavitt[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical Center, Chicago

Background/Purpose: Patients with fibromyalgia cognitive problems perform poorly on several neuropsychological tests, including the auditory consonant trigram. To date, fMRI activation differences in patients with fibromyalgia and control RA patients during the auditory consonant trigram (ACT) tasks have not been investigated.

Methods: In the present pilot study, we examined fMRI activation during an analog of the ACT task in 2 patients with fibromyalgia (FIBRO) (ages 46 and 54) and 2 patients with RA (ages 37 and 47). These participants completed an event-related fMRI protocol while performing the ACT task. Individual consonants were presented for 1000ms, followed by a distracter task of either a blank screen, or a forced choice between names of colors and anagrams of color names. The target during the distracter task was to choose the color name using MRI compatible responses devices. The duration of the distracter task was 15000ms. Following the distracter task, the participants were presented to two consonant trigrams, one of which was the trigram seen at the beginning of the event. Their task was to choose the matching trigram. These events were repeated for a total of 40 trials. fMRI data were processed in SPM 8, and examined activation contrast between distractors with blanks and words, and recognition of the trigrams following distraction with blanks or words.

Results: Behavioral results indicated that the FIBRO patients were slightly slower in reaction time compared to RA patients during recognition (Fibro = 1967ms; RA = 1222ms) and distracter tasks (FIBRO = 1914ms; RA = 1167ms) and correctly recognized fewer trigrams after distraction (FIBRO = 92% correct: RA = 98% correct).Using a statistical threshold of p = 0.01, imaging results revealed similar activation patters during recognition of the trigrams following the blank distracter task. Both FIRBO and RA subjects demonstrated activation in orbital frontal, inferior frontal, medialtemporal, cingulate and parietal lobes. Different patterns of activation were found between the FIBRO and RA patients during recognition following the color-name distracter task, however. RA patients demonstrated activation in middle frontal, inferior frontal, cingulate and insular lobes during recognition following the color-name distracter task, but FIBRO patients did not show any frontal lobe activation, but instead activated inferior temporal lobes and fusiform gyrus.

Conclusion: Behavioral differences in ACT performance has been noted in patients with FIBRO, but the underlying neural substrates involved in this deficit performance has not been explored. In this pilot study, we found that FIBRO patients demonstrate similar activation patterns to RA patients during ACT recognition following a non-demanding distraction task (blank screen). However, when the distraction task was difficult (color-name distraction), the FIBRO activation pattern of the FIBRO patients differed from that seen in the RA patients during recognition. These pilot data may provide insights into the underlying neural substrates supporting ACT performance and behavioral differences observed in FIBRO patients.

ACR/ARHP Poster Session B
Imaging of Rheumatic Disease II: X-ray, Magnetic Resonance Imaging, Computed Tomography, and Positron Emission Tomography
Monday, November 7, 2011, 9:00 AM–6:00 PM

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MRI Synovitis Is Prevalent in ACPA Positive Patients with Musculoskeletal Symptoms. Jackie L. Nam[1], Edith Villeneuve[1], Sudipto Das[1], Dennis McGonagle[1], Richard Hodgson[1], Andrew Grainger[1], Richard J. Wakefield[1], Philip G. Conaghan[1] and Paul Emery[2]. [1]University of Leeds and Leeds Teaching Hospitals, Leeds, United Kingdom, [2]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA) associated autoantibodies including anti-cyclic citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) may be present years before clinical presentation. Modern imaging modalities have proven their sensitivity for subclinical synovitis detection. The aim of this study was to explore whether the preclinical phase of RA was associated with clinically occult small joint synovitis as determined by MRI.

Methods: 21 patients identified from primary care and rheumatology clinics who were ACPA positive with musculoskeletal symptoms but without clinical synovitis, underwent MRI scans. MRI of one hand and wrist and both forefeet was performed using a 3T MRI scanner employing pre- and post-contrast sequences. Images were scored blindly by two musculoskeletal radiologists.

Results: 91% (19/21) patients were female, median age was 51 years and median duration of early morning stiffness (EMS) 12.5 min (range 0 to 240 min). All were ACPA+ and 57% (12/21) were RF+. Median ESR at study entry was 14.5 mm/h (range 1–40 mm/h) and median CRP using a high sensitivity CRP (hs-CRP) test was 2.7 mg/L (range <0.01 to 29 mg/L). CRP levels for 14/21 (66.7%) patients fell within the normal range (<10mg/L). X- rays of the hands and feet reported by experienced musculoskeletal radiologists showed no erosions or other radiographic features of RA.

All 21 cases had MRI determined synovitis. Synovitis was most frequently detected in the wrist (90.5% (19/21)). MCP synovitis reported in 52.4% (11/21) and involvement of one or both forefeet in 66.7% (14/21). MRI determined bone oedema was evident in 52.4% (11/21) cases with 23.8% (5/21) documented in the wrists, 14.3% (3/21) in the MCPs and 33.3% (7/21) in the forefeet. There was erosive change in 13/21 (61.9%) of patients on MRI–28.6% (6/21) in the wrists, 14.3% (3/21) in the MCPs and 42.9% (9/21) in the forefeet.

Similar proportions of MRI changes were documented in patients who had (1) elevated CRP levels (>10mg/L) and (2) normal CRP levels (<10mg/L), including the subgroup with (3) low CRP levels detected only using a high sensitivity test (hs-CRP 0.1–5 mg/L). Synovitis was documented in each of the 3 subgroups in 7/7(100%), 14/14 (100%) and 11/11 (100%) patients, bone oedema in 3/7(42.9%), 8/14(57.1%) and 5/11(45.5%) patients and erosions in 5/7(71.4%), 8/14(57.1%) and 6/11 (64.5%) patients respectively.

Conclusion: This MRI imaging study of small joints in ACPA positive patients who do not have clinical evidence of joint inflammation showed that patients already have MRI determined small joint synovitis, irrespective of CRP levels. In ACPA positive patients, musculoskeletal symptoms may be an early indicator of the presence of clinical synovitis. The study is ongoing to determine the specificity of these findings.

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Comparison of High-Resolution Multi-Pinhole SPECT and MRI for Monitoring Early Arthritis Patients Under Methotrexat Therapy: First Results. Christian Buchbender[1], Philipp Sewerin[1], Axel Scherer[1], Falk Miese[1], Oliver Sander[1], Katalin Mattes-György[1], Hans-Jörg Wittsack[1], Christof Specker[2], Gerald Antoch[1], Matthias Schneider[1] and Ben Ostendorf[1]. [1]Heinrich-Heine-University, Düsseldorf, Germany, [2]Kliniken Essen Süd, Essen, Germany

Background/Purpose: To compare Magnetic Resonance Imaging (MRI) and Multi-pinhole Single-Photon-Emission Computed Tomography (MPH-SPECT) for the detection of joint inflammation in early rheumatoid arthritis (ERA) after six months Methotrexate therapy.

Methods: The clinically dominant hand of five consecutive ERA patients (4 f, 1 m, disease duration < 6 months, therapy-naive for DMARD, mean-values: CRP 15 mg/l, DAS 28 4.9, CCP 115.6 U/l, Rheumatoid factor 628 U/l) and involvement of the metacarpophalangeal (MCP) joints was imaged with a MPH-SPECT system at baseline (T0) and six months (T1) after initiation of methotrexate (MTX) therapy (15 mg/weekly p.o. or s.c.). SPECT (Picker PRISM 2000 S camera (Philips Medical Systems), MPH pyramidal collimator reaching a spatial resolution < 1 mm)) imaging was performed with 550 megabequerel (MBq) of technetium-99m dicarboxy propane disphosphonate (Tc99m-DPD). SPECT FoV was 110 × 100 mm covering the MCP, proximal and distal interphalangeal joints. Ratios of Tc99m-DPD uptake in MPH-SPECT were calculated intra-individually for MCP joints in relation to a non-involved joint in each patient. MR imaging of the same hand was contemporaneously performed on a 3T system (Magnetom Trio; Siemens Healthcare, Germany) using a 4 channel flex coil (imaging protocol: coronal STIR, coronal T1-TSE, dynamic T1 contrast enhanced, contrastenhanced coronal T1-TSE, axial contrast-enhanced T1-FS SE. MRI was evaluated based on the RAMRIS subset scores for synovitis, bone marrow edema (BME), and erosions. MPH-SPECT and MRI data of the two time points were compared (T0 and T1). Mann-Whitney-U test was used to test for differences in Tc99m-DPD uptake between the two time points.

Results: Clinically all patients respond to MTX (mean values (T1) DAS 28 1.4, CRP 2 mg/l). MPH-SPECT at T0 revealed increased bone metabolism in 12 out of 20 MCP joints. The mean Tc99m-DPD uptake ratio at baseline was 2.1 ± 1.2 (Range 1.2 –5.7). All 12 joints showed synovitis on baseline MRI scans. BME and erosions were found in one MCP joint. 10/12 showed a decreased bone metabolism after six month compared to baseline SPECT. The mean Tc99m-DPD uptake ratio of the follow up SPECT was 1.5 ± 0.46 (Range 1.1–2.7). We found that bone metabolism on follow-up was significantly decreased compared to baseline ($p = 0.013$). Bone metabolism showed an average decrease of 35%. The follow-up MRI scans revealed improvement of synovitis in 10/12 MCP joints. Despite improvement, synovitis was still present in 6/12 joints. No change or progression of erosions—detected on baseline MRI—was found at T1. No change of BME (1 MCP) was seen.

Conclusion: In comparison to MRI, MPH-SPECT more frequently reveals early inflammatory involvement of the bone (potentially prior to BME). In ERA, therapy monitoring using MRI was limited to soft tissue inflammation. Thus MPH-SPECT might represent an additional tool for monitoring initial bony alterations in inflammatory joints diseases, such as ERA. Further studies are needed to support this hypothesis.

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Construct Validity and Responsiveness of Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Early Rheumatoid Arthritis – A Comparison with Conventional Magnetic Resonance Imaging and Clinical Measures of Disease Activity. Mette Bjørndal Axelsen[1], Bo J. Ejbjerg[2], Merete L. Hetland[1], Kim Hørslev-Petersen[3], Mikael Boesen[4], Olga Kubassova[5], Ulrik B. Lauridsen[1], Ole Majgaard[2], Henning Bliddal[4], Niels Steen Krogh[6] and Mikkel Østergaard[1]. [1]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [2]Copenhagen University Hospital at Slagelse, Slagelse, Denmark, [3]University of Southern Denmark, Graasten, Denmark, [4]The Parker Institute, Copenhagen University Hospital at Frederiksberg, Frederiksberg, Denmark, [5]Image Analysis Ltd., Leeds, United Kingdom, [6]ZiteLab ApS, Copenhagen, Denmark

Background/Purpose: The aim of the study was to assess the responsiveness and construct validity of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) parameters during aggressive treatment of early rheumatoid arthritis (RA), by comparison with conventional MRI and clinical measures of disease activity.

Methods: DCE-MRI and conventional contrast-enhanced MRI of the non-dominant hand (wrist and 2.−5. metacarpophalangeal joints (MCP)) and clinical assessment were performed at months 0, 6 and 12 in 14 patients with early RA treated with disease modifying antirheumatic drugs (DMARDs) (methotrexate +/− cyclosporine) and intra-articular glucocorticoid in an investigator initiated clinical trial [1]. Conventional MRI was evaluated using the Rheumatoid Arthritis MRI score (RAMRIS). DCE-MRI (one coronal slice) was analysed using a computer-aided approach by which the temporal contrast uptake is characterized by parameters such as the Initial Rate of Enhancement (IRE), Maximal Enhancement (ME) and number of enhancing voxels (N_{voxel}) [2]. The analysis was performed for 2 manually outlined Regions of Interest

(ROIs) covering the wrist and 2.–5. MCP, respectively, and for the sum of wrist and MCP ROIs, ('Wrist+MCP').

Results: All DCE-MRI parameters in the 'Wrist+MCP' declined significantly from month 0 to 12 (see table for separate wrist and MCP values and SRMs). The SRMs for RAMRIS synovitis was −0.67 to −1.05 from month 0–6 and 0–12. DAS28, and tender and swollen joint counts declined similarly (SRMs −0.51 to −1.11). Correlations with RAMRIS synovitis were high for ME (rho 0.56–0.87, $p<0.04$), N_{voxel} (rho 0.76–0.80, $p\leq0.002$) and $IRExN_{voxel}$ (rho 0.73–0.81, $p\leq0.003$), and low–moderate for IRE (0.09–0.56, $p \leq 0.04$–0.76).

Table 1. Responsiveness of DCE-MRI, Conventional MRI and Clinical Parameters

	Baseline Median (range)	6 months Median (range)	12 months Median (range)	Change 0–6 months Median (range)	Change 0–12 months Median (range)	SRM 0–6 months	SRM 0–12 months
Dynamic Contrast-Enhanced Magnetic Resonance Imaging Parameters							
Wrist+MCP IRE (%/s)	1.79 (1.37 – 3.54)	1.58 (0.91 – 2.68)	1.55 (0.93 – 3.06)	−0.22 (−2.12 – 1.00)*	−0.42 (−2.22 – 1.38)*	−0.49	−0.53
Wrist+MCP ME	1.53 (1.19 – 2.04)	1.43 (1.15 – 1.80)	1.32 (1.16 – 1.83)	−0.21 (−0.53 – 0.28)	−0.13 (−0.48 – 0.31)*	−0.55	−0.61
Wrist+MCP N_{voxel} (voxels)	1241 (267 – 7964)	642 (12 – 2712)	505 (16 – 2189)	−665 (−6158 – 1867)	−644 (−424 – 1344)**	−0.49	−0.65
Wrist+MCP $IRExN_{voxel}$ (%voxels/s)	2193 (365 – 23943)	1168 (11 – 7281)	741 (15 – 6699)	−1192 (−21353 – 5859)	−1337 (−21162 – 5277)**	−0.43	−0.53
Wrist IRE (%/s)	1.88 (1.36 – 3.74)	1.63 (0.91 – 2.98)	1.55 (1.08 – 3.33)	−0.28 (−2.33 – 1.31)	−.54 (−2.42 – 1.66)*	−0.49	−0.54
Wrist ME	1.58 (1.19 – 2.16)	1.44 (1.14 – 1.92)	1.33 (1.15 – 1.93)	−0.16 (−0.64 – 0.37)	−0.13 (−0.60 – 0–38)*	−0.49	−0.57
Wrist N_{voxel} (voxels)	759 (193 – 5473)	552 (12 – 1732)	356 (9 – 1547)	−238 (−4687 – 958)	260 (−773 – 4511)*	−0.37	−0.56
Wrist $IRExN_{voxel}$ (%voxels/s)	1394 (269 – 17951)	936 (11 – 5161)	522 (10 – 5151)	−467 (−16756 – 3869)	−679 (−16287 – 3858)*	−0.36	−0.46
MCP IRE (%/s)	1.61 (1.21 – 2.66)	1.51 (0.00 – 1.84)	1.56 (0.50 – 1.95)	−0.07 (−1.59 – 0.44)	−0.05 (−1.3 – 0.28)	−0.41	−0.37
MCP ME	1.48 (1.16 – 1.75)	1.26 (0.00 – 1.60)	1.25 (1.08 – 1.83)	−0.12 (−1.27 – 0.29)	−0.064 (−0.38 – 0.29)	−0.54	−0.38
MCP N_{voxel} (voxels)	389 (69 – 2491)	131 (0.00 – 1020)	90 (6 – 900)	−278 (−1676 – 909)*	−215 (−1913 – 571)*	−0.61	−0.70
MCP $IRExN_{voxel}$ (%voxels/s)	536 (96 – 5082)	196 (0 – 1803)	135 (4 – 1647)	−484 (−3694 – 1675)*	−342 (−3972 – 1123)*	−0.58	−0.65
Rheumatoid Arthritis Magnetic Resonance Imaging Scores (RAMRIS)							
Wrist+MCP RAMRIS Synovitis	13 (3 – 18)	5.5 (3 – 19)	5 (3 – 21)	−4.5 (−14 – 1)*	−3.5 (−15 – 4)*	−1.05	−0.89
Wrist RAMRIS synovitis	7 (3 – 9)	3 (3 – 6)	4 (2 – 8)	−3 (−6 – 2)**	−2 (−6 – 2)**	−1.04	−1.02
MCPRAMRIS synovitis	6 (1 – 9)	3 (0 – 7)	2 (0 – 6)	−2 (−9 – 2)**	−1.5 (−9 – 4)*	−0.88	−0.67
Clinical Parameters							
DAS28(crp)	3.99 (2.76 – 6.85)	2.78 (1.66 – 3.46)	2.23 (1.67 – 4.45)	−0.63 (−3.68 – 1.83)*	−0.78 (−4.54 – 1.81)**	−0.52	−0.53
Swollen Joint Count (28 joints)	3 (1 – 14)	0 (0 – 2)	0 (0 – 1)	−3.5 (−12 – 0)***	−3.0 (−14 – 0)**	−1.11	−1.10
Tender Joint Count (28 joints)	5 (0 – 19)	0 (0 – 5)	0 (0 – 8)	−2 (−17 – 4)*	−2.5 (−19 – 4)*	−0.69	−0.51

Wilcoxon Signed Rank test: p≤0.05:*, p≤0.01:**, p≤0.001:***
Correlations between parameters (Spearman's Correlation Coefficient, rho), changes over time (Wilcoxon Signed Rank test) and responsiveness (Standardized Response Mean (SRM)) were calculated.

Conclusion: All DCE-MRI parameters declined significantly during treatment. With regard to responsiveness, DCE-MRI was comparable to DAS28 but inferior to RAMRIS synovitis. DCE-MRI demonstrated construct validity and moderate responsiveness.

References:

1 Hetland ML et al. *Arthritis Rheum* 2006;54:1401–1409

2 Kubassova O et al. *Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv* 2007;10:261–269.

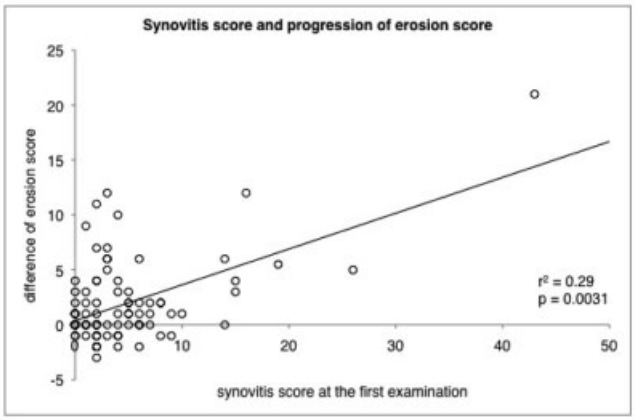
947

Evaluation of Activity, Making Diagnosis and Prediction of Future Bone Destruction by Using Low Field Compact Magnetic Resonance Imaging Machine in Patients with Rheumatoid Arthritis. Makoto Sugihara[1], Takeshi Suzuki[1], Yoshikazu Okamoto[2], Masanobu Horikoshi[1], Masahiro Yokosawa[1], Shinya Hagiwara[1], Tomoya Hirota[1], Yohei Takano[1], Naoto Umeda[1], Yuya Kondo[1], Hiroto Tsuboi[1], Hiroshi Ogishima[1], Taichi Hayashi[1], Yusuke Chino[1], Daisuke Goto[1], Isao Matsumoto[1] and Takayuki Sumida[1]. [1]Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan, [2]Division of Radiology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan

Background/Purpose: The aim of this study was designed to evaluate activity of rheumatoid arthritis (RA), to make a diagnosis of RA using a new low field compact magnetic resonance imaging (cMRI), and to predict future bone destruction in individual RA patients.

Methods: We have developed cMRI with 0.3tesla magnetic field and set it in outpatient booth of Tsukuba University Hospital. We took hand images of coronal T1 weighted image and coronal short tau inversion recovery image without gadolinium enhancement. (1) Five hundreds and sixty four hands of 283 patients were included and evaluated by cMRI. Sixty eight hands of 84 patients were RA treated with biologic agents (infliximab 37 patients, etenercept 23, tocilizumab 13, adalimumab 6 and abatacept 5), 209 hands of 105 patients were RA treated without biologic agent, 54 hands of 27 patients had arthralgia caused by other connective tissue diseases (CTD) and 133 hands of 67 patients were unclassified arthritis (UA). Bone erosion, bone marrow edema and synovitis were scored by cMRI scoring system. In cMRI scoring system, 32 sites of bone erosion, 32 sites of bone marrow edema and 11 sites of synovitis were evaluated. Bone erosion, bone marrow edema and synovitis are graded on a scale from 0 to 3 by imaging, respectively. The total cMRI score (cMRIS) is calculated by the sum of total bone erosion score multiplied by 1.5, total bone marrow edema multiplied by 1.25 and total synovitis score. (2) One hundred and three hands of 53 RA patients were evaluated by cMRI at first time and 6 to 12 months later, scored by cMRI scoring system. We analyzed the correlation between synovitis score at first time and the difference of erosion score between two examinations.

Results: (1) Total cMRIS were 37.17 points ± 26.94 for RA treated with biologics ($p<0.0001$ versus RA treated without biologics, $p<0.0001$ versus patients with other CTD and $p<0.0001$ versus UA patients), 21.94 ± 21.19 for RA patients treated without biologics ($p<0.0001$ versus patients with other CTD and $p<0.0001$ versus UA patients), 10.45 ± 16.57 for patients with other CTD ($p=0.0056$ versus UA patients) and 3.83 ± 5.32 for UA (t test). (2) Mean synovitis score at first examination was 3.95 ± 5.99. Erosion score of the second examination (14.60 ± 12.60 was significantly higher than score of the first (12.93 ± 11.43, $p < 0.0001$, t test). Synovitis score at the first evaluation by cMRI is significantly correlated with progression of erosion score 6 to 12 months later ($r^2=0.29$, $p=0.0031$, Spearman correlation rate).



Conclusion: cMRI might be a useful tool to prospect disease activity of RA and distinguish RA from the other diseases. Synovitis observed by cMRI would predict future bone destruction in individual RA patients.

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Is Experience Necessary to Accurately Score Low-Field Non-Contrast Magnetic Resonance Imaging of Rheumatoid Arthritis Joints? Comparison of Readings by Inexperienced Rheumatology Fellow to Scores of Experienced Musculoskeletal Radiologist. Fahed Hamadeh[1] and Ewa Olech[2]. [1]University of Oklahoma, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Radiography is a standard imaging technique for assessing destructive joint lesions in rheumatoid arthritis (RA). Magnetic Resonance Imaging (MRI) is more sensitive than conventional x-ray for the detection of RA joint pathology and it is increasingly being used for detecting and monitoring of this disease. It is not known if interpretation and scoring of small joints MRI requires more training and experience than reading x-rays. In this study we compare results of MRI scoring between inexperienced and experienced readers.

Methods: MR images of bilateral hand and wrist of 16 randomly selected RA patients were performed using 0.2 Tesla extremity unit (C-Scan) on two occasions, 1 year apart. The imaging protocol included coronal T1-weighted 3-dimensional gradient echo and coronal fat-suppressed short tau inversion recovery of the wrist and hand. Subsequently, the images were independently scored by inexperienced rheumatology fellow (IR) and experienced musculoskeletal radiologist (ER), according to RAMRIS system for erosions, osteitis and synovitis. IR had experience in evaluating RA x-rays. He was familiarized with RAMRIS definitions and scoring by reviewing the EULAR–OMERACT RA MRI reference image atlas[1]. He also reviewed several normal hand and wrist MRI studies. Agreement between the two readers was calculated as intraclass correlation coefficient (ICC) per patient per MRI.

Results: The patients' characteristics at baseline were as follows: mean age–49 years old, 31% male, mean disease duration–7 years, 81% RF-positive, 62.5% anti-CCP-positive, mean DAS28-ESR–4.96, DAS28–CRP–4.7. A total of 2944 bones were evaluated. IR reported lower number of erosions and erosion scores, but higher osteitis and synovitis scores than ER (Table 1). However, cross-sectionally, the ICCs between the 2 readers were high for erosions and osteitis (both wrists and metacarpophalangeal (MCP) joints), and moderate for synovitis (Table 2). There was no correlation between the readers for erosion, osteitis and synovitis scores change over time.

Table 1. Total erosion number and erosion, osteitis and synovitis scores per visit by ER and IR.

		Number of Erosions	Erosion Score	Osteitis Score	Synovitis Score
Baseline MRI	**ER**	127	342	45	76
	IR	58	161	120	149
MRI at 1 year	**ER**	126	345	36	74
	IR	53	184	114	104

Table 2. ICCs between the two readers' scores for MCP, wrist, and total joints.

	MCP joints	Wrist joints	Total joints
Erosions	0.95**	0.91**	0.95**
Bone edema	0.82**	0.94**	0.94**
Synovitis	0.49*	0.56*	0.73**

*p<0.05, **P<0.005

Conclusion: Despite high intraclass correlation coefficient values, the inexperienced reader underscored erosions and overestimated osteitis and synovitis. In order to accurately evaluate hand and wrist MRI of RA patients, experience is required.

Reference:
1. Østergaard M, et al. Ann Rheum Dis 2005;64(Suppl I)

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Stability of Automated Quantitation of Dynamic Contrast Enhanced (DCE) 3T Wrist Magnetic Resonance Imaging (MRI) in Healthy Volunteers; A Year Long Longitudinal Study. A. Rastogi[1], Olga Kubassova[2], Mikael Boesen[3], J.V. Hajnal[4] and Peter Taylor[5]. [1]Barts and the London NHS Trust, London, United Kingdom, [2]Image Analysis Ltd., Leeds, United Kingdom, [3]The Parker Institute, Copenhagen University Hospital at Frederiksberg, Copenhagen, Denmark, [4]Imperial College, London, United Kingdom, [5]Kennedy Institute of Rheumatology, London, United Kingdom

Background/Purpose: A desirable property of new therapeutics is to arrest progression of joint damage at early stages of rheumatoid arthritis (RA). Dynamic Contrast Enhanced (DCE)-MRI has recently been recognized as a promising biomarker of disease modification in early phase inflammatory arthritis as it permits quantitative assessment of perfusion. To recommend DCE-MRI for quantification of treatment effect in patients, thorough validation should be conducted using the data from healthy volunteers where no disease related changes are expected over the course of imaging. This study is concerned with validation of variability inherent in newer automated DCE-MRI methods by testing software performance in healthy cohorts over a year.

Methods: Dominant wrists of 7 healthy volunteers (3 males:4 females, age range:24–40 years) were imaged by 3T MR at baseline, week 12, 24 and 52 using T2w TSE, pre and post contrast T1wFFE, DCE-MRI sequences with the following parameters: TR/TE/FA: 3.8 ms/2.1 ms/20°, slices: 127, 40 frames (scan mode: 3D) and T1wFFE Proset. DCE-MRI data were analysed using Dynamika, Image Analysis, UK. Using the software, parameters of maximum enhancement (ME), initial rate of enhancement (IRE) and the number of pixels (e.g. volume of enhancing synovium) with persistent and wash-out pattern of enhancement were measured using pixel-by pixel model based approach in the entire image and within regions of interest (ROI) drawn around the wrist and placed precisely around enhancing synovium.

Results: The average ± standard deviation for baseline parameters and change over time is shown in Table 1. In wrist ROI analysis and precise ROI analysis, ME and IRE change are consistently low and less then 0.1. The number of pixels with persistent, plateau and washout pattern of enhancement, reflecting the volume of synovium become more accurate as a % of the ROI size and are low too (normalised persistent voxel change over 12 weeks: 0.2±1.1%(wrist ROI) & −0.2±2.1% (precise ROI), normalised plateau voxel change over 52 weeks: 3.7±3.4% (wrist ROI) & 1.0±10.9% (precise ROI) and normalised washout voxel change over 52 weeks: 1.9±0.9% (wrist ROI) & 5.8±7.4% (precise ROI)).

Table 1. Shows baseline values of parameters and their change over time.

	Baseline	Wk12-baseline change	Wk24-baseline change	Wk52-baseline change				
	Average	Std dev	Average	Std dev	Average	Std dev	Average	Std dev
ROI Wrist								
ME_{mean}	1.266095	0.0786	−0.007619	0.0632	0.007595	0.0940	0.041133	0.0239
$ME_{st.\ dev.}$	0.105619	0.0758	−0.000228	0.0576	0.033142	0.1001	0.041866	0.0265
IRE_{mean}	0.001952	0.0008	−0.000285	0.0009	9.52381E-05	0.0011	0.0006	0.0009
$IRE_{st.\ dev.}$	0.000904	0.0007	0.000809	1	0.001476	0.0014	0.002066	0.0015
Normalised Persistent: (%)	0.885665	0.7006	0.202174	1.1978	−0.427921	0.8410	−0.305485	0.3177
Normalised Plateau: (%)	11.283851	10.2615	0.938550	8.9309	0.469898	8.8623	3.790429	3.4510
Normalised Wash-out (%)	1.233881	1.1631	0.874174	0.6031	−0.383588	1.471956	1.951587	0.9091
ROI Precise								
ME_{mean}	1.285428	0.0903	−0.016619	0.0675	0.035595	0.1381	0.048966	0.0428
$ME_{st.\ dev.}$	0.106076	0.0798	0.006590	0.0694	0.034757	0.1100	0.041333	0.0382
IRE_{mean}	0.001761	0.0008	0.000285	0.0011	0.000809	0.0019	0.0008	0.0009
$IRE_{st.\ dev.}$	0.000952	0.0004	0.001142	0.0021	0.001809	0.0021	0.0013	0.0009
Normalised Persistent: (%)	1.578668	1.6659	−0.209247	2.1411	−0.540966	2.3994	−0.824105	1.5893
Normalised Plateau: (%)	22.432640	21.2280	−4.270537	13.8230	−3.060829	11.9250	1.078427	10.9669
Normalised Wash-out (%)	1.728650	1.5729	1.475777	1.8877	−0.619386	1.8319	5.819983	7.4759

Conclusion: This study shows that in healthy subjects, we can expect DCE-MRI parameters remain stable for as long as a year. The absence of variability associated with analysis methodology give confidence that these parameters can be used as imaging biomarkers in patients with inflammatory arthritis where early and sensitive quantification of change due to therapeutic intervention is desirable. Both wrist and precise ROI give similar results in healthy volunteers over a year and thus either could be used alone as part of the analysis.

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Importance of Field Strength, Coil Type and Image Resolution for Visualization of Bone Marrow Edema in Magnetic Resonance Imaging (MRI)—a Comparison of Contrast-to-Noise Ratio, Signal-to-Noise Ratio and Contrast on 0.23 T, 0.6 T, 1.5 T and 3 T MRI Units. Simon Krabbe[1], Susanne Juhl Pedersen[2], Pernille Bøyesen[3], J.M. Møller[4], Flemming R. Therkildsen[5], Ole Rintek Madsen[2] and Mikkel Østergaard[1]. [1]Copenhagen University Hospital in Glostrup, Glostrup, Denmark, [2]Copenhagen University Hospital in Gentofte, Copenhagen, Denmark, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Copenhagen University Hospital in Herlev, Copenhagen, Denmark, [5]Copenhagen, Denmark

Background/Purpose: MRI bone marrow edema (BME) represents inflammatory infiltrates in trabecular bone and is an important predictor of joint damage in patients with RA. Earlier studies of BME at different MRI units did not measure parameters of image quality. The objective of this study was to compare three parameters of image quality (contrast-to-noise ratio (CNR), signal-to-noise ratio (SNR), and contrast) between: (1) 4 MRI scanners with different field strength and the same coil type and voxel size, (2) different coil types (flex coils versus dedicated hand-wrist coils), and (3) two different image resolutions (voxel sizes).

Methods: Coronal STIR (short tau inversion recovery) and T1-weighted images of wrist and 2^{nd}–5^{th} MCP joints were obtained in 40 RA patients with ≥1 swollen joint and 12 healthy controls on 4 Philips MRI

units with different field strengths (0.23 T, 0.6 T, 1.5 T (TR: 4000, TE: 26–30; TI: 85, 110 and 150 (all ms)) and 3 T (TR: 6000, TE: 30, TI: 100 (all ms))) within 24 hours. Voxel size was 1×1×3 mm in all 4 MRI units, and in addition a smaller voxel size (0.5×0.5×2 mm) was applied at the 1.5 T MRI unit. BME was identified and manually delineated on the 1.5 T images. Afterwards the area was copied onto the other STIR sequences as close as possible to the original anatomical position. The signal intensities (S) of BME and normal fatty marrow (FM) and the noise were measured. CNR = $(S_{BME}-S_{FM})$/noise, SNR = S_{BME}/noise, and contrast = $(S_{BME}- S_{FM})/(S_{BME}+ S_{FM})$ were compared with 30 predefined paired t-tests. The intra-observer reliability was assessed on the MRIs of 10 patients.

Results: BME was identified in 140 out of 920 assessed bones in the patients, and in 1 out of 276 assessed bones in the controls. CNR was highest at 0.6 T (CNR = 23.6), lower at 1.5 T (20.7), still lower at 3 T (17.0) and lowest at 0.23 T (8.6). SNR was higher at 1.5 T (SNR = 36.3), 0.6 T (33.3) and 3 T (30.4) in pairwise comparisons with 0.23 T (14.7). Contrast was highest at 0.6 T (contrast = 0.53) in pairwise comparison with 1.5 T (0.39), 0.23 T (0.40) and 3 T (0.37). A dedicated hand-wrist coil was superior to a flex coil at 1.5 T (CNR 37.2 vs. 20.7 and SNR 68.9 vs. 36.3), but not at 0.6 T. Smaller voxel size gave lower CNR (11.1 vs. 20.7), SNR (22.6 vs. 36.3) and contrast (0.32 vs. 0.37) than the larger voxel size (each of these results was statistically significant, $p<0.05$). The intra-observer reliability was κ (kappa) = 0.81 for BME/no BME, and ICCs for CNR, SNR, and contrast were good (0.72–0.79).

Contrast-to-noise ratios (CNRs)	N	Mean difference	Paired t-test, p-values
Field strength (all with flex coils):			
0.23 T - 0.6 T	28	−15.3	<0.001*
0.23 T - 1,5 T	33	−12.0	<0.001*
0.23 T - 3 T	28	−8.3	<0.001*
0.6 T - 1.5 T	27	3.9	0.020*
0.6 T - 3 T	23	4.9	0.015*
1.5 T - 3 T	27	4.3	0.014*
Coil type:			
Flex coil (0.6 T) - Wrist coil (0.6 T)	26	−1.6	0.43
Flex coil (1.5 T) - Hand-wrist coil (1.5 T)	33	−17.0	<0.001*
Voxel size (at 1.5 T):			
Large voxel (flex coil) - Small voxel (hand-wrist coil)	29	10.4	<0.001*
Large voxel (hand-wrist coil) - Small voxel (hand-wrist coil)	30	28.0	<0.001*

N = number of observations. Positive mean values indicate a higher CNR for the first mentioned field strength/coil/voxel size.

Conclusion: The 0.6 T MRI unit provided better CNR and contrast than the other MRI units, and similar SNR. As expected, a smaller voxel size resulted in lower CNR, SNR and contrast. It is important to appreciate these advantages and disadvantages of different field strengths, coils and image resolutions, when optimizing the MRI acquisition strategy in RA.

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Tocilizumab Improves in Rheumatoid Arthritis Patients with Longstanding but Still Active Disease the Clinical Disease Activity (DAS28) and Ameliorates MRI Findings within the First Three Months of Therapy. Herbert Kellner[1] and Wolfgang Kellner[2]. [1]Centre for Inflammatory Joint Diseases, Munich, Germany, [2]Radiologische Praxis im Josephinum, Munich, Germany

Background/Purpose: Longstanding, but still active rheumatoid arthritis (RA) is often a therapeutic challenge. Tocilizumab (TCZ) has shown to be an effective biologic agent in mono as well as combination therapy. To assess therapeutic response in RA, the clinical disease activity score DAS 28 as well as MRI have shown to be value diagnostic tools. In the present study the therapeutic effect of TCZ in treatment experienced RA patients with active disease was examined.

Methods: 12 RA patients (m/f=1/11, age 53,8 y (41 –72), RF + n=8, CCP + n=7) with a disease duration of > 5 years (range 5–34 y) underwent tocilizumab mono (n=5) or combination therapy (n=7) over a 12 months period (8 mg/kg every 4 weeks). RA was active in all patients (DAS28 > 5). Pretreatment included DMARDs (average 3, range 2–5) and biologics (average 1,75, range 1–3). DAS28 and MRI (low-field, 0,2 T) was performed at baseline, week 12 and 52. The images were evaluated semiquantitatively using the RAMRIS scoring system and correlated with clinical results.

Results: DAS 28 at baseline was 6,0 (range 5,1 – 8,2) and decreased to 3,8 (3,2–51) in week 12 and 3,4 (2,8 –4,1) in week 52 respectively. The RAMRIS score improved from baseline values of a mean of 110 (range 64–188) to 58 (range 30–156) at week 12 and continued to stay there until week 52 (mean 58, range 26–140). During the first 12 weeks of therapy synovitis and bone edema improved significantly whereas erosions due to longstanding disease persited but did not impair.

Conclusion: Tocilzumab can even in treatment experienced patients with longstanding RA disease improve the clinical condition. DAS28 decreased within 12 weeks of therapy and there was no significant difference in therapeutic efficacy between mono and combination treatment. Low-field MRI could demonstrate improvement of especially synovitis and bone edema already within the first 3 months of therapy and progression of already established joint erosions could be prevented.

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Early Response to Tocilizumab in Patients with Treatment Resistant Rheumatoid Arthritis—Assessment Using 3 Tesla MRI. Joerg C. Henes[1], Marius Horger[1], Florian Haas[1], Gunther Zeh[1], Daniel Spira[1] and Ina Kötter[2]. [1]University Hospital Tuebingen, Tuebingen, Germany, [2]University Hospital Tuebingen, Tübingen, Germany

Background/Purpose: The monoclonal interleukin (IL)-6-antibody tocilizumab (TCZ) has been proven to be effective in rheumatoid arthritis (RA). Magnetic resonance imaging (MRI) is a very exact measurement in assessing inflammation as well as cartilage or bone damage in RA patients.

Methods: In this prospective trial we included 10 patients with RA refractory to at least 1 non-biological and 1 biological disease modifying antirheumatic drug (DMARD). TCZ was given in a standard dosing of 8mg/kg bodyweight every 4 weeks. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), disease activity score 28 (DAS28) as well as the clinical disease activity score (CDAI) were assessed at baseline, week 4 and 12. MRIs were performed on a 3 T whole-body MRI unit (Magnetom Trio, Siemens Healthcare). One trained musculoskeletal radiologist performed the procedure by using MRI definitions for erosion, edema, and synovitis, in accordance with the OMERACT RAMRIS recommendations. In order to achieve maximal image quality we consciously modified the RAMRIS criteria by reducing the examination area to the clinically leading affected joints and added 2 additional scores: Bone marrow hyperemia is considered to be a very early marker of inflammation. Its presence correlates with increased levels of acute phase reactants (ESR, CRP) and scales for the clinical evaluation of disease activity analogous to bone edema. Tenosynovitis includes fluid in the tendon sheath, increased thickness or contrast enhancement of the tendon sheath synovium, or a combination thereof. Normal fluid in the tendon sheaths has a thickness of less than 1mm. As with the joint synovium, contrast enhancement of the tendon sheath synovium is considered a specific sign of tenosynovitis. We scored this sign similarly with articular synovitis (0–3).

Results: Two male and 8 female patients with a median age of 49 years were included. Patients had inadequate response to a median of 3 (range 1–6) DMARDs and 1.5 (1–5) biologicals. At baseline the median DAS28 was 4.8 (range 2.1–6.7) and the median CDAI 22 (12–40). Using Wilcoxan test a significant reduction of DAS28 ($p=0.007$), ESR ($p=0.005$) and CRP ($p=0.005$) was documented at week 4 and 12. CDAI reduction from 22 to 15.5 missed significance ($p=0.06$). 3 patients showed progressive erosions during the 12 weeks, all other had stable erosive manifestations. Synovitits, tenosynovitis, bone marrow edema and hyperemia all were reduced at week 12, but only synovitis reached significance ($p=0.042$). Six patients experienced a DAS28 remission with a score <2.8 at week 12. Two patients did not respond to treatment. No serious adverse events occurred.

Conclusion: Even in this negative selection treatment with TCZ significantly reduced disease activity. The fast response is one of the leading characteristics of TCZ, this could be demonstrated with a significant reduction of ESR, CRP and DAS28 after only 1 infusion. As these clinical measurements are known to be overestimated when using TCZ we added very early MRI for the evaluation. Using this sensitive method the effectiveness of TCZ was confirmed, but after 12 weeks at the earliest with a significant improvement of synovitis.

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Reduction In MRI Inflammation During Adalimumab Therapy In Patients with Psoriatic Arthritis – Implementation of the OMERACT PsAMRIS Scoring Method In a Follow-up Study.

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Background/Purpose: To evaluate the changes in magnetic resonance imaging (MRI) parameters of disease activity and structural damage in patients with psoriatic arthritis (PsA) during 48 weeks of adalimumab therapy.

Methods: Patients were included if they had 1) PsA according to Moll and Wright's criteria; 2) ≥3 tender and ≥3 swollen joints; 3) ≥1 swollen finger joint and/or ≥1 dactylitis and 4) clinical indication for TNFα inhibitor. MRI (0.6 T) was performed at weeks 0 (at initiation of adalimumab 40 mg sc eow), 6, 24 and 48, of the 2nd-5th fingers (metacarpophalangeal, and proximal and distal interphalangeal joints) of the hand with the highest clinical disease activity at inclusion. MRIs were scored according to PsAMRIS (1) by a trained reader. MRI total inflammation score was calculated by adding the components of the synovitis, flexor tenosynovitis, periarticular inflammation and bone marrow oedema. Clinically, patients were evaluated according to PsARC-response at week 24. Responders continued treatment with adalimumab, whereas non-responders changed therapy at the discretion of the treating rheumatologist.

Results: Patient (n=41) characteristics were: 18 (44%) males, median (interquartile range) age 49 (39–60) years, disease duration 9 (5–15) years, skin disease duration 23 (12–35) years, CRP 7 (4–14) mg/L, SJC 8 (5–16), TJC 21 (11–39), VAS pain 62 (49–73) mm, VAS global 65 (49–77) mm, VAS physician 50 (39–64) mm, HAQ-score 0.9 (0.4–1.4), MASES 13-enthesitis score 1 (0–2), dactylitis count 0 (0–2) and body surface area affected by psoriasis (BSA) 2 (1–5) %. SJC and TJC decreased significantly from baseline to week 6, 24 and 48 for clinical responders, whereas no decreases were seen in non-responders.

The table shows the PsAMRIS scores during 48 weeks of treatment with adalimumab.

Time (week)	0	6	24	48
All patients/PsARC-responders (n)	41/-	37/29	34/30	33/29
Synovitis (0–36)	9(6–14)	9(5–12)*; [10(5–12)]	8(4–12); [8(4–12)]	6(3–9)*; [7(4–9)]*
Flexor tenosynovitis (0–36)	2(0–6)	1(0–5)**; [2(0–5]**	1(0–4)*; [1(0–4)]*	1(0–3)**; [1(0–3]**
Periarticular inflammation (0–24)	0(0–1)	0(0–1); [0(0–2)]	0(0–1); [0(0–2)]	0(0–1); [0(0–1)]
Bone oedema (0–72)	0(0–2)	0 (0–2); [0(0–2)]	0(0–1); [0(0–0)]*	0(0–1); [0(0–1)]
Bone erosion (0–240)	2(1–6)	2(1–4); [3(1–4)]	2(0–6); [3(0–6)]	3(0–5); [3(0–5)]
Bone proliferation (0–12)	0(0–1)	0(0–1); [0(0–2)]	0(0–2); [0(0–2)]	0(0–1); [0(0–1)]
Total MRI inflammation (0–168)	16(8–22)	14(9–19)*; [15(9–19)]*	13(7–19)*; [13(8–18]	9(6–14)**; [9(7–14)]**

Values are medians (IQR). *p<0.05, **p<0.005, Wilcoxon signed-rank test. Values are for all examined patients at weeks 0, 6, 24 and 48 weeks, with values for PsARC responders given in squared brackets.

The baseline MRI very frequently showed synovitis (40 patient (98%)), whereas bone oedema was less common (18 patients (44%)). After 6 weeks, there was a significant decrease in synovitis, flexor tenosynovitis and total MRI inflammation scores. Flexor tenosynovitisand total MRI inflammation significantly had improved in the PsARC-responders (table). After 48 weeks both the pooled patient group and the responder group (but not non-responders) showed significantly decreased synovitis, flexor tenosynovitis and total MRI inflammation scores. Scores of periarticular inflammation, bone proliferation and bone erosion did not change significantly.

Conclusion: Treatment with adalimumab in patients with active PsA reduces MRI signs of inflammation as assessed by the PsAMRIS method.

Reference

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Diffusion Tensor and Perfusion Magnetic Resonance Imaging Delineates Microstructural Changes of Inflammation and Differentiates Between Tuberculosis and Chronic Inflammatory Arthritis.

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Background/Purpose: Conventional MRI does not differentiate between infective and non-infective chronic inflammatory arthritis. Synovial histology and culture are the only means to differentiate between these two. Chronic inflammation is characterized by cellular infiltration and increased vascularity. We hypothesize that Diffusion tensor imaging (DTI), a non-contrast MRI technique, delineates synovial inflammation. DTI derived metrics [fractional anisotropy (FA), mean diffusivity (MD), linear anisotropy (CL), planar anisotropy (CP) and cylindrical isotropy (CS)] and perfusion parameters [blood flow (BF) and blood volume (BV)] assess cellular infiltration and vascularity, respectively, in inflamed synovium. Also, increased inflammation during infection should lead to greater variation in DTI and perfusion parameters that should differentiate between the two conditions.

Methods: Patients with knee arthritis (>3 months duration) underwent conventional and DTI (3T scanner) followed by arthroscopic biopsy. Synovial tissue was subjected to histopathology, immunohistochemistry (IHC), and culture and multiplex PCR for Mycobacterium tuberculosis. In-house developed software was used to process DTI and perfusion data. Pearson correlation coefficient was used to evaluate correlation between DTI and perfusion and IHC parameters. Independent samples t-test was used to compare parameters between tubercular and non-tubercular patients. Discriminant analysis was done to ascertain imaging parameters discriminant of tuberculosis.

Results: There were 41 patients (mean age 38 years, [range 18–75], 27 male). Ten patients had tuberculosis and rest had; chronic monoarthritis (n=11), undifferentiated spondyloarthropathy (n=12), osteoarthritis (n=3), reactive (n=2) and rheumatoid, juvenile idiopathic and lepra reaction one each. There was significant correlation between the DTI, perfusion and IHC parameters (Table-1). DTI, perfusion and IHC parameters were significantly different in the tubercular as compared to the non-tubercular group (Table-2). FA and blood volume were 100% sensitive and specific in discriminating and predicting tuberculosis.

Table 1. Correlation coefficient (R) between DTI, Perfusion and IHC markers (n=41)

Parameter	CD3	CD4	CD8	CD68	Total cells	CD34	CD54	TNFα	IL-1β
FA	0.59*	0.64*	0.46@	0.63*	0.77*	0.84*	0.45@	0.69*	0.67*
MD	−0.41@	−0.39#	−0.28	−0.32#	−0.46@	−0.49@	−0.27	−0.3	−0.48#
CL	0.44@	0.53*	0.32#	0.36#	0.49@	0.62*	0.18	0.38#	0.54*
CP	0.36#	0.24	0.33#	0.21	0.26	0.17	0.05	0.33#	0.13
CS	−0.3	−0.44@	−0.18	−0.28	−0.42@	−0.51@	−0.56*	−0.41@	−0.42@
Blood flow	0.39@	0.42@	0.23	0.49@	0.58*	0.73*	0.4@	0.58*	0.55*
Blood volume	0.59*	0.66*	0.53*	0.53*	0.75*	0.90*	0.50@	0.64*	0.77*

*p<0.001, @p<0.01, #p<0.05

Table 2. Comparison of DTI, perfusion and IHC markers between tubercular and non-tubercular groups

Parameters	Tuberculosis (n=10) Mean ± SD	Non-tubercular (n=31) Mean ± SD	P value
DTI			
FA	0.27 ± 0.01	0.21 ± 0.00	<0.001
MD	1.01 ± 0.04	1.6 ± 0.54	0.002
CL	0.08 ± 0.02	0.05 ± 0.02	<0.001
CP	0.16 ± 0.04	0.14 ± 0.05	0.27
CS	0.69 ± 0.05	0.76 ± 0.03	<0.001
Perfusion			
BV	16.24 ± 1.99	3.23 ± 2.22	<0.001
BF	161.26 ± 16.9	99.22 ± 36.55	<0.001
IHC			
CD3	193.40 ± 61.99	112.87 ± 39.56	<0.001
CD4	97.80 ± 33.80	48.03 ± 18.40	<0.001
CD8	72.80 ± 17.51	42.90 ± 25.29	0.001
CD68	253.90 ± 64.10	157.94 ± 70.72	<0.001
CD34	194.60 ± 51.73	41.42 ± 18.35	<0.001
CD54	90.30 ± 62.34	33.71 ± 13.63	<0.001
TNFα	33.10 ± 7.90	18.77 ± 7.94	<0.001
IL-1β	55.90 ± 14.50	21.30 ± 11.93	<0.001

Conclusion: DTI and perfusion scan clearly differentiates between the tubercular and non-tubercular arthritis.

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Erosions on MRI of the Sacroiliac Joints in Patients with Ankylosing Spondylitis: Can They Be Reliably Detected? Ulrich Weber[1], Susanne Juhl Pedersen[2], Mikkel Ostergaard[3], Kaspar Rufibach[4], Robert GW Lambert[1] and Walter P. Maksymowych[1]. [1]University of Alberta, Edmonton, AB, [2]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [3]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [4]University of Zurich, Zurich, Switzerland

Background/Purpose: Erosions of the sacroiliac joints (SIJ) on pelvic radiographs of patients with ankylosing spondylitis (AS) are the most important feature of the modified New York classification criteria (mNYc). Assessment of SIJ erosions by computed tomography (CT) in clinical practice is limited given recent reports indicating an association of malignancy with pelvic CT. Recent studies have shown that erosions can be detected also on magnetic resonance imaging (MRI) of the SIJ early in the disease course before they can be seen on radiography [1]. Erosions may extend across major portions of the iliac and sacral subchondral bone (extended erosion (EE)). We have also recently observed a novel appearance of erosions on MRI where tissue metaplasia re-fills the excavated erosion and have termed this phenomenon "backfilling" (BP). However, data on the reliability of detection of erosions and these related features on MRI are scarce.

Objectives: To assess the reproducibility of erosions, EE and BP in the SIJ detected by MRI in 30 AS patients and in 30 controls using the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI standardized methodology.

Methods: 30 patients with AS meeting the mNYc (15 patients each with symptom duration of ≤5 and ≥5/≤10 years) and 30 controls (15 healthy volunteers and 15 patients with mechanical back pain (MBP)) underwent an MRI with STIR and T1 spin echo sequences of the SIJ. A standardized erosion definition was applied and lesion reference images served to calibrate the 4 readers. Erosions in all 8 quadrants on each slice of the SIJ, EE and BP were scored on an internet-based reading program of the SPARCC method. The frequency of erosions was analyzed descriptively by concordant observations of the 6 possible reader pairs. Kappa statistics (erosions as binary variable on a patient level) and intraclass correlation coefficients (ICC) (erosion sum scores per patient) for all readers jointly were used to assess the reproducibility of erosions.

Results: Erosions on SIJ MRI were detected in all 30 AS patients by ≥2 readers, whereas 5 MBP patients and 1 healthy control also showed lesions meeting the definition of erosion. EE and BP were recorded in 22 (73.3%) and 19 (63.3%) AS patients, respectively. The median frequency of erosions recorded by 4 readers jointly in 30 AS patients was 4.3 in the ilium and 1.1 in the sacrum ($p < 0.0001$). The kappa value for all 60 subjects showed an agreement for erosions between the 4 readers of 0.70 (95% CI 0.56–0.81), for EE of 0.73 (CI 0.59–0.85) and for BP of 0.63 (CI 0.47–0.77). For all 4 observers, the ICC values for the erosion score were 0.76, for EE 0.72, and for BP 0.55, respectively. For comparison, the kappa and ICC values for bone marrow edema (BME) were 0.61 and 0.89, respectively.

Conclusion: Erosions were detected significantly more frequently in the iliac portion of the SIJ. The agreement between 4 readers regarding erosions on SIJ MRI was substantial and comparable to BME.

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The Reliability of a New Juvenile Arthritis MRI Scoring System for the Knee; JAMRIS. Robert Hemke[1], Marion A.J. Van Rossum[2], Mira van Veenendaal[2], J. Merlijn van den Berg[2], Koert M. Dolman[3], Taco W. Kuijpers[2] and Mario Maas[4]. [1]Academic Medical Center (AMC)/Emma Children's Hospital, Amsterdam, Netherlands, [2]Emma Children's Hospital/ Academic Medical Center (AMC), Amsterdam, Netherlands, [3]St. Lucas Andreas Hospital and Reade Institute, Amsterdam, Netherlands, [4]Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: MRI provides unequalled visualization of all the anatomical structures involved in Juvenile Idiopathic Arthritis (JIA). The increasing evidence that early therapeutic intervention improves long-term outcome and the development of highly effective treatments highlight the need for reliable and accurate measures in the quantification of disease activity. Therefore, the aim of our study is to assess the reliability of a new composed Juvenile Arthritis MRI Scoring (JAMRIS) system for evaluating JIA activity of the knee.

Methods: A collaborative program between two tertiary pediatric rheumatology centers in the Netherlands was established, incorporating rheumatologists and radiologists with experiences in the research field of imaging in JIA. After an extensive search of all relevant literature a MRI grading score was developed. After a training session, the initial scoring system was re-evaluated. The scoring development exercise was focused to refine the MRI features, to remove redundant items, and to develop a more reader-friendly assessment score. After tailoring the initial grading score, four MRI features were included in the Juvenile Arthritis MRI Scoring system.

The JAMRIS method assesses synovial hypertrophy at six anatomical regions, scaling from 0–2. Bone marrow edema, cartilage lesions and bone erosions are scored at eight sites of the joint, scaling from 0–3.

Results: A MRI dataset from 40 JIA patients (mean age 12.8 years [SD 2.3]) was scored by two experienced readers using the JAMRIS method. The interreader agreement (ICC) for the different JAMRIS key features ranged from 0.85 for bone erosions up to 0.92 for synovial hypertrophy scores. The reliability for bone marrow edema was 0.91 and for cartilage lesions 0.86.

Conclusion: Our newly developed scoring system for the evaluation of inflammatory and destructive changes in knees of JIA patients (JAMRIS) shows good reliability for the evaluated variables. The score's sensitivity to change and its correlation with clinical assessment is topic of ongoing research.

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Non-Invasive MRI by Omitting Intravenous Contrast Injection; Does It Change the Radiologic Assessment of Knee Joint Pathologies in JIA? Robert Hemke[1], Taco W. Kuijpers[2], Mira van Veenendaal[2], J. Merlijn van den Berg[2], Koert M. Dolman[3], Marion A. J. van Rossum[2] and Mario Maas[4]. [1]Academic Medical Center (AMC)/Emma Children's Hospital, Amsterdam, Netherlands, [2]Emma Children's Hospital/Academic Medical Center (AMC), Amsterdam, Netherlands, [3]St. Lucas Andreas Hospital and Reade Institute, Amsterdam, Netherlands, [4]Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: MRI is the most preferred imaging modality in detecting joint pathologies in Juvenile Idiopathic Arthritis (JIA), despite practical limitations such as the risk of allergic reactions when intravenous (IV) contrast is administered, and the evaluation of one joint because of time constraints. IV Gadolinium (Gd) contrast use prolongs examination time, increases invasiveness and patient discomfort, and thereby reduces feasibility of MRI in JIA patients. Therefore, our objective is to evaluate if JIA joint pathologies can be reliably assessed by MRI without Gd injection compared with Gd-enhanced MRI as the reference.

Methods: MRI data-sets (open-bore, 1.0T) of 46 JIA patients (mean age 12 years [range 4–18]) were prospectively scored twice by two experienced readers for the presence of knee joint pathologies. MRI features were evaluated using a literature-based assessment score, comprising synovial hypertrophy, bone marrow edema (BME), cartilage lesions and bone erosions. The first reading included unenhanced images (−Gd), whereas complete image sets were available for the second reading (+Gd).

Results: Using +Gd MRI as the reference, sensitivity and specificity of -Gd MRI in the detection of BME (89%, 99%), cartilage lesions (73%, 100%) and erosions (100%, 99%) were high. Good -Gd and +Gd interreader agreements (ICC) were found regarding BME (0.87, 0.88), cartilage lesion (1.00, 0.97) and bone erosion scores (0.90, 0.93).

Regarding the assessment of synovial hypertrophy the specificity of −Gd MRI was 98%, though the sensitivity was 60%. ICC for +Gd MRI was 0.88, however omitting post-Gd acquisitions increased interreader variation (ICC=0.76).

Conclusion: Omitting intravenous contrast injection is unimportant in the assessment of presence of bone marrow edema, cartilage lesions or bone erosions in knees of JIA patients, but decreases the reliability of the evaluation of synovial hypertrophy.

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Patients with Juvenile Idiopathic Arthritis and Rheumatoid Arthritis in "Physician Determined Clinical Remission" Have Evidence of Persistent Inflammation Revealed by 3T MRI. Amanda G. Brown[1], Raphael Hirsch[2], Tal Laor[3], Kimberly A. Francis[4], Michael J. Hannon[5] and C. Kent Kwoh[6]. [1]Children's Hospital Pittsburgh of UPMC, Pittsburgh, PA, [2]Children's Hospital Pittsburgh, Pittsburgh, PA, [3]Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH, [4]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [5]University of Pittsburgh School of Medicine, Pittsburgh, PA, [6]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, PA

Background/Purpose: It has been reported that up to 90% of adults with RA who are in clinical remission have persistent synovitis and/or bone marrow lesion (BMLs) on MRI. Similar MRI abnormalities have been observed in unaffected joints in JIA patients with active oligoarthritis, but MRI findings in JIA patients in clinical remission have not been well described. In order to determine whether JIA patients in clinical remission have evidence of subclinical inflammation, we utilized 3T MRI with contrast enhancement to examine individuals with a history of JIA involving the hand and/or wrist who were in clinical remission. We compared this JIA cohort with a cohort of adult RA patients.

Methods: Eleven JIA patients and ten RA patients with hand and/or wrist involvement were included due to physician determined clinical remission. Physician determined clinical remission was defined as the absence of signs or symptoms of active arthritis, and no medication changes for at least 6 months. For the JIA cohort there could be no sign or symptom of systemic disease activity. A study rheumatologist performed an evaluation of hands and wrists for tenderness, swelling, and limitation of motion. Study participants self-reported tender joint counts. The participants under went MRI with contrast enhancement of one currently asymptomatic hand and wrist that had a history of arthritis symptoms and exam findings. A single musculoskeletal radiologist, blinded to the clinical data, scored the MRIs for the presence of synovitis, tenosynovitis, and/or BMLs. Synovitis and tenosynovitis in the hand and wrist were recorded as none, mild, moderate, or severe. BMLs were recorded as none, focal or diffuse. Wilcoxon-Mann-Whitney test was used to compare the disease activity scores, and Fisher's exact test to compare the MRI scores between cohorts.

Results: Sixty-three percent of the JIA cohort and 70% of the RA cohort had MRI findings of synovitis, BMLs, and/or tenosynovitis. Eighty-two percent of the JIA cohort met the recent JIA remission criteria, while 56% of RA patient met the revised ACR remission criteria. All pediatric patients with MRI abnormalities had normal physician tender and swollen joint counts. Patients' self-report of painful joint counts did not predict MRI abnormalities. Three of the JIA patients were in clinical remission without any therapy. The RA cohort trend was higher pain scores and more affected joints on physician joint count. The JIA cohort trended toward lower CHAQ compared to adult HAQ scores. The DAS28 tended to be higher in the RA cohort compared to the JIA cohort. In the RA cohort, there was a trend towards more synovitis and more BMLs when compared to the JIA cohort.

Conclusion: In this study, over half of the patients with a history of JIA in clinical remission had MRI evidence of persistent inflammation, as defined by the presence of synovitis, tenosynovitis, or BMLs. This suggests that, as in RA, a substantial proportion of patients with JIA who are in clinical remission may have persistent subclinical disease activity. Additional longitudinal studies are needed to determine whether this subclinical inflammation results in progression of joint destruction and/or impacts long-term outcomes in JIA.

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Identification of Magnetic Resonance Imaging Morphologic Features Associated with Different Knee Pain Patterns. C. Kent Kwoh[1], Ali Guermazi[2], Michael J. Hannon[3], Robert M. Boudreau[4], Stephanie M. Green[4], John M. Jakicic[5] and Frank Roemer[6]. [1]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, PA, [2]Boston Medical Center, Boston, MA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA, [5]University of Pittsburgh, PA, [6]Boston University, Boston, MA

Background/Purpose: Knee pain (KP) is the main reason for patients to seek care for knee osteoarthritis, but the cause for KP is unclear. The Knee Pain Map is a validated measure to assess different KP patterns in regard to specific joint locations. The aim of the study was to examine the association of joint morphologic features on MRI with KP in specific locations, regions or global pain patterns.

Methods: The Joints on Glucosamine (JOG) study includes 177 subjects aged 35–65 (95 men and 82 women) with chronic, frequent KP in at least one knee. 3T magnetic resonance imaging (MRI) of both knees was performed at baseline on a Siemens Trio using the same pulse sequence protocol as in the Osteoarthritis Initiative (OAI). All MRI features were scored semi-quantitatively using a modified WORMS system. All MR features were divided into two categories: present (score $\geq$1) and absent (score=0). Knees were characterized into localized, regional or global pain patterns using the Knee Pain Map, an interviewer-administered assessment of location-specific KP patterns based on the presence of pain in the past 30 days. Associations of MRI abnormalities in any subregion of the medial and lateral compartments with pain localized in that joint line and with regional or global pain patterns in each respective compartment were evaluated. Multinomial logistic regression was used to compare the KP patterns, controlling for clustering by person.

Results: A total of 46 knees had no KP, 83 had localized medial joint line KP, 36 had medial regional KP, 68 had localized lateral joint line KP, 31 had lateral regional KP, and 27 had global KP. The medial and lateral joint lines were the most common localized KP patterns. The association of KP patterns with a separate model for each individual MRI abnormality is shown in the table below. Compared to those with no KP in the past 30 days, individuals with local medial joint line KP, medial regional KP or global KP were more likely to have MRI abnormalities such as cartilage damage, bone marrow lesions, or meniscal extrusion. Those with the medial regional KP were also more likely to have meniscal damage (Table 1).

Table 1.

	Local Medial Joint Line Pain (n = 83)			Regional Medial Pain (n = 36)			Global Pain (n = 27)		
Compartment-specific MRI features*	RRR	[95%CI]		RRR	[95% CI]		RRR	[95% CI]	
Cartilage damage	2.52	1.07	5.92	3.97	1.28	12.35	4.65	1.37	15.81
Bone marrow lesions	9.89	2.04	47.99	12.10	2.27	64.60	12.44	2.24	69.05
Synovitis/effusion**	0.99	0.46	2.14	1.62	0.61	4.28	0.94	0.31	2.79
Meniscal damage	1.46	0.56	3.77	3.72	1.10	12.60	2.65	0.77	9.11
Meniscal extrusion	1.08	0.47	2.49	8.77	2.18	35.23	3.46	1.00	12.05

* adjusted for age, sex and BMI and compared to knees with pain in the past 30 days;
RRR=relative risk ratio, CI=confidence interval
** Synovitis/effusion was read for the whole knee

Conclusion: The presence of MRI-detected pathology was associated with medial localized joint line, medial regional and global pain patterns. These findings may help to identify more homogenous populations for targeted knee OA interventions.

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Progression of the MRI-Detected Osteoarthritis Features in Radiographic 'End-Stage' Knee Osteoarthritis (Kellgren-Lawrence grade 4) - the Multicenter Osteoarthritis Study. Ali Guermazi[1], Daichi Hayashi[1], Frank Roemer[1], David T. Felson[1], Ke Wang[1], John Lynch[2], Shreyasee Amin[3], James Torner[4], C.E. Lewis[5] and Michael C. Nevitt[6]. [1]Boston University, Boston, MA, [2]UCSF, San Francisco, CA, [3]Mayo Clinic, Rochester, MN, [4]University of Iowa, Iowa City, Iowa City, IA, [5]University of Alabama, Birmingham City, AL, [6]University of California-San Francisco, San Francisco, CA

Background/Purpose: Kellgren-Lawrence grade 4 (KL4) knees are considered radiographic 'end-stage' knee OA (bone-on-bone appearance) which theoretically does not progress further. We evaluated what proportion of KL 4 knees at baseline demonstrate further progression longitudinally in regard to features only detectable by MRI, i.e. cartilage, bone marrow lesion (BML), meniscus, Hoffa-synovitis, and effusion-synovitis.

Methods: We studied subjects from the Multicenter Osteoarthritis Study who had KL4 knees at baseline and had baseline and 30-month MRI. Cartilage, BML, meniscus, Hoffa-synovitis, and effusion-synovitis were semiquantitatively scored using the WORMS system in the 5 subregions of the medial and lateral tibiofemoral (TF) compartments of the knee: central and posterior femoral, anterior, central and posterior tibial subregions. WORMS cartilage grading ranges from 0 – 6 where 6 represents full-thickness cartilage loss in >75% of the subregion. Analysis was performed for the compartment showing bone-on-bone appearance ("index") on radiograph and also for the other TF compartment of the same knee. Hoffa-synovitis and effusion-synovitis were assessed for the whole knee. Changes in

scores at follow-up were noted for each feature. For cartilage and BML, within-grade changes were also recorded.

Results: 63 subjects (67 knees) were included (51% women, 84% White, mean age 65.1±8.6 years, mean BMI 30.2±5.2 kg/m^2). At baseline, in the index TF compartment, all knees showed severe cartilage loss (max WORMS score from 5 subregions was 5 in 1 knee and 6 in 66 knees), 54 knees (80%) showed moderate to large BMLs (max WORMS score 2 or 3), and 62 knees (94%) had severe meniscal lesions (i.e. displaced tear or maceration). In the other TF compartment, 12 knees (18%) had severe cartilage loss, but 47 (71%) had no BML and 57 (97%) had no meniscal damage. 39 knees (58%) had moderate to severe effusion-synovitis, 56 knees (86%) had mild or moderate Hoffa-synovitis. Longitudinally, 22 index compartments (35%) showed an increase in the sum of cartilage scores from all subregions, and 2 (3%) showed increase in the maximum cartilage score. In the other TF compartment, 22% showed an increase in the sum score for cartilage damage, while 15% showed increase in maximum score. For BMLs in the index TF compartment, 19 knees (31%) showed an increase in maximum score and 11 (18%) showed a decrease. Fluctuation of BMLs was also seen in the other TF compartment, but to a lesser extent. Meniscal status mostly remained the same in the index (98%) and other TF (95%) compartments. Effusion-synovitis worsened in 15 knees (27%) and improved in 2 knees (4%). Hoffa-synovitis worsened in 6 knees (11%) and improved in 2 knees (4%).

Conclusion: In KL4 knees, MRI detected progression of cartilage loss, and fluctuation of effusion-synovitis, Hoffa-synovitis and BMLs was observed over a 30-month period. Meniscal damage remained stable. Our findings support the idea that disease progression still occurs in KL4 knees. KL4 knees can be a potential target for assessing therapeutic interventions and should not necessarily be excluded from clinical trials.

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The Association Between Bone Marrow Lesion Detected by Magnetic Resonance Imaging and Knee Pain in the Community Residents in Korea. Inje Kim[1], Yeong Wook Song[2], Hyun Ah Kim[3] and Ali Guermazi[4]. [1]Hallym University Kangdong Sacred Heart hospital, Seoul, South Korea, [2]Seoul National University College of Medicine, Seoul, South Korea, [3]Hallym University Sacred Heart Hospital, Kyunggi, South Korea, [4]Boston Medical Center, Boston, MA

Background/Purpose: The presence of bone marrow lesion (BML) detected by magnetic resonance imaging (MRI) has been associated with knee pain among patients with osteoarthritis (OA). The purpose of this study was to investigate the prevalence of BML and its association with knee pain in community residents in Korea.

Methods: Participants (n=346) were randomly chosen regardless of knee OA or knee pain from the population-based Hallym Aging Study. Demographic data were obtained by questionnaire including knee pain and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index. Radiographic evaluations consisted of weight-bearing knee anteroposterior radiographs and 1.5-tesla MRI scans. We assessed the BML in the dominant knee or in the more symptomatic knee, and scored BML using Whole-Organ MRI score in the medial femorotibial, lateral femorotibial and patellofemoral compartment. The association between BML and knee pain was examined by logistic regression analysis after adjustment of age, sex, body mass index and radiographic knee OA.

Results: Radiographic knee OA in either knee was present in 33.4% of subjects. The prevalence of BML and large BML in any compartment of the knee were 80.3% and 40.4%, respectively. BML was more common in women and was most common in the patellofemoral compartment. The prevalence of BML in any compartment was 98.3% and 70.6% in subjects with and without knee OA, respectively. BML in any compartment and in medial compartment were found in 46.2% and 57.6% of subjects with knee pain, and in 53.8% and 42.4% of subjects without knee pain, respectively. After multivariate analysis, BML was found to be significantly associated with radiographic knee OA (OR 18.58, 95% CI [4.31–80.09]). After adjusting for age, sex and radiographic knee OA, knee pain was significantly associated with BML in medial compartment (OR 2.18, 95% CI [1.29–3.66]).

Conclusion: Incidental BML on MRI of the knee are very common in the middle- aged and elderly community residents in Korea. BML in the medial compartment of knee is related with knee pain.

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Correlation of Bony Enlargements with Radiological Findings in Hand Osteoarthritis. Niveditha Mohan[1], Michael J. Hannon[2] and C. Kent Kwoh[3]. [1]Univ of Pittsburgh Arth Inst, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, PA

Background/Purpose: A strong association between the presence of bony enlargement (BE) and x-ray evidence of hand osteoarthritis (HOA) has been reported. We assessed the validity of this relationship and attempted to delineate the association between BE on clinical exam and different grades of osteophytes (OST) and joint space narrowing (JSN).

Methods: The study utilized data from the Osteoarthritis Initiative (OAI), a community based cohort aged 49–75 years with symptomatic knee OA or with risk factors for developing knee OA. The dominant hand films of 400 women were read using the ICRS/OARSI Atlas. The 1st CMC, 2nd–5th DIP and PIP joints were read for JSN and OST on a 0–3 scale. Only the presence of Heberden's nodes was assessed by trained OAI clinic staff at enrollment. The relationship between BE and JSN and OST was evaluated using the four DIP joints in a logistic regression model adjusted for age, race, BMI, smoking history, and family history of arthritis. The model was controlled for clustering by person.

Results: The sample was 84% white with a mean age of 61.6 (SD 9.3). 33% were overweight and 39.5% obese. 47% were current or former smokers. 26% were premenopausal with 26% reporting a family history of arthritis.

A total of 1586 DIP joints were read, 589 (37.1%) with BE on exam. Of these joints, 285 (48.4%) had OST, 142, 80 and 63 of which were grade 1, 2, and 3 OST, respectively. Of the 997 without BE, only 93 (9.7%) had x-ray evidence of OST and 80, 10 and only 3 were grade 1, 2 and 3 respectively. 427(72.5%) had JSN, 258, 87, 82 of which were grade 1, 2 and 3 respectively. Of the 997 without BE, only 303 (30.4%) had x-ray evidence of JSN and 296, 37 and 4 were grade 1, 2 and 3 JSN respectively.

Odds ratios were calculated for the association of BE with JSN and OST (Table 1). When JSN and OST were combined, of the 589 joints with BE, 445 (75.6%) had an x-ray finding of some problem while only 352 (35.3%) of those with no BE had such a finding. The presence of any x-ray findings was associated with a large increase in risk of BE (adjusted OR 4.9, 95% CI of 3.6–6.7).

Table 1. Adjusted OR for BE and presence of JSN and OST

BE	Odds ratio	95% CI
Grade 1 JSN	2.29	1.62–3.24
Grade 2 JSN	3.75	2.07–6.81
Grade 3 JSN	10.83	3.03–38.74
Grade 1 OST	3.17	2.16–4.66
Grade 2 OST	9.04	4.38–18.65
Grade 3 OST	9.71	1.62–58.29
Age	1.46	1.02–2.07
Race (Caucasian)	1.19	0.76–1.89
BMI overweight	0.67	0.44–1.03
BMI obese	0.78	0.52–1.17
Family history	1.81	1.21–2.70
Smoking history	0.98	0.71–1.37

Conclusion: The presence of BE strongly associated with x-ray evidence of HOA, and the strength of the association increases as the grade of OST and JSN increases. The interaction between OST and JSN was not significant. This association is validated at the earliest radiological changes as well as when OST and JSN are adjusted for OA risk factors. However, having a BE clinically does not always indicate having x-ray findings. This suggests that x-ray changes may be preceded by soft tissue changes that may be clinically consistent with a BE. Further prospective studies may provide us with pathophysiological insights into characteristics that predispose to HOA and may provide an ideal therapeutic window for intervention, prior to onset of irreversible x-ray changes.

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Correlation of Hand Pain and Radiological Findings in Hand Osteoarthritis. Niveditha Mohan[1], Michael J. Hannon[2] and C. Kent Kwoh[3]. [1]Univ of Pittsburgh Arth Inst, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, PA

Background/Purpose: Symptomatic hand osteoarthritis (HOA) affects 20% of patients above the age of 55 years. We assessed the association between hand pain as reported on a homunculus by patients with the presence of HOA based on x-ray findings.

Methods: The study utilized data from the Osteoarthritis Initiative (a community based cohort aged 49–75 years with symptomatic knee OA or with risk factors for developing knee OA). The dominant hand films of 400 women were read using the ICRS/OARSI Atlas. The 1st CMC, 2nd–5th DIP and PIP joints were read for Joint Space Narrowing (JSN) and Osteophytes (OST) on a scale of 0–3 and the presence of central erosions (CE) and lateral deviation (LD>15 degrees). Hand pain was self-reported by participants using a whole body homunculus as part of a general pain assessment (individual hand joints were not delineated). The relationship between hand pain and radiological findings was evaluated using logistic regression adjusted for age, race, BMI, smoking history, and family history of arthritis.

Results: The sample was 84% white with a mean age of 61.6 (SD9.3). In the sample 33% of the women were overweight and 39.5% obese. 47% were current or former smokers. 26% were premenopausal, with 26 % reporting a family history of arthritis. 140 of 400 patients (35%) reported hand pain within the past 30 days in any/either hand. Of these, 126 (31.5%) reported pain in the dominant hand (which was the hand x-ray that was read in our study). All measures of radiological HOA changes were highly intercorrelated (α=0.92). We formed a hand scale for measuring presence or absence of x-ray features of HOA (OST>1, JSN>1, CE or LD). X-ray features of HOA associated strongly with hand pain after adjusting for multiple factors (Table 1). The strength of the association increased with increase in number of joints involved (Table 2).

Table 1. Association of hand pain and x-ray changes adjusted for multiple factors (age, race, obesity, family history of OA and menopausal status)

Joint	Odds ratio	95% CI
1st CMC joint	1.89	1.15–3.10
2nd DIP joint	3.53	1.96–6.34
3rd DIP joint	3.14	1.69–5.84
4th DIP joint	3.45	1.86–6.42
5th DIP joint	4.11	2.26–7.49
2nd PIP joint	3.16	1.36–7.3
3rd PIP joint	2.93	1.38–6.21
4th PIP joint	2.04	0.96–4.30
5th PIP joint	2.23	1.06–4.71

Table 2. Association of hand pain with number of joints with x-ray changes of HOA adjusted for multiple factors (age, race, obesity, family history of OA and menopausal status)

Number of joints affected	Odds ratio	95% CI
1	2.08	1.07–4.05
2–3	3.11	1.54–6.29
4–6	3.90	1.65–9.19
7 or more	12.96	4.58–36.67

Conclusion: There is a strong association between overall hand pain and radiological evidence of HOA with increasing strength of the association with increase in the number of joints involved. The association of hand pain with x-ray changes at the CMC joint was not significantly stronger than that noted at other joints, which is in contrast to previously published data.

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Biomarkers of Bone Resorption and Bone Formation Are Specifically Linked to Catabolic and Anabolic Skeletal Changes Assessed by High Resolution CT Scans in Patients with Rheumatoid Arthritis. Sophie Aschenberg, Stephanie Finzel, Sarah Schmidt, Matthias Englbrecht, Juergen Rech and Georg Schett. University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Biomarkers of bone metabolism may emerge as powerful tool to monitor and predict structural joint damage in patients with rheumatoid arthritis (RA). Based on rather large patients cohort, several bone biomarkers, i.e. biomarkers for bone resorption have been successfully correlated to bone damage visualized in conventional radiographs. We hypothesized that improvement of sensitivity for detection of joint damage by high resolution micro computed tomography (μCT) may allow to better correlate bone biomarkers and structural bone damage and allow to proof this link even in small cohorts of RA patients.

Methods: Forty RA patients received a simultaneous μCT scan and analysis of serum markers of bone resorption (collagen type1 crosslaps: CTX1, tartrate resistant acid phosphatase 5b:TRAP5b) and formation (bone alkaline phosphatase: BAP, osteocalcin) at baseline and one year follow up. Erosions (erosion count and score) as well as osteophytes (osteophyte count and score) detected by μCT in the metacarpophalangeal (MCP) joints 2–4 of the dominantly affected hand were recorded. Bone biomarkers were related to the imaging data by partial correlations including age, sex, disease duration, DAS 28 and autoantibody status.

Results: All erosions and osteophytes detected at baseline were also visible at follow up with a slight progression in both numbers of erosions and of osteophytes (mean erosion count 5.112 ±7.120 at baseline versus 5.432 ±7.338 at follow up; mean osteophyte count 3.233 ±2.498 vs. 3.294 ±2.150respectively). Erosion score did not change (5.001 ±7.452 vs. 5.002 ±6.907) whereas osteophyte score did increase (4.094 ±3.815 vs. 4.343 ±3.412). The mean levels (±SD) of bone metabolism parameters were as follows: CTX1 at baseline 0.354 ng/ml ±0.205 and 0.351 ng/ml ±0.220 at follow-up, tartat-resistent acid phosphatase 5b (±Trap5b) at baseline 2.464 U/l ±1.294, at follow-up 2.537 U/l ±1.134, BAP at baseline 19.360 E/l ±6.299, follow-up 19.731 E/l ±5,945 and osteocalcin 12.577 ng/ml ±7.791 vs. 11.600 ng/ml ±6,209. Bone erosions in the MCP joints detected by μCT were strongly correlated with the serum level of the osteoclast-specific protease TRAP5b, a marker for bone resorption and osteoclast activity at both baseline and 1-year follow-up (baseline: p=0.030, r= 0.426, follow-up: p=0.004, r=0.493). In contrast, osteophytes detected by μCT were strongly correlated to bone alkaline phosphatase being a marker for bone formation (baseline: p=0.022, r= 0.447, follow-up: p=0.004, r=0.499).

Conclusion: These data suggest that specific biomarkers of bone formation and bone resorption can be correlated to different forms of structural joint damage, such as bone erosions and osteophytes formation in patients with RA. Detailed assessment of structural bone changed in the joints by μCT allows a validation of bone biomarkers in patients with RA. Moreover, these data are stimulating for small proof-of-concepts studies with novel therapeutics, by suggesting that biomarkers can be related to structural bone damage even in small patient cohorts.

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High Resolution Peripheral Quantitative Computed Tomography Bone Health Outcomes in the Metacarpal Head and Ultra-Ultra Distal Radius: A Precision Study Using Novel Scan Acquisition and Custom Semi-Automatic Contour and Evaluation Protocols. Lynne M. Feehan[1], Helen R. Buie[2], Eric C. Sayre[3], Steve K. Boyd[2], Heather A. McKay[4] and Linda C. Li[1]. [1]Arthritis Research Centre of Canada and University of British Columbia, Vancouver, BC, [2]University of Calgary, Calgary, AB, [3]Arthritis Research Centre of Canada, Vancouver, BC, [4]University of British Columbia, Vancouver, BC

Background/Purpose: High Resolution Peripheral Quantitative CT (HR-pQCT) imaging can assess early changes in microstructural bone health in the metacarpal head (MH) and ultra-ultra distal radius (DR); two sites commonly affected in early inflammatory arthritis. The purpose of this study was to determine the precision of HR-pQCT measures of density and microstructure in these two regions using novel scan acquisition and custom semi-automatic contour and evaluation protocols. The advantages of these new protocols include: 1) more stable and comfortable positioning of the upper body and arm for scanning; 2) more consistent positioning of hand and forearm alignment and joint angles; and 3) more efficient image analyses with low risk of operator bias.

Methods: The MH and DR in 12 healthy adults were scanned using HR-pQCT (XtremeCT, Scanco Medical AG), with 2 repeat scans at 3–7 days. Participants sat facing the scanner, leaning forward with their upper body and head supported by pillows. The dominant arm was scanned in a custom-made positioning device that held the wrist and metacarpal joints in a neutral joint angle. Scans were done using standard parameters (82 μm, 60kVp, 900 μA,100 ms). DR scans were 110 slices starting 1 mm proximal to the distal-medial end of the radius and MH scans were 220 slices starting 1 mm distal to the 3rd MH. A previously described semi-automated contouring and evaluation method for standard DR scans was adapted for the MH and ultra-ultra DR and applied to 110 slices at each site. Analyses included Total (ToD), Cortical (CtD) and Trabecular (TbD) bone density; Cortical thickness (CtTh) and Trabecular bone volume fraction (BV/TV), thickness (TbTh) and number (TbN). Reliability was assessed with an intraclass correlation coefficient (ICC) of up to 3 repeated measures. Coefficient of variation (CV) was calculated as the standard deviation of up to 3 repeated measurements divided by the mean.

Short-term precision errors (PE) were calculated as the root mean square coefficient of variation (RMSCV) of at least 2 paired images.

Results: *Participants:* 8 females and 4 males, mean age 44 (range 23–71) *Findings:* Our novel scan acquisition and custom semi-automated analyses protocols demonstrate excellent precision for repeated measurement of both microstructure and density in the ultra-ultra DR and 3rd MH sites; with ICCs ranging from 0.894 to.994, CVs ranging from 1 to 6% and PEs ranging from 1 to 7%. DR measures were slightly less precise than MH measures and measures of cortical thickness were less precise than other parameters, See Table 1.

Table. Summary of Results

	ICC (0.000–1.000)		Mean CV (%)		PE (RMSCV%)	
	DR	MH3	DR	MH3	DR	MH3
ToD (mgHA/cm3)	0.986	0.994	2.33	1.07	3.19	1.40
CtD (mg/HA/cm3)	0.962	0.963	3.48	1.98	3.75	2.82
TbD (mgHA/cm3)	0.993	0.993	1.31	1.03	1.61	1.44
CtTh (mm)	0.959	0.937	5.92	4.85	7.29	6.21
TbBV/TV (%)	0.990	0.981	1.66	1.23	2.04	1.60
TbTh (mm)	0.956	0.981	0.79	0.76	1.07	1.08
TbN (1/mm)	0.908	0.894	3.09	1.99	4.35	2.39

Conclusion: Our findings using novel HR-pQCT scan acquisition and analyses protocols for the evaluation of the ultra-ultra DR and MH are consistent with previously published estimates for precision of bone microstructure and density measures using microCT in the ultra-ultra DR in cadavers [Mueller et al,2009; DR region 1] and in the MH in humans using HR-pQCT [Fouque-Aubert et al, 2010; MH3 – 71 slices].

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Correlation of [18f]FDG PET Assessments with Disease Activity and Markers of Inflammation in Patients with Early Rheumatoid Arthritis Following Initiation of Antirheumatic Therapy. Anne M. Roivainen[1], Sannamari Hautaniemi[1], Timo Möttönen[1], Pirjo Nuutila[1], Vesa Oikonen[1], Riitta Parkkola[1], Luminita Pricop[2], Rudyard Ress[2], Nicholas Seneca[3], Marko Seppänen[1] and Timo Yli-Kerttula[1]. [1]Turku University Hospital, Turku, Finland, [2]Hoffmann-La Roche Inc, Nutley, NJ, [3]F. Hoffmann-La Roche Ltd., Switzerland

Background/Purpose: In patients with early rheumatoid arthritis (RA), the quantitative assessment of disease activity is still challenging. Identification of patients who are likely to respond to therapy early in a course of the disease should be the valuable key for the successful treatment. This observational, single center, imaging study evaluated the potential for advanced functional imaging techniques to monitor disease activity and the efficacy of treatment in patients with early, DMARD naïve RA.

Methods: Functional imaging focused on two important pathological features of RA, e.g. synovial metabolism was evaluated by [^{18}F]FDG PET/CT, and tissue perfusion and vascular permeability was evaluated by Gd-DOTA enhanced MRI. Seventeen RA patients with active disease, committed to initiate combination oral therapy with hydroxychloroquine 5 mg/kg per day, sulfasalazine 2.0 g per day, and methotrexate 7.5–15 mg per week plus low dose prednisolone, were enrolled in this study. Clinical disease activity was assessed by using disease activity scoring (DAS), numbers of tender and swelling joints (TJC, SJC) and measuring erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at screening, baseline and after 2, 4, 8, and 12 weeks of the therapy. Whole-body [^{18}F]FDG PET/CT and Gd-DOTA MRI of the most affected joints (wrist, knee or ankle) were performed at baseline and at weeks 2 and 4. Quantification of [^{18}F]FDG uptake was performed by the calculation of the standardized uptake value (SUV), fractional uptake rate (FUR) and glucose uptake rate (GU). Positive enhancement integral and maximum slope of increase at the site of inflamed synovium were determined from Gd-DOTA MRI. The mean PET and MRI imaging measures of all regions of interest per patient were calculated and used for statistical analysis. For PET analysis, only the DAS-28 joints with detectable [^{18}F]FDG uptake were taken into account.

Results: Based on [^{18}F]FDG PET/CT evaluation, 76% of patients had reduction in SUV_{max} from baseline to week 2 (mean±SD reduction 22±13%) and 81% from baseline to week 4 (mean±SD reduction 29±13%), respectively. The percentual decrease in SUV_{max}, FUR_{max} and GU_{max} from baseline to week 2 predicted clinical outcome as measured by DAS-28 (ESR) and DAS-28 (CRP) at week 12. In addition, changes in CRP and ESR levelswere positively associated with changes in all PET imaging measures-.Interestingly, the PET measures at baseline showed a positive correlation with CRP and TJC measured at week 12. Although the maximum slope of increase of MRI correlated with SUV_{mean}, FUR_{mean} and GU_{mean}, none of the MRI measures up to week 4 correlated with clinical outcome measures in this patient population.

Conclusion: Our results suggest that [^{18}F]FDG PET/CT but not Gd-DOTA MRI findings at weeks 2 and 4 predicted treatment efficacy and clinical outcome in patients with early active RA treated with combination hydroxychloroquine-sulfasalazine-methotrexate therapy. Future studies utilizing these methods may aide in predicting therapeutic response using novel drug treatments.

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Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography Is Useful for the Visualization of Reticulo-Endotheliao System and Prediction of Steroid-Resistant Cases in Adult Onset of Still's Disease. Tomohiro Kameda[1], Kentaro Susaki[1], Yuka Yamamoto[2], Miharu Izumikawa[3], Junichi Danjo[1], Shusaku Nakashima[1], Hiromi Shimada[1], Yohei Takeuchi[1], Yoshihiro Nishiyama[2], Hiroaki Dobashi[1] and Takuya Matsunaga[1]. [1]Kagawa University, Kagawa, Japan, [2]Kagawa University, Kita-gun, Japan, [3]Kagawa University, Kita-Gun, Japan

Background/Purpose: Adult onset of Still's disease (AOSD) is rare inflammatory disease characterized by the fever, rash, polyarthritis, sore throat, splenomegaly, lymphadenopathy, and serological examination as follows; increasing the level of CRP or ESR, hyperferritinemia and leukocytosis. Among these serological markers, serum ferritin level is associated with disease activity of AOSD relatively, but not be specific. Furthermore, though AOSD is considered as autoimmune disorder, autoantibody such as anti-nuclear antibodies or rheumatoid factor are commonly negative. Additionally, there are no reports to analyze the activity of AOSD visually. These are reason why the diagnosis of AOSD is difficult for us. On the other hand, fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has been an established in a field of oncology. Recently, the indications for ^{18}F-FDG PET are expanding rapidly. ^{18}F-FDG PET is used as diagnostic tool for inflammatory disorder such as infection or collagen vascular disease. As for treatment, AOSD patients are treated with corticosteroid mostly. However, we encounter the cases that are difficult to taper corticosteroid. These cases are needed salvage therapy such as immunosuppressant or biologics. If we can predict a refractory AOSD cases before treatment, the disease activity of AOSD can be controlled earlier. We investigate the features and the usefulness of ^{18}F-FDG PET in the diagnosis of AOSD. Additionally, we examine the predictive marker of refractory AOSD patients.

Methods: Eleven patients with the diagnosis of AOSD were treated in our hospital. Ten patients with AOSD had undergone ^{18}F-FDG PET, and the inflammatory lesion was evaluated by using the standardized uptake value (SUV). Laboratory data showing disease activity of AOSD such as CRP, WBC counts, LDH, sIL-2R and ferritin was measured in all patients. We examined the correlation of FDG accumulation and serological markers such as CRP, WBC, LDH, sIL-2R or ferritin. In addition, all patients were treated with only corticosteroid (responder group) or combined with immunosuppressant (non-responder group). We investigated the difference between two groups by using serological markers or FDG accumulation.

Results: ^{18}F-FDG PET revealed hepatosplenomegaly and FDG accumulation in the bone marrow, lymph node or spleen with AOSD patients. Two serological markers (sIL-2R, ferritin) showed close correlation with FDG accumulation. Additionally, SUV levels and the titer of ferritin were significantly high in non-responder group.

Conclusion: In AOSD patients, ^{18}F-FDG PET is useful for the diagnosis of AOSD with the serological markers equally. Furthermore, FDG accumulation can visually reveal a disease activity. Additionally, we suggest the possibility that high level of SUV and high titer of ferritin become predictive factor of refractory AOSD cases.

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PET-CT, Interleukins and Metalloproteinases to Assess Disease Activity in Takayasu Arteritis Patients. Anne E.D. Arraes[1], Alexandre W.S. Souza[1], Eduardo N.P. Lima[2] and Emilia I. Sato[1]. [1]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Hospital AC Camargo, São Paulo, Brazil

Background/Purpose: Takayau arteritis (TA) is a large vessel arteritis affecting mainly aorta and its branches. One of the great difficulties to treat TA patients is a lack of reliable criteria to assess disease activity. There is study showing that even in TA patients with no complaints and no abnormal acute phase reactants (classified as inactive disease), at surgical procedure it was found an inflammatory process at vessel wall, characterizing a histologically active disease. The aim of this study was to quantify 18F-fluorodeoxyglucose (FDG) uptake on PET-CT and measure serum levels of IL-2, IL-6, IL-8, IL-12, IL-18, TNF-alfa, MMP-3 and MMP-9 to assess disease activity in TA patients. We also evaluate correlation between FDG uptake on PET-CT and level of these serum biomarker.

Methods: Thirty-six TA patients (≥3 ACR criteria, 1990) followed at Vasculitis unitis of a University hospital and 36 age-and-sex matched controls participated in the study. The serum level of IL-2, IL-6, IL-8, IL-12 and TNF-alfa were measured by LUMINEX (HSCYTO-60SK-05 Milliplex, Millipore, USA). IL-18 (Med & Biol Lab CO, Japan), MMP-3 and MMP-9 (R&D System, EUA) were measured by ELISA assay. Maximum standard uptake value (SUVmax) in arterial walls was registered by PET-CT (Gemini, Phylips, EUA). The TA activity was evaluated using NIH criteria

Results: The mean age of patients and controls was respectively 36.2 and 37.0 years and 92% of them were female. The serum level of IL-6 [13.3 pg/ml (95% CI 7.0–19.6) vs 3.4 pg/ml (95%CI 1.9–4.8) $P<0.001$] and of MMP-3 [647.8 pg/ml (95%CI 494.7–800.8) vs 563.7pg/ml (95%CI 439.4–688.0); $P<0.001$] were higher in TA patients than in controls. Comparing the serum level of these interleukins and metalloproteinases between patients classified as active vs inactive disease, only IL-6 was significantly higher in patients with active disease (22.5 pg/ml vs 7.5 pg/ml; $P=0.027$). Regarding SUVmax on PET-CT, patients with active disease had higher SUVmax values than those with inactive disease ($P=0.042$). ROC curve analysis showed that the value of SUVmax as a predictor of clinical activity ($P=0.043$; AUC=0.703; IC 95%=0.534–0.832). SUVmax ≥ 1.3 was associated with clinical activity ($P=0.039$). TNF-alfa levels were higher in patients with SUVmax ≥ 1.3, when compared to those <1.3 ($P=0.045$) and to controls ($P=0.012$). IL-6 and MMP3 levels were higher in patients with SUVmax ≥ 1.3 than in controls ($P<0.001$ and $P=0.006$, respectively). There was no significant difference regarding others serum biomarkers comparing TA patients and controls.

Conclusion: This is the first study evaluating various interleukins and metalloproteinase to assess disease activity in TA patients. The serum level of IL-6 was associated with disease activity. This study also finds a correlation between 18F-FDG uptake in PET-CT and disease activity. Therefore PET-CT and serum level of IL-6 appear to be promising tools to assess Takayasu arteritis disease activity.

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The Value of Positron Emission Tomography – Computed tomography in Patients with Large Vessel Vasculitis. Man Wai Tang, Danielle Marie Gerlag, A. Elisabeth Hak, Berthe L.F. van Eck-Smit and Paul-Peter Tak. Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Positron emission tomography - computed tomography (PET-CT) scan has become a promising, noninvasive diagnostic test in various diseases, such as large vessel vasculitis. It is currently unknown what the influence of corticosteroids on the outcome of this technique is in this disease. The purpose of this research is to study the correlation between the inflammatory markers, erythrocyte sedimentation rate and C-reactive protein (respectively ESR and CRP) and outcome of PET-CT. Furthermore, the influence of corticosteroids on the outcome of PET-CT in large vessel vasculitis will be studied.

Methods: 24 patients with a suspicion of large vessel vasculitis were evaluated between November 2007 – January 2010 using PET-CT. Levels of ESR and CRP were measured and correlated to vascular FDG-uptake. The levels of ESR and CRP were categorized in both normal values, elevated ESR or CRP and both elevated levels. The use of corticosteroids at the time the PET-CT was performed, was also evaluated. Clinical outcome was also studied, which was defined as starting with corticosteroids in patients with and with no pathological vascular FDG-uptake.

Results: Patients with the suspicion of vasculitis who showed pathological vascular FDG-uptake in the large vessels on PET-CT had a higher level of ESR compared to patients without vascular FDG-uptake, respecitively mean ± SD: 72 ± 45 versus 30 ± 20 mm/hr (p=0,011). Similar results were found for the CRP levels with positive and negative FDG-uptake, respectively median 43 (4,2–220) versus 6,2 (1–221) mg/L (p=0,053). Using the three categories, 90% of the patients who have both elevated markers showed pathological vascular FDG-uptake, compared to 50% of patients with elevated ESR or CRP level and only 20% of patients with normal levels (p=0.011), see figure 1. Overall, the area under the curve (ROC) of the three groups of normal and/or high ESR and/or CRP increased from 0.731 (p=0,063) to 0.804 (p=0,014) after addition of the PET-CT scan.

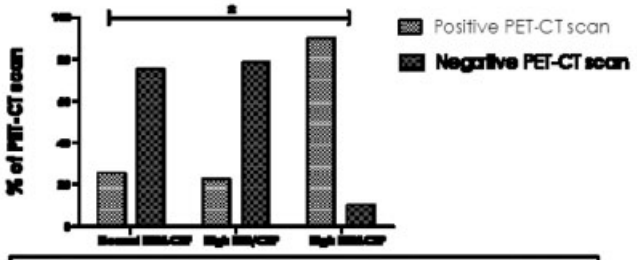

Fig. 1 Elevated levels of ESR and CRP were significantly more correlated with a positive PET-CT scan.

As expected, lower ESR levels were measured in the group of patients who used corticosteroids compared to patients who did not use corticosteroids, respectively 35 ± 30 versus 78 ± 45 mm/hr (p=0.016). Use of corticosteroids was not related to FDG-uptake itself (p=0.680).

Conclusion: The PET-CT scan seems to have more additional value in patients suspected of vasculitis who have normal ESR or CRP levels compared to patients who have elevated levels of ESR and CRP. Corticosteroids decrease inflammatory markers in the peripheral blood, but do not seem to have a direct effect on FDG-uptake.

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Reduced Insular Gamma-Aminobutyric Acid in Fibromyalgia. Bradley Foerster[1], Myria Petrou[1], Richard Edden[2], Pia Sundgren[1], Tobias Schmidt-Wilcke[1], Suzan E. Lowe[1], Steven Harte[1], Daniel J. Clauw[1] and Richard E. Harris[1]. [1]University of Michigan, Ann Arbor, MI, [2]Johns Hopkins, Baltimore, MD

Background/Purpose: Recent findings indicate that chronic pain patients diagnosed with fibromyalgia (FM) display elevated levels of glutamate, a major excitatory neurotransmitter, within the insula and other brain regions. This has led our group and others to suggest that some individuals with FM have augmented central glutamatergic neurotransmission and that this may play a role the pathology of this disorder. Here we quantified the level of γ-aminobutyric acid (GABA), the brain's major inhibitory neurotransmitter, in individuals with FM. We hypothesized that decreased inhibitory neurotransmission may also play a role in the pathology of FM.

Methods: 16 female FM patients (mean±SD age in years: 37.2±12.8) and 17 age- and sex-matched healthy controls (36.1±11.7; p-value = 0.79) underwent a single 3 Tesla proton magnetic resonance spectroscopy (H-MRS) session. Single voxels were placed in the right anterior insula, the right posterior insula, the anterior cingulate and the occipital cortex. The insula cortex was chosen based on our previous findings of elevated glutamate, whereas the cingulate and occipital cortex were selected as exploratory and negative control regions respectively. For voxel placement, each subject underwent a 3D-MPRAGE sequence with 0.9 mm^3 isotropic voxel resolution. MR spectra were acquired from using 3.0 cm × 2.0 cm × 3.0 cm^3 volumes. Single-voxel point resolved spectroscopy (PRESS) spectra (TR/TE=2000/35 ms) were acquired from each region of interest. GABA was isolated using MEGA-PRESS with the following parameters: TE = 68 ms (TE1 = 15ms, TE2 = 53 ms); TR= 1.8s; 256 transients of 2k datapoints; spectral width= 2 kHz; frequency selective editing pulses (14 ms) applied at 1.9 ppm (ON) and 7.46 ppm (OFF). Refocusing was performed using amplitude-modulated pulse 'GTST1203' (length = 7 ms, bandwidth = 1.2 kHz). MEGA-PRESS spectroscopy was analyzed using in-house post-processing software in Matlab with Gaussian curve fitting to the GABA and inverted N-acetylaspartate

(NAA) peaks. The concentration of GABA (in arbitrary institutional units, AIU) was then calculated by multiplying the ratio of GABA:NAA by the absolute NAA concentration determined from LCModel analysis of PRESS data.

Results: Compared to healthy pain free controls, FM patients had significantly lower levels of GABA within the right anterior insula (AIU mean ± SD 1.02 ± 0.21 versus 1.24 ± 0.28; p=0.015). There was a trend towards increased GABA in the anterior cingulate of FM patients (p=0.06). No significant differences between groups were detected in the posterior insula or occipital cortex (all $p > 0.05$). Within the right posterior insula, higher levels of GABA were positively correlated with pressure pain thresholds for the FM patients (r=0.70; p=0.008).

Conclusion: Diminished inhibitory neurotransmission resulting from lower concentrations of GABA within the insula may play a role in the pathophysiology of FM. Moreover, reduced GABA may partially explain the efficacy of GABA receptor agonists such as sodium oxybate in this condition.

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Pregabalin Reduces Posterior Insula Combined Glutamate and Glutamine in Fibromyalgia. Richard E. Harris[1], John P. Huggins[2], Lynne Pauer[2], Pia Sundgren[1], Craig Urwin[1], Kathy Scott[1] and Daniel J. Clauw[1]. [1]University of Michigan, Ann Arbor, MI, [2]Pfizer Inc., Sandwich, United Kingdom

Background/Purpose: Pregabalin has been shown to reduce pain in fibromyalgia (FM) however its clinical mechanism of action is unknown. Preclinical studies *in vitro* and *in vivo* both indicate that pregabalin binds to the $\alpha 2\delta$-subunit of voltage gated calcium channels thereby potentially down regulating glutamate (Glu) release at the synapse as well as inhibiting glutamatergic synapse formation. Recently our group has demonstrated that patients diagnosed with FM display elevated levels of Glu and combined Glu + glutamine (Glx) within the posterior insula, suggesting augmented glutamatergic neurotransmission in this disorder. Here we quantify the levels of insular Glu and Glx in individuals with FM before and after treatment with pregabalin and placebo. We hypothesized that pregabalin, as compared to placebo, would decrease the amount of Glu and/or Glx within the posterior insula.

Methods: 17 female FM patients (mean±SD age in years: 38.0±10.9), with complete data, completed a randomized double-blind two-period cross-over study of pregabalin versus placebo. During the pregabalin period, drug concentration was dose escalated to 450mg/day over the course of 14 days. During the placebo period, sugar pills were taken over the course of 14 days to match the pregabalin period. Prior to and following each period (pregabalin or placebo), patients underwent proton magnetic resonance spectroscopy (H-MRS) imaging at 3 Tesla at rest. Single voxels were placed in the right anterior insula and the right posterior insula. The insula cortex was chosen based on our previous findings of elevated Glu and Glx in this structure. Single-voxel point resolved spectroscopy (PRESS) spectra were acquired from each region of interest with the following parameters:TR 3000ms/TE 30ms, 90 degree flip angle, NEX 8, FOV 16, with a voxel size of 2×2×3cm. Spectra were analyzed offline with LCModel. Values for Glu and Glx were calculated as ratios to the internal standard creatine (Cr; eg. Glu/Cr). Data were analyzed with SPSS v.19.

Results: FM patients displayed a significant reduction in Glx/Cr within the posterior insula following pregabalin treatment (post minus pre; mean difference ± SD: 0.116 ± 0.177; p=0.016) but not placebo (post minus pre; mean difference ± SD: −0.028 ± 0.308; p=0.71). There was a trend towards decreased Glu/Cr in the posterior insula following pregabalin (post minus pre; mean difference ± SD: 0.070 ± 0.157; p=0.08) but not placebo (p=0.44). No significant changes following either pregabalin or placebo were detected for Glx/Cr and Glu/Cr in the anterior insula (all $p>0.05$). No significant changes were detected for any of the other H-MRS detected metabolites within the anterior and posterior insula (all $p>0.10$).

Conclusion: Consistent with preclinical data, pregabalin reduces combined glutamate and glutamine within the posterior insula of individuals with FM. This may be related to the clinical efficacy of this drug.

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Feasibility of Bone Density Evaluation Using Plain Digital Radiography. Margot B. Kinds, Anne C. A. Marijnissen, Koen L. Vincken, Lambertus W. Bartels, Max A. Viergever, Hugo WAM de Jong and Floris P.J.G. Lafeber, University Medical Center Utrecht, Utrecht, Netherlands

Background/Purpose: For the evaluation of subchondral bone density (BD) changes due to OA, Dual Energy X-ray Absorptiometry (DEXA) is the most validated method. The need for DEXA might be reduced if the quantitative measurement of clinically relevant BD changes on radiographs is proved feasible, since radiographs are commonly acquired to evaluate structural changes due to OA. Precision of BD evaluation might be influenced by variations in acquisition settings that commonly occur in clinical practice and by post-processing (PP) that was introduced with the transition from conventional film-screen radiography to digital radiography. The objective of this study was to evaluate the effects of PP and acquisition settings on the precision and with that feasibility of BD measurement using plain digital radiography.

Methods: A bone density standard (BDS) was created consisting of eight cups with hydroxyapatite (HA: range 1.0–5.75 g/cm^2). Digital radiographs of the BDS were taken (Philips Digital Diagnost), with variations in the acquisition and PP settings. Tube voltage (in kilovolt: kV), exposure (in milliampere seconds: mAs), tube added filtering, and BDS position in the field-of-view were systematically varied and the default clinical PP was compared with minimal PP (at minimal strength). An aluminum step wedge served as an internal reference to express gray values of the BDS in mm aluminum equivalents (mmAl), by use of custom made software. In all cases a human (cadaver) knee joint was added to simulate clinical conditions. The relation (R^2) between the BD values normalized to the reference wedge (in mmAl equivalents) and actual BD (HA in g/cm^2), with variations in acquisition and PP settings was evaluated with linear regression analyses. Precision of BD measurement of the BDS was calculated in early OA (Cohort Hip & Cohort Knee: CHECK) to evaluate the relevance for clinical (research) practice.

Results: The BDS was validated by DEXA scanning and the relation between actual HA (g/cm^2) and DEXA values was strongly linear: $R^2=0.99$. In general for digital radiographs a strong correlation between actual BD and BD in mmAl was found for all settings. The correlation improved by changing PP from clinical ($R^2=0.96$) to minimal ($R^2=0.98$). Higher kV improved the correlation further. Even, for clinical PP mean SD was 0.97 mmAl, much smaller than the change of 2.51 mmAl clinically observed during two-year follow-up in early OA which implies the feasibility of BD measurements using plain digital radiography.

Conclusion: Accurate bone density measurement using digital radiography is feasible in a clinically relevant range, which removes the need for additional DEXA scans since plain radiographs are acquired for to evaluate structural changes due to osteoarthritis. Care should be taken in changing post-processing and acquisition settings, which can have profound effect on outcome.

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Alterations of Bone Geometry, Volumetric Density and Microarchitecture in Women with Systemic Lupus Erythematosus on Chronic Corticosteroids: A Case-Control Study Using High Resolution-Peripheral Quantitative Computed Tomography. Xiao Lin Tang, Tracy Y. Zhu, Lai Shan Tam and Edmund K. Li. The Chinese University of Hong Kong, Hong Kong, Hong Kong

Background/Purpose: To assess the alterations of bone geometry, volumetric bone mineral density (vBMD) and microarchitecture and areal BMD (aBMD) in women with systemic lupus erythematosus (SLE) on chronic corticosteroid.

Methods: One hundred and twenty-one Chinese women with SLE taking chronic corticosteroid with mean (SD) age of 44.78 (8.47) and 121 age- and sex-matched healthy controls with mean (SD) age of 45.19 (8.31) were recruited. Bone geometry, vBMD and microarchitecture were measured by high resolution peripheral quantitative computed tomography (HR-pQCT) at the non-dominant distal radius. aBMD was measured by dual-energy x-ray absorptiometry at femoral neck, total hip, lumbar spine and non-dominant distal radius

Results: At all 3 sites, aBMD was not significantly different between patients with SLE and controls. Prevalence of osteoporosis was significantly higher in patients with SLE than controls (8.3% vs. 2.5%, p=0.046). Using HR-pQCT, average bone density (p=0.02) and cortical bone density (p=0.002) were lower in patients than controls. Patients with SLE developed more deterioration in cortical area (p=0.014) and cortical thickness (p=0.002). After adjusting for body mass index and menopausal status, cortical area and cortical thickness remained significantly lower in patients than controls. There was a trend toward deterioration in trabecular bone quality, including trabecular bone density, trabecular bone volume fraction

and trabecular number in patients with SLE, although not statistically significant.

aBMD and geometry, volumetric density, microarchitecture measured by DXA and HR-pQCT in SLE women and age-matched controls

	Patients (n=121)	Controls (n=121)	p
aBMD (g/cm^2)			
Femoral neck	0.72±0.15	0.74±0.11	0.197
Total hip	0.85±0.12	0.88±0.11	0.053
L1-L4 spine	1.02±0.93	0.99±0.15	0.744
Distal radius	0.56±0.05	0.56±0.07	0.457
Geometry			
Total bone area (cm^2)	209.18±32.42	203.94±34.86	0.227
Cortical area (cm^2)	54.43±9.63	57.28±8.26	0.014
Trabecular area (cm^2)	151.80±31.72	144.49±33.64	0.083
Volumetric BMD			
D100 (mg HA/cm^3)	365.70±73.42	386.63±65.14	0.020
Dcomp (mg HA/ cm^3)	940.19±51.91	958.30±39.03	0.002
Dtrab (mg HA/cm^3)	140.48±43.11	142.17±38.15	0.747
Dmeta (mg HA/cm^3)	198.45±40.89	204.23±36.11	0.245
Dinn (mg HA/cm^3)	100.16±45.91	98.90±40.46	0.821
Microarchitecture			
Ct.Th (mm)	0.91±0.17	0.97±0.15	0.002
Ct.Pm (mm)	60.30±4.95	59.34±4.99	0.135
BV/TV	0.12±0.04	0.12±0.03	0.748
Tb.N (1/mm)	1.54±0.28	1.55±0.26	0.759
Tb.Th (mm)	0.08±0.02	0.08±0.01	0.615
Tb.Sp (mm)	0.60±0.15	0.59±0.15	0.669
Tb.1/N.SD (mm)	0.26±0.10	0.26±0.10	0.944

Conclusion: Patients with SLE on chronic corticosteroid developed lower vBMD and deterioration of bone microarchitectural that can be assessed noninvasively by HR-pQCT. HR-pQCT appears sensitive to detect bone loss, especially cortical bone loss, in patients with SLE.

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Disease Damage Has Deleterious Effect on Trabecualr Bone Microarchitecture in Female Patients with Systemic Lupus Erythematosus On Chronic Corticosteroids. Xiao Lin Tang, Tracy Y. Zhu, Lai Shan Tam and Edmund K. Li. The Chinese University of Hong Kong, Hong Kong, Hong Kong

Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease. It can affect almost all the organs of the body, for example the musculoskeletal system. Patients have higher risk of osteoporosis and fracture than general population. Recently, with advances in high resolution imaging techniques, such as high-resolution peripheral quantitative computed tomography (HR-pQCT), interest in investigating bone microarchitecture as an important role in the development of osteoporosis has increased. We aimed to investigate the effect of various clinical parameters on bone geometry, volumetric density and microarchitecture in female SLE patients on chronic corticosteroids using HR-pQCT.

Methods: One hundred and twenty Chinese females with SLE on long-term corticosteroids, with mean age (SD) of 42 (9) and 37.5% being post-menopausal, were selected to participate in a cross-sectional study. Areal bone mineral density (aBMD) at the total hip, lumbar spine and non-dominant distal radius was measured by dual-energy X-ray absorptiometry (DXA). Bone geometry, volumetric density and microarchitecture at the non-dominant distal radius were measured by HR-pQCT. Clinical parameters of interest included disease activity, disease damage, major organ involvement (lupus nephritis and neuropsychiatric damage), and use of corticosteroids and cyclophosphomade were recorded.

Results: Disease damage measured by the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) was the only variable constantly associated with bone loss in patients with SLE. Other clinical parameters had minimal effect on bone quality. The median SDI score of the cohort was 0 (interquartile range: 0–1, range 0–4), among which 51 (42.5%) had a SDI score ≥ 1. Ocular (12.5%), neuropsychiatric (10%) and cardiovascular damage (5%) were the most common damages. Forty-two (35%) patients were osteopenic or osteoporotic at total hip, 43 (36%) at lumbar spine, 25 (21%) at radius and 60 (50%) at either 1 site. Strong correlations were found between aBMD and all volumetric/architecture parameters. More organ damage were significantly correlated with more deterioration in trabecular bone quality, including trabecular bone density, trabecular bone volume fraction, trabecular thickness, trabecular separation and standard deviation of 1/trabecular number. After adjusting for age, body mass index, menopausal status and trabecular area, significant correlations still remained between higher SDI score and all the above trabecular bone parameters.

Conclusion: Disease damage has deleterious effect on trabecular bone microarchitecture in female SLE patients on chronic corticosteroids. Preventing disease damage may be effective in preserving bone quality, especially trabecular bone quality in SLE.

ACR/ARHP Poster Session B
Innate Immunity and Rheumatic Disease
Monday, November 7, 2011, 9:00 AM–6:00 PM

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A Toll-Like Receptor 1 Polymorphism Is Associated with Heightened T Helper 1 Responses and Antibiotic-Refractory Lyme Arthritis. Klemen Strle, Junghee J. Shin, Lisa Glickstein and Allen C. Steere. Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background/Purpose: Single nucleotide polymorphisms (SNPs) have been identified in several genes encoding Toll-like receptors (TLRs) that lead to modified cellular immune responses, decreased cytokine production, and altered disease susceptibility. The TLR SNPs with the best evidence for affecting immune function are TLR1 (1805GG), TLR2 (2258GA) and TLR5 (1174CT). We studied the frequency and functional outcome of these polymorphisms in patients with various manifestations of Lyme disease.

Methods: PCR amplification-restriction fragment length polymorphism assays were used to determine the genotypes of TLR1 at position 1805, TLR2 at position 2258, and TLR5 at position 1174 in 71 patients with erythema migrans (EM) an early disease manifestation, and in 76 patients with antibiotic-responsive and 101 patients with antibiotic-refractory Lyme arthritis, a late disease manifestation. To assess the functional outcome of the polymorphisms, protein levels of 12 cytokines and chemokines were determined in serum of EM patients, and in joint fluid of Lyme arthritis patients using bead-based multiplex assays. In addition, the protein levels of these mediators were assessed in supernatants of *Borrelia burgdorferi*-stimulated PBMC from 43 patients with Lyme arthritis.

Results: The frequency of TLR1 polymorphism (1805GG) was greater in patients with antibiotic-refractory arthritis compared to patients with EM (62% vs, 49%, odds ratio = 1.7, P = 0.1) or antibiotic-responsive arthritis (62% vs. 47%, odds ratio = 1.9, P=0.05). Early in the illness, patients with EM who had 1805GG, primarily those infected with *B. burgdorferi* RST1 strains, had higher serum levels of IFNγ, CXCL9 and CXCL10, and more severe infection than patients with 1805TG/TT. These inflammatory responses were amplified in patients with Lyme arthritis, and the highest responses were observed in patients with antibiotic-refractory arthritis who had 1805GG and had been infected with RST1 strains. When PBMC from Lyme arthritis patients were stimulated with a *B. burgdorferi* RST1 strain, the 1805GG group had significantly larger fold changes in the levels of IFNγ, CCL2, CXCL9 and CXCL10, than those with 1805TG/TT (P<0.001). In contrast, the frequencies of TLR2 (2258GA) and TLR5 (1174CT) were not significantly different among the groups, and cytokine and chemokine values were similar in those with or without the polymorphism.

Conclusion: We concluded that the TLR1 1805GG polymorphism in *B. burgdorferi* RST1-infected patients was associated with stronger T_H1-like immune responses, more symptomatic infection, and antibiotic-refractory arthritis. This is the first innate immune factor identified associated with antibiotic-refractory arthritis.

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Toll Like Receptor-2 Activation Prevents Cartilage Damage in Osteoarthritis Models That Display Synovial Activation. Arjen Blom, Peter van Lent, Shahla Abdollahi-Roodsaz, Peter M. van der Kraan and Wim B. van den Berg. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: There has been a huge interest in the role of Toll-Like Receptors (TLR) in human and experimental arthritis. Several endogenous ligands for TLR2 are present in osteoarthritic joints. However, the involvement of TLR2 in osteoarthritis (OA) has not been studied extensively. This study was performed to evaluate the role of TLR2 in experimental OA pathology.

Methods: Three models for OA were used, collagenase induced OA (CIOA), destabilization of the medial meniscus (DMM) and spontaneous OA in IL-1ra$^{-/-}$ murine knee joints. CIOA was induced by injection of collagenase into murine knee joints. Due to instability, OA-like pathology develops within 42 days. DMM

was induced by transsecting the medial meniscotibial ligament, which results in OA-like pathology within 56 days. The role of TLR2 was studied by induction of CIOA and DMM OA in TLR2$^{-/-}$ mice (n=16) and C57BL/6 controls (n=15), and by backcrossing of TLR2$^{-/-}$ mice to IL-1ra$^{-/-}$ mice. At end point, knee joints were isolated and OA-like changes in the cartilage were scored. At several time points after induction, synovial tissue was isolated to study TLR2 expression in the wild type (WT) mice by Q-PCR.

Results: In CIOA and to a lesser extent in the IL-1ra$^{-/-}$ mice, synovial activation, indicated by thickening of the synovial lining layer, was clearly present during the whole course of the disease. However, no synovial activation was observed in the DMM model. At day 7 after induction of CIOA in WT mice, synovial TLR2 levels were upregulated up to 56 fold, probably reflecting cellular influx at this time point. At day 21 TLR2 levels were up 2-fold and 42 days after induction, TLR2 levels in the synovium were down to baseline levels. In the DMM model, TLR2 was not regulated at any of these time points.

During CIOA in TLR2$^{-/-}$ mice, OA cartilage pathology increased from 10,0 in the WT controls to 15,5 ($p<0,02$). Changes were observed in both medial and lateral joint compartment. Incidence of severe cartilage damage was increased in the medial femur, medial tibia, lateral femur and lateral tibia respectively from 13% to 44%, from 27% to 69%, from 60% to 81% and from 53% to 81%. In knee joints of IL-1ra$^{-/-}$ mice, damage was mild compared to CIOA WT mice with a mean score of 2,2 and showed an increase in the IL-1ra$^{-/-}$/TLR2$^{-/-}$ up to a score of 4,1. In contrast, cartilage pathology during DMM OA in TLR2$^{-/-}$ was not changed in the medial compartment of the joints, compared to WT mice, respectively 13,7 and 14,7. Severe cartilage damage did not differ between WT and TLR2$^{-/-}$. In all models, synovitis in TLR-2$^{-/-}$ mice was comparable to the WT, indicating no direct role for TLR2 in synovitis.

Conclusion: Unexpectedly, this study indicates that in TLR2 deficient mice OA pathology is more severe in experimental OA that involves synovial activation. This suggests a protective role for this receptor in OA. This protective role was abolished in the absence of synovial activation, as was found in the DMM model. Stimulation of TLR2 by endogenous ligands such as biglycan, hyaluronan or HMGB-1 has been shown to induce IL-10, TGFb and HGF, which are protective mediators for OA. Although further research is needed, these results indicate that the TLR2 pathway protects cartilage from developing OA and that this effect is mediated by the synovium.

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NI-0101, a Therapeutic TLR4 Monoclonal Antibody for Rheumatoid Arthritis. Greg Elson[1], Theresa Page[2], Vanessa Buatois[1], Bruno Daubeuf[1], Laurence Chatel[1], Laura Cons[1], Carla Lippens[1], Susana Salgado-Pires[1], Walter Ferlin[1], Marie Kosco-Vilbois[1], Kim Midwood[2] and Limin Shang[1]. [1]NovImmune S.A., Plan-Les-Ouates, Geneva, Switzerland, [2]Kennedy Institute of Rheumatology, Imperial College of Science, Technology and Medicine, London, United Kingdom

Background/Purpose: Toll-like receptor 4 (TLR4) is a powerful sensor of inflammation bridging mechanisms that give rise to both innate and adaptive immunity. Dysregulation of TLR4 signaling via endogenous ligands created during chronic inflammatory processes appears to play an underlying role in the pathogenesis of autoimmune diseases. The aim of this study was to evaluate the full potential of TLR4 blockade for the treatment of rheumatoid arthritis (RA) using a novel therapeutic monoclonal antibody (mAb), NI-0101.

Methods: The anti-human TLR4 mAb, NI-0101, was generated and shown to efficiently block TLR4 activation in vitro by exploiting a mechanism involving both Fv and Fc portions. Using exogenous, endogenous or chemical ligands, the capacity to block TLR4 activation was evaluated. Subsequently, NI-0101 was tested in synovial explant cultures obtained from RA patients. Furthermore, the corresponding mouse surrogate antibody was tested in a laboratory model of RA.

Results: Due to inhibition of TLR4 dimerization, NI-0101 efficiently blocked the activation of TLR4 by different ligands, including tenascin C, the endogenous ligand of TLR4 upregulated in synovial fluid from RA patients. Consistent with this result, NI-0101 reduced the spontaneous production of TNFα and IL-6 in synovial explant cultures from RA patients. To determine the effects of NI-0101 *in vivo*, we used the mouse surrogate antibody of NI-0101, 5E3. Therapeutic administration of 5E3 efficiently ameliorated disease progression in the he IL-1Rn−/− model of RA.

Conclusion: The therapeutic anti-human TLR4 mAb, NI-0101, has the capacity to interfere with not only LPS but also signaling of TLR4 through endogenous and chemical ligands. When used in *in vitro* models with tissue from RA patients, NI-0101 reduces spontaneous pro-inflammatory cytokine production. We demonstrated that anti-TLR4 mAb therapy is efficient in abolishing disease progression in arthritic mice. Taken together, these data promote NI-0101 as a promising treatment in RA. Moreover, by targeting a central upstream mediator in the inflammatory cascade, NI-0101 may have broad effects on RA pathogenesis and promote remission.

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MiR-20a Regulates Negatively TLR4 Signalling Pathway by Targeting ASK1 in Rheumatoid Synoviocytes. Lucas Philippe[1], Ghada Alsaleh[1], Sébastien Pfeffer[2], Jacques-Eric Gottenberg[1], Jean Sibilia[1], Dominique Wachsmann[1] and Philippe Georgel[3]. [1]EA4438 Laboratoire Physiopathologie des Arthrites, Illkirch-Strasbourg, France, [2]Architecture et Réactivité de l'ARN, Université de Strasbourg, Strasbourg, France, [3]Laboratoire d'ImmunoGénétique Moléculaire Humaine, Strasbourg, France

Background/Purpose: In rheumatoid arthritis (RA), the fibroblast-like synoviocytes (FLS), resident cells of the joint space, show an aggressive phenotype. They release a broad range of cytokines and enzymes which contribute to destruction. Extrinsic factors such as microbial components (PAMPs) or damage associated molecular patterns (DAMPs) activate FLS by interacting with Pattern Recognition Receptors (PRRs) such as Toll like receptors (TLRs). But it becomes more and more evident that epigenetic factors such as miRNAs play an important regulatory role in the development of the inflammatory response in RA. Our group identified in LPS-activated RA FLS a miRNA, miR-346 which functioned as a negative regulator of IL-18 and TNF-α release by activated FLS. We also demonstrated that miR-19 (miR-17–92 cluster) controlled directly TLR2 expression in RA FLS. An online search of the miRBase target database, demonstrated that one miRNA: miR-20a belonging to the downregulated miR 17–92 cluster was predicted to potentially target the 3'-UTR region of a mitogen-activated protein 3-kinase (ASK1) selectively required for LPS-induced activation. In this study, we aimed to evaluate the role of miR-20a in the regulation of this TLR signalling component.

Methods: RA FLS were isolated from synovial tissues and stimulated with TLR2 (BLP) and TLR4 (LPS) ligands. QRT-PCR was performed to evaluate miRNA and mRNA expression. Transient transfection of FLS with mimic 20a was performed using the Human Dermal Fibroblast Nucleofector™ kit from Amaxa. All assays were performed 48 h post transfection. Transfection of HEK293 cells with reporter constructs and miR-20a mimic or antagomir was performed using Lipofectamine. Luciferase activity was determined using the dual-luciferase reporter assay system. IL-6 release was measured in culture supernatants by ELISA.

Results: We first showed by qRT-PCR that RA FLS expressed constitutively ASK1 and that ASK1 expression is significantly enhanced in response to LPS and BLP. Consistent with the downregulation of miR-17-92 cluster expression, miR-20a was strongly down regulated in RA FLS activated by LPS and BLP. As *in silico* analysis predicted that miR-20a might possibly bind to the 3'-UTR of human ASK1 transcript, we transiently transfected into HEK-293 cells, a reporter construct that contain the firefly luciferase gene fused to the ASK1 3'-UTR containing the putative miR-20a interactor site along with miR-20a. We observed a downregulation of the luciferase activity, indicating that the 3'-UTR of ASK1 mRNA is directly targeted by miR-20a. Finally, to examine the consequence of a decrease of ASK1 expression by miR-20a, we tested by transfection, whether expression of miR-20a affected IL-6 release in LPS-activated RA FLS. As compared to the control, we observed that transfection of the mimics induced a strong downregulation of IL-6 release in response to LPS and not to BLP.

Conclusion: These results illustrate a negative feedback loop that control TLR4 response. Our data strongly suggest a critical role of miR-20a in the regulation of the expression of ASK1 in response to TLR4 activation which could play an important role in the regulation of the inflammatory response in RA.

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TIR-Domain-Containing Adaptor-Inducing Interferon-β (TRIF)-Dependent Toll-Like Receptor 4 Signaling Mediates Antibody Class Switching in a Mouse Model of Histidyl-tRNA Synthetase-Induced Myositis. Lisa Harlow[1], Makoto Soejima[2] and Dana P. Ascherman[3]. [1]University of Miami Miller School of Medicine, Miami, FL, [2]University of Pittsburgh, Pittsburgh, PA, [3]University of Miami, Miami, FL

Background/Purpose: In our previously published model of myositis generated by intramuscular (IM) immunization with a recombinant fragment of murine Jo-1 fused to Maltose Binding Protein (MA/MBP), we determined that induction of IgG anti-Jo-1 autoantibodies does not require the addition of exogenous adjuvant, but is dependent on TLR4 signaling. While this observation highlighted the potential role of innate immune pathways in directing the

production of IgG autoantibodies, the relative contribution of TLR4 signaling to antibody formation versus class switching remained undefined.

Objectives: To determine the role of toll-like receptor (TLR) signaling in histidyl-tRNA synthetase (Jo-1)-induced autoantibody formation and class switching.

Methods: We used standard solid phase ELISA to determine IgM and/or IgG anti-Jo-1 antibody responses at various time points following IM immunization of different mouse strains with a recombinant amino-terminal fragment of murine Jo-1 fused to Maltose Binding Protein (MA/MBP). Mouse strains used for this analysis included C3H/HeOuJ (WT), C3H/HeJ (TLR4 loss of function mutation), C57BL/6 (B6), B6.MyD88$^{-/-}$, and B6.Ticam1 (TRIF loss of function mutation).

Results: Relative to post-immunization sera derived from C3H/HeOuJ (WT) mice, sera obtained from C3H/HeJ (functional TLR4 knockout) mice following IM immunization with MA/MBP demonstrated markedly reduced titers (5–40 fold) of IgG anti-Jo-1 autoantibodies. Although this finding implicated TLR4 signaling in anti-Jo-1 autoantibody formation/class switching, MA/MBP-immunized B6.MyD88$^{-/-}$ mice surprisingly demonstrated equivalent levels of anti-IgG Jo-1 autoantibodies relative to their WT counterparts, C57BL/6 (with some differences in the ratio of IgG_1/IgG_{2a}). In contrast, IM immunization of B6.Ticam1 (deficient TRIF signaling) mice with MA/MBP yielded markedly reduced titers of IgG anti-Jo-1 autoantibodies (similar to C3H/HeJ mice), implicating the TRIF-dependent arm of TLR4 signaling in the generation of IgG anti-Jo-1 autoantibodies. To clarify the role of TRIF-mediated TLR4 signaling in autoantibody formation versus class switching, we assessed the induction of IgM and IgG anti-Jo-1 antibodies at Days 4, 7, and 11 following IM immunization of C3H/HeJ and C3H/HeOuJ mice. These experiments demonstrated that C3H/HeJ mice produced equivalent levels of anti-Jo-1 IgM compared to C3H/HeOuJ mice at early time points following MA/MBP immunization, but failed to generate significant titers of class switched anti-Jo-1 autoantibodies.

Conclusion: IM immunization with recombinant murine Jo-1 in the absence of exogenous adjuvant induces antigen-specific, class switched autoantibodies. This humoral immune response is dependent on TRIF-mediated TLR4 signals regulating IgG class switching rather than IgM antibody formation. With relevance to the study of autoimmunity as well as vaccine biology, these findings provide insight regarding the contribution of innate immune signaling pathways to the generation of adaptive humoral immune responses.

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Presence of Fas Associated Death Domain Protein in the Synovial Fluids and Sera (ESPOIR Cohort) of Rheumatoid Arthritis Patients Mirrors the Inflammatory Attribute of the Disease. Léa Tourneur[1], Sylvie Mistou[1], Valérie Vilmont[1], Nicolas Cagnard[2], Jacques-Eric Gottenberg[3], Valerie Devauchelle[4] and Gilles Chiocchia[2]. [1]Institut Cochin, Paris, France, [2]Institut Cochin, 75014 Paris, France, [3]Strasbourg University Hospital, Strasbourg, France, [4]Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France

Background/Purpose: Fas-associated Death Domain (FADD) is the pivotal adaptor of the apoptotic signal mediated by death receptors. In rheumatoid arthritis (RA), ligands of IL-1R/TLR4 are present in the synovial fluid (SF), and FADD can act as an anti-inflammatory molecule by sequestering MyD88, the adaptor of IL-1R/TLR4 signaling. Thus, absence of FADD in synovial cells can potentially contribute to the establishment of inflammation. Recently, we identified adenosine receptors as the main regulators of a new mechanism of FADD regulation of expression by shedding of microvesicles. As adenosine is abundant in the SF of RA patients, we investigated whether FADD could be detectable in the SF and sera of RA patients compared to non-RA patients.

Methods: Detection of intracellular FADD in patients affected with RA and osteoarthritis (OA) was investigated by western blot followed by densitometry in synovial tissues (RA n=11, OA n=14) and cultured synoviocytes (RA n=7, OA n=7). A homemade protocol was used for quantification of FADD expression by ELISA. FADD was assessed in Synovial fluid (SF) from two independent cohorts (n=26 and 67) and in the sera of patients from the ESPOIR cohort (n=551 RA and 67 non-RA patients), [a French multi-centric cohort of patients having early arthritis lasting less than 6 months], and from healthy individuals (n=20). Student's *t* tests were conducted to verify statistical significance of our data.

Results: Densitometry analysis (Arbitrary Unit = AU) showed a higher concentration of cytoplasmic FADD in OA tissues and synoviocytes compared to RA tissues and synoviocytes: 0.809±0.06 vs 0.592±0.06 AU and 0.532±0.212 vs 0.317±0.143 AU respectively. Similarly nuclear FADD was higher in OA tissues and synoviocytes: 0.621±0.08 vs 0.320±0.09 and 0.247±0.05 vs 0.138±0.042AU. We detected more FADD in SF of RA patients compared to OA patients in the two cohorts: 249.4 ±72.7 vs 55 ng/ml±17 (P=0.017) and 140.2±28.5 vs 5.8±1.4 ng/ml (P=0.0015) respectively. Also FADD concentration was higher in sera of RA patients than in non-RA and healthy patients: 33.5± 5.2 vs 10.7±1.7 (P=0.00004) and vs 5.6±2.5 ng/ml (P=0.000002). The presence of FADD in RA sera at inclusion correlated with the presence of anti-CCP antibodies (P=0.035), rheumatoid factor (P=0.03) and the DAS28 (P=0.0002). Conversely no link could be made between FADD concentration and joint erosion at inclusion (P=0.2) or at 2 years post-inclusion (p=0.39).

Conclusion: This is the first demonstration that human FADD could be detected specifically during the course of an inflammatory disease. These results raised the hypothesis that low expression of FADD in joint cells could occur through a release of the protein in SF and could contribute to the development of RA.

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TLR4 on Resident Cells and Bone Marrow Derived Cells Contribute Equally to Arthritis. Ben T. van Den Brand[1], Shahla Abdollahi-Roodsaz[1], Miranda B. Bennink[2], Onno J. Arntz[2], Wim van den Berg[1] and Fons A. van de Loo[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Nijmegen, Netherlands

Background/Purpose: The IL-1 receptor antagonist (IL-1Ra) knockout mice spontaneously develop a Th17 driven arthritis. When cross bred with TLR4 knock out (TLR4−/−) these animals showed reduced inflammation, joint destruction, and diminished IL-17 levels.

Methods: An age-matched (4–5 weeks), sex-mismatched reciprocal bone marrow transplantation was performed with TLR4−/− and TLR4+/+ mice in the IL-1Ra−/− background by 7.5 Gy irradiation and intravenous injection of freshly harvested bone marrow cells. Bone marrow was stained for Y-chromosome. Peritoneal macrophages were stimulated with lipopolysaccharide. Clinical manifestation of disease was monitored macroscopically (0 to 2 per joint). Animals were sacrificed at the age of 25 weeks. Bone erosion was scored on Safranin-O stained histological slides (0–5). T cell analysis was performed on cells from spleen and draining lymph nodes using flow cytometry.

Results: Reconstitution of bone marrow was successful as determined by Y-chromosome staining. Peritoneal macrophages from animals engrafted with TLR4+/+ bone marrow showed normal IL-6 mRNA up regulation after LPS challenge, whereas IL-6 mRNA up regulation was significantly reduced by 90% in animals that received TLR4−/− bone marrow. Lack of TLR4 on either the engrafted bone marrow cells or the radio-resistant cells did not affect disease incidence, ranging from 55 to 90% between all groups and comparable to previous experiments. However, animals that lacked TLR4 on the engrafted bone marrow derived cells, radio-resistant cells, or both showed a reduced macroscopic arthritis score (mean 1.0, 0.9, and 0.9, respectively) compared to animals expressing Tlr4 on all cells (mean 1.6). This was also reflected in bone erosion scores of the joints. T-cell analysis showed no differences in Th1 or Th17 in the spleen. However, the percentage of IL-17 positive cells was reduced in the draining lymph nodes of animals lacking TLR4 on the bone marrow derived cells, resident cells, or both, averaging 0.7%, 0.7%, and 0.57% respectively, whereas lymph nodes of complete TLR4+/+ animals contained 1.1% IL-17 cells.

Conclusion: These data suggest that TLR4 plays an equally important role on both the bone marrow derived and local resident cells in Th17 development and in aggravating experimental arthritis. TLR4 could play a local role by creating a cytokine environment favouring Th17. On the other hand, TLR4 activation on the bone marrow derived antigen presenting cells might promote a more aggressive Th17 phenotype.

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Toll-Like Receptor-9 Activation Regulates Macrophage Triggering Receptor Expressed on Myeloid Cells-1 Expression and shedding. Yair Molad[1], Elisheva Shapira[2] and Vered Carmon[3]. [1]Felsenstein Medical Reseach Center, Sackler Faculty of Medicine, Tel Aviv University, and Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel, [2]Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel, [3]Laboratory of Inflammation Research, Felsenstein Medical Research Center, Tel Aviv University, Petah Tikva, Israel

Background/Purpose: Toll-like receptor (TLR)-4-mediated immune response plays a pivotal role in the initiation and progression of the chronic and destructive stages of arthritis in both human disease and rodent models of

rheumatoid arthritis (RA). In-addition, previous studies suggested TLR-9 plays a role in the pathogenesis of RA. For example, TLR-9 K.O. mice suffered of worse arthritis. Triggering receptor expressed on myeloid cells-1 (TREM-1) is a DAP12-associated receptor which its up-regulation is TLR-4-mediated and plays an essential role in innate immune response by augmenting the production of proinflammatory chemokines and cytokines. Monocyte TREM-1 expression is increased in human and mouse synovium as well as its soluble form (sTREM-1) serum level. Moreover, sTREM-1 was shown to exert anti-inflammatory effects in animal models of RA. We hypothesize that anti-inflammatory effects of CpG-oligonucleotide (ODN), an inducer of TLR-9 activation, are mediated by regulating membrane TREM-1 expression and sTREM-1 shedding. Thus, the purpose of our study was to determine the *in vitro* effects of CpG-ODN-induced TLR-9 activation on macrophage TREM-1 expression and shedding.

Methods: Membrane TREM-1 expression was assayed by FACS and sTREM-1 level was assayed by ELISA. Zymography was used to determine metalloproteinase (MMP)-9 activity.

Results: We sought to determine whether CpG-ODN-mediated TLR-9 activation affects TREM-1 expression and sTREM-1 level using mouse peritoneal macrophages and mouse macrophage cell line RAW 264.7. We found that the expression of TREM-1 is not significantly altered by CpG-ODN alone whereas lipopolysaccharide (LPS) up-regulates TREM-1 as was previously shown. However, macrophage stimulation with both LPS and CpG-ODN significantly abrogated TREM-1 LPS-induced up-regulation (For peritoneal cells MFI= 86.03 $\pm$ 8.6 vs. 229 $\pm$ 19.4, $p<0.005$; and for RAW cells MFI= 55.7 $\pm$ 5.6. vs. 97.6 $\pm$ 7.5, $p<0.05$). Moreover, supernatant soluble TREM-1 level of CpG-ODN as well as LPS-stimulated cells was increased and sTREM-1 level as result of both LPS-and CpG-ODN macrophage stimulation was significantly higher compared with LPS or CpG-ODN alone (56.4 $\pm$ 5.36 pg/ml vs. 16.2 $\pm$ 2.74pg/ml, $p = 0.05$). The release of sTREM-1 was found to be positively correlated with MMP-9 activity ($r=0.914$, $p<0.005$) and was inhibited by chloroquine (a TLR-9 and MMP-9 inhibitor).

Conclusion: Our novel results suggest that CpG-ODN-induced TLR-9 activation abrogates the effect of LPS on macrophage TREM-1 up-regulation and induces either by itself or in conjunction with LPS a significant increase of sTREM-1 level through a mechanism that involves MMP-9-mediated TREM-1 shedding. Our results suggest that the anti-inflammatory effects of CpG-ODN might be mediated through decreased membrane TREM-1 expression and increased MMP-9-mediated TREM-1 shedding. Since both CpG-ODN and sTREM-1 were found to exert anti-inflammatory effects in mouse models of RA, we suggest a novel pathway for CpG-ODN-mediated up-regulation of sTREM-1 that can be used to treat inflammatory arthritis.

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A TLR 9 Antagonist Diminishes Arthritis Severity and Inhibits Bone Erosion in a Rat Model of Rheumatoid arthritis. Sonja Herman[1], Anita Fischer[1], Markus Hoffmann[2] and Gunter Steiner[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Karolinska Institutet, Stockholm, Sweden

Background/Purpose: There is increasing evidence that release of endogenous nucleic acids may trigger autoimmune reactions crucially involved in the induction of systemic autoimmune diseases such as SLE or rheumatoid arthritis (RA). In recent years, endosomal Toll-like receptors (TLRs, i.e. TLR3, TLR7, TLR8 and TLR9) have been implicated in autoimmune processes due to their ability to recognize these nucleic acids.

To study the role of TLR7 and TLR9 in the pathogenesis of erosive arthritis by antagonizing these TLRs in rats with pristane-induced arthritis (PIA).

Methods: First, the inhibitory capacity of immunoregulatory sequences (IRS) known to antagonize TLR7 and/or TLR9 activation was investigated in cultured rat splenocytes by measuring production of pro-inflammatory cytokines. Subsequently, using the PIA model, these IRS were also tested for their efficiency to inhibit arthritis development in rats with PIA. The IRS' were applied twice a week subcutaneously at the base of the tail, a non-inhibitory IRS and PBS served as control substances. Weight changes were measured during the experiment and arthritis was assessed using an established scoring system. Expression of TLRs was analyzed in paws, lymph nodes and spleen by Western blotting, RT-PCR and immunohistochemistry. Further, the impact of antagonizing TLR7/9 in osteoclastogenesis was analyzed by performing *in vitro* osteoclast assays.

Results: IRS specific for TLR7, TLR9 or TLR7/9 inhibited in a dose-dependent manner production of pro-inflammatory cytokines in rat splenocytes pre-activated by TLR specific stimulators. However, neither the TLR7 specific inhibitor nor the inhibitor targeting both TLR7 and TLR9 showed an effect on incidence and severity of PIA. Remarkably however, antagonizing TLR9 solely led to delayed disease onset and reduced arthritis severity, which was accompanied by diminished TLR9 protein expression levels in paws and lymph nodes compared to placebo-treated control animals. Moreover, bone erosion was largely reduced in animals treated with the TLR9 antagonist. Furthermore, inhibition of TLR9 but not of TLR7 in an in vitro osteoclast formation assay diminished osteoclastogenesis significantly in a dose-dependent manner.

Conclusion: Our *in-vitro* and *in-vivo* results indicate a potential involvement of TLR9 not only in the initiation of inflammatory arthritis but also in the later phase of inflammatory bone loss pointing toward a hitherto unknown role for TLR9 in the regulation of osteoclast activity.

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Upregulated High Mobility Group Box One Acts in Synergy with Danger Signals Through the Activation of of p38 Mitogen-Activated Protein Kinases to Promote Inflammation in Patients with Lupus Nephritis. Shui-Lian Yu, Chun-Kwok Wong, Da-Peng Chen, cheuk-Chun Szeto, Edmund K. Li and Lai-Shan Tam. The Chinese University of Hong Kong, Hong Kong, China

Background/Purpose: The chromatin DNA binding protein high mobility group box one (HMGB1) has previously been demonstrated to act as an "alarm" prototypical damage associated molecular pattern (DAMP) to contribute to the pathogenesis of SLE via breaking the immunological tolerance against nucleosomes/dsDNA, yet its mode of action is still not well defined. To assess the balance between the levels of receptor for advanced glycation end products (RAGE), RAGE ligand (HMGB1) and soluble RAGE in active lupus patients (systemic lupus erythematosus disease activity index, SLEDAI > 4), and subsequently explore the modulating and synergy effects of HMGB1 with endogenous and exogenous danger signals on its downstream cytokine in lupus patients.

Methods: Plasma HMGB1 and soluble RAGE were detected in lupus patients and healthy controls (HCs) by enzyme-linked immunosorbent assay. Monocyte cell surface RAGE expression was assessed using flow cytometry. *Ex vivo* production of inflammatory cytokines (IL-1β, IL-6, IL-8, IL-10, TNF-α and IL-12p70) from monocytes of lupus patients and HCs upon 24 hours HMGB1 stimulation was assessed using human inflammatory cytokine Cytometric Bead Array with flow cytometry.

Results: Elevated plasma levels of HMGB1 in lupus patients were positively correlated with SLEDAI (both $p < 0.05$). Significantly lower concentrations of soluble RAGE were found in lupus plasma, albeit higher protein expression on monocytes than HCs. Recombinant HMGB1 (rHMGB1) could significantly induce the *ex vivo* production of IL-6 from monocytes of lupus patients. Moreover, there was an observable elevated release of proinflammatory (IL-6 and IL-12p70) from monocyte in lupus patients upon the stimulation with TLR9 ligand (CpG-ODNs) or nuclear extract alone than that of HCs. Strong enhancing effects on induction of IL-6 and IL-12p70 occurred when HMGB1 in combination with CpG-ODNs, which subsequently promoted the phosphorylation of p38 mitogen-activated protein kinases (MAPK) in monocytes.

Conclusion: Upregulated alarmin HMGB1 may act in synergy with TLR9 ligand (CpG-ODNs) through the activation of p38 MAPK to promote the production of proinflammatory (IL-6 and IL-12) in monocytes of patients with Lupus Nephritis.

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The Anti-Inflammatory Action of Nerve Growth Factor Is Mediated by Trka Signalling: Modification in Trka Expression in Juvenile Idiopathic Arthritis Mononuclear Cells Create An Unbalance Between Inflammatory and Anti-Inflammatory Pathways? Gaetana Minnone[1], Giusi Prencipe[1], Raffaele Strippoli[1], Loredana De Pasquale[1], Ivan Caiello[1], Fabrizio De Benedetti[1] and Luisa Bracci-Laudiero[2]. [1]Children Hospital Bambino Gesù, Rome, Italy, [2]Institure of Translational Pharmacology-CNR, Rome, Italy

Background/Purpose: Nerve Growth Factor (NGF) production in the organism is a strictly regulated process. Inflammation increases NGF expression and indeed high NGF levels are a feature of synovial fluid and tissue in patients with chronic arthritis. Although all mononuclear cells express NGF receptors, it is, however, unclear what are the biological effects of these high NGF levels on immune cell activity. In order to evaluate the ability of mononuclear cells to respond to NGF in vivo, we analyzed the expression of TrkA and p75-NTR in mononuclear cells of patients with juvenile idiopathic arthritis (JIA). For better understanding the possible effect of NGF during the

inflammatory response we studied how intracellular signalling pathways induced by NGF affect TLR downstream signalling in monocytes, which are key players in inflammation and a critical link between innate and adaptive immunity.

Methods: Mononuclear cells were isolated from synovial fluid and peripheral blood samples of 25 children with JIA and age matched controls by Ficoll-Hypaque density centrifugation. Healthy donor monocytes, purified using Percoll discontinuous density gradients, were stimulated with TLR ligands with or without NGF addition. The expression of TrkA and p75NTR and the effects of TrkA activation or inhibition on TLR signalling and cytokine release were evaluated using real-time PCR, western blot and ELISA.

Results: We found that mononuclear cells of JIA patients from both peripheral blood and synovial fluid are characterized by a significant decrease in TrkA expression, while p75-NTR expression remains stable. In normal monocytes, phosphorylation of TrkA after NGF binding activated intracellular pathways that interfered with TLR signalling. Indeed NGF addition increased Akt phosphorylation, inactivated GSK3 and reduced IkB phosphorylation. Blocking TrkA enhanced inflammatory cytokine production, while reducing IL-10 synthesis and resulted in a greater activation of the NF-kB pathway and in inhibition of the PI3K pathway.

Conclusion: Our results imply that NGF is a relevant component of the endogenous mechanisms limiting excessive inflammatory response. Indeed, through TrkA NGF potentiates anti-inflammatory responses usually activated after TLR stimulation. The well-known increase in NGF in chronic arthritis patients may be *de facto* not efficacious in controlling inflammation because of the decrease of TrkA expression observed in JIA patients. This down-regulation of TrkA expression may influence the balance between inflammatory and anti-inflammatory pathways.

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Dysregulation of Pyrin, the Familial Mediterranean Fever Protein, Exacerbates Endotoxin-Induced Uveitis in Mice. Holly L. Rosenzweig[1], Jenna S. Clowers[2], Jordan Allensworth[1], Emily E. Vance[1], Stephen R. Planck[1], Michael P. Davey[2], Jae Jin Chae[3], Daniel L. Kastner[4] and James T. Rosenbaum[1]. [1]Oregon Health & Science University, Portland, OR, [2]Veterans Affairs Medical Center, Portland, OR, [3]Medical Genetics Branch, National Human Genome Research Institute, MD, [4]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

Background/Purpose: Mutation of pyrin (encoded by the gene *MEFV*) is the cause of the recessively inherited autoinflammatory disorder, familial Mediterranean fever (FMF). Pyrin is involved in regulation of inflammasome activation and IL-1β production. Given the importance of IL-1β in disease and the association of uveitis with systemic autoinflammatory disorders linked with pyrin, we sought to elucidate the functional consequences of the pathogenic, variant V726A, on the onset and severity of uveitis in mice.

Methods: Knock-in (KI) mice containing the V726A mutation or littermate controls (S129SV background) were observed without intervention or were administered an intravitreal injection of 250 ng lipopolysaccharide (LPS) in one eye and saline in the contralateral eye. Ocular inflammation was assessed histologically using a scoring system. Granulocyte populations in the blood and uveitic eye tissue were quantified by flow cytometry and immunofluorescence. Arthritis was assessed histologically and by whole body, near-infrared fluorescence imaging of inflamed regions labeled by with ProSense. Multi-plex ELISA was performed to quantify cytokine levels in uveitic eye tissue.

Results: Akin to patients with FMF, carriers with 2 copies of the mutation (i.e. KI mice) exhibit granulocytosis and arthritis that coincided with conjunctivitis. While the *MEFV* mutation did not predispose to spontaneous onset of uveitis, it did render KI mice markedly sensitive to LPS-induced uveitis as these mice developed an extensive pan-uveitis that was significantly worse that litter-mate controls. Interestingly, a pathergy response was observed in saline-injected KI controls. Ocular inflammation was characterized by infiltration predominantly of neutrophils and eosinophils that coincided with dilated blood vessels and hemorrhaging within the retina. Analysis of cytokine levels in uveitic eye tissue homogenates revealed a significant increase in IL-1β production compared to litter-mate controls.

Conclusion: Our data provide insight into how dysregulation of pyrin might influence intraocular inflammatory responses, and thereby result in more severe uveitis following an environmental trigger such as LPS.

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Expression and Function of the NALP3 Inflammasome in Behçet's Disease. En Hyung Kim[1], Jae Young Shin[2], Mi-Jin Park[2], Sun Park[2] and Eun-So Lee[2]. [1]Kwan Dong University, Cheil General Hospital and Women's Healthcare Center, Seoul, South Korea, [2]Ajou University School of Medicine, Suwon, South Korea

Background/Purpose: NOD-like receptors (NLRs) are pattern recognition receptors that sense intracellular microbial products. Some NLRs sense danger signals and form large complexes called inflammasomes that link the sensing of microbial products and metabolic stress to the proteolytic activation of the proinflammatory cytokines. NALP3 and NOD2 belong to the NLR family. After activation, the NALP3 inflammasome subsequently releases pro-inflammatory cytokines such as interleukin-1β (IL-1β).There is strong evidence for pro-inflammatory role of IL-1β in Behçet's disesase (BD). Therefore we explored the expression of the different components of the NALP3 inflammasome and NOD2 in tissue and serum samples from patients with BD. We also evaluated altered function of inflammasomes in BD patients.

Methods: The expression of NALP3, apoptosis-associated speck-like protein containing CARD domain (ASC) and NOD2 in erythema nodosum lesions of 25 BD patients and 25 non-BD patients were examined by immunohistochemistry. The mRNA expression of NALP3 and NOD2 were examined by RT-PCR in 20 patients with BD and as control, 10 patients with psoriasis and 10 healthy adults were studied. The altered function of inflammasomes in 20 BD patients was evaluated by measuring the release of IL-1β and TNF-α from PBMCs and monocytes after stimulation using ELISA.

Results: The immunohistochemistry results showed that the expression of NALP3 and ASC was significantly higher in BD patients. Also RT-PCR results showed similar results. However, neither immunohistochemistry nor RT-PCR results showed any difference in NOD2 expression between the groups. When PBMCs from BD patients were stimulated with LPS, IL-1β secretion significantly increased by 58 times. And with ATP, IL-1β release was even more increased by 1.6 times compared to LPS stimulation alone. Caspase-1 inhibitor decreased IL-1β release caused by LPS, however the decrease was less dramatic when ATP was added as a second stimulus. So in PBMCs, LPS stimulation caused large IL-1β release in BD patients but not in healthy controls. But with ATP, IL-1β release increase significantly in healthy controls but not in BD patients. When monocytes from BD patients were stimulated with LPS, IL-1β secretion was increased by 5 times And with ATP, IL-1β release was even more increased by 14 times compared to LPS stimulation alone. So, in BD patients, monocytes secrete impressively greater amounts of mature IL-1β following LPS stimulation, comparable to that of healthy individuals, but fail to increase IL-1β secretion in response to ATP. However, when TNF-α release was measured in a similar way, the result was independent of crosstalk between toll like receptors and NALP3 in BD patients.

Conclusion: This study reveals a role for the NALP3 inflammasome complex in BD. In normal monocytes, 2 signals are required to activate the inflammasome, thus tightly controlling IL-1β secretion but in patients, a single stimulus, which would be unable to trigger IL-1β secretion in healthy individuals, is sufficient to drive a dramatic inflammatory cascade. Modulation of the NALP3 inflammasome activity may delay the inflammatory process and chronic morbidities noticed in patients with BD.

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Demographic and Genetic Results From the EUROFEVERS/EUROTRAPS Consortia in the Largest Series of Patients with TRAPS Yet Reported. Helen J. Lachmann[1], Antonella Meini[2], Isabelle Touitou[3], Laura Obici[4], Martina Finetti[5], Kirsten Minden[6], Luca Cantarini[7], Marine Desjonqueres[8], Joost Frenkel[9], Isabelle Kone-Paut[10], Olga Vougiouka[11], Maria Jesus Rua Elorduy[12], Nicola Ruperto[13], Patricia Woo[1] and Marco Gattorno[14]. [1]University College London Medical School, London, United Kingdom, [2]Dipartimento di Pediatria, University of Brescia, Brescia, Italy, [3]CHU Montpellier-Hôpital Arnaud de Villeneuve, Montpellier, France, [4]IRCCS Policlinico S. Matteo, Pavia, Italy, [5]IRCCS Istituto G. Gaslini, Genova, Italy, [6]Charite, Berlin, Germany, [7]Policlinico le Scotte, Sienna, Italy, [8]Hopital Femme Mere Enfant, Groupement Hospitalier Est, Lyon, France, [9]University Medical Center Utrecht, Utrecht, Netherlands, [10]CHU Le Kremlin Bicetre, Paris, France, [11]P. A. Kyriakou Childrens Hospital of Athens University, Athens, Greece, [12]Hospital de Cruces, Barakaldo, Spain, [13]Paediatric Rheumatology International Trials Organisation – IRCCS [PRINTO], Genova, Italy, [14]G Gaslini Institute, Genoa, Italy

Background/Purpose: The TNF receptor associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory syndrome due to muta-

tions in the TNFRSF1A gene. It is associated with severe morbidity and increased mortality due a high risk of AA amyloidosis. The estimated prevalence is 1 per million and experience has previously been limited to small series.

Methods: The Eurofever/Eurotraps consortia (funded by the European Union) have developed a common web-based registry for all autoinflammatory diseases. The registry is accessed from the member area of the PRINTO web-site (www.printo.it/eurofever) and is available to all interested specialists physicians.

Results: 178 patients with clinical disease and a TNFRSF1A mutation were identified from 11 countries. The series included cases with 66 different mutations and 2 low penetrance mutations/polymorphisms, R92Q and P46L. Of the 66 mutations 8 (12%) were reported in more than 1 unrelated individual or kindred; 19 (29%) mutations affected a cysteine residue and of these 5 (26%) were seen in at least 2 unrelated patients. The T50M mutation was the most widespread and was found in 5 families originating from 5 different European countries. More than 1 disease associated mutation was identified at 7 sites, including 5 cysteine residues. In total of the 122 patients with a TNFRSF1A mutation: 68 (60.7%) reported a family history of similar symptoms; 58 (51.8%) were male; 105 (93.8%) were of Caucasian ethnicity and the mean age at symptom onset was 7.6 yrs (range: neonatal to 49 yrs). Of note in 10 patients (9%) the first symptoms developed after the age of 30 yrs. The 59 patients with R92Q polymorphism were 98% Caucasian, 45.8% male and 17% gave a family history of similar inflammatory disease. They presented at an average age of 10 yrs (range: neonatal to 52.6 yrs). The 7 patients with the P46L polymorphism included 2 patients of African ancestry, 1 Turk and a Gulf Arab, they presented at an average age of 16.6 yrs (range: 2.5 to 66.3 yrs) and 2 of them reported that other family members had similar disease.

Conclusion: The EUROFEVERS/EUROTRAPS consortia have collected data on 178 mutation positive TRAPS patients from 11 countries constituting the most extensive clinical series to date. The patients were largely contributed by European centres which may explain the dominance of Caucasian ethnicity. It confirms that TRAPS usually presents in childhood with a median age at presentation of less than 5 yrs but 9% of patients present well into adult life. 60% of patients report a family history of disease and most reported kindreds are small and mutations are family specific. Mutations affecting cysteine residues in extracellular domains are over represented but the most widespread disease causing mutation is T50M. Symptomatic patients with the well recognised polymorphism of R92Q and P46L make up 38% of the patients and appear to have a later onset of disease symptoms with lower penetrance. The availability of a large patient cohort will facilitates interpretation of the significance of TNFRSF1A mutations/polymorphism and understanding of genotype phenotype correlations.

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The Pattern-Recognition Receptor NOD1 Promotes Production of Inflammatory Mediators in Different Cell Types of the Synovium in Rheumatoid Arthritis. Kazuhiro Yokota[1], Toshihide Mimura[2], Renate E. Gay[1], Steffen Gay[1], Christoph Kolling[3] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Saitama Medical University, Saitama, Japan, [3]Schultess Clinic, Zurich, Switzerland

Background/Purpose: We previously reported that the functional pattern-recognition receptor NOD1 is significantly increased in rheumatoid arthritis (RA) compared to osteoarthritis (OA) synovial tissues and that stimulation of RA synovial fibroblasts (SFs) with the NOD1 ligand induces expression of pro-inflammatory cytokines. Now, we looked at the expression and regulation of NOD1 in RASFs, OASFs, monocyte-derived macrophages (MDMs) and peripheral blood mononuclear cells (PBMCs) and analyzed its interaction with TLR pathways.

Methods: Expression of NOD1 mRNA and protein in RASFs, OASFs, healthy control PBMCs and MDMs was analyzed by real-time PCR and flow cytometry. RASFs, MDMs and PBMCs were stimulated with TNF, IL-1β, NOD1 ligand, TLR2 ligand, TLR3 ligand and TLR4 ligand. ELISA was used to quantitate protein levels of IL-6 and IL-1β. Silencing of NOD1 was performed with transfection of RASFs siRNA targeting NOD1 mRNA by Amaxa Nucleofector Technology. Phosphorylation levels of interleukin-1 receptor-associated kinase 1 (IRAK1) were measured by western blotting.

Results: Basal expression levels of NOD1 mRNA (n=4–5) and protein (n=5–6) were not different in RASFs, OASFs, healthy control PBMCs and MDMs. Only stimulation with TLR3 induced the expression of NOD1 mRNA (2.67±0.29-fold, $p<0.05$) and protein (2.30±0.59-fold, $p<0.05$) in RASFs, but not in PBMCs or MDMs. Thus, NOD1 is constitutively similarly expressed among different cell types of the RA synovium, but is upregulated by TLR3 stimulation only in RASFs. Even though PBMCs (n=6) and MDMs (n=6) did not produce IL-6 or IL-1β by NOD1 stimulation alone, there was a strong synergistic effect of NOD1 with TLR2 as well as TLR4 in the production of IL-1β and IL-6 in these cells. Similar synergisms were found in the production of IL-6 by RASFs (n=6), showing that NOD1 and TLRs strongly synergize in the induction of pro-inflammatory effects in RASFs, MDMs and PBMCs. Most interestingly, IL-6 production induced by TLR2 ligand or IL-1β stimulation was significantly decreased by silencing of NOD1 compared with that of controls in RASFs (n=6). Silencing of NOD1 significantly reduced the phosphorylation of IRAK1 induced by TLR2 stimulation (n=9).

Conclusion: In the current study we show a strong interaction of NOD1 with other pattern recognition receptors in different synovial cells. In addition to a synergistic response of the parallel activation of these receptors, our data indicate a role of NOD1 in the promotion of TLR2 and IL-1β signaling pathways in RA.

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Innate Immune Stimulation Triggers Early-Onset Spondyloarthritis in HLA-B27/Human beta2 Microglobulin Transgenic Rats. Leonie M. van Duivenvoorde[1], Gleb M. Slobodin[2], Nimman Satumtira[2], Martha L. Dorris[2], Paul P. Tak[3], Dominique L. Baeten[1] and Joel D. Taurog[2]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]UT Southwestern Medical Center, Dallas, TX, [3]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam The Netherlands, Amsterdam, Netherlands

Background/Purpose: We recently proposed that spondyloarthritis (SpA) is driven by altered innate immune responses rather than by autoantigen-specific T or B cell responses[1].

The objective of this study aimed to test directly the hypothesis that stimulation of the innate immune system triggers experimental SpA.

Methods: Rats were injected subcutaneously with *Mtb* in oil or IFA with doses of 30 – 100 μg *Mtb*, which is lower than doses typically used to trigger arthritis adjuvant arthritis in non-tg LEW rats. In the first experiments, HLA-B27/hb2m rats from several different tg lines[2], HLA-B7/hb2m tg rats[2] and non-tg LEW control rats were injected with 30, 60 or 100 mg *Mtb* in IFA. The second set of experiments, used (21-3×283-2)F1 HLA-B27/hb2m tg and (120-4×283-2)F1 HLA-B7/hb2m control rats, both with high copy hb2m, and non-tg LEW controls. These rats were immunized with 30, 60 or 90 mg *Mtb* in IFA at 6 wk of age. Arthritis and spondylitis were monitored clinically.

Results: In the first set of experiments, arthritis was induced in both HLA-B27/hb2m and HLA-B7/hb2m tg rats at doses of ≤60 μg of *Mycobacterium tuberculosis* (*Mtb)* (B27/hb2m: 10/22; B7/hb2m: 8/17 vs. 1/24 non-tg controls). To test whether this effect was more specifically related to HLA-B27 and to assess the effect on spondylitis, which only occurs spontaneously in (21-3×283-2)F1 males, the second set of experiment was carried out as described in Methods. In the spontaneous SpA of (21-3×283-2)F1 rats, the males develop arthritis and spondylitis beginning at 110 d of age, reaching an incidence of 70% and 40% respectively. The female (21-3×283-2)F1 and both sexes of the (120-4×283-2)F1 B7/hb2m rats remain healthy. Data obtained in these rats are depicted in the table.

	Mycobacterium tuberculosis/IFA					
	90 μg Arthritis	Spondylitis	60 μg Arthritis	Spondylitis	30 μg Arthritis	Spondylitis
Males						
HLA-B27/hβ2m	2/2 (100%)	2/2 (100%)	2/2 (100%)	2/2 (100%)	5/6 (83.3%)	6/6 (100%)
HLA-B7/hβ2m	2/3 (66.6%)	2/3 (66.6%)	2/3 (66.6%)	2/3 (66.6%)	0/3 (0%)	0/3 (0%)
Females						
HLA-B27/hβ2m	3/3 (100%)	3/3 (100%)	3/3 (100%)	3/3 (100%)	1/3 (33.3%)	0/3 (0%)
HLA-B7/hβ2m	0/3 (0%)	0/3 (0%)	0/3 (0%)	0/3 (0%)	0/3 (0%)	0/3 (0%)

In males, 30 mg *Mtb* induced arthritis and/or spondylitis in 6/6 HLA-B27/hb2m rats, but not in the HLA-B7/hb2m controls. In females, 60 or 90 mg *Mtb* induced both arthritis and spondylitis in 6/6 of the HLA-B27/hb2m tg rats, but in none of the HLA-B7/hb2m controls. Arthritis and spondylitis appeared 2–3 weeks after immunization in both genders, over 40 d before the age of earliest onset of spontaneous arthritis in males.

Conclusion: These data indicate that low dose *Mtb*, an innate immune stimulus, triggers SpA in HLA-B27/hb2m tg rats. Moreover, it induces SpA in females, increases incidence in males, and accelerates and synchronizes disease onset, all of which will facilitate use of this model for experimental and preclinical research.

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Dual Signaling Pathways Dependent Upon the Adaptor Protein SLP-76 Lead to Distinct Natural Killer Cell Effector Functions. Rebecca May[1], Chih-Jung Hsu[1], Mariko Okumura[1], Gary A. Koretzky[2] and Taku Kambayashi[1]. [1]University of Pennsylvania, Philadelphia, PA, [2]University Pennsylvania, Philadelphia, PA

Background/Purpose: Natural killer (NK) cells are innate immune cells that provide a defense against intracellular pathogens and tumors by displaying cytotoxicity and producing immune-activating cytokines. NK activation is regulated by the expression of activating receptors that are finely counterbalanced by inhibitory receptors. Although mechanisms by which activating signals are blocked by inhibitory receptors are well defined, the proximal signaling pathways that lead to NK effector function are incompletely understood. Thus, we aimed to dissect the proximal signaling pathways downstream of the Ly49D activating receptor and focused our studies on SLP-76, an adaptor molecule which is important in mediating signals downstream of activating receptors in many hematopoietic cell types.

Methods: To investigate the involvement of SLP-76 in Ly49D signal transduction, SLP-76 phosphorylation and clustering at the plasma membrane was examined in Ly49D-activated NK cells. Furthermore, the role of SLP-76 in NK cell signal transduction, activation, and development was assessed in SLP-76-knockout (KO) compared to wildtype (WT) NK cells.

Results: When NK cells were activated through Ly49D, SLP-76 was phosphorylated and recruited to the plasma membrane. Furthermore, SLP-76 was required for optimal signal transduction through Ly49D as SLP-76 KO NK cells exhibited diminished ERK and Akt phosphorylation compared to WT NK cells. This correlated with decreased IFNg production and granule exocytosis by SLP-76 KO NK cells. Although NK cells from SLP-76 KO mice appeared developmentally mature based on expression of late maturation markers, we noted a selective defect in the acquisition of Ly49 family member inhibitory and activating receptors in SLP-76 KO NK cells. Since the defective function of SLP-76 KO NK cells might be related to perturbed development, SLP-76 was inducibly deleted in NK cells after maturation. Despite normal Ly49 receptor expression, NK cells inducibly deleted of SLP-76 still displayed defective IFNg production and granule exocytosis, suggesting that SLP-76 plays an important role in Ly49D-mediated NK cell function.

We next explored the mechanisms by which SLP-76 relocalizes from the cytosol to the plasma membrane. As this process depends on membrane-resident adaptor molecules LAT and NTAL in T cells and mast cells, we tested whether LAT and NTAL were similarly crucial for SLP-76 function in NK cells. Like SLP-76 KO NK cells, LAT/NTAL double KO (DKO) NK cells displayed significant functional defects, suggesting that LAT/NTAL may be required for SLP-76 activation. Surprisingly, membrane recruitment and phosphorylation of SLP-76 were intact in LAT/NTAL DKO NK cells following Ly49D stimulation. Cellular proliferation was also independent of LAT/NTAL, but dependent on SLP-76 expression.

Conclusion: These data suggest that NK cells use a novel LAT/NTAL-independent pathway leading to SLP-76 phosphorylation and membrane recruitment. This novel pathway leads to distinct NK cell effector functions. Together, these results demonstrate a critical role of SLP-76 in NK cell activation downstream of multiple signaling pathways emanating from the Ly49D activating receptor.

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Untreated Juvenile Dermatomyositis: Altered Peripheral Blood Natural Killer Cell Receptors Associated with Increased Natural Killer Cell Localization in Inflamed Muscle. Sheela Shrestha[1], Maurice O'Gorman[2], Jordan Orange[3], Chelsea Tessler-Verville[1], Katelin Snow[1], Gabrielle Morgan[1], Deli Wang[4] and Lauren M. Pachman[2]. [1]Children's Memorial Hospital, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Children's Hospital of Philadelphia, Philadelphia, [4]Northwestern University's Feinberg School of Medicine, Chicago, IL

Background/Purpose: We have observed decreased levels of circulating $CD3^{-}CD56^{+}$ natural killer (cNK) cells in children with untreated JDM (Arthritis Rheum 58:S225, 2008).

Objectives: 1) To further characterize specific surface and intracellular receptors on cNK cells in untreated JDM with: a) low, or b) normal cNK (age-normed) at diagnosis and after clinical response to therapy, compared with healthy pediatric controls; 2) Evaluate NK localization in inflamed, untreated JDM muscle.

Methods: Definite/probable JDM and healthy pediatric controls (IRB# 2008–13457) were enrolled. We tested frozen peripheral blood mononuclear cells (PBMCs) from untreated white JDM females with low (Group 1, n=6) and normal cNK (Group 2, n=5) at diagnosis; in both groups the cNK normalized after institution of immunosuppressive therapy (19.92 ± 11.46 mo after diagnosis). Controls for the two groups (n= 7 and 8 respectively) were age matched. Marker expressions on viable $CD3^{-}CD56^{+}$ NK cell was measured by flow cytometry using FlowJo software. **Results:** were expressed as the percentage (%) NK positive for a specific marker and median fluorescence intensity (MFI) of the specific marker. Results were analyzed using the paired t-test for the two JDM groups and the student's t-test for comparing the JDM patients and controls ($p<0.05$ as significant). Using dual stain immunohistochemistry, NK cells were identified in 27 untreated JDM muscle tissue as $CD16^{+}/CD56^{+}$ cells (n=16, low cNK; n=11, normal cNK; n=7, controls) Wilcoxon Rank Sum test was used for comparisons ($p<0.05$ as significant).

Results: In Group 1 JDM (low cNK at diagnosis), 7 out of 17 NK receptors analyzed at diagnosis were significantly reduced compared to the levels observed when the cNK normalized, and to controls. The density (MFI) of 5 of these receptors (CD16, CD2, NKG2D, CD11b, and CD94) was also significantly reduced, ($p<0.05$). After cNK levels normalized following therapy, the % of NK cells expressing NKp46 increased, but % of NK cells expressing CD158b was significantly lower than controls, ($p<0.05$). The DNAM1+ cNK cells were decreased to 50% normal range at diagnosis, and remained depressed (78% of normal) after response to therapy. In contrast, in Group 2 JDM children (normal cNK at diagnosis), only CD2 was below the healthy control group (both % and MFI), but increased to normal ranges after therapy. This group also had a higher % of cNK cells expressing perforin at diagnosis (92.06 ± 5.81 vs 84.90 ± 4.16, $p=<0.05$) compared to the control group. In the diagnostic muscle biopsies, the NK cell counts from JDM with either low or normal cNKs were significantly higher than controls ($p=0.012$, $p=0.044$) respectively.

Conclusion: At diagnosis, the percentage of NK cells expressing specific receptors and the density of these receptors expressed on the cell surface differed from levels observed post therapy and from healthy control age-matched children. Irrespective of the absolute count of cNK cells, we found a significant increase in NK cells localized in inflamed muscle tissue of untreated children with JDM compared to healthy controls. These data suggest NK cells may be involved in the pathogenesis of muscle damage and disease in JDM.

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Antigen Cross-Presentation Is Essentially Required for the Pathogenesis of Lupus Nephritis: Essential Role of Endosomal Trafficking. Ken Tsumiyama[1], Mai Takimoto[1] and Shunichi Shiozawa[2]. [1]Kobe University Graduate School of Health Science, Kobe, Japan, [2]Kobe University Graduate School of Health Science and Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Background/Purpose: We repeatedly immunized mice normally not prone to autoimmune diseases with the same antigen to show that repeated immunization reproducibly led to the development of systemic lupus erythematosus (SLE). Importantly, autoantibodies are induced *via de novo* T cell receptor (TCR) revision at periphery, giving rise to a novel T cell type we term an autoantibody-inducing CD4 T (*ai* CD4 T) cell. The *ai* CD4 T cell not only stimulated B cells to generate varieties of autoantibodies including rheumatoid factor, anti-Sm and anti-dsDNA antibodies but also helped full maturation of CD8 T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to produce lupus nephritis. Here we examine the molecular detail of antigen cross-presentation in relation to lupus nephritis.

Methods: Bone marrow-derived dendritic cell (BMDC) from BALB/c mice was cultured with fluorescent-labeled ovalbumin (OVA). Early endosome antigen 1 (EEA1) and calnexin were detected to identify endosome and endoplasmic reticulum (ER), respectively, by using immunofluorescent staining. To examine whether or not engulfed antigen is exported from endosome to cytoplasm, translocon Sec61 was also detected. Localization of OVA, endosome, ER and Sec61 was examined under confocal laser scanning microscopy. For *in vivo* study, BALB/c mice were repeatedly immunized with OVA to induce tissue injuries. MG132 was co-immunized with OVA to inhibit proteasomal degradation of antigen. To investigate whether or not antigen peptide-MHC class I complex is transported from endosome to cell surface, mice were immunized with OVA in the presence of primaquine (PQ), an inhibitor of endosomal trafficking to cell surface. We also inhibited Sec61 *in vivo* by treating with exotoxin A. Proteinuria and histopathology of kidney

were assessed. IFNγ-producing CD8 T cell in spleen was detected under flow cytometry.

Results: In BMDC, OVA was first co-localized with an endosomal marker EEA1, and then gradually separated from EEA1. OVA was never co-localized with an ER marker calnexin. Instead, translocon Sec61 did co-localize with OVA, the findings indicated that OVA was exported from endosome to cytoplasm *via* Sec61. The *in vivo* treatment with MG132, an inhibitor of proteasomal degradation, inhibited the generation of fully mature CTL and lupus nephritis. Proteinuria and renal damage were not observed in the mice treated with PQ. Full maturation of CD8 T cell to IFNγ-producing CTL was also inhibited. Since PQ inhibits transport from endosome to cell surface, the finding indicates that antigen peptide-MHC class I complex is directly transported from endosome to cell surface for antigen cross-presentation. Further, the treatment with exotoxin A, an inhibitor of Sec61, also inhibited the maturation of effector CTL and the development of lupus nephritis, indicating that export of antigen from endosome to cytoplasm *via* Sec61 is indispensable for antigen cross-presentation.

Conclusion: Endosomal trafficking, bypassing ER, is required for antigen cross-presentation. Inhibition of this pathway resulted in inhibition of lupus nephritis. Thus, export of antigen from endosome to cytoplasm *via* Sec61 is essential for antigen cross-presentation and induction of lupus tissue injuries.

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Immune-Complex Induced Inflammation Is Augmented in the Absence Nicotinic Acetylcholine Receptors in Mice. Milena Vukelic[1], Gloria Koo[1], Patricia M. Redecha[1] and Jane E. Salmon[2]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

Background/Purpose: Integrated neural networks influence immune responses. We reported that activation of the "cholinergic antiinflammatory pathway" by stimulation of nicotinic acetylcholine receptors (nAchR) expressed on immune cells, neutrophils and monocytes, attentuates activation triggered by innate C5a and Fcγ receptors in human phagocytes. In vitro ligation of nAchR decreased markers of activation related to tissue damage: reactive oxygen species production, phagocytosis, TNFα production and expression of adhesion molecules. Here, our goal was to analyze the role of α7 cholinergic receptors on early phase of immune complex- mediated injury in vivo by using mice deficient in a7 subunit of nAchR ($\alpha7nAchR^{-/-}$) and their wild type littermates.

Methods: Mouse (WT (C57/Bl6) or $\alpha7nAchR^{-/-}$) or human neutrophils (PMNs) were incubated with C5a (100nM) in a presence or absence of cholinergic agonists, GTS21 (specific α7nAChR agonist) (1μM) or control medium. TNFα concentrations were analyzed by ELISA. IkB phosphorylation was detected by western blot. Peritoneal reverse passive Arthus reaction was initiated by injecting OVA i.v. and anti-OVA IgG i.p. After 1.5hrs PMN recruitment in peritoneal lavage fluid was assessed by FACS.

Results: Compared to WT mice, naïve $\alpha7nAchR^{-/-}$ mice had a greater number of neutrophils, macrophages and mast cells in peritoneal cavity ($0.58\pm0.2\times10^4$ vs. $7.4\pm4.1\times10^4$ $p<0.05$; $96\pm5\times10^4$ vs $144\pm13\times10^4$ $p<0.05$; $35\pm5\times10^4$ vs $58\pm8\times10^4$) with later two expressing higher levels of C5aR and FcγR on their surface, although bone marrow granulopoesis was comparable in both strains. Bone marrow derived $\alpha7^{-/-}$ macrophages spontaneously produced higher TNFα in culture medium than WT macrophages (33±6 vs 82±23 pg/ml) and TNFα levels were higher in the peritoneal cavity of naïve $\alpha7nAchR^{-/-}$ animals (120±20 vs 197±43 pg/ml). When $\alpha7nAchR^{-/-}$ mice were challenged with the reverse passive Arthus reaction, early neutrophil accumulation was enhanced to approximately 245% of wild type levels ($51\pm12\times10^6$ vs. $124\pm27\times10^6$cell/ml; p=0.024) and TNFα in peritoneal lavage fluid was also markedly increased (243±60 vs. 439±96 pg/ml; p=0.023). To examine the basis of the suppressive effect of ligation nAchR, we stimulated PMNs with C5a in the presence and absence of specific α7nAChR agonist, GTS21. C5a mediated NFkB activation was markedly decreased by GTS21 in association with blockade of phosphorylation of its inhibitor IKB; GST21 did not alter phosphorylation of IKB in unstimulated cells.

Conclusion: These results indicate that α7nAchR expressed on innate immune cells play critical role in suppressing inflammation at sites of immune complex deposition and suggest that tonic stimulation of α7nAchR attenuates the FcγR- and C5aR-mediated activation of the NFkB-proinflammatory cytokine axis, a pathway that activates resident and newly recruited leukocytes. Our findings have implications for tissue injury in SLE and RA and suggest new strategies to reduce damage at the sites of immune complex deposition.

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Association of Functional *Fcgammariic* (*FCGR2C*) Polymorphisms with Rheumatoid Arthritis in African Americans. Jianming Wu[1], Xinrui Li[2], Rui Lin[3], Howard Wiener[4], Hemant Tiwari[4], Cunren Liu[4], Travis Ptacek[2], Jeffrey C. Edberg[5], S. Louis Bridges Jr.[6] and Robert P. Kimberly[4]. [1]University of minnesota, St. Paul, MN, [2]University of Alabama at Birmingham, Brimingham, AL, [3]University of Minnesota, St. Paul, MN, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [6]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Functional polymorphisms in human Fcg receptor (FcgR) genes play important roles in the pathogenesis of various autoimmune diseases. *FcgRIIC* (*FCGR2C* or CD32C), an activating Fcg receptor gene, contains a stop codon/open-reading frame polymorphism (SNP 202T>C, rs10917661) and two novel SNPs at the intron 6 splicing junctions. The current study was intended to investigate whether *FcgRIIC* polymorphisms (SNPs) are associated with rheumatoid arthritis (RA) and to examine biological functions of the *FcgRIIC* SNPs.

Methods: *FcgRIIC* SNP 202T>C and the intron 6 SNPs (SNP6L-A>G and SNP6R-C>G) were genotyped in 833 African American (AA) healthy controls and 764 AA RA patients using Pyrosequecing methodology. SNP allele, genotype, and haplotype distributions were compared between RA and healthy controls. The functions of the *FcgRIIC* SNP were investigated in mini-gene and transfected cell systems.

Results: Our genotyping data demonstrated that the SNP 202C (open-reading frame allele) is significantly associated with RA susceptibility ($P = 0.0002$, Odds Ratio 1.584; 95% CI: 1.238–2.027) in AA. In addition, the frequency of the SNP-6L G allele (which forms a canonical splicing donor motif) is significantly increased in AA RA patients compared to controls ($P = 0.0007$, OR = 1.923, 95% CI 1.312–2.819). No association of SNP-6R alleles with RA susceptibility was observed in AA ($P = 0.9400$, OR = 1.005, CI = 0.874–1.156). The haplotype 202C/6L-G/6R-G is a major risk factor for RA in African Americans ($P = 0.015$, OR 3.533; 95% CI: 1.278–9.772). Functionally, the expression of SNP 202T allele enhanced the inhibitory FcgRIIB expression in human B cells. Furthermore, the intron 6 SNPs are the main origin of the various FcgRIIC mRNA species and the 202C/6L-G/6R-G is the sole FcgRIIC SNP haplotype capable of producing an activating receptor.

Conclusion: The functional *FcgRIIC* SNP haplotype 202C/6L-G/6R-G is a genetic marker for RA in AA and may have important biological consequences.

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Low Copy Number of Fcgamma Receptor 3B Gene Is a Disease Susceptibility and Severity Factor in Primary Sjøgren's Syndrome. Johannes C. Nossent[1], Maureen Rischmueller[2], Andrea Becker-Merok[1] and Sue Lester[2]. [1]University of Tromsø, Tromso, Norway, [2]Queen Elizabeth Hospital, Adelaide, Australia

Background/Purpose: Cross linking of immune-complexes (IC) with the neutrophil specific Fc-gamma receptor 3b (Fcgr3b) initiates IC clearance. IC contribute to the complications of and primary Sjøgren's syndrome (pSS) and Systemic Lupus Erythematosus (SLE). Copy number (CN) variation of the Fcgr3b gene alters the Fcgr3b function on the cell membrane and thus influence the clearance of IC. We investigated whether FcgR3b CNV is associated with disease susceptibility and severity in adult patients with pSS.

Methods: Cross sectional study of patients with established pSS (n= 174), SLE (n=107) and healthy controls (n= 162). FcGr3b CNV was determined by three different RT-PCR parameter estimations (Ct-, Cy0 and CpD1) and confirmed by the Fcgr2c/Fcgr2a paralog ratio test. Clinical and serological data were analyzed for their association with FcGr3b CN.

Results: Low FcGr3b CN was significantly more frequent in SLE (OR 4.15, p=0.003) and pSS (OR 2.67, p=0.013) patients than in controls. In pSS patients, low FcGr3b CN was associated with daytime sleepiness, absence of anti-Ro/La and lower levels of RF and IgG. In contrast, low FcGr3b CN was associated with increased levels of antibodies against dsDNA, C1q and ribosomal P and nephritis in SLE patients. FcGr3b CN did not associate with serum levels of B-cell activating factor in either disease.

Conclusion: Low FcGr3b CN is a susceptibility factor for both pSS and SLE and associates with more severe disease and pathogenic autoantibodies in SLE and extraglandular features in pSS. The contrasting findings for low FCGr3B CN and levels of anti-dsDNA and anti-Ro/La antibodies indicates selective handling of autoantibodies by Fcgr3b on neutrophils in autoimmune diseases.

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C1q Diverts Lupus Immune Complexes Away From CD14^{dim}CD16+ "Patrolling" Monocytes. Pradipta Ghosh*, Alice Wiedeman*, Deanna M. Santer, Vivian E. Vlamakis and Keith B. Elkon. University of Washington, Seattle, WA

Background/Purpose: Immune-complexes (IC) cause inflammation in systemic lupus erythematosus (SLE) in significant part by engagement of FcγR on neutrophils, monocyte/macrophages and plasmacytoid dendritic cells (pDCs). We previously observed that in the absence of C1q, IC bind to FcγRII on pDCs and potently stimulate IFN-α production; whereas IC containing C1q bind predominantly to monocytes leading to a reduction in IFN-α production by pDCs. Heterogeneity of human peripheral blood monocytes is known, but recently 3 subpopulations have been defined based on surface expression of CD14 and CD16. Both the CD14+CD16- and the CD14+CD16+ monocytes were described in mice as having "inflammatory" properties while the CD14^{dim}CD16+ population is thought to be a "patrolling" monocyte that responds to invading pathogens as well as to circulating ICs. Given the differing profiles of these newly defined monocyte subsets, we asked whether SLE-IC show preferential binding to the different monocyte subsets, how this binding is altered in the presence of C1q and what are the functional consequences in regards to inflammatory cytokine signaling.

Methods: IC were formed with diluted SLE serum (1:2000) and 0.5% U937 necrotic cell extract as a source of antigen or diluted SLE serum (1:1000) and Alexa Fluor 647 labeled RNP. Monocyte subsets were purified by flow sorting (FACSAria). IC were added to peripheral blood mononuclear cells (PBMCs) or purified monocyte subsets (> 95% pure) prepared from healthy donors in the presence or absence of C1q for 30 minutes on ice (binding studies) or 20 hours (ELISA and flow cytometry). Cytokines in culture supernatants were quantified by ELISA and expression of cell surface markers and the monocyte activation marker CD86 were determined by flow cytometry.

Results: When monocytes subsets were flow sorted according to cell surface markers, CD14 and CD16, and incubated with SLE-IC in the absence of C1q, the IC bound to all monocyte subsets. Similar to one published study, CD14^{dim}CD16+ monocytes (but not the CD14+CD16+ or CD14+CD16- populations) uniquely responded to SLE-IC stimulation by producing TNF-α. In addition, these IC induced strongest up-regulation of CD86 on the CD14^{dim} subset (two-fold increase of MFI). Whereas the addition of C1q enhanced SLE-IC binding to all monocyte subsets as determined by MFI of the labeled RNP antigen, the distribution of binding changed to favor the CD14+CD16+ monocytes (fold increase = 6.13±0.93) and the CD14+CD16- monocytes (fold increase =7.17±0.91) compared to the pro-inflammatory CD14^{dim} (fold increase = 3.00±0.48, $p<0.05$ compared to the other subsets).

Conclusion: Under steady state conditions SLE immune complexes bind to all of the presently described monocyte subsets, but induce CD86 up-regulation most strongly on the CD14^{dim} population. The presence of C1q diverts the IC away from the TNF-α producing CD14^{dim} "patrolling" monocytes and towards the less inflammatory CD14+CD16+ and CD14+CD16- monocyte subsets. Our findings point to a novel mechanism by which C1q may protect against inflammation in SLE.

*Contributed equally to the work

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Functional Effects Attributable to the R77H Lupus Susceptibility Variant Encoded by *ITGAM*. Benjamin Rhodes[1], Barbara G. Fürnrohr[1] and Timothy J. Vyse[2]. [1]King's College London, London, United Kingdom, [2]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom

Background/Purpose: Variation at *ITGAM* (CD11b – the alpha chain of complement receptor 3 (CR3)) is among the strongest genetic susceptibility effects identified in human lupus, with rs1143679, encoding an R77H amino acid change, implicated by genetic analysis as the functional variant.

Methods: We studied COS7 cells transiently transfected with wild-type (WT) and 77H variant *ITGAM* alongside the invariant beta chain to reconstitute CR3. Transfected cells were used for a static adhesion assay in 96-well plates coated with various protein ligands and for a phagocytic assay using iC3b opsonised sheep erythrocytes (sRBC). Assays were replicated using *ex-vivo* monocytes (adhesion) and monocyte-derived macrophages (phagocytosis) from healthy genotyped volunteers.

Results: Phagocytosis of iC3b coated sRBC by COS cells was significantly impaired for cells expressing the 77H mutant compared with WT (mean at 30 minutes 0.48 sRBC/phagocyte vs. 0.87sRBC/phagocyte, $P<0.001$). The adhesion of sRBCs to the transfected cells was not impaired. Transfected cells bound specifically to 96-well plates coated with known CR3 ligands, most strongly iC3b and DC-SIGN in this static adhesion assay. However, the binding of the 77H transfects to protein coated wells was 39% lower than WT transfects to iC3b and 19% lower to DC-SIGN. Only 1% of the healthy European population are homozygous for the rs1143679, making the recruitment of healthy human participants for study difficult. Nonetheless we also have preliminary data in *ex-vivo* monocytes that demonstrates functional differences in adhesion and phagocytosis consistent with those found in our cell line model.

Conclusion: We demonstrate functional consequences of the R77H variation in a cell line model and extend this to provide preliminary evidence that these effects are also observed in *ex-vivo* myeloid cells from healthy individuals. Although further work is required it is apparent that the functional consequences of the rs1143679 mutation may fit within existing theories of lupus pathogenesis that include complement mediated clearance of apoptotic cells and immune complexes.

999 WITHDRAWN

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Anti-Inflammatory Profile of AS2444697, A Novel Interleukin-1 Receptor-Associated Kinase-4 Inhibitor. Junko Imanishi, Takeshi Ishikawa, Emiko Imamura, Hidekazu Mizuhara, Haruna Iwaoka, Ball Evelyn, Hiroshi Inami, Tsuyoshi Mizutani, Junko Watanabe, Hiroyuki Usuda, Shinya Nagashima, Tomonori Ito, Toru Kontani, Yasuaki Shimizu and Seitaro Mutoh. Astellas Pharma Inc., Tsukuba, Japan

Background/Purpose: Toll-like receptors (TLRs) function in the innate immune response by recognizing pathogen-associated molecular patterns or host-derived "danger signals" produced during tissue injury or inflammation. Interleukin-1 (IL-1) receptor-associated kinase-4 (IRAK-4) is known to be a pivotal mediator on the TLR/IL-1R signaling pathway, as both IRAK-4-knockout mice and IRAK-4-deficient human patients exhibit functional defects in this pathway. Observations of increased expression of TLRs and TLR ligands in patients with rheumatoid arthritis (RA) suggest that these receptors may contribute to RA pathogenesis. Here, we report the pharmacological profile of AS2444697, a novel IRAK-4 inhibitor.

Methods: In vitro IRAK-4 inhibitory activities of AS2444697 were evaluated using recombinant human and rat IRAK-4 enzymes and synthetic substrates (FGL ARF SRF AGS SPS QSS MVA RTQ TVR GTL A). IL-1β-mediated IRAK-1 degradation in A549 (human alveolar basal epithelial cell line) was assessed with western blot analyses using anti-IRAK-1 antibody (Cell Signaling Technology). The effect of AS2444697 on IL-1β-, TNF-α- and TLR ligands- (LPS for TLR-4, peptidoglycan for TLR-2, imiquimod for TLR-7) stimulated cytokine production were examined using A549 and two primary cells, PBMCs (Peripheral Blood Mononuclear Cells from healthy volunteers) and HFLS-RA (Human Fibroblast-Like Synoviocytes-Rheumatoid Arthritis from RA patient). In vivo anti-inflammatory activity was evaluated using lipopolysaccharide (LPS) induced cytokine production and adjuvant-induced arthritis (AIA) in rats.

Results: AS2444697 inhibited human and rat IRAK-4 with the same IC_{50} values of 21 nM. It also suppressed IL-1β-mediated IRAK-1 degradation in A549 in a concentration-dependent manner with a range of 10 nM–10 μM. It also inhibited IL-1 (1 ng/mL) and TNFα (3 ng/mL) stimulated IL-6 production from A549 with IC_{50} of 250 nM and 3900 nM, respectively. AS2444697 inhibited LPS- (0.01 ng/mL) induced TNF and IL-6 production from PBMCs, with IC_{50} values of 47 and 59 nM, respectively. In addition, AS2444697 was also effective on IL-6 production from HFLS-RA stimulated with IL-1β 1 pg/mL and TNFα 10 pg/mL (IC_{50}: 170 and 380 nM respectively). AS2444697 inhibited TNFα production from LPS (3 ng /animal) injected rat dose dependently with an ED_{50} of 3.4 mg/kg. Further, prophylactic administration of AS2444697 ameliorated paw swelling in AIA rats with an ED_{50} of 4.5 mg/kg (p.o. b.i.d).

Conclusion: AS2444697 inhibited not only TLR, IL-1β but also TNFα pathway. These results suggest that AS2444697 will an attractive agent for the treatment of RA.

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MicroRNA-15a Regulates Etk/BMX Expression and IL-6 Release In Activated Rheumatoid Synoviocytes. Ghada Alsaleh[1], Lucas Philippe[1], Angélique Pichot[1], Sébastien Pfeffer[2], Jacques-Eric Gottenberg[1], Jean Sibilia[1], Philippe Georgel[3] and Dominique Wachsmann[1]. [1]EA4438 Laboratoire Physiopathologie des Arthrites, Illkirch-Strasbourg, France, [2]Architecture et Réactivité de l'ARN, Université de Strasbourg, Strasbourg, France, [3]Laboratoire d'ImmunoGénétique Moléculaire Humaine, Strasbourg, France

Background/Purpose: The Toll like receptor family is the best characterized group of innate immune receptors in term of known ligands, signaling pathways and functional relevance. TLRs are expressed by immune cells and also by resident cells of the joint such as fibroblast-like synoviocytes (FLS) which play a crucial role in RA. Etk/BMX, a Btk Family Tyrosine Kinase, is a key adaptor involved in signaling downstream of TLR2, TLR4, and integrin $\alpha 5\beta 1$, linking pathogen-associated molecule detection to the initiation of proinflammatory response by activated rheumatoid fibroblast-like synoviocytes (RA FLS). We previously demonstrated that the inhibition of Etk impaired IL-6 release by LPS activated-FLS. Many data indicate that miRNA can exert negative effects in inflammatory pathways and this prompted us to look for miRNA which could target directly TLRs signaling and control negatively cytokine release in response to TLRs stimulation, such as Etk.

Methods: RA FLS were isolated from synovial tissues from different patients. Cells were stimulated with TLR2 (BLP) and TLR4 (LPS) ligands and quantitative RT-PCR was performed to evaluate miRNA and mRNA expression in RA FLS. Transient transfection of FLS with mimic 15a was performed using the Human Dermal Fibroblast NucleofectorTM kit from Amaxa. All assays were performed 48 h post transfection. Transfection of HEK293 cells with reporter constructs and miR-15a mimic or antagomir was performed using Lipofectamine. Luciferase activity were determined using the dual-luciferase reporter assay system. IL-6 release was measured in culture supernatants by ELISA according to the manufacturer's instructions.

Results: We first showed that RA FLS expressed constitutively Etk, and that its expression is up-regulated in response to LPS and BLP. To identify miRNA targeting Etk mRNA, RA FLS were activated with LPS for six hours and a miRNA microarray analysis was performed. Among the down-regulated miRNAs, miR-15a was predicted to target Etk. This down regulation was confirmed by quantitative RT-PCR. As *in silico* analysis predicted that miR-15a might possibly bind to the 3'-UTR of human Etk transcript, we transiently transfected into HEK-293 cells a reporter construct that contain the firefly luciferase gene fused to the Etk 3'-UTR containing the putative miR-15a interactor site along with miR-15a. We observed a downregulation of the luciferase activity, indicating that the 3'-UTR of Etk mRNA is directly targeted by miR-15a. Moreover transfection of RA FLS using miR-15a mimics decreased IL-6 release in response to LPS and BLP.

Conclusion: These results suggest an important role of miR-15a in the control of Etk expression and IL-6 synthesis and indicate that its expression may be critical to prevent an excessive inflammatory response.

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Knock-Down of Galectin-3 Inhibits Spontaneous and Lipopolysaccharide -Induced IL-6 Secretion In Fibroblast-Like Synoviocytes. Uri Arad, Avital Angel-Korman, Sharon Amir, Sharon Tzadok, Ortal Seagal, Ori Elkayam and Dan Caspi. Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Background/Purpose: Galectin-3 is a β-galactoside-binding lectin that plays an important role in the modulation of immune responses. Galectin-3 levels are increased in rheumatoid arthritis (RA) synovial tissue, synovial fluid and peripheral blood. Recombinant exogenous galectin-3 stimulates proinflammatory cytokine secretion by fibroblast-like synoviocytes (FLS). Our objective was to examine the effect of galectin-3 knock-down on spontaneous and lipopolysaccharide (LPS)-induced secretion of IL-6 in FLS from RA and osteoarthritis (OA) patients.

Methods: FLS from RA and OA patients were harvested from synovial fluid aspirates or directly from synovial tissue obtained during orthopedic surgery. The expression of galectin-3 was knocked-down by transfection of siRNAGal3 vs. siRNACtrl. The XTT test was used to evaluate cell viability, and galectin-3 knock-down was confirmed by western blotting. IL-6 secretion with and without lipopolysacharide (LPS)-stimulation was determined by ELISA.

Results: Maximal knock-down of galectin-3 expression was observed on the 3rd day post transfection, in both RA and OA FLS (50–75% knock-down). Galectin-3 knock-down caused a significant decrease in IL-6 secretion in both cell types (OA – 46%, RA – 21.5%, $p<0.05$). The inhibition of IL-6 secretion was not caused by decreased cell viability. LPS-stimulation caused a 35-fold increase in IL-6 secretion, and galectin-3 knock-down substantially inhibited LPS-induced IL-6 secretion (OA- 74%, RA- 33%, $p<0.05$).

Conclusion: siRNA-transfection is an effective means of suppressing galectin-3 expression in FLS. Knock-down of galectin-3 inhibited both spontaneous and LPS-induced IL-6 secretion. It appears that galectin-3 is an important component in the regulation of IL-6 secretion in FLS and may be targeted for suppressing joint inflammation.

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Vimentin Suppresses the Production of Reactive Oxygen Species and the Antimicrobial Response Via p47phox. Nirit Mor-Vaknin, Maureen Legendre, Yue Yu, Carlos H.C. Serezani, Sanjay Garg, Anna Jatzek, Michael D. Swanson, Seagal Teitz-Tennenbaum, Antonello Punturieri, N. Cary Engleberg, Ruma Banerjee, Marc Peters-Golden and David Markovitz. University of Michigan, Ann Arbor, MI

Background/Purpose: Vimentin, a widely expressed intermediate filament, is considered to function mainly as a structural protein that stabilizes the intracellular architecture. However, vimentin is particularly abundant in macrophages and is secreted in response to inflammatory cytokines and apoptosis. It was recently reported that mutation and citrullination of vimentin can trigger autoantibodies responses in arthritis patients. Susceptibility to mutations and general instability of the genome found in the RA synovium is thought to be the cause of DNA damage induced by persistent oxidative stress. Here we report that vimentin impedes production of reactive oxygen species (ROS) by interfering with the assembly and function of the NADPH oxidase complex. Remarkably, the absence of vimentin conferred significant resistance to death by bacterial septicemia *in vivo*.

Methods: Peritoneal and bone marrow macrophages were obtained from vimentin knockout and wild-type controls. Cells were analyzed for bacterial phagocytosis, bacterial killing and production of reactive oxygen species by chemiluminescence, H2O2 and NADPH production measurements. Redox was measured by high-performance liquid chromatography. Immunopreceipitation and Western blot analysis were performed to show the interaction between the p47 phox subunit of the NADPH oxidase complex with vimentin at the plasma membrane. Co-localization of p47phox and vimentin at the plasma membrane was confirmed via confocal fluorescence microscopy analysis.

Results: Here we report that peritoneal and bone marrow-derived macrophages of vimentin knockout (Vim KO) mice generated higher levels ROS upon activation compared with wild-type (WT) controls leading to reduced intracellular redox potential. This enhanced production of ROS by Vim KO phagocytes correlated with an improved capacity to mediate *in vitro* bacterial killing. Lack of vimentin accelerated the p47phox subunit of the NADPH oxidase complex from the cytosol to the plasma membrane via its interaction with the trans-located p47phox subunit at the plasma membrane. Challenging Vim KO and WT mice with a lethal dose of *Escherichia coli* (*E. coli*) demonstrated that lack of vimentin improved bacterial clearance and prolonged mouse survival.

Conclusion: These findings suggest that vimentin impedes production of ROS by interfering with the assembly and function of the NADPH oxidase complex. Remarkably, the absence of vimentin conferred significant resistance to death by bacterial septicemia. Based on our results, we propose that vimentin modulates the intensity of the innate immune response by attenuating ROS production, a surprising role for this highly abundant but poorly understood intermediate filament protein that has been recently implicated in the pathogenicity of arthritis.

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SNAPIN Is Overexpressed in Rheumatoid Arthritis Synovial Tissue and Involved in Endosomal Lysosomal Pathway. Bo Shi[1], Qi Quan Huang[1], Andrea Dorfleutner[1], Christian Stehlik[1], Paul P. Tak[2] and Richard M. Pope[1]. [1]Northwestern University, Feinberg School of Medicine, Chicago, IL, [2]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: We identified Snapin, a SNARE complex protein required for synaptic vesicle docking and fusion, as a TLR2 binding molecule

in yeast two-hybrid system in screening cDNA library constructed from synovial tissue of RA patients. We further confirmed Snapin is a TLR2 agonist. Besides, Snapin was also reported to play a critical role in late endosome trafficking and endosome-lysosome fusion. In this study, we examined Snapin expression in synovial tissue of RA patients by immunohistochemistry. Further, we explored the Snapin's role in endosome-lysosomal pathway in macrophages.

Methods: Snapin expression in synovial tissue was examined by histology, and single and two-color immunohistochemistry. Snapin knock down in macrophages were performed using siRNA technique. Snapin, Lamp1, 2 and Lac3 protein levels were checked by Western blot analysis. The localization and co-localization of Snapin with Rab7 in macrophages were studied with confocal immunofluorescence microscopy.

Results: Snapin was significantly increased in RA synovial tissue compared to control synovial tissues from arthritis-free controls. The percentage of Snapin positive cells (lining: 21 vs 60%, sublining: 18 vs 54%; $p < 0.01$) and the Snapin expression score (lining: 18 vs 124, sublining: 10 vs 144; $p < 0.05$), reflecting the percent positive and intensity of staining, were both significantly increased in the synovial lining and in the sublining of the RA synovial tissues compared to the controls. Snapin expression level was correlated with inflammation. Two color immunohistochemistry showed that CD68 positive macrophages, especially those in the sublining region, strongly expressed Snapin in RA synovial tissue. Additionally, within lymphoid aggregates some CD3 positive T cells also expressed Snapin. Therefore, studies were performed to determine the homeostatic function of Snapin in macrophages. Employing in-vitro differentiated macrophages, Snapin was present in a diffuse granular pattern and it co-localized with Rab7, a marker for late endosomes. The forced reduction of Snapin by siRNA in macrophages resulted in increased Lamp-1, Lamp-2, two lysosomal markers, and LC3-II, a marker of autophagosomes, suggesting that Snapin might be functionally involved in endosome to lysosome fusion in macrophages. Studies are underway to determine the potential role of Snapin in the autophagy-lysosomal pathway, which may contribute to the pathogenesis of RA.

Conclusion: Snapin was highly expressed in RA synovial tissue, especially in sublining macrophages. Snapin was localized in the late endosomes and may play an important role in endosome to lysosome fusion in macrophages.

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Mechanisms of Human Monocytes and Macrophages to Adapt to Hypoxia. Monique Fangradt[1], Timo Gaber[1], Martin Hahne[1], Paula Hoff[1], Manuela Jakstadt[1], Cindy Strehl[1], Gerd-Rüdiger Burmester[2] and Frank Buttgereit[1]. [1]Charité University Medicine, Berlin, Germany, [2]Charité University Hospital, Berlin, Germany

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease of diarthrodial joints, characterized by infiltration of immune cells and local tissue hypoxia. Migrating monocytes and differentiated macrophages are forced to adapt their energy metabolism to hypoxia. Hypoxia-inducible factor (HIF)-1a is known to act as key regulator for the adaptation of migrating cells into hypoxic areas. The aim of this study was to investigate the mechanisms used by human monocytes and macrophages to adapt to hypoxia.

Methods: Isolated human $CD14^+$ monocytes were incubated for 5h under normoxic and hypoxic conditions with or without PMA stimulation, respectively. Cell survival rates were measured by 7-AAD staining and subsequent FACS analyses. Using a Nuclear Extract Kit (Actife Motiv), nuclear and cytosolic fractions were prepared in order to detect HIF-1a and NFkB by immunoblot. For the experiments with macrophages, primary human monocytes were differentiated into monocyte derived macrophages (hMDM) using M-CSF. The effects of normoxia and hypoxia on gene expression were compared between monocytes and hMDMs using quantitative PCR.

Results: Hypoxia was found to improve the survival of primary human monocytes. Furthermore, monocytes stabilize HIF-1a under hypoxic conditions in a time dependent manner. Interestingly HIF-1a was detected exclusively in the cytoplasm, but not in the nucleus of unstimulated cells. PMA stimulation, however, resulted in the translocation of HIF-1a into the nucleus with PKC-a/b_1 being an essential regulator of this process. Also differentiation of monocytes into macrophages was found to be accompanied by the translocation of HIF-1a into the nucleus. In monocytes, hypoxia does induce the expression of glycolytic genes despite the absence of HIF-1a in the nucleus. NFkB1 turned out to be the transcription factor which mediates the regulatory effect under these conditions.

Conclusion: Monocytes migrate into inflamed and non-inflamed tissues where they differentiate into macrophages. During this differentiation process, HIF-1a translocates from the cytoplasm (monocytes) into the nucleus (macrophages). Therefore, while in macrophages HIF-1a seems to serve as key regulator for the adaptation to hypoxia, this function is fulfilled by NFkB1 in monocytes.

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The Key Apoptotic Cell Receptor Mer and Its Ligand Gas6 Are Differentially Regulated in M2 Macrophage Subsets. Gaetano Zizzo, Brendan A. Hilliard, Marc Monestier and Philip L. Cohen. Temple University School of Medicine, Philadelphia, PA

Background/Purpose: Mer is a receptor tyrosine kinase that binds to apoptotic cells via protein S and Gas6. Ligation of Mer leads to profound macrophage functional changes, with diminished production of inflammatory cytokines. Because little is known about the control of Mer expression in humans, we aimed to identify immunological mechanisms regulating Mer expression and Gas6 release in human monocytes and in macrophage subsets.

Methods: Expression of Mer and other surface markers in normal human monocytes and monocyte-derived macrophages was assessed by flow cytometry and Western blot. Gas6 and soluble Mer levels were measured by ELISA.

Results: Among fresh circulating monocytes, Mer was detectable in a small population of CD16+CD14dimHLA-DR+SR-A1+ cells. Macrophages differentiated in the presence of M-CSF (M2 conditions) showed enhanced Mer expression, yet GM-CSF (M1 conditions) was inhibitory. Other M1 stimuli, such as IFNγ, also caused Mer down-regulation, and LPS exposure led to generation of soluble Mer in supernatants. Among M2 macrophages, Mer was overexpressed in CD14brightCD163+SR-A1+CD206brightCD209-CD16+ "M2c" cells, and was driven by dexamethasone and by M-CSF (in the presence of serum) or M-CSF+IL-10 (in serum-free conditions). TGFβ had a negative effect on Mer and CD163 expression, although it up-regulated CD16 and CD206. Except for rare cells, prototypical M2 macrophages driven by IL-4 ("M2a"), defined as CD14dim/nullCD209+CD206+CD163-CD16-, did not express Mer. Mer's ligand Gas6 was released by IL-10- and glucocorticoid-differentiated "M2c" macrophages, though the highest levels were found in supernatants of IL-4-treated cells. In contrast, TGFβ inhibited Gas6 release. Down-regulation of Mer was dependent on PPARγ activation: in fact, GW9662 (PPARγ-antagonist) up-regulated Mer and CD163 in M1 and "M2a" cells; conversely, Rosiglitazone (PPARγ-agonist) suppressed Mer and CD163 expression in otherwise untreated macrophages.

Conclusion: The expression pattern of Mer and Gas6 in macrophages, sustained by anti-inflammatory cytokines and associated with other receptors involved in phagocytosis of apoptotic cells (SR-A1, CD14) and IL-10 production (CD163, FcγRs), reinforces the importance of Mer as a key regulator of inflammation and localizes its role mostly to "M2c" macrophages. In particular, the induction of Mer by glucocorticoids and cytokines may be of importance in the control of inflammation and has therapeutic implications. The role of PPARγ in Mer regulation may also be of clinical significance.

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Ly-6C^{high} Monocytes Are Key Cells in Pathogenesis of Autoimmune Arthritis and May Be An Interesting Target for Immunotherapy. Jessy Presumey[1], Gabriel Courties[1], Virginie Escriou[2], Daniel Scherman[2], Diego Kyburz[3], Steffen Gay[4], Yves-Marie Pers[5], Christian Jorgensen[5] and Florence Apparailly[1]. [1]Inserm, Montpellier, France, [2]Inserm, Paris, France, [3]University hospital of Zurich, Zurich, Switzerland, [4]University Hospital of Zürich, Zürich, Switzerland, [5]CHU Lapeyronie, Montpellier, France

Background/Purpose: Monocytes are important players in immunity and their heterogeneity reveals multiple functions. Recent publications suggest that the mouse Ly6C^{high} monocyte subset and its human counterpart $CD14^+/CD16^{low}$ may represent a valuable target for innovative immunotherapeutic strategies against immune-mediated inflammatory disorders. The present work aims at evaluating such hypothesis in vivo in a preclinical model of rheumatoid arthritis (RA) and in vitro in human $CD14^+/CD16^{low}$ primary monocytes. PBEF (Pre-B cell colony-enhancing factor/Visfatin), a pro-inflammatory adipokine described as a new marker of inflammation in RA, is expressed by monocytes and induces IL-6 production. Using RNAi-mediated gene silencing of PBEF, we investigated the therapeutic potential of the

targeting of the mouse Ly6C^{high} and the human CD14^{+}/CD16^{low} monocyte subsets for immuno-intervention in RA.

Methods: Collagen-induced arthritis (CIA) was induced in male DBA/1 mice. We first provided an in-depth characterization of the monocyte subsets in CIA mice using multiparametric analysis by flow cytometry. Small interfering (si)RNAs against mouse PBEF (siPBEF) or non targeting siRNAs (siCT) sequences were formulated with the cationic liposome RPR209120/DOPE and injected intravenously from arthritis onset (0,5 mg/kg). Clinical and biological features of the disease were investigated. In vitro, human CD14^{+}/CD16^{low} monocytes were transfected with human siPBEF or siCT formulated with the cationic liposome. Inhibition of PBEF expression and impact on pro-inflammatory cytokines was quantified.

Results: CIA mice present Ly-6C^{high} monocytosis that infiltrate into the arthritic joints and highly express TNFα. The lipoplex formulation used is preferentially uptaken by the Ly-6C^{high} monocytes from the blood, spleen and joints of CIA mice and by human CD14^{+}/CD16^{low} monocytes from PBMCs in vitro. Weekly systemic injection of siPBEF lipoplexes significantly decreased clinical disease activity scores compared with siCT treated animals as evidenced by paw swelling measures. The anti-PBEF siRNA lipoplexes efficiently triggered in vivo the inhibition of PBEF protein expression within Ly-6C^{high} monocytes/macrophages from blood and inflamed joints. Importantly, PBEF silencing significantly decreased several pro-inflammatory mediators including TNF-α, IL-6, IFN-γ and IL-17A, while increasing anti-inflammatory IL-10 cytokine production in the spleen. Finally, inhibition of PBEF expression in human primary CD14^{+}/CD16^{low} monocytes leads to a decreased IL-6 production.

Conclusion: These results provide novel evidence that silencing of PBEF within Ly-6C^{high} monocytes efficiently reduces experimental arthritis, and within CD14^{+}/CD16^{low} monocytes decreases their pro-inflammatory profile, emphasizing the therapeutic potential of Ly-6C^{high} / CD14^{+}/CD16^{low} monocytes targeting for anti-inflammatory intervention in RA.

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Myeloid-Derived Suppressor Cells Present in the Synovial Fluid of Mice with Proteoglycan-Induced Arthritis Are Potent Suppressors of Dendritic Cell Maturation and T Cell Proliferation. Julia Kurko, Colt Egelston, Timea Besenyei, Beata Tryniszewska, Tamas Kobezda, Tibor A. Rauch, Tibor T. Glant and Katalin Mikecz. Rush University Medical Center, Chicago, IL

Background/Purpose: Innate immune cells with a myeloid phenotype and suppressor activity towards T cells have been recently described in cancer patients. Similar myeloid-derived suppressor cells (MDSCs) have been also found in transplant recipients. While such suppressor cells can weaken anti-tumor T cell responses with detrimental consequences in cancer, they have the potential to suppress transplant rejection or autoimmunity. If MDSCs were present in patients with autoimmune diseases such as rheumatoid arthritis (RA), their suppressor activity could be exploited to curtail the expansion of autoreactive T cells. The goal of the present study was to identify potential MDSCs in mice with cartilage proteoglycan-induced arthritis (PGIA), an autoimmune model of RA.

Methods: Various organs of naïve BALB/c mice and BALB/c mice with PGIA were screened for the expression of MDSC-related genes and phenotypic markers using RT-PCR, Western blot, and flow cytometry. MDSCs (which were found predominantly in the synovial fluid and spleen of arthritic mice) were then isolated and tested for suppressor activity towards proteoglycan (PG)-specific T cells using PG-loaded bone marrow-derived dendritic cells (DCs) and T cells from naïve PG-specific T cell receptor transgenic (PG-TCR-Tg) mice. The effect of MDSCs on DC maturation (expression of MHC-II and the co-stimulatory molecule CD86) was also examined. The mechanisms of MDSC-mediated suppression were investigated using inhibitors of MDSC-produced effector molecules such as arginase-1 (arg-1), nitric oxide (NO), and reactive oxygen species (ROS).

Results: We identified cells expressing a myeloid phenotype (CD11b+ Gr-1+) and co-expressing MDSC-specific molecules including arg-1 and inducible NO synthase (iNOS) in the synovial fluid (SF) of arthritic joints and spleens of mice with PGIA. Such MDSC-like cells were detectable at much lower numbers in the blood and bone marrow of the same animals, and were virtually absent in naïve mice. Upon co-culture with PG-TCR-Tg T cells in the presence of PG-loaded DCs, SF MDSCs profoundly inhibited the proliferation of T cells, thereby confirming their suppressor activity. Phenotypically similar CD11b+ cells isolated from the spleens of arthritic mice were much less potent suppressors of T cell proliferation. Intriguingly, SF MDSCs also significantly inhibited the maturation of DCs through down-regulation of MHC-II and CD86 expression. SF-MDSCs did not suppress the PG/DC-independent proliferation of anti-CD3/CD28-stimulated T cells, suggesting that they exhibited suppressor activity, at least in part, via inhibition of DC activation and antigen presentation. Experiments with inhibitors of arg-1, iNOS, and ROS reveled that the primary mechanisms of suppression of both DC maturation and T cell proliferation involved NO and ROS production by SF MDSCs.

Conclusion: Our study is the first to identify MDSCs in the SF of arthritic joints and spleen in an animal model of RA. As potent suppressors of DC maturation and antigen-specific T cell proliferation, MDSCs have a potential to down-regulate autoimmunity, and by doing so, prevent further inflammatory attacks on the joints in RA.

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Analysis of the Expression of Interferon Regulatory Factors on Dendritic Cells From Systemic Lupus Erythematosus Patients. Karina Santana-de Anda, Adriana Elizabeth Monsivais-Urenda, Diana Gomez-Martin, Jose Cruz-Ruiz and Jorge Alcocer-Varela. Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico city, Mexico

Background/Purpose: Dendritic cells (DC) are a key element between the innate and the adaptative immune responses, they are considered professional antigen presenting cells, and the main source (plasmacytoid DC) of type-I interferon (IFN-I). Elevated levels of IFN- I have been detected in many autoinmune diseases in humans. The genomic and proteomic studies have shown that elevated serum levels of IFN-I and the interferon related genes overexpression are the molecular signature of systemic lupus erythematosus (SLE). The interferon regulatory factors (IRF) are among these upregulated genes. These transcription factors are induced by many different receptors, mainly toll-like receptors and interferon receptors. Diverse genetic association studies have found relationship between many IRF-5 polymorphisms and increased susceptibility to SLE in different ethnic groups. However these studies have been done with total mononuclear cells, which may not reflect specific DC alterations. It is not known if there are alterations in the expression of IRF on DC from SLE patients. The aim of this study was to evaluate the expression of IRF-3 and IRF-5 on DC from SLE patients.

Methods: We included 10 SLE patients (4 with SLEDAI=0, 6 with SLEDAI>6) as well as 10 healthy controls. Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque centrifugation. Monocytes were purified by positive selection with anti-CD14 mAb coated microbeads. DC were generated by culturing monocytes for 6 days in presence of GM-CSF, IL-4 and for 2 additional days in presence of LPS to induce maturation. In vitro generated DC as well as peripheral blood DC defined by the following phenotype, Lin^{-}HLA-DR^{+}CD11c^{-}BDCA-4^{+}, were analyzed for HLA-DR, CD40, IRF3, and IRF5 expression by flow cytometry and Western Blot.

Results: We found that immature DC from SLE patients shown significantly diminished levels of the CD40 molecule (percentage of CD40+ DC: control median= 48.8, SLE median= 28, p=0.03). In addition, we observed that expression of IRF-3 and IRF-5 on mature DC from SLE tended to be higher compared with controls (IRF3 MFI mean= 17.7 in controls versus 32.5 in SLE; IRF5 MFI mean=22.1 in controls versus 30.01 in SLE). Furthermore, we found that the expression of these molecules was increased in peripheral blood Lin^{-}HLA-DR^{+}CD11c^{-}BDCA-4^{+} DC from SLE patients compared with healthy controls (percentage of IRF3 positive cells= 29 in controls versus 76 in SLE; percentage of IRF5 positive cells= 3.6 in controls versus 34.6 in SLE). We found no differences on IRF expression on DC from active SLE and those with inactive disease.

Conclusion: Our results suggest that the previously reported elevated levels of IFN-I observed in SLE might be explained by the altered expression of IRF on DC from SLE patients. Furthermore, the impaired expression of these factors might be considered as an intrinsic defect in SLE.

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Expression of Caspase 8 in Dendritic Cells Is More Potent Than in Myeloid Cells in the Prevention of SLE-Like Disease Onset. Carla M. Cuda[1], Jaime Chowaniec[1], Jack Hutcheson[2], G. Kenneth Haines III[3], Chandra Mohan[2] and Harris R. Perlman[4]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]Yale University, New Harven, CT, [4]Northwestern University, Chicago, IL

Background/Purpose: Caspase 8 has been referred to as the initiator caspase of the death receptor mediated extrinsic apoptotic pathway. The death receptor Fas can trigger the extrinsic apoptotic pathway, and loss of Fas in macrophages and dendritic cells (DCs) results in autoimmunity. Deletion of caspase 8 revealed non-apoptotic roles for this molecule in regulating embryonic development,

lymphocyte activation and proliferation, and NFκB activation, though its effect on non-proliferating immune cells such as macrophages or DCs remains unknown. Due to caspase 8's involvement in the activation of apoptosis triggered by multiple death receptors as well as signaling via non-apoptotic pathways, it was of interest to assess how loss of caspase 8 in either macrophages or DCs would affect development of systemic autoimmunity.

Methods: Mice with caspase 8 flanked by *loxP* sites ($Casp8^{flox/flox}$) were crossed with mice expressing Cre under control of either the lysozyme M gene promoter (Cre^{LysM}), which functions in mature lysozyme-expressing cells of the myelomonocytic lineage, or the CD11c gene promoter (Cre^{CD11c}), which is expressed by dendritic cells. Both $Cre^{LysM}Casp8^{flox/flox}$ and $Cre^{CD11c}Casp8^{flox/flox}$ mice were verified by RT-PCR. Flow cytometric analysis was employed to characterize both myeloid and lymphoid cell distribution and activation in bone marrow, blood, lymph node, and spleen. Luminex-based assays and ELISAs were used to detect serum cytokine and Ig levels. Immunohistochemical staining revealed kidney pathology.

Results: With age, both $Cre^{CD11c}Casp8^{flox/flox}$ and $Cre^{LysM}Casp8^{flox/flox}$ mice presented with a break in tolerance, as indicated by splenomegaly, lymphadenopathy, and autoantibody production, though these phenotypes were more exaggerated in $Cre^{CD11c}Casp8^{flox/flox}$ mice. While central and peripheral lymphoid organ analysis revealed that this break occurs via peripheral mechanisms, it also strikes early in development. Peripherally, both myeloid cell and DC-specific loss of caspase 8 not only increased circulating granulocytes and $Gr\text{-}1^+$ monocytes, as well as splenic and lymph node antigen presenting cells. Additionally, increased peripheral effector T cells coincided with decreased peripheral naïve T cell populations. Moreover, not only did loss of caspase 8 in DCs and myeloid cells intrinsically amplified DC and macrophage activation, respectively, while affecting activation of other immune cells in a paracrine fashion. In an *in vitro* antigen-specific MLR, $Cre^{CD11c}Casp8^{flox/flox}$ DCs induced T cell proliferation, while $Cre^{LysM}Casp8^{flox/flox}$ macrophages inhibited proliferation. Elevated serum IL-12, TNFα, sRANKL levels were common to both strains, though $Cre^{CD11c}Casp8^{flox/flox}$ mice presented with heightened IgG2b levels and more severe kidney pathology.

Conclusion: These results demonstrate that while loss of caspase 8 in both DCs or myeloid cells initiates inflammatory phenotypes, intact caspase 8 signaling appears to be more crucial in DCs than in myeloid cells to prevent systemic autoimmunity. These data have implications for autoimmunity by elucidating previously unknown functions of a potentially useful target for therapy.

1011

Analysis of the Bioactive Molecules That Promote the Induction of Human Tolerogenic Dendritic Cells. Takuya Matsumoto, Hitoshi Hasegawa, Jin Lei, Koichiro Suemori, Sachiko Onishi and Masaki Yasukawa. Ehime University Graduate School of Medicine, Toon, Japan

Background/Purpose: Tolerogenic dendritic cells (DCs) and regulatory T cells (Treg) play a critical role in immune tolerance and are involved in the pathogenesis of autoimmune diseases such as rheumatoid arthritis. Suppression by tolerogenic DCs is primarily mediated via the induction of Treg cells. Tolerogenic DCs and Treg cells are induced or differentiated in the presence of specific biological agents, but little is known about harmless, potent inducers, especially in humans. Previously we isolated some agents that induced human Treg cells and reported that peroxisome proliferator-activated receptor (PPAR) agonist together with TGF-beta induced functional human Treg cells. Therefore, in this study, we screened the molecules that enhanced induction of tolerogenic DCs and analyzed the mechanism of these molecules in induction of tolerogenic DCs.

Methods: DCs were prepared from human monocytes by treatment of GM-CSF and IL-4 for 5 days, and then cultured with TNF-alpha for 48h, in the presence of the molecule. From the libraries of lipids, nuclear receptor ligands, and kinase inhibitors, we screened the molecules that suppressed the expression of CD80, CD83, and CD86 for immature DCs and that induced the production of IL-10 for IL-10-producing DCs. Furthermore, we examined the effects of these molecules on stability and plasticity of DCs, antigen presenting, allogenic T cell response, and induction of cytokines and Treg cells.

Results: We screened 24 kinds of lipids, nuclear receptor ligands, and kinase inhibitors that suppressed the expression of CD80, CD83, and CD86 similar to the phenotype of immature DCs. DCs treated with PPAR-gamma, dexamethazone, and indirubin remained phagocytosis, suppressed allogenic T cell responses and production of IL-12, and enhanced induction of Treg cells. On the other hand, we screened 10 kinds of the molecules that produced IL-10 from DCs. DCs treated with prostaglandin and GSk 3-beta inhibitor such as kenpaullone decreased allogenic T cell responses and enhanced induction of Tregs through IL-10 production. Moreover, induction of tolerogenic DCs was enhanced by combination with two molecules. We show the details of mechanism and other molecules in congress.

Conclusion: We identified some bioactive molecules that promoted the induction of tolerogenic DCs. We aim at the development of efficient induction of both human tolerogenic DCs and Treg cells using these molecules.

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Active involvement of "alarmins" S100A8 and A9 in regulation of Synovial Activation and Joint Destruction During Mouse and Human Osteoarthritis. Peter Van Lent[1], Arjen Blom[1], Rik Schelbergen[1], Annet Sloetjes[1], Thomas Vogl[2], Johannes Roth[2], Wim B. Van Den Berg[1] and and The NOAC study group[3]. [1]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [2]University of Munster, Munster, Germany, [3]Maartens Clinic, Nijmegen, Netherlands

Background/Purpose: Prominent proteins released by activated macrophages are the "alarmins" S100 A8 and A9. There is increasing belief that synovial tissue activation contributes to OA cartilage pathology. The aim was to explore active involvement of S100A8/A9 in cartilage destruction in experimental osteoarthritis models that differ in degree of synovial activation and to evaluate the presence of S100A8/S100A9 in sera and synovia of patients with early symptomatic OA.

Methods: Experimental OA was either induced by transection of the medial anterior meniscotibial ligament which leads to destabilisation of the medial meniscus (DMM) or by injection of collagenase into murine knee joints, which causes overall ligament damage and broad instability. Collagenase-induced-osteoarthritis involves chronic synovial activation in contrast to DMM. Synovial expression of S100A8 and S100A9 was measured using immunolocalisation. Both models were induced in $S100A9^{-/-}$ deficient mice (myeloid cells also lack S100A8 at the protein level). Primary chondrocytes were stimulated with S100A8 and A9 and MMP levels were measured using RT-PCR.

Arthroscopic biopsies (30) and sera (200) were taken from patients with early symptomatic OA (CHECK cohort, The Netherlands). Protein levels of S100A8 and A9 was determined using immunolocalisation or ELISA and related to joint destruction (Kellgren Lawrence score) at year two.

Results: In collagenase-induced osteoarthritis, showing marked synovial activation S100A8 and S100A9 was strongly upregulated in synovium at day 7 and remained high at days 14, 28 and 42. In contrast IL-1β was expressed in early stages only. Using $S100A9^{-/-}$ mice, we found a major impact of s100A8 and A9 on synovial activation and OA cartilage destruction. Synovial activation was 62% lower at day 42. Cartilage destruction was significantly lower in all surfaces and ranged from a 45% reduction in the lateral tibia to 73% reduction in the medial femur. When primary mouse chondrocytes were stimulated with S100A8 or S100A9, a strong upregulation of particularly MMP-3 mRNA level was found indicating a direct role of S100A8/A9 in cartilage destruction. In contrast, in the DMM model in which synovial involvement is scant no role of S100A8/A9 was found for the focal OA cartilage destruction.

Arthroscopic synovial biopsies taken from patients in the early symptomatic OA CHECK cohort identified substantial S100A8 and A9 mRNA and protein expression and levels correlated with synovial lining thickness, cellularity in subintima and joint destruction. Serum S100A8/A9 protein levels were significantly enhanced at base line in patients showing pronounced progression of joint destruction in 2 years.

Conclusion: Alarmins S100A8/S100A9 are crucial proteins involved in synovial activation and cartilage destruction during OA and high levels may predict joint destruction in human OA.

1013

Rilonacept for Gout Flare Prevention in Patients on Uric Acid-Lowering Therapy: Results of a Double-Blind, Placebo-Controlled, Phase 3, International Safety Study. John S. Sundy[1], H. Ralph Schumacher[2], Judith Kirstein[3], Essack Mitha[4], Steven P. Weinstein[5], Jian Wang[5], Shirletta King-Davis[5] and Robert R. Evans[5]. [1]Duke University Medical Center, Durham, NC, [2]VA Medical Center and University of Pennsylvania, Philadelphia, PA, [3]Advanced Clinical Research, West Jordan, UT, [4]Newtown Clinical Research, Johannesburg, Gauteng, South Africa, [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background/Purpose: Previous studies with rilonacept, an interleukin (IL)-1 antagonist, have confirmed that IL-1 plays an essential role in initiation of gout flares and is an appropriate target for flare prevention. RE-SURGE was a large double-blind, placebo-controlled, phase 3 study evaluating the safety and efficacy of rilonacept in patients with gout at risk of a gout flare (GF).

Methods: This phase 3 study was conducted in the US, South Africa, Europe, and parts of Asia. Adults (N=1315; 18–80 years of age) with gout at risk of a GF due to initiation of uric acid-lowering therapy (ULT) or continuation of ULT in the setting of high uric acid body stores were randomized in a 3:1 ratio to treatment with weekly subcutaneous injections of rilonacept 160mg (R160) or placebo (PBO) for 16 weeks. On day 1 a loading dose of rilonacept 320mg or PBO was administered. The primary endpoint was safety, assessed by type and incidence of adverse events (AEs) and changes in lab values over the 20-week study period. Secondary efficacy endpoints included the mean number of GFs per patient, and proportions of patients with ≥1 and ≥2 GFs.

Results: 985 patients were treated with R160 and 330 with PBO. Most patients were male (87.8%) and white (66%); median age was 53 years, and median weight was 95 kg. Tophi were present in 29% of patients. Baseline comorbidities included hypertension (53%), hypercholesterolemia (17%), renal and urinary disorders (14%) and cardiac disorders (11.5%); a history of polypharmacy was common. Through week 20, AEs were reported in 67% of R160 vs 59% of PBO patients. AEs reported in ≥5% of R160 patients are shown below:

Adverse Event	PBO (n=330)	R160 (n=985)
Infections	19.1%	20.1%
Injection site reactions	3.3%	15.2%
Headache	7.9%	9.1%
Arthralgia	6.1%	6.6%
Pain in extremity	4.5%	5.3%

Withdrawals due to treatment emergent AEs were seen in 4.7% and 3.0% of patients in R160 and placebo, respectively. Injection site reactions were the most common reason for withdrawal in the R160 group with 1.2% of rilonacept-treated patients experiencing an injection site reaction leading to withdrawal. Treatment emergent serious AEs were observed in 3.1% of R160 and 3.9% of PBO patients. Serious infections were uncommon, occurring in 0.5% of patients in the R160 group and 0.9% of patients in the PBO group. Six deaths occurred, 3 (0.3%) in R160 (none assessed as related to study drug) and 3 (0.9%) in PBO. For secondary efficacy endpoints, R160 resulted in a 70.3% reduction in mean number of total GFs per patient relative to PBO (0.51 vs 1.73; $P<0.0001$) at week 16. Treatment with R160 also resulted in a 49.6% reduction in patients experiencing 1 or more GFs (25.7% vs 51.1%; $P<0.0001$); 11.7% of patients in R160 vs 34.7% in PBO experienced 2 or more GFs ($P<0.0001$; 66.4% reduction).

Conclusion: Rilonacept demonstrated an acceptable safety and tolerability profile in gout patients with typical comorbid conditions. The rate of serious infections was low. Rilonacept resulted in a substantial reduction in gout flares in patients at high risk of flaring.

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Rilonacept Efficacy for Gout Flare Prevention in Patients with Tophi and/or Polyarticular Disease Who Initiate Uric Acid-Lowering Therapy. Robert Terkeltaub[1], H. Ralph Schumacher[2], A. Kivitz[3], Steven P. Weinstein[4], Richard Wu[4], Rebecca Gall[4] and Robert R. Evans[4]. [1]VA Medical Ctr, San Diego, CA, [2]VA Medical Center and University of Pennsylvania, Philadelphia, PA, [3]Altoona Center for Clinical Research, Duncansville, PA, [4]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background/Purpose: Patients (pts) with greater disease burden, those with tophi and/or polyarticular disease, may be at greater risk of gout flares (GFs) when initiating uric acid-lowering therapy (ULT). This analysis used data from three Phase 3 clinical trials of the IL-1 antagonist rilonacept to evaluate the risk of these clinical features for occurrence of GFs during initiation of ULT, and to determine the efficacy of rilonacept in these pts.

Methods: PRE-SURGE 1, PRE-SURGE 2, and RE-SURGE were randomized, double-blind, placebo (PBO)-controlled trials evaluating safety and efficacy of weekly subcutaneous doses of rilonacept 80mg (R80) and 160mg (R160) for prevention of GFs during initiation of ULT. Treatment duration was 16 wks and pts analyzed had baseline serum urate ≥7.5 mg/dL and >2 GFs in the past year and were initiating allopurinol. GF rate ratios were calculated in the PBO group for each study by comparing pts with tophi and/or polyarticular disease vs pts without these features. GFs per pt and proportion of pts with ≥1 GF were estimated for pts within each study as well as pooled from the 3 studies. GFs were defined as pt-reported acute articular pain typical of a gout attack that required anti-inflammatory treatment.

Results: Pts with tophi and/or polyarticular disease had significantly higher rates of GFs than those with monoarticular, non-tophaceous disease: GF rate ratios (95% confidence intervals) were 1.97 (1.02, 3.79), 3.69 (1.51, 9.02), and 1.93 (1.30, 2.86), in PRE-SURGE 1, PRE-SURGE 2, and RE-SURGE, respectively. Among pts with these risk factors, rilonacept significantly reduced the mean number of GFs per pt (Table). These reductions were generally similar to those observed for the total population of all pts with serum urate ≥7.5 mg/dL, ≥2 GFs in the past year, and initiating allopurinol. Pooling the data within treatment groups showed that for pts with these risk factors, R80 resulted in a 69.5% reduction in mean number of GFs per pt versus PBO (from 1.81±2.52 (PB0) to 0.55±1.20 (R80); P≤0.0001); the reduction with R160 was 67.7% (to 0.59±1.19; P≤0.0001). The proportion of pts with ≥1GF in the pooled population of pts with risk factors was 59.4%, 29.8%, and 30.7% for PBO, R80, and R160, respectively, representing almost a 50% reduction with rilonacept.

Study	Treatment	GFs per patient, mean±SD	
		Total population (n)	Patients with tophi/polyarticular disease (n)
PRE-SURGE 1	PBO	1.19±1.75 (79)	1.31±1.83 (64)
	R80	0.40±0.91 (80)*	0.39±0.85 (56)†
	R160	0.28±0.62 (81)†	0.35±0.70 (56)†
PRE-SURGE 2	PBO	1.51±1.87 (82)*	1.68±1.92 (71)
	R80	0.62±1.32 (82)*	0.69±1.44 (65)*
	R160	0.48±0.99 (84)*	0.58±1.08 (68)*
RE-SURGE	PBO	1.99±2.89 (145)	2.17±3.05 (121)
	R160	0.55±1.20 (420)*	0.63±1.27 (340)*

* P≤0.0001 vs PBO; †P<0.005 vs PBO.
Subgroup = Pts with baseline serum urate ≥7.5 mg/dL and ≥2 GFs in the past year and initiating allopurinol; SD = standard deviation.

For the total study population in these 3 studies, the most commonly reported adverse event (AE), infections, was balanced among treatment groups; the most frequently reported treatment-related AE was injection site reaction.

Conclusion: The presence of tophi and/or polyarticular disease represents a risk factor for gout flares in patients initiating uric acid-lowering therapy. Among patients with these risk factors, rilonacept demonstrated efficacy for gout flare prevention that was generally similar to that observed for the overall population.

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Integrated Safety Analysis of Four Trials of Interleukin-1 Blockade with Rilonacept for Gout Flare Prevention in Patients Taking Uric Acid-Lowering Therapy. Robert Terkeltaub[1], H. Ralph Schumacher[2], Essack Mitha[3], John S. Sundy[4], Kenneth G. Saag[5], Steven P. Weinstein[6], Jian Wang[6] and Robert R. Evans[6]. [1]VA Medical Ctr, San Diego, CA, [2]VA Medical Center and University of Pennsylvania, Philadelphia, PA, [3]Newtown Clinical Research, Johannesburg, Gauteng, South Africa, [4]Duke University Medical Center, Durham, NC, [5]Univ of Alabama-Birmingham, Birmingham, AL, [6]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background/Purpose: The IL-1 antagonist rilonacept has demonstrated efficacy for gout flare prevention in a phase 2 and three phase 3 clinical trials. This pooled analysis of the 4 trials provides an integrated summary of safety.

Methods: The phase 2 and phase 3 studies (PRE-SURGE 1, PRE-SURGE 2, RE-SURGE) were randomized, double-blind, placebo (PBO)-controlled trials evaluating the safety and efficacy of weekly subcutaneous doses of rilonacept 80mg (R80) and 160mg (R160) for the prevention of gout flares in patients at risk for flares while initiating or continuing uric acid-lowering therapy (ULT). Treatment duration was 16 weeks in all studies. Safety assessments in patients taking at least 1 dose of study drug included the incidence, type, severity and seriousness of adverse events (AEs), and changes in clinical lab values. Data from the 4 studies were pooled for the R80 (n=162), R160 (n=1191), and PBO (n=533) groups.

Results: Demographic characteristics were generally well-balanced across the pooled treatment groups. Most patients were male (89.5%) and white (67.2%), with a mean age of 52.3±11.5 years. AEs were reported in 59.7%, 64.8%, and 66.0% of PBO, R80, and R160 patients, respectively (Table), and were generally of mild or moderate severity. The incidences of serious AEs and AEs leading to withdrawal were similar among the groups (Table). Although AEs leading to withdrawal were infrequent, the main cause in the rilonacept groups was injection site reactions (1.0%). Six deaths occurred, 3 in PBO (0.56%) and 3 in R160 (0.25%); none of the deaths in the R160 group were assessed as related to study drug. Infections were the most commonly reported category of AEs and were similar among the treatment groups (Table). Serious infections were infrequent with 1 event, which occurred in the PBO group, considered treatment-related (Table). Injection site reactions, headache, and arthralgia were the most frequently reported individual AEs (Table); injection site reactions were dose-related, with 7 patients (0.6%) reporting severe injection site reactions, all in the R160 group. Changes in lab analytes were consistent with IL-1 inhibition with potentially clinically significant laboratory values for a given analyte generally <1.0% in any treatment group.

Treatment-Emergent AEs	Percent (number) of patients			
	PBO (n=533)	R80 (n=162)	R160 (n=1191)	All rilonacept doses (n=1353)
Any AE	59.7 (318)	64.8 (105)	66.0 (786)	65.9 (891)
Serious AEs	4.1 (22)	4.9 (8)	3.2 (38)	3.4 (46)
AEs leading to withdrawal	3.2 (17)	4.3 (7)	4.2 (50)	4.2 (57)
Infection AEs	20.8 (111)	23.5 (38)	20.2 (241)	20.6 (279)
Serious infections	0.6 (3)	1.9 (3)	0.4 (5)	0.6 (8)
Individual AEs in '5% patients in any treatment group				
Joint related signs and symptoms	6.8 (36)	4.9 (8)	7.0 (83)	6.7 (91)
Arthralgia	5.4 (29)	3.7 (6)	6.1 (73)	5.8 (79)
Injection site reactions	2.6 (14)	10.5 (17)	15.5 (185)	14.9 (202)
Injection site erythema	0.2 (1)	6.2 (10)	6.0 (72)	6.1 (82)
Headaches NEC	6.4 (34)	6.2 (10)	8.2 (98)	8.0 (108)
Headache	5.6 (30)	6.2 (10)	7.8 (93)	7.6 (103)
Individual treatment-related AEs in ≥5% of patients in any treatment group				
Any treatment-related AE	12.6 (67)	24.7 (40)	27.6 (329)	27.3 (369)
Injection site reactions	2.1 (11)	10.5 (17)	14.8 (176)	14.3 (193)
Injection site erythema	0.2 (1)	6.2 (10)	5.9 (70)	5.9 (80)

Conclusion: An integrated safety analysis of 4 trials indicates that a 16-week course of weekly 80mg or 160mg rilonacept for gout flare prevention in patients initiating or continuing uric acid-lowering therapy has a generally acceptable safety and tolerability profile. The rate of serious infections was low, and injection site reactions were the most common adverse event leading to discontinuation in only 1.0% of rilonacept patients.

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Long-Term Efficacy and Safety of Canakinumab Versus Triamcinolone Acetonide in Acute Gouty Arthritis Patients. J.P. Brown[1], A. So[2], A. Dikranian[3], R. Alten[4], T. Bardin[5], H. R. Schumacher[6], A. Gimona[7], G. Krammer[7], A. Karpov[7] and N. Schlesinger[8]. [1]CHUQ-CHUL Research Centre, Laval University, Quebec City, QC, [2]CHUV, Lausanne, Switzerland, [3]San Diego Arthritis Medical Clinic, San Diego, CA, [4]Charité Teaching Hospital–Schlosspark-Klinik, Berlin, Germany, [5]Hôpital Lariboisière, Paris, France, [6]University of Pennsylvania and VA Medical Center, Philadelphia, PA, [7]Novartis Pharma AG, Basel, Switzerland, [8]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ

Background/Purpose: Gouty arthritis (GA) is a painful, progressive, destructive, chronic inflammatory disease. Targeting the inflammatory pathway through IL-1β inhibition with canakinumab, a fully human anti-IL-1β monoclonal antibody, is a novel therapeutic approach that may provide significant long-term benefits in this patient group. In 2 pivotal 12-week controlled trials (β-RELIEVED and β-RELIEVED-II), canakinumab showed superiority to triamcinolone acetonide (TA) in relieving pain, inflammation and delaying risk of new flares in GA patients with limited treatment options. We report the results of two extension studies that assessed long-term efficacy, safety and tolerability.

Methods: In two 12-week, multicenter, active-controlled trials, acute GA patients (meeting preliminary ACR-1977 criteria for acute GA and unresponsive, intolerant or contraindicated to NSAIDs and/or colchicine) were randomized to receive canakinumab 150mg sc or TA 40mg im, followed by two 12-week extension studies. Patients received canakinumab 150mg sc or TA 40mg im for the baseline flare and only "on demand" for any new flare. Time to first new flare, mean number of flares, physician's and patient's global assessment of treatment response (Likert scale) and safety over 24 weeks are assessed.

Results: 416 patients completed the core studies (β-RELIEVED: 214; β-RELIEVED-II: 202). 335 patients (β-RELIEVED: 175; β-RELIEVED-II: 160) entered the extension studies and 317 completed (β-RELIEVED E1: 167; β-RELIEVED-II E1: 150). Over 24-weeks following randomization, canakinumab delayed the time to first new flare vs TA with a statistically significant relative risk reduction of 52% in β-RELIEVED E1 and 60% in β-RELIEVED-II E1 (Table). The mean number of flares per patient was significantly reduced with canakinumab. At Week 24, a higher percentage of patients taking canakinumab achieved a better assessment of treatment response from physicians and patients. Incidence of AEs for canakinumab and TA in both studies was: β-RELIEVED E1: 62.8% vs 48.7%; β-RELIEVED-II E1: 69.6% vs 57%, respectively. Most AEs were mild to moderate in severity. No discontinuations due to AEs were observed in β-RELIEVED E1. 2 (1.8%) patients treated with canakinumab in β-RELIEVED-II E1 discontinued. SAEs [β-RELIEVED E1: canakinumab, n =11; TA n=6; β-RELIEVED-II E1: canakinumab n=7; TA n=2] were not considered to be related to study medication by the investigators. Most patients had no injection site reactions [β-RELIEVED E1: canakinumab, n=0; TA n=0; β-RELIEVED-II E1: canakinumab n=2; TA n=1].

Table. Efficacy assessments over 24 weeks: β-RELIEVED E1 and β-RELIEVED-II E1

	β-RELIEVED E1		β-RELIEVED-II E1	
Efficacy	Canakinumab N=113	TA N=115	Canakinumab N=112	TA N=114
Probability of new gout flare (Kaplan-Meier estimates) (%)	35.5	57.5	29.1	54.3
Hazard ratio to TA 40 mg im	0.48		0.40	
95% CI	(0.32–0.73)		(0.25–0.64)	
One sided p-value	0.0003		<0.0001	
Mean number of flares per patient	0.40	0.87	0.35	0.80
Estimated rate ratio (p-value)	0.45 (0.0001)		0.42 (0.0001)	
Assessment of response to treatment at Week 24				
Patient's global assessment, %				
Excellent	31.0	17.9	59.5	40.3
Good	46.0	44.9	26.6	44.4
Physician's global assessment, %				
Very Good	43.7	27.8	77.2	66.2
Good	50.6	50.6	16.5	29.6

Conclusion: In frequently flaring patients with limited treatment options, canakinumab demonstrated superior 24 week efficacy against TA with comparable safety and tolerability to 12-week data.

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No Dosing Adjustments Are Required for Colchicine in Patients Over Age 60 Years Compared to Younger Adults on the Basis of Age and Mild Renal Impairment. Suman Wason[1], Robert D. Faulkner[1], Darin B. Brimhall[2] and Matthew W. Davis[1]. [1]URL Pharma, Philadelphia, PA, [2]Novum Pharmaceutical Research Services Clinical Studies Inc., Pittsburgh, PA

Background/Purpose: Gout affects 4% of adults in the United States. Patients ≥65 yrs of age experience higher prevalence (~8%-12%). The objective of this study was to evaluate the pharmacokinetics (PK) of colchicine in subjects aged 18–30 yrs compared to ≥60 yrs to determine if older subjects require dose adjustments when prescribed colchicine.

Methods: Thirty-eight subjects (ages 18–30 [n=20], and ≥60 [n=18] yrs of age) received a single, oral 0.6-mg dose of colchicine after a 10-hr fast. Plasma samples for PK analyses were collected pre-dose and up to 72 hrs post-dose and analyzed for colchicine by a validated liquid chromatographic-tandem mass spectrometry method.

Results: Plasma samples from all subjects were included in the analyses. As seen in the Table, creatinine clearance (CrCl) at baseline was significantly lower ($P<0.0001$) in subjects ≥60 yrs of age compared with subjects 18–30 yrs of age. Mean colchicine maximum concentrations (C_{max}) were similar in both groups. There was marginally higher exposure (AUC) to colchicine in the older group; however, this difference was not significant ($P>0.05$). The mean $T_{1/2}$ (elimination half-life) was slightly longer in subjects aged ≥60 yrs than those 18–30 yrs of age; however, this was not significant ($P=0.0944$). Further, there were no differences between oral clearance (CL/F; $P=0.987$) or apparent volume of distribution (V/F; $P=0.785$) of colchicine between groups.

Table. Creatinine Clearance and Pharmacokinetic Parameters in Young Versus Older Subjects (N=38) Following a Single Dose of Colchicine Tablets USP, 0.6 mg

	Young Adults 18–30 years	Older Adults 60–70 years
Creatinine Clearance (mL/min)		
Mean (Range)	132.56 (99.2 – 182.6)	87.02 (56.8 – 119.9)
Pharmacokinetic Parameter (Units)	**Arithmetic mean ± SD (% CV)**	
AUC $_{0\text{-}t}$ (ng·hr/mL)	20.1362 ± 5.8576 (29.0897)	21.8804 ± 6.2248 (28.4490)
AUC $_{0\text{-}\infty}$ (ng·hr/mL)	22.3852 ± 6.9451 (31.0254)	25.0134 ± 6.922 (27.6743)
C_{max} (ng/mL)	2.6071 ± 0.707 (27.1332)	2.5559 ± 0.9701 (37.9553)
T_{max} (hr)	1.3824 ± 0.4157 (30.0708)	1.2500 ± 0.4287 (28.7140)
$T_{1/2}$ (hr)	24.9178 ± 5.3389 (21.4259)	30.0580 ± 10.779 (24.2464)
CL (mL/min)	0.0321 ± 0.0091 (28.2270)	0.0292 ± 0.0071 (24.1464)
Vd	1.1296 ± 0.3336 (29.5315)	1.2725 ± 0.5745 (45.1482)

There were 16 females and 22 males enrolled. Subgroup analysis showed that there was a difference ($P<0.05$) in AUCs; however, the mean ratios for female to male was 1.21, indicating this difference was not clinically significant. There were no significant differences between males and females in Tmax, T1/2, or body-weight adjusted CL/F, V/F, and CrCl. There were 14 African Americans, 15 Caucasians, and 9 "other" enrolled. There were no significant differences in the aforementioned PK parameters between the racial groups.

Adverse events (AEs) were reported in 15 subjects. The most commonly reported AEs were increased blood pressure and somnolence. All AEs were considered mild, were not related to colchicine, and resolved spontaneously prior to study completion.

Conclusion: Following administration of a single 0.6-mg dose of colchicine, there were no significant differences in PK parameters between young and older adults (including those with mild decreases in renal function estimated by creatinine clearance), suggesting there is no need to modify the dose of colchicine based on age alone.

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BCX4208 Synergistically Lowers Serum Uric Acid (sUA) Levels When Combined with Allopurinol in Patients with Gout: Results of a Phase 2 Dose-Ranging Trial. Alan S. Hollister[1], Michael A. Becker[2], Robert Terkeltaub[3], Anita Waugh[1], Scott Lyman[1], Amy Flynt[4] and David Fitz-Patrick[5]. [1]BioCryst Pharmaceuticals, Inc., Durham, NC, [2]University of Chicago Medical Center, Chicago, IL, [3]VA Medical Ctr, San Diego, CA, [4]PharPoint Research, Inc., Chapel Hill, NC, [5]East-West Medical Research Institute, Honolulu, HI

Background/Purpose: BCX4208 is an oral, once-daily, novel purine nucleoside phosphorylase inhibitor in clinical development for the chronic management of gout. Because BCX4208 blocks production of uric acid earlier in the metabolic pathway than xanthine oxidase inhibitors, there is a strong mechanistic rationale for expecting synergistic reduction of sUA when combined with xanthine oxidase inhibition. This is important because >50% of gout patients fail to meet the therapeutic goal of sUA <6.0 mg/dL during treatment with 300 mg allopurinol daily. This study assessed the dose-response relationship of BCX4208 on sUA when administered as monotherapy and in combination with allopurinol.

Methods: Adults (n=87) with gout and sUA ≥8.0 mg/dL were randomized to placebo (Plc) or 20, 40, or 80 mg/d BCX4208 in combination with Plc or with 100, 200, or 300 mg/d allopurinol using a 4 × 4 factorial study design. Drugs were administered in a double-blind manner for 3 weeks with weekly assessments of sUA and adverse events (AEs). The key efficacy endpoints were the change in sUA from baseline on Day 22 and the percentage of patients achieving the goal (sUA <6.0 mg/dL).

Results: When BCX4208 was combined with allopurinol, there was a synergistic reduction in sUA (by Combination Index test). BCX4208 produced a significant reduction in sUA compared with Plc when administered as monotherapy and in combination with allopurinol. Both BCX4208 and allopurinol demonstrated dose-related reductions in sUA and increases in the proportion of patients achieving goal sUA (Table).

		BCX4208		
Cotreatment	**Placebo**	**20 mg**	**40 mg**	**80 mg**
Placebo	(n=5) 0%	(n=4) 0%	(n=6) 17%	(n=5) 40%
Allopurinol 100 mg	(n=5) 0%	(n=4) 0%	(n=5) 60%	(n=5) 40%
Allopurinol 200 mg	(n=4) 0%	(n=5) 20%	(n=5) 80%	(n=5) 80%
Allopurinol 300 mg	(n=5) 40%	(n=4) 75%	(n=4) 100%	(n=5) 100%

Seventy-five percent to 100% of patients achieved sUA <6.0 mg/dL with BCX4208 in combination with 200 mg allopurinol (>20 mg BCX4208) or 300 mg allopurinol (≥20 mg BCX4208) daily. Patients in the 300 mg allopurinol monotherapy group had a 1.8 mg/dL reduction in sUA, whereas the addition of 20 mg BCX4208 to 300 mg allopurinol decreased sUA by 3.9 mg/dL. AE frequency and severity were comparable across dose groups. Common AEs in the BCX4208 group included diarrhea (12% vs 5% in Plc) and headache (6% vs 5% in Plc). No serious AEs were reported. Lymphocyte counts and subsets (CD4+, CD8+, CD20+ and CD56+) were reduced, with both baseline counts and dose of BCX4208 significant factors in multivariate models for all subsets. One patient on BCX4208 experienced a reduction in lymphocytes (grade 0 at baseline to grade 2, 500–599 cells/μL, at Day 22). No severe or opportunistic infections were observed.

Conclusion: BCX4208 combined with allopurinol produces synergistic reductions in sUA in patients with gout and permitted substantially higher achievement of goal sUA compared with commonly prescribed doses of allopurinol alone. BCX4208 once-daily dosing is well tolerated when used in combination. Positive results of this trial have led to the initiation of a 6-month add-on study of BCX4208 in patients who did not achieve goal sUA with 300 mg allopurinol daily.

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Inflammation Suppression Over 24 Weeks in Patients with Gouty Arthritis: Results From Two Phase-III Core and Extension Studies Comparing Canakinumab with Triamcinolone Acetonide. A. So[1], R. Alten[2], H. R. Schumacher[3], T. Bardin[4], M. Bloch[5], D. Richard[6], A. Karpov[6], T. Kiechle[6] and N. Schlesinger[7]. [1]CHUV, Lausanne, Switzerland, [2]Charité Teaching Hospital–Schlosspark-Klinik, Berlin, Germany, [3]University of Pennsylvania and VA Medical Center, Philadelphia, PA, [4]Hôpital Lariboisière, Paris, France, [5]Holdsworth House Medical Practice, Sydney, Australia, [6]Novartis Pharma AG, Basel, Switzerland, [7]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ

Background/Purpose: Gouty arthritis (GA) is a chronic inflammatory arthritis, mainly driven by IL-1β—a proinflammatory cytokine. Canakinumab, a fully human monoclonal anti-IL-1β antibody, offers a new therapeutic option for GA that may provide significant long-term benefits.

Methods: In two, pivotal 12-week, multicenter, double blind, double dummy, active-controlled studies (β-RELIEVED and β-RELIEVED-II), GA patients (meeting preliminary ACR-1977 criteria) with flare duration ≤5 days and unresponsive, intolerant or contraindicated to NSAIDs and / or colchicine were randomized to receive a single dose of canakinumab 150mg sc or triamcinolone acetonide (TA) 40mg im and were re-dosed "on demand" on each new flare. Patients completing the core studies were enrolled into 12-week extension studies

to further investigate "on demand" use of canakinumab 150 mg sc or TA 40 mg im on new flare. Inflammatory markers (CRP, SAA), tenderness and swelling were assessed at baseline, 72h and 7 days post dose, 12, and 24 weeks, where as IL-6 and TNF-α was assessed at baseline, 12 and 24 weeks.

Results: In both core studies, 454 patients received treatment and 416 completed the studies. Of these, 335 patients entered and 317 completed the extension studies. At baseline in β-RELIEVED and β-RELIEVED-II, 17.1% and 16.8% had polyarticular GA and the mean number of flares in the previous year was 6.8 and 6.2, respectively. A large proportion (60.5%; 60.2%) of patients had a history of GA >5 years. Median CRP and SAA levels were elevated at baseline (Table). Following treatment with canakinumab, CRP decreased rapidly and normalized by 7 days post dose and SAA normalized by 3 days post dose. Both remained below upper limit of normal (ULN) over 24 weeks. Following treatment with TA, CRP remained above ULN at all post-dose time points except 24 weeks and SAA remained above ULN until Week 12. IL-6 was more effectively suppressed with canakinumab than TA over 24 weeks. No major changes in levels of TNF-α were observed, demonstrating its lack of involvement in this inflammatory cascade.

Table. Changes from baseline in inflammatory markers at 72 h, 7 days, 12 and 24 weeks post dose by treatment group

	Canakinumab N=113					TA=115				
β-RELIEVED Median (range)	**Baseline**	**72 h**	**7 days**	**12 WK**	**24 WK (EOS)**	**Baseline**	**72 hrs**	**7 days**	**12 WK**	**24 WK (EOS)**
CRP levels, *ULN=3.0mg/L*	(n=110) 13.2 (0–346)	(n=112) 4.4* (0–62)	(n=113) 2.1* (0–70)	(n=105) 1.8 (0–47)	(n=85) 2.6 (0–90)	(n=113) 9.4 (1–278)	(n=109) 5.2 (0–198)	(n=104) 3.6 (0–305)	(n=100) 3.8 (0–64)	(n=76) 3.0 (0–79)
SAA levels, *ULN=6.7mg/L*	(n=113) 18.0 (1–2500)	(n=108) 5.2* (0–444)	(n=111) 3.3* (0–202)	(n=102) 3.5 (0–70)	(n=85) 4.0 (0–198)	(n=113) 9.9 (0–1080)	(n=109) 10.1 (1–768)	(n=109) 7.9 (4–1280)	(n=100) 6.2 (1–179)	(n=75) 6.1 (0–210)
IL-6 levels	(n=80) 4.6# (0–356) (n=96) 4.1 (0–356)	NA	NA	(n=80) 0 (0–131)	(n=96) 2.7** (0–38)	(n=73) 4.80# (0–143) (n=96) 3.8 (0–143)	NA	NA	2.7 (0–75)	3.5** (0–61)

	Canakinumab (N=112)					TA (N=114)				
β-RELIEVED-II	**Baseline**	**72 hrs**	**7 days**	**12**	**24 WK (EOS)**	**Baseline**	**72 hrs**	**7 days**	**12 WK**	**24 WK**
CRP levels, *ULN=3.0mg/L*	(n=112) 10.2 (0–350)	(n=107) 4.3* (0–73)	(n=108) 1.8* (0–92)	(n=97) 1.4 (0–46)	(n=79) 1.6 (0–89)	(n=114) 8.9 (0–227)	(n=110) 7.0 (0–225)	(n=109) 3.1 (0–98)	(n=97) 3.2 (0–62)	(n=70) 2.7 (0–30)
SAA levels *ULN=6.7mg/L*	(n=106) 11.2 (0–2070)	(n=106) 5.1* (0–952)	(n=105) 2.9* (0–1070)	(n=92) 3.5 (0–109)	(n=77) 3.4 (0–180)	(n=112) 9.8 (0–2160)	(n=107) 11.1 (0–1940)	(n=108) 7.3 (0–908)	(n=96) 4.5 (1–380)	(n=70) 5.5 (0–158)
IL-6 levels	(n=81) 3.30# (0–188) (n=92) 2.75 (0–188)	NA	NA	0.0 (0–86)	0** (0–53)	(n=68) 1.0# (0–370) (n=98) 3.0 (0–370)	NA	NA	2.4 (0–117)	0** (0–177)

* denotes p <0.0001; ULN: upper normal limit, **24 weeks (EOS) in case patient discontinued prior to 24 weeks, levels for IL6 measured at discontinuation visit was included
# baseline statistics in patients who had both baseline and 12 week values
^ baseline statistics in patients who had both baseline and 24 wk (EOS) values

Patients in the canakinumab group had less tenderness and swelling (β-RELIEVED OR: 2.00, 2.25; 1.72, 2.02 at 72 h and 7 days; β-RELIEVED-II OR: 2.34, 2.07; 1.76, 1.21, at 72 h and 7 days post dose) compared to the TA group.

Conclusion: IL-1β blockade with canakinumab provided significant and sustained anti-inflammatory benefit over 24 weeks that was consistent with the clinical improvement in pain and significant delay in subsequent flares. Longer persistence of higher levels of inflammatory markers in the TA group suggests less control of ongoing inflammation.

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Effect of IL-1β Inhibition with Canakinumab Compared to Triamcinolone Acetonide on Pain Intensity and New Flares in Gouty Arthritis Patients with Chronic Kidney Disease Stage 2–5. P. Sunkureddi[1], T. Bardin[2], R. Alten[3], N. Schlesinger[4], M. Bloch[5], T. Kiechle[6], G. Krammer[6], A. Shpilsky[7] and A. So[8]. [1]Clear Lake Rheumatology Center, Nassau Bay, TX, [2]Hôpital Lariboisière, Paris, France, [3]Charité Teaching Hospital–Schlosspark-Klinik, Berlin, Germany, [4]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [5]Holdsworth House Medical Practice, Sydney, Australia, [6]Novartis Pharma AG, Basel, Switzerland, [7]Novartis Pharmaceutical Corporation, East Hanover, NJ, [8]CHUV, Lausanne, Switzerland

Background/Purpose: Most gouty arthritis (GA) patients have pre-existing comorbidities. Chronic kidney disease (CKD) is common and can limit treatment options due to intolerance and contraindications to available therapies. Canakinumab, a fully human monoclonal anti-IL-1β antibody, is a potential new therapeutic option for treating acute GA pain and delaying new flares in this difficult to treat GA patient population. Here, we report a post-hoc efficacy and safety analysis of pooled 24-week data from two pivotal Phase III studies (β-RELIEVED and β-RELIEVED-II) for a subgroup of GA patients with renal impairment.

Methods: In two 12-week multicenter, double-blind, double-dummy, active controlled studies (β-RELIEVED, N=228; β-RELIEVED-II, N=226), patients aged ≥18-≤85 yrs meeting ACR 1977 criteria for acute GA and contraindicated, intolerant or unresponsive to NSAIDs and/or colchicine received one single dose of canakinumab 150 mg sc or triamcinolone acetonide (TA) 40 mg im and were re-dosed "on demand" on each new flare, followed by a 12-week extension where study completers received canakinumab 150 mg sc or TA 40 mg im only "on demand" upon a new flare. Here, we report 24-week data in this renal impaired cohort for time to first new flare, pain intensity on visual analog scale (VAS) in most affected joint and safety.

Results: A total of 380 (83.7%) patients had renal impairment (baseline estimated Glomerular Filtration Rate (eGFR) <90mL/min/1.73m^2; corresponding to CKD stages 2–5): 188 (83.6%) in the canakinumab group and 192 (83.8%) in the TA group. At 24 weeks, significantly fewer patients on canakinumab experienced new flares vs those on TA (25.5% vs 47.4%, OR 0.38, 95% CI 0.25–0.59, p<0.0001). Mean VAS scores for the canakinumab group and TA group were 73.9mm vs 73.8mm at baseline, and 38.5mm vs 49.9mm 72 hours post dose (Diff: −10.9 mm; 95% CI: −16.1, −5.8, p<0.0001). This significant difference in pain relief was sustained up to 7 days (Table). 66.5% of patients had adverse events (AEs) with canakinumab vs 52.6% with TA. The most frequent canakinumab AEs were back pain and hypertension (n=10, 5.3% each), headache (n=9, 4.8%); whereas for TA they were hypertension (n=11, 5.7%), arthralgia (n=9, 4.7%), pain in the extremity and worsening of gout (n=8, 4.2 % each). Incidence of infections and infestations were comparable between canakinumab group (14, 7.4%) and TA group (14, 7.3%). There were no opportunistic infections. Serious AEs (canakinumab: n=15, 8%; TA: n=6, 3.1%) were not considered to be related to treatment by the investigator.

Table. Pooled analysis of pain intensity over 7 days post-dose in the CKD stages 2–5 patients

Time		***BL**	**6 hours**	**12 hours**	**24 hours**	**48 hours**	**72 hours**	**4 days**	**5 days**	**6 days**	**7 days**
Pain intensity (0–100 mm VAS)	Canakinumab 150mg sc	73.9 (12.73)	57.4 (1.40)	50.1 (1.58)	39.5 (1.78)	30.6 (1.86)	24.4 (1.84)	21.9 (1.78)	19.1 (1.76)	17.2 (1.79)	15.6 (1.72)
LS Mean (SE)	TA 40mg im	73.8 (12.64)	61.3 (1.41)	54.9 (1.60)	48.1 (1.80)	41.7 (1.88)	35.3 (1.86)	31.1 (1.80)	28.4 (1.78)	26.3 (1.81)	21.8 (1.73)
LS Mean difference canakinumab vs TA, (mm)			−4*	−4.7*	−8.7*	−11.1*	−10.9*	−9.2*	−9.3*	−9.1*	−6.2*
95% confidence intervals			−7.9, −0.0	−9.2, −0.3	−13.6, −3.7	−16.3, −5.9	−16.1, −5.8	−14.2, −4.2	−14.3, −4.4	−14.1, −4.1	−11.0, −1.4

* Baseline pain scores are presented as mean±SD; TA, triamcinolone acetonide; *p value≤0.05, LS Mean difference, least square mean. difference; SE, standard error

Conclusion: Renal impairment is a common comorbidity in GA patients. This post-hoc analysis of these two large clinical trials demonstrated that renal impairment (CKD stages 2–5) did not compromise the therapeutic efficacy and safety of canakinumab in this difficult to treat population.

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Efficacy and Safety of Lesinurad (RDEA594), A Novel Uricosuric Agent, Given In Combination with Allopurinol in Allopurinol-Refractory Gout Patients: Preliminary Results from the Randomized, Double-Blind, Placebo-Controlled, Phase 2B Extension Study. John Sundy[1], Fernando Perez-Ruiz[2], Eswar Krishnan[3], Vijay Hingorani[4], Jody Welp[4], Matt Suster[4], Kimberly Manhard[4], Matt Cravets[4], David Hagerty[4] and Barry Quart[4]. [1]Duke University Medical Center, Durham, NC, [2]Hospital De Cruces, Baracaldo, Spain, [3]Stanford University, Stanford, CA, [4]Ardea Biosciences, Inc., San Diego, CA

Background/Purpose: Lesinurad (RDEA594) is an oral investigational URAT1 inhibitor for the treatment of gout. A Phase 2B study in 208 gout patients (estimated creatinine clearance >60 mL/min) with an inadequate response to a stable dose of ALLO (200–600 mg/day for 6 weeks) confirmed the greater efficacy of the lesinurad/allopurinol combination. The lesinurad + ALLO groups showed superior reductions in sUA with 79%, 74%, and 63% of patients achieving sUA < 6 mg/dL after 28 days of dosing with 600 mg, 400 mg and 200 mg lesinurad + ALLO, respectively, compared to 25% with ALLO+placebo (p < 0.0001 with ITT analysis for all comparisons). Subjects completing the Phase 2B study could enter a long term extension, the preliminary results of which are presented here.

Objectives: To assess the ongoing efficacy and safety of lesinurad in combination with ALLO vs. ALLO and placebo (PBO) in patients with an inadequate response to standard doses of ALLO.

Methods: All subjects completing the double-blind 28-day dosing period washed out of lesinurad or PBO before entering the extension, but remained on a stable dose of ALLO. Subjects then restarted their original blinded treatment of lesinurad or PBO. All lesinurad-treated subjects started on the 200 mg dose and were to have the dose titrated stepwise to 400 or 600 mg if the sUA was not <6 mg/dL (<5 mg/dL in some regions). Formal statistical testing was not performed since this is an ongoing extension study and too few patients at this time have reached 6 months of dosing.

Results: 126 subjects enrolled into the extension study; 113 currently are continuing. Forty-one subjects completed 28 weeks and 8 subjects completed 1 year. Efficacy results are presented for all 41 subjects who completed extension week 28. Combination treated subjects continued to respond with 80% (4/5), 82% (9/11) and 92% (12/13) of ALLO + lesinurad 600 mg, 400 mg, and 200 mg, respectively, maintaining sUA < 6 mg/dL at 28 weeks, compared to 33% (4/12) of ALLO+PBO subjects; 40% (2/5), 64% (7/11) and 46% (6/13) of subjects receiving ALLO + lesinurad 600, 400 and 200 mg, respectively, also achieved sUA<5 mg/dL, compared to 17% (2/12) of ALLO+PBO subjects. 13 subjects (7 PBO/6 lesinurad) withdrew from the study for any reason before or after week 28. Two lesinurad subjects reported SAEs (angina, infected elbow) considered unrelated to lesinurad. CK elevations at baseline were common (24% of all subjects) and post-baseline elevations were also common, but rates were similar between the PBO (29%) and lesinurad (30%) groups. Transient serum creatinine elevations (increase to at least 1.5 × ULN) were observed with long term dosing in the lesinurad group (3.6%), which resolved to within the normal range at the next visit; no such elevations were observed with placebo.

Conclusion: Addition of lesinurad produced consistent, sustained reductions in sUA levels in patients not adequately responding to standard doses of ALLO. Most subjects achieved target sUA levels of <6 mg/dL on either the 200 or 400 mg lesinurad dose. Lesinurad was well-tolerated and no dose-related side effects were observed with combination treatment. Lesinurad is a promising investigational drug for the treatment of hyperuricemia in gout patients.

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Febuxostat (vs. Allopurinol) In Treating the Hyperuricemia of Gout In Diabetic Patients. Michael A. Becker[1], Patricia A. MacDonald[2], Barbara Hunt[2] and Robert L. Jackson[2]. [1]University of Chicago Medical Center, Chicago, IL, [2]Takeda Global Research & Development Center, Inc., Deerfield, IL

Background/Purpose: Patients with gout have substantially greater incidences of metabolic, cardiovascular and renal comorbidities than nongouty individuals. Diabetes mellitus is one of the disorders commonly associated with gout, but data about baseline characteristics and the efficacy and safety of urate-lowering (UL) therapy in diabetic gout patients are limited.

Methods: To report on the baseline characteristics and the efficacy and safety of UL therapy in diabetic gout subjects, we examined 312 subjects with gout and diabetes (among 2,269 with gout and baseline serum urate [sUA] ≥8.0 mg/dL) in the 6 month CONFIRMS trial. Diabetes was identified at baseline by history, with 72% (225 subjects) receiving either insulin or oral hypoglycemic agents. Subjects were randomized to daily febuxostat (FEB) 40mg or 80mg (both in subjects with eCLcr ≥30ml/min) or allopurinol (ALLO: 300mg if eCLcr ≥60 ml/min; 200 mg if eCLcr 30–59 ml/min). UL efficacy was defined as the proportion of subjects in each group achieving final visit sUA <6.0 mg/dL. Safety was evaluated by physical/lab examination and reported adverse events (AEs).

Results: Comorbidities in diabetic subjects were very prevalent: CVD (86%, including: hypertension [83%], coronary artery disease [22%], arrhythmias [18%] and MI [10%]); impaired renal function (eCLcr <90 ml/min [79%], <59 ml/min [36%]); hyperlipidemia (65%); and mean BMI of 36 kg/m^2. Serum urate levels (mean 9.6 mg/dL), a history of years with gout (mean 13 years), and tophi (18%) were similar across groups. In diabetic subjects, UL efficacy (final visit sUA <6.0 mg/dL) was comparable between FEB 40mg (38%) and ALLO (32%), but efficacy of FEB 80 mg (75%) was superior to both ($p<0.001$), a finding also seen in mild and moderate CKD (defined as eCLcr 60–89 ml/min and 30–59 ml/min, respectively). Higher serum urate levels and the presence of tophi at baseline were associated with low UL efficacy response rate in all treatment groups. Non-fasting blood glucose levels remained stable throughout the study. Regarding safety, at least 1 AE was reported in 46%, 62%, and 66% of FEB 40mg, FEB 80mg, and ALLO-treated diabetic gout subjects. Self-limiting diarrhea and upper respiratory infections were the most common AEs across treatment groups. Serious AEs occurred in 1, 8, and 8 subjects in FEB 40mg, FEB 80mg, and ALLO groups, respectively.

Conclusion: Despite very high rates of CV, renal, and additional metabolic co-morbidities, diabetic gouty subjects tolerated UL therapy with either FEB or ALLO, but FEB 80mg treatment achieved sUA <6.0 mg/dL more often than ALLO treatment at commonly prescribed doses.

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Rilonacept for Gout Flare Prevention: Subgroup Analysis of Patients Initiating or Continuing Uric Acid-Lowering Therapy in a Randomized, Placebo-Controlled Trial. John S. Sundy[1], H. Ralph Schumacher[2], Roy M. Fleischmann[3], Johannes M. Engelbrecht[4], Steven P. Weinstein[5], Jian Wang[5], Shirletta King-Davis[5] and Robert R. Evans[5]. [1]Duke University Medical Center, Durham, NC, [2]VA Medical Center and University of Pennsylvania, Philadelphia, PA, [3]MCRC, University of Texas, Dallas, TX, [4]Vergelegan Medi-Clinic, West Cape, South Africa, [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background/Purpose: Studies with the IL-1 antagonist rilonacept have established that IL-1 plays a key role in gout flare (GF) initiation.

Results from RE-SURGE, a large international, double-blind, placebo-controlled, phase 3 study demonstrated that rilonacept has a favorable safety and tolerability profile and resulted in substantial reduction in GFs in patients at high risk of flaring. A subgroup analysis was performed to evaluate efficacy in different subpopulations of RE-SURGE patients.

Methods: RE-SURGE included adults 18–80 years of age with gout who were initiating or currently on uric acid-lowering therapy (ULT). Patients were randomized in a 3:1 ratio to weekly subcutaneous injections of rilonacept 160mg (R160; n=985) or placebo (PBO; n=330) for 16 weeks; a loading dose of rilonacept 320mg or PBO was administered on Day 1. ULT was titrated to achieve uric acid <6 mg/dL. Efficacy endpoints included the mean number of GFs per patient, the mean number of GF days per patient, and proportions of patients with ≥1 and ≥2 GFs. GFs were defined as subject-reported acute articular pain typical of a gout attack and deemed by patient or investigator to require anti-inflammatory treatment. This subgroup analysis evaluated patients initiating ULT; continuing ULT; those using liquid pre-filled syringes (others used lyophilized drug in vials requiring reconstitution); and those meeting additional inclusion criteria of previous phase 3 confirmatory efficacy studies: serum uric acid concentration ≥7.5 mg/dL, ≥2 GFs within the past year, and initiating allopurinol treatment. There was no adjustment for multiple comparisons in this exploratory analysis.

Results: At 16 weeks (end of treatment), statistically significant reductions from baseline were observed with R160 relative to PBO for all efficacy endpoints in all subgroups (Table). Efficacy in all subgroups was also similar to that observed in the total population. Across subgroups, reductions ranged from 67.8%-72.3% for GFs per patient; 58.7%-69.4% for GF days per patient; 44.7%-52.4% for the proportion of patients with ≥1 GFs; and 60.4%-84.3% for the proportion of patients with ≥2 GFs.

	GFs per patient, mean (SD)	GF days per patient, mean (SD)	≥1 GFs, %	≥2 GFs, %
Total population	0.51 (1.17)*	2.66 (7.69)*	25.7*	11.7*
R160 (n=985)	1.73 (2.69)	7.66 (11.79)	51.1	34.7
PBO (n=330)				
Initiating ULT	0.50 (1.18)*	2.34 (6.67)*	24.7*	11.0*
R160 (n=614)	1.75 (2.70)	7.62 (11.55)	51.9	36.1
PBO (n=212)				
Continuing ULT	0.55 (1.15)*	3.19 (9.10)*	27.4*	12.7*
R160 (n=371)	1.70 (2.68)	7.72 (12.26)	49.6	32.2
PBO (n=118)				
Pre-filled syringe	0.46 (1.03)*	2.28 (5.49)†	29.2†	6.2*
R160 (n=120)	1.66 (1.99)	7.42 (9.73)	57.9	39.5
PBO (n=40)				
Additional inclusion criteria	0.55 (1.20)*	2.67 (7.22)*	27.9*	12.4*
R160 (n=420)	1.99 (2.89)	8.69 (12.37)	56.6	39.9
PBO (n=145)				

* P<0.0001 versus PBO; † P <0.005 versus PBO; SD = standard deviation.

Infections were reported in 20.1% of R160 patients (0.5% serious) and 19.1% of PBO patients (0.9% serious). Other AEs reported in ≥5% of R160 patients were injection site reactions (leading to withdrawal in 1.2%), headache, arthralgia, and pain in extremity. Six deaths occurred, 3 (0.3%) in R160 (none assessed as related to study drug) and 3 (0.9%) in PBO.

Conclusion: Weekly treatment with rilonacept 160mg resulted in similar efficacy in patients initiating or continuing uric acid-lowering therapy who were at risk of gout flares. Pre-filled syringes demonstrated efficacy similar to lyophilized drug in vials. Efficacy was also consistent in patients meeting the additional inclusion criteria from previous phase 3 studies. No new safety signals were observed.

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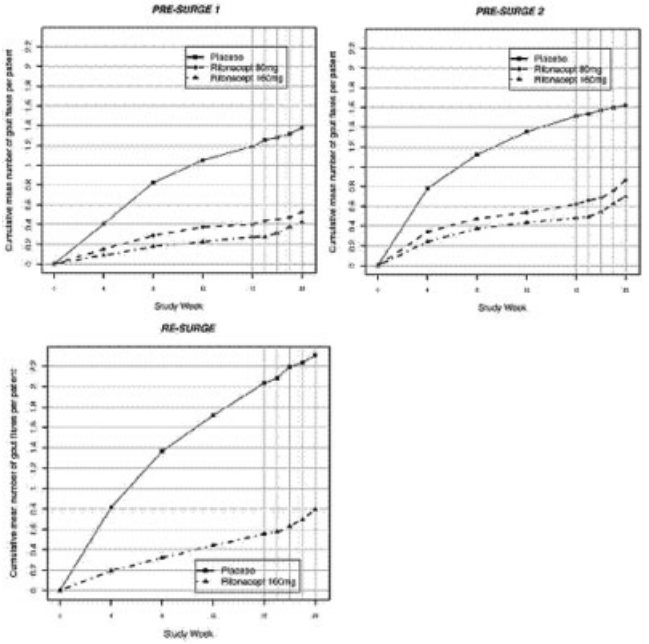
Rilonacept for Prevention of Gout Flares Associated with Uric Acid-Lowering Therapy: Response Rate Across Three Phase 3 Clinical Trials.
H. Ralph Schumacher[1], Robert R. Evans[2], Charles A. Birbara[3], Leon Fouche[4], Steven P. Weinstein[2], Jian Wang[2] and Robert Terkeltaub[5]. [1]VA Medical Center and University of Pennsylvania, Philadelphia, PA, [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [3]Univ Mass City Campus, Worcester, MA, [4]Limpopo Clinical Research Initiative, Thabazimbi, South Africa, [5]VA Medical Ctr, San Diego, CA

Background/Purpose: The efficacy of the interleukin (IL)-1 antagonist rilonacept for prevention of gout flares (GFs) associated with uric acid-lowering therapy (ULT) has been demonstrated in three phase 3 trials. While the 3 trials were of double-blind, placebo (PBO)-controlled design, they displayed some heterogeneity with regard to study populations and GF definition. This analysis evaluates the efficacy response across the 3 trials using the same GF definition (see **Methods**) for patients having similar inclusion criteria.

Methods: PRE-SURGE 1, PRE-SURGE 2, and RE-SURGE evaluated the safety and efficacy of weekly subcutaneous doses of rilonacept 80mg (R80; PRE-SURGE 1 and 2) and 160mg (R160; all 3 studies) for the prevention of GFs associated with ULT. PRE-SURGE 1 was conducted in North America, and the other two studies were conducted internationally. Double-blind treatment duration was 16 weeks (to Day 113) in all studies with a subsequent 4-week safety follow-up period. This analysis includes those patients who had baseline serum urate levels ≥7.5 mg/dL, ≥2 GFs in the past year, and were initiating treatment with allopurinol. GF rates were plotted for the individual studies and the percent reduction was estimated for the 16-week time point. GFs were defined as a subject-reported acute articular pain typical of a gout attack and deemed by patient or investigator to require anti-inflammatory treatment.



Results: Differences among the 3 studies in the GF rate curves over the 16-week treatment period manifested mainly as differences in the PBO GF rate (Figure). However, at the 16-week time point, the relative efficacy with R160 was similar across the 3 trials for reductions in GFs per patient. The mean reductions in flare rate with R160 were 76.9%, 68.1%, and 70.3%, for PRE-SURGE 1, PRE-SURGE 2, and RE-SURGE, respectively, providing an overall reduction of 69.2%. The mean reductions in flare rate with R80 were 66.4% and 58.9% for PRE-SURGE 1 and PRE-SURGE 2, respectively, providing an overall reduction of 62.3%. For the total population in the 3 studies,, infections were balanced among treatment groups. The most frequently reported treatment-related AE was injection site reaction, which led to patient withdrawal rates of 0% to 1.3% across rilonacept treatment groups. The rate of serious infections was low, ranging from 0% to 0.9% for PBO, 1.3% to 2.4% for R80, and 0% to 0.5% for R160.

Conclusion: In analyses employing the same gout flare definition in similar patient populations, the relative efficacy of rilonacept was consistent across three Phase 3 clinical trials. Rilonacept 160mg resulted in a 69.2% reduction in rate of gout flares and rilonacept 80mg resulted in a 62.3% reduction in rate of gout flares. Rilonacept demonstrated an acceptable safety and tolerability profile.

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Pharmacological Treatment of Acute Gout: A Systematic Review.
Puja Khanna[1], Manjit K. Singh[2], John D. FitzGerald[3], Sangmee Bae[2], Shraddha Prakash[3], Marian Kaldas[3], Maneesh Gogia[3], Paul Maranian[4], Robert Terkeltaub[5] and Dinesh Khanna[6]. [1]University of Michigan, Ann Harbor, MI, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, [3]UCLA, Los Angeles, CA, [4]UCLA Medical School, Los Angeles, CA, [5]VA Medical Ctr, San Diego, CA, [6]University of Michigan, Ann Arbor, MI

Background/Purpose: Acute gout flares are commonly treated with non steroidal anti-inflammatory agents (NSAIDS), colchicine, or corticosteroids. We systematically reviewed the published data on the pharmacological agents used for the treatment of acute gouty arthritis.

Methods: PubMed and CENTRAL databases were searched to find articles on gout till March 2011. From 5830 titles, 3729 titles excluded as these were duplicate, non-English, or met our exclusion criteria—leaving 1827 abstracts. Abstracts were reviewed by 2 reviewers leading to a total 128 manuscripts. We also reviewed the ACR and EULAR abstracts for last 3 years. A total of 26 manuscripts and 3 abstracts were selected for the systematic review.

Results: 27 of the 29 studies were active comparator studies, while the remaining two studies had a placebo control group. 23 studies were randomized controlled trials and 6 open pilot studies. The pooled mean (SD) age in the trials was 55 (12) years and 88% were males. 21% of studies treated patients within 24 hours of an acute gout attack, 27.5% within 48 hours, and 27.5% within 5 days; in 24% studies the duration of acute gout attack was not reported.

NSAIDs are the most frequently studied agents for the treatment of acute gout attacks. Indomethacin (INDO) has been extensively studied at doses of 50mg TID. INDO is comparable in efficacy to oral or IM NSAIDs when started within 48 hours. When compared to COX-2 selective inhibitors, indomethacin is associated with greater adverse events. Naproxen has been used at 500mg BID up to 1500mg daily for the treatment of acute gout. Naproxen is as efficacious as other NSAIDs, but has not been compared to COX-2 inhibitors. Etorocoxib and lumiracoxib (COX-2 inhibitors) has similar efficacy to NSAIDs but greater tolerability profile. High dose celecoxib (800/400mg on day 1) has similar efficacy to INDO. 2 studies showed that oral colchicine had greater efficacy in treating pain compared to placebo within first 12 hours of an acute attack. Although low dose (1.2 mg, followed by 0.6 mg) and high dose colchicine (4.8mg total over 6 hours) have comparable efficacy, low-dose colchicine has a significantly greater tolerability profile. Corticosteroids and IM ACTH have similar efficacy to therapeutic doses of NSAIDs in treating an acute gout attack. Adverse events were generally lower in patients on corticosteroids and ACTH compared to NSAIDs. Subcutaneous single-dose canakinumamb 150mg is more efficacious than single-dose 40mg IM triamcinolone acetonide for acute gout attack whose disease is refractory to or who have contraindications to NSAIDs and/or colchicine. Rilonacept was not more efficacious than indomethacin in a RCT. Topical ice was effective in reducing pain, when used with corticosteroids and colchicine. 8 studies of NSAIDs reported pain as an outcome measure. NSAIDs treatment started within 24 hours of acute onset was associated with an average weighted percent improvement of 76% vs. 61% for 48 hours (P=0.16).

Conclusion: NSAIDs and colchicine are effective in treating acute gout attack. Corticosteroid, ACTH, and canakinumamb can be used in patients who have contraindications to NSAIDs and colchicine.

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Nonclinical Drug-Drug Interaction Profile of BCX4208, An Oral, Once-Daily, Novel Nonmetabolized Enzyme Inhibitor for Chronic Management of Gout.
Paul G. Pearson[1], Shanta Bantia[2] and Leigh Harman[2]. [1]Pearson Pharma Partners, Westlake Village, CA, [2]BioCryst Pharmaceuticals, Inc., Birmingham, AL

Background/Purpose: Common comorbidities associated with gout, including obesity, hypertension, diabetes, and chronic kidney disease, may confer a greater risk of drug-drug interaction (DDI) through both polypharmacy and disease-associated alterations in drug absorption, distribution, metabolism, or excretion. Currently available antiinflammatory and urate-lowering therapies (such as colchicine, allopurinol, and probenecid) used for management of gout are

associated with significant DDIs. BCX4208 is an oral, once-daily, novel enzyme inhibitor in clinical development for the chronic management of gout. In Phase 1 pharmacokinetic (PK) studies of BCX4208, a dose-dependent reduction in serum uric acid was related to inhibition of purine nucleoside phosphorylase. In this study, we characterized the potential for BCX4208 to (1) interact with cytochrome P450 enzymes, (2) interact with drug transporters, and (3) induce or act as a substrate of metabolizing enzymes.

Methods: BCX4208 was incubated in gender-pooled human liver microsomes with marker substrates for CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5, and the catalytic activity of these isoforms was determined. BCX4208 was incubated with human primary hepatocytes from three donors, and induction of CYP1A2, CYP2B6, CYP2C9, CYP3A4/5, MDR1 (P-glycoprotein [P-gp]), and MRP2 was assessed.

Results: CYP isoforms: No significant inhibition of catalytic activity by BCX4208 was observed for CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 using gender-pooled human liver microsomal incubations. Additionally, BCX4208 was not shown to be a time-dependent inhibitor of CYP3A4/5. BCX4208 did not induce protein synthesis or enzyme activity for CYP1A2, CYP2B6, CYP2C9, and CYP3A4 in primary hepatocyte cultures from human donors. Drug transporters: BCX4208 did not induce protein synthesis of MDR1 or MRP2 in primary human hepatocytes, nor did the drug significantly inhibit OAT1 (kidney transport)–mediated uptake of p-aminohippuric acid, a substrate for OAT1. In addition, BCX4208 was not a substrate for the OAT1 transporter. BCX4208 was demonstrated to be a weak inhibitor of the kidney transporter OCT2 (11%-24% inhibition at 200 mM in CHP-OCT2 cells); however, BCX4208 is unlikely to mediate a DDI with compounds that are cleared by OCT2.

Conclusion: In summary, there is a low risk of DDIs between BCX4208 and coadministered medications. The potential for hepatic and/or renal DDIs is low given that BCX4208 does not induce or inhibit cytochrome P450 isoforms, has low potential as a P-gp substrate or inducer, and is not a substrate or inhibitor of renal organic anion and cation transporters. Furthermore, BCX4208 undergoes renal elimination and is not metabolized extensively; therefore, the clinical PK of BCX4208 will not be altered by inhibitors of drug metabolizing enzymes. These results provide good assurance in the clinical setting that drug interactions are not expected with BCX4208 in a chronic gout patient population. Indeed, in a Phase 2 trial of BCX4208 administered in combination with allopurinol, a first-dose PK assessment revealed no DDI with allopurinol or its active metabolite oxypurinol.

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Efficacy of Combined Treatment with Allopurinol and Benzbromarone in Gout Patients with Chronic Renal Impairment. Ji Seon Oh[1], Seung Won Choi[1], Bon San Koo[2], Min Wook So[2], Yong-Gil Kim[2], Chang-Keun Lee[2] and Bin Yoo[2]. [1]University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, South Korea, [2]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Background/Purpose: The management of hyperuricemia in gout patients with chronic renal impairment is difficult because of relatively high uric acid levels in such patients and a limitation in increasing doses of urate-lowering agents such as allopurinol. At the reduced doses proposed in the recommendations in such conditions, allopurinol alone may not decrease the serum urate concentration sufficiently to allow regression of tophi. Currently, the role of combination therapy with urate-lowering agents in such patients has not been well established. The purpose of this study is to evaluate the efficacy and safety of combined treatment with allopurinol and benzbromarone in hyperuricemic patients with moderate to severe renal impairment.

Methods: We retrospectively reviewed medial records of twenty gout patients with moderate to severe renal impairment (glomerular filtration rate (GFR) 15–59 mL/min/1.73m^2) who has been treated with both allopurinol and benzbromarone in our outpatient clinic between 2003 to 2011. We measured uric acid levels and GFR at baseline and during treatment with allopurinol before and after addition of benzbromarone. GFR was calculated by the Modification of Diet in Renal Disease (MDRD) equation. For statistical analysis, Wilcoxon test was used.

Results: Mean age of patients was 61.0 ± 11.2. Mean uric acid levels and GFR at baseline was 10.4 ± 1.3 mg/dL and 38.4 ± 8.3 mL/min/1.73m^2, respectively. Mean doses of allopurinol and benzbromarone were 197.5 ± 86.6 mg (range 100–400 mg) and 47.5 ± 29.1 mg (range 25–100 mg), respectively. Uric acid levels decreased from a mean of 10.4 ± 1.3 mg/dL to 5.6 ± 1.7 mg/dL ($p<0.001$). Of fourteen patients who treated with allopurinol alone at average doses of 193 mg/day before addition of benzbromarone, none had achieved the desired uric acid level (mean uric acid levels, 8.7 ± 1.4 mg/dL; mean reduction of uric acid levels, 1.9 ± 1.4 mg/dL, $p<0.001$). Fourteen (70%) of twenty patients with combination treatment reached the uric acid levels of ≤ 6.0 mg/dL. There was no serious adverse event including hepatic dysfunction during combination treatment. Benzbromarone was discontinued in one patient due to diarrhea. There were no significant changes in GFR during treatment with benzbromarone (mean changes in GFR, 1.1 ± 4.5 mL/min/1.73m^2, $p=0.298$).

Conclusion: This study results suggest that combined treatment with allopurinol and benzbromarone may be an effective strategy for achieving the goal of uric acid levels in gout patients with moderate to severe renal impairment.

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Comparison of Pain Intensity, Incidence of New Flares, Safety and Tolerability of Canakinumab Vs Triamcinolone Acetonide in Gouty Arthritis Patients with Cardiovascular Diseases or with Cardiovascular Risk Factors. N. Schlesinger[1], J. P. Brown[2], T. Bardin[3], T. Kiechle[4], A. Shpilsky[5], R. Alten[6] and A. So[7]. [1]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]CHUQ (CHUL) Research Centre, Laval University, Quebec City, QC, [3]Hôpital Lariboisière, Paris, France, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharmaceutical Corporation, East Hanover, NJ, [6]Charité Teaching Hospital–Schlosspark-Klinik, Berlin, Germany, [7]CHUV, Lausanne, Switzerland

Background/Purpose: Patients with gouty arthritis (GA) are at a higher risk of cardiovascular disease (CVD) than the general population and CVD comorbidities limit treatment options for acute flares. Acute flares are associated with an increase in inflammatory markers such as hsCRP, which is a risk factor for CVD. We report a post-hoc efficacy and safety analysis of canakinumab (a fully human, anti-IL-1β monoclonal antibody) vs triamcinolone acetonide (TA) in GA patients with CVD comorbidities.

Methods: In two, 12-week multi-center, double-blind, double-dummy, active controlled studies, patients ≥18−≤85 yrs meeting ACR 1977 preliminary criteria for GA and contraindicated, intolerant or unresponsive to NSAIDs and/or colchicine, with an onset of flares ≤5 days were randomized to receive a single dose CAN 150mg sc or TA 40mg im, and were re-dosed "on demand" on each new flare. Patients completing the core studies were enrolled into 12-week extension studies to further investigate "on demand" use of canakinumab 150 mg sc or TA 40 mg im on new flare. We report a post hoc analysis in CVD population including patients with a history of heart failure, coronary artery disease, cardiac arrhythmia, ischemic heart disease, and cerebrovascular disease and/or at least one CVD risk factor (stable hypertension, diabetes mellitus, hypercholesterolemia) at baseline. Evaluations included number of patients with new flares over 24 weeks; pain intensity in the most affected joint (0–100 mm VAS) at 72h post dose; effect on hsCRP and SAA and safety.

Results: 454 GA patients received treatment (β-RELIEVED, N=228; β-RELIEVED-II, N=226), 225 received CAN and 229 received TA. 319 (70.2%) had either a history of CVD and/or at least one CVD risk factor at baseline, 151 (67.1%) received CAN and 168 (73.4%) received TA. Pain intensity was comparable at baseline (mean±SD CAN: 74.4 mm ±12.37 mm; TA: 73.7±12.28 mm). A significantly lower pain score was reported for CAN vs TA at 72h post dose (LS mean: 25.3 mm vs 35.0 mm, Diff: −9.7 mm; 95% CI: −15.2, −4.3, $p=0.0005$). Incidence of new flares over 24 weeks was significantly lower for CAN vs TA (24.5% vs 46.4%, odds ratio = 0.37, 95% CI 0.23–0.60, $p<0.0001$). CRP levels were 39% lower in CAN vs TA 72h post dose (ratio=0.61, 95% CI: 0.50, 0.73, $p<0.0001$) and 52% lower at 7 days (ratio=0.48, 95% CI: 0.39. 0.59, $p<0.0001$). SAA levels were 59% lower in CAN vs TA 72h post dose (ratio=0.41; 95% CI: 0.32, 0.53, $p<0.0001$) and 62% lower at 7 days (ratio=0.38; 95% CI: 0.29, 0.49, $p<0.0001$). Decrease in blood pressure was observed over 24 weeks in CAN vs TA (mean±SD SBP: −5.1±17.26 mmHg vs −3.4±14.81 mmHg, DBP: −1.4±11.51 mmHg vs −0.4±9.61 mmHg). CAN had more AEs and SAEs (102 [67.5%], 12 [7.9%]) vs TA group (86 [51.2%], 5 [3.0%]). angina pectoris, arrhythmia, myocardial ischemia (1 each) was reported in canakinumab group and aortic valve incompetence and cardiac myopathy (1 each) were reported in TA group. None of the SAEs were reported by investigators as related to study drug. Infections were mostly mild to moderate.

Conclusion: CAN provided superior pain relief, reduced the risk of a new flare and lowered the level of inflammatory markers vs TA in GA patients with CVD or CVD risk factors.

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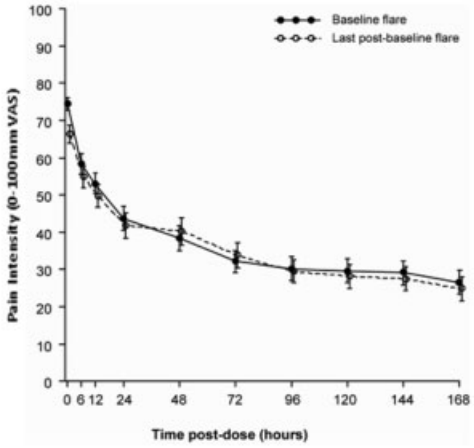
Efficacy of Canakinumab on Re-Treatment in Gouty Arthritis Patients with Limited Treatment Options: 24-Week Results From β-RELIEVED and β-RELIEVED-II Studies. R. Alten[1], A. So[2], A. Kivitz[3], T. Bardin[4], M. Bloch[5], A. Gimona[6], A. Widmer[6], G. Krammer[6], N. Schlesinger[7] and H. R. Schumacher[8]. [1]Charité Teaching Hospital–Schlosspark-Klinik, Berlin, Germany, [2]CHUV, Lausanne, Switzerland, [3]Altoona Center for Clinical Research, Duncansville, PA, [4]Hôpital Lariboisière, Paris, France, [5]Holdsworth House Medical Practice, Sydney, Australia, [6]Novartis Pharma AG, Basel, Switzerland, [7]UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, [8]University of Pennsylvania and VA Medical Center, Philadelphia, PA

Background/Purpose: Gouty arthritis (GA) is a chronic, recurrent, inflammatory arthritis affecting 1–4% of the population. A subset of patients experiencing acute flares may have limited anti-inflammatory treatment options due to contraindications, intolerance or unsatisfactory therapeutic response with current therapies. Canakinumab, a fully human anti-IL-1β monoclonal antibody, selectively targets the inflammatory cascade and is a novel therapeutic approach to treat acute GA. Here we report pooled results from two studies on time to first new flare and pain response to treatment of first and last flare.

Methods: In two, 12-week multicenter, active-controlled trials (β-RELIEVED and β-RELIEVED-II), GA patients (18–85 yrs) meeting preliminary ACR-1977 criteria and unresponsive, intolerant, or contraindicated to NSAIDs and/or colchicine were enrolled to receive one single dose canakinumab 150mg sc or triamcinolone acetonide (TA) 40mg im and were re-dosed "on demand" on each new flare. Patients completing the core studies were enrolled into 12-week extension studies to further investigate "on demand" use of canakinumab 150 mg sc or TA 40 mg im on new flare. Pooled data from 24-weeks treatment were analyzed for time to first new gout flare (Cox proportional Hazard regression model) and pain intensity in most affected joints (0–100mm VAS).

Results: 454 patients received study drug and 335 patients entered the extension studies. A total of 317 patients (95% of those entering the extension) completed 24-weeks. Over the entire 24-week period 64 patients on canakinumab and 112 patients on TA experienced ≥1 new flare and 17 patients on canakinumab and 50 patients on TA experienced ≥2 new flares. The probability of a new gout flare was lower with canakinumab (32.4%) vs TA (56.0%) corresponding to a statistically significant risk reduction of 56% (Hazard Ratio: 0.44; 95% CI 0.32–0.60; p<0.0001) over 24 weeks. The median time to first new flare per patient treated with canakinumab was >168 days (i.e. not reached within the 24 week study duration) vs 131 days with TA. For new flares in the canakinumab patients, pain was less intense than during first flare. With canakinumab, there was a good correlation between pain response during first flare and subsequent flares (r=0.60) vs TA (r=0.28). Treatment of the last new flare was as effective as treatment of the first flare (Figure).

Figure: Treatment response: Pain intensity (0-100mm VAS) during the 7 days post-dose in canakinumab patients for last new flare vs first flare



VAS Score on Y-axis displayed as Mean±Standard error

Conclusion: By targeting IL-1β, canakinumab provided effective pain-relief in all flares and reduced the risk of new flares compared to TA. Canakinumab may represent an important advance in the treatment of GA in patients whose disease cannot be appropriately managed with currently available treatments.

1030

Pharmacokinetics, Efficacy and SAFETY of Lesinurad, a Novel URAT1 Inhibitor, In Individuals with Mild to Moderate Renal Impairment. David Hagerty, Brad Kerr, Zangong Shen, Li-tain Yeh, Vijay Hingorani, Matt Cravets, Jody Welp, Jeffrey N. Miner, Kimberly Manhard and Barry Quart. Ardea Biosciences, Inc., San Diego, CA

Background/Purpose: Lesinurad is novel URAT1 inhibitor that blocks reabsorption of uric acid in the proximal tubule of the kidney. Because many gout patients exhibit varying degrees of renal insufficiency, serum urate (sUA) lowering effect, pharmacokinetics (PK), safety, and tolerability of lesinurad were examined in subjects with normal and impaired renal function in 3 clinical trials.

Methods: In 2 double-blind, placebo-controlled, Phase 2b studies, 331 gout patients were randomized to receive a 28-day once-daily course of placebo or lesinurad from 200 to 600 mg as monotherapy or in combination with allopurinol (ALLO). In a phase 1 study, 24 subjects with varying degrees of renal function were given a single oral dose of lesinurad 200 mg. Full PK profiles were obtained in the phase 1 study and in a sub-study of the Phase 2b ALLO-combination study and predose trough concentrations were measured weekly in both phase 2b studies. Urinary lesinurad concentrations and sUA levels were also evaluated.

Results: Degrees of renal insufficiency for data analysis was based on Chronic Kidney Disease staging guidelines using measured 24-hr creatinine clearance (CrCL) in the phase 1 study and estimated CrCL by Cockcroft-Gault (ideal body weight) in the Phase 2b studies. Lesinurad C_{max} increased ≤30% in the various renal impairment categories compared to subjects with normal renal function. Lesinurad AUC increased ~33% in subjects with mild renal impairment and approximately doubled in subjects with moderate renal impairment. Renal clearance of lesinurad was similar between subjects with normal renal function and with mild renal impairment, but appeared to decrease as the creatinine clearance declined below around 40 ml/min. In the phase 2b studies, there was no meaningful difference in trough plasma concentrations of lesinurad. Median sUA reduction with the 400 mg dose in patients with normal, and mild to moderate renal impairment was 32%and 28% for monotherapy and 21%and 25% for combination with ALLO, respectively. Across the 3 studies, the tolerability and safety of lesinurad was similar in patients with normal and impaired renal function.

Conclusion: In Phase 2B clinical trials, there were no meaningful differences in lesinurad exposure in patients with mild-to-moderate renal impairment. Similar urate reductions were observed in these patients compared to patients with normal renal function. The efficacy and safety profile of lesinurad was similar in patients with normal and impaired renal function

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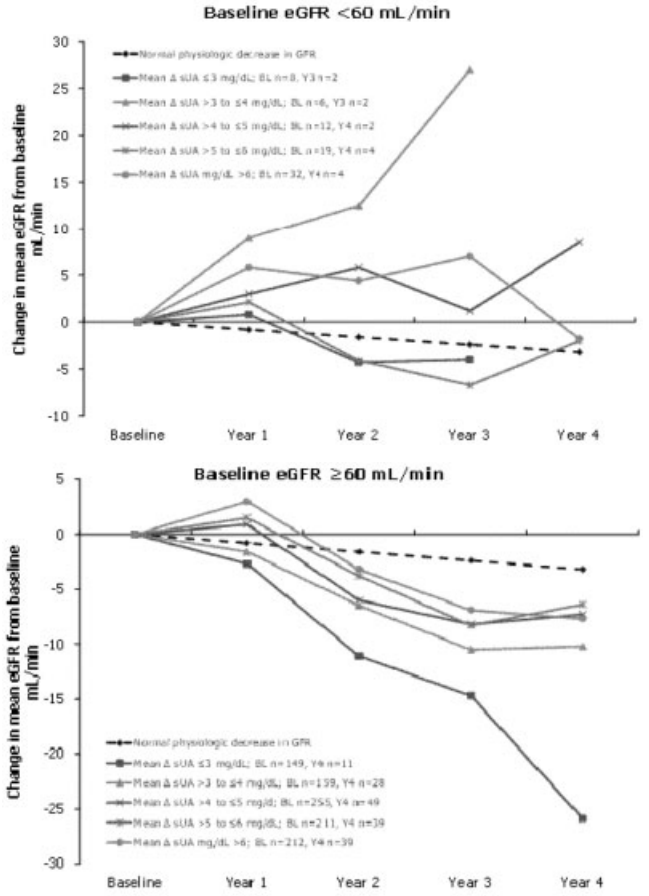
The Impact On Renal Function of Quantitative Serum Urate Reduction In Gout Patients. Andrew Whelton[1], Patricia A. MacDonald[2], Barbara Hunt[2] and Lhanoo Gunawardhana[2]. [1]The Johns Hopkins University and Universal Clinical Research Center, Inc., Baltimore, MD, [2]Takeda Global Research & Development Center, Inc., Deerfield, IL

Background/Purpose: Gout may lead to deterioration of renal function beyond that which can be attributed to aging. This analysis evaluated the effects of urate-lowering therapy (ULT) on renal function in hyperuricemic gout subjects with baseline (BL) estimated glomerular filtration rates (eGFR) of < or ≥60 mL/min.

Methods: Subjects (1086) completing 2 phase 3 trials (FACT and APEX) were enrolled in the long-term EXCEL study and received daily ULT (febuxostat 80 or 120 mg or allopurinol 300 mg) for ≤4 years. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. A repeated-measures linear model was used to assess the relationship between eGFR change and sUA change, with factors for year of treatment and BL renal function (eGFR <60 vs ≥60 mL/min).

Results: Among this mostly male (96%), Caucasian (79%), and obese (63%) cohort, 7% (n=77) had BL eGFR <60 mL/min. Long-term ULT appeared to provide greater stabilization of renal function in subjects with BL eGFR <60 (Figure 1) than for those with BL eGFR ≥60 (Figure 2). Overall, greater sustained sUA decreases were associated with less renal function deterioration (p<0.001). The model projects that, overall, every 1 mg/dL sUA reduction from BL will yield 1.25 mL/min less of a decrease in eGFR compared with no sUA reduction. The impact of BL renal impairment was significant (p<0.05): given the same treatment duration and sUA change, subjects with renal impairment (BL eGFR <60 mL/min) had 4.7 mL/min less of an eGFR decrease compared to those with BL eGFR >60 mL/min.



Conclusion: In treated gout subjects, the magnitude of treatment-induced persistent decreases in sUA is correlated with reduced deterioration of renal function, especially in patients with baseline eGFR <60 mL/min. These findings have important clinical implications in the management of gout in patients with renal impairment.

1032

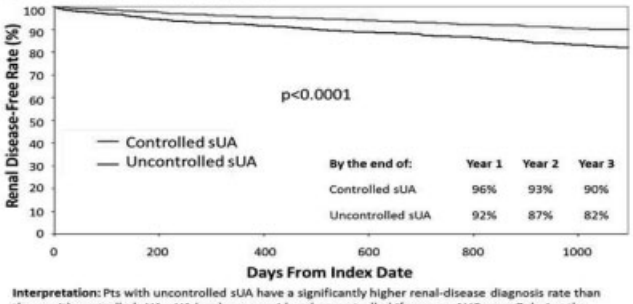
Uncontrolled Serum Uric Acid Is Associated with An Increased Risk of Developing Renal Disease In Veterans with Gout. Eswar Krishnan[1], Hari Sharma[2], Bhavik J. Pandya[3], Maryna Marynchenko[2], Andrew Yu[2], Eric Wu[2], Jinan Liu[4] and Lizheng Shi[4]. [1]Stanford University, Stanford, CA, [2]Analysis Group, Inc., Boston, MA, [3]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [4]Tulane University, New Orleans, LA

Background/Purpose: Increases in serum uric acid (sUA) levels are associated with renal function deterioration. This study aims to estimate the impact of uncontrolled sUA on the risk of developing renal disease in veterans with gout.

Methods: Adult male patients (pts) (age ≥18 yrs) with at least 2 gout diagnoses (ICD-9 CM: 274.xx) and 2 sUA measurements between 1/1/2002 and 1/1/2011 were identified from the Veterans Integrated Services Network 16 (VISN 16) data warehouse. The first sUA measurement date was assigned as the index date. Pts were required to be continuously eligible for at least 6 months prior to and 12 months following the index date and were excluded if they had history of inflammatory diseases (rheumatoid arthritis, lupus, scleroderma, vasculitis, psoriatic arthritis, autoimmune diseases, pseudogout, and other inflammatory arthritis). Renal disease was identified using ICD-9-CM codes (580–588, 250.4, 590, 593, and 791.0) and dialysis procedure codes (CPT: 90935, 90937, 90945, and 90947). Pts with history of renal disease prior to the index date were excluded. A longitudinal design was used with 6-month cycles from the index date until the end of eligibility. sUA levels were assessed for each cycle. Cycles with sUA levels >7/≤7 mg/dL were considered uncontrolled/controlled. Time to first renal disease diagnosis was compared between patients with uncontrolled vs. controlled sUAs using Kaplan-Meier (K-M) analysis and a Cox proportional hazard model. For K-M analysis, average area under the curve (AUC) for sUA measurements during the entire study period was used to classify pts into uncontrolled vs. controlled sUA cohorts. Cox proportional hazard model was used to estimate relative risk of renal disease associated with uncontrolled sUA level as a time-varying risk factor, controlling for: age at index date; year of index date; race; region; body mass index (BMI); and baseline tobacco use, hypertension, hyperlipidemia, and diabetes.

Results: 2,116 pts were selected. The majority of pts (53%) were white, with average age 62.6 yrs. Pts were generally obese (mean BMI 31.2). Average follow-up time was approximately 80 months. Major comorbidities at baseline included hypertension (93%), hyperlipidemia (67%), diabetes (20%), and smoking (8%). K-M analysis (Figure 1) showed that pts with controlled sUA had significantly higher renal disease-free rates at year 1, 2, and 3 compared to pts with uncontrolled sUAs (96% vs 92%; 93% vs 87%; and 90% vs 82%, respectively; p<0.0001). Cox proportional hazard model confirmed that the uncontrolled sUA was associated with a significantly higher risk of renal disease (hazard ratio: 1.43, 95% confidence interval: [1.20–1.70]).

Figure 1. Kaplan-Meier Survival Curve for Time to First Renal-Disease Diagnosis: Controlled sUA vs Uncontrolled sUA



By the end of:	Year 1	Year 2	Year 3
Controlled sUA	96%	93%	90%
Uncontrolled sUA	92%	87%	82%

Interpretation: Pts with uncontrolled sUA have a significantly higher renal-disease diagnosis rate than those with controlled sUA. sUA level was considered uncontrolled if average AUC was >7 during the study period.

Notes: Time to renal disease was measured from index date until: a) renal-disease diagnosis; b) death; or c) the end of data, whichever comes earlier. Pts with renal disease prior to index date were excluded.

Sample size at the end of:	Baseline	Year 1	Year 2	Year 3
Controlled sUA	912	873	805	741
Uncontrolled sUA	1,204	1,111	988	856

Conclusion: Compared to controlled sUA levels, uncontrolled sUA levels are associated with increased risk of a new diagnosis of renal disease among veterans with gout.

1033

Clinical Characteristics of Difficult-to-Treat Gout Patients: a Principal Components Analysis. Elizaveta Vaysbrot[1], Yoojin Lee[1], Sarah McLaughlin[1], Neetu Agashivala[2], Anthony Yadao[3], Timothy E. McAlindon[1] and William F. Harvey[1]. [1]Tufts Medical Center, Boston, MA, [2]Novartis Pharmaceutical Corporation, East Hanover, NJ, [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ

Background/Purpose: Difficult-to-treat gout patients have unmet medical need in symptom control due to limited treatment options and may require additional healthcare services, including ER visits and hospitalization. Understanding which clinical characteristics of this population are significant and how they are intercorrelated is vital for future research but limited at this point. Our objective was to uncover the correlation between the clinical characteristics of difficult-to-treat gout patients to identify key variables for future research.

Methods: Tufts Medical Center charts were reviewed for fiscal years 2008–2010. As no definition of difficult-to-treat gout exists, we chose inclusion criteria based on ease of electronic searching and on the principle that poor control of gout symptoms results in frequent visits/admissions. Inpatients with difficult-to-treat gout were defined as persons with ≥2 inpatient consultations in one year by a rheumatologist for gout (ICD9 274.xx) regardless of admission diagnosis. Outpatients were selected on the basis of a new rheumatologic outpatient consult and ≥5 outpatient rheumatology visits for gout in a year. From each of these two criteria sets, 75 inpatients and 75 outpatients with the highest billing codes were selected. Data were extracted on patient demographics, referral data, disease characteristics, comorbidities, and medication history over a 12 months period. Nominal dichotomous (Yes/No) variables such as "diuretics use" and comorbid conditions data were selected to perform a principal components analysis (PCA) using an orthogonal rotation (SAS version 9.2. Cary, NC. SAS Institute Inc.). Factors were selected based on the Kaiser criterion (eigenvalue >1), and components were included if their loading value was >0.4.

Results: Mean age was 63±13.7 years, 71% were male, and 67% were white. The most common referral source was primary care (43.2%). 9.3% had ≥3 attacks in the previous year. 72% were on ≥5 concomitant medications, excluding those for gout. Approximately 20% had an emergency room visit and 17% were hospitalized specifically for a gout attack. Five factors were identified in PCA (see table).

Factors (Eigenvalues) and principal components (loading values)	Patient Records (n=150)
Factor 1 (3.37): Chronic Heart Failure (0.81), Coronary Heart Disease (0.73), Cerebrovascular Disease (0.64), Diuretic Use (0.53), Dyslipidemia (0.52)	
Patients with 5 components (%(n))	5.3% (8)
Patients with 4 components (% (n))	10.7% (16)
Patients with 3 components (% (n))	4% (6)
Patients with 2 components (% (n))	19.3% (29)
Patients with 1 component (% (n))	31.3% (47)
Patients with 0 components (% (n))	29.3% (44)
Factor 2 (2.55): Cirrhosis (0.87), Chronic Liver Disease (0.86), Upper GI Ulcer (0.66), GI Bleeding history (0.48)	
Patients with 4 components (% (n))	1.3% (2)
Patients with 3 components (% (n))	0
Patients with 2 components (% (n))	4% (6)
Patients with 1 component (% (n))	8% (12)
Patients with 0 components (% (n))	86.7% (130)
Factor 3 (1.80): Hypertension (0.66), Metabolic Syndrome (0.61), Diabetes Mellitus (0.54), Chronic Kidney Disease (0.53), Arthritis other than gout (0.50)	
Patients with 5 components (% (n))	6% (9)
Patients with 4 components (% (n))	8% (12)
Patients with 3 components (% (n))	18.7% (28)
Patients with 2 components (% (n))	24.7% (37)
Patients with 1 component (% (n))	27.3% (41)
Patients with 0 components (% (n))	15.3% (23)
Factor 4 (1.37): Obesity (0.56), Alcohol Use (−0.55), Peripheral Vascular Disease (−0.51)	
Patients with 3 components (% (n))	0
Patients with 2 components (% (n))	3.3% (5)
Patients with 1 component (% (n))	52.% (79)
Patients with 0 components (% (n))	44% (66)
Factor 5 (1.14): Renal Stones (0.56), Tophi (−0.42)	
Patients with 2 components (% (n))	1.3% (2)
Patients with 1 components (% (n))	26.7% (40)
Patients with 0 components (% (n))	72% (108)

* negative loading values indicate that absence of that component is correlated with the other components.

Conclusion: The four out of five factors had components with clinical relationships: cardiovascular diseases, gastrointestinal disorders, metabolic syndrome and features of advanced gout. The components in factor 4 did not have a clear clinical relationship. The study was limited by its retrospective nature, small sample size, and an inexact, exploratory nature of PCA method. Characteristics of this population may vary if using different definitions of difficult-to-treat. Despite the limitations, our results confirm the clinical intuition that the above conditions are linked to difficult-to-treat gout and may help design future research.

1034

Predictors of Outcomes in Gout with Comorbid Chronic Kidney Disease. Ankoor Shah and John S. Sundy. Duke University Medical Center, Durham, NC

Background/Purpose: Gout in the setting of chronic kidney disease (CKD) poses particular challenges in disease management. Impaired renal function leads to reduced excretion of urate. CKD poses a challenge in terms of treatment of gout. Non-steroidal anti-inflammatory drugs and colchicine are contraindicated in the setting of CKD. The appropriate dosing of allopurinol in the setting of CKD remains controversial. We characterized the disease and treatment features of gout patients with CKD compared to gout patients without CKD in an integrated academic health system

Methods: Adult gout patients were identified by searching an institutional outpatient database for ICD-9 codes associated with gout (274.xx) in the past five years. Charts were further reviewed for conformity with the American College of Rheumatology's preliminary criteria for gout diagnosis. CKD was ascertained and staged based on the patient's estimated glomerular filtration rate from laboratory studies. The primary endpoint was the proportion of patients reaching a target serum uric acid (SUA) of less than 6.0 mg/dL. Statistical analysis was performed using JMP v9 (SAS Cary, NC).

Results: 1791 patients were identified with an ICD-9 code associated with gout, 500 of which were randomly selected for chart review. Of these, 240 met criteria for the diagnosis of gout. 130 patients had gout alone, while 110 patients had gout and comorbid CKD. The mean age at diagnosis in the gout alone group was 57 years and 67 years in the gout/CKD group ($p<0.0001$). Women represented 20% of the gout alone group compared to 47% of the gout/CKD group ($p<0.0001$). There were no significant racial differences.

45% of patients with gout alone reached a target SUA of <6.0 compared to 40% of those with CKD ($p = 0.40$). Patients with CKD had a higher baseline SUA (9.8 mg/dL v. 8.29 mg/dL, $p < 0.0001$), however there was no significant difference between their most recent treated SUA (6.49 mg/dL v. 6.96 mg/dL $p = 0.097$).

73% with gout alone and 75% of gout/CKD patients were on uric acid lowering therapy ($p = 0.675$). The mean allopurinol dose in patients with CKD was significantly less than in patients with gout alone (256 mg v. 208 mg; $p=0.01$).

30% of patients with gout alone had a rheumatologist involved in care compared to 43.7% of those in the gout/CKD group ($p = 0.029$). Among all patients, involvement of a rheumatologist led to significantly greater liklihood of reaching target SUA (54.02% v. 36.6%, $p = 0.009$). "A logistic regression model using multiple predictors found only rheumatologist involvement significantly predicted reaching a target SUA goal ($p = 0.007$).

Conclusion: Patients with comorbid gout and CKD were older at diagnosis, had a higher baseline SUA and had a greater proportion of females compared to patients with gout alone. A minority of patients in both groups reach target uric acid goals of less than 6.0 mg/dl regardless of comorbid CKD. Treatment by a rheumatologist was the only statistically significant predictor of improved outcomes. Our results indicate that the demographic features of comorbid gout and CKD are distinct from that of patients with gout alone. The presence of gout and CKD may serve as a marker of the need for referral to a rheumatologist in order to optimize care.

1035

Patient Management/Treatment and Outcomes of Gout Between Primary Care Physicians and Rheumatologists: A Chart Review of 1,039 Patients with Gout In the United States. Dinesh Khanna[1], Anna Forsythe[2] and Puja Khanna[1]. [1]University of Michigan, Ann Arbor, MI, [2]Savient Pharmaceuticals, Inc., East Brunswick, NJ

Background/Purpose: The prevalence of gout has doubled over the last two decades and estimated currently at 8.3 million patients in the U.S. (Hyon Choi NHANES IV abstract) [1]. Only 4% of patients with gout are cared for by rheumatologists (Rheums) whereas the majority are managed by primary care physicians (PCPs). Despite the availability of urate-lowering therapies (ULT), there still remains a subset of chronic gout patients whose serum urate (SUA) levels and gout symptoms are not controlled. However, the differences in treatment and management of these gout patients as well as the outcomes of therapy have not been compared between PCPs and Rheums. The purpose of this abstract is to identify the current ULT practice patterns among the PCP and Rheums in the US, understand the clinical burden of gout patients treated with ULT, and assess the differences in patient outcomes between PCPs and Rheums.

Methods: A retrospective chart audit of 1,039 US pts with gout was conducted during August and September, 2010 by BioTrends Research Group, Inc.[2] A panel of board-certified practice-based Rheums (119) and PCPs (122) who treated > 50 gout patients in US were selected. Each included chart records of the last 3–5 consecutive gout patients who had a physician-confirmed diagnosis of gout. A structured case report form was completed by each physician that included patient demographics, burden of illness (SUA levels, flare, tophi, swollen joints and presence of radiographic damage), co-morbidities, treatment and resource utilization. The data from Rheums and PCPs were compared using independent unpaired t-test for means (equal variances) and independent z-test for percentages. A difference of $p=0.05$ was considered statistically significant.

Results: Of 1,039 gout pts, 82% were male, 74% were Caucasian, mean age was 58 years and 30% had a BMI > 30. Pts under the care of Rheums had higher disease burden and co-morbidities compared to pts under care of PCPs. Burden of illness, co-morbidities, ULT treatment, and resource utilization are presented in Table.

Table.

	PCP's pts (n=522)	Rheum's pts (n=517)	P value
Burden of Illness (% total pts)			
Chronic tophaceous gout	3.1	22.5	<0.05
Tophi	14.2	37.5	<0.05
3 to 5 Annual Flares	10.7	15.9	<0.05
>6 Annual Flares	5.0	6.0	NS
High to extreme severity of recent flare	17.7	39.6	<0.05
sUA <6 mg/dl	30.3	36.0	NS
sUA >6 to <8 mg/dL	42.1	34.6	<0.05
sUA >8 mg/dL	27.6	29.4	NS
Co-Morbidities (% total pts)			
Cardiovascular disease	14.8	25.0	<0.05
Hyperlipidemia	41	34.8	<0.05
Chronic kidney Disease	11.1	22.1	<0.05
Currently on ULTs (% total pts)	63.2	84.5	<0.05
Allopurinol	49.0	59.7	<0.05
Febuxostat	12.6	23.4	<0.05
Probenecid	1.5	1.4	NS
% Allopurinol pts on >300 mg	20.7	24.0	NS
Resource Utilization over the last 12 months			
SUA labs (mean N per pt)	1.7	2.5	<0.05
Radiographic tests (mean N per pt)	14.4	35.0	<0.05
% Radiograph indicating joint damage	49.3	57.5	NS
% Flares resulting in ER visits	11.2	11.4	NS
% Flares resulting in hospitalization	1.6	2.9	NS

Conclusion: Pts under the care of Rheums had higher disease burden and co-morbidities compared to pts under care of PCPs. PCP's and Rheum's pts had similar resource utilization. Despite the availability of ULTs, 64 – 70% of patients had SUA > 6 mg/dL, 37.5% in Rheum practices have tophi, and 16% have 3–5 flares. Only 21–24% were on allopurinol > 300 mg/day. There continues to be a disconnect between the treatment guidelines for gout[3] and current practices in US.

Ref:
[1] Zhu Y, Pandya BJ, Choi KH. Prevalence of gout in the US general population: The NHANES survey 2007–2008. ISPOR 13th Annual European Congress, Prague, Czech Republic, November, 2010. [2]© 2010 BioTrends Research Group, Inc. All rights reserved. Reproduction, distribution, transmission or publication is prohibited. Reprinted with permission.[3]Zhang W, Doherty M, Bardin T, et al. Ann Rheum Dis. 2006 Oct;65(10):1312–24.

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Adverse Reactions to Allopurinol Are Not Increased In Patients Exposed to Doses Higher Than Recommended for Creatinine Clearance: A Retrospective Study of A Large Urban Multispecialty Group. Tawatchai Paisansinsup[1] and John T. Schousboe[2]. [1]Park Nicollet Health Services, St. Louis Park, MN, [2]Park Nicollet Health Services, Minneapolis, MN

Background/Purpose: Reported recommendations of allopurinol dose adjustment based on creatinine clearance to reduce adverse reactions in patients with renal insufficiency were based on case reports[1]. The efficacy of this strategy is unproved with unintended consequences of suboptimal uric acid level and poor control of gout.

Methods: We identified 551 patients who had allopurinol prescribed between 1/1/2004 and 12/31/2010 who had their serum creatinine measured while on allopurinol and who had complete covariate data. Adverse drug reactions (ADRs) to allopurinol were defined as listing of allopurinol in the ADR list of the medical record or as a physician's attribution of an adverse event to allopurinol combined with discontinuation of the drug. Patient charts were individually reviewed to adjudicate the accuracy of the reported ADRs and the reasons for prescription discontinuation. ADRs were categorized as major (severe cutaneous reactions and/or resulted in death) or minor. Each person's exposure to allopurinol was estimated to be above or below that recommended by Hande*, et al*[1] according to their creatinine clearance. The association of minor or major ADRs to allopurinol with use of allopurinol in doses above recommendation was estimated with logistic regression models.

Results: Prescribed allopurinol doses ranged from an average of 50 mg/day to 750 mg/day (mean and median, respectively, 227 and 300 mg/day). Mean creatinine clearance (Cockcroft-Gault) was 57 ml/min (range 8.5 to 125 ml/min). Three hundred forty two patients (61.5%) were prescribed doses that exceeded those recommended for their levels of renal function; 65 patients (11.7%) had a minor ADR and none had a major ADR to allopurinol. The odds ratio of an allopurinol ADR in those exposed to allopurinol doses higher than recommended for their levels of renal function compared to those treated with doses within or below the recommended dose was 0.84 (95% C.I. 0.49 to 1.46) adjusted for age, sex, diabetes mellitus, ischemic heart disease, hypertension, use of diuretics, and use of aspirin.

Conclusion: The risk of having ADRs to allopurinol is not increased in patients exposed to allopurinol doses higher than those recommended by Hande*, et al*[1]. These results support the strategy of titrating doses of allopurinol to attain a therapeutic goal of uric acid below 6 mg/dl to achieve adequate clinical control of gout.

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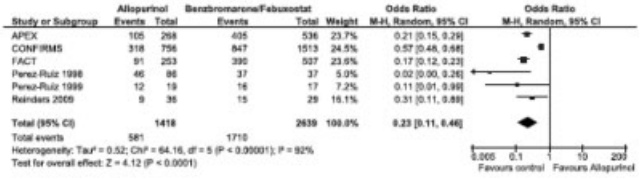
Oral Urate Lowering Therapies in Chronic Gout: A Systematic Review and Meta-Analysis. Puja Khanna[1], Manjit K. Singh[2], Sangmee Bae[2], John D. FitzGerald[3], Shraddha Prakash[4], Marian Kaldas[4], Maneesh Gogia[4], Paul Maranian[5], Robert Terkeltaub[6] and Dinesh Khanna[1]. [1]University of Michigan, Ann Arbor, MI, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, [3]UCLA David Geffen School of Medicine, Los Angeles, CA, [4]UCLA, Los Angeles, CA, [5]University of California, Los Angeles, [6]VA Medical Ctr, San Diego, CA

Background/Purpose: Urate-lowering therapy (ULT) is considered key to the optimal management of hyperuricemia in gout. We systematically reviewed the published data on the pharmacological ULT agents in gout.

Methods: PubMed and CENTRAL databases were searched to find published English language articles on gout up to March 2011. A total of 21 manuscripts were selected for this systematic review. A meta-analysis was carried out to assess the average effect size for the proportion achieving target SUA <6.0 mg/dl across studies between allopurinol (ALLO≤300mg/day) and the comparator drugs (benzbromarone [100– 200 mg/day] or febuxostat [40–120mg/day]). Mantel-Haenszel method of weighting was employed using a random-effects model. The average effect size is reported as an odds ratio (OR).

Results: The pooled mean (SD) age in the trials was 52.6 (12.0), 93.7% were males, and the disease duration 11.5 (9.2) years. ALLO at dose of 300 mg/day is largely ineffective in reaching the target goal of SUA< 6 mg/dl (24% to 53% achieved SUA< 6 mg/dl). The meta-analysis showed that the odds of achieving SUA < 6.0 mg/dl with ALLO (≤300mg/day) is 76% lower than with comparator drugs OR 0.23 [95%0.11–0.46; Figure]. Upwards dose titration every 4 weeks of ALLO, starting from 50–100 mg/day (to higher than 300 mg/day) is associated with achieving SUA < 6 mg/dl in 63% –100%. ALLO AEs in large RCTs included 2% with AST and ALT elevation> 3 ULN and 1.6% with rash. Renal impairment is associated with a significantly higher risk of severe cutaneous drug reaction with ALLO. Febuxostat (FEB) 80mg and 120 mg daily (not approved in USA) is more effective than ALLO 300 mg/day in achieving SUA< 6 mg/dl. There is lack of robust data in patients with CKD stage 4 or worse, including patients on dialysis. Rare skin hypersensitivity events also have been reported with FEB. Combination of 200–300 mg ALLO daily and probenecid 500 mg to 1 gram bid is effective in those with CrCl> 50 ml/min, at achieving SUA of <5 mg/dl. Fenofibrate and losartan also have been shown, in investigator-initiated trials, to be effective "add-on" uricosuric therapy for patients who have not achieved the target on ALLO that is not titrated above 300 mg daily.



Conclusion: Our systematic review established that ALLO ≤300mg/day fails to achieve a target SUA <6.0 mg/dl in the majority (>50%) of subjects with gout. The meta-analysis showed odds of achieving target SUA with ALLO (≤300mg/day) is 76% lower than with the comparator drugs benzbromarone and FEB. FEB at 80 and 120 mg/day is more effective than ALLO ≤300mg/day at achieving target SUA. Addition to ALLO of probenecid, or other weaker uricosurics (fenofibrate, losartan) with ALLO and probenecid is effective in patients with adequate renal function.

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A Case Series of HLA B27 Patients with a Behçet's Like Syndrome in a UK Population. Nicola Ambrose[1] and Dorian O. Haskard[2]. [1]Imperial College London, London, United Kingdom, [2]Imperial College, London, United Kingdom

Background/Purpose: This review focuses on patients referred to a UK Behçet's Syndrome (BS) Specialist Clinic who were found to be HLA B27 positive.

Methods: Patient demographics, symptoms, signs, treatments and HLA markers were recorded for the 598 patients seen in clinic from 1999 to 2011. Updates to the datasheet were made at subsequent visits.

Results: 597 patients were seen between 1999 and 2011. Of these, 319 were classified as having definite BS (DBS), 184 of having possible BS, 59 were definitely not BS and 36 were found to be HLA B27 positive and were classified as B27 BS-like syndrome (B27 group). We compared the DBS (ie B27 negative) group with the B27 group. Age and male sex were comparable (median age 36 and 38, male sex 44% and 58%, respectively). In the DBS group, 97% fulfilled ISG criteria, versus 69% of the B27 Group ($p<0.001$). Oral ulcers were found >99% of the DBS group versus 81% of the B27 group ($p=<0.001$). Genital ulcers were found in 89% of the DBS group versus 58% of the B27 group ($p<0.001$). Fewer patients in the HLA B27 group had the combination of oral and genital ulceration (B27 58% versus BS 89%, $p<0.001$). Similar numbers in both groups had inflammatory eye lesions (BS 46%, B27 56%, ($p=0.22$). Similar numbers also had skin lesions (BS 80%, B27 70%, $p=0.23$), Only a minority in either group had a positive pathergy test (BS 12%, B27 11%, $p=0.9$). While some of this B27 group present with features clinically identical to DBS, most had features that led us to suspect their B27 positivity. Thus, anterior uveitis was the predominant ocular manifestation in B27 group (85% of all), whereas posterior or panuveitis is more typical of DBS. Only 9% of our non-B27 DBS group had a history of joint swelling at any stage in their illness versus 61% of the B27 group ($p=0.001$). The latter patients also had findings which are not usual features of DBS such as psoriasis, enthesitis or plantar fasciitis. Interestingly, neurological and vascular BS manifestations were equally common in the two groups, with neurological involvement in 12% of the DBS group and in 22% of the B27 group ($p=0.06$). Neurological involvement in the B27 group included meningoencephalitis, trigeminal neuralgia, hemiparesis, intracranial hypertension and seizures. Secondly, vascular involvement was found in 18% of DBS and 25% of B27 groups respectively ($p=0.23$). In the B27 group, findings included deep vein thrombosis, subclavian vein thrombosis, superficial thrombophlebitis, dural sinus thrombosis, pulmonary embolism, development of an ischaemic digit and a radial artery aneurysm.

Conclusion: Of the 598 patients seen in this clinic, 36 have been found to be HLA B27 positive. While some of this cohort present with features identical to a classical BS, most have features that led us to clinically suspect their B27 positivity. This group may represent an extreme end of the spondyloarthropathy spectrum of disease. Importantly, they experience serious neurological and vascular BS-like manifestations to a similar extent as their classic BS counterparts.

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Dual Effects of Testosterone in Behcet's Disease: Implications for a Role in Disease Pathogenesis. Sule Yavuz[1], Tugba Akdeniz[2], Muge Bicakcigil[2], Haner Direskeneli[1] and Gulderen Yanikkaya Demir[2]. [1]Marmara University, Istanbul, Turkey, [2]Yeditepe University, Istanbul, Turkey

Background/Purpose: Behçet's Disease (BD) is a systemic inflammatory disorder characterized by vasculitis that is usually accompanied by oral and genital ulcers, skin lesions, uveitis and arthritis. Increased neutrophil activity and hyperresponsiveness to streptococci have been considered to play a role in Behçet's disease (BD) pathogenesis. We previously showed that testosterone (T) may also play a role in BD pathogenesis via increasing neutrophil activity and decreasing neutrophil apoptosis. Here we aimed further to define the effects of testosterone in detail.

Methods: Twelve BD patients who were in remission at least 6 months were included in this study. Peripheral blood from patient and 20 controls (10 ankylosing spondylitis /10 healthy donors) groups were drawn into heparinized Vacutainer tubes (BD BioSciences, USA). None of the patients were on any immunosuppressive treatment other than colchicum dispert 1.5gr/d. Neutrophils were incubated with testosterone, CpG DNA (5'-TCG ATC GGG GCG GGG CGA GC-3', XX IDT) and lipoteichoic acid (LTA) and in combinations of Ts + LTA and Ts + CpG DNA. Activation degree of neutrophils after a 2 hour incubation were analyzed by Dihydrorhodamine 123 conversion to rhodamine as a result of mitochondria activation. Culture supernatants were collected for cytokine measurements. FC500 flow cytometer and CXP software were used for analysis. IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, INF-gamma, TNF-alpha were assessed by using Th1/Th2 11plex RTU FlowCytomix Kit (BenderMed/e-Bioscience, Austria) on FC500 cytometry.

Results: Testosterone caused neutrophil activation in all groups, however, LTA and CpGDNA activated neutrophils in combination with T exclusively in BD (LTA vs LTA/T 66.2 ± 23.7 vs82.3 ± 22.5 $p<0.05$; CpGDNA vs CpGDNA/T 62.2 ± 23.6 vs 84.7 ± 13.4 $p<0.02$)When we further analyze the effect of T onto cytokines in different conditions, we observed that T induce IL-10 secretion (unstimulated vs stimulated 9.6 ± 1.01 vs 15.9 ± 4.3 $p<0.003$)in HC. Whereas, T led to elevated IL-12 levels (BD: 15.1 ± 4.6 vs 21.4 ± 5.4 $p<0.002$; AS:14.1 ± 2.4 vs20.5 ± 5.9 $p<0.006$) in both BD and AS and increased INFg only in AS. Interestingly, TNF-a levels were increased with LTA in both BD (18.5 ± 7.0 vs 28.4 ± 16.0 $p<0.01$) and AS (16.5 ± 1.7 vs 31.6 ± 25.3 $p<0.03$) compared to HC but significantly elevated IL-4 levels were observed in BD patients (103.2 ± 42.5) compared to AS (19.5 ± 2.8) and HC (17.6 ± 3.4) when stimulation occurred with LTA+T ($p<0.0001$). Similarly, CpGDNA+T induced significant upregulation of TNF-a (18.5 ± 7.0 vs 57.4 ± 52.1 $p<0.02$) in BD patients but also led to increase in IL-4 levels in BD (93.1 ± 37.2) compared to AS (18.3 ± 3.5,$p<0.0001$) and HC (20.1 ± 2.4,$p<0.01$).

Conclusion: Despite immunosuppressive behavior in healthy subjects, T causes T_H1 type immune alterations in BD patients and AS patients. The higher amount of IL-4 stimulation seen with uniquely in BD patients might be related to IL-4 gene polymorphism which is suggested to be a susceptibility factor to BD.

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Major Arterial Involvement in Behçet's Disease: Results From a Single Centre about 29 Cases. Z. Tazi Mezalek, W. Ammouri, H. Harmouche, M. Maamar, M. Bourkia, M. Adnaoui and M. Aouni. Ibn Sina Hospital, Rabat, Morocco

Background/Purpose: Behçet's disease is a multisystem pathology, and survival is closely related to vascular involvement. We analyse the clinical findings, treatment, outcome, and prevalence of arterial disease in a cohort of patients with BD from single tertiary referral medical center.

Methods: Medical records of consecutive patients with arterial involvement were reviewed to determine the clinical characteristics of BD, the sites, laboratory test results, and response to treatment. The diagnosis of BD was made according to the international criteria of BD. Statistical analysis was performed to define factors that affect prognosis.

Results: Among a cohort of 292 patients with BD, arterial involvement was present in 29 patients (10%) The over age at diagnosis was $33.9+9.6$ years, with a large predominance of males (25 cases). In 16 patients (55%), arterial involvement leads to the BD diagnosis. In the other cases, patients presented with ocular symptoms in 13, venous thrombosis in 10 and fever in 1 case. Arterial involvement was present at the initial presentation of the disease. Symptomatic lesions presented in 15 patients (55%), and asymptomatic lesions were incidentally detected in 13 (45%). There were 28 aneurysms and pseudo aneurysms: 14 in pulmonary territory, 4 infrarenal abdominal aorta, 3 cases of each superficial femoral and carotid arteries, 2 subclavian and one of each thoracic aorta and coronary artery. Were reported 2 cases of stenosis: one of the abdominal aorta and of coronary artery. Compared with BD patients without arterial involvement, those with arterial disease had higher rate of venous thrombosis ($p=0.02$), of ocular disease ($p=0.03$), were mostly man ($p= 0.003$) and had higher rate of biological inflammation ($p=0.004$). All patients were treated with corticosteroids, and 25 received immunosuppressive therapy. Surgical treatment was possible in 8 patients. For pulmonary aneurysm, an embolisation was made in 3 cases. Four patients died from pulmonary aneurysms. Recurrence was observed in 4 patients (14%) after treatment with stent graft ($n = 1$), as venous thrombosis in 2 case and as a new pulmonary aneurysm in one. The other cases remain stables.

Conclusion: The rate of arterial involvement is high in our series, probably in relation with the recruitment of a tertiary referral center. Therefore, we suggest that routine examination of symptoms and signs of arterial disease is necessary in male BD patients with venous thrombosis and/or ocular disease and/or inflammatory syndrome.

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Treatment with Infliximab Is Effective and Safty in BD Patients with Uveitis. Kayo Terauchi, Mitsuhiro Takeno, Takeaki Uehara, Atsuhisa Ueda, Nobuhisa Mizuki, Etsuko Shibuya and Yoshiaki Ishigatsubo. Yokohama City University Graduate School of Medicine, Yokohama, Japan

Background/Purpose: Infliximab (IFX) is highly effective for uveitis in Behcet's disease (BD), but the therapy does not completely suppress ocular manifestations. This study determined what factors are associated with ocular attacks during the IFX therapy.

Methods: We retrospectively examined clinical courses of 18 BD patients (female 2, male 16, age 42 + 13.7 yo) who received IFX due to uveitis. In the original regimen, IFX (5mg/kg) was given at 0, 2, 6 week, and thereafter every 8 weeks, but the intervals were shortened after major ocular attacks occurred.

Results: Mean duration was 6.4 + 5.8 years from the disease onset to initiation of infliximab therapy. Before the infiliximab therapy, 15 patients had received colchicines and 7 patients had cyclosporine A. Duration of IFX was 29 + 15.6 months (7 to 60 months, 5 to 51 times). No patients discontinued the therapy, though the infusions were suspended one or two week in 2 patients because of infection including infectious mononucleosis by cytomegalovirus. Visual acuity were improved in 17 eyes, unchanged in 10 eyes, and deteriorated in 5 eyes, except blind eyes. Frequency of ocular attacks was 2.4 + 0.6 / 6 month before and during the IFX therapy, while that was reduced to 0.34 + 0.38 / 6 months. During the therapy, total 29 ocular attacks occurred at 6.87 + 1.12 weeks after the last infusion, 1.43 + 1.53 weeks before the next expected infusion. After ocular attacks, the infusion interval was shortened from 5 to 7 weeks in 8 patients. In the other 10 patients who had no major ocular attack, visual acuity was more frequently improved. However, there was no significant difference in clinical features before initiation of IFX between two groups. Surgical ocular operations were performed in 8 and 3 eyes for cataract and glaucoma, respectively, without operation-related ocular attacks. There was no major adverse event which required hospitalization.

Conclusion: Treatment with IFX is effective, safety and tolerable in BD patients with uveitis. Ocular attacks were significantly suppressed, resulting in improvement of visual acuity. However, the attacks were accumulated in the last 2 weeks of infusion interval. It is hard to predict responsiveness to IFX therapy based on the pre-therapeutic clinical features.

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Adverse Events of Immunosuppressive Therapy in Autoimmune Uveitis Patients. Zulema Rosales, Ana B. Rodríguez-Cambrón, Oscar Fontsere, Leticia León, Pedro Arriola, Lydia Abásolo, Cristina Martínez, Cristina Lajas and Esperanza Pato. Hospital Clínico San Carlos, Madrid, Spain

Background/Purpose: Uveitis is the inflammation of the uveal tract. An immune-mediated inflammatory mechanism is the main cause of the uveitis. Non infectious autoimmune uveitis might develop a severe course with poor visual prognosis if an adequate control of the disease is not achieved. Corticosteroids (CE) are central to control acute and severe ocular inflammation and immunosuppressive drugs (IS) are used when CE are insufficient. There are no published large series and long follow-up on the effects of IS in uveitis.

Our purpose was to analyze the incidence of side effects and the withdrawal rate of the IS in a cohort of patients with autoimmune uveitis attended at the uveitis unit in our hospital.

Methods: A retrospective study from January 1992 to October 2010 was performed. Study was approved by the Ethic Committee of our hospital.

The inclusion criteria were diagnosis of chronic anterior uveitis, intermediate uveitis, posterior uveitis and panuveitis who received one of the following IS: cyclosporine A (CSA), methotrexate (MTX), azathioprine (AZA), cyclophosphamide, mycophenolate mofetil, Infliximab, Adalimumab (ADA) and/or Etanercept. We analyze IS cycles used, survival time after treatment, adverse events (AE) during the follow-up and visual acuity (VA) at baseline and last ophthalmological assessment. Survival techniques were used to estimate the incidence rate (IR) and 95% confidence interval [95% IC] of adverse events and discontinuation by drug exposure. Descriptive and bivariate analyses were also performed with Stata package.

Results: 1535 patients were evaluated in the uveitis unit during the follow up (18.9 years). 75 patients met the inclusion criteria, 41 were women (54.7%) and the mean age at diagnosis of uveitis was 42 ± 19.7 years. 23 patients had any AE. A total of 38 AE were collected during follow-up (14 digestive intolerance, 11 increase of creatinine level, 5 liver toxicity, 5 hypertension, 2 cytopenias and 1 bronchospasm) with an incidence of 6.42% (95% CI 4.67 to 8.82) during follow-up. There were no differences between men and women in the development of AE ($p = 0.43$). The risk of an AE increased with increasing age of patients ($p = 0.02$). Table 1 shows the IR per 100 patients-years (95% IC) of AE and drug discontinuation by drug exposure. There was an improvement in VA in both eyes in the follow-up: mean change (±SD) right eye 0.11 ± 0.35 and left eye 0.10 ± 0.51.

Drug	N° of patients with the drug	N° of patients with AE	IR of AE by drug exposure	N° of withdrawals	IR of discontinuation by drug exposure
MTX	37	6	2.9 (1.3–6.5)	3	1.5 (0.5–4.5)
CSA	46	22	9.3 (6.1–14.1)	8	3.3 (1.7–6.7)
AZA	29	9	6.3 (3.3–12.2)	7	4.9 (2.3–10.3)
ADA	3	1	33.3 (4.7–236.2)	1	33.3 (4.7–236.2)

Conclusion: The use of IS for the treatment of ocular inflammatory disease, particularly uveitis refractory to CE, is an effective and necessary alternative treatment. In our series, the incidence rate of AE of IS and the rate of discontinuation are low. Although the safety profile of IS used is good, it is essential to maintain a continuous monitoring during treatment. The VA in this group of patients is maintained during the follow-up.

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Relationship Between Patterns of Clinical Presentation Uveitis and Final Inmunologic Diagnosis. Esperanza Pato[1], Zulema Rosales[1], Esther Toledano[1], Pilar Macarron[1], Cristina Vadillo[1], Rosalía Mendez[1], Miguel A. Descalzo[2] and Estíbaliz Loza[2]. [1]Hospital Clínico San Carlos, Madrid, Spain, [2]Spanish Society of Rheumatology, Madrid, Spain

Background/Purpose: In our multidisciplinary uveitis unit, coordinated by ophthalmologists and rheumatologists, a predefined set of 12 clinical patterns of uveitis presentation is used to help diagnose since 1992. The routinely use of these clinical patterns leads to a decrease in the number of diagnostic test to confirm the final diagnosis.

The purpose of this study was to analyze the association between these clinical patterns and the final immunologic diagnosis and its discriminative value.

Methods: A prospective cohort study was performed. The study was approved by the ethic committee of our hospital. All patients attended in our multidisciplinary uveitis unit from January 1992 to December 2009 who were diagnosed with uveitis were selected. In all of them the following data were collected: the clinical patterns of uveitis presentation, the initial diagnosis, the medical history, the diagnostic test results and the final diagnosis. The 12 clinical patterns of uveitis presentation are: a) anterior uveitis (AU) including 1) acute recurrent unilateral AU, 2) acute nonrecurrent unilateral AU, 3) acute bilateral AU, 4) chronic AU, 5) intermediate uveitis, b) posterior uveitis as 6) unilateral chorioretinitis, 7) bilateral chorioretinitis, 8) retinal vasculitis, 9) chorioretinitis panuveitis, 10) vitritis panuveitis, 11) retinal vasculitis panuveitis and 12) exudative retinal detachment panuveitis. To measure the association between uveitis and immunologic diagnosis a correspondence analysis was performed with every pattern. According to the model coordinates, 3 different levels of association were established -mild, high and very high-, based on the distance and magnitude of the coordinates. The highest absolute number and the smallest distance, the strongest association.

Results: A total of 1,465 patients were evaluated of whom 783 were women (53 %) with a mean age at the uveitis diagnosis of 45 years ± 18 years. The most frequent final diagnoses were idiopathic anterior uveitis (29%), spondyloarthropathy (13%) ophthalmologic uveitis (10%), toxoplasmosis (9%) and herpes (8%). Table 1 shows the association of the final diagnoses with a clinical pattern of uveitis presentation.

Uveitis Pattern	Major Diagnosis	Association
Acute recurrent unilateral AU	Spondyloarthropaty	Mild
Acute nonrecurrent unilateral AU	Ophthalmologic AU	Mild
Acute bilateral AU	Idiopathic AU	Mild
Chronic AU	Juvenile Idiopathic Arthritis	Mild
Unilateral chorioretinitis	Toxoplasmosis	High
Bilateral chorioretinitis	Ophthalmological chorioretinitis	High
Vasculitis	Idiopathic retinal vasculitis	High
Intermediate uveitis	Idiopathic intermediate uveitis	High
Chorioretintis panuvelitis	Toxoplasmosis	Mild
Vitritis panuveitis	Idiopathic panuveitis	High
Vasculitis panuveitis	Behçet	High
Exudative retinal detachment panuveitis	Vogt-Koyanagi-Harada	VeryHigh

Conclusion: Our data show the central diagnostic value of the clinical patterns of uveitis presentation. The use of these patterns in daily practice could definitively be a useful tool in order to diagnose, reducing therefore he number diagnostic tests, but could also help prescribe the most appropriate treatment.

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High Dose Intravenous Methylprednisolone Induces Rapid Improvement In Severe Uveitis: A Multicenter Study. Carmen Bejerano[1], Ricardo Blanco[1], Emma Beltrán[2], Alejandro Fonollosa[3], Olga Maiz[4], Ana Blanco-Esteban[4], Miguel Cordero[5], Inés Pérez-Martín[6], Joaquín Cañal[6], Juan Ventosa[6] and Miguel Angel González-Gay[6]. [1]Hospital Universitario Marqués de Valdecilla-IFIMAV, Santander, Spain, [2]Hospital Peset, Valencia, Spain, [3]Hospital de Cruces, Barakaldo-Bilbao, Spain, [4]Hospital Donostia, San Sebastian, Spain, [5]Hospital León, León, Spain, [6]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain

Background/Purpose: Since ocular inflammation may lead to early and irreversible structural and functional damage, remission induction therapy is required in severe uveitis. High-dose intravenous methylprednisolone (IVMP) may induce rapid improvement in a broad spectrum of severe inflammatory conditions including uveitis.

Methods: We reviewed 28 patients (47 eyes) with severe ocular inflammation, attended at the Uveitis Unit from 4 tertiary Hospitals, who received IVMP. The underlying diseases were: Idiopathic uveitis (n=11, 39%), Vogt Koyanagy Harada syndrome (n=9, 32%), Behçet disease (n=2), Ankylosing Spondylitis (n=1), Eales Disease (n=1), Sympathetic Ophthalmia (n=1), Multiple Sclerosis (n=1), Relapsing Polychondritis (n=1), Varicella-Zoster-associated acute retinal necrosis (n=1). The inflammatory ocular patterns were: posterior uveitis (n=12, 43%), panuveitis (n=11, 39%), anterior uveitis (n=1), scleritis (n= 2), sclero-uveitis (n=1), and intermediate uveitis (n=1). Bilateral ocular involvement was observed in 19 patients (68%). Patients were assessed at day 2–3, 7, 14 and 30 after IVMP treatment.

Results: We studied 17 women/11 men with mean age 41.7±15.2 years. IVMP dose ranged from 0.25–1 g/day for 3–5 consecutive days. All of them had active intraocular inflammation at baseline. Following IVMP therapy patients with anterior uveitis experienced rapid improvement. However, improvement of retinal vasculitis was more slowly achieved **(TABLE).** Retinal detachment occurred in 10 patients (19 eyes) showing partial improvement of affected eyes in 11% at day 2–3 and a complete recovery in 74% at day 30. Optical coherence tomography showed impairment ($> 200\mu$) in 14 patients (26 eyes) at baseline, partial improvement in 46% of affected eyes at day 2–3 and a complete normalization ($< 200\mu$) in 54% at day 30. Visual acuity was reduced in 27 patients (44 eyes) at baseline. Thirty-five eyes (80%) improved in visual acuity, 5 eyes (11%) remained stable and 4 eyes (9%) had worsened at day 30. The patient with acute retinal necrosis presented progressive improvement and inactive lesions at day 30. One of 2 patients with scleritis showed progressive improvement with complete normalization at day 30. IVMP therapy was well tolerated and no important side-effects were observed.

	patients (affected eyes)	complete inactivity (% of eyes) after high-dose intravenous methylprednisolone		
	baseline	Day 2–3	Day 7	Day 30
anterior inflammation	15 (24)	72%	72%	96%
vitritis	13 (20)	25%	40%	75%
retinal vasculitis	7 (11)	0	0	73%
choroiditis/ chorioretinitis	8 (14)	14%	14%	57%

Conclusion: IVMP is an effective and safe remission induction therapy in severe ocular inflammation.

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Adalimumab in 107 Refractory Uveitis: A Multicenter Study. Orlando Pompei[1], Ricardo Blanco[2], Manuel Diaz-llopis[3], David Salom[3], Carmen Garcia-Vicuña[4], Miguel Cordero-Coma[5], Gabriela Ortega-Larrocea[6], Norberto Ortego-Centeno[7], Marta Suarez-de-Figueroa[8], J. Carlos Fernandez-Cid[9], Alejandro Fonollosa[10], Angel M. Garcia-Aparicio[11], Jose M. Benítez-del-Castillo[12], Jose L. Olea[13] and J. Fernando Arevalo[14]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla-IFIMAV, Santander, Spain, [3]La Fe University Hospital of Valencia, Valencia, Spain, [4]Hospital Sant Joan de Déu, Barcelona, Spain, [5]Hospital de León, León, Spain, [6]National Institute of Rehabilitation, D.F Mexico, Mexico, [7]Hospital Clínico San Cecilio, Granada, Spain, [8]Hospital Ramon y Cajal, Madrid, Spain, [9]Hospital de Pontevedra, Pontevedra, Spain, [10]Hospital de Cruces, Bilbao, Spain, [11]Hospital Virgen de la Salud, Toledo, Spain, [12]Hospital Clínico San Carlos, Madrid, [13]Hospital Son Dureta, Palma de Mallorca, Spain, [14]Ophthalmology Clinic Center of Caracas, Caracas, Venezuela

Background/Purpose: To assess the efficacy and safety of adalimumab therapy in refractory autoimmune uveitis.

Methods: Retrospective, multicenter study on 107 patients. All of them had a failure or intolerance of prednisone therapy and ≥1 other systemic immunosuppressive therapy. Different etiologies were diagnosed: Juvenile Idiopathic Arthritis (40 cases, 37%), uveitis of Idiopathic origin (20 cases, 19%), Pars Planitis (14 cases, 13%), Behçet Disease (11 cases, 10%), Vogt Koyanagy Harada syndrome (7 cases, 7%), Ankylosing Spondylitis (5 cases, 5%), Inflammatory Bowel Disease (2 cases, 2%), Birdshot Coriorretinopathy (1 case, 1%), Rheumatoid Arthritis (1 case, 1%), Multifocal choroiditis with panuveitis (1 case, 1%), Sarcoidosis (1 case, 1%), Sympathetic Ophthalmia (1 case, 1%), and others (2%). Adalimumab (40 mg subcutaneously) every-other-week was maintained during 6 months. If uveitis was inadequately controlled, the Adalimumab dosage was increased up to 40 mg/wk. All patients underwent an outcome assessment at month 6.

Results: 107 patients (45 males, 62 females), mean age 25.23±17.68 years (range: 4 to 65 years), with active intraocular inflammation at baseline were studied. Thirty-eight had inflammation in the anterior camera, and following Adalimumab therapy achieved significant improvement (mean tyndall improved from 1.43±0.9 to 0.2±0.4; $p<0.0001$. Also, 54 patients had inflammation in the posterior camera. Significant improvement of optic coherence tomography (OCT) was achieved: baseline; 332.35±137.62 microns; and after 6 months of Adalimumab treatment 244.56±34.17 microns; $p<0.0005$. Also, 16 patients had cystoid macular edema (CME): at baseline mean OCT 432.81±144.21 microns, and after Adalimumab 256.25±37.36 microns; $p<0.0003$. Most of the remaining patients with intermediate uveitis (15 cases) had improvement. Also, most patients were able to reduce at least 50% of the dose of the concomitant immunosuppressive drugs at the end of follow-up. Adalimumab was usually well tolerated, and only local minor side effects at the injection site were observed. Nevertheless, 11 patients (10%) had moderate to severe relapses during the follow-up period, and 28 patients (26%) had minor relapses during the follow-up that were controlled with 1 periocular steroid injection.

Conclusion: Adalimumab appears to be an effective and safe treatment for refractory uveitis and may reduce steroid requirement. However, further controlled studies of adalimumab for uveitis are warranted.

1046

Recalcitrant Orbital Inflammatory Disease Responsive to Infliximab. Mary Bach and Gregory C. Gardner. University of Washington, Seattle, WA

Background/Purpose: Orbital inflammatory disease (OID) is a general descriptor for inflammatory syndromes affecting various orbital structures such as nerves, muscle and surrounding tissues. OID can be idiopathic or associated with inflammatory diseases such as ANCA-associated vasculitis, Behcet's disease, or Crohn's disease. OID is often responsive to corticosteroids. However, many cases are not fully responsive to steroids or are resistant to steroid tapering. Agents such as methotrexate, azathioprine, cyclosporine, and even cyclophosphamide have been tried as steroid-sparing medications. Several previously reported cases of idiopathic OID have been dramatically responsive to infliximab. We present three recalcitrant cases of OID that responded to therapy with infliximab.

Methods: Chart review and literature search

Results: The three cases included 2 females and 1 male with age range 28–59 years. All three cases had imaging studies demonstrating orbital inflammation and tissue biopsies showing chronic inflammation including one case that qualified for the diagnosis of Tolosa-Hunt syndrome with granulomatous changes on biopsy and cranial neuropathies. Two patients had initial response to high dose prednisone (1 complete, 1 partial) but were unable to taper without recurrence of symptoms. The third patient had persistent symptoms in spite of up to 100 mg per day of prednisone. Other steroid sparing agents used included methotrexate in all three and azathioprine in one with no or partial benefit. The addition of infliximab 3–5 mg/kg IV every 8 weeks resulted in prompt and dramatic improvement in symptoms and signs of disease and subsequent imaging studies in all patients. All three patients were able to taper prednisone completely (2 patients) or to low dose therapy. One patient developed drug–induced lupus after infliximab-induced remission but continued in remission on methotrexate and low dose prednisone. The patient with Tolosa-Hunt syndrome has been on methotrexate 7.5 mg per week and infliximab 3 mg/kg every 12 weeks in complete remission for 3 years.

There have been 10 previous cases of resistant idiopathic orbital inflammatory disease treated with infliximab reported in the English literature since 2004. Prior to infliximab, patients had been treated with one or more of the following; high dose prednisone, methotrexate, azathioprine, cyclo-

phosphamide, 6-mercaptopurine, cyclosporine, colchicine, steroid injections, and irradiation. Two of the 10 received methotrexate plus infliximab while 8 patients received infliximab alone. Infliximab dosing range was 3–5 mg/kg every 6–8 weeks. Six of the 10 went into remission while 4 patients had residual visual changes but were reported improved and inflammatory symptoms controlled.

Conclusion: Rheumatologists are often called on to provide immunotherapy for patients with inflammatory conditions such as OID. Recognizing the benefit of infliximab in patients with OID and early introduction in recalcitrant cases will hopefully help reduce morbidity and prevent excessive steroid side effects. Presentation of these three cases reports and review of previous cases will hopefully provide useful case background for rheumatologists treating patients with OID.

1047

Giant Cell Tumor of Synovial Sheath: Of Two Cases Treated with Intra-Articular Infiltration of Infliximab. Emanuela Praino, Crescenzio Scioscia, Maria Grazia Anelli, Laura Coladonato, Michele Covelli, Florenzo Iannone and Giovanni Lapadula. D.I.M.I.M.P, Rheumatology Unit - University of Bari, Bari, Italy

Background/Purpose: The giant cell tumor of the synovial membrane, formerly called pigmented villonodular synovitis, is a rare disease, often resistant to conventional therapy and with frequent recurrence after synovectomy.

Methods: We report the case of two women aged 47 and 51 years, both with a diagnosis of giant cell tumor of the synovial membrane of the left knee, resistant to therapy with methotrexate and/or surgery. Infliximab was administered to both, by intra-articular injection with in-line filter, at a dose of 100 mg (diluted in 10 cc of saline) at time 0, 4 and 12 weeks. At each visit blood tests, clinimetric and Power Doppler ultrasound evaluations were performed. MRI was performed at baseline and four weeks after the last Infliximab injection.

Results: At baseline, hyperplastic synovitis was noted by ultrasound for both patients, with power-Doppler signal of grade 2 and grade 3, these findings correlated with MRI results. At 4 weeks after the third administration, complete remission was noted with reduction of the thickening of the synovial membrane and a complete absence of power-Doppler signal. These findings were also confirmed by MRI. Both patients, therefore, were referred to an orthopedic specialist for a radical synovectomy. Two months after surgery, the patients had no recurrence of the tumor. No adverse events were noted.

Conclusion: The giant cell tumor of the synovial membrane, if untreated, can lead to disability. Synovectomy, possibly followed by radiosynovectomy, is the usual treatment of choice. Nevertheless, the recurrence of the tumor in approximately 50% of patients treated surgically indicates that surgery is not always sufficient. Our study confirms previous literature data reporting the effectiveness of infliximab, given intra articularly, in the treatment of giant cell tumor and showing a significant reduction In the number of macrophages and TNF-alpha expression in synovial tissue. Thus, this treatement is particularly effective in reducing inflammation and hyperplasia of the synovial membrane and prepare the joint for radical synovectomy surgery. Further studies are warranted to evaluate the long term efficacy and safety of infliximab in treatement of the giant cell tumor of the synovial membrane and whether this terapy may replace synovectomy.

1048

Distinct Rheumatological Features Induced by Aromatase Inhibitors in Breast Cancer Patients: A Prospective Multicenter Cohort Study of 138 Women with Breast Cancer. Serge Perrot[1], Paul Cottu[2], Xavier Decleves[1], Laure Chauvenet[1], Christophe Tournigand[3], Jean-Yves Pierga[2], Didier Bouhassira[4] and Francoise Laroche[3]. [1]Hopital Hotel Dieu, Paris, France, [2]Curie Institute, Paris, France, [3]Saint Antoine Hospital, Paris, France, [4]Ambroise Paré Hospital, Boulogne, France

Background/Purpose: Aromatase inhibitors (AI) are prescribed to postmenopausal women with breast cancer, to decrease estrogen production and thus, prevent cancer recurrence. Musculoskeletal pain was the most frequently reported adverse effect. We carried out a cohort study on women treated with AI, to define the types of AI-induced rheumatological disorders observed, their incidence and putative risk factors.

Methods: We carried out a prospective multicenter cohort study of women with breast cancer requiring long-term AI treatment. Women with breast cancer who gave informed consent were included just before the start of AI treatment. They were followed at 1, 3, 6 and 12 months of AI treatment. At each visit, patients were examined by a rheumatologist and asked to complete self-reported pain (BPI, MPQ) and psychological questionnaires. Laboratory tests were carried out for (1) two genetic polymorphisms potentially conferring a predisposition to chronic pain (COMT (cathecol-O-methyl transferase) and mu opioid receptor (OPRM1)), (2) inflammatory markers (CRP, ESR), (3) autoimmune disorders (ANA, ACPA, RF), (4) calcium metabolism abnormalities (vitamin D, calcium). Patients referred for severe or end-stage organ involvement and those with concomitant pain syndromes were excluded.

Results: In total, 138 women with breast cancer, from four cancer centers, were enrolled. Significant pain symptoms were observed at 1 month in 15% of the patients, at 3 months in 35%, at 6 months in 31% patients, and at 1 year in 22% of patients. Most of the patients (82%) that developed pain presented early pain symptoms (1–3 months), with pain in the hand associated with tenosynovitis and flare-ups of osteoarthritis, with no biological inflammatory disorder. A few patients (18%) developed late pain symptoms (6–12 months) with widespread pain, hot flushes, fatigue and sleep disorders, resembling fibromyalgia syndrome. All these patients had the typical 18 tender points and diffuse spontaneous pain and fulfilled the ACR1990 fibromyalgia classification criteria. One patient developed typical rheumatoid arthritis at 3 month of follow-up. Two patients displayed a significant increase in rheumatoid factor and ACPA levels, with no significant pain symptoms, at 1 year of follow-up. Six patients (4.3%) had to stop AI treatment between 3 and 8 months, due to pain intensity. Neither of the two genetic polymorphisms (COMT and OPRM1) tested was associated with musculoskeletal pain symptoms.

Conclusion: Pain is frequent in women treated with AI, occurring in up to a third of cases during the first year of treatment. Two major types of pain are observed. The most frequent consists of osteoarthritis symptoms in the first three months, mostly in the hands and wrists. The second resembles fibromyalgia syndrome and may occur at a late stage, probably through different mechanisms. The adverse effects of AI treatment constitute a clinical condition in which analyses of patients developing late diffuse pain syndrome may improve our understanding of the links between hormonal dysfunction and chronic widespread pain (e.g. fibromyalgia syndrome).

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Treatment of Chemotherapy-Related Arthropathy with Disease Modifying Antirheumatic Drugs: Results of An Open-Labeled Multicenter Pilot Study. Hyoun Ah Kim[1], Hyo-Jin Choi[2], Hanjoo Baek[2], Mie Jin Lim[3], Won Park[3], Jisoo Lee[4], Sung Jae Choi[5], Bo Young Yoon[6], Sang Tae Choi[7], Jung-Soo Song[7], Sung Soo Kim[8] and Chang-Hee Suh[1]. [1]Ajou University School of Med, Suwon, South Korea, [2]Gachon University Gil Hospital, Incheon, South Korea, [3]Center for Rheumatism, Inha University Hospital, Incheon, South Korea, [4]Ewha Womans University Mokdong Hospital, Seoul, South Korea, [5]Korea University Medical Center, Ansan, South Korea, [6]Inje University Ilsan Paik Hospital, Goyang, South Korea, [7]Chung-Ang University College of Medicine, Seoul, South Korea, [8]Ulsan Univ Med Sch Gangneung, Gangneung

Background/Purpose: Various musculoskeletal manifestations can develop in a patient during chemotherapy for malignancy. We previously reported 18 patients who developed chemotherapy-related arthropathy (CRA). In this study, we evaluated whether hydroxychloroquine (HCQ) modify the disease activity in CRA.

Methods: In order to compare the efficacy of HCQ and nonsteroidal anti-inflammatory drugs (NSAIDs) to NSAIDs only for the treatment of CRA, an open-labeled clinical trial was carried out at 8 tertiary hospitals. A total of 80 patients were enrolled in this study. CRA activity was clinically assessed in tender joint count (TJC), swollen joint count (SJC), visual analogue pain score (VAPS), morning stiffness (MS), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Results: Patients comprised 65 women (81.3%) and 15 men with mean age 51.43 ± 9.2 years. Forty two patients had breast cancer, 11 had lymphoma, and 7 had stomach cancer. The most commonly used drugs were cyclophosphamide, adriamycin, 5-fluorouracil and aromatase inhibitor. Joint symptoms usually began 8.54 ± 13.32 months after the first session of chemotherapy. Patients had an average of 6 tender joints and 4.5 hours of morning stiffness. Eleven patients were positive for antinuclear antibody and 8 for rheumatoid factor. Among 80 patients, 46 patients were withdrawn during the screening and follow-up. Of the 34 patients who were followed up for 3 months, 14 received HCQ and NSAIDs and 20 received NSAIDs only. If the patients did not show improvement, they could be given low-dose oral corticosteroids, acetaminophen or tramadol. There were no significant differences between baseline characteristics of two groups except ESR (30.86 ±

23.35 mm/hr in HCQ and NSAIDs group vs. 13.16 ± 9.31 mm/hr in NSAIDs only, p=0.003). After 3 months, statistically significant reduction of TJC and VAPS were observed in both groups. Also, a statistically significant reduction of ESR was observed in the HCQ and NSAIDs group.

Conclusion: The results indicate that both HCQ and NSAIDs are effective for CRA. HCQ could be used for CRA patients with elevated ESR. This pilot study encourages future randomized controlled clinical trial for treatment of CRA.

1050

Characterization of Non-Hodgkin Lymphomas in Rheumatic Diseases. Vladimir I. Vasilyev. Research Institute of Rheumatology of RAMS, Moscow, Russia

Background/Purpose: Non-Hodgkin lymphomas (NHL) are 3 to 45 times more common in rheumatic diseases (RD) than in the general population. The spectrum of NHL varies in different studies.

To describe the most common types of NHL diagnosed in rheumatic patients from 2008 to 2010 in the Institute of Rheumatology of RAMS, Moscow.

Methods: One hundred and eighty five patients (female-148, male-27) aged 19 to 80 years (median-52 years) with various RD and predictors of NHL development (massive enlargement of lacrimal and salivary glands, cytopenia, lymphadenopathy, splenomegaly, monoclonal secretion) were conducted an oncohematological survey, including incisional biopsies with subsequent immunomorphological study, trephine biopsies and myelograms, T-and B-cell clonality determination by PCR in peripheral blood and tissue samples.

Results: One hundred and ten (65.5%) patients (primary Sjögren's syndrome (pSS)–58, rheumatoid arthritis (RA)–25, systemic scleroderma (SSD)-4 and chronic hepatobiliary diseases (CHD)-6) were diagnosed with NHL. The diagnosis of RD was withdrawn with subsequent identification of primary NHL in 8 cases, myeloproliferative diseases in 5 cases and primary AL-amyloidosis in 4 patients. B-cell NHL were found in 97 (88%) and T-cell in 13 (12%) patients respectively. Immunoglobulin-secreting variant of lymphoma was observed in 30 (29.7%) patients with NHL. In RA B-cell (48 %) and T-cell (52%) lymphomas were represented in equal proportions. Marginal zone lymphoma (MZL) was most frequently detected in pSS, SSD and CHD, whereas T-cell leukemia of large granular lymphocytes was more often diagnosed in RA (n=9). Plasma cell dyscrasia (PD) ranked second more frequent in pSS (n=5) and RA (n=5). T-cell splenic lymphoma (RA–4), chronic lymphocytic leukemia (pSS–1, RA–2) and diffuse large B-cell lymphoma (RA-1, pSS-2) were diagnosed less frequently. Seventeen (76.5%) of the 22 examined patients with RA, SSD and CHD had associated Sjögren's syndrome. Three patients simultaneously developed two types of NHL.

Conclusion: A prospective study has shown that low-grade MZL, PD, T-cell leukemia of large granular lymphocytes and γδ-T-cell splenic lymphoma are the most common in RD. Primary NHL, PD, AL-amyloidosis and myeloproliferative disorders often have clinical features similar to rheumatic diseases.

1051

Colchicine Halves, but Does Not Eliminate Recurrences in Pericarditis: Colchicine for Recurrent Pericarditis. A Randomized, Controlled Trial. A. Brucato[1], S. Maestroni[1], D. Cumetti[1], R. Cemin[2], S. Ferrua[3], R. Belli[4], D. H. Spodick[5], Y. Adler[6], R. Trinchero[4] and M. Imazio[4]. [1]Ospedali Riuniti, Bergamo, Italy, [2]San Maurizio Regional Hospital, Bolzano, Italy, [3]Savigliano Hospital, Rivoli, Italy, [4]Maria Vittoria Hospital, Torino, Italy, [5]St. Vincent Hospital, Massachusetts, [6]Sackler Faculty of Medicine, Tel-Aviv, Israel

Background/Purpose: Recurrences are the most common complication of acute pericarditis (20 to 50% of cases). Aim of this study is to evaluate the efficacy and safety of colchicine for the secondary prevention of recurrent pericarditis.

Methods: This is a prospective, randomized, double-blind, placebo-controlled, multicentric trial; 120 Italian patients with a first episode of recurrent pericarditis were enrolled. Patients were randomized to receive placebo or colchicine on top of a conventional treatment (aspirin, NSAIDs and/or corticosteroids). Colchicine was given at the dose of 1.0 to 2.0 mg for the first day followed by a maintenance dose of 0.5 to 1.0 mg daily for 6 months. The primary study end point was the recurrence rate at 18 months. The secondary end points were symptom persistence at 72 hours, remission rate at 1 week, number of recurrences, time to first recurrence, disease-related hospitalization, cardiac tamponade, and constrictive pericarditis rates.

Results: Colchicine significantly reduced the actuarial incidence of recurrences at 18 months compared to placebo (23.9% vs. 55.3%; p<0.001; number needed to treat-NNT 3). Colchicine also significantly reduced the symptoms persistence at 72 hours (23.3% vs. 53.3%; p=0.001), and the mean number of recurrences. Colchicine increased the remission rate at 1 week (81.7% vs. 48.3%; p<0.001) and prolonged the time to a subsequent recurrence. The rate of side effects and drug withdrawal were similar in the colchicine and placebo groups (respectively, 6.7% vs. 6.7% for side effects, 8.3% vs. 5.0% for drug withdrawal).

Conclusion: Colchicine is safe and efficacious for the secondary prevention of recurrent pericarditis. It halves recurrences, but does not eliminate them.

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EDTA Resistant S100A12 Complexes (ERAC) In Serum of Patients with Coronary Artery Disease (CAD) with and without Inflammatory Rheumatic Disease (IRD). Ivana Hollan[1], Anita Kåss[2], Torstein Lyberg[3], Sven M. Almdahl[4], Øystein T. Førre[3], Knut Mikkelsen[5] and Magne Fagerhol[3]. [1]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [2]Betanien Hospital, Skien, Norway, [3]Oslo University Hospital, Oslo, Norway, [4]University Hospital of North Norway, Tromsø, Norway, [5]Lillehammer Hosp for Rheumatic Diseases, Lillehammer, Norway

Background/Purpose: ERAC is a recently discovered high molecular weight protein fraction containing the leukocyte derived protein S100A12. In contrast to most S100A12 complexes, these complexes do not dissociate after addition of EDTA. The purpose of this study was to compare the occurrence of serum ERAC positivity in patients with CAD with and without IRD, in IRD patients without CAD, and in healthy controls (HC).

Methods: We examined 4 groups involved in Feiring Heart Biopsy Study: patients with IRD referred to coronary artery bypass graft (CABG) (CAD+IRD), patients without IRD, referred to CABG (CAD-nonIRD), patients with IRD without CAD (IRD-nonCAD), and HC. ERAC was examined in serum by a quantitative rapid test based on monoclonal antibodies and lateral flow principle. ERAC positivity was defined as ERAC>4μg/L.

Results: There were no significant relationships between ERAC positivity and traditional cardiovascular risk factors, CRP and acute coronary syndromes. The relationship between ERAC and CAD-IRD remained statistically significant after the adjustment for group, age and gender (OR=3.9, 95%CI:1.2–12.9, p=0.024). In age- and sex- adjusted analysis of all patients with IRD, ERAC positivity was related to CAD (OR=9.9, 95%CI:2.4–41.0, p=0.002). Similar relationship, independent of RA activity and duration, was observed also within the RA subgroup. The HC patient with ERAC highly positive (49 years old, ERAC=10000) was diagnosed with CAD (requiring CABG) within 1 year.

Table 1.

	CAD+IRD (n=56)*	CAD-nonIRD (n=46)	IRD-nonCAD (n=29)**	HC (n=26)	p
Male sex, no. (%)	35 (63)	30 (65)	8 (28)	16 (62)	0.006
Age, mean±SD	67.7±10.0	67.5±8.7	58.2±9.9	57.3±9.6	<0.0005
ERAC positive, no. (%)^	27 (48)	5 (11)	4 (14)	5 (19)	<0.0005

* Patients with RA (n=21), giant cell arteritis/polymyalgia rheumatica (17), spondyloarthritis (14), connective tissue diseases (4). There was no significant difference in ERAC positivity between these IRD subgroups. ** Patients with RA. ^ ERAC>100 μg/L occurred in three (5.4%) CAD-IRD patients, in no CAD+IRD patients, and in 1(3.8%)HC.

Conclusion: Patients with CAD and IRD had higher occurrence of ERAC than patients with CAD or IRD only, and than HC. Within IRD patients, the occurrence of ERAC was related to CAD. Thus, ERAC might be a biomarker of CAD in IRD. Further studies on ERAC may increase insights into the pathogenesis of accelerated CAD in IRD.

1053

The Baseline Characteristics and Survival of Chinese Patients with Connective Tissue Disease Associated Pulmonary Arterial Hypertension. YanJie Hao[1], Wei Zhou[1], Xin Jiang[2], Yu Wang[1], Lan Gao[1], GuangTao Li[1], Tao Hong[1], Yong Wang[3], ZhiCheng Jing[2] and ZhuoLi Zhang[1]. [1]Peking University First Hospital, Beijing, China, [2]Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China, [3]Beijing Shijitan Hospital, Capital Medical University, Beijing, China

Background/Purpose: Pulmonary arterial hypertension (PAH) is a severe complication of connective tissue disease (CTD) with a poor prognosis. There have been sporadic reports with respect to the clinical features and survival of CTD associated PAH (CPAH), however, those in Chinese with CPAH are unknown yet. The purpose of this study is to investigate the baseline characteristics, survival and risk factors of mortality in Chinese with CPAH.

Methods: All consecutive adult patients who visited the three medical centers with confirmed diagnosis of CPAH between July 2006 and May 2011 were enrolled into the study. For all these patients, PAH was confirmed by right heart catheterization.

Results: A total of 144 patients (40.6±12.6 years old) were included in the study and 44% of them were associated with SLE. The other underlying CTDs, in the descending rank order, are pSS (15%), Takayasu arteritis (12%), MCTD (10%), SSc (8%) and some others(RA 3%, PM/DM 2%, adult onset Still'disease 2%, UCTD 2%, primary APS 1%, and ANCA associated small vasculitis 1%).

The median duration between symptom onset and diagnostic catheterization was 16.5 months. At diagnosis, 57.6% of patients were in WHO functional class III/IV. The six-minute walk distance was 377.0±99.7m. Mean pulmonary artery pressure was 49.7±14.4mmHg. Eighty five percent of patients received vascular-targeted therapy.

One hundred and twenty-nine patients were followed up with a median duration of 15.8 months (ranged 1.1–55.1 months). The survival rates of these patients at 1 and 3 years were 87.8% and 53.8%. The survival rates of patients with SLE associated PAH at 1 and 3 years were 90.0% and 57.1%.

Univariate Cox analysis showed shorter 6-min walk distance, lower cardiac output, cardiac index and mixed venous oxygen saturation, higher pulmonary vascular resistance (PVR), alkaline phosphatase (ALP), total bilirubin and direct bilirubin, lower total cholesterol and low-density lipoprotein were associated with high risk of death (all $p<0.05$). Multivariate Cox analysis showed higher PVR and ALP were independent predictors of mortality [HR were 1.10 (1.01–1.20) and 1.01(1.00–1.02) respectively, both $p<0.05$]. K-M analysis demonstrated the survival rate in PVR<15 wood unit group was higher significantly than that in ≥15 wood unit group (p=0.009), and the survival rate in ALP<150U/L group higher than that in ≥150 U/L group (p=0.012).

Conclusion: SLE was the most common underlying disease of CPAH in China; however, SSc-associated PAH was fewer in Chinese patients, which were much different from Caucasians. The survival of Chinese patients with CPAH at 1 and 3 years were 87.8% and 53.8%. Furthermore, elevated PVR and ALP were independent risk factors of bad outcomes.

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Overrepresentation of Lifestyle Associated Risk Factors Along the Spectrum of Rheumatic Disease. Inger L. Meek[1], H.S.J. Picavet[2], Harald E. Vonkeman[1] and Mart AF van de Laar[3]. [1]Rheumatology Center Twente, Medisch Spectrum Twente & Twente University, Enschede, Netherlands, [2]National Institute for Public Health and the Environment, Bilthoven, Netherlands, [3]Medisch Spectrum Twente & Twente University, Enschede, Netherlands

Background/Purpose: Over the past decades many reports have shown an association between rheumatoid arthritis (RA) and increased cardiovascular morbidity and mortality. This association is thought to be due to clustering of lifestyle associated cardiovascular risk factors in patients with RA, the chronic inflammatory disease process itself, as well as the use of medication such as non steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs). Information on cardiovascular risks in patients with other chronic rheumatic diseases is lacking, although they might be exposed to similar pathofysiological processes.The aim of this study was to compare the prevalence of lifestyle associated cardiovascular risk factors among the three major disease categories attending a rheumatology outpatient clinic; RA, gout and osteoarthritis (OA), and the general population.

Methods: Comparison of individual lifestyle associated cardiovascular risk factors, i.e. hypertension, hypercholesterolemia, low HDL cholesterol, overweight (BMI > 25 kg/m^2), obesity (BMI > 30 kg/m^2) and smoking habits between the three major disease categories; RA (n=546), gout (n=129), and OA (n=168) in a cohort of all consecutive patients between 36 and 75 years of age attending the Arthritis Center Twente (ACT), a large rheumatology outpatient department in The Netherlands (n=1233), and a sample of the general population (GP) from the same geographic region (n=4523). Data were collected by direct measurements in 2009 (ACT), and from 2003 to 2007 (GP) respectively. Analyses were sex-specific and standardised by age.

Results: Compared to the GP, rheumatology outpatients have a relative higher prevalence of hypertension (P_{ACT}=68%, $P_{general}$=53%), overweight (P_{ACT}=72%, $P_{general}$=62%), obesity (P_{ACT}=30%, $P_{general}$=17%) and smoking (P_{ACT}=26%, $P_{general}$=21%) ($p<0.05$). Hypertension, overweight and obesity were overrepresented in all three major chronic disease categories, with a strong association between overweight and obesity and gout (overweight OR_{gout}8.6, OR_{RA}1.2, OR_{OA}2.1; obesity OR_{gout}4.2, OR_{RA}1.4, OR_{OA}2.5). There were specific associations between RA and smoking (OR 1.5; 95%CI 1.2–1.6), gout and hypercholesterolemia (OR 2.2; 95%CI 1.6–3.3) and lowered HDL cholesterol (OR 2.9; 95%CI 1.8–4.5), and OA and hypercholesterolemia (OR 2.3; 95%CI 1.7–3.2).

Conclusion: lifestyle associated cardiovascular risk factors are overrepresented along the whole spectrum of chronic rheumatic diseases. Risk factor patterns appear to be disease specific.

1055

Subclinical Atherosclerosis In Inflammatory Rheumatic Diseases. Dan Nemes[1], Mihai Dragoi[1], Liliana Catan[1], Elena Amaricai[1], Daniel Popa[1], Roxana Onofrei[1], Dan Surducan[1], George Puenea[1], Elena Sarbu[2], Andreea Iana[2], Mihaela Muntean[2], Rodica Mihaescu[2], Rares Olariu[2] and Camelia Nemes[2]. [1]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania, [2]City Universitary and Emergency Hospital, Timisoara, Romania

Background/Purpose: Increased cardiovascular morbidity and mortality in rheumatic patients cannot be entirely explained by traditional cardiovascular risk factors, suggesting that the systemic inflammation may accelerate atherosclerosis. The aim of the present study is to link chronic inflammation with atherosclerosis in patients with systemic rheumatic diseases.

Methods: The cohort study was performed during an eighteen-month period (between November 2009 and April 2011) and enrolled 200 patients with systemic rheumatic disorders. Patients' mean age was 55.4 ± 8.18 years. 67 patients from this cohort group were selected. Subclinical atherosclerosis was assessed by the common carotid intima-media thickness (IMT) and flow mediated vasodilatation (FMD) of the brachial artery on B-mode ultrasound images, with the use of a 10 MHz linear-array transducer.

Results: Mean value of IMT at the right common carotid was 0.9 ± 0.19mm and at the left common carotid 0.9 ± 0.34mm. FMD was 8.0 ± 5.77%. ESR (Erythrocyte sedimentation rate) was increased in 80% patients, while CRP (C-reactive protein) was increased in 50% of the studied patients. We found a negative correlation between FMD and ESR (r= −0,397) or CRP (r= −0,628). Mean values of IMT was associated with ESR (r= 0,276) and CRP (r= 0,613). Disease activity was correlated with endothelial dysfunction as measured by intima-media thickness or by flow-mediated dilatation.

Conclusion: In our study we found an increased endothelial dysfunction as measured by intima-media thickness or by flow-mediated dilatation. Endothelial dysfunction was correlated with elevated levels of ESR and CRP suggesting that chronic inflammatory status promotes atherosclerosis. Disease activity was correlated with endothelial dysfunction as measured by intima-media thickness or by flow-mediated dilatation.

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Nontuberculous Mycobacterial Infections In Rheumatological Diseases. Vivek Nagaraja[1], Joel A. Terriquez[2], Susan E. Hoover[2] and Jeffrey R. Lisse[2]. [1]University of Arizona/University Physicians Healthcare at Kino Campus, Tucson, AZ, [2]University of Arizona, Tucson, AZ

Background/Purpose: Non-tuberculous mycobacterial (NTM) infections are frequently identified in patients with rheumatologic disease, and management of these infections can be challenging. The aim of this study was to describe the management and outcomes of cases of NTM infections in patients with any form of rheumatologic disease at two healthcare facilities.

Methods: We performed a retrospective chart review of inpatient and outpatient records at two health-care facilities. ICD-9 diagnostic codes were used to identify patients with NTM infection, and patients with any pre-existent rheumatologic disease were included in the study. Chart review focused on rheumatologic disease and its treatment, other co-morbidities, the NTM infection and its treatment, and impact of the infection on the rheumatologic disease management and outcome.

Results: Of 339 patients with NTM infection, 11 with rheumatologic disease were identified. Ten were females, with a median age of 67 years at the time of diagnosis of the infection. Eight cases were pulmonary and 3 were extrapulmonary. 5/11 patients had radiologically pre-existent bronchiectasis. There were five patients with rheumatoid arthritis, two patients with systemic

lupus erythematosus and one patient each with polymyalgia rheumatica, scleroderma, polymyositis, and sarcoidosis. Patients were on the following immunosuppressive medications for a significant period of time (3–5 years): prednisone (7/11), methotrexate (4/11), and anti-tumor necrosis factor (TNF) agents (3/11). Two patients were not on any immunosuppressive medications. In 4/9 cases who were on immunosuppressive therapy, the implicated medication was discontinued. In 3/9 it was continued, and in 2/9 it was restarted after a brief discontinuation. *Mycobacterium avium* complex was the commonest species isolated. Treatment for NTM infection was started in 8/11 patients based on severity and patient's choice. 2/8 patients had recurrence of the NTM infection after completion of antibiotic therapy, both while receiving concomitant immunosuppressive therapy. 3/11 patients died, with no death directly related to NTM infection.

Conclusion: This is the first study to describe the natural history of NTM infections in a rheumatologic disease population. As in the general population with NTM infection, patients tended to be female and have pre-existing bronchiectasis. The infection could often be successfully treated, but there appears to be some risk of recurrence in patients who are continued on immunosuppressive therapy. Because NTM infection and rheumatologic disease may have a predilection for the same patient population, such cases will likely continue to be identified and more study of the optimal management is needed.

1057

A Meta-Analysis: Diagnostic Accuracy of Serum Procalcitonin Concentrations for Detecting Systemic Bacterial Infection In Patients with Rheumatic Diseases. Yoshinori Kogata, Daisuke Sugiyama, Akira Onishi, Ikuko Naka, Kosaku Tsuda, Keisuke Nishimura, Kenta Misaki, Goichi Kageyama and Akio Morinobu. Kobe university graduate school of medicine, Kobe, Japan

Background/Purpose: Procalcitonin (PCT) is reported as a useful serum marker for detection of systemic bacterial infection in variety of clinical settings. We previously reported diagnostic accuracy of PCT for systemic bacterial infections in patients with rheumatic diseases in the annual scientific meeting of American College of Rheumatology in 2006. In our study, sensitivity and specificity was 50.0% and 94.1%, respectively. And the area under the curve (AUC) of summary receiver-operating characteristic (sROC) curve for PCT was 0.861.

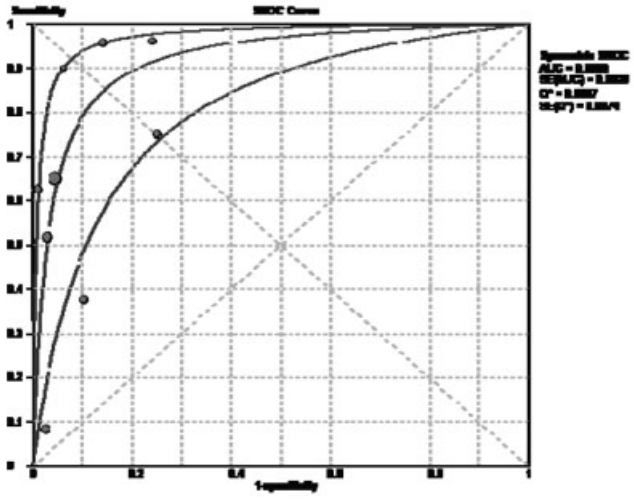
However, it is still controversial that clinical use of PCT for systemic bacterial infection in patients with rheumatic diseases. The reported diagnostic accuracy of PCT varies from study to study and their usefulness remains uncertain among the patients with rheumatic diseases. The relative rareness of rheumatic diseases has resulted in the samples for all studies being small so that no quantitative comparisons have been made of PCT for bacterial infection in patients with rheumatic diseases. We therefore systematically conducted this meta-analysis for PCT to quantitatively clarify its diagnostic accuracy of PCT.

Methods: Literature search were performed by MEDLINE (through March 7th, 2011), reference lists of retrieved studies and review articles. Included were studies in any language that examined the role of PCT in the diagnosis of adult patients with rheumatic diseases and that provided enough data to permit the calculation of sensitivity and specificity for diagnosing systemic bacterial infection. Two reviewers independently evaluated studies for inclusion, rated methodological quality, and extracted relevant data. Weighted sensitivity and specificity and an AUC of sROC curve were calculated. Meta-regression was used to identify the source of heterogeneity.

Results: We used a meta-analytic method to construct a sROC curve. Nine studies met the inclusion criteria and they involving 551 patients were relevant for the diagnostic accuracy of PCT. The diagnostic accuracy of the PCT was high, with an AUC from sROC of 0.920 (95% CI, 0.918–0.922) for patients with systemic infection. The pooled sensitivity, specificity and diagnostic odds ratio were 0.66(95% CI, 0.58–0.74), 0.94(95% CI, 0.91–0.96), and 25.1(95% CI, 11.3–55.9), respectively.

There was no heterogeneity among studies. (Cochran Q=10.9, P=0.2, I-square=26.6%)

Conclusion: Serum procalcitonin concentration showed good diagnostic capability for systemic bacterial infection among the patients with rheumatic diseases.



1058

Nutritional Deficiencies Linked to Nonspecific Complaints of Joints, Skin, and Nervous System in a University-Based Rheumatology Clinic; A Retrospective Chart Review. Shawn Macalester. University of Virginia, Charlottesville, VA; Authors: Shawn Macalester, Shikha Sarebahi, Donald L Kimpel

Background/Purpose: Nutritional and immune disorders in the context of gastrointestinal bypass surgeries and bacterial overgrowth have been linked to a variety of arthritic, dermal, and neurologic manifestations, potentially via an immune mediated process. It has been suggested that this complication of weight loss surgery was eliminated by the performance of gastric bypass procedures in place of small intestinal bypass. We carried out a two-step approach to assess 1) nutritional deficiencies, and 2) the prevalence of gastric bypass surgeries and bacterial overgrowth in this group.

Methods: A retrospective chart review was performed in individuals referred to the UVA Rheumatology clinic for nonspecific complaints including arthralgias, diffuse pain, and fatigue in order to evaluate for an enteropathic etiology and define potential areas for future intervention. Seventy three patients were evaluated in the clinic who had arthritic symptoms, and also complained of additional symptoms that could be related to gastrointestinal disorders or to malabsorption, including diarrhea, abdominal bloating and pain, Raynaud's phenomenon, sicca symptoms, muscle weakness, numbness, and tingling. These symptoms are relatively common in rheumatologic diseases as well as fibromyalgia, and symptoms could be attributed to diagnoses such as Celiac Sprue, Whipples disease, inflammatory bowel disease and post gastric bypass syndrome. We analyzed the patient results for common nutritional deficiencies, and where appropriate, for underlying gastrointestinal disorders. This group of 73 patients were tested for vitamin B1, B6, B12, 25-hydroxy-Vitamin D (D2+D3), and Serum Folate levels.

Results: Of the individuals tested, 60.3% were found to have vitamin B1 deficiency, 46.6% had B6 deficiency, 8.2% vitamin B12 deficiency, 6.8% folate deficiency, and 67.1% vitamin D deficiency. Strikingly, 30% of those evaluated had Roux-en-Y gastric bypass surgery and of those, 11 individuals underwent hydrogen breath testing for bacterial overgrowth and 9 of the 11 (81%) tested positive consistent with small intestine bacterial overgrowth (SIBO).

Conclusion: This study brought attention to common nutritional deficiencies which may lead to consultation in a rheumatology clinic, and the potential contribution of gastric bypass surgery. Further evaluation for causes of these deficiencies is indicated to evaluate for other causes such as celiac sprue. Patients with documented bacterial overgrowth, in this case associated with gastric bypass, are at risk for development of immune and nutritional disorders previously described in patients with jejunoileal small bowel bypass performed for weight loss. Our understanding of the role of gastric flora and gut-associated lymphoid tissue (GALT) on health, nutrition, and the immune system, is in its infancy. Further study to evaluate the effects of vitamin replacement, probiotics, or antibiotic treatment for bacterial overgrowth will be important.

1059

Vitamin D Deficiency in Patients with Systemic Lupus Erythematosus and Rheumatoid Artrhitis in a Tropical Country. Claudia D.L. Marques, Thiago Sotero Fragoso, Andrea Tavares Dantas, Aline Jurema G. Costa, Henrique A. Mariz, Aline Ranzolin and Angela Luzia B. P. Duarte. Hospital das Clínicas - Universidade Federal de Pernambuco, Recife - PE, Brazil

Background/Purpose: In recent years, vitamin D has been target of an increasing number of studies which have shown that, besides its role in calcium metabolism and bone formation, it interacts with the immune system through its action on the regulation and differentiation of immune cells. Current studies have linked vitamin D deficiency with multiple autoimmune diseases, emphasizing its participation in the pathogenesis, treatment and activity of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). In Brazil, a tropical country, studies on vitamin D deficiency in patients with RA and SLE are limited, and previous studies have shown that in our country the vitamin D deficiency occurs even in normal individuals, despite the high rate of solar incidence. The objectives of this study was to determine serum levels of 25-hydroxyvitamin D_3 (25(OH)D) in RA and SLE patients and verify the association of insufficiency/deficiency of 25(OH)D with clinical parameters and laboratory tests.

Methods: A cross-sectional and prospective study, between April 2009 and March 2010. Recife, capital city of Pernambuco's state – Brazil, where the study was performed, has a tropical climate, hot and humid, with average annual temperature of 25.2 ° C. The city is located at latitude 8° 04 '03''S and longitude 34° 55' 00''O, with high rates of insolation throughout the year. We included 78 patients with SLE, 58 with RA and 79 health volunteers (comparison group).

Results: It was found insufficiency/deficiency 25(OH)D (<30 ng/mL) in 43/78 (55.1%) patients with SLE, in 21/58 patients with RA(36.2%) and 32/79 (40.5%) in the comparison group. The mean serum levels of 25(OH)D were 29.8 ng/mL in patients with SLE, 33.9 ng/mL in AR group and 33.40ng/mL in comparison group. The difference between the LES group was statistically significant when compared with both group AR ($p=0.11$) and comparison group ($p=0.026$). There was no statistically significant difference in the mean vitamin D serum levels of the RA and comparison group, and there were no statistically significant association between the time of diagnosis, the clinical parameters of activity or treatment in the LES or AR group.

Conclusion: There was a high prevalence of insufficiency/deficiency of 25(OH)D in patients with SLE (55.1%) who had significantly lower serum levels of 25(OH)D than in the AR or comparison group. Thus, taking into account the multiple "roles" of vitamin D, we emphasize the importance of determination of serum 25 (OH) D in all patients with SLE regardless where they live and the time of diagnosis.

ACR/ARHP Poster Session B
Orthopedics, Low Back Pain, and Rehabilitation
Monday, November 7, 2011, 9:00 AM–6:00 PM

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Predictors of Outcomes of Total Knee Replacement Surgery. Andrew Judge[1], Nigel K. Arden[2], Cyrus Cooper[3], M. Kassim Javaid[2], Andrew Carr[1], Richard E. Field[4] and Paul A. Dieppe[5]. [1]Oxford University, Oxford, United Kingdom, [2]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK, Oxford, United Kingdom, [3]Southampton General Hospital, Southampton, United Kingdom, [4]Elective Orthopaedic Cnetre, Epsom, United Kingdom, [5]University of Exeter, Plymouth, United Kingdom

Background/Purpose: Total knee replacement (TKR) is, on average, an effective and cost-effective intervention for severe arthritis. However, a significant minority of patients are dissatisfied with the outcome and have persistent joint pain and disability.

The aim of this study was to identify pre-operative predictors of those who have poor outcomes after a TKR.

Methods: We analysed data from a large prospective cohort of patients undergoing a TKR in the UK. Pre-operative data was available on: age, gender, BMI, diagnosis, Oxford Knee Score (OKS), EQ-5D, ASA status as a proxy for general health, and socio-economic status. The primary outcome measure was the 6-month post-operative OKS. We calculated a patient-acceptable symptom state (PASS) by relating OKS outcomes to patient satisfaction with the surgery. Regression modelling was used to identify predictors of outcome.

Results: Full data were available from 1991 patients (mean age 71.7 years, 61% female). The majority improved after surgery, but in some there was either no change or worsening of the OKS score. Using a cut-point of a post-operative OKS of 30 points or more, we identified that 71.7% had achieved an acceptable PASS.

The strongest determinant of outcome was pre-operative pain and function (less severe patients had the best outcomes, multivariate ANCOVA 1.70, 95% confidence intervals 1.43–1.96)). Other significant predictive factors included diagnosis (those with RA did better than those with OA), socio-economic status (poor status associated with a poor outcome), anxiety and depression, age and sex. BMI was not an important predictor of outcome. Differences were observed between predictors of pain relief and functional gain. Those with OA and anxiety or depression were most likely to have post-operative pain; women, older people were most likely to have a poor functional outcome. However, less than 20% of the variance in outcome was explained by the variables in the model.

Conclusion: Predictors of the pain response to a TKR maybe different from those predicting functional improvement. Although significant predictors of poor pain or functional outcomes were detected in this study, the majority of the variance remained unexplained; other predictive factors need to be identified to improve our ability to select the patients who are most likely to improve.

1061

Pain After Hip or Knee Joint Replacement for Osteoarthritis: A Systematic Review. Andrew Beswick[1], Vikki Wylde[2], Ashley Blom[2], Rachael Gooberman-Hill[1] and Paul A. Dieppe[3]. [1]University of Bristol, Bristol, [2]University of Bristol, Bristol, United Kingdom, [3]University of Exeter, Plymouth, United Kingdom

Background/Purpose: The view of the public, encouraged by orthopaedic surgeons, is that total hip or knee joint replacement (TJR) nearly always relieves the pain of osteoarthritis (OA). TJR is indeed highly successful when judged by prosthesis related outcomes, such as the radiographic appearance of the prosthesis, implant survival, or surgeon assessed outcomes. Nevertheless, registry data show that many people are dissatisfied with the outcome, and it is clear that some patients continue to experience severe pain.

The aim of this study was to establish the frequency of moderate or severe pain in the operated joint after TJR.

Methods: We conducted a systematic literature review to identify longitudinal studies reporting the proportion of people with significant long-term pain after total hip or knee replacement. To reduce the biases of loss to follow-up or highly selected patient groups, the only reports included were those that were prospective studies of consecutive or generally unselected osteoarthritis patients with total hip or knee arthroplasty followed for 3 months to 5 years that reported a patient-centred pain outcome. MEDLINE and EMBASE databases were searched from inception to January 2011. Citations of key articles in ISI Web of Science, and reference lists were checked. Two authors screened titles and abstracts. One author extracted data and this was checked independently against original articles by a second. We summarised the proportions of people with different severities of pain in the operated hip or knee.

Results: Searches identified 1308 articles of which only 119 reported patient-centred pain outcomes in representative populations followed for 3 months to 5 years. Fourteen articles describing 17 cohorts (6 in hip and 11 in knee patients) presented appropriate results, but the diversity of outcome measures reported and their interpretation precluded meta-analysis. Studies excluded from analysis mainly presented outcomes as mean values only. Applying the conservative assumption that patients in whom the outcome was unclear had a similar distribution of pain, an unfavourable pain outcome (moderate or severe pain in the operated joint) was reported in 7 to 23% of hip and 10 to 34% of knee arthroplasty patients.

Conclusion: For many people, total hip or knee arthroplasty is an effective treatment for OA pain. However a significant proportion of people continue to have painful joints after surgery. There is an urgent need to improve general awareness of this, and to address the determinants of good and bad outcomes.

1062

Efficacy of Total Arthroplasty Combined with Anti-Tumor Necrosis Factor Agents on Systemic Disease Activity in Patients with Rheumatoid Arthritis. Masatoshi Hayashi[1], Toshihisa Kojima[2] and Naoki Ishiguro[3]. [1]Nagoya University Graduate School, Nagoya, Japan, [2]Nagoya Univeristy, School of Medicine, Nagoya, Japan, [3]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan

Background/Purpose: To assess the effect of total large-joint arthroplasty combined with anti-tumor necrosis factor (TNF) therapy for rheumatoid arthritis (RA).

Methods: We studied 45 RA patients (age: 57.91 ± 12.74 years, RA duration: 13.43 ± 8.28 years) who underwent 58 total arthroplasties (35 knees, 19 hips, 3 elbows, and 1 ankle) between August 2002 and November 2009. All received anti-TNF agents during their operative periods (infliximab, 22; etanercept, 33; adalimumab, 3). Changes in clinical variables in 58 cases were investigated at baseline (just before operation), and at 4, 12, and 52 weeks after operation. We assessed means of DAS28-ESR in all patients and divided all into 2 equal groups (n = 29, each) based on the median of CRP and MMP-3 at baseline.

Results: Means of DAS28 in all patients significantly improved from baseline (4.32 ± 0.99) to 1 year after operation (3.35 ± 0.93) in contrast with the fact that the average values of DAS28 remained unchanged from 1 year before the operation to the baseline. Average values of CRP, ESR, and MMP-3 in all operations improved relative to baseline in a time-dependent manner, and were lowest 1 year after the operation (Table 1). Improvement of CRP was statistically significant ($P = 0.016$). Compared with high value groups, those with low CRP and MMP-3 values gained better results and reached low disease activity on an average (Table 2).

Table 1. Values of CRP, ESR and MMP-3 in all TNF blockers (n=58 operations) at baseline, 4w, 12w and 52w after operations

	Baseline		4w		12w		52w	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CRP (mg/dl)	1.71	2.48	1.72	2.35	1.28	2.03	0.90*	1.08
ESR (mm/h)	40.34	28.81	44.81	25.85	39.13	25.74	34.43	23.02
MMP-3 (ng/ml)	230.79	242.32	181.13	174.51	197.55	209.61	165.98	145.75

* denotes significant difference from baseline. $P < 0.05$.
CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *MMP-3* matrix metalloproteinase-3, *TNF* tumor necrosis factor, *SD* standard deviation

Table 2. DAS28 of low and high groups devided by median of each CRP and MMP-3 at baseline

	Median	Group	Baseline DAS		DAS+1Y		DAS+1Y*f*3.2 (%)
			Mean	SD	Mean	SD	
CRP	0.52 (mg/dl)	low	3.93	0.87	3.00**	0.74	70.0##
		high	4.96	0.84	3.83*	0.99	11.1
MMP-3	136 (ng/ml)	low	3.97	0.92	2.95**	0.72	60.0
		high	4.65	0.97	3.80*	0.96	22.2

*,** denotes significant difference from baseline. *: $P < 0.05$. **: $P < 0.01$.
denotes significant difference from high group. $P < 0.01$.
DAS disease activity score, *DAS+1Y* DAS28 1 year after operation

Conclusion: Overall, the DAS28 of both the groups improved 1 year after operation. Large joint arthroplasty may be beneficial in RA patients using anti-TNF agents not only for pain relief from destructive joints but also for systemic improvement in RA activity.

1063

Peptic Ulcer Disease Is Associated with Periprosthetic Fractures After Total Hip Replacement. Jasvinder A. Singh[1] and David Lewallen[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Mayo Clinic College of Medicine, Rochester, MN

Background/Purpose: To assess if medical comorbidity is associated with risk of periprosthetic fractures after total hip replacement (THR).

Methods: We used the prospectively collected data from 1989–2008 in the Mayo Clinic total joint registry for two cohorts, primary THR and revision THR. Main variables of interest were Deyo-Charlson comorbidities at the time of the surgery. Outcome of interest was postoperative periprosthetic fracture at postoperative day one onwards. Multivariable Cox regression models additionally adjusted for gender, age, body mass index, American Society of Anesthesiology (ASA) class and operative diagnosis.

Results: We identified 14,065 primary THRs and 6,281 revision THRs with mean follow-up of 6.3 and 5.6 years respectively. There were 305 postoperative periprosthetic fractures in primary THR and 330 in revision THR cohort. In patients who underwent primary THR, two comorbidities were associated with higher risk of periprosthetic fracture: peptic ulcer disease with adjusted hazard ratios of 1.68 (95% confidence interval (CI): 1.16, 2.42; p=0.006); and cardiac disease with adjusted hazard ratio of 1.51 (95% CI: 1.07, 2.15; p=0.02). In patients with revision THR, peptic ulcer disease was associated with higher adjusted hazard of periprosthetic fracture, 1.58 (95% CI: 1.10, 2.29; p=0.015).

Conclusion: Peptic ulcer disease and cardiac disease in primary THR and peptic ulcer disease in revision THR patients were significantly associated with higher postoperative periprosthetic fracture risk. Further studies are needed to understand whether disease severity or specific medications used for treatment or both are responsible for this association. This may allow identification of modifiable factors amenable to interventions.

1064

Prognostic Factors for Surgical Intervention After Steroid Induced Avascular Necrosis of the Femoral Head. Ryo Hiroshima[1], Katsunori Ikari[1], Ikuko Masuda[2] and Shigeki Momohara[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]International University of Health and Welfare, Sanno Hospital, Tokyo, Japan

Background/Purpose: The MR imaging classification system of osteonecrosis proposed and revised in 2001 by the Japanese Investigation Committee characterizes osteonecrosis of the femoral head with respect to the size and location on T1-w imaging. We evaluated the prognostic value of the MR imaging classification in patients undergoing surgical intervention after avascular necrosis of the femoral head associated with connective tissue disease in Japanese patients.

Methods: We applied the MR imaging classification in 146 hips (104 patients; 87 % of the patients were female, 40% had bilateral AVN, the mean age of the patients at the diagnosis was 37.9 years and the mean observational period was 6.25 years) with connective tissue disease diagnosed with avascular necrosis of the femoral head (AVN). The classification is based on the extent of the lesion of low-signal-intensity or normal fat signal intensity demarcated by a low-signal-intensity band in the central coronal section of the femoral head as observed on T1-w images. The image consists of four types (A, B, C1, and C2): Type A, lesions occupying the medial one-third or less of the weight-bearing portion; Type B, lesions occupying the medial one-third to two-thirds; Type C1 and C2, lesions occupying more than two-thirds, in which type C2 lesions extend laterally to the acetabular edge while type C1 lesions do not. To define the prognostic factors for future surgical intervention after AVN, Cochran-Armitage trend test and multivariate logistic regression analysis (dependent variables: MRI classification, gender, age at diagnosis, unilateral or bilateral AVN, history of steroid pulse therapy and arthrodynia on the diseased hips) were performed.

Results: Regarding lesion volume and location, 12 hips were type A, 36 hips were type B, 56 hips were type C1, and 42 hips were type C2. Among them, 0/12 hips, 2/36 hips, 16/56 hips and 22/42 hips had future surgical intervention, respectively for type A, B, C1 and C2 ($P=5.0^{-7}$ by trend test). The results of the multivariate logistic regression analysis indicate that types C1 and C2 of the MRI classification (P=0.001, OR=11.6 [95%CI 2.6–52.7]) and bilateral cases (P=0.049, OR=2.7 [95%CI 1.0–7.1]) were associated with future surgical intervention after AVN.

Conclusion: Type C (C1 and C2) on the MR imaging classification at the time of diagnosis of AVN and bilateral AVN cases are the risks for future surgical intervention after diagnosis of AVN.

1065

Relationship Between Synovitis and Two-Year Post-Surgical Outcomes in Patients Undergoing Arthroscopic Partial meniscectomy. Carla R. Scanzello[1], Edward F. DiCarlo[2], Veero Kanda[1], Anthony Albert[3], Steven R. Goldring[2], John C. Richmond[3] and Brian McKeon[4]. [1]Rush University Medical Center, Chicago, IL, [2]Hospital for Special Surgery, New York, NY, [3]New England Baptist Hospital, MA, [4]New England Baptist Hospital, Boston, MA

Background/Purpose: In established OA, the presence of synovitis is associated with pain and progression of disease. We previously demonstrated that synovitis is also associated with worse pre-operative symptoms in patients undergoing arthroscopic partial meniscectomy, even in the absence of radiographic OA. Synovial inflammation in these patients was associated with expression of CCL19 and CCR7. Despite no radiographically evident disease,

the majority (80%) of these patients had intra-operative evidence of early-stage OA. The present study is the longitudinal follow-up of these patients to test whether synovial inflammation predicts progressive knee symptoms up to 2 years post-operatively.

Methods: Thirty-three patients undergoing athroscopic partial meniscectomy were recruited from Orthopedic practices at the New England Baptist Hospital. Synovial biopsies were taken at the time of surgery, and inflammation was previously scored on H&E stained sections using our published histologic scale based on the extent of perivascular lymphocytic infiltration. Symptoms were measured by the Lysholm score (a questionnaire measuring knee-specific symptoms and dysfunction) pre-operatively, at 16 weeks, 1 year and 2 years post-arthroscopy. Synovial chemokine expression was determined by quantitative real-time pcr.

Results: There were significant improvements from the pre-operative baseline Lysholm scores at all three post-operative time points (Kruskal-Wallis $p<0.0001$), with a mean (+/−SD) improvement at 2 years of 27 (+/−16) points. Despite having worse pre-operative Lysholm scores (Mann Whitney $p= 0.0008$), patients with synovial inflammation did not generally have worse Lysholm scores compared to patients without inflammation in follow-up ($p>0.05$). Patients with synovitis showed greater mean improvement in Lysholm scores at 16 week and 1 year ($p = 0.02$ and $p=0.03$), but only a trend by 2 years ($p=0.054$) compared to patients without synovial inflammation. mRNA relative expression levels of CCL19 and CCR7 were also associated with greater improvements in Lysholm scores at the 16 week (CCL19: Spearman $r=0.71$, $p = 0.049$; CCR7: $r = 0.71$, $p = 0.02$), and 2 year timepoints (CCL19: $r= 0.85$, $p = 0.004$; CCR7: $r = 0.79$, $p = 0.002$).

Conclusion: In this cohort of patients with meniscal tears and pre-radiographic OA undergoing arthroscopic partial meniscectomy, synovitis identified histologically did not predict worse Lysholm scores up to 2 years post-operatively. Patients with inflammation, measured both histologically and by expression of CCL19 and CCR7, demonstrated greater symptom improvement which was significant at multiple follow-up time points, indicating that these patients may be more responsive to surgical intervention. Radiographic evidence of OA at the time of arthroscopy has been associated with poorer outcomes. It is possible that in this radiographically normal population, longer follow-up is needed to identify patients who develop progressive knee symptoms after surgical intervention for meniscal tears.

1066

Ultrasound Guided Hip Joint Injection, Its Safety and Efficacy. Srijana Pandit[1], Charles H. Pritchard[2], Elana Eisner[2] and Mary Naglak[1]. [1]Abington Memorial Hospital, Abington, PA, [2]Rheumatic Disease Associates, Willow Grove, PA

Background/Purpose: Osteoarthritis (OA) is a leading cause of disability and the most common joint disorder in United States. Intra-articular hip injections is one of the treatment modalities for OA which is challenging because the joint lines are not palpable and the femoral nerve, artery and veins lie in the close proximity to the anterior hip joint. For many years intra-articular hip injection has been done under fluoroscopic guidance for direct visualization and confirmation may requires iodized contrast. Disadvantages to this include frequent radiologic referral, the need for the patient to transfer to another facility, use of ionizing radiation and cost. The literature has documented the safety and effectiveness of this procedure in the outpatient setting using ultrasound (US). US visualize the hip joint well and can perform accurate and safe musculo-skeletal fluid aspiration and injection.

Methods: We evaluated 85 patients who underwent US guided arthrocentesis in one rheumatology center during the period of January 2009 to August 2010. Most patients received triamcinolone 40 mg and 2–4 cc of lidocaine. The time frame of a pain relief and the presence of adverse reaction were evaluated by subsequent chart review. Several patients had multiple hip joint injections; each injection was counted. There were 120 total numbers of injections. Patients with chronic pain syndrome, patients with trochanteric bursitis and patients with low back pain were excluded from the study. Data was summarized using descriptive statistics including means and frequencies. US machine used was a GE Logiq e with a LA 5–13 MHz probe.

Results: We had 85 patients with 120 injections, 72.9 % (n=62) were female with mean age of 67.44 years and mean BMI of 31.1. 64.2 % (n=77) were right hip injections compare to 32.5% (n=39) on the left and only 3.3 % (n=4) were both hip joint injections. 87.05 % (n=74) of the patients were on pain medication with NSAIDS being the most common followed by tramadol and others were on combination of the NSAIDS, tramadol, fentanyl patch or oral opoids. Out of 120 injections 73.3 % (n=88) had a pain relief, 16.7 % (n=20) had no relief, 10 % (n=12) were lost in follow up. 20 patients who had no pain relief were later found to have other causes e.g. trochanteric bursitis or back pain. A total of 42 %(n= 37) had pain relief period of 1 –3 months, 26 % (n= 23) had pain relief period of 3–6 months, 12.5 % (n= 11) for 6–12 months, 16 %(n= 14) for >1 year, 3.5 % (n=3) patient had a pain relief of <1 month. 31% (n=26) of 85 patient underwent joint replacement. Only one patient complained of difficulty managing her blood sugar. No signs of infection, bleeding, increase in blood pressure or OA flare were noted.

Conclusion: We evaluated the safety and efficacy of the US guided hip joint injection on 85 patients (120 injections**)**. This retrospective study concludes that the US guided hip joint injection is safe and efficacious. There was no complication documented except for one patient complaining of elevated blood sugars. Two third of the patient had a pain relief period of 1–6 months and those who did not have pain relief were found to have some other source of pain mainly trochanteric bursitis and back pain. Most of the patient was female and most of the injection was done in the right side.

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Pilates to Treat Chronic Non-specific Low Back Pain. Jamil Natour, Andreia S. Baptista, Luciana A. Cazotti, Luiza H. C. Ribeiro and Anamaria Jones. Universidade Federal de Sao Paulo, Sao Paulo, Brazil

Background/Purpose: Low back pain (LBP) is a common problem among adults. Approximately 70–85% of the adult population experiences this painful complaint at some point in their lives, making LBP the second most common reason for a visit to a clinician. Despite the frequency of this diagnosis, conventional treatment does not always provide patients the desired results of reduced pain and return of normal function. For these patients, alternative modalities are available to assist in the control of pain. These options include chiropractic care, physical therapy, massage therapy, and modalities that fall under the auspices of complementary and alternative medicine, such as acupuncture. Unfortunately, Clinical trials evaluating the efficacy of a variety of interventions for chronic non-specific low back pain indicate limited effectiveness for most commonly applied interventions and approaches. Our purpose were to evaluate the effectiveness of a mat and studio Pilates program on pain, function, quality of life and NHAI consumption for chronic non-specific low back pain patients.

Methods: Eligible patient include: chronic non-specific low back pain; age between 18 and 65 years; pain ranging from 4 to 8 in a numerical pain scale. Patients with previous surgery, other causes of low back pain, fibromyalgia, regular physical activity (three or more times per week for at least three months); labor lawsuit and body mass index more than 30 were excluded. Sixty patients were randomized to the Experimental Group (EG) or Control Group (CG). Patients in EG participated in 90 days of mat and studio Pilates program twice a week (50 minutes per class) and the CG remained with their usual medicament treatment and were included in a waiting list for physiotherapy. Assessment for pain (VAS), function (Roland Morris questionnaire), quality of life (SF-36) and NHAI consumption were done at baseline, after 45 days (T45), after 90 days (T90 - end of the program), after 90 days (T180 – follow up) by a blinded assessor.

Results: The groups were homogenous for all evaluated parameters at baseline. The EG patients show improve in pain score ($p<0.001$), Roland Morris score ($p<0.001$) and some domains of SF-36 (functional capacity $p=0,046$, pain $p=0,010$ and vitality $p=0,029$) and NHAI consumption ($p<0,001$) when compared with CG.

Conclusion: A mat and studio Pilates program is effective in reducing pain and NHAI consumption and improving function and some domains of quality of life in patients with chronic non-specific low back pain.

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Some Clinical Features Are Associated with MODIC I Changes in Patient with Chronic Low Back pain; Results of a Case Control Study. Florian Bailly[1], Jean-Yves Maigne[2], Stéphane Genevay[3], Marc Marty[4], Frédérique Gandjbakhch[1], Sylvie Rozenberg[5] and Violaine Foltz[6]. [1]Hopital Pitié Salpétrière, Paris, France, [2]Hôpital Hôtel Dieu, Paris, France, [3]Hospital-Beau-Sejour, Geneva, Switzerland, [4]Hôpital Henri Mondor, Créteil, France, [5]Hopital La Pitie, Paris, France, [6]Hôpital Pitié Salpétrière, Paris, France

Background/Purpose: Modic 1 signal changes on lumbar MRI have been associated with chronic low back pain. However, it is still not clear whether specific clinical features are associated with these MRI changes in vertebral body marrow adjacent to the endplates of degenerative discs.

Purpose. To compare the clinical characteristics of low back pain (LBP) patients with and without Modic 1 changes on MRI

Methods: A case control study in which patients with Modic I and patients without Modic I were prospectively included, after informed consent, if they had a chronic LBP, no significant leg radiating pain and had a MRI taken in the previously 6 months.

Patients with Modic I and those without were matched for sex and age.

Demographic data (sedentary work, sick leaves), pain characteristics (including a standardized functional scale: Dallas Pain Questionnaire (DPQ), efficiency of NSAID or oral steroids and physical examination were recorded.

Inflammatory pain pattern was defined by the presence of at least one of the 3 characteristics: maximal pain when waking up, awakening at night because of pain, morning stiffness superior to 60mn.

Wilcoxon and Fisher tests were performed for ordinal and categorial variables respectively. Multivariate analysis (logistic regression, stepwise, backfit) were also performed.

The number of subjects included to achieve statistical significance were 60 patients per group.

Results: Table 1 summarizes the characteristics of the 2 groups. On multivariate analysis for clinical characteristics, sedentary work (OR=0.22 [0.05–0.93]), Pain in extension (OR=11.2 [3.1–40.4]) and inflammatory pain (OR=4.5 [1.2–16.9]) were significantly associated with Modic I changes.

Table 1. Characteristics of patients

	Patients with Modic I (n=60)	Patients without Modic 1 (n=60)	p
Number of years since the first episode, med(IQR)	6 (4–18)	4 (2–14)	**0.03**
Sedentary work, n(%)	32 (57)	40 (68)	0.25
Morning stiffness superior to 60 mn, n(%)	16 (27)	8(14)	0.1
Awakening at night because of LBP, n(%)	25 (42)	15(26)	0.08
Maximal pain intensity when waking up, n(%)	35 (58)	24 (40)	0.07
Inflammatory type of pain, n(%)	48 (80)	33 (55)	**0.006**
Scoliotic list, n(%)	8(14)	8(14)	1.00
Presence of morning stiffness, n(%)	36 (64)	26 (49)	0.12
Worst pain in lumbar flexion, n(%)	32 (55)	29 (54)	0.99
Worst pain in lumbar extension, n(%)	47 (80)	25 (46)	**<0.005**
Lumbar pain at straight leg raising test, n(%)	16 (27)	15 (28)	0.99
Radiculalgia, n(%)	8(14)	6(19)	0.55
DPQ impact on Daily Activities, %(SD)	62 (+/−18)	55 (+/−19)	0.053
DPQ impact on Work/Leisure, %(SD)	53 (+/−28)	53 (+/−26)	0.88
DPQ impact on Anxiety/Depression,%(SD)	35 (+/−28)	38 (+/−27)	0.56
DPQ impact on Social Activities, %(SD)	29 (+/−27)	31 (+/−23)	0.38
NSAID prescription n(%)	53 (88)	53 (88)	1.00
Good clinical response to NSAID, n(%)	18/53 (35)	14/54 (33)	0.83
Oral corticosteroids prescription, n(%)	34/58 (59)	15/50 (30)	**0.0037**
Good clinical response to oral corticosteroids, n(%)	17/34 (50)	1/15 (7)	**0.0039**

Conclusion: In this comparative cross sectionnal study, patients with Modic I changes on MRI complained more often from inflammatory pain pattern and felt the worst pain during back extension.

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The Efficacy of ThermaCare Heat Wraps on Relieving Lower Back Pain and Reducing Muscle Stiffness. Jerrold Petrofsky[1], Lee Berk[1], Gurinder Bains[1], Benny Hau[1], Geraldine Doyle[2], Shijie Chen[2] and Jill Stark[2]. [1]Loma Linda University, Loma Linda, CA, [2]Pfizer Consumer Healthcare, Madison, NJ

Background/Purpose: Lower back pain (LBP) is among the most common and costly healthcare problems throughout the world. Even when back injuries appear to resolve, they typically reoccur later in life on a continuous basis. The purpose of the present investigation was to assess the effect of ThermaCare heat wraps on relieving pain and reducing stiffness in a population with LBP.

Methods: The subjects' age range was 18–55 with primary muscular LBP which was atraumatic (e.g., no traumatic injury within 48 hrs of enrollment) and not caused by, or related to, any clinically significant medical diseases (e.g., multiple myeloma, metastatic carcinoma, spinal arthritis, etc.). Subjects were randomized into one of 2 primary efficacy groups: a heat wrap group (n=26) and an oral placebo group (n=25). For blinding purposes only, a small number of subjects were randomized to an unheated sham wrap group and an oral ibuprofen group, and are not included in the analysis. Two measures were assessed: pain (TOTPAR 0–8: sum of pain relief (PR) scores) hourly for 8 hrs and muscle stiffness (rating from 0, no muscle stiffness to 100, most stiffness).

Results: As shown in Figures 1 and 2, there was a statistically significant increase in pain relief in the ThermaCare heat wrap group over the entire 8 hrs compared to the oral placebo group (Fig. 1); furthermore, the mean back stiffness improvement from baseline was also significant, except at the 4th hr, with the ThermaCare heat wrap group compared to the oral placebo control (Fig. 2).

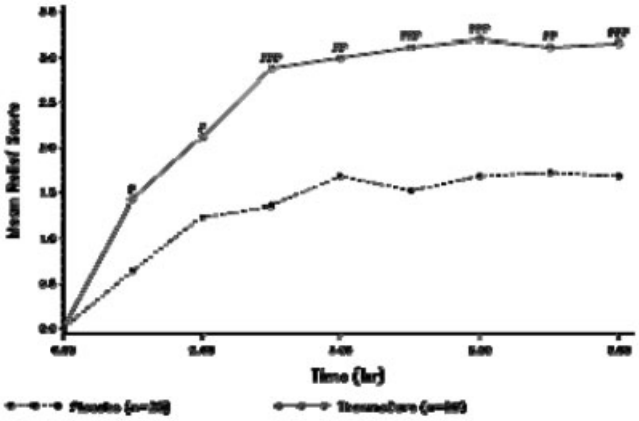

Figure 1. Mean pain relief over time. PPP: Significant compared to placebo at 0.001 level; PP: at 0.01 level; P: at 0.05 level.

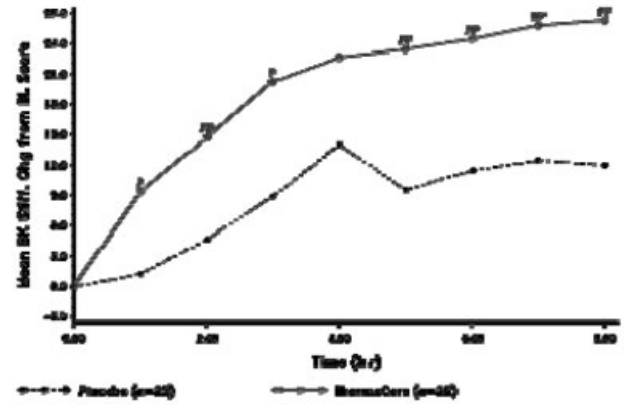

Figure 2. Mean back stiffness – change from baseline over time. PPP: Significant compared to placebo at 0.001 level; PP: at 0.01 level; P: at 0.05 level.

Conclusion: ThermaCare heat wraps provide significant back pain relief and reduce back stiffness in a measurable and sustained way over the 8 hrs of the application period. Additionally, there was no loss of pain relief at the end of the 8 hrs.

ACR/ARHP Poster Session B
Osteoarthritis - Clinical Aspects I
Monday, November 7, 2011, 9:00 AM–6:00 PM

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Hand Osteoarthritis: A Predictor of Accelerated Progression in Knee OA? Jonathan Samuels[1], Catherine Petchprapa[2], Elizabeth Carpenter[2], Mukundan Attur[1], Leon Rybak[2], Svetlana Krasnokutsky[3], Cheongeun Oh[4] and Steven B. Abramson[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]NYU Langone Medical Center, New York, NY, [3]NYU Hospital for Joint Disease, New York, NY, [4]New York University, New York, NY

Background/Purpose: There is insufficient understanding regarding how generalized OA involving the hand and knee differs from isolated knee OA, which may result from other factors such as obesity or trauma. The purpose of these studies is to determine whether the presence of hand OA involving interphalangeal (IP) and first carpometacarpal (CMC) joints, alone or in combination, predicts progression of patients with symptomatic knee OA.

Methods: Hand radiographs were obtained on 146 patients at NYUHJD who met ACR criteria for symptomatic knee OA, and who were enrolled in a two-year NIH-sponsored prospective study. The patients completed standardized fixed-flexion knee radiographs at baseline and 24 months, with progression of the signal (more painful) knee OA determined by ≥ 30% decrease change in joint space width (JSW) or ≥1 grade increase in KL score. For each set of hand x-rays, 2 radiologists evaluated 18 IP joints and 2 CMC joints for joint space narrowing and/or osteophytes, and whether or not there was erosive change at the IP joints; we averaged the scores from the two readers whose scores provided excellent Kappa values.

Results: We identified 79 percent of the knee OA patients to have at least 2.0 IP joints with OA (5% with erosive OA), and 53% with at least 1.0 1st CMC OA joint - both consistent with other studies in the literature. While the overall mean IP score was 5.6 and 1st CMC score was 0.9, Caucasians had significantly higher scores for IP and CMC ($p=0.0019$ and 0.0037). Knee progressors by JSW had higher IP scores approaching significance, 7.0 vs. 4.6 ($p=0.11$). Since the IP scores were not normally distributed, we further analyzed data by dichotomizing the study populations into two groups using 2 IP joints with OA as the cutoff point. When so analyzed, the presence of "hand OA" increased the odds ratio of knee OA progression to 2.5 ($p=0.1797$). This burden of IP OA also associated with a trend towards knee progression by delta KL increase. Conversely, knee progressors defined by a KL increase to a score of 3 or 4 over 24 months were 3.5 times as likely to have ≥2 IP joints with OA ($p=0.008$) The 7 knee OA patients with radiographic evidence of *erosive* IP disease, as compared with the rest of the non-erosive IP OA patients and those without IP OA, had a higher percentage of knee OA progression ≥ 30% JSN (57% vs. 22% vs. 19%) approaching significance. None of the permutations involving the 1st CMC revealed significant differences in knee OA progression. In addition, while we had hypothesized that OA patients with prior knee trauma or surgery would have less hand OA given the external causation, we instead found no significant differences in hand OA prevalence in either of those analyses.

Conclusion: In our completed pilot cohort, the quantitative "burden" of hand OA at the IP joint associates with the radiographic severity of knee OA and a trend towards more rapid progression of knee OA, by either JSN or increased KL grade. Erosive IP disease may be an even stronger predictor than non-erosive IP disease of accelerated progression of knee OA.

Funding: This study is funded by NIAMS (R01- AR052873).

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Erosive Osteoarthritis Is Associated with Preclinical Atherosclerosis. Athanasios Koutroumpas, Athanasios Giannoukas, Aikaterini Exarchou, Aristeidis Baliakos, Konstantinos Makaritsis and Lazaros I. Sakkas. Thessaly University School of Medicine, Larissa, Greece

Background/Purpose: Chronic inflammatory disorders have been associated with accelerated atherosclerosis and increased cardiovascular risk. Recent evidence suggests that erosive osteoarthritis (EOA) has considerable inflammation; therefore, we examined the presence of subclinical atherosclerosis and endothelial dysfunction in EOA

Methods: Twenty-four patients with EOA and 24 age and sex-matched healthy individuals without clinical OA were included in the study. No subject had a history of cardiovascular disease. Intima media thickness (IMT) and atheromatous plaques in the common carotid and common femoral arteries were measured by Doppler ultrasonography. The endothelium-dependent, flow-mediated vasodilatation was assessed by measuring the diameter of brachial arteries at baseline and after compression of the forearm with a sphygmomanometer at pressure above 30 mmHg of the individual's systolic blood pressure. The endothelium-independent vasodilatation was assessed after administration of 0.4 mg glyceryl trinitrate.

Results: The two groups were comparable for all demographic characteristics. The EOA patients had significantly elevated systolic and diastolic blood pressure ($p<0.001$ for both). IMT of both common carotid and common femoral artery was increased in EOA ($p=0.012$ and $p<0.01$, respectively). There was no difference in endothelium-dependent and independent vasodilatation, and the prevalence of atherosclerotic plaques between the two groups. The mean 10-year risk of general cardiovascular disease, as predicted with the Framingham Risk Score, was similar in patients and controls ($p=0.18$).

Table. Patients characteristics and results.

Parameter	EOA (n=24)	Controls (n=24)	p
Age (mean. SD)	62.5 (6.6)	60.7 (5.8)	0.33
Sex (Female)	22	22	1
Hypertension, n (%)	16 (66.6)	12 (50)	0.38
Hyperlipidemia, n (%)	7 (29.2)	13 (54.2)	0.14
Diabetes Melitus, n (%)	0 (0)	2 (8.3)	0.49
Smoking, n (%)	3 (12.5)	4 (16.7)	0.99
Statin use, n (%)	4 (16.7)	8 (33.3)	0.32
ACE inhibitor, n (%)	6 (25)	3 (12.5)	0.46
B blocker. n (%)	2 (8.3)	6 (25)	0.24
Angiotensin II receptor antagonist, n (%)	5 (20.8)	3 (12.5)	0.46
Diuretics, n (%)	6 (25)	5 (20.8)	0.74
Cholesterol, mean (SD) (mg/dl)	237.6 (49.5)	230 (35.4)	0.55
HDL, mean (SD) (mg/dl)	59.4 (14.3)	59.1 (13.1)	0.94
LDL, mean (SD) (mg/dl)	157.5 (48.8)	147 (33.3)	0.37
Triglycerides, mean (SD) (mg/dl)	141.8 (75.2)	124.4 (56)	0.63
Systolic Blood Pressure, mean (SD) (mmHg)	160 (32.9)	143.4 (32.1)	<0.001
Diastolic Blood Pressure, mean (SD) (mmHg)	99.9 (20.4)	83.4 (11.9)	<0.001
Intima media thickness, common carotid artery, mean (SD) (mm)	0.91 (0.17)	0.82 (0.19)	0.012
Intima media thickness, common femoral artery, mean (SD) (mm)	0.7 (0.19)	0.6 (0.2)	<0.01
Ultrasound Biopsy Score, mean (SD)	14 (3.3)	12 (2.8)	0.03
Patients with carotid and femoral artery plaques, n (%)	15 (62.5)	13 (54.2)	0.77
Δ brachial artery diameter- reactive hyperemia, mean (SD) (mm)	0.36 (0.39)	0.36 (0.44)	0.92
Δ brachial artery diameter after glyceryl trinitrare administration, mean (SD) (mm)	0.62 (0.49)	0.45 (0.48)	0.057
Framingham Risk Score (10-year risk of general cardiovascular disease), mean % (SD)	23.9 (14.7)	18.8 (11.2)	0.18

Conclusion: In this cross-sectional, controlled study, we found an association between EOA and subclinical atherosclerosis that cannot be fully attributed to traditional cardiovascular risk factors, as assessed by the Framingham score. These results suggest that chronic, low-grade inflammation could be implicated in the process of atherosclerosis in EOA.

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More Inflammatory Signs on Ultrasound in Interphalangeal Joints in Erosive Hand Osteoarthritis. Marion C. Kortekaas[1], Wing-Yee Kwok[1], M. Reijnierse[1], T.W.J. Huizinga[2] and Margreet Kloppenburg[3]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Centre, Leiden, Netherlands, [3]Department Rheumatology and Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands, Netherlands

Background/Purpose: Erosive hand osteoarthritis (EOA) is a subset of hand osteoarthritis (HOA) associated with a higher clinical burden than non-erosive disease. The aetiology of erosive evolution is still unknown. Based on observations that underlying systemic processes may be involved and that during the clinical course inflammatory signs are often seen in EOA, we hypothesized that inflammatory signs are implicated in erosive evolution. We therefore investigated the presence of inflammatory signs assessed by US in erosive and non-erosive interphalangeal joints in patients with EOA in comparison to interphalangeal joints from patients with non-erosive HOA.

Methods: Consecutive patients with HOA (fulfilling ACR criteria) were included. Eighteen interphalangeal joints were scored on radiographs using the Verbruggen-Veys anatomical phase score; E and R-phases were defined as erosive. Effusion, synovial thickening, greyscale (GS) synovitis and power Doppler signal (PDS) were scored with US on a 4-point scale. Generalized estimated equation (GEE) analyses were used to study the association between erosiveness and anatomical phases with US features. Odds ratios (OR) with 95% confidence intervals were calculated with adjustments for patients effects and confounders.

Results: Of 55 HOA patients (mean age 61 years, 86 % females) 51% showed at least one erosive joint. In 94 erosive joints GS synovitis, synovial thickening, effusion and PDS were found in 57%, 13%, 50% and 15%, respectively; in 896 non-erosive joints in 29%, 10%, 26% and 8%, respectively. Summated scores of PDS, GS synovitis and effusion were higher in EOA than in non-erosive HOA. GS synovitis was more frequent in S, J, E and R-phases compared to N-phases. PDS was only associated with E-phase (5.3 (1.3–20.5)) not with other phases. Non-erosive joints in EOA demonstrated more PDS (3.2 (1.6–6.4)), GS synovitis (2.2 (1.3–3.7)) and effusion (2.2 (1.2–3.8)) in comparison to joints in non-erosive HOA.

Conclusion: Inflammatory signs are more frequent in EOA than in non-erosive HOA, not only in erosive joints but also in non-erosive joints, suggesting an underlying systemic cause for erosive evolution.

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The Association Between Erosive Hand Osteoarthritis and Systemic Bone Mineral Density. Ida K. Haugen[1], David T. Felson[2], Martin Englund[3], Ke Wang[2], Piran Aliabadi[4], Ali Guermazi[2], Frank Roemer[2] and Tuhina Neogi[2]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Boston University, Boston, MA, [3]Lund University, Lund, Sweden, [4]Brigham and Women's Hospital, Boston

Background/Purpose: Erosive hand osteoarthritis (OA) is characterized by attrition of the joint plate, which could be due to inadequate bone quality. However, the knowledge about bone mineral density (BMD) in erosive hand OA is scarce. Thus, our aim was to examine the association between erosive hand OA and systemic BMD.

Methods: We included 2236 participants from the Framingham OA study with hand radiographs and femoral neck BMD (DEXA). The bilateral distal (DIP) and proximal interphalangeal (PIP), metacarpophalangeal (MCP), thumb base and wrist joints were scored for radiographic hand OA (Kellgren-Lawrence grade (KLG)≥2) and central erosions. Central erosions were present in DIP/PIP joints only. Thus, we defined erosive OA as ≥1 DIP/PIP joint with KLG≥2 and central erosion in the same joint, and non-erosive OA as ≥1 DIP/PIP joint with KLG≥2 and no central erosions. The unexposed group included those with no DIP/PIP OA (i.e., no OA or isolated MCP/thumb base/wrist OA). We used logistic regression to explore whether BMD (as continuous variable or age- and sex-specific BMD tertiles) was associated with presence of any DIP/PIP OA. We also performed linear regression with presence of erosive or non-erosive OA as independent variable and BMD as continuous outcome variable (one model). The analyses were repeated with the number of erosive and non-erosive joints as independent variables (one model). All analyses were adjusted for age, sex and BMI.

Results: The 2236 participants (1281 women) had a mean (SD) age of 64.5 (9.0) years and a mean (SD) BMI of 28.6 (5.5) kg/m^2. Erosive and non-erosive OA were present in 221 (9.9%) and 761 (34.0%) persons respectively. In those with erosive OA, the median (IQR) numbers of erosive and non-erosive joints were 3 (1–5) and 5 (3–8) respectively. In those with non-erosive OA, the median (IQR) number of OA joints was 2 (1–5).

In adjusted analyses, higher BMD was associated with higher odds of any OA (OR=1.90, 95%CI 0.91–3.98; p=0.09). The odds of any OA was significantly higher in those with the highest BMD tertile (OR=1.37, 95%CI 1.08–1.73; p=0.01), while not significant for those in the middle tertile (OR=1.21, 95%CI 0.96–1.53; p=0.11) compared to those in the lowest tertile.

There were small differences in BMD between the unexposed, erosive and non-erosive OA participants: The adjusted LS-mean (SD) BMD was 0.92 (0.01), 0.93 (0.02) and 0.93 (0.01), respectively. There was a trend towards higher BMD in participants with erosive and non-erosive DIP/PIP OA compared to the unexposed group (table).

Table. The association between erosive and non-erosive hand OA and BMD of the femoral neck (linear regression adj. for age, sex and BMI).

	Adjusted beta (95% CI); p-value
Presence of erosive and non-erosive DIP/PIP OA vs. no DIP/PIP OA as reference (one model)	
No DIP/PIP OA (reference)	0.00
Erosive DIP/PIP OA	0.01 (−0.01, 0.03); p=0.33
Non-erosive DIP/PIP OA	0.01 (0.00, 0.02); p=0.08
Number of erosive and non-erosive DIP/PIP joints (one model) among all participants:	
Number of erosive joints	−0.001 (−0.005, 0.003); p=0.65
Number of non-erosive joints	0.002 (−0.001, 0.004); p=0.15

Analyses with exclusion of those with isolated MCP/thumb base/wrist OA from the unexposed group did not appreciably change the results.

Conclusion: There was a trend towards higher BMD in participants with DIP/PIP OA. Erosive hand OA was not associated with lower systemic BMD, suggesting that local structural impairment of periarticular bone quality may play a role in erosive hand OA not sufficiently covered by systemic BMD measurements.

1074

Magnetic Resonance Imaging in Hand Osteoarthritis: Validation of the Oslo Hand Osteoarthritis MRI-Scoring Method and Association with Pain, Radiographs and Ultrasound. Wing-Yee Kwok[1], Marion C. Kortekaas[1], M. Reijnierse[1], Desirée van der Heijde[1], J.L Bloem[1] and Margreet Kloppenburg[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Department Rheumatology and Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands, Netherlands

Background/Purpose: Magnetic Resonance Imaging (MRI) is able to visualise abnormalities in cartilage, subchondral bone and synovium at once in osteoarthritis (OA). We investigated the reproducibility of the newly developed Oslo Hand Osteoarthritis (OHOA)-MRI scoring method and validated it against other imaging modalities in hand OA patients. Furthermore, we associated MRI features in hand OA with pain and investigated the presence of MRI features in different stages of hand OA.

Methods: Sixteen patients (median age 57 years (range 42–71), 62% female) were recruited from the Rheumatology department of the LUMC. Pain per joint (yes/no) was assessed for the distal and proximal interphalangeal joints (DIPJs, PIPJs). MRI scans of 2nd–5th DIPJs and PIPJs of the right hand were made, using a 3.0T MRI unit. Coronal and sagittal T1-weigthed images pre-and post gadolinium contrast and fat-suppressed T2-weigthed images were obtained. MRI features were scored according to the OHOA-MRI scoring method (based on 1.0T images) for synovitis, erosions, osteophytes (OP) and bone marrow lesions (BML) (grade 0–3). Ultrasound was performed with a 10–14 MHZ linear array transducer and scored for greyscale synovitis and OP. Hand radiographs were scored following the Verbruggen-Veys scoring method. An pre-erosive joint was defined as J-phase (loss of joint space), erosive joint as E-phase and remodeled joint as R-phase (irregular, sclerotic subchondral plate).

To validate the OHOA-MRI scoring method, intra-reader reliability was assessed on 6 MRI scans, measured with single measurements (ICC, 95% confidence interval (CI)). Validity of MRI features versus US was tested with Spearman's rank correlation coefficients, ρ (p-value). With Generalized Estimated Equations associations between MRI features and pain per joint were calculated to account for within-patient effects, age, sex and BMI. Results were given in odds ratios (OR) with 95% CI.

Results: Thirteen patients (81%) had erosive OA (EOA). The ICCs for synovitis, erosions, OP and BML ranged from 0.66–1.00. Any/moderate-severe synovitis was seen in 98%/43% of joints on MRI, respectively, compared to 39% greyscale synovitis on US. BML was seen in 27% of the joints, OP in 77% and 99% of the joints on MRI and US, respectively. MRI was not correlated with US grayscale synovitis (Spearman's ρ 0.02, p=0.79) and only weakly with US OP (ρ 0.16, p=0.07). The correlation of MRI with radiographs was weak for OP and erosions (Spearman's ρ 0.35 (p<0.001) and 0.33 (p<0.001), respectively).

Pain was associated with the presence of moderate/severe synovitis (OR 2.4 (95%CI 0.1–3.2)), BML (OR 3.5 (95%CI 1.6–7.7)), erosions (OR 4.5 (95%CI 1.7–11.9)) and OP (OR 2.4 (95%CI 1.1–5.3)). Having BML on MRI is associated with J- or E-phase presence in that joint (ORs 5.0 (2.2–11.4) and 36.4 (5.1–260.3), respectively).

Conclusion: The OHOA-MRI scoring system is reproducible and valid. MRI detects more synovitis ompared to US, but less osteophytes. Presence of moderate/severe synovitis, BML, erosions and osteophytes are associated with pain per joint. BML is associated with having an (pre)erosive joint, suggesting that BML could be part of the process in EOA.

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MRI and Histologic Evidence for the Role of Synovitis in Bone Erosions in Erosive Osteoarthritis. Allen P. Anandarajah[1], Laura A. Paxton[2], Ellen Giampoli[3], Kenneth Badillo[3], Johnny Monu[3] and Christopher T. Ritchlin[4]. [1]Univ of Rochester Medical Ctr, Rochester, NY, [2]University of Rochester Strong Hospital, Rochester, NY, [3]University of Rochester Medical Ctr, Rochester, NY, [4]University of Rochester School of Medicine and Dentistry, Rochester, NY

Background/Purpose: Patients with erosive osteoarthritis (EOA) often develop disfiguring deformities and decline in hand function. Approximately 15% of patients with symptomatic hand OA have radiographic erosions but the relative contribution of synovitis, bone marrow edema (BME) and cartilage degradation in the development of EOA is poorly understood. To examine the role of synovitis in this disease we reviewed magnetic resonance images (MRI) and histologic data in a cohort of EOA patients.

Methods: The medical records from a cohort of 107 EOA patients were reviewed for MRI of hands and for synovial biopsies regardless of the joint or presence of erosions. The MRIs were assessed for the presence of synovitis, BME, osteophytes, erosions, joint effusions and subchondral cysts in all proximal (PIP) (5) and the second to fourth distal (DIP) (4) joints, by 2 musculoskeletal radiologists. Tissue specimens were examined for the presence of synovitis, inflammatory cells, new bone formation and cartilage pathology.

Results: A total of 11 patients had MRI of hands and 4 had biopsies (2 finger and 2 knees). The 11 MRIs were performed on 8 females and 3 males with a median age of 59 ± 13. All patients with MRI had evidence for progressive erosive disease on plain radiographs. A total of 54 PIPs and 44 DIPs were assessed for erosions, BME, osteophytes and subchondral cysts and 49 PIPs and 40 DIPs were assessed for synovitis and effusion. Erosions were noted in 29 PIP (54%) and 23 (53%) DIP joints, synovitis in 31 PIP (63%) and 14 DIP joints (35%), BME in 15 PIP (27%) and 11 DIP (25%) joints, osteophytes in 31 PIP (57%) and 25 DIP (57%), subchondral cysts in 25 PIP (46%) and 22 DIP (50%) joints and effusion in 4 PIP (8%) and none of the DIP joints. Erosions, synovitis and osteophytes were most frequently seen in the 3rd PIP and 5th DIP joints. Positive correlations were noted between the presence of synovitis and erosions (0.3) and the presence of BME and erosions (0.3). BME was noted more frequently near the central erosions.

A total of 4 biopsies, stained with haematoxylin and eosin, were retrieved. To date, 2 of the 4 biopsies, one from a finger with erosive disease and one from a knee joint have been analyzed and were compared with synovial biopsies from patients with rheumatoid arthritis (RA), by a pathologist. Histology revealed synovitis and new bone formation in both EOA specimens and increased inflammatory infiltrate. The frequency of inflammatory cells was however less than in patients with RA. A predominance of lymphocytes with few plasma cells were observed in EOA compared with abundant lymphoplasmacytic cell infiltrate in RA. The cartilage in EOA demonstrated central ossification, a finding not seen in RA.

Conclusion: Synovitis was a common finding on MRI and histology in patients with EOA and along with BME was associated with the presence of erosions on MRI. Osteophytes were also seen in most of the joints in patients with EOA and along with histologic new bone formation helped distinguish EOA from RA. Synovial inflammation was associated with bone erosions in EOA and was mainly lymphocytic. Future studies will determine if synovitis precedes bone erosions or is secondary to cartilage loss.

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Cartilage Damage in the Tibio-Femoral and Patello-Femoral Joints and Risk of Progression: Role of Prevalent Damage Severity – the MOST Study. Frank Roemer[1], David T. Felson[2], Ke Wang[1], Michel Crema[1], Monica D. Marra[1], Michael C. Nevitt[3], Yuqing Zhang[4], Cora E. Lewis[5], James Torner[6] and Ali Guermazi[7]. [1]Boston University, Boston, MA, [2]Department of Clinical Epidemiology, Boston University School of Public Health, Boston, MA, USA, Boston, MA, [3]University of California-San Francisco, San Francisco, CA, [4]Boston University School of Medicine, Boston, MA, [5]University of Alabama, Birmingham City, Birmingham, AL, [6]University of Iowa, Iowa City, Iowa City, IA, [7]Boston Medical Center, Boston, MA

Background/Purpose: Several studies suggest that one of the strongest predictors of subsequent cartilage loss seems to be prevalent cartilage damage. However, it is unknown if prevalent cartilage damage is only an intermediate for more severe subsequent damage or an independent predictor. Aims were to assess the risk of progressive cartilage loss for subregions with different grades of baseline cartilage damage severity in the tibio-femoral and patello-femoral joint and also to define baseline damage severity grade at highest risk for progression.

Methods: The Multicenter Osteoarthritis (MOST) Study is a longitudinal observational study of subjects with knee OA or at risk of OA. The MRI protocol included axial and sagittal proton density-weighted fat-suppressed and a coronal STIR sequence (1.0 T extremity system). MRIs were assessed semiquantitatively according to the modified WORMS scoring system, where cartilage is assessed on a scale from 0 to 6. Included were all knees with available baseline and 30 months MRIs. Ordinal logistic regression was used to estimate the risk of cartilage los in the same subregion at 30 months. Analyses were performed separately for the different baseline severity grades. Subregions without any associated articular pathology were assessed separately from subregions with associated pathology (i.e. bone marrow lesions, meniscal damage and meniscal extrusion). Analyses were performed on a whole knee basis, and for the tibio-femoral and patello-femoral joints separately. Additional adjustment was performed for possible confounders of cartilage loss.

Results: Altogether 18825 subregions of 1367 knees were included. Of these 786 (4.2 %) showed small focal superficial defects (=grade 2), 213 (1.1%) exhibited small focal full thickness defects (=grade 2.5), 3244 (17.2%) showed widespread superficial damage < 75% of subregion (=grade 3), 114 (6.1%) exhibited diffuse superficial damage >75% of subregion (=grade 4) and 1772 (9.4%) showed diffuse full thickness cartilage loss (grades 5 and 6). 6120 (32.5%) subregions exhibited adjacent pathology. Altogether 1508 (8.0%) subregions showed progressive cartilage loss at follow-up. Risk of progressive cartilage loss was markedly increased for subregions with any grade of prevalent cartilage damage (Figure 1). Focal superficial defects in subregions without adjacent pathology showed the highest risk of subsequent cartilage loss (adjusted odds ratio [aOR] 9.4, 95% confidence interval [95% C] 7.0–12.1). Results were comparable for subregions with adjacent subregional pathology.

Figure 1. Risk of cartilage loss at 30 months for subregions with normal cartilage and with different grades of prevalent baseline damage severity

Cartilage morphology status	Subregions without adjacent pathology			Subregions with adjacent pathology		
	TF and PF[1]	TF[1]	PF[2]	TF[1] and PF[2]	TF[1]	PF[2]
Reference: Grade 0 and 1 combined: Subregions with cartilage loss at FU (%)	262/10110 (2.6)	180/7286 (2.5)	82/2824 (2.9)	187/2586 (7.2)	172/2461 (7.0)	15/125 (12.0)
aOR[3] 95% CI p	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Grade 2.0: Subregions with cartilage loss at FU (%)	102/518 (19.7)	66/292 (22.6)	36/226 (15.9)	93/268 (34.7)	67/184 (36.4)	26/84 (31.0)
aOR[3] 95% CI	9.38 (7.12, 12.36)	11.3 (8.06, 16.0)	6.65 (4.30, 10.29)	6.99 (5.12, 9.53)	7.74 (5.43, 11.06)	3.15 (1.56, 6.35)
p	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*	<.0013*
Grade 2.5: Subregions with cartilage loss at FU (%)	14/127 (11.0)	11/103 (10.7)	3/24 (12.5)	25/86 (29.1)	23/70 (32.9)	2/16 (12.5)
aOR[3] 95% CI	4.80 (2.67, 8.64)	4.83 (2.49, 9.38)	5.00 (1.44, 17.39)	5.22 (3.11, 8.78)	6.49 (3.67, 11.48)	1.13 (0.23, 5.53)
p	<.0001*	<.0001*	0.01*	<.0001*	<.0001*	0.88
Grade 3: Subregions with cartilage loss at FU (%)	173/1558 (11.1)	106/753 (14.1)	67/805 (8.3)	395/1686 (23.4)	321/1230 (26.1)	74/456 (16.2)
aOR[3] 95% CI	4.70 (3.70, 5.98)	6.53 (4.78, 9.38)	3.02 (2.10, 4.34)	3.76 (3.01, 4.70)	4.38 (3.44, 5.57)	1.52 (0.85, 2.71)
p	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*	0.16
Grade 4: Subregions with cartilage loss at FU (%)	12/55 (21.8)	1/9 (11.1)	11/46 (23.9)	16/59 (27.1)	10/40 (25.0)	6/19 (31.6)
aOR[3] 95% CI	10.66 (5.51, 20.64)	4.94 (0.80, 30.58)	11.03 (5.37, 23.08)	4.14 (2.28, 7.50)	3.43 (1.62, 7.27)	3.66 (1.17, 11.47)
p	<.0001*	0.09	<.0001*	<.0001*	0.01*	0.03*
Grades 5 and 6 combined: Subregions with cartilage loss at FU (%)	29/337 (8.6)	11/148 (7.4)	18/189 (9.5)	200/1435 (13.9)	151/948 (15.9)	49/487 (10.1)
aOR[3] 95% CI	3.51 (2.28, 5.41)	3.27 (1.60, 6.71)	3.45 (1.96, 6.09)	1.89 (1.46, 2.44)	2.18 (1.62, 2.92)	0.98 (0.52, 1.84)
p	<.0001*	0.001	<.0001*	<.0001*	<.0001*	0.95

* significant at p <0.05
[1] adjacent pathology: meniscal damage and/or meniscal extrusion and/or bone marrow lesion
[2] adjacent pathology: bone marrow lesion
[3] adjusted for age, gender, BMI, malalignment, radiographic OA severity, synovitis, effusion
TF-tibio-femoral, PF - patello-femoral, FU - follow-up, aOR - adjusted odds ratio, 95% CI - 95% confidence interval

Conclusion: In comparison to subregions without cartilage damage, risk of subsequent cartilage loss is markedly increased for subregions with prevalent damage regardless of adjacent pathology. Small superficial defects have the highest risk of further deterioration in the tibio-femoral and patello-femoral joints.

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Prevalence of Cam and Pincer-Type Deformities on Hip MRI in a Swiss Female Population: A Cross-Sectional Study. Stephan Reichenbach[1], Peter Jüni[1], Stefan Werlen[2], Andreas Limacher[1], Christian W. Pfirrmann[3], Reinhold Ganz[1] and Michael Leunig[4]. [1]University of Bern, Bern, Switzerland, [2]Hospital Sonnenhof, Bern, Switzerland, [3]Balgrist University Hospital, Zurich, Switzerland, [4]Schulthess Clinic, Zurich, Switzerland

Background/Purpose: Femoroacetabular impingement (FAI) has been proposed to cause early osteoarthritis (OA) in the non-dysplastic hip. FAI usually occurs as one of two different types, either "cam" or "pincer". Cam impingement is caused by the presence of a cam-type deformity with a non-spherical femoral head and/or a decreased anterior head-neck offset. Pincer impingement results from increased acetabular depth with over-coverage of the femoral head, while the head-neck configuration may be normal.

We previously reported the prevalence of cam-type deformities in a young asymptomatic male population to be 24%. The prevalence of increased acetabular depth was 6%. The aim of this study was to determine the prevalences of both types of impingement as potential risk factors for hip OA in a quasi population-based cross-sectional cohort study of young females.

Methods: Study subjects were young females aged 18 to 19 attending grammar school or selected vocational schools for manual or non-manual occupations. Participants completed a set of questionnaires pertaining to pain, stiffness, and physical function, and internal rotation was measured reliably using a validated examination chair. A random sample of the examined participants was subsequently invited to obtain magnetic resonance images

(MRI) of the hip. Cam-type deformities were assessed semiquantitatively using scores from grades 0 to 3: 0=normal, 1=mild, 2=moderate, 3=severe. The depth of the acetabulum was defined as the distance (in mm) between the center of the femoral neck and the line connecting the anterior acetabular rim to the posterior acetabular rim. The value was positive if the center of the femoral neck was lateral to the line connecting the acetabular rim. Values ≤3 mm were considered to represent increased acetabular depth. Overall prevalence estimates with 95% confidence intervals (95% CI) accounted for the oversampling of participants with decreased (<40°) and increased (≥50°) internal rotation using post-stratification weights. Prevalences were calculated separately for participants with decreased, normal, and increased internal rotation.

Results: Subjects who underwent imaging included 80 asymptomatic participants with a mean age of 19.3 years and a mean body mass index of 21.2 kg/m^2. Grade 1 cam-type deformities were found in 22% (95% CI 13 to 34). No MRI showed evidence of a definite cam-type deformity (grade ≥2). The prevalence of increased acetabular depth was 10% (95% CI 5 to 19). This prevalence did not differ between participants with decreased internal rotation and those with normal or increased internal rotation (Table 1, p-value for trend 0.71).

Table 1. Prevalence of increased acetabular depth in the general female population

Internal rotation (IR)	Number of MRIs examined	Number with increased acetabular depth	Prevalence [%] of increased acetabular depth (95% CI)
IR < 40°	26	4	15 (6 to 35)
40° ≤ IR < 50°	30	2	7 (2 to 23)
50° ≤ IR	24	3	13 (4 to 32)
Overall	**80**	**9**	**10 (5 to 19)**

Conclusion: Definite cam-type deformities on MRI in young women are rare compared to men, whereas the prevalence of increased acetabular depth is higher, suggesting that FAI has different gender-related biomechanical mechanisms.

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Systemic Bone Mineral Density Change and Body Mass Index, but Not Bone Mineral Density Are Related to Knee Cartilage Loss in Knee Osteoarthritis. Ji Yeon Lee[1], Timothy E. McAlindon[1], Lori Lyn Price[1] and Eric Miller[2]. [1]Tufts Medical Center, Boston, MA, [2]Tufts University, Medford, MA

Background/Purpose: Longitudinal studies that examined BMI and BMD in relation to cartilage loss in KOA have generated rather inconsistent results. These could be due to the methods that these studies used to detect progression. Therefore, we conducted a longitudinal study to examine relationship of systemic BMD, BMD change, and BMI with progression of KOA using continuous outcome measurements that are sensitive to small changes and are not constrained by ceiling effects.

Methods: We studied participants in a double-blinded randomized controlled trial of vitamin D for KOA (Kellgren Lawrence grade 2–4). The treatment effect of vitamin D was null. BMD of the femoral neck was measured in g/cm^2 at baseline and 2 year visits. BMI was measured in kg/m^2 at baseline. 1.5 Tesla knee MRIs were obtained at baseline, 1 and 2 year follow-up visits. A single reader used ANALYZE© software to register baseline and follow-up knee MRIs for each participant, and segmented the femoral and tibial cartilage volumes (Intra-tester reliability ICCs were 0.96 & 0.90 for cross-sectional volume and volume loss). Using a MatLab (The MathWork, Natick, MA) custom program, cartilage thickness was derived from cartilage segmentation. We expressed cartilage volume % loss per year, femoral and tibial cartilage thickness loss per year as continuous outcomes. We used linear regression to evaluate the effect of BMI, femoral neck BMD and BMD change over 2 years as predictors of change, adjusting for possible confounders (age, sex, alignment status, and vitamin D treatment).

Results: Among 146 study participants, analyzable data were available from 124 for total cartilage volume %loss, 123 for femoral cartilage thickness change and 126 for tibial cartilage thickness change. Their mean age was 62.7yrs (sd 8.58), 61% were female, mean femoral neck BMD was 0.95g/cm^2 (sd 0.14), mean change of BMD over 2 years was −0.01 g/cm^2 (sd 0.04), mean baseline BMI was 30.3 kg/m^2 (sd 5.71), 48.8% had varus alignment,18.6% valgus; 52% received vitamin D. The mean cartilage volume loss per year was 2.25%, mean femoral cartilage thickness loss per year was 0.035 mm, and mean tibial cartilage thickness loss per year was 0.030 mm. No correlation was found between BMI and BMD (r=0.14, p=0.12). BMD was not associated with any cartilage parameters. However, BMD change and baseline BMI were both significantly related to cartilage volume loss in the univariate linear models (beta= −8.00, p=0.02 for BMD change; beta= 0.06, p=0. 007 for BMI), and this trend persisted when adjusted for potential confounders (see Table).

Table. Ajusted associations of BMI, BMD, BMD change with cartilage loss

	Cartilage volume loss per year(%)		Femoral cartilage thickness loss per year(mm)		Tibial cartilage thickness loss per year(mm)	
	Estimate	**Pr(>|t|)**	**Estimate**	**Pr(>|t|)**	**Estimate**	**Pr(>|t|)**
Model 1*						
BMI	0.06	0.005	0.0005	0.19	0.0009	0.08
Femoral BMD	−0.40	0.66	−0.003	0.84	−0.018	0.38
Model 2*						
BMI	0.07	0.005	0.0006	0.14	0.0009	0.09
BMD change	−6.64	0.06	−0.086	0.17	−0.143	0.06

* Adjusted for age, sex, alignment status and treatment group.

Conclusion: We have confirmed that greater BMI predicts cartilage volume loss in knee OA. We also found a modest association of cartilage volume loss with longitudinal loss of femoral neck BMD but not baseline BMD. These findings highlight the need to intervene on body weight to reduce progression of knee OA, and also suggest a role for interventions on bone loss.

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Adiposity and Serum Inflammatory Markers Are Associated with Increases in Knee Pain Over 5 Years in Old Adults. Chang-Hai Ding[1], Oliver Stannus[2], Flavia Cicuttini[3] and Graeme Jones[2]. [1]University of Tasmania & Monash University, Hobart, Australia, [2]University of Tasmania, Hobart, Australia, [3]Monash University, Central and Eastern Clinical School, Melbourne, Australia

Background/Purpose: The associations between adiposity, inflammation and increase in knee pain over time are uncertain. This study aimed to determine if body fat and serum levels of inflammatory markers were associated with change in knee pain over 5 years in older adults.

Methods: A total of 755 randomly selected subjects (mean 62 years, range 51–81, 50% female) were studied at baseline, 2.6 and 5 years later. Knee pain (on flat surface, going up/down stairs, at night, sitting/lying and standing upright) at baseline and 5 years was assessed using WOMAC. Fat-suppressed MRI of the right knee was performed to determine knee cartilage volume and defects at baseline and 2.6 years. Fat mass and lean mass (both in kg) were measured by a Hologic Delphi dual X-ray absorptiometry (DXA) scanner. In first 149 subjects, serum levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6 and high-sensitivity C-reactive protein (hs-CRP) were measured by radioimmunoassay at baseline and 2.6 years.

Results: In multivariable analysis, increase in total knee pain score over 5 years was significantly and positively associated with female sex, knee radiographic osteoarthritis, medial tibiofemoral cartilage defects, lateral tibiofemoral cartilage defects, change in medial cartilage defects over 2.6 years and loss of medial tibial cartilage volume over 2.6 years. Increase in knee pain was positively associated with the adiposity measures including weight (OR = 1.03 per kg, P<0.001), body mass index (OR=1.07 per kg/m^2, P=0.004), percentage body fat (OR = 1.05 per %, P=0.019), percentage trunk fat (OR = 1.05 per %, P=0.007), waist-hip ratio (OR=32.72, P=0.012) and waist circumference (OR=1.03 per cm, P<0.001), but negatively associated with percentage total lean mass (OR=0.96 per %, P=0.009). Increase in knee pain was also associated with baseline TNF- α (OR=1.15, P=0.046) and change in TNF- α over 2.6 years (OR=1.52, P=0.046). When change in knee pain was used as the outcome measure, both baseline (β=0.27per mL/pg, P=0.029) and change per annum (β=0.91 per mL/pg, P=0.010) in TNF-α were positively associated with change in total knee pain. In addition, baseline IL-6 levels were positively associated with change in the standing sub-scale of pain (β=0.18per mL/pg, P=0.046), and baseline hs-CRP was positively associated with change in total knee pain (β=0.38 per ml/pg, P=0.048), as well as change in the sub-scales for pain while lying in bed (β=0.14 per mL/pg, P=0.019) and sitting (β=0.13 per mL/pg, P=0.004).

Conclusion: Multiple factors contribute to an increase in knee pain over 5 years. This is the first study to report that adiposity and inflammatory markers predict increased knee pain, while total body lean mass is protective against an increase in knee pain in older adults.

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Serum Adipokines in End-Stage Osteoarthritis; Comparison with Healthy Controls and Relations with Intra-Articular Joint Characteristics. T.N. de Boer[1], Simon C. Mastbergen[1], A.M. Huisman[2], J.W.J. Bijlsma[1] and F.P.J.G. Lafeber[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Sint Franciscus Gasthuis, Rotterdam, Netherlands

Background/Purpose: Obesity is an important risk factor for osteoarthritis (OA). Body mass index (BMI) is strongly associated with the prevalence and incidence of knee OA. It is established that metabolic factors exert an extra systemic effect on top of the mechanical effect of overweight in OA. Adipose tissue is considered an endocrine tissue releasing cytokines (IL-1β and TNFα) and adipokines (adiponectin, leptin, and resistin). Adipokines have been reported to be involved in the disease process. The exact mechanisms by which adipokines exert their effects in OA are still unclear. The aim of this study is to compare serum adipokines in end-stage OA with healthy controls and to evaluate the relationship of serum adipokines with actual cartilage damage and synovial inflammation in the affected joint.

Methods: 172 severe knee OA patients selected for total knee replacement (TKR) surgery were included. Serum was collected shortly before TKR surgery. Serum was also collected from a healthy control (HC) group of 132 individuals without any sign of radiographic knee OA. Characteristics were collected and serum adipokine (adiponectin, leptin and resistin) levels measured by ELISA. Of the OA patients cartilage and synovial tissue were collected at TKR surgery. Histological damage, proteoglycan turnover, histological inflammation, IL-1β and TNFα production were measured in cartilage and synovium. The study was conducted according to the declaration of Helsinki and received ethics approval of the hospital.

Results: Adipokine levels were higher in OA compared to HC, even after correction for age and BMI. In both OA and HC differences between men and women were seen: Adiponectin and leptin levels were higher in women than in men (Adiponectin: 24$\pm$13 vs. 14$\pm$7 μg/ml, p=0.000 and leptin: 90$\pm$64 vs. 33$\pm$28 ng/ml, p=0.000 in OA and 22$\pm$11 vs. 5.3$\pm$3 ng/ml, p=0.000 in HC). Resistin levels did not differ between women and men. In OA adiponectin levels were inversely related with BMI (R=-0.218, p=0.004) and positively correlated with age (R=0.283, p=0.000). Leptin levels showed a positive correlation with BMI (R=0.604, p=0.004 and R=0.495, p=0.000, for OA and HC, resp.). Resistin levels were inversely related with age (R=-0.206, p=0.012). In OA all adipokines correlated positively with synovial inflammation. Adiponectin, leptin and resistin with synovial tissue IL-1β production (p=0.02 all (p=0.04 for women), p=0.09 all, and p=0.02 men, resp.). Leptin and resistin with synovial tissue histological inflammation (p=0.06 all (p=0.02 in men) and p=0.09 all, resp.). And resistin with TNFα (p=0.09 all, p=0.02 for men). None of the adipokines were associated with histological or biochemical cartilage characteristics.

Conclusion: In this study we demonstrate that adipokine levels are significantly increased in end-stage knee OA patients considered for TKR surgery compared to a healthy control group. Also a clear relation of these adipokines with age and with BMI is demonstrated and a clear difference between men and women. Most interestingly, the serum (peripheral) adipokines correlated with local parameters of inflammation of OA joints. This implies that systemically measured adipokines play a role locally at the joint level in the OA disease process.

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Synovial Fluid Leptin Levels and Joint Pain in End-Stage Osteoarthritis: A Potential Explanation for Increased Pain in Women and in Obese Patients. Anne Lübbeke[1], Axel Finckh[2], Gabor J. Puskas[1], Domizio Suva[1], Alexandre Lädermann[1], Sylvette Bas[2], Daniel Fritschy[1], Cem Gabay[1] and Pierre Hoffmeyer[1]. [1]Geneva University Hospitals, Geneva, Switzerland, [2]University Hospital of Geneva, Geneva, Switzerland

Background/Purpose: Synovial leptin levels are increased in osteoarthritis (OA), particularly in women and in obese patients. Furthermore, in these two patients groups higher pain levels before joint replacement have been described. A possible link between obesity, adipocytokines and pain severity has been suggested in studies on weight loss. Weight reduction has consistently resulted in decreased joint pain in patients with OA, and in addition, weight loss decreased blood leptin levels.

We hypothesized that synovial fluid (SF) leptin concentrations correlate with pain severity, and thus mediate the association between increased joint pain and (1) female gender and (2) obesity

Methods: Cross-sectional study including all patients with primary hip and knee OA undergoing total joint arthroplasty in a large orthopedic center, between January and December 2010. On the day of intervention, SF and serum were sampled and leptin concentrations were assessed using an ELISA kit. The main outcome was severity of joint pain measured preoperatively with the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) and the VAS pain scale.

Results: 250 patients were included, 134 total hip and 116 total knee arthroplasties. Mean ($\pm$SD) age was 72 ($\pm$9) years, 62% were women (n=155). Mean BMI was 27.3 kg/m^2 in the hip and 29.1 kg/m^2 in the knee group. Mean SF leptin levels were 22.5 ($\pm$ 25.3) ng/ml in women and 5.3 ($\pm$5.5) ng/ml in men (p<0.001). SF leptin levels strongly correlated with BMI (r=0.518) and serum leptin levels (r=0.910). SF leptin concentrations > 19.6 ng/ml (highest quartile) were significantly associated with increased pain levels on both WOMAC and VAS pain scale (see Table). The association remained unchanged after adjusting for presence of contra-lateral arthritic joints and diabetes (WOMAC adjusted mean difference $-$10.8 (95% CI: $-$16.5; $-$5.1) and VAS pain adjusted mean difference 0.7 (95% CI: 0.1; 1.3)). Significant associations between increased joint pain and (1) female gender and (2) BMI observed in univariate analysis disappeared after adjusting for FS leptin concentrations, suggesting that these associations are mediated by leptin levels.

Patient characteristics and preoperative pain levels according to leptin concentration (in quartiles*) in synovial fluid of patients undergoing hip or knee arthroplasty (n=250)

	Leptin 1st quartile ≤3.2 ng/ml (n=61)	Leptin 2nd quartile 3.21–9.1 ng/ml (n=62)	Leptin 3rd quartile 9.11–19.6 ng/ml (n=65)	Leptin 4th quartile >19.6 ng/ml (n=62)	p –value*	4th vs. other quartiles:** RR (95% CI) Mean difference (95% CI)
Men (%)	43 (45.3)	35 (36.8)	14 (14.7)	**3 (3.2)**		
Women (%)	18 (11.6)	27 (17.4)	51 (32.9)	**59 (38.1)**	<0.001	12.1 (3.9; 37.4)
Age, mean, SD	72.7 (±8.9)	71.3 (±10.0)	73.1 (±9.2)	**70.9 (±8.8)**	0.535	−1.4 (−4.1; 1.2)
BMI, mean, SD	24.8 (±3.5)	27.6 (±4.1)	27.8 (±3.5)	**32.2 (±5.4)**	<0.001	5.5 (4.0; 6.9)
BMI ≥ 30kg/m^2 (%)	5 (7.1)	12 (17.1)	16 (22.9)	**37 (52.9)**	<0.001	3.8 (2.5; 5.8)
<>Hip arthroplasty (%)	34 (25.4)	40 (29.9)	36 (26.9)	**24 (17.9)**		
Knee arthroplasty (%)	27 (23.3)	22 (19.0)	29 (25.0)	**38 (32.8)**	0.034	1.8 (1.2; 2.9)
Arthritic contralateral joint (%)	30 (21.1)	35 (24.6)	36 (25.4)	**41 (28.9)**	0.079	1.5 (0.9; 2.4)
Diabetes (%)	10 (29.4)	12 (35.3)	8 (23.5)	**4 (6.5)**	0.059	0.4 (0.2; 1.1)
Leptin blood level, mean, SD	4.1 (±2.7)	12.3 (±7.4)	27.2 (±14.2)	**68.9 (±45.6)**	<0.001	53.6 (45.7; 61.5)
Pain assessment						
WOMAC pain, mean, SD	43.8 (±17.9)	38.4 (±18.7)	41.9 (±18.9)	**31.0 (±15.0)**	0.004	−10.5 (−16.1; −4.9)
VAS pain, mean, SD	5.8 (±1.7)	6.0 (±1.9)	5.8 (±2.0)	**6.5 (±1.8)**	0.079	0.6 (0.1; 1.2)

* p-value obtained with use of linear regression (leptin, continuous as dependent variable) for continuous variables and with use of chi-squared test for trend for categorical variables
** The 4th quartile was compared to the other three quartiles taken together. Relative risks (RR) and their 95% CIs were presented for categorical variables and mean differences and their 95% CIs for continuous variables.

Conclusion: Joint pain is strongly associated with SF leptin concentrations. Increased pain observed in women and in obese patients may be related to high leptin levels.

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Comparison of Cytokine Levels in the Synovial Joint Fluid Between Rapidly Destructive Coxopathy, Hip Osteoarthritis, Rheumatoid Arthritis, and Hip Oseteonecrosis. Hirohito Abe[1], Takashi Sakai[1], Wataru Ando[2], Masaki Takao[1], Takashi Nishii[1], Nobuo Nakamura[3], Hideki Yoshikawa[1] and Nobuhiko Sugano[1]. [1]Osaka University Graduate School of Medicine, Suita, Osaka, Japan, [2]Kansai Rousai Hospital, Amagasaki, Japan, [3]Kyowakai Hospital, Suita, Japan

Background/Purpose: Rapidly destructive coxopathy (RDC) represents destruction of the femoral head and/or acetabulum within 6 to 12 months mostly in elderly females. RDC causes severe hip pain and disabilities and results in total hip arthroplasty (THA). Several conditions have been suggested as the primary causes of RDC, including increasing pelvic posterior inclination as a mechanical factor, and high serum concentration of MMP-3, MMP-9 as biological factors. However, the cytokine levels of the synovial joint fluid with RDC and other hip diseases have not been well documented. The purpose of this study is to determine the characteristics of the cytokine levels compared between RDC, hip osteoarthritis (OA), rheumatoid arthritis (RA), and hip oseteonecrosis (ON) using synovial joint fluid collected during THA.

Methods: 56 hips in 55 patients were investigated in this study. The mean age was 67.3 years (range; 25 to 85 years). They consisted of 9 males and 46 females. There were 22 hips with RDC, 13 hips with OA, 6 hips with RA, and 15 hips with ON which were divided into 6 hips with collapsed ON and 9 hips with terminal ON. The diagnosis of RDC was done on plain radiographs or MRI of the hip, which showed diffuse low signal intensity area in the femoral head and neck on T1WI, and high signal intensity area on T2WI with or without rapidly destructive findings. All hips with RDC and terminal ON showed widespread obliteration of the joint space. The synovial joint fluid was collected during THA and was stored at −80°C. The cytokine levels including IL-1β, IL-6, IL-8, and TNF-α were measured by using Homogenous Time Resolved Fluorescense (HTRF). We compared the cytokine levels between hip diseases. In ON group, we also compared the cytokine level between the collapsed ON and the terminal ON to investigate the influence of the severity of joint destruction on the cytokine level. The statistical analysis was performed by Kruskal-Wallis test and Mann-Whitney U test. The level of significance was set at $p<0.05$.

Results: The mean IL-8 level (pg/ml) was 3536±2678 in RDC, 1521±1319 in OA, 2171±1176 in RA, and 2885±3232 in ON, respectively. IL-8 level in RDC were significantly higher than that in OA ($p=0.02$). There were no differences in IL-1β and TNF-α between all the hip disease categories. IL-6 level (pg/ml) in the collapsed ON was significantly higher than that in the terminal ON (collapsed ON: 2478±2026 vs terminal ON: 707±708, $p=0.03$).

Conclusion: There were few reports concerning the cytokine levels of the synovial joint fluid in hip diseases. In the present study, IL-8 levels were significantly higher in RDC hips. Although some studies had reported that knee with RA had significantly higher level of IL-8 than that with OA, there was no difference between RA and OA in the present study. Some studies have also reported that the severity of joint destruction had influenced on the Il-1β level of the joint fluid of the knee. In the ON group, IL-6 level in the collapsed ON was significantly higher than that in the terminal ON. The staging of the hip joint destruction have influenced on the cytokine level of the joint fluid of the hip. IL-8 in synovial joint fluid may be useful to diagnose the RDC.

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Presence of Gout Is Associated with Increased Osteoarthritis Prevalence and Severity. Rennie N. G. Howard[1], Jonathan Samuels[1], Soterios Gyftopoulos[1], Svetlana Krasnokutsky[2], Joseph Leung[3], Christopher Swearingen[4] and Michael H. Pillinger[1]. [1]NYU Langone Medical Center/NYU Hospital for Joint Diseases, New York, NY, [2]NYU Hospital for Joint Disease, New York, NY, [3]New York, NY, [4]University of Arkansas for Medical Sciences, Little Rock, AR

Background/Purpose: There is a pressing need to identify biomarkers of osteoarthritis (OA) presence/progression, and remediable risk factors that may promote OA therapeutic approaches. Uric acid (UA) in both soluble and crystalline forms is biologically active, and gout often occurs in a similar age group as OA. We tested whether subjects with gout or asymptomatic hyperuricemia (AH) have increased prevalence/severity of knee OA.

Methods: Male subjects age 55–85 were consecutively recruited during primary care visits to an urban VA hospital. Subjects were interviewed and assessed for gout (ACR Clinical Criteria). Background medical histories and serum UA levels were obtained. Exclusion criteria included non-gout inflammatory arthritis, psoriasis, inflammatory bowel disease, hemodialysis, severe knee trauma or knee replacement. Enrolled subjects were categorized into 3 groups: gout, AH (no gout, UA ≥ 6.9 mg/dL), and controls (no gout, UA ≤ 6.8 mg/dL). On a 2nd visit subjects underwent OA assessment: knee pain history, WOMAC and RAPID3 surveys, musculoskeletal exam, weight-bearing bilateral knee X-ray, and knee/MTP ultrasound (US) to assess MSU crystal deposition. OA was diagnosed using ACR Clinical and Clinical/Radiographic criteria, and differences in summary statistics between groups were estimated using the Kruskal-Wallis and Chi-square tests. Images were read on a blinded basis (US by 2 independent reviewers, X-rays by a musculoskeletal radiologist).

Results: Of 129 subjects screened, 119 were enrolled and 75 completed both visits: 25 gout, 25 AH, and 25 controls. Mean age/race were similar among all groups, but BMI was highest in the gout group. 68% of gout, 52% of AH and 28% of control subjects had knee OA by Clinical/Radiographic criteria (gout vs control, $p=0.017$). The unadjusted odds ratio for knee OA in gout vs control was 5.46 (95% CI [1.63, 18.36], $p=0.040$), and remained significant after BMI adjustment (OR 3.80, 95% CI: [1.06, 13.57, $p=0.040$]). Mean Kellgren-Lawrence grades were significantly higher in gout vs control for right ($p=0.013$) and left ($p=0.049$) knees. Bilateral knee OA was also more common in the gout group. WOMAC (knee pain, stiffness and functional limitation) and RAPID3 scores among gout subjects were higher compared to the other groups, but not statistically different. Crystal deposition detected by US was more common in subjects with vs without knee OA (40.5% vs 16.2%, $p=0.020$), but was not associated with OA in specific joints. Subjects with AH had knee OA prevalence/severity intermediate between control and gout patients.

Conclusion: Our data suggest that presence of gout puts subjects at significantly higher risk for increased knee OA prevalence and severity. AH may independently convey knee OA risk but our sample size was inadequate for statistical confirmation. MSU crystal deposition as detected by US was also significantly higher in subjects with knee OA. Presence of gout or AH, as well as MSU crystal deposition on US, could potentially serve as useful biomarkers for knee OA risk, severity and progression. The possibility that gout and/or AH might contribute to OA risk suggests that UA management should be assessed as a potential intervention in OA patients.

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Expression of Human Endogenous Retrovirus Herv-K18 In Osteoarthritis Patients. Benjamin Fernandez-Gutierrez[1], Marta Garcia-Montojo[2], Jose Hoyas[1], Inmaculada Dominguez-Mozo[2], Esther Villafuertes[1], Pilar Tornero-Esteban[1], Ana Arias-Leal[2], Lydia Abasolo[1], Roberto Alvarez-Lafuente[2] and Jose Ramon Lamas[2]. [1]Department of Rheumatology, Hospital Clinico San Carlos, Madrid, Spain, [2]Hospital clinico San Carlos, Madrid, Spain

Background/Purpose: The etiology of OA remains to be completely understood; however, epidemiological studies have revealed that there are both endogenous and exogenous risk factors for OA. Human endogenous retroviruses (HERV) are assumed to be remnants of ancient exogenous retroviral infections of our ancestors germ-line cells, DNA, resulting in vertical transmission in a Mendelian fashion. HERV sequences constitute approximately 3–8% of the human genome. These include endogenous retrovirus 3 (ERV-3) [4], HERV-W [5], and a number of members of the HERV-K family, suggesting the potential for involvement in autoimmunity [6]. Thus, it has been suggested that ERV-3 may provide a biomarker for osteoarthritis [7]; also, the HERV-K family, that contains some of the most active retroviral elements in the human genome, it has been related with active rheumatoid arthritis [8]. Recently, it has been described a superantigen activity for HERV-K18 [9], and a significantly elevated expression in patients with juvenile rheumatoid arthritis has been found [10].

The purpose of this study was to evaluate the involvement of HERV-K18 in Osteoarthritis (OA), through the analysis of the expression levels in OA patients in comparison with healthy controls, and through the analysis of different qualitative and quantitative clinical variables.

Methods: One hundred and thirteen OA patients and 62 controls were included. To analyze HERV-K18 mRNA expression, quantitative RT-PCR was performed; the transcriptional expression was expressed in a relative manner as a normalization ratio (NR), and for controls were assigned a NR=1. The Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), Lequesne Index, and the Stanford Health Assessment Questionnaire (HAQ) were analyzed in relation to the expression levels of HERV-K18.

Results: We found that 54/113 (47.8%) of OA patients and 22/62 (35.5%) of controls had detectable expression levels of HERV-K18. We found statistical significant differences when we compared the results of the Womac Index, Lequesne Index for knee and hip, and HAQ between OA patients with higher expression (NR>10) vs. OA patients without HERV-K18 expression ($p=0.0003$, $p=0.0005$, $p=0.002$, and $p=0.05$, respectively), and also when the comparison was made between OA patients with higher expression (NR>10) vs. OA patients with low expression of HERV-K18 (NR=1) for the Womac Index, and Lequesne Index for knee and hip ($p=0.002$, $p=0.013$, and $p=0.006$, respectively).

Conclusion: It seems to be a relation between the health status measurement systems and severity index for OA with the levels of expression of HERV-K18. These results suggest the possible involvement of HERV-K18 in the etiopathogenesis of the disease.

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Varus Thrust and Knee Frontal Plane Dynamic Motion in Persons with Knee Osteoarthritis. Alison Chang, Joan Chmiel, Kirsten Moisio, Orit Almagor, Yunhui Zhang, September Cahue, Clifton Saurel and Leena Sharma. Northwestern University, Chicago, IL

Background/Purpose: Varus thrust visualized during walking is associated with a greater peak external knee adduction moment and an increased likelihood of medial knee osteoarthritis (OA) disease progression. Gait observation for a thrust is a simple and inexpensive clinical screening tool that enables identification of some individuals at higher risk for disease progression. How observed varus thrust relates to quantitative gait kinematic data is

not known. We hypothesized that varus thrust presence is associated with greater knee frontal plane dynamic movement during the stance phase of gait.

Methods: Participants all had knee OA (by osteophyte presence) in at least one knee. Knee motion in the frontal plane during ambulation on a 35 × 4 foot walkway was captured at a rate of 120 Hz, using external passive reflective markers and an 8-camera Digital Real-Time Eagle motion analysis system. Frontal plane motion was measured using the peak knee varus angle during stance (and each subdivision of stance), peak knee varus angular velocity, and total knee varus-valgus motion during stance. Following a protocol and blinded to the knee frontal plane motion data, trained examiners assessed participants for varus thrust presence during ambulation in a 10-meter walkway. To examine the relationship between varus thrust and frontal plane knee dynamic motion, we used multivariable regression analysis with generalized estimating equations (GEE) to account for correlations between knees within persons; presence of thrust was coded using an indicator variable. Models were adjusted for age, gender, BMI, and gait speed. Findings are reported as mean differences between knees with vs. without thrust and 95% confidence intervals (CIs).

Results: The study sample consisted of 236 persons [mean age 64.9 (SD 10.4), BMI 28.5 (5.5), 179 (76%) women] contributing 440 knees for analysis. 82 knees (19%) had a definite varus thrust. Table 1 shows the mean (SD) for each frontal knee motion measure. As shown in Table 2, knees with varus thrust had a greater peak knee varus angle during the entire stance and each sub-phase as well as greater peak knee varus angular velocity.

Table 1. Means (SDs) Knee Frontal Plane Quantitative Motion Measures during Gait by Varus Thrust Status

Measures of frontal plane motion during gait	All knees n = 440 Mean (SD)	Knees *with* varus thrust n = 82 Mean (SD)	Knees *without* varus thrust n = 358 Mean (SD)
Peak knee varus angle during stance (°)	1.77 (1.28)	2.51 (1.55)	1.60 (1.15)
Peak knee varus angle during early stance (°)	0.72 (0.98)	1.55 (1.29)	0.53 (0.79)
Peak knee varus angle during mid-stance (°)	1.32 (1.50)	2.27 (1.64)	1.10 (1.38)
Peak knee varus angle during terminal stance (°)	1.42 (1.22)	2.03 (1.47)	1.28 (1.11)
Peak knee varus angle during pre-swing (°)	−0.16 (1.51)	0.66 (1.67)	−0.35 (1.40)
Peak knee varus angular velocity (°/sec)	0.29 (0.16)	0.36 (0.15)	0.28 (0.16)
Total knee varus-valgus range of motion (°)	8.69 (3.37)	8.53 (3.07)	8.72 (3.44)

Table 2. Estimated Differences in Means for Knee Frontal Plane Motion Measures Based on Presence vs. Absence of Varus Thrust, from the GEE Regression Models

Measures of frontal plane motion during gait	Difference* (95% confidence interval)		
	Unadjusted	Adjusted for age, gender, and BMI	Adjusted for age, gender, BMI, and gait speed
Peak knee varus angle during stance (°)	**0.91 (0.52, 1.30)**	**0.97 (0.56, 1.37)**	**0.98 (0.57, 1.38)**
Peak knee varus angle during early stance (°)	**1.02 (0.68, 1.35)**	**1.03 (0.69, 1.38)**	**1.04 (0.70, 1.38)**
Peak knee varus angle during mid-stance (°)	**1.16 (0.73, 1.60)**	**1.31 (0.85, 1.77)**	**1.30 (0.84, 1.77)**
Peak knee varus angle during terminal stance (°)	**0.75 (0.36, 1.14)**	**0.82 (0.42, 1.23)**	**0.83 (0.43, 1.23)**
Peak knee varus angle during pre-swing (°)	**1.01 (0.56, 1.45)**	**0.94 (0.48, 1.41)**	**0.94 (0.48, 1.41)**
Peak knee varus angular velocity (°/sec)	**0.08 (0.04, 0.12)**	**0.08 (0.04, 0.12)**	**0.08 (0.04, 0.12)**
Total knee varus-valgus range of motion (°)	−0.19 (−0.96, 0.58)	0.40 (−0.39, 1.20)	0.45 (−0.34, 1.23)

* Positive difference indicates greater mean value for knees with varus thrust vs. those without varus thrust. 95% CI that excludes 0 indicates a statistically significant difference between the groups.

Conclusion: Knees with a varus thrust during gait had greater peak knee varus angle and knee varus angular velocity during stance than knees without a thrust. These findings provide evidence that visualized varus thrust is associated with objective and quantitative measures of dynamic frontal plane instability.

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Shoe Flexibility Reduces Dynamic Joint Loads in Knee Osteoarthritis: Results of a Pilot Study. Najia Shakoor[1], Roy H. Lidtke[1], Louis F. Fogg[2], Markus A. Wimmer[1], Kharma C. Foucher[1], Rachel A. Mikolaitis[1] and Joel A. Block[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical Center

Background/Purpose: Recent evidence suggests that footwear can significantly affect dynamic knee loading and that flat, flexible shoes may result in lower knee loads compared to more supportive, stiff-soled shoes. Here, we further evaluate the longitudinal effects of flexible footwear ("mobility" shoe) compared to an identical stiff-soled "control" shoe on knee loading.

Methods: Subjects with radiographic (KL grades ≥ 2) and symptomatic (at least 30mm pain of 100mm scale while walking) medial compartment knee OA were recruited and randomized to receive a flexible soled shoe (mobility shoe) or identical appearing "control" shoe with stiffer sole. The stiffness of the soles was evaluated using a biomaterial testing system and was substantially different between the shoes. Investigators and participants were blinded to shoe assignment. Baseline gait analyses were performed using an optoelectronic camera system and multi-component force plate in subjects' "own shoes", study shoes, and barefoot. Subjects were instructed to wear the study shoes at least 6 hours/day for 6 days/week. Gait analysis was repeated at 6 and 12 weeks. The peak knee adduction moment (PAddM), a validated marker of medial compartment loading, was evaluated. Since this was a pilot trial and group sizes were not expected to demonstrate statistically significant differences, relative load reduction and effect sizes (ES) were evaluated between groups.

Results: 13 participants (10 women, mean age 54±8 years) were assigned to the control shoe and 8 (6 women, mean age 58±8 years) to the mobility shoe. Compared to their own shoes at baseline, the mobility group experienced an 11% reduction in the PAddM by 6 weeks (3.75±1.29 to 3.35±1.02 %BW*ht) while the control group experienced no change (3.28±0.69 to 3.29±0.65 %BW*ht), yielding an ES of 0.5 for the active intervention compared to control. By 12 weeks, the overall reduction in the PAddM was 20% for the mobility group (3.01±1.19 %BW*ht) while the control group also experienced a 13% reduction (2.85±0.66 %BW*ht) compared to their own shoes at baseline (ES=0.36). The Figure shows the changes in the PAddM over 12 weeks with participants own shoes, study shoes, and barefoot for both groups. The mobility shoe loads very closely approximated those during barefoot walking while the control shoe loads were similar to those of the participants own shoes.

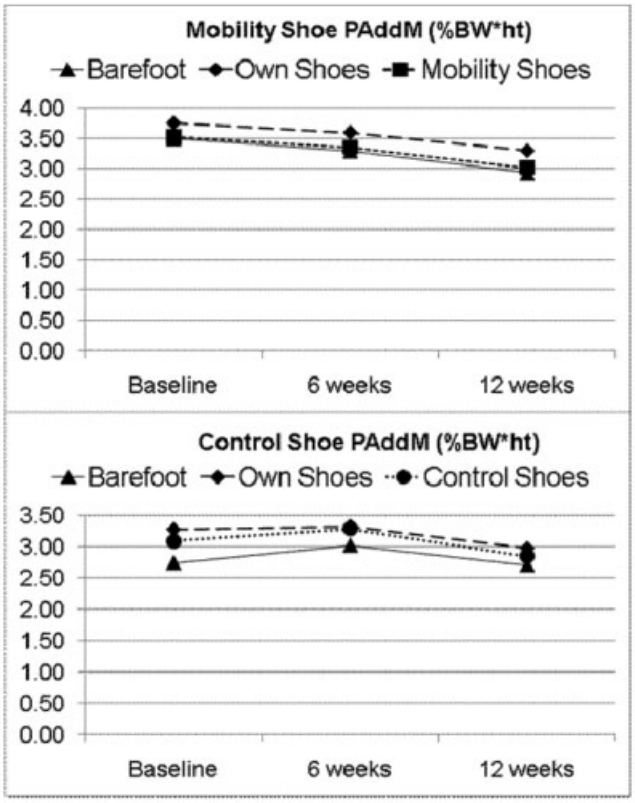

Figure. PAddM over 12 weeks in Mobility and Control groups

Conclusion: This pilot study suggests that shoe sole flexibility has a moderate effect in reducing knee loads in participants with knee OA. The "control" shoe in this study also yielded an expected load reduction compared to the participants own shoes, but this occurred entirely after 6 weeks and could be related to "wearing in" of the shoe sole stiffness with use. These results suggest that shoe sole flexibility may be one feature of footwear to consider when targeting biomechanical interventions for knee OA.

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Sagittal Plane Hip Motion During Gait and Function and Disability in Knee Osteoarthritis. Kirsten Moisio, Carmelita J. Colbert, Orit Almagor, Joan S. Chmiel, Alison Chang, Yunhui Zhang, September Cahue, Karen W. Hayes, Clifton Saurel and Leena Sharma. Northwestern University, Chicago, IL

Background/Purpose: Studies have established that sagittal plane range of knee motion during gait is associated with physical function in knee osteoarthritis (OA) (Maly 2006). The impact of knee OA on range of knee motion during gait may lead to a greater reliance on the hip. Even when knees are healthy, hips play a critical role in daily activities. With knee OA, the compensatory role of the hip may be considerable. In persons with knee OA, reduced range of hip motion during gait may be a result of shortness of two joint hip flexor muscles such as the rectus femoris or the tensor fascia lata-iliotibial band complex. We hypothesized that reduced sagittal plane range of hip motion during gait is associated with worse function and greater disability in persons with knee OA.

Methods: We studied 250 persons with knee OA (defined by osteophyte presence in at least one knee). Quantitative gait analysis was performed at the participant's self-selected normal walking speed to calculate kinematic and kinetic data for the hip and knee. Function was evaluated using: WOMAC function scale (higher score worse); Late Life Function Instrument (LL-FI), basic and advanced lower extremity function scales (lower score worse); and 20 m walk time. Disability was measured using: Late Life Disability Instrument (LL-DI), activity frequency and activity limitation scales (lower score worse). To evaluate the relationship between sagittal range of motion during gait (independent variable) and function or disability (dependent variables), linear regression models were used (analyzing the data from the limb with less sagittal motion). The results are reported as regression coefficients (slopes) and associated 95% confidence intervals (95% CIs), separately for each dynamic range of motion variable, adjusted for age, gender, and BMI.

Results: 250 persons had a mean age of 64.8 years (SD 10.2), BMI 28.6 kg/m^2 (5.6), and 76% were women. Mean (SD) sagittal range of hip motion during gait was 43.1° (5.6), and mean (SD) sagittal range of knee motion was 60.9° (5.5). The table shows adjusted coefficients per 5° (95% CI); significant values are bolded. Range of hip motion during gait was significantly associated with function by self-report, performance function, and both measures of disability; range of knee motion during gait was associated with function measures but not these measures of disability.

Table. Dynamic Sagittal Plane Hip and Knee Motion and Measures of Function and Disability

	WOMAC function scale	20 meter walk time	LL-FI, basic LE function	LL-FI, advanced LE function	LL-DI, activity frequency	LL-DI, activity limitation
Sagittal *hip* motion (°)	**−2.37 (−3.60, −1.15)**	**−1.53 (−1.77, −1.29)**	**3.04 (1.61, 4.47)**	**2.86 (1.54, 4.17)**	**1.37 (0.64, 2.11)**	**2.35 (0.95, 3.74)**
Sagittal *knee* motion (°)	**−1.75 (−3.06, −0.44)**	**−0.89 (−1.20, −0.58)**	1.49 (−0.06, 3.05)	**1.47 (0.02, 2.93)**	−0.50 (−1.30, 0.31)	1.12 (−0.40, 2.63)

Conclusion: Sagittal range of hip motion during gait was consistently associated with measures of function and disability, supporting a compensatory role played by the hip in the setting of knee OA. Longitudinal studies will help to elucidate whether range of hip motion during gait should be a rehabilitative target (e.g., stretching the hip flexors with concomitant strengthening of hip extensors, gait training) to potentially enhance outcome for persons with knee OA.

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Vibratory Sense in Patients At High Risk of Knee Osteoarthritis. Jonas B. Thorlund[1], Najia Shakoor[2], Eva Ageberg[3], Louise F. Sandal[1], Joel A. Block[2] and Ewa M. Roos[1]. [1]Research Unit for Musculoskeletal Function and Physiotherapy, Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark, [2]Rush University Medical Center, Chicago, IL, [3]Department of Health Sciences, Lund University, Lund, Sweden

Background/Purpose: Patients with knee osteoarthritis (OA) have impaired proprioception and vibratory sense. Vibratory sense is a separate yet closely related sensory pathway to proprioception, but is able to be more reliably tested than proprioception. It remains unclear if sensory deficits, which may alter neuromuscular activity and affect mechanical knee joint load, precede or follow as a consequence of OA. Young patients with previous anterior cruciate ligament injury are at high risk of knee OA. Furthermore, middle-aged patients with degenerative meniscus tears are suggested to be at high risk of knee OA or have early changes of knee OA. As such, they represent two distinctly different groups of patients to study early factors involved in OA pathogenesis. The aim of this study was to investigate the hypothesis that patients at high risk or with very early changes of knee OA would already display characteristic OA sensory deficits compared with age-matched controls.

Methods: *Patients:* 39 ACL injured patients (ACL) (24.0±5.2 yrs, BMI 24.0±2.9 kg/m^2, time since injury 21.9±21.6 month) were compared with 28 controls (ACL-C) (25.6±4.4 yrs, BMI 23.6±2.2 kg/m^2). Furthermore, 22 patients meniscectomized for a degenerative tear (APM) (49.6±4.8 yrs, BMI 24.7±2.7 kg/m^2, time since surgery 49.6±5.0 month) were compared with 25 controls (APM-C) (49.4±5.2 yrs, BMI 25.2±4.9 kg/m^2).

Self-reported outcomes: The Knee Injury and Osteoarthritis Score (KOOS) was used to assess knee-related pain, symptoms, function in daily life (ADL), sports and recreation function (Sport/Rec) and quality of life (QOL). Separate subscale scores from 0 to 100, worst to best, were calculated.

Vibratory perception threshold (VPT): VPT was assessed using a biothesiometer at two different sites (i.e. the most prominent point of the medial malleolus (MM) and the medial femoral condyle MFC)). The mean of two measurements was noted as the VPT (i.e. higher value indicates worse vibration sense).

Results: ACL self-reported substantially worse than ACL-C on all KOOS subscales ($p<0.001$). APM self-reported worse QOL ($p=0.007$) than APM-C and a tendency for more pain ($p=0.079$) and symptoms ($p=0.084$) than controls. No difference was observed between APM and APM-C in ADL and Sport/Rec. In contrast, no evidence of somatosensory deficit was observed in either the ACL or the APM group. Linear regression (adjusting for age and sex) showed no sign of sensory deficits (i.e. increased VPT score) in ACL compared with ACL-C at either of the two sites (MM: 9.4 (8.6 – 10.3) vs. 11.0 (9.7 – 12.3) volts, $p=0.034$ MFC: 15.7 (14.0 – 17.5) vs. 18.1 (15.8 – 20.4), $p=0.122$ in the patients and controls, respectively) or in APM compared with APM-C (MM: 14.4 (12.2 – 16.6) vs. 16.6 (13.6 – 19.6), $p=0.182$ MFC: 18.9 (15.9 – 21.9 vs. 23.0 (19.3 – 26.8), $p=0.092$ in the patients and controls, respectively).

Conclusion: These data do not support the hypothesis that sensory deficits precede overt OA in post-traumatic OA, at least in young ACL-injured patients and middle-aged meniscectomized patients at high risk or in the very early phase of knee OA. Further study is necessary to distinguish the time course of somatosensory loss in OA.

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Generalized Sensory Deficits in Radiographic Knee Osteoarthritis: The MOST Study. Najia Shakoor[1], Tuhina Neogi[2], David T. Felson[3], Jingbo Niu[3], Laura Frey-Law[4], Cora E. Lewis[5] and Michael C. Nevitt[6]. [1]Rush University Medical Center, Chicago, IL, [2]Boston University, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]University of Iowa, Iowa City, IA, [5]University of Alabama, Birmingham City, Birmingham, AL, [6]University of California-San Francisco, San Francisco, CA

Background/Purpose: Somatosensory abnormalities have been observed in knee osteoarthritis (OA). Whether sensory deficits are localized abnormalities at an affected OA joint versus part of a generalized neurologic process is still not clear. We evaluated vibratory sense in participants in a large cohort study of knee OA.

Methods: MOST is a NIH-funded longitudinal study of persons with symptomatic knee OA or at increased risk of OA. At the 60-month visit, participants underwent bilateral evaluation of vibratory perception threshold (VPT), using a biothesiometer. The applicator tip of the instrument was placed on the dorsum of the first MTP joint, the tibial tuberosity and, the radial styloid. The voltage was initially set at "0" and then increased by 1 volt/second until the participant acknowledged sensation and this was defined as the VPT. Participants had bilateral weight bearing x-rays which defined radiographic knee OA (RKOA) if Kellgren Lawrence grade was ≥2. Those with baseline total knee replacement or diabetes (participants taking medication for diabetes) were excluded in this analysis. In light of the large differences in VPT with age, participants were divided into age subgroups, < and ≥65 years. Because unaffected knees of persons with unilateral RKOA may be intermediate in VPT between knees with OA and knees without RKOA, for the lower extremity sites, a knee-based analysis was performed with three knee groups: 1) RKOA 2) contralateral "normal" knee of unilateral RKOA and 3) control knee (no RKOA in either knee). For the upper extremity (radial styloid), a person based analyses was performed (bilateral or unilateral RKOA and control). Linear regression was used to compare VPT between groups adjusted for age, BMI, gender, race and clinical site. In limb based analyses, GEE was used to account for between limb correlations.

Results: 977 women and 630 men with a mean age (SD) of 67±8 years were included. In men and women age ≥65, VPT was worse at the MTP and tibial tuberosity both in knees with RKOA as well as the contralateral "unaffected" knee of those with unilateral RKOA (Table). At the radial styloid, VPT was worse in those with unilateral but not bilateral RKOA, compared to controls (Table). There were no significant associations of VPT with RKOA status in men and women < 65 years of age.

Table

		Mean VPT (95% CI) adjusted for age, gender, race, BMI, and clinical site	P value (compared to control)
Men and Women Age ≥65 years			
MTP (n=knees)	RKOA (n=734)	23.7 (22.5, 25.9)	0.026
	Contralateral (n=207)	23.9 (22.1, 25.7)	0.048
	Controls (n=827)	22.0 (20.7, 23.3)	
Tibial tuberosity (n=knees)	RKOA (n=750)	25.8 (24.7, 26.8)	0.015
	Contralateral (n=209)	26.3 (24.6, 28.0)	0.019
	Controls (n=835)	24.0 (22.9, 25.2)	
Radial styloid (n=persons)	Bilateral RKOA (n=257)	9.0 (8.5, 9.5)	0.284
	Unilateral RKOA (n=210)	10.3 (9.7, 10.8)	0.004
	Controls (n=422)	9.4 (8.9, 9.8)	

Conclusion: In this cohort study, among persons age ≥65 vibratory sense was decreased at the affected as well as the unaffected contralateral limb of those with RKOA. Upper extremity vibration sense was also reduced in those with unilateral RKOA. These results suggest that alterations in vibratory sense may be part of a more generalized neurologic process in OA. The association of VPT with OA was only observed in those greater than 65 years of age in this cohort, suggesting that there may be an age-related component to sensory alterations in OA.

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The Impact of a Community-Based Aerobic Walking Program for Older Individuals with Mild to Moderate Knee Osteoarthritis: A Knowledge Translation Randomized Controlled Trial. Lucie Brosseau[1], George A. Wells[2], Glen Kenny[3], Robert Reid[4], Andreas Maetzel[5], Peter Tugwell[6], Maria Huijbregts[7], Carolyn McCullough[7], Lily Chen[8] and Gino De Angelis[9]. [1]University of Ottawa, Ottawa, ON, [2]Univ of Ottawa Faculty of Med, Ottawa, ON, [3]School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, Ottawa, ON K1N 6N5, Canada, Ottawa, ON, [4]University of Ottawa Heart Institute, Ottawa (Ontario), Canada, [5]Univ Health Network, Toronto, ON, [6]Institute of Population Health, Ottawa, ON, [7]Baycrest Centre, (Toronto), Canada, Toronto, ON, [8]University of Ottawa Heart Institute, Ottawa (Ontario), Canada, Ottawa, ON, [9]Univeristy of Ottawa, Ottawa, ON, Ottawa, ON

Background/Purpose: The objective of this study was to determine whether, after 3, 6, 9, 12, 15 and 18 months, the integration of a 12-month structured/supervised community-based aerobic walking program (SCAWP) with a behavioural strategy (WB) is more effective in improving compliance in older individuals with OA than a SCAWP only (W)? How does each of these treatment arms compare to a low cost, unsupervised/self-directed control group in which subjects receive an educational pamphlet on walking and OA (C) at 3, 6, 9, 12, 15 and 18 months?

Methods: A single-blind, randomized control trial was conducted which included 223 individuals with a confirmed diagnosis of OA of the knee. Subjects were randomized to one of three groups: 1) Group WB received an integrated behavioural strategy in combination with a structured community-based aerobic walking program (SCAWP) based on Ottawa Panel guidelines (implementation strategy); 2) Group W was provided with a SCAWP only(implementation strategy); 3) Group C was a self-directed and non structured walking program using an educational pamphlet only (dissemination strategy). All three comparative groups received an educational pamphlet on the benefits of regular walking, a logbook and a pedometer. The supervised walking sessions for groups W and WB were scheduled 3 times a week for 12 consecutive months.

Results: Individuals is the WB group demonstrated better short-term adherence when compared to the C group ($p<0.012$) after 3 months. For long term adherence (up to 6 to 12 month), WB had better adherence than the other two groups (W and C), but did not demonstrate statistical significance. As expected, all participants from each group showed improvements for all the clinical and quality of life (QoL) outcomes measured as the walking component has already proven to be effective. With the exception of a few situations, there was no statistical significance among the groups regarding clinical outcomes and QOL.

Conclusion: All participants from each group showed improvements. There is marginal significance when both types of SCAWP are combined (W +WB) to enhance long-term adherence, thereby producing greater improvements in QoL and functional status. The three KT strategies appear to be equivalent in implementing a walking program for older individuals with OA. This study was financially supported by the Canadian Institute of Health Research (CIHR) (CIHR # RCT-161122).

1091

Self-Efficacy Status Is Associated with Pain, Partially Mediating the Effect of Communication Style in Acupuncture Treatment for Knee Osteoarthritis. Grace H. Lo[1], Vanessa Cox[2], Richard L. Street Jr.[3] and Maria E. Suarez-Almazor[4]. [1]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, [2]UT MD Anderson Cancer Center, Houston, TX, [3]Texas A&M University, College Station, TX, [4]University of Texas. M.D Anderson Cancer Center, Houston, TX

Background/Purpose: In a recent study of acupuncture, high expectation style of communication of the interventionist showed greater improvement of pain in the treatment and sham acupuncture arms. Because the mind-body relationship is potentially important in acupuncture, self-efficacy status could be an important determinant of response to treatment. For this ancillary study, we had two aims: (1) to evaluate the relationship between self-efficacy and pain in knee OA and (2) to evaluate whether self-efficacy status is a mediator for the relationship between communication style and treatment effect.

Methods: This is an ancillary study of a 3 arm (traditional acupuncture, sham acupuncture, and wait list) randomized controlled trial for symptomatic knee OA. Those with a baseline and 3 month follow-up visit were included. Participants receiving either traditional or sham acupuncture were equally randomized to a high expectation and neutral communication style.

Self-Efficacy status was assessed using an abbreviated version of the Arthritis Self-Efficacy Questionnaire at the baseline and 3 month follow-up visit. Seven questions were averaged together to provide an overall self-efficacy score. Knee pain was assessed using the WOMAC pain subscale. The WOMAC pain scale was re-scaled to have a maximum score of 100. We performed correlations between baseline self-efficacy and pain; subsequently between change over 3 months of these two variables. For those in the traditional acupuncture and sham acupuncture arms, we then performed a linear regression with change in WOMAC pain score as the outcome, allocation of communication style as the predictor, and change in self-efficacy as a covariate. We repeated the model, including an interaction term between change in self-efficacy and communication style.

Results: Participants (N=485), 62% female, had a mean age of 64.7 (SD 9.2), BMI 32.4 (SD 7.5), baseline self-efficacy score 3.5 (SD 0.8) and baseline WOMAC pain 45.1 (SD 17.9). At baseline, the self-efficacy score was correlated with the WOMAC pain score, $R = -0.23$ ($p < 0.0001$). The mean change in self-efficacy over 3 months was 0.08 (SD 0.80), mean change in WOMAC pain was −12.9 (SD 18.3). Change in self-efficacy was correlated with change in WOMAC pain with an $R = -0.25$, $p < 0.0001$. In the linear regression model, allocation of communication style had a $p = 0.74$ while self-efficacy had a $p < 0.0001$. In the subsequent model, the interaction term had a $p = 0.20$.

Conclusion: In a randomized controlled trial of acupuncture for symptomatic knee OA, arthritis self-efficacy was highly correlated with knee pain scores cross-sectionally and longitudinally with higher self-efficacy being associated with lower pain severity level. As previously reported, communication style has an important effect on pain reduction. This effect may be partially mediated by change in arthritis self-efficacy. Identification ofadditional interventions effective in modifying self-efficacy may have the potential of improving pain in knee OA.

1092

Double Blind Cross-Over Study of the Efficacy of a Tart Cherry Juice Blend In Treatment of Osteoarthritis (OA) of the Knee. H. Ralph Schumacher[1], Sally W. Pullman-Mooar[2], Smita R. Gupta[3], Janet E. Dinnella[4], Rosa Kim[5] and Malachy McHugh[6]. [1]VA Medical Center and University of Pennsylvania, Philadelphia, PA, [2]Philadelphia Veterans Hospital, Philadelphia, PA, [3]University of Pennsylvania, Santa Monica, CA, [4]University of Pennsylvania, Philadelphia, PA, [5]The Children's Hospital of Philadelphia, Philadelphia, PA, [6]Nicholas Institute of Sports Medicine and Athletic Trauma, New York, NY

Background/Purpose: Consumption of cherries or cherry juice has been claimed to alleviate pain in arthritis, have anti-inflammatory and anti-oxidant

effects, alleviate muscle pain after exertion, and decrease pain (and uric acid levels) in gout. We tested effects of cherry juice (CJ) in patients with OA.

Methods: This double-blind cross-over study tested 6 weeks use of a tart cherry juice preparation (blended with apple juice to decrease tartness) given daily as 2 8-ounce bottles each containing the equivalent of 45 tart cherries. The comparator was Kool-aid (Kraft, Ryebrook, NY) with an added clouding agent to produce similar appearances. Both CJ and control servings contained 31 grams of sugar. Non-diabetic patients with Kellgren grade 2–3 OA and VAS pain of 4–9 were withdrawn from NSAIDS for at least 1 week. After 1 week washout treatments were crossed over for an additional 6 weeks. The primary outcome measures were WOMAC scores at 6 weeks; walking times, hsCRP levels, any acetaminophen use, and serum urate (because of past reports in gout) were also recorded.

Results: 59 patients were enrolled with 27 randomized to begin with CJ and 32 with the control. There were 53 completers for each group. WOMAC and pain scores decreased significantly after CJ but not after the control (Table 1), but differences between the treatments were not significant. Acetaminophen use and walking times did not change. hsCRP levels declined on CJ and rose on the control possibly related to initial withdrawal from NSAIDs and later withdrawal from CJ (Fig. 1) ($p<0.01$). WOMAC improvement correlated with hsCRP falls ($p<0.01$). Serum urate levels were mostly normal and did not change. 7 AEs lead to early discontinuations (4 with CJ and 3 control). AEs possibly related to CJ included one rash, and one "GI symptoms". 1 subject during the control treatment and 1 after the CJ had elevated blood sugar. Blinding was considered adequate. At the end of the CJ arm only 57% of subjects believed they were on CJ.

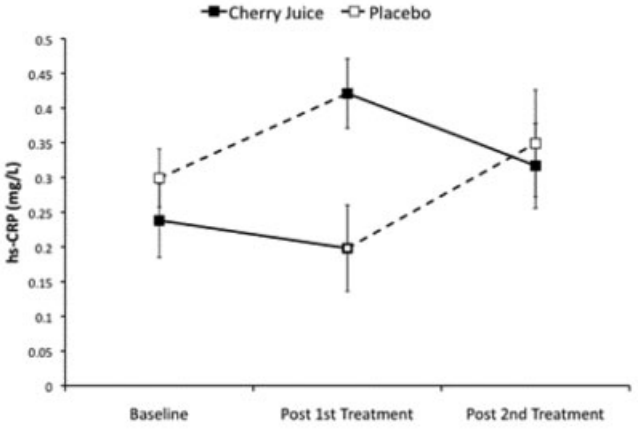

Figure 1. hsCRP values for cherry juice and placebo treatments displayed according to treatment order. Time by treatment order $P<0.01$. Mean±SE displayed.

Table 1. WOMAC Results

		Cherry Juice n=53	Placebo n=53	Difference n=49	P Value
WOMAC Score	Pre Treatment	46.1 ± 23.2	45.8 ± 23.5	1.7 ± 17.1	P=0.98
	Post Treatment	39.2 ± 25.1	43.0 ± 27.0	−2.7 ± 17.6	P=0.58
	Difference	6.9 ± 13.7	2.8 ± 16.9	4.4 ± 23.6	P=0.2*
	P Value	P=0.002	P=0.23	P=0.2*	
Pain Score	Pre Treatment	42.1 ± 22.9	41.5 ± 24.4	0.9 ± 18.0	P=0.99
	Post Treatment	36.3 ± 27	40.0 ± 26.6	−3.6 ± 20.5	P=0.46
	Difference	5.8 ± 17.7	1.5 ± 17.4	4.5 ± 27.3	P=0.20*
	P Value	P<0.05	P=0.99	P=0.20*	

mean±SD; *Significance of time by treatment interaction; other P values adjusted for planned pairwise comparisons (P values times 2).

Conclusion: Patients taking cherry juice had improved WOMAC scores and had significantly decreased hsCRP levels compared to controls. Both CJ and control were generally well tolerated.

1093

Fish Oil in Knee Osteoarthritis: A Two Year Randomized, Double-Blind Clinical Trial Comparing High Dose with Low Dose. Catherine L. Hill[1], Graeme Jones[2], Lynette March[3], Ruth Battersby[1], Kristen Hynes[2], Tanya Fedorova[4], Sue Lester[5], Susanna Proudman[6] and Leslie G. Cleland[6]. [1]The Queen Elizabeth Hospital, Woodville, Australia, [2]University of Tasmania, Hobart, Australia, [3]University of Sydney, Insitute of Bone and Joint Research, Royal North Shore Hospital, St Leonards NSW, Australia, [4]University of Sydney, St Leonards NSW, Australia, [5]Queen Elizabeth Hospital, Woodville South, Australia, [6]Royal Adelaide Hospital, Adelaide, Australia

Background/Purpose: Fish oil is widely used for the symptomatic treatment of osteoarthritis. However, its effect has not previously been investigated in an RCT. The objective of this study was to determine whether high dose fish oil is superior to low dose fish oil in the treatment of symptomatic knee osteoarthritis.

Methods: Investigator initiated, government funded, randomized, double-blind, multicenter 24 month trial. Patients older than 40 years, with knee OA as defined by the ACR clinical criteria, suffering from regular knee pain were randomized 1:1 to (1) high dose fish oil liquid (EPA 18% and DHA 12%) 15mL/day or (2) low dose fish oil (blend of fish oil and sunola oil in a ratio of 1:9) 15mL/day. Each oil was also flavored with citrus to provide a comparable taste and ensure masking. Prior to randomization, a 4- week run in period with a similar oil was performed to exclude patients who were intolerant to liquid fish oil. Baseline knee radiographs were scored according to OARSI atlas. The primary end point was change in pain scale (WOMAC index) from baseline to 3,6, 12 and 24 months. Secondary endpoints included changes in disability scale (WOMAC index) and OMERACT-OARSI Responder Index. Intention-to-treat analysis (LOCF) was undertaken.

Results: Participants (N=202) were 49% female, mean age 60.9 yrs (SE 0.7), mean BMI 29.0 (SE 4.7), with comparable baseline characteristics. There was significantly greater and earlier dropout in the high dose group (34.6%, median 3 months), compared to the low dose group (19.8%, median 7.5 months). In intention to treat analysis, both groups demonstrated a clinically important improvement in WOMAC pain and disability scores compared to baseline (Table 1, $p<0.003$). There was no difference between the 2 groups for change in WOMAC pain or function in the first year, however, the low dose group were superior to the high dose group for both pain and function at month 24. There was a trend towards better OARSI response at 24 months in the low dose group over the high dose group (Table 2, $p=0.06$).

Table 1.

	Change in WOMAC pain		Change in WOMAC disability	
	Low dose	High dose	Low dose	High dose
Month 3	−2.0	−2.5	−5.7	−8.3
Month 6	−3.2	−2.8	−8.6	−9.2
Month 9	−2.7	−2.7	−8.3	−10.7
Month 12	−4.5	−2.9	−13.8	−10.2
Month 18	−4.1	−2.5	−11.9	−8.9
Month 24	−5.2	−2.8	−12.7	−8.0

Table 2.

	PROPORTION OF RESPONDERS		
	low dose	high dose	p-value
Month 3	17%	22%	0.37
Month 6	21	23	0.66
Month 9	21	27	0.99
Month 12	32	28	0.27
Month 18	33	26	0.16
Month 24	39	27	0.06

Conclusion: Fish oil in either low dose or high dose improves the symptoms of knee OA. In contrast to RA, however, high dose fish oil was not superior to low dose particularly in the second year of treatment. This may reflect the effect of non-differential drop out rates or may suggest that low dose is sufficient for OA due to lower levels of inflammation.

1094

The Efficacy and Safety of Duloxetine Treatment in Older Patients with Osteoarthritis Knee Pain: A Post Hoc, Subgroup Analysis of Data From 2 Placebo-Controlled Trials. Joseph L. Micca[1], Richard C. Risser[2], Jonna Ahl[2] and Madelaine M. Wohlreich[2]. [1]Patient Centered Healthcare, Altanta, GA, [2]Lilly USA, Indianapolis, IN

Background/Purpose: Osteoarthritis (OA) of the knee is common in the elderly and a leading cause of disability. Alleviation of pain symptoms should be the focus of knee OA treatment. The purpose of this study was to examine the efficacy and safety of duloxetine (DLX) treatment in older aged patients with OA knee pain.

Methods: This was a post-hoc analysis of data from two 3-month randomized double-blind placebo-controlled trials in patients with symptomatic knee OA. In both studies, patients were randomized to DLX 60mg QD vs. placebo for 7 weeks. For the remaining 6 weeks, in Study I, DLX patients were re-randomized to receive either DLX 60 mg QD or 120 mg QD. In Study II, only DLX non-responders (defined as <30% improvement from baseline on Brief Pain Inventory 24-h average pain item score) had their dose increased to 120 mg. For each study, patients were stratified according to age:

<65 (younger) and ≥ 65 years (older). Dosing arms for each age group were: DLX 60 mg for patients who remained on this dose, and DLX 120 for patients who had their dose increased, and placebo. Pain severity (0–10) was assessed daily and recorded in patient diaries. Change in weekly average pain was analyzed with a mixed-models repeated measures model including terms up to and including the 3-way interaction between treatment, age group, and week, which assesses differential treatment effects between age groups over time. Treatment-emergent adverse events (TEAEs) were compared between treatments and subgroups using a logistic regression model including the terms up to and including the interaction between treatment and age group, which assesses the differential treatment effects between age groups.

Results: Across both studies, average age in years was 56 for younger subgroup and 72 for older subgroup. Average pain duration in younger and older groups was 7 and 10 years, respectively, and average baseline pain score was 6 in both age groups. The older subgroup included: DLX 60, n=68; DLX 120, n=35; PLA, n=136; and the younger subgroup included: DLX 60, n=95; DLX 120, n=41; PLA, n=154. After 13 weeks treatment, in Study I, there was significantly greater pain reduction in older patients with DLX 60 mg and 120 mg vs. PLA (−3.3 (60 mg) and −4.1 (120 mg) vs. −2.0; both p<.01). Among younger patients, those receiving DLX 120 had significantly greater pain reduction vs. PLA (−3.1 vs. −2.2; p=.03); improvement in pain did not differ from PLA in patients receiving DLX 60 mg. In Study II, all patients receiving DLX 60 mg had significantly greater improvement in pain vs. PLA (older: −3.2 vs. −1.8, p<.01; younger: −3.0 vs. −2.0, p<.01); improvement in pain did not differ from PLA in patients receiving DLX 120 mg. Among TEAEs with frequency ≥ 2% for DLX, only dizziness showed significant treatment by subgroup interaction (p =.022), with greater incidence over placebo in younger patients (6.6% vs 0.6%, p =.024) but not in the older patients (1.0% vs 3.2%, p =.292).

Conclusion: In older patients, duloxetine 60 mg/day for the treatment of OA knee pain was efficacious and well tolerated.

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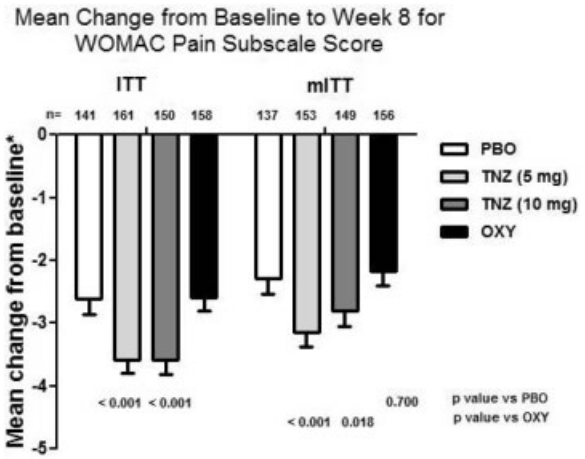
A Phase 3 Placebo- and Oxycodone-Controlled Study of Tanezumab in Adults with Osteoarthritis. James Fidelholtz[1], Marvin Tark[2], Egilius Spierings[3], Gernot Wolfram[4], Karen Annis[4], Michael D. Smith[4], Mark T. Brown[4] and Christine R. West[5]. [1]Hilltop Physicians, Inc., Cincinnati, OH, [2]Pain Solutions Treatment Centers, Marietta, GA, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Pfizer, Groton, CT, [5]Pfizer, Williamston, MI

Background/Purpose: A randomized, double-blind, placebo (PBO)- & active-controlled study, investigated efficacy & safety of tanezumab (TNZ), a humanized monoclonal antibody that specifically inhibits nerve growth factor, vs. oxycodone (OXY) continuous release as analgesic treatment for knee or hip osteoarthritis (OA).

Methods: Eligible patients had moderate to severe pain from knee or hip OA, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale score ≥5, WOMAC Physical Function subscale score ≥4, Patient Global Assessment of OA of 'Fair', 'Poor' or 'Very Poor', & Kellgren-Lawrence Grade of ≥2 at Baseline. Patients received up to two doses of TNZ (10 or 5 mg IV in 8-week intervals), OXY (10–40 mg every 12 hours; up-titrated & modified according to tolerability & pain relief) or PBO after appropriate prior analgesic pain medication washout. The primary endpoint was WOMAC Pain subscale score. The study was partially completed due to a FDA-imposed clinical hold so primary endpoint timing was amended from Week 16 to Week 8 to maximize planned analyses. Primary efficacy comparisons of TNZ vs. PBO were made in the intent-to-treat population (ITT; patients who received ≥1 IV injection) whereas comparisons of TNZ vs. OXY & OXY vs. PBO were conducted on the modified intent-to-treat population (mITT; all ITT patients with Week 8 visit or discontinued on or before clinical hold). Incidence of adverse events (AEs) was assessed.

Results: Both TNZ doses (p<0.001), but not OXY (p=0.700) resulted in significant improvements in WOMAC Pain subscale vs. PBO at Week 8 (Figure). WOMAC Pain subscale improvements with TNZ 10 mg & TNZ 5 mg were also superior to OXY (p≤0.018). Overall AE rate was higher with OXY (63.3%) than TNZ (40.7 – 44.7%) or PBO (35.5%). AEs reported in >5% of patients were nausea, constipation, vomiting, dizziness, pruritus, & headache with OXY & arthralgia with TNZ 10 mg. Incidence of patients who discontinued due to an AE was highest with OXY (10.1%), followed by TNZ 10 mg (2.7%), PBO (1.4%), & TNZ 5 mg (1.2%). Incidence of serious AEs was similar among treatments & <3%. The AE profile for TNZ was similar to that of previous TNZ studies. Two patients in TNZ 10 mg group were reported to have osteonecrosis (ON; 2/150; 1.3%; one was reported as worsening of pre-existing ON) & underwent total joint replacement (TJR). An external adjudication committee did not confirm ON, but indicated one patient had rapidly progressing OA & the other had normally progressing OA. One additional patient in the TNZ 10 mg group, one in TNZ 5 mg and one in PBO underwent TJR not associated with an AE. One patient in the OXY group underwent TJR for an AE of OA.



Conclusion: Treatment with TNZ (10 mg or 5 mg) resulted in superior analgesic efficacy as measured by WOMAC Pain subscale compared to PBO & OXY. Results from this study indicate that TNZ is efficacious in the treatment of OA pain. No new safety signals were identified.

1096

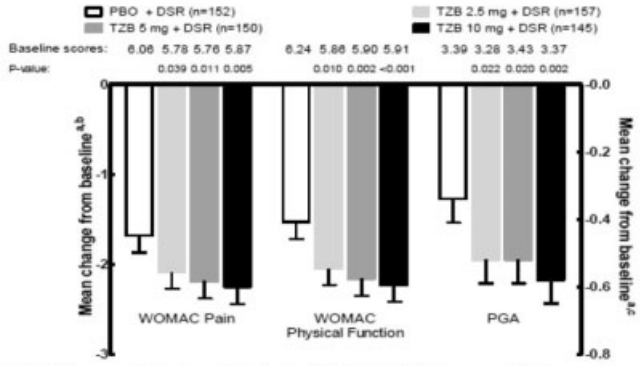
Efficacy and Safety of Tanezumab Added on to Diclofenac in Patients with Knee or Hip Osteoarthritis (NCT00864097). Eugen Feist[1], Andra Balanescu[2], Gernot Wolfram[3], Isabelle Davignon[3], Michael D. Smith[3], Mark T. Brown[3] and Christine R. West[4]. [1]Charité Medical School, Berlin, Germany, [2]Sf. Maria Hospital, Bucharest, Romania, [3]Pfizer, Groton, CT, [4]Pfizer, Williamston, MI

Background/Purpose: Tanezumab (TZB), a monoclonal antibody that inhibits nerve growth factor, reduces hip or knee osteoarthritis (OA) pain. A European randomized, double-blind, controlled multicenter study was conducted to evaluate efficacy and safety of intravenous (IV) TZB added to oral diclofenac sustained release (DSR) in patients with hip or knee OA.

Methods: Patients (N=604) with moderate to severe knee or hip OA tolerating stable oral diclofenac 150 mg/day were randomized and treated in a 1:1:1:1 ratio to IV TZB 2.5, 5, or 10 mg, or placebo (PBO) at weeks 0, 8, and 16, combined with oral DSR 75 mg BID. Co-primary efficacy endpoints (Western Ontario and McMaster Universities OA Index [WOMAC] Pain subscale, WOMAC Physical Function subscale, and Patient Global Assessment [PGA] of OA) were assessed at Week 16. Statistical analysis was made using Analysis of Covariance (ANCOVA), with model terms for baseline value, OA type (knee or hip) and treatment group, with Last Observation Carried Forward as primary imputation for missing data. Comparisons were made by prespecified step-down testing for TZB dose + DSR versus PBO + DSR, in the order of tanezumab doses of 10 mg, 5 mg then 2.5 mg. Each treatment comparison across co-primary endpoints had to be significant to conclude superiority.

Results: For all TZB doses, mean changes from baseline to Week 16 with TZB + DSR were statistically significant versus PBO + DSR for all co-primary endpoints (p≤0.039; 9 of 9 comparisons; Figure). Safety was similar to previous TZB trials although incidence of adverse events (AEs) of abnormal peripheral sensation was lower. No new safety signals emerged. Overall incidence of AEs was higher with TZB + DSR (45.2–49.7%) than with PBO + DSR (34.9%). Serious AE rates were similar across treatments (5.3–7.6%) with OA and osteonecrosis (ON) the most frequently reported (in 6 patients each across treatments). ON was reported as a serious AE in 6 of 452 patients with TZB + DSR (1.3%), but an external adjudication committee was unable to confirm ON in any patient. Three patients had insufficient x-ray information to allow

adjudication, 1 had rapidly progressing OA, 1 had subchondral fracture and 1 had an old femoral neck fracture at baseline. Overall combined incidence of total joint replacement due to reported ON, OA or arthralgia was 2.8% with TZB 10 mg + DSR, 2.0% with TZB 5 mg + DSR, 1.3% with TZB 2.5 mg + DSR and 0.7% with PBO + DSR. Incidence of AEs causing withdrawals was 3.9% for PBO + DSR and 5.1–7.3% in TZB + DSR groups. Treatment-emergent serious AEs involving fractures were reported more frequently in TZB + DSR (6 of 452 patients; 1.3%) versus PBO + DSR (0 of 152 patients) other serious AEs were not observed in ≥1 patient in any group.



DSR, diclofenac sustained release; PBO, placebo; PGA, Patient Global Assessment; TZB, tanezumab; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; [a]Least square mean change from baseline; [b]WOMAC subscales were assessed on a 0-10 numerical rating scale; [c]PGA was assessed on a 5-point Likert scale; Last Observation Carried Forward used as the primary imputation for missing data

Conclusion: Addition of TZB to stable oral diclofenac in OA patients resulted in greater improvement in pain, function, and global assessments than diclofenac alone across co-primary endpoints with no new safety signals.

ACR/ARHP Poster Session B
Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogenesis
Monday, November 7, 2011, 9:00 AM–6:00 PM

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Is Femoral Neck Fracture Associated with Hip Structural Analysis Measurements? Alexander G. S. Oldroyd[1], John P. Halsey[2], Bronwen Evans[2], Cathi Greenbank[2], Nicola Goodson[3] and Marwan Bukhari[2]. [1]Lancaster University, Lancaster, United Kingdom, [2]Royal Lancaster Infirmary, Lancaster, United Kingdom, [3]University Hospital Aintree, Liverpool, United Kingdom

Background/Purpose: The association between a lower femoral neck bone mineral density (BMD) and a higher fragility fracture risk is well known. Studies have also identified the dependency of bone fracture resilience upon morphometric shape of bone. Densitometry scans have the ability to measure the shape of the proximal femur, called hip structural analysis (HSA).

This study aimed to investigate if the shape and density of the proximal femur are associated with previous femoral neck fracture.

Methods: Dual X-ray Absorptiometry (DXA) scan results between 1996 and 2010 from a single scanner in the North west of England were collated. The following basic information of each individual was recorded: age, sex, body mass index (BMI) and social deprivation score of place of residence. The BMD of the femoral neck was collated. All HSA measurements were collated, including the hip axis length (HAL), cross-sectional moment of inertia (CSMI) and proximal femur strength index (SI). The previous femoral neck fragility fracture status of each patient was ascertained. Densitometry data of those who had previously sustained a unilateral femoral neck fracture was collated from their contralateral un-fractured femoral neck.

Logistic regression analysis, adjusted for age, sex, BMI, social deprivation score and femoral neck BMD, was used to investigate for significant differences of HSA measurements between those who had and had not sustained a femoral neck fracture. Differences of femoral neck BMD was also investigated for, adjusted for age, sex, BMI and social deprivation score.

Results: 580 (75.69% female) subjects had previously sustained a unilateral fracture of the femoral neck. 8389 (84.45% female) subjects had not previously sustained a fragility fracture of any body site.

Analysis revealed a significant difference of HAL, CSA, length and diameter of the femoral neck (represented by d1, d2, d3, y) and SI between the two fracture groups, independent of age, sex, BMI and social deprivation score.

Following further adjustment for femoral neck BMD, the only HSA measurements that varied between the two fracture groups were those of the diameter and length of the femoral neck: d1, d2, d3 and y; femoral neck fracture was significantly associated with a shorter and wider femoral neck. Femoral neck BMD of the fracture group was significantly lower compared to the non-fracture group.

	Adjusted for age, sex, BMI and social deprivation score Odds ratio (95% CI)	Adjusted for age, sex, BMI, social deprivation score and femoral neck BMD Odds ratio (95% CI)
HAL/mm	1.05 (1.03, 1.07)	0.96 (0.91, 1.02)
CSMI/m^4	0.99 (0.95, 1.03)	1.03 (0.90, 1.17)
CSA/mm^2	0.98 (0.97, 0.98)	1.01 (0.98, 1.04)
d1/cm - distance from centre of femoral head to centre of femoral neck	1.04 (1.01, 1.07)	0.87 (0.78, 0.97)
d2/cm - distance from centre of femoral head to axis intersection of femoral neck and shaft	0.98 (0.97, 0.99)	0.96 (0.91, 0.99)
d3/cm - mean diameter of femoral neck	1.11 (1.07, 1.15)	1.13 (1.03, 1.24)
y/cm - distance from centre of mass of femoral neck to superior neck margin	1.26 (1.19, 1.35)	1.22 (1.04, 1.44)
Neck/shaft angle^o	0.98 (0.96, 1.00)	0.99 (0.94, 1.05)
SI	0.58 (0.41, 0.79)	1.38 (0.91, 2.10)
Mean femoral neck BMD g/cm^2	0.05 (0.01, 0.90)	–

Conclusion: Femoral neck fracture is significantly associated with a shorter and wider femoral neck. Measurement of a patient's shape of their proximal femur may allow for more accurate assessment of their femoral neck fracture risk. Further work on the fragility-fracture predictive ability of HSA measurements is warranted.

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The Analysis of Denosumab Discontinuation and Associated Fracture Incidence in the FREEDOM Trial. Jacques P. Brown[1], Jens-Erik Beck Jensen[2], Chris Recknor[3], Christian Roux[4], Ove Tørring[5], Matt Austin[6], Andrea Wang[6], Andreas Grauer[6] and Rachel B. Wagman[6]. [1]CHUQ-CHUL Research Centre, Laval University, Quebec City, QC, [2]Hvidovre Hospital, Hvidovre, Denmark, [3]United Osteoporosis Centers, Gainesville, GA, [4]Paris Descartes University, Paris, France, [5]Institution for Clinical Science and Education Södersjukhuset Karolinska Institutet, Stockholm, Sweden, [6]Amgen Inc., Thousand Oaks, CA

Background/Purpose: Denosumab, a reversible RANKL inhibitor, decreases osteoclast formation, function, and survival. In the pivotal phase 3 fracture trial, FREEDOM, denosumab 60 mg administered every 6 months decreased the risk for new vertebral, nonvertebral, and hip fractures over 3 years compared with placebo (Cummings *NEJM* 2009). Osteoporosis is a chronic disease, and continued treatment is required to provide anti-fracture efficacy. While cessation of denosumab treatment has been associated with transient increases in bone remodeling and declines in bone mineral density (BMD) (Miller *Bone* 2008; Bone *JCEM* 2011), the effect on fracture risk is not as well characterized.

Methods: To understand fracture incidence in an osteoporotic population after treatment cessation, we evaluated subjects in FREEDOM who discontinued treatment after receiving 2 to 5 doses of investigational product (IP), either denosumab or placebo, and continued study participation for ≥ 6 months since the last dose + 1-month study visit window (≥ 7 months). The off-treatment observation period, which varies from subject to subject, began 7 months after the last dose of IP and lasted for approximately 6 to 24 months (for subjects who received 5 and 2 doses, respectively).

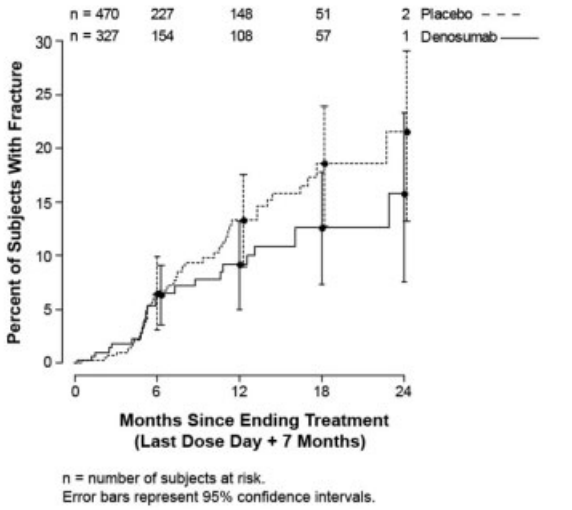
Table. Subject Characteristics at Treatment Discontinuation

	Placebo (N = 470)	Denosumab (N = 327)
Number of doses received		
2	114 (24)	86 (26)
3	138 (29)	99 (30)
4	90 (19)	68 (21)
5	128 (27)	74 (23)
Fracture during treatment*	90 (19)	36 (11)
Significant BMD reduction† during treatment*	80 (17)	4 (1)
Treatment discontinuation due to requiring alternative therapy or disease progression	116 (25)	29 (9)
Started alternative therapy after last dose	197 (42)	90 (28)

Values are number (%) of subjects. N = number of subjects who discontinued treatment after receiving 2 to 5 doses of investigational product, either denosumab or placebo, and continued study participation for ≥ 7 months after the last dose. *Treatment period = first dose through last dose + 7 months. †Significant BMD reduction is defined as > 7% BMD reduction at the total hip within any 12-month period, ≥ 10% BMD reduction at total hip from baseline at any time point, or total hip BMD T-score < −4 at any time point.

Results: This subgroup of 797 subjects (470 placebo, 327 denosumab) showed similar baseline characteristics for age, prevalent fracture, and lumbar spine and total hip BMD T-scores. During the treatment period, more subjects treated with placebo as compared with denosumab sustained a fracture and had significant decreases in BMD (Table). In addition, 42% of placebo-treated subjects vs 28% of denosumab-treated subjects initiated an alternative therapy after the last dose. After treatment discontinuation, similar percentages of subjects in both groups sustained a new fracture (9% placebo, 7% denosumab), resulting in a fracture rate per 100 subject-years of 13.5 for placebo and 9.7 for denosumab (HR 0.82; 95% CI: 0.49, 1.38), adjusted for age and total hip BMD T-score at baseline. There was no apparent difference in fracture occurrence pattern between the treatment groups during the off-treatment period (Figure).

Figure: Time to First Osteoporotic Fracture During the Off-treatment Period



Conclusion: We conclude from this analysis that there was not an excess in fracture risk after treatment cessation with denosumab compared with placebo during the off-treatment period for up to 24 months.

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Vertebral and Femoral Strength Increased In Postmenopausal Women with Osteoporosis Treated with Teriparatide for 18 Months. Tony M. Keaveny[1], Michael Maricic[2], David Kopperdahl[3], Valerie Ruff[4], Xiaohai Wan[5] and Kelly Krohn[6]. [1]University of California, Berkeley, CA and O.N. Diagnostics, LLC, Berkeley, CA, [2]Catalina Pointe Rheumatology, Tucson, AZ, [3]O.N. Diagnostics, LLC, Berkeley, CA, [4]Lilly USA, LLC, [5]Eli Lilly and Company, [6]Lilly USA, LLC, Indianapolis, IN

Background/Purpose: Finite element analysis of quantitative CT scans is a widely accepted method for non-invasive assessment of vertebral and femoral strength in clinical studies. Since very few finite element data have been reported on changes in vertebral and femoral strength for patients treated with teriparatide [rhPTH (1–34)], the biomechanical effects of teriparatide treatment in postmenopausal women with osteoporosis are not well known. To address this issue, we used finite element analysis to assess the effects of 18 months of treatment with teriparatide on vertebral and femoral strength in postmenopausal women with osteoporosis. We also assessed changes in volumetric bone mineral density (BMD), areal BMD, and early changes in bone turnover markers (P1NP and CTX).

Methods: 30 postmenopausal women (T-score of −2.0 or lower with ≥1 minimal trauma vertebral/nonvertebral fracture or T-score of −3.0 or lower with no prior fracture) received teriparatide 20 μg administered subcutaneously once daily for 18 months in this open-label study. Quantitative CT of the lumbar spine and hip was performed at baseline and 18 months (or early termination visit). All patients with 2 evaluable CT scans at both time points were included in the analysis. Volumetric density was measured for the trabecular, peripheral (outer 2–3 mm of bone that contained both cortical and some adjacent trabecular bone), and both ("integral") compartments. Nonlinear finite element analysis was performed for uniform compression for the spine and a sideways fall for the hip to provide estimates of vertebral and femoral strength. DXA of the spine and hip was performed at baseline and 18 months (or early termination) to determine areal BMD. Serum P1NP and CTX were assessed at baseline, 3 and 6 months.

Results: Vertebral and femoral strength increased compared to baseline. Significant increases were observed at 18 months in both trabecular and peripheral volumetric densities for the spine, and a significant increase was seen in the trabecular density for the hip, with no change in the peripheral density (Table). Areal BMD also increased significantly at the lumbar spine. Both P1NP and CTX showed significant increases at Months 3 and 6 (Figure).

Table. % Change from Baseline to Month 18 Median (interquartile range)

Outcome	Vertebra (n=30)	Femur (n=26)
Strength	16.6 (7.4, 24.7)*	2.3 (−1.6, 6.8)*
Strength-to-Density Ratio[a]	5.5 (2.8, 10.0)*	0.0 (−1.4, 1.5)
Volumetric Bone Density		
Integral	9.9 (4.4, 14.4)*	2.2 (0.0, 4.7)*
Trabecular	12.8 (4.9, 18.2)*	3.9 (1.5, 7.0)*
Peripheral	5.8 (3.8, 9.2)*	0.0 (−1.6, 1.9)
Mean (standard deviation)		
Areal BMD	(n = 25)	(n = 28)
Lumbar spine	6.3 (5.0)**	
Femoral neck		1.8 (4.8)
Total hip		0.2 (3.4)

[a] Ratio of strength to integral density
* $P < 0.05$ vs baseline; ** $P < 0.0001$ vs baseline

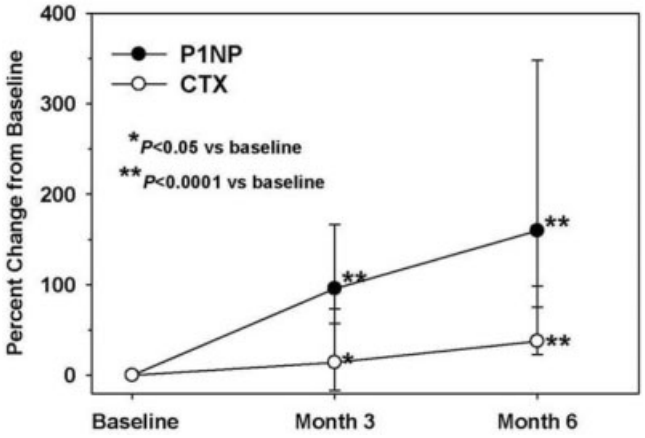

Figure. % Change from Baseline, Median (interquartile range), in Bone Turnover Markers

Conclusion: In women with postmenopausal osteoporosis, both vertebral and femoral strength increased after 18 months of treatment with teriparatide.

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Risk Factors for Osteoporosis in Patients with Rheumatoid Arthritis (TOMORROW STUDY). Tadashi Okano[1], Masahiro Tada[1], Yuko Sugioka[1], Kenji Mamoto[2], Shigeyuki Wakitani[1], Hiroaki Nakamura[1] and Tatsuya Koike[1]. [1]Osaka City University Medical School, Osaka, Japan, [2]Higashisumiyoshi Morimoto Hospital, Osaka, Japan

Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease characterized by inflammation of the synovial joint, cartilage degradation, and subsequent bone destruction. Bone damage is often manifested as localized juxta-articular bone loss, or generalized bone loss. The later is likely attributed to a number of factors including disease activities itself, reduced daily physical activity, glucocorticoid use or common postmenopausal osteoporosis. We have started prospective cohort study (TOMORROW research) to investigate comorbidities of the RA patients. In this study, we examined the risk factors that affected osteoporosis in RA patient.

Methods: Subjects included 208 RA patients (112 patients receiving biological agents and 96 patients receiving conventional therapy) and 205 age- and sex-matched healthy volunteers (N=413). Measurements of body composition, bone mineral density (BMD, QDR-4500, Hologic), urine pentosidine, urine NTX, ucOC and homocysteine levels were performed. In the analysis of BMD, the patients who had the prosthesis in their joints were excluded.

Results: In the baseline data, lean body mass was lower and fat mass was higher in RA patients than volunteers (table 1). The arms, lower limbs, the thoracic vertebra and the lumbar vertebra significantly indicated a low value

in the bone density in the RA group compared to the volunteer group ($p<0.05$) (Table 2). Moreover, urine pentosidine, urine NTX and homocysteine levels were significantly higher in RA patients (Table 2). Bone density correlated with lean body mass positively, and showed negative correlations with the fat mass. Stepwise multiple regression analysis using whole body BMD as a dependent variable resulted in age, weight, whole body lean mass, whole body % fat and NTX as independent variables. Age and whole body lean mass were also selected as independent variables for upper arm, thoracic spine, lumber spine and leg BMD.

Table 1. Clinical data at baseline

Parameter	Whole population (n=413)	Control (n=205)	RA (n=208)	P*
Age	57.9 ± 12.9	57.4 ± 13.1	58.4 ± 12.8	NS
Women (n [%])	349 (85)	172 (84)	177 (85)	NS
Height (cm)	156.4 ± 8.4	157.6 ± 7.8	155.3 ± 8.8	NS
Body weight (kg)	55.6 ± 10.2	56.3 ± 10.4	54.9 ± 10.1	NS
BMI (kg/m^2)	22.7 ± 3.4	22.6 ± 3.2	22.7 ± 3.6	NS
Girth of the abdomen (cm)	81.1 ± 10.0	81.6 ± 9.3	80.6 ± 10.6	NS
Whole body lean mass	38377.5 ± 7538.0	39566.2 ± 7662.2	37206.0 ± 7242.8	<0.01
Whole body % Fat	28.3 ± 6.6	27.2 ± 6.2	29.4 ± 6.8	<0.01

(* comparison between control and RA subject)

Table 2. BMD and biomarker

Parameter	Whole population (n=413)	Control (n=205)	RA (n=208)	P*
Left arm BMD	0.607 ± 0.098	0.632 ± 0.085	0.582 ± 0.104	<0.01
Right arm BMD	0.613 ± 0.105	0.639 ± 0.091	0.587 ± 0.111	<0.01
Thoracic spine BMD	0.725 ± 0.128	0.750 ± 0.126	0.701 ± 0.125	<0.01
Lumbar spine BMD	0.913 ± 0.164	0.930 ± 0.163	0.896 ± 0.164	<0.05
Left leg BMD	0.993 ± 0.144	1.022 ± 0.126	0.961 ± 0.155	<0.01
Right leg BMD	1.005 ± 0.144	1.034 ± 0.123	0.973 ± 0.158	<0.01
Whole body BMD	0.989 ± 0.129	1.005 ± 0.123	0.968 ± 0.134	<0.01
Urine pentosidine (pmol/mg Cr)	63.8 ± 33.7	54.2 ± 23.1	73.6 ± 39.5	<0.01
Urine NTX (nmolBCE/mmolCr)	51.7 ± 32.5	44.3 ± 22.4	59.0 ± 38.7	<0.01
ucOC (ng/ml)	4.06 ± 2.73	3.97 ± 2.34	4.16 ± 3.07	NS
Homocysteine (μmol/l)	10.0 ± 4.0	9.1 ± 2.6	10.9 ± 4.8	<0.01

(* comparison between control and RA subject)

Conclusion: RA patients showed lower BMD at any part of body compared to age- and sex- matched volunteers. Lower BMD in RA patients might be explained by lower lean mass and higher % fat. The effects of other factors such as medication, duration of inflammation might be explored by our continuous cohort study.

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Adherence with Intravenous Zoledronic Acid and Ibandronate for Osteoporosis Among U.S. Medicare Beneficiaries. Jeffrey R. Curtis[1], Huifeng Yun[2], Robert Matthews[2], Kenneth G. Saag[1] and Elizabeth S. Delzell[2]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: To evaluate adherence beyond one year among new users of zoledronic acid and IV ibandronate among U.S. Medicare enrollees.

Methods: We used Medicare data for the random 5% sample from January 2005 through December 2009 to evaluate new users of IV zoledronic acid and ibandronate. Eligible individuals must have had continuous Medicare part A + B + D coverage and not be enrolled in a Medicare Advantage plan. Results were multiplied by 20 to extrapolate to the national U.S. Medicare Fee for Service population. A one year base period was used to characterize covariates of interest. All patients must have had 18 months of follow-up time after their first infusion to assess adherence.

The outcome of interest during the 18 month follow-up period was high adherence. For zoledronic acid, adherence was defined as receiving at least 2 infusions of zoledronic acid or switching to IV ibandronate; for ibandronate, adherence was defined as receiving at least 5 ibandronate infusions or switching to zoledronic acid. Factors hypothesized to be associated with adherence with zoledronic acid beyond 1 year were evaluated with multivariable logistic regression.

Results: Among 22,220 eligible Medicare beneficiaries, 15,100 were new users of zoledronic acid (Z) and 7,120 were new, users of IV ibandronate (I). The median (IQR) age of the zoledronic acid and ibandronate users was 78 (8) and 78 (9) years. Of these, approximately 95% were women and 95% were white. A majority of patients received at least one prescription for oral glucocorticoids (62 and 73%, respectively). For both drugs, 43% of first infusions were given in the outpatient hospital setting; for those given in physician offices, 26 (Z) and 31% (I) were administered by rheumatologist/endocrinologists, 15 (Z) and 6% (I) by oncologists, and 10 (Z) and 13% (I) by internal medicine doctors.

The proportion of zoledronic acid users persistent beyond one year was 65.7% and was greater than the proportion persistent with IV Ibandronate (34.6%, $p < 0.0001$). After adjustment, factors associated with zoledronic acid adherence (referent to those non-persistent with zoledronic acid) included male gender (odds ratio [OR] = 0.35, 95% CI 0.11 – 1.11), age 85+ (referent to age 65–69) (OR = 0.41, 95% CI 0.21 – 0.80), glucocorticoid use (OR = 0.74, 0.53 – 1.03), prior non-adherence with osteoporosis medications (OR = 0.66, 95% CI 0.42 – 1.04) and prior factures (OR=0.89, 95% CI 0.51–1.56). Compared to infusions administered by an oncologist, adherence was greater among patients receiving infusions administered by an internal medicine physician (OR = 1.84, 0.92 – 3.70) and rheumatologists/endocrinologists (OR = 1.45, 0.86 – 2.45).

Conclusion: Adherence beyond 1 year with IV zoledronic acid and IV ibandronate was comparable or somewhat greater than prior reports of adherence with oral bisphosphonates. However, more than 1/3 of IV bisphosphonate users did not continue beyond 12 months. Less frequently dosed medications may improve adherence but ongoing efforts are still needed to maximize long term adherence with osteoporosis therapies.

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Glucocorticosteroids but Not Hand Bone Density Is Associated with Distal Radius Fracture Severity in Elderly Women. Alvilde Dhainaut[1], Adalstein Odinson[2], Kamil Daibes[3], Mari Hoff[2], Unni Syversen[1] and Glenn Haugeberg[1]. [1]The Norwegian University of Science and Technology, Trondheim, Norway, [2]St Olavs Hospital, Trondheim, Norway, [3]Sørlandet Hospital, Kristiansand, Norway

Background/Purpose: Distal radius is one of the most common sites for fractures (fx) in elderly people. Both reduced bone mineral density (BMD) and the use of glucocorticosteroids (GC) have been identified as independent risk factors for fragility distal radius fx [1]. GC do not only reduce BMD, but do also impair bone quality. Reduced BMD measured in the hand with Digital X-ray Radiogrammetry (DXR) has been shown to predict distal radius fx [2]. The aim of this study was to explore if there is an association between severity of distal radius fx and hand DXR-BMD or other potential associates including GC.

Methods: The study population consisted of 110 women > 50 years with a recent low-energy distal radius fx assessed 10 days after fx. Demographic, clinical and treatment data were collected. BMD at the spine (L2–4) and femoral neck was assessed by dual energy X-ray absorptiometry (DXA) and hand BMD was assessed by the Sectra DXR software calculating cortical BMD from hand radiographs. Fx were scored according to the AO Classification of Fractures of Long Bones on the primary X-rays where fx were divided into A, B and C types, each with 3 subgroups. A is extra-articular, B partial articular and C intra-articular. Intraarticular fx were defined as more severe than extra-articular fx. The association between extraarticular or intraarticular fx as dependent variable and BMD, clinical and treatment variables were tested separately in unadjusted logistic regression analyses. Variables with a p value ≤ 0.20 were included in adjusted analyses. Statistical tests were applied using SPSS and significance level was $p < 0.05$.

Results: Mean age was 68 years. 75% had an extraarticular fx (34 A2; 49 A3) and 25% had an intraarticular fx (4 B1, 1 B2, 17 C1, 3 C2 and 2 C3). In the intraarticular group a significant higher proportions of patients were ever user of GC compared to the extraarticular group (5/81 vs 5/24 $p=0.016$). No significant differences between the two groups were found for age, height, weight, smoking, alcohol use, current exercise, presence of chronic inflammatory or endocrine disease, use of calcium, vitamin D, bisphosfonate orestrogen, DXA BMD at spine or femoral neck or DXR hand BMD. In logistic regression analyses none of the BMD measurements were significantly associated to fx severity in univariate analyses. Ever use of GC had a significant result with an increased risk of having an intraarticular fx both in univariate and adjusted analyses (Table 1). In the adjusted analyses DXA BMD showed a reverse effect with higher BMD increasing the risk for intraarticular fx.

Table 1.

	Univariate		Adjusted		Adjusted	
	OR	P	OR	P	OR	P
GC, ever use	5.07	0.01	5.87	0.04		
GC, current use	3.71	0.12			1.15	0.89
Spine BMD mg/cm^2	1.00	0.14	1.00	0.01	1.00	0.01
Exercise†	0.44	0.09	0.53	0.28	0.22	0.50
Chronic disease‡	2.28	0.09	2.01	0.24	2.78	0.09
Calcium, current use	0.99	0.14	0.99	0.12	0.99	0.04

Conclusion: We found no association between cortical hand DXR BMD and the severity of distal radius fx expressed with the AO classification. However, our data indicate a potential association between the use of GC and the risk for intraarticular fx.

1 Oyen J et al Osteoporos Int 2010; 21
2 Bouxsein ML et al Osteoporos Int 2002; 13

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Extended Safety Observations From Denosumab Administration in Postmenopausal Women From the FREEDOM and FREEDOM Extension Trials. J. P. Brown[1], H. G. Bone[2], R. Chapurlat[3], C. Libanati[4], M. L. Brandi[5], E. Czerwinski[6], M.-A. Krieg[7], Z. Man[8], D. Mellström[9], S. C. Radominski[10], J.-Y. Reginster[11], H. Resch[12], J. A. Román Ivorra[13], Christian Roux[14], N. S. Daizadeh[4], A. Grauer[4], S. R. Cummings[15] and S. Papapoulos[16]. [1]CHUQ-CHUL Research Centre, Laval University, Quebec City, QC, [2]Michigan Bone & Mineral Clinic, Detroit, MI, [3]Hôpital Edouard Herriot, Lyon, France, [4]Amgen Inc., Thousand Oaks, CA, [5]University of Florence, Florence, Italy, [6]Krakow Medical Center, Krakow, Poland, [7]University Hospital of Lausanne, Lausanne, Switzerland, [8]Centro TIEMPO, Buenos Aires, Argentina, [9]Sahlgrenska University Hospital, Göteborg, Sweden, [10]Universidade Federal do Paraná, Curitiba, Brazil, [11]University of Liège, Liège, Belgium, [12]St. Vincent Hospital, Vienna, Austria, [13]Hospital Universitario La Fe, Valencia, Spain, [14]Paris Descartes University, Paris, France, [15]San Francisco Coordinating Center, CPMC Research Institute, San Francisco, CA, [16]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Denosumab (DMAb) is an approved therapy for the treatment of postmenopausal women with osteoporosis at increased risk for fracture. A favorable DMAb risk/benefit profile was demonstrated in the pivotal, 3-year FREEDOM trial. All women who completed FREEDOM, did not discontinue investigational product, and did not miss > 1 dose were eligible to participate in an extension study to investigate the safety and efficacy of DMAb treatment for up to 10 years. We previously reported that 5 years of DMAb treatment maintained bone turnover reduction, increased BMD, and was associated with low fracture rates. Here, we provide details on the yearly incidence of serious adverse events (SAEs) of infection and adverse events (AEs) of malignancy in FREEDOM and the extension.

Methods: Of the 5928 women eligible for the extension, 4550 (77%) enrolled. During the extension, all women receive 60 mg DMAb every 6 months and supplemental calcium and vitamin D daily. For the analyses reported here, women from the FREEDOM DMAb group received 2 more years of DMAb for a total of 5 years of exposure (long-term group; N=2343) and women from the FREEDOM placebo group received 2 years of DMAb exposure (cross-over group; N=2207). The analyses of AEs were descriptive and are reported as exposure-adjusted subject incidence rates.

Results: The year-to-year observed subject incidence rates of SAEs of infection (Table 1) and AEs of malignancy (Table 2) in the placebo group exhibited some variation during the 3 years of the FREEDOM trial. The yearly subject incidence rates in the first 2 years of the extension for the long-term and cross-over groups were similar to or lower than the observed yearly rates in the FREEDOM placebo group. This was also the case for individual SAEs of infection (by preferred term) including cellulitis or erysipelas (Table 1) and individual malignancies (by preferred term; Table 2). One case of oral osteomyelitis and one case of bone necrosis in the cross-over group were adjudicated as consistent with ONJ.

Table 1. Yearly Incidence of Serious Adverse Events of Infection

		FREEDOM			Extension	
		Year 1	Year 2	Year 3	Year 1	Year 2
		r (n)	r (n)	r (n)	r (n)	r (n)
All SAEs of Infection	Cross-over (Pbo/DMAb)	1.1 (42)	1.4 (50)	1.4 (48)	1.5 (33)	1.6 (32)
	Long-term (DMAb/DMAb)	1.5 (56)	1.6 (58)	1.6 (54)	1.3 (30)	1.2 (26)
Pneumonia	Cross-over (Pbo/DMAb)	0.3 (12)	0.4 (13)	0.4 (12)	0.4 (9)	0.4 (8)
	Long-term (DMAb/DMAb)	0.3 (12)	0.3 (9)	0.4 (13)	0.3 (7)	0.3 (7)
Urinary tract infection	Cross-over (Pbo/DMAb)	0.1 (4)	0.1 (5)	< 0.1 (1)	< 0.1 (1)	0.2 (4)
	Long-term (DMAb/DMAb)	< 0.1 (3)	0.2 (8)	0.1 (5)	< 0.1 (1)	< 0.1 (1)
Diverticulitis	Cross-over (Pbo/DMAb)	0	0.1 (5)	< 0.1 (1)	0.1 (3)	< 0.1 (1)
	Long-term (DMAb/DMAb)	0.1 (4)	< 0.1 (2)	< 0.1 (3)	< 0.1 (2)	< 0.1 (2)
Gastroenteritis	Cross-over (Pbo/DMAb)	< 0.1 (3)	< 0.1 (2)	< 0.1 (2)	0	< 0.1 (2)
	Long-term (DMAb/DMAb)	< 0.1 (3)	0.1 (4)	< 0.1 (2)	0	< 0.1 (1)
Appendicitis	Cross-over (Pbo/DMAb)	0.1 (4)	< 0.1 (1)	< 0.1 (2)	0	< 0.1 (1)
	Long-term (DMAb/DMAb)	0.1 (4)	< 0.1 (3)	0	< 0.1 (2)	< 0.1 (1)
Cellulitis or erysipelas	Cross-over (Pbo/DMAb)	0	0	< 0.1 (1)	0	< 0.1 (1)
	Long-term (DMAb/DMAb)	0.1 (4)	< 0.1 (1)	0.2 (8)	< 0.1 (2)	< 0.1 (1)
Bronchopneumonia	Cross-over (Pbo/DMAb)	< 0.1 (2)	0	0.1 (5)	< 0.1 (1)	0
	Long-term (DMAb/DMAb)	< 0.1 (1)	< 0.1 (3)	< 0.1 (2)	0	< 0.1 (2)
Lower respiratory tract	Cross-over (Pbo/DMAb)	< 0.1 (1)	< 0.1 (2)	0	0	< 0.1 (1)
	Long-term (DMAb/DMAb)	< 0.1 (2)	0.1 (4)	< 0.1 (2)	< 0.1 (1)	0

Treatment groups are the original randomized assignments in the FREEDOM study. All subjects in the extension study receive denosumab. Denosumab treatment is shown in gray. Events are listed if ≥ 4 subjects reported an adverse event in any group in any year.
r = exposure-adjusted subject incidence per 100 subject-years. n = total number of subjects with ≥ 1 adverse event.

Table 2. Yearly Incidence of Adverse Events of Malignancy

		FREEDOM			Extension	
		Year 1	Year 2	Year 3	Year 1	Year 2
		r (n)	r (n)	r (n)	r (n)	r (n)
All AEs of Malignancy	Cross-over (Pbo/DMAb)	1.8 (69)	1.6 (57)	1.5 (50)	1.8 (39)	1.4 (29)
	Long-term (DMAb/DMAb)	1.8 (69)	1.5 (53)	2.2 (74)	1.8 (42)	2.2 (47)
Skin	Cross-over (Pbo/DMAb)	0.6 (24)	0.3 (10)	0.5 (17)	0.5 (11)	0.6 (12)
	Long-term (DMAb/DMAb)	0.6 (22)	0.3 (10)	0.5 (17)	0.6 (13)	0.8 (17)
Gastrointestinal	Cross-over (Pbo/DMAb)	0.2 (9)	0.3 (11)	0.1 (4)	0.4 (9)	0.1 (3)
	Long-term (DMAb/DMAb)	0.3 (11)	0.3 (11)	0.4 (13)	0.3 (7)	0.4 (9)
Breast (including nipple)	Cross-over (Pbo/DMAb)	0.2 (9)	0.3 (11)	0.2 (8)	0.1 (3)	0.2 (5)
	Long-term (DMAb/DMAb)	0.3 (10)	0.3 (10)	0.4 (14)	0.3 (6)	0.2 (5)
Respiratory	Cross-over (Pbo/DMAb)	0.3 (11)	0.3 (10)	0.1 (4)	< 0.1 (2)	< 0.1 (2)
	Long-term (DMAb/DMAb)	< 0.1 (3)	0.1 (4)	0.2 (7)	0.2 (4)	0.1 (3)
Reproductive	Cross-over (Pbo/DMAb)	0.2 (6)	< 0.1 (2)	< 0.1 (2)	< 0.1 (1)	0.1 (3)
	Long-term (DMAb/DMAb)	0.2 (7)	0.2 (6)	0.2 (6)	< 0.1 (1)	< 0.1 (2)
Metastases	Cross-over (Pbo/DMAb)	0.1 (5)	0.1 (4)	< 0.1 (1)	< 0.1 (1)	< 0.1 (1)
	Long-term (DMAb/DMAb)	0.1 (4)	0.1 (4)	< 0.1 (1)	< 0.1 (1)	< 0.1 (2)
Renal and urinary tract	Cross-over (Pbo/DMAb)	0.1 (4)	< 0.1 (2)	< 0.1 (3)	0.2 (4)	0
	Long-term (DMAb/DMAb)	< 0.1 (1)	0.1 (4)	< 0.1 (1)	0.1 (3)	0
Plasma cell	Cross-over (Pbo/DMAb)	0	< 0.1 (2)	< 0.1 (2)	< 0.1 (2)	< 0.1 (1)
	Long-term (DMAb/DMAb)	< 0.1 (1)	0	0.1 (5)	< 0.1 (1)	< 0.1 (2)
Endocrine	Cross-over (Pbo/DMAb)	0	0	< 0.1 (2)	< 0.1 (1)	< 0.1 (1)
	Long-term (DMAb/DMAb)	0.1 (5)	< 0.1 (1)	< 0.1 (1)	0.1 (3)	0
Nervous system	Cross-over (Pbo/DMAb)	< 0.1 (1)	0	0.2 (6)	< 0.1 (1)	0
	Long-term (DMAb/DMAb)	< 0.1 (2)	< 0.1 (1)	< 0.1 (2)	0	0

Treatment groups are the original randomized assignments in the FREEDOM study. All subjects in the extension study receive denosumab. Denosumab treatment is shown in gray. Events are listed if ≥ 4 subjects reported an adverse event in any group in any year.
r = exposure-adjusted subject incidence per 100 subject-years. n = total number of subjects with ≥ 1 adverse event.

Conclusion: The year-to-year observed AE rates in placebo subjects provide a valuable indicator of the expected variation in untreated subjects and assist in the interpretation of safety results associated with therapy. Yearly incidences of SAEs of infection and AEs of malignancy did not increase over 5

years of continuous DMAb treatment of postmenopausal women with osteoporosis. The imbalances in SAEs of skin infections reported in the original FREEDOM study were not observed with DMAb treatment in the extension study.

1104

Strontium Ranelate in the Treatment of Male Osteoporosis. One Year Results of a Placebo Controlled Study. Jean-Marc Kaufman[1], Maurice Audran[2], Gerolamo Bianchi[3], Steven Boonen[4], Robert Josse[5], Roger M. Francis[6], Stefan Goemaere[1], S. Palacios[7], M. Diaz-Curiel[8], Johann-Diederich Ringe[9] and Dieter Felsenberg[10]. [1]Ghent University Hospital, Ghent, Belgium, [2]CHU Angers, Angers, France, [3]Ospedale La Colletta, Arenzano-GE, Italy, [4]Leuven University Hospital, Leuven, Belgium, [5]St Michael's Hospital, Toronto, [6]Institute for Ageing and Health, Newcastle, United Kingdom, [7]Instituto Palacios, Madrid, Spain, [8]Fundacion Jimenez Diaz, Madrid, Spain, [9]Klinikum Leverkusen, University of Cologne, Cologne, Germany, [10]Charité Campus Benjamin Franklin, Berlin, Germany

Background/Purpose: Male osteoporosis is increasingly recognised as a major public health issue. The efficacy and safety of strontium Ranelate (Sr Ran) have been established for treatment of post menopausal osteoporotic women. The male Osteoporosis study assessed the efficacy and safety of SrRan in men with primary osteoporosis.

Methods: The study was a 2-year double-blind placebo-controlled randomised trial (SrRan 2g/day/placebo 2:1). Bone mineral density (BMD) at the lumbar and femoral sites was measured every 6 months. Primary endpoint was relative changes from baseline of lumbar BMD L2-L4 (LS BMD) at 1 year. An ITT analysis was applied.

Results: Baseline characteristics were similar in both groups (mean ±SD): age: 73.1±6.1 vs 72.6±5.7 yrs; LS T-Score: − 2.7±0.9 vs – 2.4±1.2, femoral neck T-score: − 2.3±0.6 vs – 2.3±0.7, prevalent vertebral fractures and prevalent peripheral osteoporosis fracture = 28.2% vs 25.3% and 11.5% vs 10.3% respectively.

Over 1 year, LS BMD increased significantly in the SrRan group compared to placebo from baseline to endpoint, by 5.3%±0.75 ($p<0.001$); femoral neck BMD increased by 2.9%±0.62, ($p<0.001$). There was a decrease in bone resorption (estimate of adjusted means difference (SrRan-placebo) for s-CTX: –25.9%(7.86), p=0.0011) and a maintenance of bone formation (estimate of adjusted means difference for bALP:4.5%(3.0),NS). An improvement (i.e. score decrease) in both groups of the Quality of life was observed, more marked in the SrRan group (−0.16±0.6 vs. −0.07±0.5 in the placebo group,NS), particularly regarding 'pain interfering with patient sleep' (16.2% vs 5.1%, p=0.016).

Furthermore, the serum strontium levels and the magnitude of the increases in lumbar (6.38%±0.81) and femoral neck (3.19%±0.70) BMD at M12 in this male population, were similar to those previously observed in PMO women studies as shown in the table below:

Relative changes (M0–M12) versus placebo (%)		Maleo N=243	PMO studies N=6551	Effects in Men versus Women
Lumbar spine BMD %	E(SE)	6.38% (0.81)	7.04% (0.35)	p-value[1] = 0.442
	95% CI	[4.1,8.0]	[6.7,7.4]	
	p-value	p<0.001	p<0.001	
Femoral neck BMD %	E(SE)	3.19% (0.7)	3.52% (0.14)	p-value[1] = 0.655
	95% CI	[1.8,4.6]	[3.3,3.8]	
	p-value	p<0.001	p<0.001	

E(SE): Estimate and Standard Error of the adjusted mean difference (S 12911 2g minus Placebo)
(1) p-value of the Student test
No new safety concern has been detected in this male population.

Conclusion: In a male population at high risk of fractures, a marked increase in the mean lumbar L2-L4 and femoral neck BMD were observed, similar to that previously observed in women. Considering the present results in men and the previously established relationship between change in BMD and reduction in new vertebral and hip fractures risk with SrRan treatment in women, a similar anti-fracture efficacy is expected in men. Safety results did not reveal any unexpected adverse events in men exposed to SrRan.

1105

The Lancaster Osteoporosis Predictor—a Novel Tool to Identify Individuals with Osteoporosis. Alexander G. S. Oldroyd[1], John P. Halsey[2], Nicola Goodson[3], Bronwen Evans[2], Cathi Greenbank[2], David Gore[2] and Marwan Bukhari[2]. [1]Lancaster University, Lancaster, United Kingdom, [2]Royal Lancaster Infirmary, Lancaster, United Kingdom, [3]University Hospital Aintree, Liverpool, United Kingdom

Background/Purpose: A number of tools have been developed to predict an individual's OP risk and guide referral for a densitometry scan, including SCORE, FRAX, pBW and OST. Apart from FRAX, currently available tools were developed with only small cohorts. No currently available tool considers the presence of less common osteoporosis risk factors alongside the traditional.

Methods: Data was collated from 25912 individuals that attended for a DXA scan at the Royal Lancaster Infirmary (UK) between 1992 and 2010. The following data was collated: age, body mass index (BMI kg/m^2), diagnosis of rheumatoid arthritis, post-menopausal status (females only), diagnosis of osteoporosis (t-score of the lumbar spine or femoral neck less than −2.5). The presence of less common osteoporosis risk factors was collated, which included: more than 1 year of amenorrhoea, untreated early menopause before 45 years of age, previous breast cancer, inflammatory bowel disease, coeliac disease, hyperthyroidism. The total number of osteoporosis risk factors of each individual was ascertained.

The cohort was randomly divided into development and validation cohorts. Logistic regression models for males and females were formed separately, using a diagnosis of osteoporosis (binary) as the outcome variable and the following as predictor variables: age, BMI, diagnosis of rheumatoid arthritis (binary), number of osteoporosis risk factors and post-menopausal status (only included in the female model). Only variables with a p-value less than 0.05 were included in the final model. The logistic regression models were translated into receiver operator characteristic (ROC) curves. Tools were validated using the validation cohorts. Individual tools for males and females were developed.

Results:

	Female n = 22003		Male n = 3909	
Variable	Development n = 14661	Validation n = 7342	Development n = 2554	Validation n = 1355
Mean Age/years (SD)	62.30 (12.47)	62.26 (12.31)	64.79 (12.17)	64.54 (13.76)
Mean BMI/kg/m^2 (SD)	26.60 (5.27)	26.58 (5.37)	26.74 (4.57)	26.67 (4.47)
No. rheumatoid arthritis (%)	423 (2.89)	214 (2.91)	120 (4.70)	53 (3.91)
No. post-menopausal (%)	5661 (38.61)	2804 (38.19)	—	—
No. osteoporotic (%)	4500 (30.69)	2196 (31.27)	895 (35.04)	462 (34.10)
Mean no. osteoprosis risk factors (SD)	1.65 (1.40)	1.65 (1.40)	1.73 (1.37)	1.66 (1.33)

The coefficients of the female logistic regression model were: intercept −4.44, age/years 0.06, BMI kg/m^2 −0.06, number of osteoporosis risk factors 0.51, post-menopausal status 1.67. The area under the ROC curve was 0.85. A threshold of −1.3 gave 86% sensitivity and 68% specificity. Therefore, individuals with a score higher than −1.3 were deemed to be osteoporotic. Validation of this tool gave 86% sensitivity and 68% specificity.

The coefficients of the male logistic regression model were: intercept −2.40, age/years 0.03, BMI kg/m^2 −0.05, number of osteoporosis risk factors 0.61. The area under the ROC curve was 0.74. The threshold that gave a sensitivity of 85% was −1.2, of which the specificity was 44%. Therefore, males with a score higher than −1.2 were deemed to be osteoporotic. Validation of the tool gave a sensitivity of 85% and a specificity of 43%.

Conclusion: Use of this tool, which was developed with a large cohort, can reduce the number of DEXA scans by 51% in females and 32% in males; 8.6% of females and 16% of males not scanned will be osteoporotic. Further validation and optimal threshold identification is required before clinical implementation.

1106

Allowing Patient Self-Referral of Dual Energy X-Ray Absorptiometry Significantly Improves Osteoporosis Screening in Two Regional Healthcare Systems. Amy H. Warriner[1], Ryan C. Outman[1], Jeffery R. Curtis[1], Adrianne C. Feldstein[2], Roslin Nelson[3], David T. Redden[1], Junling Ren[3], Mary M. Rix[2], Brandi E. Robinson[3], Douglas W. Roblin[3], A. Gabriela Rosales[2], Monika M. Safford[1] and Kenneth G. Saag[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Kaiser Permanente Center for Health Research, Portland, OR, [3]Kaiser Permanente Center for Health Research, Atlanta, GA

Background/Purpose: Current U.S. guidelines recommend bone density screening with central dual energy x-ray absorptiometry (DXA) in all women 65 years or older. However, less than one-third of eligible U.S. women undergo this testing. We evaluated whether a simple, low-cost intervention for patients to more easily schedule DXAs might improve osteoporosis screening rates compared to the current requirement of physician referral.

Methods: We conducted a group randomized controlled trial involving 14 primary care clinics within the Kaiser Permanente Northwest Region (KPNW) and 15 primary care clinics within the Kaiser Permanente Georgia Region (KPG). Women 65 years or older with no identifiable DXA scan in the past 5 years and no identifiable anti-osteoporosis treatment in the past 12 months were eligible for the study. Clinics were randomized into 1 of 3 groups: A self-referral intervention (SELF) (eligible patients invited by mail to get a DXA and provided opportunity to self-schedule a DXA); self referral + DVD (SELF+DVD) (consisting of

SELF, plus an educational brochure and DVD promoting patient-provider communication about osteoporosis screening, enhanced through patient story-telling); and, Usual Care (UC) (No DVD or self referral). Providers in all groups were directed to web-based CME training on osteoporosis screening and treatment.

Results: Of 8800 eligible women from KPNW, 3191 women were randomized to SELF, 3720 to SELF+DVD, and 1889 to UC. A total of 24.3% of women in SELF and 24% in SELF+DVD completed a DXA scan, compared to 6% of women in UC; the risk difference for DXA receipt in SELF and DVD+SELF vs. UC was 18.1 (95% CI 16.6–19.6). Of 3239 eligible women from KPG, 1064 women were randomized to SELF, 1005 to SELF+DVD, and 1170 to UC. A total of 16.4% of women in SELF and 14.5% in SELF+DVD completed a DXA scan, compared to 5.2% of women in UC; the risk difference for DXA receipt in SELF and DVD+SELF vs. UC was 10.3 (95% CI 8.2–12.3).

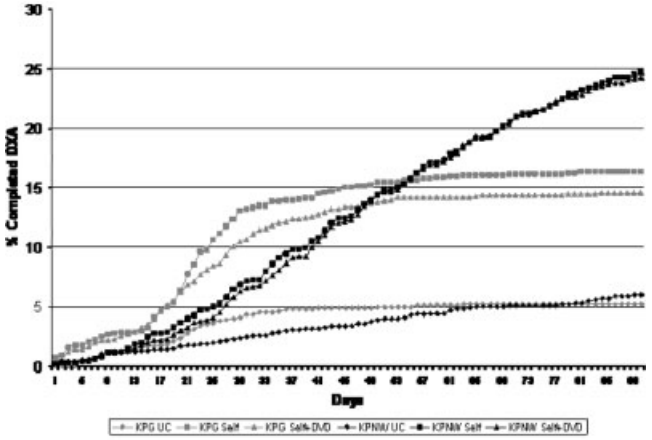


Figure. Receipt of DXA scans by Day

Conclusion: In both regions, DXA scan scheduling and receipt was improved significantly by allowing patients to self-schedule their own scans. The addition of an educational DVD using patient story-telling to promote patient-provider communication did not significantly improve DXA screening over DXA self-scheduling alone. Allowing eligible women to self-schedule screening DXA scans (similar to mammography self-scheduling) may be an effective low cost strategy to increase rates of osteoporosis screening.

1107

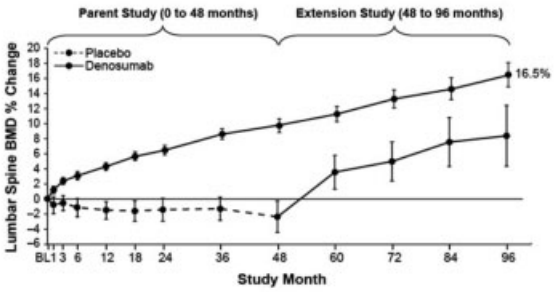
Effects of Denosumab on Bone Mineral Density and Biochemical Markers of Bone Turnover Over 8 Years. Michael R. McClung[1], E. Michael Lewiecki[2], Michael A. Bolognese[3], Munro Peacock[4], Richard L. Weinstein[5], Beiying Ding[6], Michelle L. Geller[6], Andreas Grauer[6], Rachel B. Wagman[6] and Paul D. Miller[7]. [1]Oregon Osteoporosis Center, Portland, OR, [2]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, [3]Bethesda Health Research Center, Bethesda, MD, [4]Indiana University, Indianapolis, IN, [5]Diablo Clinical Research, Inc., Walnut Creek, CA, [6]Amgen Inc., Thousand Oaks, CA, [7]Colorado Center for Bone Research, Lakewood, CO

Background/Purpose: Denosumab is a fully human monoclonal antibody that inhibits RANKL, reduces bone resorption, increases BMD, and reduces the risk of new vertebral, hip, and nonvertebral fractures at 3 years compared with placebo (Cummings *NEJM* 2009). With its unique mechanism of action, long-term experience with denosumab therapy is of clinical interest. Here we present the effects of 8 years of continuous denosumab treatment on bone mineral density (BMD) and bone turnover markers (BTM) from a phase 2 study.

Methods: In the 4-year, phase 2 parent study, postmenopausal women with a BMD T-score between –1.8 and –4.0 (lumbar spine) and/or –1.8 and –3.5 (total hip or femoral neck) were randomized to receive placebo, alendronate, or 1 of 7 different doses of denosumab. After 2 years on study, subjects were reallocated to maintain, discontinue, or discontinue and reinitiate denosumab; discontinue alendronate; or maintain placebo for an additional 2 years (Miller *Bone* 2008). The parent study was then extended for 4 years. All subjects in the extension study received open-label denosumab 60 mg every 6 months (Q6M). Here our results focus on subjects who received denosumab treatment for 8 years total in the parent and extension studies, and those who received placebo for 4 years in the parent study followed by denosumab for 4 years in the extension study.

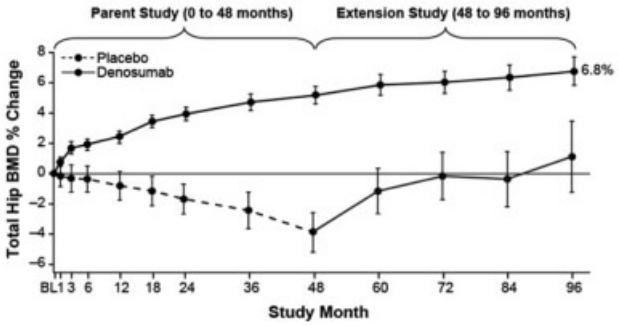
Results: Of the 262 subjects who completed the parent study, 200 enrolled in the extension study and of these, 138 (69%) completed the 4-year extension study. For the 88 subjects who received 8 years of continuous denosumab treatment, BMD at the lumbar spine and total hip increased on average by 16.5% and 6.8%, respectively, compared with their parent study baseline, and by 5.7% and 1.8%, respectively, compared with their extension study baseline (Figures 1 and 2). For the 12 subjects in the previous placebo group, 4 years of denosumab treatment resulted in gains in BMD comparable with those observed during the first 4 years of 60 mg Q6M in the parent study. Reductions in CTX and BSAP were sustained over the course of continuous denosumab treatment. Reductions in these BTMs were also observed when the placebo group transitioned to denosumab treatment. The adverse event profile was overall similar to what has been reported previously. There were no atypical fractures or ONJ events.

Figure 1: Percent Change in Lumbar Spine BMD From Parent Study Baseline



Data are least squares mean (95% CI). Subjects with parent study baseline and ≥ 1 post-baseline measurement were included.

Figure 2: Percent Change in Total Hip BMD From Parent Study Baseline



Data are least squares mean (95% CI). Subjects with parent study baseline and ≥ 1 post-baseline measurement were included.

Conclusion: These data demonstrated that continuous denosumab treatment for up to 8 years was associated with continued gains in BMD and persistent reduction in markers of bone turnover, and was well tolerated.

1108

Transitioning to Denosumab Leads to Further Increases in BMD throughout the Skeleton in Postmenopausal Women Who Received 5 or More Years of Continuous Alendronate Therapy. Michael A. Bolognese[1], Henry G. Bone[2], David L. Kendler[3], Maria Luisa Brandi[4], Anthony Hodsman[5], Philippe Orcel[6], Hoi-Shen Radcliffe[7], Andreas Grauer[8] and Cesar Libanati[8]. [1]Bethesda Health Research Center, Bethesda, MD, [2]Michigan Bone and Mineral Clinic, Detroit, MI, [3]University of British Columbia, Vancouver, BC, [4]University of Florence, Florence, Italy, [5]University of Western Ontario St. Joseph's Health Center, London, ON, [6]Lariboisière University Hospital, Paris, France, [7]Amgen Inc., Cambridge, United Kingdom, [8]Amgen Inc., Thousand Oaks, CA

Background/Purpose: Denosumab treatment led to significantly greater BMD gains throughout the skeleton in women who transitioned from alendronate to denosumab compared with those who remained on alendro-

nate, as reported in STAND (Study of Transitioning from Alendronate to Denosumab; Kendler DL, et al. *JBMR*. 2010;25:72). To participate in STAND, women had to have received alendronate for ≥ 6 months. The median alendronate exposure in STAND was 36 months (range 6 to 192 months); the primary endpoints have been previously reported. Because an increasing number of women are presently discontinuing their treatment after 5 or more years of bisphosphonate administration, we now report on the efficacy and safety from a subset of women from STAND who transitioned to denosumab after 5 or more years of continuous alendronate therapy.

Methods: STAND was a randomized, double-blind, double-dummy study in 504 postmenopausal women aged 67.6 ± 7.8 years with low BMD. Women were transitioned to denosumab (60 mg every 6 months subcutaneously) or were continued on branded alendronate therapy (70 mg weekly) for 12 months. All analyses were post-hoc and exploratory.

Results: In STAND, 149 women aged 70.0 ± 7.6 years had received alendronate for ≥ 5 years. These women were slightly older and had worse total hip but not lumbar spine BMD than those treated with alendronate for < 5 years. A total of 70 women transitioned to denosumab and 79 women remained on alendronate. Transitioning to denosumab for 12 months led to further significant increases in BMD of 2.95% (lumbar spine), 1.66% (total hip), and 1.02% (femoral neck). In contrast, those who remained on alendronate had smaller changes in BMD of 1.55% (lumbar spine), 0.97% (total hip), and 0.25% (femoral neck). A treatment-by-prior alendronate exposure interaction analysis did not indicate any differences in greater gains in BMD observed with the transition to denosumab in the subgroup exposed to alendronate for ≥ 5 years compared with the overall STAND population results at all measured sites.

Of the women who received alendronate for ≥ 5 years, a similar number of adverse events were reported by those who transitioned to denosumab and those who continued to receive alendronate (81.4% and 84.8%, respectively). The most frequently reported adverse events were nasopharyngitis (16.1%), back pain (11.4%), nausea (7.4%), bronchitis (7.4%), pain in extremity (7.4%), and arthralgia (7.4%). There were no cases of osteonecrosis of the jaw, delayed fracture healing, or atypical femoral fractures.

Conclusion: Consistent with the results from the overall STAND study, transitioning to denosumab after ≥ 5 years of continuous alendronate treatment led to further significant gains in BMD at the lumbar spine, total hip, and femoral neck, and demonstrated a similar safety profile compared with those who continued on alendronate.

1109

Current Vs. Past Exposure to Corticosteroids: Which Is Most Associated with Osteoporotic Fractures in Systemic Lupus Erythematosus Patients?
Laurence S. Magder[1] and Michelle Petri[2]. [1]University of Maryland, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: SLE patients are at excess risk for osteoporotic fractures. It is widely thought that this excess risk is explained, in part, by exposure to corticosteroids, but there is uncertainty whether cumulative past exposure or current levels of exposure are most important to fracture risk. In addition, other possible risk factors in SLE such as avoidance of sunlight for those with cutaneous SLE, renal failure, or chronic arthritis have been postulated but not confirmed. We explored risk factors for incident osteoporotic fracture in a large cohort of SLE patients.

Methods: The cohort consists of patients with SLE who are followed quarterly. This analysis was based on the cohort experience of 2044 patients who did not have an osteoporotic fracture prior to cohort entry. The patients were 90% women, 56% Caucasian, and 37% African-American. Osteoporotic fracture was defined as fracture by x-ray, CT or MRI in a patient with known osteopenia/osteoporosis. We calculated fracture rates in subgroups, and assessed the effect of predictors controlling for confounders using pooled logistic regression.

Results: 184 incident fractures were experienced over 12,039 person-years of observation (Rate=15.3 per 1000 person years). Adjusting for age, rates were significantly higher among Caucasians and those with hyperlipidemia (Table). A slight increased rate was seen among those with cutaneous SLE, but no increase was seen with renal or musculoskeletal involvement. The effect of corticosteroids was mainly seen for those with both current use and cumulative exposure. Rates were not significantly higher among those with current use if they had low levels of cumulative exposure, or for those with moderate levels of cumulative exposure but no current use. These relationships persisted after adjustment for all the above variables in a multivariable model.

Table. Rates of fracture, by patient exposures and characteristics

	Subgroup	Observed Number of Fractures	Rate of events per 1000 person-years	Rate Ratios based on a model that adjusts for age (95% CI)	P-value
Age	18–39	56	9.5	1.0 (Ref. Gp)	0.056
	40–49	45	14.0	1.5 (1.0, 2.2)	<0.0001
	50–59	52	26.8	2.8 (1.9, 4.1)	0.0016
	60–69	18	22.4	2.4 (1.4, 4.0)	<0.0001
	70+	13	62.0	6.5 (3.6, 11.9)	
Sex	Female	174	15.7	1.0 (Ref. Gp)	0.12
	Male	10	10.4	0.6 (0.3, 1.1)	
Race	Caucasians	126	20.1	1.0 (Ref. Gp)	<0.0001
	African-Americans	52	10.0	0.5 (0.4, 0.7)	0.31
	Other	6	10.1	0.7 (0.3, 1.5)	
Most recent Cholesterol	<150	15	7.2	1.0 (Ref. Gp)	0.022
	150–199	73	15.0	1.9 (1.1, 3.3)	0.0001
	200+	70	26.0	3.0 (1.7, 5.3)	
History of Arthritis	No	92	14.5	1.0 (Ref. Gp)	0.99
	Yes	91	16.4	1.0 (0.7, 1.3)	
History of Cutaneous lupus	No	56	12.5	1.0 (Ref. Gp)	0.084
	Yes	127	17.5	1.3 (1.0, 1.8)	
Renal Involvement	None	99	15.3	1.0 (Ref. Gp)	0.87
	Protein in urine	34	13.0	1.0 (0.7, 1.4)	0.32
	Nephrotic syndrome	10	9.1	0.7 (0.4, 1.4)	0.54
	Renal Insufficiency	41	21.9	1.4 (1.0, 2.1)	
Mean Serum Creatinine during cohort	<1.0	105	15.4	1.0 (Ref. Gp)	0.71
	1.0–1.2	23	20.3	1.1 (0.7, 1.7)	0.85
	1.2+	14	17.7	0.9 (0.5, 1.7)	
BMI	<20	13	15.2	1.0 (Ref. Gp)	0.91
	20–25	51	16.1	1.0 (0.5, 1.8)	0.38
	25–30	41	14.3	0.8 (0.4, 1.4)	0.76
	30+	61	17.6	0.9 (0.5, 1.7)	
Corticosteroids					
Current dose of corticosteroids	none	71	13.0	1.0 (Ref. Gp)	0.14
	1–9 mg/day	50	17.2	1.3 (0.9, 1.9)	0.0001
	10–19 mg/day	41	24.4	2.2 (1.5, 3.2)	0.0144
	20+ mg/day	15	19.9	2.0 (1.2, 3.5)	
Cumulative past dose of corticosteroids	None	21	14.0	1.0 (Ref. Gp)	0.94
	<3650 mg	17	12.8	1.0 (0.5, 1.9)	0.40
	3650–10,950	25	15.4	1.3 (0.7, 2.3)	0.071
	10,950–36,499	55	20.0	1.6 (1.0, 2.6)	0.0090
	36,500+	26	26.5	2.2 (1.2, 3.8)	
Current vs. Cumulative Dose	Low current[1], low cumulative[2] dose	55	14.0	1.0 (Ref Gp)	0.35
	Low current, high cumulative dose	41	17.0	1.3 (0.8, 1.8)	0.53
	High current, low cumulative dose	8	13.7	1.2 (0.6, 2.7)	<0.0001
	High current, high cumulative dose	40	31.5	2.8 (1.8, 4.2)	

[1] Low current means < 10mg/d
[2] Low cumulative means <3650 mg

Conclusion: Our data suggest that both cumulative and current exposure to corticosterioids are needed to incur an increased risk of fracture. This suggests that rates return to close to baseline after stopping corticosteroids, and are not increased with short-term use. However, additional studies are needed to confirm these findings.

1110

Severe Vitamin-D Deficiency in HIV-Infected Patients: Relationships with Inflammation, Bone Metabolism and Functional Status.
Thiphaine Ansemant[1], Paul Ornetti[1], Christine Piroth[1], Sophie Mahy[2], Jean C. Guilland[3], Laurence Duvillard[3], Delphine Croisier[2], Stephanie Ewing[3], Christian Tavernier[1], Pascal Chavanet[2], Jean Francis Maillefert[1] and Lionel Piroth[2]. [1]Rheumatology, Dijon, France, [2]Infectious diseases department, Dijon, France, [3]INSERM U866 and laboratory of biochemistry, Dijon, France

Background/Purpose: to assess the relationships between severe hypovitaminosis D (SHD) with lifestyle habits, comorbidities, HIV infection and antiretroviral history, and inflammation in HIV infected patients.

Methods: 263 unselected HIV infected outpatients consulting during spring 2010 were included in a cross sectional study. Apart from clinical examination, data on their medical history, food habits, sun exposure and addictions were collected. Fasting blood samples were taken for immunological, virological, inflammation, endocrine and bone evaluations.

Results: SHD (<10ng/ml) was found in 95 (36%) patients, and mild deficiency (10–30 ng/ml) in 135 (51%). In multivariate analysis, SHD was associated i) with mean daily sun exposure (OR +1 hour: 0.84, 95% CI: 0.74–0.94, p=0.03), current (OR: 2.63; CI95%: 1.27–5.45, p=0.009) or past (OR: 2.74; 95% CI: 1.17–6.43, p=0.02) smoking, Hepatitis C (OR: 1.87; 95% CI: 0.92–3.85, p=0.09) and B (OR: 2.76; CI95%:1.17–6.54, p=0.005) coinfections, functional status (OR for past history of fall: 1.80 95% CI: 1.00–3.27, p=0.02), and ii) with increased IL-6 levels (OR +1 pg/ml, 1.13, 95% CI: 1.02–1.25, p=0.02), and elevated C-Telopeptides × (CTX) (OR:2.44 95% CI: 1.23–4.81, p=0.01).

Conclusion: SHD appears to be more closely associated with comorbidities and functional status than with the history of HIV infection and the therapies used. Certain antiretroviral drugs may have a negative impact, which could be counterbalanced by a positive impact on inflammation. Increased CTX reflects higher oscteoclastic activity and the risk of bone fracture, and underlines the need to improve functional status and the management of comorbidities, in addition to vitamin D supplementation.

1111

Inhibitory Effects of 1′,2′-Dihydrorotenone On Osteoclast Differentiation and Bone Resorption. Chang-Hoon Lee[1], Myung-Soon Sung[2], Eun-Gyeong Lee[2], Myong Joo Hong[2] and Wan-Hee Yoo[2]. [1]Department of Internal Medicine, School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea, [2]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea

Background/Purpose: Osteoclasts, which are bone-resorbing multinucleated cells, are derived from hematopoietic cells of the monocyte-macrophage lineage and play a key role in bone resortion. Regulation of osteoclast fusion is important to treat of bone resorbing disease such as osteoporosis and rheumatoid arthritis. The aim of this study was to identify a new compound that inhibits osteoclast differentiation and bone resorption.

Methods: Osteoclast formation was evaluated in bone marrow cells (BMC) in the presence or absence of 1′,2′-dihydrorotenone. The expression of c-fos and NFATc1 mRNA in osteoclast precursor were assessed by RT-PCR. The levels of c-fos and NFATc1 protein were assessed by western blot. Also the MAPKs and NF-κB pathways were measured using Western blot analysis. Osteoclast function was evaluated with resorption pit assay. With LPS treated mouse model, We evaluated the effects of 1′,2′-dihydrorotenone on LPS induced bone loss when co-treated with it by using micro CT and histomorphometric analysis.

Results: 1′,2′-dihydrorotenone inhibited receptor activator of NF-kB ligand (RANKL)-induced osteoclast differentiation of cultured bone marrow macrophages (BMMs) in a dose-dependent manner. However, 1′,2′-dihydrorotenone did not exert cytotoxic effect on BMMs. 1′,2′-dihydrorotenone suppressed the expression of c-fos and NFATc1 as well as osteoclast specific genes in BMMs treated with RANKL. Treatment with RANKL inhibited the expression of inhibitors of differentiation/DNA binding (Id)1, 2, and 3; however, in the presence of 1′,2′-dihydrorotenone, RANKL did not suppress the expression of Id1, 2, and 3. Furthermore, 1′,2′-dihydrorotenone inhibited bone resorption and considerably attenuated the erosion of trabecular bone induced by lipopolysaccharide treatment.

Conclusion: Taken together, these results suggest that 1′,2′-dihydrorotenone has the potential to be applied in therapies for bone-related diseases.

1112

Interesting Roles of IL-1 in Osteoclast Differentiation. Chang-Hoon Lee[1], Myung-Soon Sung[2], Eun-Gyeong Lee[2], Myong Joo Hong[2] and Wan-Hee Yoo[2]. [1]Department of Internal Medicine, School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea, [2]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea

Background/Purpose: Osteoclast differentiation plays key role in bone resorption in many erosive bone disease and inflammatory situation. Osteoclasts are multinucleated cells that are formed by the fusion of mononuclear osteoclasts, which is an essential process in bone resorption leading to bone remodeling. The aim of this study was to evaluate the exact effects of IL-1, known as proinflammatory cytokine, on osteoclasogenesis, especially on fusion of mononuclear osteoclasts.

Methods: Prefusion osteoclasts (pOCs) were generated from bone marrow macrophages treated with M-CSF and RANKL. pOC cultures have been used to investigate the effect of IL-1 on multinuclear cell formation. Expression of c-Fos, NFATc1, and DC-STAMP were determined by RT-PCR and Western blot analysis. We used constitutively active (CA)- MKK6 adenovirus to evaluation of the signaling of p38 induced by IL-1

Results: we showed that IL-1 promoted the fusion of prefusion osteoclasts (pOCs). IL-1 induced the expression of DC-STAMP and Atp6v0d2 that were mediated by inducing NFATc1 via induction of c-Fos. The expression of c-Fos and NFATc1 was regulated by the p38 signaling pathway. Inhibition of p38 and NFATc1 suppressed the expression of DC-STAMP Atp6v0d2 and led to the inhibition of pOC fusion. However, retrovirus-mediated expression of NFATc1 in pOCs rescued the defect in pOC fusion, despite the presence of SB. The ectopic expression of CA-MKK6 induced DC-STAMP and Atp6v0d2 expression and fusion of pOCs under stimulation of IL-1. DC-STAMP and Atp6v0d2 expression increased with constitutively active (CA)-NFATc1. Expression of DC-STAMP and Atp6v0d2 with NFATc1 inhibitor, cyclosporine was reduced.

Conclusion: IL-1 induced fusion of pOCs to form multinucleated osteoclast by inducing expression of c-fos, NFATc1 through p38 pathway.

1113

Application of Combined Algorithms with Peripheral Bone Mineral Density (BMD) and Risk Indeces to Reduce the Requirement for Central Dual X-Ray Absorptometry (DXA). María América López-Lasanta[1], Francisco G. Jiménez-Núñez[1], Carmen M. Romero-Barco[1], Sara Manrique-Arija[1], Verónica Rodriguez-García[1], Miguel A. Descalzo[2], Blanca Panero[1], Jose Mancera Romero[3], Silvia Mesa González[3], Maria Carmen Ordóñez[1], Inmaculada Ureña[1], Manuel Rodríguez-Pérez[1] and Antonio Fernandez-Nebro[4]. [1]Hospital Regional Universitario Carlos Haya., Málaga, Spain, [2]Spanish Society of Rheumatology, Madrid, Spain, [3]Health Center "Ciudad Jardín", Malaga, Spain, [4]Hospital Regional Universitario Carlos Haya, Málaga, Spain

Background/Purpose: Currently the diagnosis of osteoporosis (OP) by BMD as defined by the WHO is applied to central DEXA. PIXI devices are smaller, portable, and faster, and cheaper than central DEXA, so that a PIXI scan may cost 70–85% less than a DEXA scan. However, PIXI results cannot be interpreted using the WHO definition and do not correlate perfectly with BMD at central DEXA. Objective: To analyse if using risk indices and PIXI scans jointly would reduce requirement for central DEXA to diagnose postmenopausal OP.

Methods: A stratified sample of postmenopausal women was selected: a random sample of 305 postmenopausal women from Primary care, and 200 consecutive postmenopausal women referred for central DXA measurement from tertiary care. Inclusion criteria: Caucasian female, age ≥50 yrs, and full menopause (amenorrhea ≥12 mo.). Exclusion criteria: previous diagnose of OP, previous treatment with OP drugs (calcium and/or vitamin D and/or estrogens for menopausal symptoms treatment were allowed) or steroids and other drugs related with low BMD, and institutionalized persons OR Steinbrocker's functional grade 4. Informed consent was obtained. Four risk indices were calculated: SCORE, ORAI, OSIRIS, and OST. All participants underwent two different BMD measurements: a non-dominant heel BMD-(PIXI Lunar, Software #50699, GE Corp.), and a central DXA of the hip and lumbar spine (Lunar Prodigy Advance, Software ENCORE 2006, PA+300274, GE Corporation). OP definition according to the WHO was used. Statistical analyses: The diagnostic utility was measured by ROC curves. We calculated the sensitivity and specificity for risk indices, PIXI, and all possible combinations. Logistic regression was performed to build a risk model with the presence or absence of osteoporosis at the central DEXA as dependent variable. The thresholds was established in 2 ways: 1) a cutoff point where the sensitivity and specificity are maximized, and 2) with two cutoff points, where both it sensitivity and specificity reached 90%.

Results: 505 Caucasian women with a mean (SD) 61 (8) yrs, were recruited. Median (p25-p75) scores for each risk index were: OST 1 (0–3), ORAI10(7–14), and SCORE 8(6–11). The mean (SD) PIXI T-score of the calcaneus was −0.33 (1.14). The mean (SD) femoral neck T-score was −1.01 (1.05), total femur was −0.59 (1.19) and lumbar T-score was −1.18 (1.36). The prevalence of osteoporosis by central DXA was 20%(n = 102), 19% (57) in primary care and 23% (45) in tertiary care. The combined algorithm PIXI + OST + SCORE was the greatest area under the curve obtained: 75%(95%CI, 71 to 79). Most favorable threshold for this algorithm stratified subjects into high, medium, and low risk according to 2 cutoff (−20 and −5, respectively), and the most favorable subsequent decision was referral for central DXA if the medium or high risk categories were reached. According to this algorithm (table) 11 (2.2%) false positives were obtained, but 257 (52%) central DEXA were avoided and a 20 – 35% in costs could have been saved.

Conclusion: A triage based on a combined algorithm composed of PIXI + OST + SCORE reduces reduce the requirements of central DEXA a 52%, and may savings cost.

1114

Fractures and Mortality in Relation to Different Osteoporosis Treatments. Huifeng Yun[1], Elizabeth S. Delzell[1], Robert Matthews[1], Meredith Kilgore[1], Kenneth G. Saag[1], Cathleen Colon-Emeric[2], Christopher M. O'Connor[3], Kenneth W. Lyles[3], Michael Morrisey and Jeffrey R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Duke University Medical Center and the Durham VA GRECC, Durham, NC, [3]Duke University School of Medicine, Durham, NC

Background/Purpose: Few studies have assessed the effectiveness of different drugs for postmenopausal osteoporosis (OP). We compared fracture incidence and mortality among Medicare beneficiaries initiating various OP medications.

Methods: Using the Medicare national random 5% sample, we identified new users of oral bisphosphonates (BPs), intravenous (IV) ibandronate (IBN), IV zoledronic acid (ZOL), calcitonin (CAL), raloxifene (RAL) and parathyroid hormone (PTH). Eligible subjects were >=65 years; continuously enrolled in fee for service and part D Medicare; and newly treated during 2006–2008. New treatment was defined as therapy initiated after 12 month baseline during which no prescription was filled for the drug. Subjects remained in their initial drug category regardless of any switching of medication during follow-up. Cox proportional hazards models evaluated associations between different OP drugs and mortality and also first hip, distal radius/ulna, clinical vertebral, or humerus fracture. Analyses used IV ZOL as the referent and adjusted for multiple confounders. Further confounder control was examined using propensity score (PS) quintile adjusted and PS matched analyses.

Results: We identified 24537 new users for oral BPs, 750 for IV IBN, 1962 for IV ZOL, 7231 for CAL, 986 for PTH and 2222 for RAL. These cohorts experienced, respectively, 8.4%,, 12.9%, 8.8%, 17.0%, 13.6%, 7.8% fractures and 8.8%, 7.6%,6.1%, 21.2%,12.9% and 6.4% deaths during follow-up. After multivariable adjustment (ZOL referent), hazard ratios for fracture were 1.41 (95% CI: 1.03–1.93) for IV IBN, 1.33 (1.06–1.66) for oral BPs; 1.47 (1.16–1.86) for CAL, 1.27 (0.97–1.67) for RAL and 1.05 (0.78–1.42) for PTH; and for mortality were 0.84 (0.60–1.22) for IBN, 0.94 (0.76–1.18) for oral BPs, 1.47 (1.17–1.85) for CAL, 0.99 (0.75–1.31) for RAL and 1.31 (0.98–1.75) for PTH.

Table. Compare the crude and adjusted hazard ratios between different osteoporosis drugs

	Fractures		Death	
Treatment	**Crude**	**Adjusted**	**Crude**	**Adjusted**
IV Zoledronic acid	Ref	Ref	Ref	Ref
IV Ibandronate	2.30 (0.95–1.76)	1.41 (1.03–1.93)	0.86 (0.60–1.22)	0.84 (0.59–1.20)
Oral BP	0.82 (0.67–1.00)	1.33 (1.06–1.66)	1.04 (0.84–1.28)	0.94 (0.76–1.18)
Calcitonin	1.63 (1.30–2.04)	1.47 (1.16–1.86)	2.48 (1.99–3.09)	1.47 (1.17–1.85)
Raloxifene	0.73 (0.56–0.95)	1.27 (0.97–1.67)	0.75 (0.57–0.98)	0.99 (0.75–1.31)
Parathyroid Hormone	1.21 (0.90–1.62)	1.05 (0.78–1.42)	1.46 (1.10–1.93)	1.31 (0.98–1.75)

Note: We adjusted age, gender, race, geographic region, income, osteoporosis related conditions, other comorbidities and medications at baseline.

Conclusion: Compared to IV ZOL, fracture rates among users of other BPs or CAL were 33–47% higher; mortality was 47% greater among users of CAL. While fracture benefit may be in part mediated through improved adherence to IV ZOL, the mechanism for a possible mortality benefit remains unclear.

1115

Bach1 Regulates Osteoclastogenesis Via Heme Oxgenase-1 Dependent and Independent Pathways. Maasa Hama[1], Yohei Kirino[1], Mitsuhiro Takeno[1], Kaoru Takase[1], Ryusuke Yoshimi[1], Atsuhisa Ueda[1], Akihiko Muto[2], Kazuhiko Igarashi[2] and Yoshiaki Ishigatsubo[1]. [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Tohoku University Graduate School of Medicine, Sendai, Japan

Background/Purpose: Bone destruction of rheumatoid arthritis (RA) is caused by abnormally activated osteoclasts (OCs). It is suggested that induction of heme oxygenase (HO)-1 is beneficial for the treatment of RA by reducing inflammation. However the function of HO-1 in bone metabolism remains unclear. The objective of this study is to clarify the influence of HO-1 and its repressor BTB and CNC homolog 1 (Bach1) on osteoclastogenesis.

Methods: *In vitro* osteoclastogenesis was compared between Bach1 deficient and wild type mice. OCs were generated from bone marrow derived macrophages (BMM) by stimulation with M-CSF and RANKL. Osteoclastogenesis and OC function were assessed by tartrate-resistant acid phosphatase staining, expression of OC-related genes, and the pit resorption assay. Intracellular signal pathways in OC precursors were also assessed. HO-1 shRNA was transduced into *Bach1*$^{-/-}$ BMM to examine the role of HO-1 in osteoclastogenesis.

Results: Transcription of HO-1 was down-regulated by RANKL stimulation in the early stage of OC differentiation. *Bach1*$^{-/-}$ BMM were partially resistant to the RANKL dependent HO-1 reduction and showed impaired osteoclastogenesis, which was associated with reduced expression of RANK and components of the downstream TRAF6-c-Fos-NFATc1 pathway as well as the expression of Blimp-1. Treatment with HO-1 shRNA increased the number of OCs and expression of the OC-related genes except Blimp-1 during the *in vitro* osteoclastogenesis from *Bach1*$^{-/-}$ BMM. Furthermore, osteoclastogenesis in *Bach2*$^{-/-}$ BMM was similar to WT whereas *Bach1*$^{-/-}$*Bach2*$^{-/-}$ similar to *Bach1*$^{-/-}$.

Conclusion: Bach1 regulates osteoclastogenesis via both HO-1 dependent and independent mechanisms. Inhibition of Bach1 function thus may be a promising therapy for inflammatory bone loss in diseases including RA.

1116

Maintenance of Antifracture Efficacy Over 10 Years with Strontium Ranelate in Postmenopausal osteoporosis. J.-Y. Reginster[1], Jean-Marc Kaufman[2], Jean-Pierre Devogelaer[3], Claude-Laurent Benhamou[4] and Christian Roux[5]. [1]University of Liège, Liège, Belgium, [2]Ghent University Hospital, Ghent, Belgium, [3]St-Luc University Hospital, Brussels, Belgium, [4]Hopital de la Source, Orleans, [5]Paris Descartes University, Paris, France

Background/Purpose: Postmenopausal osteoporosis is a chronic disease requiring long-term treatment. Strontium ranelate (SrRan) 2g/day has proven efficacy against vertebral and non vertebral fractures including hip over 5 years in postmenopausal women. Results showing the continuous benefit on osteoporotic fractures and bone mineral density (BMD) over 8 years have already been reported (1). This abstract presents efficacy results over 10 years.

Methods: The two double blind placebo-controlled phase III studies included a total of 6740 Caucasian women with postmenopausal osteoporosis. In SOTI, patients were randomly assigned to receive SrRan 2g/day or placebo for 4 years and during the 5th year, half of the SrRan group continued with SrRan. In TROPOS, patients were randomly assigned to receive SrRan 2g/day or placebo for 5 years. Patients having participated in both studies up to 5 years were invited to enter a 3-year open-label extension study, subsequently extended by 2 years, and then received strontium ranelate up to 10 years. Here are presented the efficacy results in patients treated with SrRan for 10 years.

Results: At SOTI and TROPOS baseline, patients treated for 10 years (n= 233) had a profile similar to the whole population with a mean (SD) age of 72.0(5.5) years, a mean (SD) lumbar spine and femoral neck BMD T-score of –3.30(1.38) and –2.95(0.57) respectively. Over the 10-year period, lumbar BMD increased continuously and significantly ($p<0.05$ up to year 10) with, at 10 years, a relative change from baseline of 34.5%±20.2. At the femoral neck and total hip sites, the BMD increased significantly until year 7, with a relative change from baseline of 10.7%±12.1 and 11.7%±13.6 respectively, and then remained stable.

The cumulative incidences of new vertebral and non vertebral fractures (20.6% and 13.7% respectively) over the 5-year extension were not statistically different ($p=1.00$ and 0.672 respectively) to the cumulative incidences over the 5 years in the original studies (18.5% and 12.9% respectively). To assess the anti-fracture efficacy of SrRan in the absence of placebo group, we searched for a matching population in the placebo group of TROPOS using the 10-year probability of major osteoporotic fracture calculated with FRAX® as matching variable. The mean 10-year probability of major osteoporotic fracture, calculated with FRAX®, in the 233 patients treated for 10 years with SrRan was 25.8% at the time of their inclusion in the extension study. The incidences of vertebral and non-vertebral fracture observed over the 5 years of TROPOS were significantly higher ($p<0.05$) in the matching placebo group than those observed in the "10-year" population over the 5- year extension, with a relative risk reduction with SrRan of 35% and 38% for vertebral fractures and non-vertebral fractures respectively.

Strontium ranelate remained safe and well tolerated over 10 years with no unexpected adverse event.

Conclusion: These results are in favour of the maintenance of the efficacy of strontium ranelate over 10 years, with a good safety profile.

1. Reginster JY et al. Long-term treatment of postmenopausal osteoporosis with strontium ranelate: results at 8 years Bone 2009;45(6):1059–1064

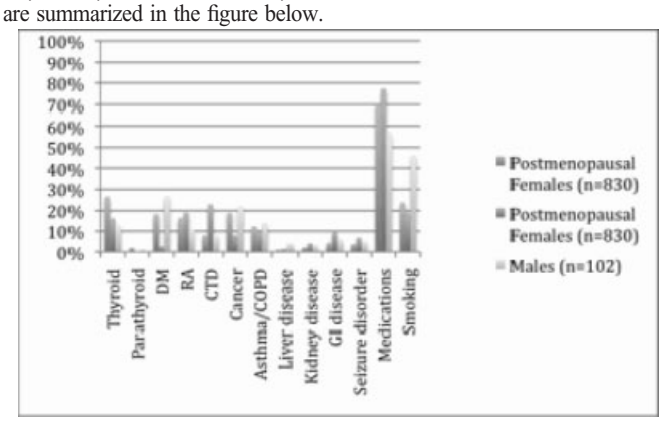
1117

Analysis of Prevalence of Low Bone Mineral Density and Secondary Causes In Patients Undergoing Bone Density Measurement. Andrew Wilson, Anuj Patel, Toni Peters and Vikas Majithia. University of Mississippi Medical Center, Jackson, MS

Background/Purpose: There are a number of known secondary causes (SC) of low bone mineral density (BMD) i.e. osteopenia and osteoporosis. These have not been well quantified and may be prevalent at different rates in younger populations and males. This study aims to describe the prevalence of number and kind of SC in men and women with low BMD.

Methods: Retrospective chart review of patients who had a DEXA scan performed at center between Jan 2009 - Dec 2009. Prevalence of Low BMD, defined as presence of a T-score less than −1.0, co-morbid illness, medications and SC was calculated.

Results: A total of 1,339 patient charts were reviewed (112 premenopausal, 1,088 postmenopausal, 139 men). We found low BMD was common and seen in 75% (1,007/1,339) of patients. Low BMD was seen in 67% (75/112) of pre-menopausal patients, 76% (830/1088) of post-menopausal patients, and 73% (102/139) of men. The SC were also very prevalent among these patients with about 80% having at least one and 40 % of these patients had a normal Z-score. The most prevalent SC and co-morbid conditions were medication use including steroids, smoking, thyroid disease, diabetes mellitus, cancer, rheumatoid arthritis, and connective tissue disease. These results are summarized in the figure below.



The prevalence of these variables was different among the patients with low BMD among 3 subgroups—postmenopausal females, premenopausal females and males. Postmenopausal women had a significantly higher prevalence ($p<0.05$) of thyroid disorders, hyperparathyroidism, diabetes, cancer, asthma/COPD and GI diseases than premenopausal females, who had a higher prevalence of other CTD. Male had significantly higher prevalence ($p<0.05$) of liver disorders, smoking and a lower prevalence of thyroid disorders, diabetes and medication use. There was no significant difference among the white and African-Americans.

Conclusion: The results show a high prevalence of low BMD in this cohort of patients across all 3 subgroups including young females and males, who traditionally are felt to have normal bone mass. In addition there was a high prevalence of the secondary causes in this cohort and presence of multiple SC. There were significant differences in their prevalence across the subgroups as highlighted above. Although population prevalence cannot be calculated from this cohort study, these findings suggest that low bone density is fairly prevalent and is usually associated with a contributing co-morbidity or SC in both females and males even with normal Z-score. Low BMD on DEXA scan even with a normal Z-score should prompt work-up for secondary causes. Conversely, presence of known secondary causes should alarm the clinician to obtain the measurement of BMD to prevent serious consequence of fractures.

1118

Long-Term Warfarin Use Is Not Associated with Fracture Risk. Devyani Misra[1], Yuqing Zhang[2], Christine Peloquin[2], Hyon K. Choi[2] and Tuhina Neogi[2]. [1]Boston University Medical Centre, Boston, MA, [2]Boston University School of Medicine, Boston, MA

Background/Purpose: Vitamin K deficiency has been associated with osteoporotic fractures but the mechanism for this association is unclear. Skeletal effects of vitamin K are mediated through Gla-proteins, which require vitamin K for conversion into their functional forms. Osteocalcin, a skeletal Gla-protein, promotes binding of calcium to hydroxyapetite in bones in its functional form. Warfarin, a vitamin K antagonist, has been shown to reduce functional osteocalcin levels, thus potentially increasing the risk for osteoporosis and related fractures. While some studies have reported increased risk of fracture, mainly at vertebral site, others have not found an association. We examined the association of long-term warfarin use with hip and wrist fractures, which are two common osteoporotic fracture sites, in a large population based cohort of elders with atrial fibrillation and long follow-up time.

Methods: Participants were men and women 65 years or older with incident atrial fibrillation followed between 1990–2010 from The Health Improvement Network (THIN), an electronic medical records database of more than 7.3 million patients in the UK containing clinical diagnoses and prescription data. Long-term warfarin use was defined in two ways: 1) warfarin use ≥1year; 2) warfarin use ≥3 years. Non-use was defined as never use of warfarin over the follow-up period. For each subject we calculated a propensity score using logistic regression with long-term use of warfarin as the dependent variable and age, sex, body mass index (BMI), high fall risk, heart failure, neuropsychiatric impairment, beta blockers, corticosteroids, bisphosphonates, smoking and alcoholism as independent variables. Each long-term warfarin user was matched to a non-user based on propensity score using the "greedy matching" method. We examined the association between long-term warfarin use and risk of hip and wrist fractures separately, using Cox-proportional hazards model adjusting for the covariates.

Results: We included 23,616 participants (48% women, mean age 77± 6.3y, mean BMI 27± 5.1 kg/m^2) in the hip fracture analysis and 23,302 participants with similar demographics in the wrist fracture analysis. Average follow up time was 1260±1020 days and 1258± 1024 days for hip and wrist fractures, respectively. There were 419 incident hip fractures and 197 incident wrist fractures. Long-term warfarin use, either ≥1 years or >3 years, was not associated with the risk of either incident hip fracture or incident wrist fracture (Table).

Table. Warfarin use and Risk of Hip and Wrist Fracture

	Hip Fracture			Wrist Fracture		
	Cases	Rates per 1000 person-years	Hazards Ratio* (95% CI)	Cases	Rates per 1000 person-years	Hazards Ratio* (95% CI)
Warfarin use ≥ 1 year	219	0.015	1.18 (0.91, 1.51)	101	0.007	1.0 (0.71, 1.41)
Non-use	200	0.014	1.0 (reference)	96	0.007	1.0 (reference)
Warfarin use ≥ 3 years	128	0.016	0.98 (0.71, 1.34)	52	0.007	1.17 (0.70, 1.97)
Non-use	136	0.017	1.0 (reference)	48	0.006	1.0 (reference)

* Adjusted for age, sex, body mass index (BMI), high fall risk, heart failure, neuropsychiatric impairment, beta blockers, corticosteroids, bisphosphonates, smoking and alcoholism.

Conclusion: In this large cohort of elderly men and women, we did not find an association between warfarin use and risk of hip or wrist fracture, despite a plausible biologic mechanism. Thus, warfarin use may not necessitate increased surveillance or prophylactic therapy for osteoporosis in elders.

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Possible Hypophosphatasia in Personalized Medicine Research Project. Less K. Shrestha, Fergus E. McKiernan, Richard L. Berg and Jay T. Fuehrer. Marshfield Clinic, Marshfield, WI

Background/Purpose: Personalized Medicine Research Project (PMRP) at Marshfield Clinic is a population-based cohort of ~20,000 adult subjects receiving care almost exclusively at Marshfield Clinic for whom we have comprehensive, searchable electronic medical record lab data since 1960, ICD-9 diagnosis codes since 1980 as well as stored DNA, plasma and serum. Hypophosphatasia (HPP) is a genetic metabolic disorder of skeletal mineralization with an estimated prevalence for severe disease of 1/100,000. We postulated that mild forms of HPP are more prevalent in an adult population than currently appreciated. The purpose of our study is to identify subjects with possible hypophosphatasia (HPP) in Personalized Medicine Research Project (PMRP).

Methods: The Marshfield Clinic electronic medical record of all PMRP enrollees with recorded serum alkaline phosphatase (ALP) values mostly ≤ 30 IU/L (normal 40–120 IU/L) were manually searched for diagnostic terms, ICD-9 codes and laboratory values suggesting the presence of HPP. Individual radiographic reports and all available radiographs were reviewed for chondrocalcinosis and metatarsal stress fractures. Previously unrecognized HPP was considered possible when, in the judgment of the PIs, the available clinical, biochemical and radiographic evidence suggested its presence.

Results: 21 subjects (14 Females/7 Males) were identified whose serum ALP was mostly ≤ 30 IU/L. Chondrocalcinosis was present in 7/21(33%) and often characterized as extensive. 6/21(29%) had suspected or proven acute crystalline arthritis or calcific tendonitis. 5/21(24%) had calcaneal spurs or symptomatic foot exostoses. 4/21(19%) had ≥ 1 metatarsal or femur shaft fracture. 2/21(10%) had hip dysplasia. 2/3 subjects with available DXA scans had axial Z-scores ≥ +2.5. One subject each had kyphoscoliosis, mild hypermobility, clavicular osteolysis or fibromyalgia. Onset of acute crystalline arthritis and metatarsal fractures was typically 20–40 years of age. No subject had alternate explanations for these conditions (e.g., hyperparathyroidism) or previously diagnosed HPP. At least 7 of 21 (33%) subjects in PMRP with serum ALP mostly ≤30 IU/L were considered likely to have previously unrecognized mild HPP. 5 of these 7 subjects have since been

personally evaluated (FM) and the clinical impression of mild adult HPP has been confirmed.

Conclusion: Subjects with persistently low serum ALP appear to have significant musculoskeletal disease burden and some may have previously unrecognized HPP. Further clinical and biochemical investigations are warranted.

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Acute-Phase Response After Zoledronic Acid: Role of Vitamin D and of Previous Treatment with Oral Amino-Bisphosphonates. Marco Massarotti, Chiara Crotti, Nicola Ughi, Gianluigi Fabbriciani, Laura Belloli and Bianca Marasini. IRCCS Humanitas Clinical Institute, Rozzano (Milan), Italy

Background/Purpose: Amino-bisphosphonates (N-BPs) are currently considered the most important class of drugs used for the inhibition of osteoclast activity in common metabolic bone diseases, such as osteoporosis (OP), Paget disease, bone metastases, multiple myeloma and hypercalcemia. Recently, intravenous zoledronate has been licensed for the treatment of postmenopausal and male osteoporosis. The major adverse event of i.v. zoledronate is the development of an acute-phase response (APR), characterized by a transient mild flu-like syndrome with fever, fatigue, myalgia and malaise. The APR usually develops within 24 to 36 hours from the first infusion and resolves spontaneously within 2 to 3 days. The symptoms are due to an increased circulating level of interleukin 6 (IL-6), tumor necrosis factor β (TNF- β), and interferon-γ (IFN- γ). Recently an association between post-N-BPs APR and 25(OH)D has been disclosed, suggesting an interesting interplay among N-BPs, 25(OH)D and the immune system. The purpose of this study was to: a) Evaluate whether previous treatment with oral N-BP may influence APR after first zoledronate infusion; b) Confirm the association between 25(OH)D levels and APR.

Methods: We retrospectively evaluated 130 OP patients treated for the first time with i.v. zoledronate between October 2008 and April 2010 and selected a sample of 80 patient for which serum 25(OH)D levels had been dosed in the month preceding the infusion. We also recorded for these patients (81 F e 9 M; 72 $\pm$ 8 years of age): 1) previous treatment with oral N-BPs, 2) previous treatment with strontium ranelate and teriparatide, 3) serum calcium and PTH levels before the infusion, 4) concomitant treatments [corticosteroids; immunosuppressive drugs (eg MTX, AZA, CTX); aromatase inhibitors; statins].

Results: We verified the development of APR in 34 of the 80 patients in analysis (37.8% APR+ versus 62.2% APR-). 25(OH) D levels were significantly lower in the APR+ group than in the APR- subjects (29.9 $\pm$ 24.5 versus 39.4 $\pm$ 21.0; $p<0.05$) and the PTH levels resulted significantly higher in the APR+ group than in APR- subjects (60.7 $\pm$ 23.3 versus 50.4 $\pm$ 20.5; $p<0.0396$). Calcium levels were not significantly lower in the APR- group than in APR+ subjects (9.59 $\pm$ 0.4 versus 9.79 $\pm$ 0.5; $p=0.058$). Forty eight of the eighty patients were previously treated with orally N-BP (N-BPs+ 60% versus N-BPs- 40%). The APR frequency were significantly lower among the N-BPs+ subjects than the naive ones (31.3% vs 59.4%; $p=0.013$). We didn't find any relationship between the APR onset and age, previous treatment with teriparatide or strontium ranelate and the concomitant treatments evaluated (corticosteroids; immunosuppressive drugs; aromatase inhibitors; statins).

Conclusion: Our study confirms the association between low serum 25 (OH) levels and the development of APR and shows that a previous N-BPs treatment could reduce the APR incidence after the first i.v. zoledronate infusion; it also underlines, for the first time, the role of serum 25 OH levels in preventing APR induced by zoledronate, even in patients with previous treatment with N-BPs.

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Use of Pharmacologic Agents for the Prevention of Osteoporosis Among Older Women with Low Bone Mass Is Discordant with National Osteoporosis Foundation Guidance. Jie Zhang, Jeffery R. Curtis, Elizabeth S. Delzell and Kenneth G. Saag. University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: To determine if treatment with pharmacologic agents among postmenopausal women with low bone mass (T score between -1.0 and -2.5) was in concordance with the current and recent National Osteoporosis Foundation (NOF) clinical guidelines.

Methods: Cross-sectional analysis from 2007 to 2009 among participants of the Global Longitudinal Study of Osteoporosis in Women (GLOW) recruited from one study site. Eligible subjects had a bone density test within 2 years prior to a GLOW survey and had their lowest T score (of either total hip, femoral neck, lumbar spine, or 1/3 radius) between -1.0 and -2.5. Those who reported a history of hip or spine fracture were excluded. Fracture risk factors and the use of anti-osteoporosis medications were self-reported. We examined the proportions of women managed in concordance with the NOF 2003 and 2008 guidelines, with concordance defined as ever (current or past) received treatment among those recommended for treatment and never received treatment among those not recommended for treatment. Univariate odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results: Mean age among 770 eligible women was 70$\pm$7 years. When NOF 2003 guidelines were applied, 463 (61%) women were managed in concordance with the guidelines. Those who met NOF 2003 criteria were more likely to have ever received treatment (OR, 2.5; 95% CI, 1.9–3.4). Women with lower T scores were more likely to be treated (Table 1). Among those not recommended for treatment, women with T scores between -2.0 and -1.5 and absent of major risk factors were more likely to be treated than women with T scores between -1.5 and -1.0. Three hundred and nine (52%) women were managed in concordance with NOF 2008 guidelines. Those who met NOF 2008 criteria were not more likely to have ever received treatment (OR, 1.1; 95% CI, 0.8–1.6). Compared to women not recommended for treatment, those satisfying both NOF FRAX criteria were more likely to be treated (OR, 1.7; 95% CI, 1.1–2.6), while those satisfying only one of the criteria were not more likely to be treated (OR, 0.8; 95% CI, 0.5–1.4).

Table 1. Univariate associations between meeting and not meeting National Osteoporosis Foundation criteria and having ever received anti-osteoporosis treatment

	N (%) Treated	Odds Ratio (95% Confidence Interval)
NOF 2003 Guidelines$^{\mu}$		
Overall		
Treatment recommended	262 (60.4)	2.5 (1.9–3.4)
Treatment not recommended	122 (37.8)	Reference
*By BMD category and presence of major risk factors**		
Treatment recommended		
T score ≤ -2.0	168 (63.9)	3.8 (2.6–5.7)
$-2.0 <$ T score ≤ -1.5 and presence of at least one of the following risk factors*	94 (55.0)	2.7 (1.7–4.1)
Treatment not recommended		
$-2.0 <$ T score ≤ -1.5 and absent of the following risk factors*	64 (46.0)	1.9 (1.2–2.9)
$-1.5 <$ T score < -1.0	58 (31.5)	Reference
NOF 2008 Guidelines$^{\mu}$		
Overall		
Treatment recommended	168 (54.2)	1.1 (0.8–1.6)
Treatment not recommended	147 (51.0)	Reference
By FRAX risk score		
Treatment recommended		
10 year probability of hip fracture $\geq$ 3% and 10 year probability of major osteoporotic fracture $\geq$ 20%	98 (64.1)	1.7 (1.1–2.6)
Either 10 year probability of hip fracture $\geq$ 3% or 10 year probability of major osteoporotic fracture $\geq$ 20%, but not both	70 (44.6)	0.8 (0.5–1.4)
Treatment not recommended		
10 year probability of hip fracture $<$ 3% and 10 year probability of major osteoporotic fracture $<$ 20%	147 (51.0)	Reference

$^{\mu}$ The NOF 2003 and 2008 criteria could not be evaluated in 13 and 172 women respectively due to missing values on key fracture risk factors.
* Risk factors include fracture since turning 45, parental hip fracture, body weight $<$ 127 lbs, current smoking, and current glucocorticoid use

Conclusion: Up to 50% of the women with osteopenia were not treated in concordance with NOF guidelines. Those having one but not both of the NOF FRAX criteria for intervention were not more likely to be treated than those having neither. These results may reflect a lack of awareness of and insufficient dissemination of the guidelines among physicians.

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The Relationship Between the Level of Serum Lipids and Bone Metabolism Among Pre and Postmenopausal Women. Yun Sung Kim[1], Hae-Rim Kim[2], Sang-Hyon Kim[3] and Hyun-Sook Kim[1]. [1]Internal Medicine, Chosun University Hospital, Gwangju, South Korea, [2]Konkuk University Medical Center, Seoul, South Korea, [3]Dongsan Medical Center, Keimyung University, Daegu, South Korea

Background/Purpose: Previous in vitro and animal studies showed that high serum cholesterol reduced bone mass densitometry (BMD) by

affecting the cell differentiation of osteoblasts, and hyperlipidemic drugs (HMG-CoA reductase inhibitors) were shown to help preserve bone mass and prevent osteoporosis induced fracture. However there were only few studies which investigated the correlation between human serum lipid levels with biochemical bone markers reflecting bone metabolism. Therefore, this study was done to investigate the correlation between the two.

Methods: The subjects included 133 female adults who visited a health promotion center from November 2005 to May 2006. Urine deoxypyridinoline osteocalcin, and alkaline phosphatase (ALP) were used as bone markers and BMD was measured.

Results: There was a positive correlation between urine deoxypyridinoline and triglyceride ($r = 0.20$, $P = 0.02$), and a negative correlation with HLD-cholesterol ($r = -0.24$, $P < 0.01$). No correlation was found between osteocalcin and serum lipids but a positive correlation was noted between ALP and HLD-cholesterol ($r = 0.21$, $P = 0.01$). In an effort to study the relationship between bone marker and serum lipids, multiple regression analysis was conducted after adjusting for age, menopause status, the period of menopause, BMI (Body mass index), muscle mass, fat mass, and exercise amounts. According to the analysis, deoxypyridinoline had a statistically significant correlation with total cholesterol ($P < 0.01$), triglyceride ($P < 0.01$), HDL-cholesterol ($P = 0.013$), and LDL-cholestrol ($P < 0.01$), but osteocalcin showed no correlation. ALP was found to have a significant correlation with triglyceride ($P = 0.014$) and LDL-cholesterol ($P = 0.045$).

Conclusion: Significant correlation was noted between serum lipid level and deoxypyridinoline as bone absorption index and ALP as bone formation index. Therefore, lipid metabolism can affect the bone metabolism, and dyslipidemia patients should be managed in order to prevent osteoporosis.

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Vitamin D in Obesity (VIDeO): Assessing Vitamin D Deficiency in the Bariatric Population. Arthur N. Lau[1], Maria Tiboni[1], Zara Khalid[1], Roman Jaeschke[1], Mehran Anvari[1] and Jonathan D. Adachi[2]. [1]McMaster University, Hamilton, ON, [2]Hamilton, ON

Background/Purpose: Gastric bypass surgery (GBS) is becoming an increasingly common intervention for the morbidly obese. Little is known about the effects of GBS on bone metabolism. Adiposity has been inversely associated with vitamin D levels across a range of BMI and cultural groups. Our goal was to assess the prevalence of vitamin D deficiency pre-operatively, and post-operatively. As a quality assurance initiative, we also wanted to assess if our center was doing a satisfactory role in promoting vitamin D and calcium supplementation in this population, and if aggressive screening and treatment of deficiency had any effect on 25-hydroxyvitamin D levels.

Methods: In a retrospective chart review of 173 bariatric patients, baseline 25-hydroxyvitamin D, PTH and calcium levels were obtained pre-operatively and post-operatively at 3 and 6 months. We also assessed the percentage of patients on oral vitamin D and calcium supplementation at baseline and at each follow-up visit, and the number of patients receiving aggressive treatment with 50,000 IU of Vitamin D2 weekly. All patients with vitamin D deficiency during the follow-up period (below 50 mmol/L) were treated with 50,000 IU of vitamin D2 weekly for eight week duration.

Results: Of the 173 patients, 170 had undergone laparoscopic roux-en-y bypass, 3 received a gastric sleeve. Their mean baseline BMI was 46.0 and weight of 126.8 kg. Baseline 25-hydroxyvitamin D levels were 55.4, PTH levels of 5.68, and Calcium of 2.46. From the 164 patients with baseline blood work, 76 had baseline vitamin D deficiency (<50mmol/l) and 130 had vitamin D insufficiency (77.8%). A total of 32/93 (34.4%) patients were vitamin D insufficient at 3 months, and 19/67 (28.4%) were at 6 months follow-up. Regarding vitamin D deficiency, 5/93 (5.4%) patients were found to have a 25-hydroxyvitamin D level in the deficient range at 3 months, and 2/67 (3.0%) at the 6 month follow-up. All 100% of patients at the 3 month follow-up assessment were on oral supplementation with calcium and vitamin D, and 75% were on supplementation at the 6 month follow-up.

Conclusion: Our study shows a majority of bariatric patients have vitamin D deficiency at baseline. After GBS, much lower rates of vitamin D deficiency/insufficiency were seen compared to the current literature. We also found a high percentage of our patients were supplemented with calcium and vitamin D post-operatively. The aggressive screening for vitamin D deficiency, aggressive treatment when it was found, and emphasis on preventing vitamin D deficiency post-operatively with routine oral supplementation likely accounted for the low rates of vitamin D deficiency seen in our cohort.

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Osteogenesis and Osteoclast Inhibition Effects of Bisphosphonates Administered for Over 4 Years Alone or in Combination with Statin in Rheumatoid Arthritis Patients During a 12 Month Follow-up. Masakazu Nagashima. Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan

Background/Purpose: To investigate the effects of bisphosphonates (Bis) alone or in combination therapy with Bis (etidronate, alendronate, and risedronate) and statin on the BMD and bone metabolism of rheumatoid arthritis (RA) patients.

Methods: Seventy-five RA patients receiving prednisolone (PSL) and Bis for over 4 years were divided into 2 groups: Bis and Bis + statin (n=40 and35; average age, 66.1 and 65.3 years; average disease duration, 25.3 years and 20.8 years; average PSL dose, 2.5 and 2.9 mg, respectively). During a 12-month treatment and follow-up, we measured the serum levels of NTX, TRACP-5b, PICP, and RANKL. BMD levels of the 2 groups at the radius, lumbar spine, and femoral neck were compared by using QDR.

Results: A significant increase was observed in the BMD of the lumbar spine in the Bis + statin group and significant decreases were observed in the BMD of the radius and femoral neck in the Bis group. The serum level of NTX in the Bis group decreased during the follow-up period. The serum RANKL levels were significantly decreased at 12 months after the start of statin administration in the Bis + statin group, compared with the Bis group.

Conclusion: The combination of the Bis + statin had no significant influence on bone resorption and increased osteogenesis. However, the Bis group had inhibited bone resorption and decreased osteogenesis. These results suggest that the combination therapy regulated bone resorption and osteoclast induction via a decrease in RANKL levels, and up-regulated osteogenesis.

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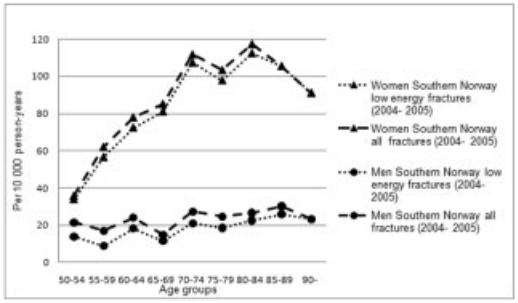
The Epidemiology of Low and High Energy Distal Radius Fracture in Middle-Aged and Elderly Men and Women in Southern Norway. Andreas P. Diamantopoulos[1], Gudrun Rohde[1], Inger M. Skoie[1], Irene Johnsrud[1], Marc Hochberg[2] and Glenn Haugeberg[1]. [1]Hospital of Southern Norway, Kristiansand, Norway, [2]University of Maryland School of Medicine, Baltimore, MD

Background/Purpose: Distal radius is among the most frequent sites for fractures in the elderly population. The overall incidence of distal radius fracture has been reported to be highest in the Scandinavian countries. There is a lack of epidemiology data on distal radius fractures in particular where low and high energy fractures have been studied separately. Thus our aim was to study the incidence of low and high energy distal radius fracture in middle-aged and elderly men and women in Southern Norway.

Methods: Patients with low and high energy distal radius fractures aged 50 years or older were identified from four hospitals in southern Norway in 2004 and 2005. Low energy fracture was defined as a result of minimal trauma, e.g. falling from standing height or less. Age adjusted and age specific incidence rates for men and women were calculated.

Results: A total of 799 (118 men and 681 women) individuals aged $\geq$ 50 yrs with low energy and 84 (48 men and 36 women) with high energy distal radius fracture were identified. Mean age for the low energy fracture patients was 70.1 yrs (66.8 men, 70.7 women) and for the high energy fracture patients 63.7 yrs (61.7 men, 66.3 women). A difference of approximately 5 years was found for age between low and high energy fracture patients both in men and women.Age specific incidence rates were significantly higher in women than in men for all age groups.The overall age adjusted incidence rate per 10.000 person years was 18.9 for men (low energy 12.8 vs. high energy 6.1) and 75.1 for women (low energy 71.1 vs. high energy 4.0). The prevalence of distal radius fractures in the two year period was significantly higher in winter compared with the other seasons ($p<0.001$). Between rural and urban areas a statistically significant difference in age adjusted incidence rates for all distal radius fractures was found for men (12.8 vs. 23.8, $p<0.005$) but not for women (69.0 vs. 82.6, $p< 0.06$). For low energy distal radius fracture the difference between rural and urban areas was statistically significant both for men ($p<0.008$) and women ($p<0.013$).

Fig.1. Age specific incidence rates of low energy and all distal radius fracture among women and men in Southern Norway (2004- 2005)



Conclusion: A fourfold higher age adjusted incidence rate for distal radius fracture was found for women compared with men. However the proportion of patients with high energy distal radius fracture is higher in men than in women (28.9% vs 5.9%). Our data indicate that individuals living in urban areas are at higher risk for low energy distal radius fracture than individuals living in rural areas. Increased awareness and better preventive strategies and treatment methods are still needed to reduce the risk of low energy distal radius fracture in the aging population of the western society.

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The Efficacy and Mechanism of Bisphosphonate on Glucocorticosteroid-Induced Osteoporosis in Systemic Lupus Erythematosus Patients. Xiao Zhang and Yu-xing Qin. Guang Dong General Hospital, Guang Dong Academy of Medical Sciences, Guangzhou, China

Background/Purpose: Glucocorticoids (GCs) is a mainstay of treatment in many inflammatory and immune-mediated disorders. However, persistent use is associated with side-effects, such as bone loss and increased fracture risk. Bisphosphonate is an available medicine by FDA for the prevention and treatment glucocorticoid-induced osteoporosis(GIOP). And this trial was to investigate the clinical effect and mechanism of Alendronate in preventing Glucocorticosteroid-Induced Osteoporosis

Methods: 1.Clinical Study: 78 SLE patients, divided into 3 groups according to Bone Density (BMD). ① Standard Glucocorticoids (GCs) group(Blank Placebo), ② Standard GCs+ vitamin D3+calcium tablet group, ③ Standard GCs+ alendronate group (treatment group), All of the patients were examined bone mineral density(BMD) of lumbar and left femur in 0 week, 12 week and 24week.

2. Basic Sciences Study: ① 13 case in blank placebo group, 9 cases with GCs+ alendronate therapy group (treatment group), compared PPARγ and β-catenin expression with immunohistology and histomorphometry with HE staining after 24w. ② To inductd human bone mesenchymal stem cells (hBMSCs) to osteoblasts and adipocyte with addition different concentration Alendronate during the induction, PPRAγ-mRNA and β-catenin-mRNA were measured by Q-PCR after induction.

Results: 1. In alendronate group, there was significant difference before and after treatment(F value 15.622, *P* value 0.001; F value 11.294, *P* value 0.003) in BMD of lumbar and left femur; There were no significante in vitamin D3+calcium group (F 0.542, *P* 0.466; F 0.389, *P* 0.537).

2. The results of histomorphometry between treatment group and control group had statistically significant(trabeculae surface area percentatge, trabeculae thickness; *P* 0.033, 0.009),treatment group PPARγ average photodensity was lower than blank placebo group (*P*0.037); there were no statistical difference of β-catenin immunohistochemistry between two groups (*P*0.569). 3. Oil red O stain, PPARγ Q-PCR analysis indicated 10^{-5}mol/L, 10^{-7}mol/L Alendronate group and adipogenic induced group presents significant difference (*P* 0.000, 0.041), while β-catenin Q-PCR indicated no intergroup statistical difference (F 1.999, *P* 0.193).

Conclusion: Bisphosphonate presents determined efficacy in the treatment of GIOP, increasing patient bone mass to a certain degree; bisphosphonates increase trabeculae surface area density as well as thichness; and through the inhibition of PPARγ expression, reduces bone marrow matrix stem cell lipid differentiation, indirectly increasing bone formation, thus decreasing GIOP incidence.

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Changes in Serum Receptor Activator for Nuclear Factor κB Ligand and Osteoprotegerin After Glucocorticoid Therapy Reflect Regulation of Their Expression by Glucocorticoid in Osteoblasts *in Vitro*. Kaichi Kaneko, Natsuko Kusunoki, Nahoko Tanaka, Tatsuhiro Yamamoto, Yoshie Kusunoki, Kenji Takagi, Hirahito Endo and Shinichi Kawai. Toho University School of Medicine, Tokyo, Japan

Background/Purpose: Osteoporosis is serious complication of systemic glucocorticoid (GC) therapy. RANKL (receptor activator for nuclear factor κB ligand) is a major ligand that increases differentiation of osteoclast *in vitro*. Osteoprotegerin (OPG) is a decoy receptor for RANKL showing inhibitory effects of action of RANKL *in vitro*. However, the significance of serum RANKL and OPG in GC-induced osteoporosis have not clarified yet. To clarify the significance of serum RANKL and OPG in patients with systemic autoimmune diseases under GC therapy.

Methods: (1) This study was approved by the ethics committee of Toho University. Sixty patients (female 36, postmenopausal 20) with systemic autoimmune diseases (systemic lupus erythematosus 18, vasculitis syndrome 18, polymyositis/dermatomyositis 10/5, adult onset Still's disease 5, mixed connective tissue disease 4) who were started to receive prednisolone at 30 mg or higher (up to 60 mg) daily dose were prospectively included in this study. Regular doses of bisphosphonate (alendronate n=26 or risedronate n=34) were co-administered in all the patients. Serum samples were obtained just before and 1 to 4 weeks after the start of GC therapy. Serum levels of RANKL and OPG were determined by ELISA (enzyme-linked immunosorbent assay) (Biomedica, Vienna, Austria). (2) NHOst, normal human osteoblast cells (Lonza Inc, Williamsport, OH) were cultured in a humidified environment of 5% CO_2. The effects of dexamethasone (Dex) on mRNA and protein productions of RANKL and OPG were evaluated by reverse transcription-polymerase chain reaction and ELISA, respectively.

Results: (1) Serum mean RANKL level in all patients remained unchanged after GC therapy. However, RANKL levels in these patients were broadly distributed at baseline. Mean serum RANKL level in patients above the 75th percentile was significantly ($P<0.0001$) decreased [from 0.52 ± 0.12 (SE) to 0.29 ± 0.08 pmol/L] after GC therapy. In contrast, mean serum RANKL level in patients below the 75th percentile was significantly ($P<0.05$) increased (from 0.035 ± 0.009 to 0.072 ± 0.019 pmol/L) after GC therapy. The serum CRP levels in patients whose RANKL levels above the 75th percentile were significantly ($P<0.05$) increased when compared with those in patients below the 75th percentile. Mean serum OPG level in all patients was significantly ($P<0.0001$) decreased (from 2.2 ± 1.5 to 1.4 ± 1.4 pmol/L) after GC therapy. (2) mRNA and protein expressions of RANKL were increased, while those of OPG were decreased by addition of Dex in the culture medium of unstimulated NHOst. Expressions of mRNA and protein of RANKL and OPG were increased by IL-1β. IL-1β-stimulated expressions of mRNA and protein of RANKL and OPG were both suppressed by Dex treatment in NHOst.

Conclusion: We suggested that the effects of GC on RANKL and OPG in systemic autoimmune diseases showed dual regulations both *in vivo* and *in vitro*, possibly depending upon disease activity.

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Effects of Technetium-99 Conjugated with Methylene Diphosphonate on Rats with Glucocorticoid Induced Osteoporosis. Ying Ning, Xuewu Zhang, Jiaxin Zhu, Min Feng and Zhanguo Li. Peking University People's Hospital, Beijing, China

Background/Purpose: Yunke (technetium-99 conjugated with methylene diphosphonate, ^{99}Tc-MDP), a drug patented in China (patent No. ZL94113006.1), has been used in Chinese patients since 1997 and proven to be effective in the treatment of rheumatoid arthritis. In this study, we examined whether ^{99}Tc-MDP has therapeutic effect on glucocorticoid-induced osteoporosis, comparing with MDP (methylene diphosphonate)

Methods: Forty-eight Sprague-Dawley rats were randomly divided into six groups: blank group, negative control group, high dose group, medium dose group, low dose group and positive control group. During the induction period, dexamethasone is given to all five groups except the blank group. In the treatment period, blank and negative control groups were given 5mg/kg physiological saline, 10mg/kg,5mg/kg and 2.5mg/kg ^{99}Tc-MDP were given to high dose, medium dose and low dose groups respectively, and positive control group was given 5mg/kg MDP. Both tibiae from each rat were subjected to micro-computed tomography (micro-CT) and histomorphology analysis (hematoxylin-eosin staining) respectively.

Results: 1. Micro-CT quantitative analysis: (A) Analysis of cancellous bone: (1) compared to the blank group, rats in the negative control group had decreased Bone Volume/Total Volume(BV/TV) and Trabecular Number(Tb.N) as well as increased Bone Surface Area/Bone Volume (BSA/BV),Trabecular Spacing(Tb.Sp) and Trabecular Pattern Factor (TPF); (2) compared to the negative control group, rats in the low dose group had increased BV/TV and Tb.N, and decreased Tb.Sp and TPF; (3) For medium dose, high dose and positive control groups, the number of parameter improvement with statistical significance increases to five and six, respectively; (4) For positive control group, improvement of all six parameters has statistical significance. (B) Analysis of cortical bone: Cortical Thickness (Co.Th) decreased in the negative control group in contrast to the blank group; after treatment, Co.Th in all doses of ^{99}Tc-MDP groups increased comparing to the negative group; however, no improvement of Co.Th was noted in the positive control group comparing to the negative group. 2. Histomorphology: compared to the blank group, rats in the negative control group has sparse, disordered trabeculae; compared to the negative control group, all doses of ^{99}Tc-MDP groups and MDP group have denser and regular trabecular arrangement.

Conclusion: Our study suggests that: ^{99}Tc-MDP can reverse the microarchitecture changes of glucocorticoid-induced osteoporotic rats. Low dose of ^{99}Tc-MDP is effective and the efficacy improves as dose increases; ^{99}Tc-MDP and MDP show similar effect on cancellous bone while ^{99}Tc-MDP excels in improving cortical bone thickness.

1129

Prevention of Glucocorticoid-Induced Osteoporosis - We Are Not Doing Enough; What Else to Consider. Lucy E. Durham[1], Sima Patel[1], Leena Yalakki Jagadeesh[1] and Taher Mahmud[2]. [1]Kent and Sussex Hospital, Tunbridge Wells, United Kingdom, [2]Pembury Hospital, Tunbridge Wells, United Kingdom

Background/Purpose: Royal College of Physicians 2002 guidelines(1) recommend that people aged over 65 years on long term glucocorticoids are prescribed osteoporosis prophylaxis (bisphosphonates alone, or in combination with calcium and vitamin D supplementation) in order to reduce the risk of fragility fractures. In February 2011 we audited the extent to which these guidelines were met in a district general hospital.

Methods: All hospital inpatients were screened over a period of one week. Their drug charts and clinical notes were reviewed, patients were interviewed and their general practitioner contacted as needed. Patients aged over 65 years taking glucocorticoids for longer than 3 months or more than 3 short courses in 12 months were identified and the presence or absence of osteoporosis prophylaxis noted.

Results: 240 inpatients were screened. 27(19 female) met the criteria for the need for osteoporosis prophylaxis. Common indications for glucocorticoid use were chronic obstructive pulmonary disease (n=8) and polymyalgia rheumatica (n=8). Results showed that 12 (44%) of 27 patients in whom osteoporosis prophylaxis was indicated were actually receiving prophylaxis.

Conclusion: These results identify a failure of clinicians to prescribe prophylaxis and/or poor patient adherence. These results are infact worse than the results from a similar audit 2 years ago 44% now vs 68% then; we are using new appriaches to raise awareness about the need for steroid induced osteoporosis prevention. In addition to presenting the findings at the hospital clinical governance meeting we are using other strategies including training of new medical staff and nurses at induction, flagging the audit results, placement of osteoporosis guidelines on the hospital intranet and spot checks by inpatient pharmacy staff with use of fluorescent stickers on drug charts to identify patients eligible for prophylaxis.

We also plan to use social media to raise awareness about the need for secondary prevention of osteoporosis by using Tweeter and Facebook. We will re-audit after after 6 months to assess whether these measures have been effective.

Reference:

1. Guidelines Working Group for the Bone and Tooth Society, National Osteoporosis Society and Royal College of Physicians. *Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment* (Royal College of Physicians, London, 2002).

1130

Modeling Human Rheumatoid Arthritis In Non-Human Primate: Type II Collagen Induced Arthritis In Cynomolgus Macaques. Hong Zhang[1], June Liu[1], Jilin Deng[1], Liangtang Chang[1], Hellen Zheng[1], Cheng Yu[1], Jun Lu[1], Alison Bendele[2], Yunfeng Fu[1] and Jeff Duan[1]. [1]PharmaLegacy Laboratories, Shanghai, China, [2]Bolder BioPATH. Inc., Boulder, CO

Background/Purpose: Collagen induced arthritis (CIA) rodent models have been extensively used in rheumatoid arthritis (RA) research. An RA model in non-human primate (NHP) is particularly demanded because of the close phylogenesis that provides the cross-reactivity to human for different development compounds using most modern drug technologies. However, NHP RA model has been reported extremely difficult because of the low and inconsistent disease incidence.

Methods: We studied type II collagen induced arthritis in Cynomolgus monkeys. Following immunization with collagen, the disease progression was monitored for 8 weeks.

Results: Overall the arthritic incidence reached 87% and the average arthritic incidence of proximal interphalangeal (PIP) joint reached near 90%, significantly higher than what was previously reported. The average swelling of PIP joint increased approximately by 45%. Radiography, histopathology and histomorphometry analysis of the joint bones well supported the arthritic disease with the similar characteristics of human RA joints. The average arthritic score was significantly reduced with the single agent treatment of Methotrexate or Dexamethasone.

Conclusion: Our results demonstrated the successful establishment of an reliable CIA in Cynomolgus monkeys, providing a valuable tool for studies of RA disease in pathogenesis, biomarker, translational research, and most importantly, anti-arthritic therapeutics as well as other relevant diseases, such as anemia of chronic disease and arthritic pain.

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Interferon Regulatory Factor 7 Deficiency Inhibits Collagen-Induced Arthritis: Regulation of Interleukin-6 and Matrix Metalloproteinase 3 Production. Susan E. Sweeney. UCSD School of Medicine, La Jolla, CA

Background/Purpose: Innate immune responses activate synoviocytes and recruit inflammatory cells into the rheumatoid joint. Transcription of many IFN response and pro-inflammatory cytokine genes is activated by IFN-regulatory factors (IRF) in response to innate sensor recognition. This study examined the effect of genetic deficiency of IRF7 in a murine collagen-induced model of arthritis (CIA).

Methods: CIA was induced in wild type DBA/1 (WT) and IRF7−/− DBA/1 mice by immunizing with type II collagen. Clinical arthritis scores and paw measurements were determined and histology was performed. Gene expression was evaluated by synovial tissue and splenic Q-PCR. Mouse serum was analyzed by ELISA. Draining lymph node cells from CIA were evaluated in vitro for cytokine production and proliferation.

Results: Arthritis severity and joint destruction was significantly decreased in IRF7−/− mice compared with WT CIA. Anti-type II collagen IgG levels were not significantly different in sera of IRF7−/− mice compared with WT. Synovial and splenic gene expression of IL-6 and synovial MMP-3 gene expression was significantly decreased in IRF7−/− mice compared with WT CIA mice. In addition, serum protein levels of IL-6 and MMP-3 were significantly decreased in IRF7−/− mice.

Conclusion: Genetic deficiency of IRF7 resulted in a significant decrease in both arthritis severity and joint destruction in CIA. Consistent with the clinical effect, IL-6 and MMP3 synovial gene expression and serum protein production were significantly decreased in IRF7−/− CIA. This study demonstrates an important role for IRF7-driven immunity in production of MMP as well as IL-6 in experimental arthritis and suggests the therapeutic potential for targeting IRF7 in RA patients.

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Improving Therapy Effect on Arthritic Rats by Co-Expression of CD40LIg and IκBα. Ping Fan, Lan He, Dan Pu, Wenxu Zhou, Xiaohong Lv, Yining Sun and Nan Hu. The First Affiliated Hospital Xi'an Jiaotong University School of Medicine, Xi'an, China

Background/Purpose: Rheumatoid arthritis (RA) is one of chronic autoimmune diseases that harm the human health for a long time. The pathogenesis of RA is still unknown, which refers to several aspects of the immune system. Especially, the aberrant activation of the lymphocytes and the NFκB dependent nonspecific inflammatory response are the two main points of joint inflammatory damage in RA. CD40/CD40L is the key co-stimulated molecular in the recognition and activation of the T cells. IκBα can suppress the inflammatory response and injury of joint synovium by cytokine at the key point by inhibiting the NFκB signaling. In this study, we used CD40LIg-IRES2- IκBα co-expressiong adenovirus vector to transfect the synovium tissue of arthritic rats to investigate the genes expression as well as the effect on the arthritic rats. In addition, we will compare the therapeutic effect of the co-expression gene adenovirus and the single gene adenovirus vector, to explore the potential gene therapy for RA.

Methods: Construction of pAdCD40LIg, pAdIκBα and pAdCD40LIg-IRES2-IκBα adenovirus vector had completed. Wistar rats were rendered arthritic by multi-subcutaneous injection of complete Freund's adjuvant. Arthritic rats were divided into four groups: group A with distal joint cavity injection of sterile water as control (n=5); group B with injection of pAdCD40LIg vector (n=5); group C with pAdIκBα vector injection (n=5); and group D with injection of pAdCD40LIg-IRES2-IκBα vector (n=5). Therapy effects were measured by the method of arthritis index score of rats. The levels of TNF-α/IL-2/IL-6 in synovial fluid collected by joint puncture were measured by ELISA methods 21 days after treatment.

Results: The mean arthritis index score of rats in group D was significantly lower than those in other three groups ($P<0.05$). The index in group B and C were significantly lower than that in group A ($P<0.05$). The rats in group D had the lowest TNF-α, IL-2 and IL-6 levels in synovial fluid followed by group C, B and A ($P<0.05$).

Conclusion: The expression CD40LIg and IκBα can effectively inhibit inflammatory reaction of arthritic rats. Simultaneous expression CD40LIg and IκBα can improve the therapeutic effect by synergistic effect.

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Mimicking Disruption of the Brain—Immune System—Joint Communication Results in Expression of Collagen Type II-Induced Arthritis in Non-Susceptible PVG Rats. Christine Wolff[1], Johannes Wildmann[2], Anke Randolf[2], Hugo O. Besedovsky[2], Adriana del Rey[2] and Rainer H. Straub[1]. [1]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, Department of Internal Medicine I, University Hospital, Regensburg, Germany, [2]Department of Immunophysiology, Institute of Physiology, Philipps University, Marburg, Germany

Background/Purpose: Disruption of brain-immune system-joint-communication has been demonstrated during collagen type II (CII) induced-arthritis in susceptible DA rats. In this study, we investigated whether immunization of non-susceptible PVG rats with CII results in changes in central and peripheral neuroendocrine mechanisms different from those observed in DA rats. We also investigated whether mimicking the disruption of the communication between the systems results in expression of arthritis in PVG rats.

Methods: PVG rats were immunized with CII in incomplete Freund adjuvant. Plasma corticosterone levels were evaluated by ELISA and joint innervation by immunofluorescence. Hypothalamic neurotransmitters were determined by HPLC and hypothalamic cytokine expression by real-time RT-PCR. Adrenalectomy was performed 14 days before immunization.

Results: Compared to DA rats, which developed a severe arthritis (score 16), only 12 out of 28 PVG rats showed minor arthritis symptoms (score 1–2). In PVG rats, plasma corticosterone levels and the sympathetic innervation in the joints did not change after immunization with CII. Also as opposed to arthritic DA rats, hypothalamic serotonin metabolism and tyrosine content were decreased on day 28 after immunization and there was an early increase in hypothalamic TNF gene expression in PVG rats. Following adrenalectomy, immunized PVG rats developed a severe arthritis in the hind paws (score 8), indicating that adrenal hormones contribute to control the expression of the disease.

Conclusion: In conclusion, immunization of non-susceptible PVG rats with CII results in changes in hypothalamic neurotransmitters and peripheral neuroendocrine mechanisms different from those observed in susceptible DA rats. Thus, disruption of immune-neuro-endocrine interactions seems to be relevant for the predisposition and course of arthritis, since mimicking such a disruption results in a marked change of arthritis severity.

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Regulation of Inflammatory Arthritis by the Upstream Kinase MKK7 in the c-Jun N-Terminal Kinase (JNK) Pathway. Sang-il Lee, David L. Boyle and Gary S. Firestein. UCSD School of Medicine, La Jolla, CA

Background/Purpose: The mitogen-activated protein (MAP) kinase JNK is a key regulator of matrix metalloproteinase (MMP) and cytokine production in rheumatoid arthritis (RA), and JNK deficiency markedly protects mice in animal models of inflammatory arthritis. JNK is regulated by two upstream kinases, namely MKK4 and MKK7. Previous studies demonstrated that cytokine-induced JNK activation and MMP production are solely dependent on MKK7 in fibroblast-like synoviocyte (FLS) and do not require MKK4. Therefore, we evaluated whether selective targeting of MKK7 in vivo using anti-sense oligonucleotides (ASO) would block arthritis-associated JNK activation and decreased severity of K/BxN serum transfer arthritis.

Methods: 2'-O-Methoxyethyl chimeric ASO for MKK7 and control ASO (25 and 50 mg/kg) were injected intravenously to assess their knockdown effect in normal C57BL6 mice. Arthritis was induced by injecting mice with K/BxN serum. Treatment included intravenous injections of PBS, control ASO, or MKK7 ASO (50 mg/kg twice a week, n = 7–8 for each group) from day −8 to 10. Arthritis severity was assessed using semiquantitative clinical scoring system. Ankle histology was scored for inflammation, bone erosion, and cartilage damage. Expression of MKK7 and JNK pathways were evaluated by quantitative PCR and western blot analysis of ankle joints.

Results: MKK7 ASO decreased MKK7 mRNA and protein levels in ankle joints of normal C57BL6 mice within 3 days in a dose-dependent manner, with greatest inhibition of nearly 40% at a dose of 50 mg/kg (n = 4 for each group). There was no effect of control ASO on MKK7 expression and MKK7 ASO did not decrease MKK4 levels. In the K/BxN serum transfer model, mice injected with MKK7 ASO had significantly less severe arthritis from day 4 to day 10 compared with control ASO. The peak clinical scores were: 11.1 ± 0.2 in control ASO, 4.9 ± 1.0 in MKK7 ASO; $p < 0.01$) and the changes in ankle diameter were: 0.59 ± 0.06 mm in control ASO and 0.22 ± 0.06 mm in MKK7 ASO; $p < 0.01$). The ankle joints from MKK7 ASO injected mice had significantly lower inflammation, bone erosion, cartilage damage, and overall histology scores than control ASO (overall scores: control ASO 2.7 ± 0.3 and MKK7 ASO 1.5 ± 0.3; $p < 0.05$). MKK7 deficiency decreased phospho-JNK by 67% and phospho-c-Jun by 62% in ankle extracts ($p < 0.05$). In addition, synovial MMP3 and MMP13 mRNA were decreased by 76.2%, and 70.8%, respectively ($p < 0.05$).

Conclusion: The upstream kinase MKK7 plays a critical regulatory in a murine model of inflammatory arthritis. MKK7 deficiency suppresses the entire JNK pathway, including key JNK-dependent genes like synovial MMPs. Targeting MKK7 rather than JNK could provide site and event specificity when treating synovitis, potentially decreasing side effects by blocking pathogenic JNK activation while permitting non-pathogenic MKK4-mediated events.

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Gingiva-Derived Mesenchymal Stem Cells-Mediated Therapeutic Intervention for Experimental Arthritis. Maogeng Chen[1], Xiao-Shun He[2] and Song G. Zheng[3]. [1]University of Southern California, Los Angeles, CA, [2]1st Affiliated Hospital of Sun Yat-sen University, [3]USC Keck School of Medicine, Los Angeles, CA

Background/Purpose: Current approaches are unable to cure rheumatoid arthritis. Accumulated evidence has revealed that manipulation of bone-marrow mesenchymal stem cells (BMSCs) has a potential promise to treat these diseases. Nonetheless, isolation and expansion of BMSCs for therapeutic usage is less feasible in the clinic. In the current study, we have observed that use of gengival-derived mesenchymal stem cells (GMSCs), mostly sharing similar phenotypic and functional characteristics with BMSCs, resulted in significantly therapeutic effects on the established collagen induced arthritis (CIA).

Methods: CIA, an experimental animal model of human rheumatoid arthritis (RA), has been induced with the immunization of type II collagen (CII) and CFA in DBA/1J mice. 2×10^6 GMSCs were injected i.v. into DBA/1J mice on day 0, 14 or 28 after immunization. Arthritic index was evaluated, the levels of CII-specific autoantibodies and pro- and antiinflammatory cytokines IL-10, IFN-γ, IL-17A, IL-4, and TNF-α in sera, spleens or draining lymph nodes were determined using ELISA and quantitative RT-PCR. The joint pathology was examined with H&E staining. In some experiments, injection of PC61 i.p. was used to delete Tregs in arthritis mice. Additionally, GMSCs were injected to the DBA/1J GFP knock-in mice immunized or not with CII and CFA, and numbers and function of Foxp3 (GFP+) regulatory T cells were examined with flow cytometry. Co-culture of GMSCs and naïve CD4 T cells were used to induce Foxp3+ Treg cells *in vitro* with or without transwell. To test the clinical relevance, the therapeutic effect of GMSCs was tested in humanized animal xeno-GVHD model. Injection of 20×10^6 human PBMC to SCID common γ chain KO mice can induce the typical syndromes of xeno-GVHD.

Results: Compared with CIA model, infusion of GMSCs to DBA/1J mice at day 14 or day 28 after CII/CFA immunization significantly decreased the severity of arthritis and pathology scores. Injection of GMSCs also significantly down-regulated inflammatory cytokine (IFN-γ, IL-17A) and CII-specific autoantidody levels. The role of GMSCs in controlling the diseases may partially depend upon the induction of CD4+Foxp3+ Tregs. Co-cultures of GMSCs and naïve CD4+Foxp3- cells induced the differentiation of CD4+Foxp3+ Tregs through soluble factors dependent mechanism and infusion of GMSCs resulted in the increase of CD4+Foxp3+ cells in naïve and CIA mice. Infusion of GMSCs to DBA/1J mice at day 14 after immunization partially interfered with the progress of the arthritis when Foxp3+ Tregs were depleted. Co-transfer of GMSC and human PBMCs significantly prolonged the survival of SCID mice.

Conclusion: Injection of GMSC to evident arthritis resulted in significantly therapeutic effects on CIA. The therapeutic effect of GMSCs was partially mediated by the increased frequency of CD4+Foxp3+ regulatory T cells. Transfer of GMSCs significantly suppressed the GVHD initiated from human donor cells in SCID mice, suggesting that GMSCs have clinical relevance. GMSCs can function as an immunomodulatory and anti-inflammatory component of the immune system *in vivo* and use of GMSC may provide a promising approach for the treatment of rheumatoid arthritis and other autoimmune diseases.

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VX-509, An Orally Available Janus Kinase 3 (JAK3) Specific Inhibitor, Showed Robust Activity in Pre-Clinical Models of Aberrant Immune/Inflammatory Function. Thomas Hoock[1], James Hogan[1], Sudipta Mahajan[1], Dina Shlyakhter[1], Luke Oh[2], Larry Park[2], George Ku[2], Ian Catlett[1], Meryll Corbin[1], Francesco Salituro[2] and Mark Namchuk[1]. [1]Vertex Pharmaceuticals Incorporated, Cambridge, MA, [2]Formerly of Vertex Pharmaceuticals Incorporated, Cambridge, MA

Background/Purpose: JAK3 is a promising target for the design of orally available, targeted immunosuppressive drugs. Cytokines, which signal through JAK3, are critical for lymphocyte development and T cell-mediated immune responses. JAK3 expression is largely restricted to the lympho-hematopoietic system while the other members of the JAK kinase family are more broadly expressed. Hence developing specific inhibitors of JAK3 may potentially provide future oral therapies for a number of autoimmune diseases.

Methods: The investigational compound, VX-509, is a potent inhibitor of JAK3 (enzyme K_i 2.5 nM + 0.7 nM) and has demonstrated potent inhibition of endogenous cellular JAK3 activity with IC_{50}s ranging from 50–170 nM. The compound showed excellent selectivity against non-JAK family kinases of nearly three orders of magnitude. Enzymatic selectivity over isolated protein kinase domains of the other JAK family members (JAK1, JAK2 and TYK2) was less than 10-fold, however a more physiologically relevant measure of JAK isotype selectivity using cellular assays dependent on different JAK family members demonstrated a selectivity window of approximately 25–150 fold, depending on the assay comparators.

Results: VX-509 was examined for activity following oral administration in animal models of aberrant immune/inflammatory function. In a rat model of rheumatoid arthritis (CIA), VX-509 showed a dose-dependent reduction in ankle swelling and paw weight and improved histological scores in affected paws, with the effects/potency exceeding the reference standard etanercept (Enbrel®). In the mouse oxazolone DTH model, VX-509 displayed dose-dependent effects in alleviating the T-cell mediated skin inflammatory response, which was comparable to the reference standard prednisolone.

Conclusion: Overall, VX-509 is a JAK3-specific inhibitor that was effective in several preclinical models of aberrant immune/inflammatory function with oral dosing that support BID and QD regimens. These results support the clinical testing of VX-509 in chronic, autoimmune/inflammatory disorders and VX-509 is currently undergoing clinical evaluation in rheumatoid arthritis.

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A New Derivative of Roxithromycin Modulates Immunological Responses and Ameliorates Collagen-Induced Arthritis. Noriko Otsuki[1], Satoshi Iwata[1], Emi Kumagai[1], Taketo Yamada[2], Tomoki Katayose[1], Yoshiko Kichikawa[1], Osamu Hosono[1], Hiroshi Kawasaki[1], Hirotoshi Tanaka[1], Nam H. Dang[3] and Chikao Morimoto[1]. [1]The Institute of Medical Science, The University of Tokyo, Tokyo, Japan, [2]School of Medicine, Keio University, Tokyo, Japan, [3]University of Florida Shands Cancer Center, Gainesville, FL

Background/Purpose: Macrolide antibiotics have many biological activities distinctly different from antibacterial functions. Previously we showed that Roxithromycin (RXM), a macrolide antibiotic with a 14-member macrocyclin ring, inhibited in vitro production of proinflammatory cytokines such as TNF-α and IL-6 by T cells and macrophages. More interestingly, oral administration of RXM in mice with collagen-induced arthritis (CIA) reduced the severity of arthritis and serum level of IL-6 as well as leukocyte migration into the affected joints and destruction of bones and cartilages. In the present study, we synthesized the new derivertive of RXM named 5-I with less antimicrobial activity and studied the immunomodulatory effects of 5-I both in vitro and in vivo.

Methods: Proliferative response and cytokine production by human PBMCs and T cells stimulated with anti-CD3 plus anti-CD28 mAbs, cytokine production by human monocytes stimulated with lipopolysaccharide, and transendothelial migration of human T cells were analyzed in the presence or absence of various concentration of 5-I and RXM. In addition, 5-I and RXM-mediated alteration of mRNA expressions were evaluated by cDNA microarray anaysis and RT-PCR using human $CD4^+$ T cells. The in vivo effect of the oral administration of 5-I or RXM was evaluated using collagen-induced arthritis model mice (DBA/1J strain) by scoring of arthritis and pathological examination.

Results: 5-I did not affect the proliferation of lymphocytes and the production of Th2-type cytokines, whereas it specifically inhibited production of Th1, Th17, and proinflammatory cytokines, such as IL-2, IFN-γ, TNF-α, IL-6, and IL-17A by human T cells and/or monocytes. Microarray analysis revealed that 5-I reduced the expression of RORγt which is the master regulator of Th17. 5-I also inhibited the activated T cells migration. We found that the administration of 5-I to collagens-induced arthritis mice reduced the severity of the desease in the comparable level to RXM. The effectiveness was also observed in the delayed administration after onset of the disease, suggesting 5-I may be useful in the treatment of CIA as well as its prevention.

Conclusion: Our findings strongly suggest that 5-I is a promising low molecular compounds for the possible clinical application in the treatment of rheumatoid arthritis in human. Furthermore, 5-I may be a useful lead compound to regulate the differentiation of Th17 population.

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IL-6 Overproduction Is Predominantly Related to Arthritis in TNFα-Induced Adipose-Related Protein (TIARP) Deficient Mice. Asuka Inoue[1], Isao Matsumoto[1], Naoto Umeda[1], Yuki Tanaka[1], Satomi Tamaki[1], Masahiko Mihara[2], Satoru Takahashi[3] and Takayuki Sumida[1]. [1]University of Tsukuba, Tsukuba city, Ibaraki, Japan, [2]Chugai Pharmaceutical, Gotemba, Japan, [3]Department of Anatomy and Embryology, Doctoral Program in Biomedical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba city, Ibaraki, Japan

Background/Purpose: TNFα-induced adipose-related protein (TIARP) is a six-transmembrane protein induced by TNFα, IL-6 and IL-1β in adipose tissue. Recently, we found that TIARP is dominantly expressed in splenic macrophages and joints of two arthritic mouse models (collagen induced arthritis; CIA and glucose-6-phosphate isomerase (GPI) induced arthritis). In human, TIARP is also observed in human joints from patients with rheumatoid arthritis and clearly upregulated by TNFα stimulation, although the pathogenic mechanisms of arthritis remain unclear. In this study, to elucidate the role of TIARP in the development of arthritis, we have generated TIARP-deficient ($TIARP^{-/-}$) mice.

Methods:
(1) We generated TIARP$^{-/-}$ in C57BL/6 (B6) background. We investigated several organs in aged (12months old) TIARP$^{-/-}$ mice.
(2) Peritoneal macrophages were collected using thioglycolate and were cultured with TNFα for 96h. Then, the production of IL-6 in culture supernatant was measured by enzyme-linked immunosorbent assay (ELISA).
(3) We also examined the susceptibility of young (8–12weeks old) TIARP$^{-/-}$ mice to CIA. CIA was induced by immunization with 200ug of chicken type II collagen (CII) emulsified in complete freund's adjuvant (CFA) to B6 mice, followed by boost immunization after 21 days of primary immunization. The severity of arthritis was monitored by clinical score and evaluated histologically on day 60.
(4) Draining lymph nodes and splenocytes were isolated on day 10 and were cultured with CII for 72h in vitro. IFNγ, IL-17 and IL-4 in their culture supernatant were measured by ELISA.
(5) The level of IL-6 and TNFα in the serum on day 60 after CII immunization were measured.
(6) We examined the effects of anti-IL-6 receptor mAb (MR16-1) on the development of arthritis in TIARP$^{-/-}$ mice. We injected 2mg of MR16-1 intraperitoneally on day 21 after CII immunization.

Results:
(1) Aged TIARP$^{-/-}$ mice spontaneously developed weak synovitis with enthesitis.
(2) Peritoneal macrophages from TIARP$^{-/-}$ mice produced high amount of IL-6 with TNFα stimulation.
(3) The severity of arthritis score in TIARP$^{-/-}$ mice was higher than that in WT mice. Histological analyses showed that enhanced neutrophil infiltration, synovial proliferation, and cartilage destruction.
(4) The amount of IFNγ, IL-17 and IL-4 was comparable between TIARP$^{-/-}$ and WT mice.
(5) The serum IL-6 was significantly increased in TIARP$^{-/-}$ mice, whereas serum TNFα was not detected.
(6) Administration of MR16-1 on day 21 significantly suppressed the progression of arthritis in TIARP$^{-/-}$ mice.

Conclusion: These findings suggest that TIARP deficiency relates the development of arthritis via the overproduction of IL-6.

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Inhibitory Effect of c-Fos/AP-1 Inhibitor T-5224 on the Levels of Cytokines and Chemokines in the Arthritic Lesion of Mice with Collagen-Induced Arthritis. Tomomi Date[1], Yukihiko Aikawa[1], Akira Hashiramoto[2], Tetsuya Yamamoto[1], Masaaki Mikami[1], Hirokazu Narita[1], Shuichi Hirono[3] and Shunichi Shiozawa[2]. [1]Research Laboratories, Toyama Chemical Co., Ltd, Toyama, Japan, [2]Department of Biophysics, Kobe University Graduate School of Health Sciences/Department of Medicine, Kobe University Graduate School of Medicine/The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, [3]Department of Pharmaceutical Sciences, School of Pharmacy, Kitasato University, Tokyo, Japan

Background/Purpose: Activator protein-1 (AP-1) directly regulates the expressions of inflammatory cytokines and matrix-degrading matrix metalloproteinases important in rheumatoid arthritis (RA). We have previously reported that a small molecule c-Fos/AP-1 inhibitor T-5224 prevented the development of arthritis and joint destruction in mice with collagen-induced arthritis (CIA). The purpose of this study was to investigate its effect on the expression profile of cytokines and chemokines in the arthritic hind paw of mice with CIA after a single administration of T-5224.

Methods: CIA was induced in DBA/1J mice by the immunization with bovine type II collagen twice on day 0 and 21. On day 35, hind paws and serum were collected at 0, 1, 3, and 6 hours after a single oral administration of 30 mg/kg of T-5224. The tissue extracts were prepared from each paw. The amounts of 23 cytokines/chemokines in the tissue extracts and sera were measured using Bio-Plex Mouse Cytokine 23-Plex Panel or ELISA.

Results: The arthritis developed from several days after the secondary immunization, and mice showed severe arthritis on day 35. When analyzing each of hind paws with full-blown arthritis, the levels of 9 cytokines/chemokines [IL-1β, IL-3, IL-6, IL-12 (p40), G-CSF, KC/groα, MCP-1, MIP-1β, and RANTES] significantly increased compared with those in the normal paws. Especially, the amounts of IL-1β, IL-6, and KC/groα in the arthritis hind paws were approximately 40 times higher than those in normal paws. A single administration of T-5224 at the dose of 30 mg/kg significantly decreased the levels of IL-1β, IL-6, and KC/groα within several hours. Eight cytokines/chemokines including TNFα could not be determined in the paws. The significant elevations of the levels of IL-1β, IL-3, IL-6, G-CSF, KC/groα, MCP-1, and MIP-1β were also observed in the sera from the same individuals. The serum levels of IL-1β and KC/groα were significantly decreased by the treatment of T-5224.

Conclusion: T-5224 immediately reduced the levels of inflammatory cytokines and chemokines in the arthritic lesion. The results suggest that the prompt inhibitory effect of T-5224 on the overexpression of cytokines and chemokines contributes to the anti-arthritic effects in the therapy of RA.

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Colony Stimulating Factor 1 Receptor Inhibition Has Anti-Inflammatory and Potent Early Onset Bone and Cartilage Protective Effects. Myew-Ling Toh[1], Jean-Yves Bonnefoy[1], Nathalie Accart[1], Sandrine Cochin[1], Christophe Zemmour[1], Helene Haegel[1], Philippe Ancian[1], Bettina Sehnert[2], Sandy Pohle[2], Falk Nimmerjahn[3], Reinhard Voll[4] and Georg Schett[2]. [1]Transgene SA, Illkirch, France, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Erlangen, Germany, [4]Freiburg, Germany

Background/Purpose: The colony stimulating factor 1 (CSF-1)/CSF-1 receptor (CSF-1R) network plays a key role in macrophage and osteoclast differentiation which are current therapeutic targets in rheumatoid arthritis (RA). We determined CSF-1R expression in human RA synovium/bone, and the efficacy of CSF-1R antagonism using a humanized anti-CSF-1R monoclonal antibody (mAb) and an anti-murine CSF-1R MAb in arthritis models.

Methods: CSF-1R immunostaining was performed with a murine anti-human CSF-1R MAb (murine CXIIG6) in RA, osteoarthritis (OA) and healthy human synovium/bone. The efficacy of a humanized anti-CSF-1R MAb (H27K15) or anti-murine CSF-1R MAb (clone AFS98) was examined in a human osteoclast differentiation assay from CD34+ bone marrow precursors (TRAP5b activity, CTX levels) *in vitro* or collagen-induced and serum transfer induced arthritis *in vivo* respectively.

Results: CSF-1R expression was increased in RA synovium/bone compared to OA or healthy controls, in predominantly lining and sublining CD68+ macrophages, TRAP+ multinucleated mature osteoclasts and a small proportion of vimentin+ RA fibroblast-like synoviocytes and CD21+ follicular dendritic cells in germinal centre-like structures. CSF-1R expression was not detected in osteoblasts, T cells, B cells or immature or mature DC. *In vitro,* H27K15 significantly inhibited osteoclast differentiation and activity. *In vivo,* an anti-murine CSF-1R MAb reduced arthritis scores and synovial inflammation within 14 days of arthritis onset, associated with rapid inhibition in serum TRAP5b activity and complete abrogation of local bone and cartilage erosion in collagen-induced arthritis. Complete abrogation of serum TRAP5b activity and local bone erosion was confirmed in serum transfer-induced arthritis.

Conclusion: CSF-1R expression was abundant in macrophages and mature osteoclasts in human RA synovium/bone, and a humanized anti-CSF-1R MAb markedly inhibited human osteoclast differentiation and activity. We demonstrate an anti-inflammatory as well as early onset potent bone and cartilage protection by a specific anti-CSF-1R MAb in murine arthritis models. This supports evidence for CSF-1R as a therapeutic target in arthritis, inflammatory bone loss and other diseases associated with osteoclastic bone damage.

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Overexpression of T-Bet Gene Regulates Collagen Induced Arthritis Via IFNγ Independent Suppression of IL-6 Signal Transduction. Yuya Kondo, Masahiro Tahara, Mana Iizuka, Hiroto Tsuboi, Satoru Takahashi, Isao Matsumoto and Takayuki Sumida. University of Tsukuba, Tsukuba city, Ibaraki, Japan

Background/Purpose: Recent studies reported that IL-17 producing Th-17 cells appear to play a critical role in the generation of several autoimmune arthritis models, and that IFNγ has anti-inflammatory effect in the development of autoimmune arthritis via the suppression of Th-17 cells. However, the function of Th-1 specific master transcriptional factor T-bet in the development of arthritis is not clarified. The aim of this study is to elucidate the role of T-bet on the pathogenesis of collagen induced arthritis (CIA).

Methods:
1) T-bet transgenic (T-bet Tg) mice under the promoter of CD2 gene were generated. CIA was induced in T-bet Tg mice and wild-type C57BL/6 (B6) mice.
2) Collagen type II (CII) reactive T-bet and RORγt mRNA expression level was analyzed by real-time PCR.

3) Criss-cross experiments using $CD4^+$ T cells of B6 or T-bet Tg mice, as well as $CD11c^+$ splenic dendritic cells (DCs) of B6 or T-bet Tg mice with CII were carried out, and then IL-17 and IFNγ in the supernatants were measured by ELISA. T-bet and RORγt expression on $CD4^+$ T cells was analyzed by FACS.
4) T-bet Tg × $IFN\gamma^{-/-}$ mice were generated by crossing T-bet Tg mice and $IFN\gamma^{-/-}$ mice. $CD4^+$ T cells from B6, T-bet Tg, or T-bet Tg × $IFN\gamma^{-/-}$ mice were cultured in the condition favoring Th-17 differentiation, then cytokine production and transcription factor expression (RORγt, SOCS3, and STAT3) were analyzed by real-time PCR and FACS.
5) IL-6 receptor expression and phosphorylation of STAT3 on $CD4^+$ T cells were analyzed by FACS.

Results:

1) T-bet Tg mice did not develop collagen-induced arthritis compared with B6 mice.
2) T-bet Tg mice showed overexpression of T-bet and downregulation of RORγt in CII reactive T cells.
3) Criss-cross experiments with $CD4^+$ T cells and splenic DCs showed significant reduction in IL-17 production from CII reactive $CD4^+$ T cells in T-bet Tg mice even upon co-culture with DCs of B6.
4) FACS analyses revealed that IL-17 production and RORγt expression were inhibited under Th-17 differentiation conditions in T-bet Tg mice and T-bet Tg × $IFN\gamma^{-/-}$ mice. SOCS3 and STAT3 mRNA expression was equivalent for among these mice.
5) IL-6 receptor expression was suppressed in T-bet Tg mice and T-bet Tg × $IFN\gamma^{-/-}$ mice. Phosphorylation of STAT3 on $CD4^+$ T cells were inhibited in T-bet Tg mice and T-bet Tg x $IFN\gamma^{-/-}$ mice.

Conclusion: Overexpression of T-bet in T cells suppressed the development of autoimmune arthritis. The regulatory mechanism of arthritis might involve inhibition of CII reactive Th17 differentiation by overexpression of T-bet via IFNγ-independent suppression of IL-6 signal transduction.

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Lapatinib Ameliorates Experimental Arthritis in Rats. Metin Ozgen[1], Suleyman Serdar Koca[1], Ahmet Karatas[1], Adile Ferda Dagli[2], Fazilet Erman[3], Baris Gundogdu[1], Kazim Sahin[4] and Ahmet Isik[1]. [1]Department of Rheumatology, Faculty of Medicine, Firat University, Elazig, Turkey, [2]Department of Pathology, Faculty of Medicine, Firat University, Elazig, Turkey, [3]School of Health Sciences, Firat University, Elazig, Turkey, [4]Department of Animal Nutrition, Faculty of Veterinary Science, Elazig, Turkey

Background/Purpose: Angiogenesis and synovial hyperplasia have important roles in the pathogenesis of cartilage-bone destruction in rheumatoid arthritis (RA). Members of the epidermal growth factor receptor (EGFR) family and their associated ligands are commonly expressed by synovial cells, and may be involved in the synovial hyperplasia seen in RA and its disease progression. Lapatinib is an orally available, small-molecule, reversible inhibitor of both EGFR and human EGFR-2 (HER2) tyrosine kinases. Thus, we suggested that lapatinib may have potential joint-protective properties in RA. The purpose of this study was to investigate the therapeutic effect of lapatinib on collagen-induced arthritis (CIA) in rats**.**

Methods: Thirty Wistar albino female rats were randomized to three groups (n=10 in each group): Group-I as the control group, Group-II as the arthritis group, Group-III as the lapatinib group were assigned. Arthritis was induced by intradermal injection of chicken type II collagen combined with incomplete Freund's adjuvant in Group-II and III rats. One day after the onset of arthritis, Group-III rats were given lapatinib (30 mg/kg/day) via oral gavage until they were killed on day 29.

Animals were sacrificed at the 15th day after the onset of arthritis. The trunk bloods and paws of the rats were obtained for further analysis. Tumor necrosis factor (TNF)-α, interleukin (IL)-17, malondialdehyde (MDA) levels and superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) activities in serum, and articular tissue nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxgenase-1 (HO-1) expressions, perisynovial inflammation and cartilage-bone destruction were determined in the paws.

Results: When compared with Group-I, TNF-α, IL-17, and MDA levels were increased, and SOD, CAT, GPx activities and the expressions of Nrf2 and HO-1 were decreased in Group-II (Table). Histopathological analysis demonstrated the extensive perisynovial inflammation and marked cartilage-bone destruction in Group-II rats. Lapatinib treatment decreased the levels of TNF-α, IL-17, MDA, and increased the activities of SOD, CAT, GPx and the expressions of Nrf2 and HO-1, and decreased the perisynovial inflammation and cartilage-bone destruction in the paws.

Table: Clinical and laboratory data in the study groups

	Group-I (Control) (n=10)	Group-II (Arthritis) (n=10)	Group-III (Lapatinib) (n=10)
14th day arthritis score	—	1.4 ± 0.7	1.6 ± 0.5
29th day arthritis score	—	2.4 ± 0.5	0.3 ± 0.5[e]
Inflammation score	—	4.0 ± 0.0	2.1 ± 0.7[e]
Cartilage-bone destruction score	—	3.9 ± 0.3	1.2 ± 0.4[e]
TNF-α (pg/mL)	25.6 ± 5.0	62.7 ± 12.9[b]	26.4 ± 3.3[d]
IL-17 (pg/mL)	29.5 ± 8.3	65.7 ± 8.9[b]	47.0 ± 6.5[b,d]
MDA (μmol/L)	0.58 ± 0.23	1.6 ± 0.2[b]	0.92 ± 0.13[b,d]
SOD (U/mL)	12.0 ± 7.3	3.4 ± 1.6[b]	5.4 ± 1.1[b,c]
CAT (nmol/min/mL)	0.33 ± 0.07	0.12 ± 0.08[b]	0.24 ± 0.02[a,d]
GPx (nmol/min/mL)	335 ± 179	179 ± 45[b]	307 ± 62[d]

Data were presented as mean±standard deviation. TNF: Tumor necrosis factor, IL: Interleukin, MDA: Malondialdehyde, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase. vs. Control group [a] $p<0.05$, [b] $p<0.01$; vs. Arthritis group [c] $p<0.05$, [d] $p<0.01$, [e] $p<0.001$

Conclusion: Our present study is the first report to identify that lapatinib suppresses inflammatory pathways and oxidative stress, and prevents synovial hyperplasia in CIA model. Lapatinib may be an effective option for the treatment of RA.

1143

IL-33 Mediates a Mast Cell-Fibroblast Amplification Loop That Primes Mast Cells for Activation Via Immune Complexes. Shinjiro Kaieda[1], Jun-Xia Wang[1], Ruslan Shnayder[1], Richard Lee[1], Richard Stevens[1] and Peter A. Nigrovic[2]. [1]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [2]Children's Hospital Boston and Harvard Medical Scool, Boston, MA

Background/Purpose: Mast cells (MCs) have been recognized as potential participants in inflammatory arthritis. Recent studies have suggested that the IL-1 family cytokine IL-33 directly activates synovial MC in murine arthritis. However, knowing that MC participation in this condition requires expression of the immune complex receptor FcγRIII, we examined the possibility that the major role of IL-33 might instead be to promote the responsiveness in MC to immune complexes.

Methods: Arthritis was initiated in mice lacking the IL-33 receptor IL1RL1, as well as wild-type (WT) littermates, via intraperitoneal administration of K/BxN mouse serum. $FcgRII^{-/-}$ and WT mouse bone marrow-derived MCs (mBMMCs) were preincubated with or without recombinant mouse IL-33 for 4 h; they were activated by plate-bound anti-FcgRII/III antibody for 16h and assayed by multiple cytokine and chemokine array as well as by specific cytokine ELISA. Co-culture of WT or IL-1RL1-deficient mBMMCs with fibroblast-like synoviocytes (FLS), a known source of IL-33, was performed in a transwell system. Transcripts for IL-6, IL-1β and IL-33 in mBMMCs and FLS during co-culture were evaluated by RT-qPCR.

Results: $IL1RL1^{-/-}$ animals exhibited less severe arthritis than WT mice. Correspondingly, histological measures of arthritis were reduced, as was tissue expression of IL-1β and IL-6. Further, we found that MC-dependent acute vascular edema was reduced in the $IL\text{-}1RL1^{-/-}$ mice, in a timecourse inconsistent with direct activation via IL-33. A multiplex array revealed that preincubation of mBMMC with recombinant mouse IL-33 amplified the FcγRIII-mediated MC release of chemokine CXCL2 and the cytokines IL-1β, IL-6 and TNF-α. IL-1β is of particular significance, since MC represent a key source of this cytokine in early synovitis, whereas CXCL2 is implicated in IL-33-mediated neutrophil recruitment. In co-culture experiments, FLS induced mBMMCs to increase their levels of transcripts for IL-6 and IL-1β, and mBMMCs induced expression of IL-33 as well as IL-6 in co-cultured FLS. This reciprocal effect on FLS required MC expression of IL1RL1, indicating the presence of an IL-33-mediated MC-FLS pro-inflammatory loop in which IL-33 from FLS elicits MC mediators that further enhance IL-33 release from FLS.

Conclusion: These findings confirm a novel role for IL-33 as an amplifier of immune complex-mediated inflammation and identify a MC-FLS amplification loop dependent on IL-33 and its receptor. We conclude that "priming" of MCs via synovial fibroblast-derived IL-33 potentiates their activation via FcγRIII.

1144

A High Fat Diet Causes Fat Uptake by Synovial Lining Macrophages and Enhances Joint Inflammation and Cartilage Destruction During Experimental Arthritis. Peter van Lent, Wouter de Munter, Arjen Blom, Annet Sloetjes and Wim van den Berg. Rheumatology, Nijmegen, Netherlands

Background/Purpose: Earlier studies have shown that synovial lining macrophages are crucial in mediating joint inflammation and cartilage destruction during experimental arthritis (1). Oxidised LDL (ox-LDL) has been shown to activate macrophages which may enhance joint inflammation and cartilage destruction. Uptake of Ox-LDL by macrophages is clearly seen in atherosclerotic lesions of mice made deficient for the LDL receptor which were given a high fat diet. In the present study, we investigated the effect of a high fat diet in $LDLr^{-/-}$ mice on uptake of fat by synovial lining macrophages and development of joint inflammation and cartilage destruction during experimental arthritis.

Methods: $LDLr^{-/-}$ mice were given a high fat or a normal fat diet for 50 days. Autoantibody-induced arthritis was elicited by giving 0,2 ml K/BxN serum systemically twice at alternate days. Arthritis was scored macroscopically using an arbitrary score and histologically using sections of forepaws. Sections were stained with Haematoxylin/eosin, Safranin-O or red oil. Cartilage destruction was measured as either proteoglycan depletion, cartilage matrix erosion and chondrocyte death. MMP mediated neoepitopes were determined using immunolocalisation and VDIPEN antibodies. Bone marrow derived macrophages were stimulated by oxidized LDL and expression of chemokines was determined using RT-PCR. Protein levels of cytokines was measured using Luminex.

Results: Induction of K/BxN arthritis in $LDLr^{-/-}$ mice given a high fat diet for 50 days showed a higher joint inflammation in the wrist of the fore-paws when compared to $LDLr^{-/-}$ which received a normal diet. At days 2, 5 and 12, the macroscopic score was 171%, 46% and 63% higher respectively. Cryostate sections of total knee joints stained with red oil showed strong accumulation of fat within the lining macrophages which was much lower in the $LDLr^{-/-}$ fed with a normal diet. Histology of forepaws taken at day 12 after arthritis induction showed significantly higher amounts of mainly PMN as seen after immunostaining with NIMPR14 antibody. When bone-marrow macrophages were stimulated with Ox-LDL for 24 hours, protein levels of PMN attracting chemokine KC was significantly higher whereas that of macrophage attracting chemokine MCP-1 was comparable to the production by control macrophages. Serum levels of triglyceride, cholesterol and IL-6 were significantly higher in high fat treated $LDLr^{-/-}$ mice when compared to $LDLr^{-/-}$ mice fed with a normal diet whereas levels of IL-1β and TNFα were undetectable. Cartilage destruction measured in four different distal carpals of the wrist was significantly higher in the fat-rich treated group when compared to the normal diet group. Proteoglycan depletion, erosion of the cartilage matrix and chondrocyte death were respectively 65%, 333% and 283% higher. In line with that a significantly higher VDIPEN expression was observed in the cartilage layers of the high fat diet group.

Conclusion: $LDLr^{-/-}$ mice given a high fat diet accumulate fat within synovial lining macrophages and exhibit enhanced joint inflammation and cartilage destruction during experimental arthritis.

Ref:

1) Blom AB et al. Arthritis Rheum. 2007;56(1):147–57.

1145

Inhibition of Murine Collagen-Induced Arthritis by Overexpression of Glucocorticoid-Induced Leucine Zipper Locally in the Joints Using a Gene Therapy Approach. Devi Ngo[1], Elaine Beaulieu[1], Scott Loiler[2], Margriet Vervoordeldonk[3] and Eric Morand[1]. [1]Monash University, Melbourne, Australia, [2]Arthrogen B.V, Amsterdan, Netherlands, [3]Arthrogen B.V, AMC/University of Amsterdam, Amsterdan, Netherlands

Background/Purpose: Glucocorticoid-induced leucine zipper (GILZ) is an intracellular protein expressed in T cells, macrophages, synovial fibroblasts and endothelial cells, which inhibits NFkB- and ERK-dependent signaling. We previously have shown that silencing endogenous GILZ exacerbates murine collagen-induced arthritis (CIA) (Beaulieu et al, Arthritis Rheum 2010). Here, we investigated the therapeutic potential of exogenous GILZ in inflammatory arthritis, and the function of endogenous GILZ in adaptive and innate immune responses.

Methods: To study the therapeutic effect of GILZ in established arthritis, CIA was induced in DBA/1 mice. After onset of disease (day 27), recombinant adeno-associated virus-5 (rAAV5) expressing the gene for murine GILZ was injected in both knee and ankle joints ($3.85\times10\hat{}13$ vg/ml), and the therapeutic effect observed over 15 days. The activity of rAAV5-GILZ against NF-kB was studied in a human microvascular endothelial cell line. $GILZ^{-/-}$ mice were generated on a C57BL/6 background by targeting the canonical mouse GILZ isoform. Adaptive immune responses in $GILZ^{+/+}$ and $GILZ^{-/-}$ mice were studied in response to injection of chicken type II collagen (CCII)/CFA at the base of the tail on day 0 and 21. Innate immune responses mice were studied by measuring serum cytokines induced by intra-peritoneal injection of LPS (10mg/kg).

Results: In established CIA in DBA/1 mice, intra-articular rAAV5-GILZ injection resulted in significant decrease of clinical disease severity ($P<0.05$), associated with a significant increase in joint GILZ mRNA expression. TNF-induced NF-kB luciferase activity in vitro was significantly inhibited by rAAV5-GILZ. Adaptive immune responses, as evidenced by CII-induced proliferation of T cells from immunized mice, were significantly increased in $GILZ^{-/-}$ mice ($P<0.01$). No significant clinical arthritis or anti-CII antibodies were induced in $GILZ^{+/+}$ C57BL/6 mice, and GILZ deficiency did not result in increased arthritis susceptibility or anti-CII antibodies in this strain. GILZ expression was low in $GILZ^{+/+}$ mice in the setting of LPS administration, and LPS-induced serum IL-1, IL-6 and TNF concentrations were unaffected by GILZ deficiency.

Conclusion: These results suggest that intra-articular GILZ overexpression can inhibit established arthritis. Endogenous GILZ inhibits T cell responses to CII, but no effect of GILZ-deficiency on LPS-induced cytokines was observed. These findings provide proof of concept for the therapeutic potential of a GILZ-based therapy in arthritis, but suggest further investigation of the mechanism of action of GILZ is required.

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Inhibiting IL-6 *Trans*-Signalling with Soluble gp130Fc Potently Reduces the Incidence and Severity of Collagen-Induced Experimental Arthritis. Shaun Smale[1], Sara Carty[1], Rhian Goodfellow[1], Ernest Choy[1], Stefan Rose-John[2], Simon Jones[3] and Anwen S. Williams[4]. [1]Cardiff University, Cardiff, ENGLAND, United Kingdom, [2]Christian Albrechts University, Kiel, Germany, [3]Cardiff University, Cardiff, Wales, [4]Cardiff University, Cardiff, United Kingdom

Background/Purpose: Cytohistomorphological analysis of the synovial joint provides researchers with an opportunity to unmask specific intra- and extra- cellular mechanisms that regulate the switch from acute to chronic pathology in arthritis. The signal transducer and activator of transcription (STAT) pathway orchestrates this transition and steers the effector functions of interleukin-6 (IL-6) within the inflamed joint. We used a pertinent inflammatory arthritis model, murine collagen-induced arthritis (mCIA), to define the timecourse of STAT3 expression within the inflamed joint and to test the potency of timely targeted therapy with an inhibitor of IL-6 *trans*-signalling (sgp130Fc).

Methods: Joint tissues were collected (pre and post arthritis) over the timecourse of mCIA. IL-6, soluble IL-6 receptor (sIL-6R) and STAT3 were measured in joint tissue homogenates by ELISA. To test sgp130Fc's efficacy, 2.5mg/Kg was injected daily. Control mice received either etanercept (2.5mg/Kg daily) or vehicle; they were administered using an identical dosing regimen. Arthritis severity was gauged macroscopically in each paw; the sum of scores provided a clinical arthritis index (CAI) for each mouse. Therapeutic outcome was determined microscopically in serial histological sections taken from joint tissue specimens at end point.

Results: In early mCIA, joint tissue homogenates recorded significant increases in IL-6 ($P<0.01$), sIL-6R ($P<0.05$) and STAT3 ($P<0.05$) levels; they coincided with arthritis onset. sgp130Fc treatment was therefore initiated at arthritis onset. sgp130Fc and etanercept delayed mCIA onset, after 5 doses arthritis incidence was 0% (sgp130Fc) versus 17% (etanercept) and 83% (vehicle). At endpoint (day 7 therapy) all mice had arthritis; CAI ($P<0.05$) and paw diameters ($P<0.05$) were significantly reduced in sgp130Fc and etanercept compared with vehicle controls. Histological damage was less severe in the etanercept group versus vehicle controls, but not statistically significantly different. All histological parameters were significantly lower in sgp130Fc vs vehicle controls (synovial hyperplasia ($P<0.01$), synovial tissue infiltrate ($P<0.01$)). Cytomorphometric analysis revealed that synovial $Ly\text{-}6G^{+}$-neutrophils ($P<0.05$), $F4/80^{+}$-macrophages ($P<0.01$) and $CD3^{+}$-T-cells ($P<0.01$) counts were also significantly lower in sgp130Fc vs. vehicle controls. Tissue protective functionality of sgp130Fc was highlighted further by the absence of lymphoid aggregates, diminutive tartrate resistant acid

phosphatase staining for osteoclasts and significantly less bone erosions ($P<0.05$) compared with vehicle controls. At the dosing regimen under investigation, electrophoretic mobility shift assays revealed that sgp130Fc lowered the level of nuclear factor-kappa B (NFkB) and STAT activation (predominantly STAT3) in joint tissues at endpoint whilst etanercept caused a partial reduction in NFkB.

Conclusion: Timely targeted inhibition of IL-6 *trans*-signalling with sgp130Fc potently reduces clinical disease severity in an experimental model of arthritis. Selective blockade of IL-6 *trans*-signalling could have therapeutic applicability in the management of rheumatoid arthritis.

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Safety and Biodistribution of An Adeno-Associated Virus Vector, AAV5 hIFN beta (ART-I02), Delivered Via Intra-Articular Injection to Rhesus Monkeys with Collagen-Induced Arthritis. Caroline J. Aalbers[1], L. Bevaart[1], K. de Cortie[1], M.P.M. Vierboom[2], J.F. Wright[3], Paul P. Tak[4] and Margriet Vervoordeldonk[5]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Biomedical Primate Research Centre, Rijswijk, Netherlands, [3]Children's Hospital of Philadelphia, Philadelphia, PA, [4]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam The Netherlands, Amsterdam, Netherlands, [5]Arthrogen B.V, Amsterdan, Netherlands

Background/Purpose: Recombinant AAV5.NFkB.hIFNβ (ART-I02) is an adeno-associated type 5 (rAAV5) vector expressing the human interferon β (hIFNβ) gene under control of an inflammation-inducible promoter, which is under development for the treatment of rheumatoid arthritis (RA). We investigated biodistribution and initial safety of the vector after intra-articular (ia) injection of the gene construct in rhesus monkeys with collagen-induced arthritis.

Methods: Mild arthritis was induced in 3 male and 3 female monkeys with chicken type II collagen (ChCII, 3 mg). All monkeys were naïve or showed limited (1:3.1–1:10) neutralizing antibody (Nab) titers to AAV5 at the start of the study. All animals were treated with a single dose of ART-I02 ia in the first involved PIP joint and in the ipsilateral knee and ankle joint (0.1, 0.5 and 1×10e13 vector genomes (vg), respectively). Clinical signs and symptoms were monitored for a maximum of 4 weeks until the human end-point in the study was reached. Serum, joints and organs were collected for histological analysis. Serum was analyzed for acute phase response (CRP, IL-6 levels) and Nab. Presence of ART-I02 vector genomes in 16 tissues was analyzed using qPCR. Expression of hIFNβ was analyzed in serum and knee synovial tissue (ST) samples by ELISA. Histological evaluation by an experienced pathologist was performed on all organs collected to evaluate potential toxicity induced by the vector.

Results: No adverse events were observed after ia injection of a high dose of ART-I02. All animals experienced a mild acute phase response (CRP > 50 mg/L-500 mg/L) with simultaneous rising of IL-6 levels and the production of anti-ChCII IgG antibodies, as expected in this model, associated with the development of mild arthritis. High titers of Nab to rAAV5 were observed (between 1:3.160 and 1:100.000) at the end of the study. Vector DNA was detected in ST of the injected knee joint and the popliteal (draining) lymph node (injected side) at the highest copy numbers. In 1 out of 3 animals one ovary tested positive for the vector DNA (100 copies/ug DNA). Importantly, no vector DNA was detected in testes (3/3) or brain (6/6). No abnormalities were observed after histological evaluation of all organs. In knee ST samples minimal expression of hIFNβ was observed due to low arthritis activity in the knee joints, preventing activation of the NFkB promoter in the vector. In serum no hIFNβ protein could be detected.

Conclusion: Intra-articular injection of a high dose of ART-I02 is well-tolerated and does not induce adverse events in the monkey collagen-induced arthritis model of RA. This study represents an important next step towards a phase I clinical trial in RA patients.

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Anti-IL17 and Etanercept Display An Overlapping Gene Profile for Inflammation and Osteoclastogenesis in Mice with Collagen-Induced Arthritis. Daigen Xu[1], Yong Kim[1], Kai-Yeung Lau[2], Mario Giron[2], Palanikumar Ravindran[2], Holly Hilton[2], Hans Bitter[2], Catherine Tribouley[2], Deborah Cockayne[1] and Jay S. Fine[1]. [1]Inflammation Discovery, Hoffmann-La Roche, Nutley, NJ, [2]Translational Research Sciences, Hoffman-La Roche, Nutley, NJ

Background/Purpose: Anti-TNFa and anti-IL-17 treatment are beneficial to patients with rheumatoid arthritis (RA). Both agents produce efficacy by suppressing chronic inflammation and joint destruction. To explore the mechanisms underlying these effects, we assessed the impact of an anti-IL17 (aIL17) and the TNFa blocker Etanercept on global gene expression in a mouse model of collagen-induced arthritis (CIA).

Methods: CIA was induced in adult male DBA1/J mice by 2 immunizations with bovine type II antigen. Upon the 2nd immunization (day 21), test agent (aIL17 or Etanercept), vehicle (PBS) or isotype control (rat IgG) was injected ip (10 mg/ml) every 48 hours. At the end of the study (day 35), both hind paws were collected for mRNA extraction and Affymetrix array (Mouse 430 2.0). Genes upregulated by ≥2 fold were assigned to different pathways based on their known functions. Effects of disease and drug treatment on gene expression were determined by comparing CIA (isotype) mice respectively with naive and test agent-treated CIA animals. % inhibition=100-($F_{treatment}$-1)/($F_{isotype}$ −1)*100, where F is fold/ naïve.

Results: Among 14340 genes, 458 were increased by ≥2 fold in isotype-treated CIA mice over naïve animals. Genes with the greatest degree of induction belong to pro-inflammatory cytokines/chemokines, neutrophil granule proteins, MMPs or acute phase proteins. Clusters of multiple genes critical for osteoclastogenesis, Wnt signaling, Adam/Adamts activities, monocyte/macrophage or eosinophil functions were also significantly upregulated, albeit to a lesser extent. Treatment with aIL7 or Etanercept inhibited the expression of highly induced pro-inflammatory genes (>5 fold, IL-6, IL-1b, CXCL1, 2, 3, 5, COX-2, Saa3), and that of genes implicated in joint destruction, including osteoclastogenesis (RANKL, cathepsin K, Atp6v0d2 and TRAP5, Oscar, Tm7sf4 and Ibsp), Wtn (Cthrc1, Rspo2, Sfrp2, Sai1, Wisp1 and Wisp2) and matrix metalloproteases (Adam8 and12, Adamts1, 3, 4, 9 and 12, MMP3, 8, 9 and 13) by ~80%.

By comparison, both agents displayed a smaller suppressive effect on the expression of markers for monocytes/macrophages (Chi3L3, Csf1r, Emr1 and Msr1; 50% for Etanercept vs. ~60% for aIL17) and neutrophils (Ngp, Camp, Elane, Lcn2, Prtn3, Mpo, Ltf, S100a8, S100a9, CD177; 19% for Etanercept vs. ~50% for aIL17). Moreover, neither agent inhibited the up-regulation of immunoproteasome subunits (Psmb8, 9 and 10) or eosinophil markers (Ear1, Epx, Prg2 and 3). Instead, Etanercept increased the expression of eosinophil markers by an average of ~30%.

Conclusion: Together, our data demonstrate that both Etanercept and aIL17 produced their anti-inflammatory and joint protective effects by suppressing the expression of pro-inflammatory genes (cytokines, chemokines and prostaglandins), as well as genes critical for osteoclastogenesis, Wnt signaling and extracellular matrix degradation. The data further show that these therapies are not as effective at eliminating effector inflammatory cells, which may cause sustained inflammation and prevent remission. Therefore, targeting these cells for removal may represent a useful strategy for treating RA.

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Importance of the Chymase-Family Member Mouse Mast Cell Protease-5 in Inflammatory Arthritis. Richard Stevens[1], H. Patrick McNeil[2], Kichul Shin[3] and David M. Lee[4]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]University of New South Wales, Sydney, Australia, [3]Seoul National University Hospital, Seoul, South Korea, [4]Brigham and Womens Hospital, Boston, MA

Background/Purpose: Human mast cells (MCs) contain large amounts of hTryptase-β and hChymase-1 bound to heparin proteoglycans. The ortholog of hTryptase-β is mouse MC protease (mMCP) −6. Mouse MCs express many chymase-like proteases but the amino acid sequence of mMCP-5 is most similar to that of hChymase-1. Although the MCs in the synovium of arthritic C57BL/6 mice store substantial amounts of mMCP-5- and mMCP-6-heparin complexes in their granules, the biologic significance of the coordinate expression of these two serine proteases and their preferred recognition of heparin has not been deduced. Targeted inactivation of the gene that encodes N-deacetylase N-sulfotransferase-2 results in the biosynthesis of undersulfated heparin which leads to diminished granule accumulation of mMCP-5, mMCP-6, and other neutral proteases. Experimental arthritis is markedly reduced in MC-deficient *W/W^v* mice, and the adoptive transfer of Kit^+/mMCP-5^+/mMCP-6^+ MCs into these Kit-defective animals restores arthritis when the mice are then given K/BxN mouse serum. Although arthritis is also reduced in mMCP-6-null C57BL/6 mice, inflammation and joint destruction are more pronounced in heparin-deficient mice than in the tryptase-deficient animals. These data raised the possibility that a second protease exocytosed from activated MCs bound to heparin contributes to experimental arthritis. The purpose of this study was to identify that neutral protease.

Methods: Using a homologous recombination approach, an mMCP-5-

null C57BL/6 mouse was created that was then backcrossed ten times with wild-type (WT) C57BL/6 mice. The resulting mMCP-5-null mice were characterized, and then subjected to the K/BxN mouse serum-transfer and methylated albumin/interleukin-1β arthritis models.

Results: mMCP-5-null C57BL/6 mice were healthy, and contained normal numbers of MCs in their tissues. However, these MCs were less granulated than the corresponding MCs in WT mice due to their mMCP-5 deficiency. mMCP-5 and mMCP-6 are functionally distinct in all disease models that have been evaluated so far. For example, mMCP-6 is more important in chemical-induced colitis and in bacterial and helminth infections, whereas mMCP-5 is more important in ischemia-reperfusion and burn injury. Because mMCP-6 participates in inflammatory arthritis, we anticipated that extensive arthritis would develop in mMCP-5-null mice as occurs in WT mice. Surprisingly, we discovered that arthritis was much less severe in mMCP-5-null mice than in WT mice, whether the mice had been given K/BxN mouse serum or methylated albumin and IL-1β. These data suggest that mMCP-5 and mMCP-6 work together to control the magnitude of MC-dependent inflammatory arthritis in mice.

Conclusion: The finding that arthritis is reduced in both mMCP-5- and mMCP-6-null mice suggests that these unrelated serine proteases are coordinately expressed in MCs so that they sometimes can act in synergy in normal and disease processes. In terms of the human relevance of our mouse data, it is likely that an anti-protease approach will be more effective in treating patients with rheumatoid arthritis if inhibitors are used that inactivate both hChymase-1 and hTryptase-β.

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Deficiency of the Wnt-Inhibitor Sclerostin Promotes Inflammatory Joint Destruction in the Human Tumor Necrosis Factor Alpha Transgenic Mouse Model of Rheumatoid Arthritis. Corinna Wehmeyer[1], Christina Wunrau[1], Athanasios Stratis[1], Ina Kramer[2], Michaela Kneissel[2], George Kollias[3], Thomas Pap[1] and Berno Dankbar[1]. [1]University Hospital Muenster, Muenster, Germany, [2]Basel, Switzerland, [3]Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece

Background/Purpose: Progressive joint destruction is a hallmark of rheumatoid arthritis (RA) and results from increased bone resorption and the lack of repair mechanisms. TNFalpha contributes to both aspects of pathologic joint remodelling by increasing the number of bone-resorbing osteoclasts and decreasing the number of bone-forming osteoblasts. The Wnt-inhibitor sclerostin inhibits osteoblast differentiation by antagonizing the Wnt/beta-catenin signalling pathway. Since it has been shown that sclerostin is upregulated in response to TNFalpha, we studied its expression under inflammatory conditions in human RA and in hTNFtg mice, which develop an RA-like destructive arthritis. Moreover, we analyzed the effects of sclerostin deficiency on the development and severity of arthritis in these mice.

Methods: Sclerostin expression was assed by immunohistochemistry, western-blot-analysis, and RT-PCR. Sclerostin knockout ($SOST^{-/-}$) mice were crossed with hTNFtg mice to determine the functional role of sclerostin *in vivo*. The assessment of the clinical severity of disease in $SOST^{-/-}$/hTNFtg and hTNFtg mice, bone erosion, cartilage destruction and inflammation were evaluated by histomorphometric, x-ray and micro-CT analysis. TRAP staining was used to quantify the number of osteoclasts. DKK-1 expression was analyzed by immunohistochemistry and western-blot-analysis.

Results: Immunohistochemistry and western-blot-analysis revealed an increased sclerostin expression in synovial tissues of RA compared to OA patients. Ankle joints of hTNFtg mice showed high levels of sclerostin, especially in the infiltrating pannus, whereas only negligible staining was observed in wildtype animals. *In vitro*, expression of sclerostin was only found in osteoblasts, osteoclasts and hTNFtg synovial fibroblasts but could be induced in human RA synovial fibroblasts by TNFalpha. Surprisingly, knockout of sclerostin did not improve the clinical severity of arthritis in hTNFtg mice but most dramatically accelerated joint damage in this mouse model of RA. $SOST^{-/-}$/hTNFtg mice displayed significant higher bone erosion, synovial hyperplasia and osteoclast numbers compared to hTNFtg mice. Moreover, immunohistochemistry revealed higher levels of DKK-1 in joints of SOST-deficient hTNFtg mice.

Conclusion: We hypothesise that under inflammatory conditions, higher levels of DKK-1 in joints of sclerostin-deficient arthritic mice counteract the beneficial effect of sclerostin deficiency by increasing osteoclast development through enhanced blockade of the Wnt/beta-catenin signalling pathway by DKK-1. These results may have an impact on the use of blocking sclerostin antibodies in inflammatory joint diseases.

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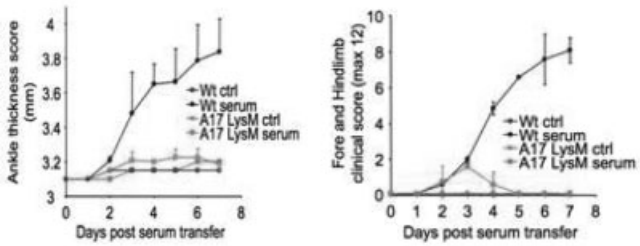
Deficiency of TACE in Myeloid Cells Prevents Arthritis in Mice. Priya Issuree[1], Thorsten Maretzky[2], Kei Horiuchi[3], Jane E. Salmon[4] and Carl Blobel[5]. [1]Weill Cornell Graduate School of Medical Sciences, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan, [4]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [5]Weill Cornell Medical College, Hospital for Special Surgery, New York, NY

Background/Purpose: The role of TNF-α in RA has been underscored by the success of anti-TNF-a therapies in the clinic. TNF-α is first synthesized as a homotrimeric 26-kDa membrane-bound protein and is proteolytic cleaved by the TNF-α-converting enzyme (TACE), also known as ADAM17, into an active 17-kDa soluble form. Small molecules that inhibit TACE and thus release of soluble TNF-α might provide an alternate approach to existing therapies. Since neutrophils and monocytes are the predominant cell types involved in the pathogenesis of the disease in patients as well as in various mice model of arthritis, such as the K/BxN passive serum transfer and the collagen antibody-induced arthritis, we investigated the benefit of inhibiting TACE in myeloid cells in the K/BxN passive serum transfer arthritis mouse model.

Methods: To generate mice lacking *Adam17* in myeloid cells, *Adam17flox/flox* mice were mated with *LysM-Cre* transgenic mice. *Adam17flox/flox/LysM-Cre* mice were maintained on a mixed genetic background (129Sv/C57BL6). K/BxN mouse serum was collected from 8-week-old K/BxN mice and pooled for each experiment. Arthritis was induced by intraperitoneal injection of 150 μl serum per mouse on day 0 and day 2. Ankle thickness was measured with a J15 micrometer (Blet) and inflammation was scored using a standard protocol.

Results: See Graph.



Conclusion: Inhibiting TACE in myeloid cells confers protection in K/BxN serum transfer arthritis and confirms the importance of myeloid cells in the effector phase of the disease. Furthermore, our data shows that myeloid cells are an importance source of TNF-α release and that inhibiting TACE on these cells may be an effective approach to limit TNF-α-driven joint damage.

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Cell Penetrating Recombinant Foxp3 Protein Enhances Treg Function, Suppresses Th17 Cells and Ameliorate Arthritis. Kentaro Yomogida[1], Yong Zhu[2], Shili Wu[2] and Cong-Qiu Chu[3]. [1]Oregon Health & Science University, Portland, OR, [2]VivoScript, Inc, Costa Mesa, CA, [3]Oregon Health & Science Univ, Portland, OR

Background/Purpose: Foxp3 is the key transcription factor for T regulatory (Treg) cell differentiation and function. Deficiency in Foxp3 results in severe autoimmune inflammation. Foxp3 induces itself expression in Treg cells and negatively regulates Th17 cell differentiation by repressing RORγt. SKG mice have impaired Treg function and develop chronic arthritis closely resembling human rheumatoid arthritis. Arthritis in SKG mice is dependent on Th17 cells. This study aimed to test the therapeutic potential of cell penetrating recombinant Foxp3 protein in treating arthritis.

Methods: Recombinant Foxp3 protein was fused to a cell penetrating polyarginine (11R) tag to facilitate intracellular transduction. Arthritis was induced in SKG mice by intraperitoneal (i.p.) injection of 2 mg zymosan. Foxp3–11R was injected i.p. daily one week after arthritis induction and continued for seven days. Severity of arthritis was assessed by using a score system and followed up for 8 weeks. Treg function was assessed by inhibition of CD4+ T effector cell proliferation using CFSE dilution assay. Th1 and Th17 cells in lymph nodes and spleens from mice treated with Foxp3–11R were detected by intracellular cytokine staining.

Results: In vitro Foxp3–11R treated CD4+ cells showed a 50% increase in suppressive function compared with control protein treated cells. Severity of arthritis in Foxp3–11R treated SKG mice was reduced compared with those treated with a control protein (see Table 1). CD4+ T cells of lymph nodes and spleen from Foxp3–11R treated mice showed increased levels of Foxp3 expression compared with those of control protein treated with mean fluorescence intensity 38 ± 3 vs 30 ± 4 in draining lymph nodes and 40 ± 2 vs 30 ± 5 in the spleen ($p<0.05$). The number of IL-17 producing CD4+ T cells in the spleen was decreased in Foxp3–11R treated mice with 1.3% vs 2.5% in control protein treated. However, the number of IFN-γ producing cells was similar between Foxp3–11R and control protein treated groups.

Table 1. Arthritis score in SKG mice treated with Foxo3–11R or a control protein.

Week after arthritis induction	4	6	8
Foxp3 treated (n=5)	1.36 ± 0.93	1.08 ± 0.72	1.84 ± 1.90
Control (n=6)	1.47 ± 0.76	3.13 ± 2.95	4.18 ± 3.21
p	0.78	0.02	0.33

Conclusion: These results demonstrate that Foxp3–11R can enhance T cell suppressive function, suppress Th17 cells and ameliorate experimental arthritis. The data suggest that cell penetrating recombinant Foxp3 is a potentially useful agent in therapy of arthritis.

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Macrophage-Specific SHIP-1 Depletion Leads to Greatly Enhanced Arthritis. Shawn M. Rose and Harris R. Perlman. Northwestern University, Chicago, IL

Background/Purpose: Macrophages are critical effectors of innate immunity, as they are involved in the detection, response, and resolution phases of inflammation. The Src homology 2-domain-containing inositol-5'-phosphatase (SHIP-1) is an important negative regulator of the phosphatidylinositol 3-kinase (PI3K) pathway, and hence acts as a molecular rheostat to keep inflammation in check. Mice with a systemic deficiency of SHIP-1 demonstrate autoimmunity characterized by increased production of auto-antibodies, hematologic abnormalities, and lung and kidney disease. It has been reported that macrophages in SHIP-1-deficient mice are skewed toward the alternative M2 phenotype, which results from the exogenous effects of basophils in these animals *in vivo*. It is unknown whether macrophage-intrinsic properties contribute to this phenotype. We have exploited the Cre-LoxP system to generate animals with a macrophage-specific deletion of SHIP-1. To test whether M1 macrophage inflammatory activity occurs in these mice *in vivo*, we utilized the serum transfer induced arthritis model.

Materials & Methods: 8 week-old B6.SHIPflox x LyzCre and B6.SHIPflox control mice were injected intraperitoneally with K/BxN serum. Arthritis severity was assessed every other day for 2–3 weeks using measurements of joint width (mm) and a clinical inflammation index (0–3 scale, 4 paws). After euthanasia, ankle joints were harvested from the animals, fixed in paraformaldehyde, decalcified, processed for immunohistochemistry, and stained with Hematoxylin & Eosin.

Results: Both measures of arthritis were significantly greater in B6.SHIPflox x LyzCre compared to B6.SHIPflox control mice. Remarkably, joint inflammation did not resolve in B6.SHIPflox x LyzCre animals even out to 3 weeks. Pathologic analysis of ankle joint specimens confirmed more severe inflammatory infiltrates in B6.SHIPflox x LyzCre mice compared to B6.SHIPflox controls.

Conclusion: Our findings suggest that B6.SHIPflox x LyzCre mice develop very severe joint inflammation in the serum transfer induced model of arthritis. Hence, there may be an intrinsic M1 macrophage component in SHIP-1-deficient mice, although effects of the loss of SHIP-1 on neutrophils in this model cannot be excluded. Studies on the mechanism of arthritic inflammation in these animals are forthcoming.

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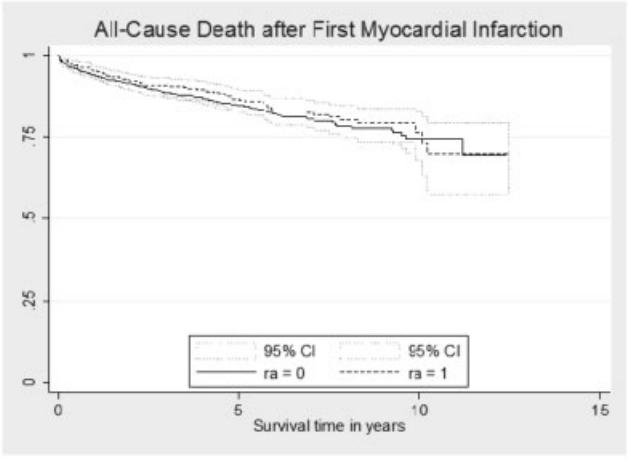
Treatment and Mortality After Myocardial Infarction in Rheumatoid Arthritis—a Cohort Study of Incident Rhematoid Arthritis in Sweden. Marie Holmqvist[1], ängla Mantel[1], Tomas Jernberg[2], Lennart TH Jacobsson[3], Lars Alfredsson[4], Stefan James[5] and Johan Askling[1]. [1]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Solna, Sweden, [2]Department of medicine, Section of Cardiology, Karolinska University Hospital, Huddinge, Sweden, [3]Section of Rheumatology, Malmo, Sweden, [4]Institute of Environmental Medicine, Karolinska Institutet, Solna, Sweden, [5]Department of Cardiology, Uppsala University Hospital

Background/Purpose: To investigate whether RA-patients are at increased risk of dying after an MI and whether level of care and treatment intensity differs between RA-patients and general population comparators after an event.

Methods: RA-patients included in the Swedish Rheumatology Quality Register (SRQ) between 1 Jan 1995 and 1 Jan 2007 who had a symptom duration ≤12months when included and were free from ischemic heart disease prior to inclusion were matched on sex, calendar period, county, and age to an ischemic heart disease free general population comparator. 6,735 RA-patients and 33,692 general population comparators were identified. An index date was assigned to all individuals; date of inclusion in SRQ in RA and corresponding in comparators. Information on all first time hospitalizations for MI and on all who for the first time were treated in intensive coronary care units (ICCU) after index date was retrieved from Swedeheart, a nationwide register of all ICCU care given in Sweden, and the Swedish Inpatient register. Information on deaths was retrieved from the census register. To compare the risk of death after event, Cox models were constructed using time since event as time scale, adjusted for age and sex. Survival curves were fitted using the product limit estimator.

Results: 70% of the RA-patients and comparators were women. Mean age at index date was 57 in RA and comparators. 8% of RA-patients and 6.6% of the comparators were hospitalized with an MI after index date. 41% of RA-patients and 31% of the comparators hospitalized with an MI were treated in an ICCU. Of those hospitalized in an ICCU, there was no difference in the proportion of RA-patients and comparators undergoing coronary bypass surgery or percutaneous coronary interventions. The proportion of individuals prescribed with beta-blocking agents (85%), statins (66%), and nitrates (17 vs 21%) at discharge was similar in the two groups. Oral anticoagulants and antiplatelet medications were somewhat more common in RA-patients at discharge (56.5% vs 49.8%, p non-significant). 63.5% of RA-patients and 65.7% of comparators were assigned followup in a cardiology or internal medicine department. Overall survival after being hospitalized with an MI was similar in RA-patients and comparators (fig 1), RR 1.0 (95% CI 0.7, 1.3). 28-day survival and 1-year survival was also similar in the two groups.



Conclusion: In Sweden, patients with early RA who suffer an MI are as well treated and as likely to survive as the general population.

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Diastolic Heart Failure in Rheumatoid Arthritis Correlates with Reduction in Global Longitudinal Strain and Occurs Independent From Therapy with Tumor Necrosis Factor Inhibitors. A Study with Tissue Doppler, Strain Imaging, and NTproBNP Measurement. Demian A. Ridjab[1], Michael Gottwald[2], Andreas Krause[3], Thomas Schau[1], Christian Butter[1] and Michael Zaenker[2]. [1]Cardiology Dept., Immanuel Klinikum Bernau Heart Center Brandenburg, Bernau, Germany, [2]Immanuel Klinikum Bernau, Rheumatology Center North Brandenburg, Bernau, Germany, [3]Immanuel Krankenhaus Berlin-Buch, Berlin, Germany

Background/Purpose: Risk of heart failure is increased in patients with rheumatoid arthritis (RA) and is more likely to occur in RA patients with a preserved ejection fraction. It has been postulated that fibrosis plays an important role in the structural changes in the heart of patients with RA. Until now little is known about the prevalence of diastolic heart failure and its related structural changes. Therefore we examined RA patients with and without anti-TNFa therapy for diastolic heart failure using measurement of NT-pro-BNP level and echocardiography, including tissue doppler and strain imaging.

Methods: In a prospective consecutive study 74 patients from our outpatient clinic with RA according to ACR-Criteria treated with (n = 38) or without (n = 36) anti-TNFa-therapy were included. The cohort underwent blood sampling for NT-pro-BNP and echocardiography with assessment of left ventricular end-diastolic (LVEDV), end-systolic volume (LVESV), septal thickness, LV ejection fraction, LV diastolic function and global longitudinal strain with speckle-tracking. Diastolic heart failure was diagnosed when (1) E/E'-ratio > 15 or (2) NT-pro-BNP > 220 pg/ml with E/E'-ratio > 8 or in presence of atrial fibrillation.

Results: Sixty-six percent of the patients (n=49/74) were female. Mean age was 59.8 ± 13 years. RA activity score DAS28 showed a mean of 2.8 (± 0.9) with 32 % of patients in remission (DAS28 ≤ 2.6). Function score FFbH showed a mean of 66% (± 25). Mean BMI was 29.0 ± 4.7 kg/m^2. Twenty-three percent of the patients had hypertension (mean blood pressure 130.9 / 79.5 mmHg (± 19.9 /8.1). LV hypertrophy was found in 78 %, with mean septal thickness of 10.8 ± 1.4 mm. The following mean values were present: heart rate 81 ± 13 bpm, GLS –18.7 ± 2.8%, LVEDV and LVESV 70.7 ± 23.2 and 23.9 ± 9.7 ml, reps., LV ejection fraction 67.5 ± 6.4, E/A-ratio 1.03 ± 0.42, E/E'-ratio 8.37 ± 3.02. Only five percent of patients had relevant valvular disease (n=3 tricuspidal regurgitation II°, n=1 moderate aortic stenosis). According to the above mentioned criteria diastolic heart failure was diagnosed in 31 % of patients. Using a GLS value of −19% as a cut off, patients with diastolic heart failure showed a significant reduction in GLS in comparison to those with normal diastolic function (p = 0.02, OR 3.2 (95% CI:1.04–10.3)). There were no significant differences in LVEDV, LVESV, E/A-ratio, E/E′-ratio, NT-BNP, and mean GLS between groups, when anti-TNFa-therapy was considered.

Conclusion: In the studied RA cohort, there is a surprisingly high rate of diastolic heart failure (31 %) with preserved ejection fraction independent from concomitant anti-TNFa therapy. Imaging data revealed a significant reduction in the global longitudinal strain in patients with diastolic heart failure. This finding suggests the role of fibrotic changes in diastolic heart failure in RA. The endocardium is most susceptible to the deleterious effects of interstitial fibroris and GLS measurements detect abnormal longitudinal function of the subendocardial level at an earlier stage. We therefore suggest the use of global longitudinal strain measurement in addition to conventional echocardiography in diastolic heart failure.

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Progression of Subclinical Atherosclerosis Over Five Years in Patients with Early Rheumatoid Arthritis. Anna Södergren[1], Kjell Karp[2], Kurt Boman[3], Catharina Eriksson[4], Elisabeth Lundström[2], Torgny Smedby[5], Bozen Möller[6], Solbritt Rantapää Dahlqvist[1] and Solveig Wållberg Jonsson[1]. [1]Dept of Rheumatology, Umeå, Sweden, [2]Department of Surgical and Perioperative Sciences, Umeå, Sweden, [3]Department of Medicine, Skellefteå, Sweden, [4]Department of Clinical Immunology, Umeå, Sweden, [5]Östersunds Rehab Centrum, Östersund, Sweden, [6]Department of Rheumatology, Luleå, Sweden

Background/Purpose: Patients with rheumatoid arthritis (RA) have an increased mortality and morbidity due to cardiovascular disease (CVD). A premature atherosclerosis as measured by ultrasound of intima media thickness (IMT) has been demonstrated in patients with long-standing RA (1, 2). Endothelial dysfunction, shown to precede atherosclerosis in general population (3), can be measured by flow-mediated dilation (FMD). In patients with RA of recent onset we have found IMT and FMD to be similar as in controls (4). In this prospective 5-year follow up, we aimed to investigate for increased progression of atherosclerosis, as measured by FMD and IMT, in the patients with early RA compared to the controls. We also aimed to analyze the relationship between these measurements and biomarkers of endothelial dysfunction (5), taking inflammation and traditional CVD risk factors into account.

Methods: Patients from northern Sweden diagnosed with early RA are followed in an ongoing prospective study of co-morbidity. From these patients a subgroup of patients (n=71), aged ≤60 years, was consecutively included for measurements of IMT of the common carotid artery and FMD of the brachial artery. The ultrasound measurements were taken at inclusion (T0) and after 5 years (T5). Forty-two age/sex matched controls were included. The patients were clinically assessed (DAS28, TJC, SJC, DMARDs) and blood was drawn from all individuals for initial analysis of cholesterol, HDL-cholesterol, triglycerides, ESR, CRP, MCP-1, PAI-1, tPA-mass, VWF, sICAM, sVCAM, sE-selectin and sL-selectin.

Results: Patients with RA had a significant aggravation in both IMT (0.052 at T0 and 0.058 at T5, p<0.001) and FMD (0.090 at T0 and 0.070 at T5, p<0.001). Among the controls the increase was less evident and only significant for IMT (0.055 at T0 and 0.060 at T5, p<0.001). There was a trend towards a more pronounced worsening in the FMD among patients with RA (−0.022 in RA vs −0.010 on ctrls, p=0.097). In linear regression analyses among patients with RA, the IMT at T5 was significantly associated with several variables measured at T0: systolic and diastolic blood pressure (BP), cholesterol, triglycerides, tPA, VWF, and MCP-1 and it was inversely associated with sL-selectin. In the corresponding analyses of FMD at T5 it was significantly associated with sL-selectin and inversely associated with diastolic BP and VWF at T0. Amongst the controls, the IMT at T5 was significantly associated with cholesterol, HDL, triglycerides, body mass index, systolic and diastolic BP, and tPA at T0, whilst FMD related inversely with VWF at T0.

Conclusion: In five years, the increase in subclinical atherosclerosis was more evident among patients with early RA compared to the controls. The IMT at T5 was more highly predicted by baseline levels of biomarkers of endothelial activation in patients with RA compared to controls.

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Treat to Target: Normal Cholesterol Values in Low Disease Activity Established RA. Inger L. Meek[1], H.S.J. Picavet[2], Harald E. Vonkeman[1] and Mart AF van de Laar[3]. [1]Rheumatology Center Twente, Medisch Spectrum Twente & Twente University, Enschede, Netherlands, [2]National Institute for Public Health and the Environment, Bilthoven, Netherlands, [3]Medisch Spectrum Twente & Twente University, Enschede, Netherlands

Background/Purpose: Over the past decades many reports have demonstrated the association between RA and dyslipidemia, the unfavourable lipid profiles having been observed >10 years before disease onset. Some have reported an association between disease activity and low HDL cholesterol levels, however in other studies no associations between disease duration or activity and lipid spectrum abnormalities could be found. Also, after treatment with biologicals improvement, as well as deterioration of lipid profiles has been observed. Dislipidemia might contribute to the observed raised cardiovascular mortality in RA, therefore more data concerning lipid profiles in currently treated RA patients are needed. The aim of this study was to compare the lipid profiles of RA outpatients with the general population, and to investigate risk factors for an artherogenic lipid profile in RA.

Methods: Comparison of lipid profiles, i.e. total cholesterol (TC), HDL cholesterol (HDL), and TC/HDL-ratio in a cohort of all consecutive patients between 36 and 75 years of age attending the Arthritis Center Twente (ACT), a large rheumatology outpatient department in The Netherlands (n=546), and a sample of the general population (GP) from the same geographic region

(n=4523). Multivariate analysis of the relationship between potential risk factors, i.e. disease activity (remission by DAS-28 or expert opinion), ESR, disease duration, biological use, and smoking and TC/HDL-ratio. Data were collected by direct measurements in 2009 (ACT), and from 2003 to 2007 (GP) respectively. Analyses were sex-specific and standardised by age.

Results: The RA cohort consisted of 341 women and 205 men, mean age 56 years, and mean disease duration 81 months, 19% being treated with biologicals, and 69% being in remission of RA. Preliminary analyses show that RA patients had similar frequencies of hypercholesterolemia (TC>6.5 mmol/L and/or use of lipid lowering medication; GP 18%, OR_{ACT} 1.1, 95% CI 0.9–1.4) and lowered HDL<1.0 mmol/L; GP 7.2%, OR_{ACT} 1.0, 95% CI 0.7–1.4) compared to the GP. TC/HDL ratios were lower in RA patients (GP 4.2, RA 3.9, p<0.05). In RA patients non-smoking and biological use were associated with lower TC/HDL ratios (p, 0.05), controlling for lipid lowering therapy.

Conclusion: Dislipidemia is not increased in RA patients treated according to the current standards aiming at remission. Non-smoking and biological use are associated with lower TC/HDL ratios.

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Vitamin D Levels Are Independently Associated with the Metabolic Syndrome and Metabolic Dyslipidemia In Rheumatoid Arthritis. Joshua Baker[1], Nehal Mehta[2], Gary Toedter[3], Daniel G. Baker[4], Joan Marie Von Feldt[5] and Mary Beth Leonard[6]. [1]University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania, PA, [3]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Malvern, PA, [4]Centocor R & D, a division of Johnson & Johnson Pharmaceutical Research and Development, LLC, Malvern, PA, [5]Univ of Pennsylvania/Philadelphia VAMC, Philadelphia, PA, [6]The Children's Hospital of Philadelphia, Philadelphia, PA

Background/Purpose: Vitamin D deficiency has been associated with an increased risk of cardiovascular disease through unknown mechanisms. The association between vitamin D, dyslipidemia, and metabolic syndrome has not been evaluated in patients with rheumatoid arthritis (RA).

Methods: Baseline serum 25(OH)vitamin D levels were measured at baseline in a random sample of 499 participants, ages 18–85, enrolled in a randomized trial of golimumab (GO-Before Trial). Participants met ACR criteria for RA, had active disease, and were naïve to methotrexate and biologic therapy. Multivariable linear regressions were performed to assess associations between vitamin D and lipoprotein fractions at baseline. Multivariable logistic regression was performed to determine the risk of metabolic syndrome and hyperlpidemia in participants with low vitamin D.

Results: Low-density lipoprotein (LDL) and triglyceride (TG) levels were correlated with vitamin D (Spearman's Rho:-0.16 p=0.0006 and −0.16 p=0.0002, respectively). In linear regression analysis, the association was present controlling for age, sex, race, BMI, GFR, exercise, smoking, steroid use, diabetes, hypertension, CRP, geographic region, disease activity (DAS28), and season. Vitamin D deficiency (<20 ng/mL) was independently associated with an increased risk of hyperlipidemia (1.66 (1.10–2.45) p=0.014) as well as an increased risk of metabolic syndrome (OR 3.45 (1.75–6.80) p<0.001).

Conclusion: Vitamin D deficiency is independently associated with the metabolic syndrome and metabolic dyslipidemia in subjects with RA.

Table 1. Multivariable logistic regression analyses evaluating the odds of hyperlipidemia (defined as TG>150, LDL>160, HDL<40 for men or <50 for women of current use of lipid lowering therapy) by vitamin D status.

Variable	Odds Ratio	95% CI	P value
Model 1*			
< 20 ng/mL	1.64	1.14–2.35	0.008
Model 2†			
< 20 ng/mL	1.52	1.04–2.20	0.032
Model 3‡			
< 20 ng/mL	1.62	1.10–2.40	0.015
Model 4μ			
< 20 ng/mL	1.72	1.10–2.45	0.014

* Adjusted for age, sex, race
† Adjusted for age, sex, race, BMI, diabetes, hypertension, and smoking.
‡ Adjusted for age, sex, race, BMI, GFR, exercise, smoking, diabetes, hypertension, and CRP.
μ Adjusted for age, sex, race, BMI, GFR, exercise, smoking, steroid use, diabetes, hypertension, CRP, region, DAS28, and season.

Table 2. Multivariable logistic regression analysis for the odds of the presence of 1, 2, 3, or 4 components of the metabolic syndrome in vitamin D deficient subjects (<20 ng/mL). The adjusted mean vitamin D level for subjects with increasing components of the metabolic syndrome is also presented.

Components of Metabolic Synd.*	OR	95% CI	P value	Adjusted Mean Vitamin D*
0	1	—	—	21.68
1	1.29	0.78–2.14	0.32	20.77
2	1.65	0.93–2.93	0.085	19.86
3	2.93	1.40–6.16	0.004	19.01
4	4.84	1.44–16.30	0.011	18.15
				(P for trend = 0.016)

* Adjusted for age, sex, race, GFR, exercise, smoking, steroid use, CRP, region, DAS28, and season.

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Endothelial Dysfunction Improves in Patients with Rheumatoid Arthritis by Reducing Disease Activity. Lodewijk de Groot[1], Johanna Westra[2], Nynke Jager[1], Marcel D. Posthumus[2] and Marc Bijl[2]. [1]University Medical Centre Groningen, Groningen, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: The incidence of cardiovascular disease (CVD) is increased in rheumatoid arthritis (RA). Disease activity is supposed to be an important factor in the development of CVD in RA and reducing disease activity is one of the recommendations in the EULAR criteria for "cardiovascular risk management" in RA.

Aims of the study: To evaluate whether reduction of disease activity will influence markers of endothelial dysfunction, which is regarded an early marker of atherosclerosis.

Methods: In a prospective, longitudinal study 58 RA patients with recent onset of disease and 58 age and sex matched healthy controls were included. Endothelial dysfunction was measured by small artery elasticity (SAE), presence of atherosclerosis was determined by intima media thickness (IMT). Disease activity was measured by DAS-28. Patients were treated according to a predefined protocol. After one year all measurements were repeated in the RA patients and in 10 healthy controls.

Results: At entry endothelial dysfunction was increased in RA (median 3.4 ml/mmHg ×100, range 1.2–9.0) vs. HC (6.1, 1.7–12.9, P<0.0001). There was no difference in IMT between RA (0.70mm, 0.44–1.54) vs. HC (0.68, 0.49–1.46, P= 0.55). SAE had an inverse correlation with DAS-28 (r=-0.3066, P=0.0228). After 1 year SAE was improved in RA (3.9, 1.5–10.3, P=0.0115), in particular in patients who achieved remission (DAS-28 score < 2.6): in these SAE increased from 3.3, (1.2–7.7) to 5.7, (1.5–10.3), P=0.0269. In healthy controls SAE did not change after one year (6.8, (1.7–10.5) to 6.6 (1.6–10.0), P=0.56). DAS-28 scores decreased from 4.6, (2.1–7.8) to 2.1, (1.0–5.5), (P<0.0001). IMT showed no significant change after one year.

Conclusion: Endothelial dysfunction is present in early RA and is correlated inversely with disease activity. By reducing disease activity endothelial dysfunction improves, although not to normal values. This implicates that disease activity is probably not the only factor responsible for the increased risk for CVD in RA.

1160

Statin Use Is Associated with Decreased Incident Coronary Artery Events in Rheumatoid Arthritis Patients. Chad P. Walker[1], Xiaoqin Tang[2], H. Lester Kirchner[2], Steven Steinhubl[3], Stephanie J. Morris[4], Jana L. Antohe[3] and Androniki Bili[5]. [1]Geisinger, Bloomsburg, PA, [2]Geisinger Center for Health Research, Danville, PA, [3]Geisinger Health System, Danville, PA, [4]Rose Tree Medical Associates—Riddle Memorial Hos, Danville, PA, [5]Geisinger Medical Center, Danville, PA

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased morbidity and mortality from cardiovascular disease (CVD). Statins have been associated with decreased coronary artery disease (CAD) events in the general population and have immunomodulatory effects, but this relationship has not been studied in RA. We examined the association of statin use with incident CAD in an inception cohort of RA patients.

Methods: Patients with newly diagnosed RA between 1/1/2001–12/31/2009 were identified through electronic health records (n=1881). Patients with preexisting CVD (CAD, cardiac revascularization procedure, abdominal aortic aneurysm, stroke, transient ischemic attack, peripheral artery disease, arterial revascularization procedure), primary care physician outside the institution, previous

statin use or liver disease were excluded (n=1331). The primary outcome was time to CAD (ICD-9 code ICD-9 410, 410.**-414.99 or revascularization procedure CPT codes 33510, 33548, 92982, 92984, G0290, G0291, 92930, 92981). Secondary analysis used time to development of CVD. Cox regression models were used to estimate the association between exposure to statin use and development of disease after adjusting for age, gender, race, hypertension, hyperlipidemia, diabetes, body mass index, low density lipoprotein level, systolic and diastolic blood pressure, rheumatoid factor, sedimentation rate and medications (TNF inhibitors, MTX, HCQ, steroids and NSAIDs).

Results: Analyses included 550 RA patients. Table 1 shows the patients' characteristics by statin use. Of the 39 cases developing CAD during observation, 14 were ever- and 35 were never-statin users. The median duration of statin exposure was 17.3 months. Of the 14 cases developing CAD in statin ever-users, 7 were exposed ≤ 17 months and 7 were exposed >17 months. The incidence rate ratio (95% CI) for statin use >17 months vs. ≤ 17 months vs. statin never use was 0.87 (0.39, 1.95; p-value=0.74) and 2.03 (1.06, 3.88; p-value=0.03) compared to never-use respectively. Results of the fully adjusted Cox model are shown in Table 2.

Table 1. Characteristics of RA patients by Duration of Statin Usage

		Post-RA Statin use[1]		
	Never (n = 432)	≤17 month (n = 58)	>17 month (n = 60)	P-value*
Male sex	105 (24.3%)	14 (24.1%)	16 (26.7%)	n.s.
White race	411 (95.1%)	54 (93.1%)	58 (96.7%)	n.s.
Positive CCP IgG Ab	126 (54.3%)	16 (57.1%)	10 (45.5%)	n.s.
Positive rheumatoid factor	272 (76.4%)	36 (80.0%)	41 (82.0%)	n.s.
Medication use (ever)				
TNF	139 (32.2%)	24 (41.4%)	21 (35.0%)	n.s.
Hydroxychloroquine	185 (42.8%)	23 (39.7%)	24 (40.0%)	n.s.
Methotrexate	256 (59.3%)	37 (63.8%)	41 (68.3%)	n.s.
NSAIDs	331 (76.6%)	52 (89.7%)	50 (83.3%)	.049
Steroid	377 (87.3%)	49 (84.5%)	55 (91.7%)	n.s.
Hypertension	227 (52.6%)	43 (74.1%)	48 (80.0%)	<.001
Hyperlipidemia	16 (3.7%)	49 (84.5%)	54 (90.0%)	<.001
DM	67 (15.5%)	20 (34.5%)	30 (50.0%)	<.001
Age at RA diagnosis	54 (44, 67)	59 (53, 68)	58 (52, 71)	.002
Median BMI (95.3% known)	28.4 (24.4, 32.3)	30.3 (27.6, 35)	32.1 (28.2, 36.2)	<.001
Median LDL (77.3% known)	107 (89, 128)	123 (102, 142)	103 (82, 120)	.001
Median SBP	74 (70, 80)	76.5 (72, 80)	72 (70, 80)	.047
Median DBP	124 (118, 132)	130 (122, 134)	131 (123, 139)	<.001
Pt Max CRP result (35.8% known)**	6.9 (2.4, 19)	7.4 (3.2, 19.7)	7.8 (3.1, 19.8)	n.s.
Pt Max Sedimentation Rate (81.3% known)	30 (16, 50)	34 (20, 54)	46 (21, 77)	.024

1. Ever Post-RA statin usage prior to DM diagnosis or censor date.
* P-values obtained either from Chi-square tests (frequencies) or Wilcoxon's test (medians)
** Not included in modeling due to the high percentage of missing data.
^ These are ever in time-frame. All else are post-RA.
n.s. = not significant

Table 2. Risk of developing CAD and CVD Based on Statin Use in RA patients

			HR (95% CI)	p-value
Coronary Artery Disease	Cumulative duration of statin exposure	Continuous (in months)	0.96 (0.96, 0.99)	.009
	Cumulative duration of statin exposure	≤17 months vs. never use	1.12 (0.42, 2.97)	n.s.
		>17 months vs. never use	0.30 (0.10, 0.94)	.039
Cardiovascular Disease	Cumulative duration of statin exposure	Continuous (in months)	0.97 (0.98, 0.10)	.021
	Cumulative duration of statin exposure	≤17 months vs. never use	1.52 (0.69, 3.31)	n.s.
		>17 months vs. never use	0.45 (0.16, 1.25)	n.s.
Coronary Artery Disease*	Cumulative duration of statin exposure	Continuous (in months)	0.963 (0.935, 0.991)	.009
	Cumulative duration of statin exposure	≤17 months vs. never use	1.121 (0.423, 2.974)	n.s.
		>17 months vs. never use	0.303 (0.098, 0.940)	.039
Cardiovascular Disease*	Cumulative duration of statin exposure	Continuous (in months)	0.971 (0.947, 0.996)	.021
	Cumulative duration of statin exposure	≤17 months vs. never use	1.515 (0.694, 3.306)	n.s.
		>17 months vs. never use	0.445 (0.159, 1.246)	n.s.

* Fully adjusted using time-variance where applicable for age, gender, race, hypertension, hyperlipidemia, diabetes, body mass index, low density lipoprotein level, systolic and diastolic blood pressure, rheumatoid factor, sedimentation rate and medications (TNF inhibitors, MTX, HCQ, steroids and NSAIDs)
n.s. = not significant

Conclusion: Statin use was associated with a 4% per month decrease in incident CAD risk in RA patients. For RA patients using statins for >17 months the risk of incident CAD decreased by 70%. Secondary analysis for incident CVD showed similar trends, although this did not reach statistical significance. This is a novel finding that may allow the study of statin use for primary CAD prevention in RA patients.

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Endothelial Progenitor Cells and Cardiovascular Risk in Patients with Rheumatoid Arthritis. Nynke Jager, Steven Wenker, Lodewijk de Groot, Marcel D. Posthumus, Marc Bijl and Johanna Westra. University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: The incidence of atherosclerosis and therefore cardiovascular disease (CVD) is increased in rheumatoid arthritis (RA). The chronic inflammatory status is seen as an important factor in activation and damage to the endothelium. This leads to endothelial cell dysfunction and subsequently to atherosclerosis. Endothelial progenitor cells (EPCs) are stem cell like cells, and can be found in the peripheral blood. EPCs are supposed to play a role in repair of endothelial damage. The aim of this study is to evaluate whether the increased cardiovascular risk of RA patients is determined by lower EPC numbers, and whether these numbers correlate with endothelial dysfunction and atherosclerosis.

Methods: Thirteen RA-patients, with recent onset of disease (< 1 year), and thirteen healthy controls (HC) where included. EPC counts were measured in peripheral blood by flow cytometry using anti-CD34 en anti-CD133 antibodies. Colony-forming units (CFUs) were counted by culturing peripheral blood mononuclear cells on fibronectin coated plates (CFU-Hill) (1). In all participants SAE (small artery elasticity) was determined as measure of endothelial dysfunction and IMT (intima media thickness) was determined as measure for atherosclerosis.

Results: The numbers of circulating CD34 positive cells were lower in RA patients compared to HC (p=0.09), while CFU counts were significantly decreased in RA patients compared to healthy controls (p=0.005). The number of CD34 positive cells, the number of double positive cells (CD34/CD133) and the CFU counts were all significantly positively correlated to SAE measurement (p=0.02, p=0.02 and p=0.007 respectively). No correlations could be demonstrated between EPC or CFU numbers and IMT values.

Conclusion: Circulating EPCs and CFU counts are reduced in RA patients, and EPC numbers correlate with endothelial dysfunction. A shortage of EPCs in the peripheral blood could play a role in reduced repair and accelerated development of atherosclerosis in RA patients. As such, determination of the number of EPCs might be of value to predict the cardiovascular risk in RA patients.

Reference List

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1162

Ischemic Stroke in RA—a Cohort Study of Risks, Relative Risks and Predictors. Marie Holmqvist[1], Emma Gränsmark[2], Solveig Wållberg Jonsson[3], Lennart TH Jacobsson[4], Lars Alfredsson[1] and Johan Askling[5]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Dept of Rheumatology, Umeå, Sweden, [4]Section of Rheumatology, Malmo, Sweden, [5]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Solna, Sweden

Background/Purpose: To investigate the risk of ischemic stroke (IS) in rheumatoid arthritis (RA) relative to the risk in the general population; to find out when after RA-diagnosis the risk is increased; to explore predictors of IS in the RA population.

Methods: RA-patients included in the Swedish Rheumatology Quality Register (SRQ) between 1 Jan 1995 and 1 Jan 2010 who had a symptom duration ≤12months when included and were free from ischemic stroke prior to inclusion were matched on sex, calendar period, county, and age to an ischemic stroke free general population comparator. 9,412 RA-patients and 46,242 general population comparators were identified. An index date was assigned to all individuals; date of inclusion in SRQ for RA-patients and corresponding in the matched comparators. Information on all first time hospitalizations for IS and potential predictors was retrieved from the Swedish Inpatient register. Information on deaths was retrieved from the census register. Follow-up with respect to hospitalization for IS ended at event, death, emigration or 31 Dec 2009. To estimate the relative risk (RR) and calculate 95% confidence intervals (CI), Cox models were constructed using time since RA-diagnosis as time scale. The models accounted for the matched design. To assess the impact of comorbidities such as hypertension (HT), diabetes mellitus (DM), atrial fibrillation/flutter (AF), peripheral venous events including deep venous thrombosis and pulmonary embolism (DVT/PE) and ischemic heart disease (IHD) on the risk of having an IS, Cox models were constructed and each potential predictor assessed separately using time-dependent covariates adjusted for age at index date and sex.

Results: Median follow-up was 4.7 years in RA and in comparators. Mean age at index date was 57.9 years in RA and 57.8 years in the comparators. 65.3% of the patients with RA were seropositive. 2.7% of RA-patients and 2.4% of the comparators were hospitalized with an IS after index date, corresponding to an age- and sex-adjusted RR of 1.14 (95% CI 0.99, 1.31). Women with RA had a significantly increased risk of IS compared to the general population (RR= 1.2, 95% CI 1.01, 1.44) but men did not. The risk increased compared to the general population after 10 years with RA (table). HT, IHD AF were statistically significant predictors of IS in RA. DVT/PE did not predict IS in RA but did in the general population (table).

Relative risk of ischemic stroke in RA stratified on time since RA-diagnosis

	<1 year since RA diagnosis	1–4 years since RA diagnosis	5–10 years since RA diagnosis	10–15 years since RA diagnosis
Relative risk (95% CI)	1.19 (0.84, 1.67)	1.06 (0.86, 1.30)	1.08 (0.84, 1.40)	2.00 (1.24, 3.22)
N events in RA/comp	45/190	110/516	73/336	27/78

Time-dependent covariates adjusted for age at index date and sex

	RA-patients RR (95% CI)	Comparators RR (95% CI)
Hypertension	1.74 (1.30, 2.32)	2.20 (1.92, 2.52)
Diabetes mellitus	1.34 (0.86, 2.10)	2.18 (1.82, 2.61)
Ischemic heart disease	1.64 (1.22, 2.22)	1.54 (1.33, 1.79)
Atrial fibrillation/flutter	1.91 (1.32, 2.75)	2.61 (2.22, 3.07)
Peripheral venous emboli	0.97 (0.55, 1.70)	1.32 (1.00, 1.75)

Conclusion: The risk of IS is increased in RA but first after 10 years with RA. Traditional risk factors might have a weaker association with IS in RA than in the general population, prompting us to search for other, RA-specific, predictors of IS.

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Myocardial Ischemia in Asymptomatic Patients with Rheumatoid Arthritis: A Comparative Study with Diabetes Mellitus. A. Karanasos[1], I. Felekos[1], C. Aggeli[1], E. Zampeli[1], A. Protogerou[1], C. Stefanadis[1], G. Kitas[2], K. Toutouzas[1] and PP Sfikakis[1]. [1]Athens University, Medical School, Athens, Greece, [2]The Dudley Group of Hospitals NHS Foundation Trust, Dudley, and Arthritis Research Campaign Epidemiology Unit, University of Manchester, UK, Manchester, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased ischemic events. The possible presence of myocardial ischemia, by dobutamine stress-contrast echocardiography was studied in asymptomatic patients and compared to patients with diabetes mellitus and a control group.

Methods: We prospectively enrolled 18 (12 women) consecutive non-diabetic RA patients with no evidence of coronary artery disease (68±7 years old with disease duration of 11±7 years, 50% smokers, 72% hypertensives, 33 % dyslipidemics) who developed new carotid plaques during the past 3 years. All underwent stress contrast echocardiography using the 17-segment model of the left ventricle for wall-motion and perfusion evaluation; consented patients with a positive stress test underwent coronary angiography. RA patients were compared to 18 asymptomatic patients with diabetes mellitus (matched 1:1 for traditional cardiovascular risk factors), as well with 36(matched 1:2) asymptomatic 'healthy' individuals.

Results: A positive stress result was found in 12 RA patients (67%), 14 diabetics (78%) and 11 controls (31%; $p<0.05$ for RA vs. control, $p<0.01$ for diabetes vs control group, p=NS for RA vs diabetes). Median number of myocardial segments with perfusion defect was 1 (interquartile range [IQR] 2) in RA, 2 (IQR 3) in diabetes and 0 (IQR 1.5) in controls ($p<0.05$ for RA vs. control, $p<0.01$ for diabetes vs control, p=NS for RA vs diabetes). Median wall motion score index was 1.05 (IQR 0.1) in RA, 1.1 (IQR 0.05) in diabetes and 1 (IQR 0.075) in the control group ($p<0.05$ for RA vs. control, $p<0.01$ for diabetes vs control, p=NS for RA vs DM). Among subjects with positive stress results either the number of segments with perfusion defect (median of 2) or wall motion score index (median of 1.1) was similar between RA, diabetes and controls. Of the 12 RA patients with positive stress result, coronary angiography performed in 8 revealed normal findings in 4, non significant coronary atheromatic lesions in 2 and lesions requiring angioplasty in 2 patients.

Conclusion: Asymptomatic patients with RA displayed high myocardial ischemic burden which was comparable to diabetes mellitus. In the absence of obstructive coronary artery disease myocardial ischemia, potentially caused by microvascular coronary dysfunction, was common in these patients.

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Radiographic Joint Damage in Rheumatoid Arthritis Is More Strongly Associated with Peripheral Arterial Stiffness Than with Peripheral or Carotid Artery Obstruction. Jose Felix Restrepo[1], Agustin Escalante[1], Daniel F. Battafarano[2], Daniel H. O'Leary[3] and Inmaculada Del Rincon[1]. [1]University of Texas Health Science Center, San Antonio, TX, [2]Brooke Army Medical Ctr, San Antonio, TX, [3]Tufts University-Boston Campus, Boston, MA

Background/Purpose: The mechanism for RA's increased cardiovascular(CV) morbidity and mortality are incompletely understood. One hypothesis is that shared mechanisms underlie joint damage and atherosclerosis in RA. The present study examined the association between radiographic joint damage, and markers of peripheral or carotid atherosclerosis and arterial stiffness in RA patients.

Methods: We studied RA patients using the ankle-brachial index (ABI), calculated as the systolic pressure of the lower limb arteries divided by that of the brachial arteries. The normal ABI varies from 0.91 to 1.3. An ABI ≤.9 indicates arterial obstruction, usually due to atherosclerosis, while an ABI ≥ 1.3 is incompressible, indicating arterial stiffness due to medial sclerosis or calcification. We used high resolution ultrasound to assess carotid plaque, a marker of atherosclerosis. We measured joint damage from radiographs of the hands and wrists, which we scored for erosions and joint-space narrowing using the method of Sharp and colleagues.

Results: We measured the ABI in 644 RA patients, among whom it was normal in 489 (76%), obstructed in 83 (13%) and incompressible in 72 (11%). Joint damage was significantly greater in the patients with obstructed arteries (Mean Sharp score = 72, SD = 71) and those with incompressible arteries (Sharp = 108, SD = 86), compared to the ones with normal arteries (Sharp score 52, SD = 58), $P \leq 0.001$ by one way ANOVA. The association between joint damage and incompressibility remained after age- and sex-adjustment, but was attenuated for obstruction, although it remained significant. Patients with carotid plaque also had significantly more joint damage (Sharp 73, SD = 74) than those without plaque (Sharp = 52, SD = 58), $P \leq 0.001$, but with age- and sex-adjustment the difference attenuated, loosing significance.

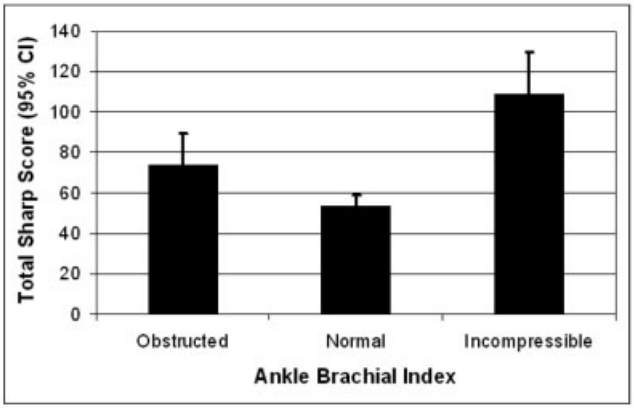

Figure. Sharp score in 642 RA patients, according to results on the ABI. Patients with either obstructed or incompressible peripheral arteries had significantly greater joint damage (ANOVA $P \leq 0.001$). With age- and sex-adjustment, the higher Sharp among incompressible patients remained highly significant ($P \leq 0.001$), but that with obstructed patients was attenuated ($P = 0.02$).

Conclusion: Radiographic joint damage in this group of RA patients was associated with peripheral arterial stiffness, and less so with markers of peripheral or carotid atherosclerosis. These findings support the hypothesis that CV disease in RA may share mechanisms with joint damage. Further research is needed to understand the mechanisms linking joint damage and arterial stiffness in RA.

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Determinants of Insulin Resistance in Patients with Rheumatoid Arthritis. Seong Hu Park[1], SungIl Kim[1], Young Eun Park[1], Seung Geun Lee[1], SeungHoon Baek[1], Geun Tae Kim[2] and JoungWook Lee[3]. [1]Pusan Nationl University Hospital, Busan, South Korea, [2]Kosin University Gopsel Hospital, Pusan, South Korea, [3]Busan st. Mary's Medical Center, South Korea

Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased cardiovascular events. These may be related to insulin resistance (IR). We evaluated status of IR and analyzed the relationship between IR and clinical and laboratory characteristics in patients with RA.

Methods: We examined 110 RA patients (93 females) and 110 age and sex matched healthy controls. We measured homeostasis model assessment (HOMA) IR, calculated according to fasting serum glucose and insulin. Univariate analysis was used to determine the relationship between baseline variables and IR (assessed by HOMA IR). Multiple linear regression analysis was used to select independent predictive factors.

Results: In patient group, age was 51.9±11.3 years old, disease duration was 58.5±43.2 months. HOMA IR was significantly high in patient group (1.73±2.07) compared with age and sex matched control group (0.88±0.69) ($p<0.001$). In patient group, 42 were early RA (disease duration less than 36 months) and 68 were established RA (more than 36 months). HOMA IR was significantly higher in patients with established RA (1.99±2.51) than those with early RA (1.31±0.90) ($p=0.001$), and correlated with disease duration ($r=0.393$, $p<0.01$), CRP($p=0.210$, $p=0.028$), age ($r=0.212$, $p=0.026$), triglyceride($r=0.236$, $p=0.023$), BMI ($r=0.231$, $p=0.015$). Disease duration and CRP were independent predictors for HOMA IR ($p\leq0.01$, $p=0.023$).

Conclusion: In patients with RA, IR measured by HOMA IR was significantly increased compared with that of healthy control. Independent predictive factors for HOMA IR in RA patients were disease duration and CRP.

Table 1. Clinical characteristics of patients with RA and controls

Variables	Controls (N = 110)	Patients with RA (n = 110)	P-value
Age, year	51.3 ± 9.0	51.8 ± 11.3	0.713
Women, n (%)	93 (84.5%)	93 (84.5%)	0.855
BMI, Kg/m2	23.3 ± 3.4	23.0 ± 3.1	0.534
WC, cm	79.0 ± 8.5	77.4 ± 7.8	0.155
Systolic BP, mmHg	119.7 ± 19.7	122.9 ± 12.7	0.169
Diastolic BP, mmHg	74.2 ± 10.7	79.8 ± 8.7	0.000
Fasting insulin, μIU/mL	3.7 ± 2.3	7.1 ± 5.7	0.000
Fasting glucose, mg/dL	90.6 ± 16.2	91.2 ± 24.8	0.840
TC, mg/dL	202.6 ± 40.4	189.3 ± 41.3	0.017
HDL mg/dL	57.1 ± 12.7	63.0 ± 18.9	0.008
LDL mg/dL	125.0 ± 37.8	113.3 ± 33.0	0.021
Triglycerides, mg/dL	93.5 ± 46.8	116.3 ± 72.4	0.007
HOMA IR	0.88 ± 0.69	1.73 ± 2.07	0.000
CRP, mg/dL	0.1 ± 0.2	1.0 ± 2.4	0.000
ESR, mm/hour	—	38.7 ± 29.1	—
Disease duration, month	—	58.4 ± 43.2	—
Mean 6 month prednisolon, mg	—	4.3 ± 2.8	—
Total prednisolon dose, mg	—	4558.9 ± 4866.5	—

n: number, BMI: body mass index, BP: blood pressure, WC: waist circumference, TC: total cholesterol, HDL-C: high density lipoprotein, LDL-C: low density lipoprotein, HOMA IR: homeostasis model assessment of insulin resistance, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, NS: non-significant

Table 2. Correlations of HOMA IR with variables

variables	HOMA IR r	P-value
Age, year	0.212	0.026
BMI, Kg/m2	0.231	0.015
WC, cm	0.233	0.014
Systolic BP, mmHg	0.006	0.951
Diastolic BP, mmHg	−0.108	0.267
Fasting insulin, μIU/mL	0.933	0.000
Fasting glucose, mg/dL	0.597	0.000
TC, mg/dL	−0.084	0.384
HDL, mg/dL	−0.122	0.845
LDL, mg/dL	−0.075	0.473
Triglycerides, mg/dL	0.236	0.023
CRP, mg/dL	0.210	0.028
ESR, mm/hour	0.187	0.051
RF, positive, n (%)	0.124	0.200
Disease duration, month	0.393	0.000
Mean 6 month prednisolon, mg	−0.032	0.741
Total prednisolon dose, mg	0.063	0.514

BMI: body mass index, BP: blood pressure, WC: waist circumference, TC: total cholesterol, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoproteincholesterol, RF: rheumatoid factor, HOMA IR: homeostasis model assessment of insulin resistance, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

Table 3. Clinical characteristics according to disease duration

Variables	Control (N = 110)	Early RA (n = 42)	Established RA (n = 68)	P-value*
Age, year	51.3 ± 9.0	50.4 ± 12.8	52.7 ± 10.2	0.038
BMI, Kg/m2	23.3 ± 3.4	22.5 ± 2.8	23.3 ± 3.3	0.353
WC, cm	79.0 ± 8.5	77.5 ± 1.1	77.3 ± 8.1	0.204
Systolic BP, mmHg	119.7 ± 19.7	122.0 ± 10.0	123.4 ± 14.2	0.006
Diastolic BP, mmHg	74.2 ± 10.7	79.8 ± 6.4	79.8 ± 9.9	0.006
Fasting insulin, μIU/mL	3.7 ± 2.3	5.6 ± 2.6	8.0 ± 6.9	0.001
Fasting glucose, mg/dL	90.6 ± 16.2	89.8 ± 26.7	92.0 ± 23.8	0.217
TC, mg/dL	202.6 ± 40.4	185.1 ± 36.9	192.0 ± 43.8	0.886
HDL, mg/dL	57.1 ± 12.7	64.2 ± 15.8	62.3 ± 20.7	0.007
LDL, mg/dL	125.0 ± 37.8	107.6 ± 29.8	117.0 ± 34.7	0.441
Triglycerides, mg/dL	93.5 ± 46.8	108.2 ± 72.1	121.6 ± 72.7	0.004
HOMA IR	0.88 ± 0.69	1.30 ± 0.90	1.99 ± 2.51	0.001
CRP, mg/dL	0.1 ± 0.2	0.9 ± 1.8	1.1 ± 2.8	0.000
ESR, mm/hour	—	41.1 ± 30.6	37.2 ± 28.3	0.561
Disease duration, month	—	24.7 ± 20.1	79.2 ± 40.4	0.000
Mean 6 month prednisolon, mg	—	4.5 ± 2.8	4.2 ± 2.8	0.772
Total prednisolon dose, mg	—	2405.8 ± 2870.6	5888.8 ± 5365.1	0.000

* Statistical significances were tested by one way analysis of variances among groups. RA: rheumatoid arthritis, BMI: body mass index, BP: blood pressure, TC: total cholesterol, HDL-C: high density lipoprotein-cholesterol, HOMA IR: homeostasis model assessment of insulin resistance, RF: rheumatoid factor, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

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Inflammation-Dependent Insulin Resistance Is Present in Rheumatoid Arthritis but it Is Not Associated with Retinol Binding Protein 4. Vanesa Hernandez-Hernandez[1], Esmeralda Delgado-Frías[1], Ivan Ferraz-Amaro[1], Jose A. Garcia-Dopico[2], Lilian Medina[2], Antonieta Gonzalez-Diaz[3], Maria A. Gomez-Rodriguez-Bethencourt[3], Jose Ramon Muñiz[4], Ana I. Rodriguez-Vargas[1], M. Angeles Gantes-Mora[1], M.Teresa Arce-Franco[1], M. Jesus Dominguez-Luis[5] and Federico Diaz-Gonzalez[1]. [1]Rheumatology Service, La Laguna, Spain, [2]Laboratorio Central, La Laguna, Spain, [3]Medicina Nuclear, Spain, [4]Resonancia Magnetica IMETISA, [5]Hospital Universitario de Canarias, La Laguna, Spain

Background/Purpose: Insulin resistance has been associated with rheumatoid arthritis (RA) disease activity. These correlation suggests that inflammation and hyperinsulinemia somehow interact and facilitate one another. Mechanistic data for inflammation-associated insulin resistance in RA are sparse. Retinol binding protein 4 (RBP4), an adipokie that contributes to insulin resistance, is increased in insulin-resistant states like diabetes and obesity. The role of this RBP4 has not been explored in inflammation-associated insulin resistance of RA patients. The purpose of this study was to estimate beta cell function, and resistance and sensitivity to insulin in patients with AR compared to controls, and to describe the potential relationship between peripheral bloods levels of RBP4 and inflammation-associated insulin resistance in RA patients.

Methods: 216 subjects, 101 RA patients and 115 age and sex matched controls were included in this cross-sectional study. Demographic data regard body mass index, presence of hypertension and corticosteroids intake were collected. Diabetes patients or controls were excluded. We measured in both groups fasting insulin and C-peptide, glucose, lipid levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), retinol binding protein 4, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFalpha). Insulin sensitivity was measured using the homeostasis model assessment index (updated HOMA model 2) to estimate beta cell function (%B), insulin sensitivity (%S) and insulin resistance index (IR). The Health Assessment Questionnaire Disability Index (HAQ) and the Disease Activity Score (DAS 28) were determined in RA patients.

Results: RA patients included were 55.2±10.0 years old, had a mean disease duration of 7.4±5.8 years and show a DAS28 3.99±1.41 and HAQ 0.80±0.76. In the univariate analyses the presence of RA was associated with a higher IR (β coefficient 0.8, 0.2–1.4 IC95%, $p=0.01$), and %B (β 20%, 2–39 IC95%, $p=0,03$). Insulinemia was also higher in AR patients, 73.3 vs 95.9 pmol/L, $p=0,04$ but they did not express higher levels of RBP4. This data remained statiscally significant when adjusted for body mass index, age, presence of comorbility and corticoids intake. DAS28 and HAQ did not correlate with insulin resistance indexes neither RBP4 levels. Similarly, ESR, RCP, IL6 and TNFalpha levels in RA patients were not associated with insulin resistance except for a strong positive association between RCP and %S ($r^2=0.48$, $p=0.00$). Multivariate analysis was perform to assess whether AR specific factors like ESR, RCP, corticoids intake, DAS28, HAQ, disease duration, and TNFalpha and IL6 levels were able to predict insulin sensitivity, resistance or beta cell function. DAS28, HAQ, corticoids, IL6, TNFa were capable to explain nearly the 20% of IR. For beta cell production, disease duration, corticoids, CRP and TNFalpha, IL6 levels predict 32% of %B variability.

Conclusion: Our data suggest that inflammation and IR interact and facilitate one another. IR states are presence in RA. RBP4 does not seem to play a role in IR related to RA.

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Low Serum Levels of Soluble Receptor for Advanced Glycation End Products Are Associated with Increased Augmentation Index in Patients with Early Rheumatoid Arthritis. Lai Shan Tam[1], Qing Shang[1], Edmund K. Li[1], Ka Lai Lee[2], Ying Ying Leung[3], King Yee Ying[4], Cheuk-wan Yim[5], Emily Kun[6], Alexander M. Leung[7], Martin Li[1], Tena K. Li[1], Tracy Y. Zhu[1], Ricky K. Chui[1], Lorraine Tseung[1], Shui Lian Yu[1], Woon Pang Kuan[8] and Cheuk-Man Yu[1]. [1]The Chinese University of Hong Kong, Hong Kong, Hong Kong, [2]Pamela Youde Nethersole Eastern Hospital, Hong Kong, Hong Kong, [3]North District Hospital, Hong Kong, Hong Kong, [4]Princess Margaret Hospital, Hong Kong, Hong Kong, [5]United Christian Hospital, Hong Kong, Hong Kong, [6]Tai Po Hospital, Hong Kong, Hong Kong, [7]Queen Elizabeth Hospital, Hong Kong, Hong Kong, [8]Hospital Selayang, Kuala Lumpur, Malaysia

Background/Purpose: There is growing evidence of premature atherosclerosis in patients with rheumatoid arthritis (RA), leading to a higher rate of cardiovascular events than in the general population. Recent evidence suggested that this phenomenon also occurs in patients with early RA. Whether the prevalence of subclinical atherosclerosis was increased in early RA patients

remained controversial. We assessed whether carotid intima-media thickness (IMT) and arterial stiffness indexes as determined by pulse wave velocity (PWV) and augmentation index (AIx) were increased in a cohort of early RA patients as compared to non-RA controls. We also ascertained the potential explanatory variables associated with an increased AIx in early RA patients.

Methods: Ninety-five early RA patients (age, 52.5 +/− 11.4 years; 85 female) and 70 age- and sex-matched (age, 52.4 +/− 10.5 years; 60 female) community controls were recruited for this cross-sectional study. Patients and controls were eligible for analysis if they had no overt cardiovascular (CV) diseases. PWV and AIx were assessed noninvasively during pulse wave analyses. For large artery remodeling the intima-media thickness (IMT) was measured in both common carotid arteries with ultrasound. Traditional CV risk factors were measured in patients and controls, while novel CV risk factors (soluble receptor for advanced glycation end products [sRAGE]) and inflammatory markers (ESR, CRP, IL-12p, TNF-alpha, IL-10, IL-6, IL-1beta, IL-8) were assessed in early RA patients.

Results: The mean disease duration for this group of early RA patient was 13.5 +/− 7.9 months and the DAS 28 score was 3.9 +/− 1.3. The prevalence of traditional CV risk factors was similar between the two groups, although the use of anti-hypertensives (26.5% versus 8.2%, $p<0.005$) and statins (7.1% versus 1.0%, $p<0.05$) were more prevalent in patients with early RA. Despite treatment, early RA patients had a significantly increased diastolic blood pressure (82 +/− 12 mmHg versus 77 +/− 11 mmHg, $p<0.005$). The levels of total cholesterol (4.6 +/− 1.1 mmol/L versus 5.3 +/− 0.8 mmol/L, $p<0.001$), HDL-cholesterol (1.5 +/− 0.4 mmol/L versus 1.7 +/− 0.4 mmol/L, $p<0.001$) and LDL-cholesterol (2.6 +/− 0.8 mmol/L versus 3.1 +/− 0.8 mmol/L, $p<0.005$) were significantly lower in early RA patients. AIx was statistically significantly higher in early RA patients as compared with controls (31.6 +/− 11.2 % versus 28.0 +/− 11.5%; $P<0.05$), while PWV (14.9 +/− 0.3m/s versus 14.9 +/− 0.3m/s, p=NS) and IMT (0.60 +/− 0.09mm versus 0.62mm +/− 0.08mm, p=NS) were similar between patients and control. Increased AIx in early RA patients was associated with the use of anti-hypertensives (36.3 +/− 8.7% versus 29.8 +/− 11.5%, $p<0.05$), older age ($r = 0.29$, $p<0.05$), higher glucose level ($r = 0.21$, $p<0.05$) and lower sRAGE level ($r = -0.24$, $p<0.05$).

Conclusion: AIx, a marker of arterial stiffness, is increased in early RA patients without overt CV diseases. Increase in AIx may be a sensitive indicator for early subclinical atherosclerosis in patients with early RA, which was associated with traditional as well as novel CV risk factors including a lower sRAGE level. Measuring AIx might assist in better assessing the increased cardiovascular risk in early RA patients.

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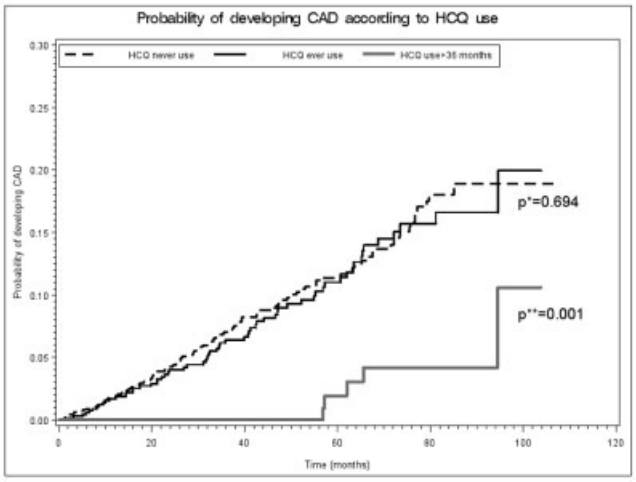
Prolonged Hydroxychloroquine Use Is Associated with Decreased Incidence of Cardiovascular Disease in Rheumatoid Arthritis Patients. Androniki Bili[1], Xiaoqin Tang[2], H. Lester Kirchner[2], Jana L. Antohe[1], Stephanie J. Morris[3] and Mary Chester Wasko[4]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Center for Health Research, Danville, PA, [3]Rose Tree Medical Associates—Riddle Memorial Hos, Danville, PA, [4]West Penn Allegheny Health System, Pittsburgh, PA

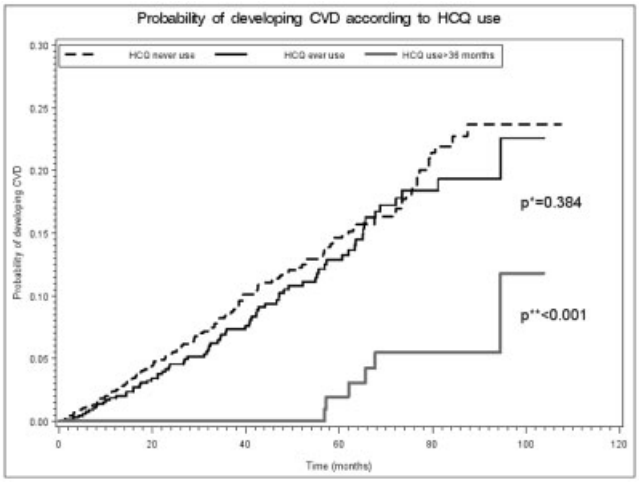
Background/Purpose: Hydroxychloroquine (HCQ) use has been associated with decreased incidence of diabetes (DM) and improved lipid profile in rheumatoid arthritis (RA) patients, but no studies have reported on the relationship between HCQ and cardiovascular disease (CVD) in RA. Given the long half-life of HCQ, we looked at the effect of long-term HCQ use (>36 mo.) and risk of incident CVD in RA patients.

Methods: 1,881 incident adult RA patients (ICD-9 code 714.0 at ≥ 2 outpatient encounters with a rheumatologist), diagnosed between 1/1/2001 – 3/31/2008 were identified. Prevalent cases of CVD [coronary artery disease (CAD), cardiac revascularization procedure, abdominal aortic aneurysm, stroke, transient ischemic attack, peripheral artery disease, arterial revascularization procedure] were excluded (n=52). Primary outcome was time to CAD [ICD-9 code 410, 410–414.99 or revascularization procedure (CPT codes 33510, 33548, 92982, 92984, G0290, G0291, 92930, 92981)]. Secondary outcome was time to development of CVD. Cox proportional regression models were used to calculate hazard ratios (HR) of exposure after adjustment for age, gender, race, BMI, LDL, BP, HTN, hyperlipidemia, DM, RF, ESR, TNF-α inhibitors, methotrexate, statin and corticosteroid use. Exposure to HCQ and all other variables were treated as time-variant in the models.

Results: Of the 1,829 patients included in the analysis, 684 (37.4%) patient were ever on HCQ, 138 on HCQ >36 mo. and 546 on HCQ ≤ 36 mo. Of the 166 cases developing CAD during observation, 102 were HCQ nonusers, 6 in the HCQ > 36 mo. and 58 in the HCQ ≤ 36 mo. user groups, yielding incidence of 25.4, 7.3 and 31.6 events per 1000 person-years (py), respectively, with incidence rate ratio (IRR) 0.29 (0.13–0.65, p=0.003) in the >36 months users vs. nonusers. HCQ use >36 months was associated with a reduction in the hazard for developing CAD (HR= 0.28, 95% CI:0.12–0.68, p=0.005) compared to nonusers. Of the 200 cases developing CVD during observation,126 were never on HCQ, 7 in the HCQ > 36 months and 67 in the HCQ ≤ 36 months users, yielding incidence of 31.7, 8.6 and 36.9 events per 1000 py, respectively, with IRR 0.27 (0.17–0.58, p=0.001) in the HCQ >36 mo users vs. nonusers. A similar association was found between HCQ use > 36 months, compared to nonusers, and hazard for developing CVD (HR 0.27, 0.12–0.60, p=0.005).

Conclusion: In patients with RA, HCQ use for >36 months is associated with a 72% and 73% reduction in the risk of incident of CAD and CVD respectively. These findings support the use of HCQ as an adjunct to other first line DMARDs in RA patients at high risk for CVD.





1169

Vitamin D Deficiency, Interleukin 17, and Vascular Function in Rheumatoid Arthritis. Prabha Ranganathan[1], Shokoufeh Khalatbari[2], Srilakshmi Yalavarthi[3], Wendy Marder[4], Robert Brook[2] and Mariana J. Kaplan[4]. [1]Washington University School of Medicine, St. Louis, MO, [2]University of Michigan at Ann Arbor, MI, [3]University of Michgan at Ann Arbor, MI, [4]University of Michigan, Ann Arbor, MI

Background/Purpose: Although the effects of vitamin D deficiency on cardiovascular (CV) disease risk in health and in chronic kidney disease have been previously reported, no studies have examined the link between vitamin D deficiency and CV risk in rheumatoid arthritis (RA). Our aim was to determine the effects of vitamin D deficiency on vascular function, and

inflammatory markers potentially associated with CV risk, in a cohort of patients with RA.

Methods: Serum levels of 25 hydroxyvitamin D (25 [OH]D) were quantified in a cohort of 87 patients with RA, with an age of 55.2±12.1(mean ± standard deviation). The majority of this cohort was female (n=70 [80.5%]), and had been on stable doses of traditional disease-modifying anti-rheumatic drugs and/or biologics for at least 3 months. At the same visit, patients underwent assessment of flow mediated dilatation (FMD) of the brachial artery in response to reactive hyperemia to assess endothelium-dependent responses of conduit vessels; pulse wave velocity (PWV) to assess aortic compliance, and microvascular reactive hyperemia index (RHI) using Endopat-2000 device. Various markers of CV risk were quantified in plasma. RA disease activity was assessed by Disease Activity Score of 28 joints (DAS28). Serum interleukin 17 (IL-17) was quantified by enzyme linked immunosorbent assay (ELISA). Regression analysis was performed to determine the effects of vitamin D deficiency on vascular function and inflammatory markers in patients who were vitamin D insufficient ([25 (OH)D] < 30 ng/ml), and vitamin D deficient ([25 (OH)D] < 20 ng/ml).

Results: Of the 87 RA patients, 59 (68%) were vitamin D insufficient (25[OH]D <30 ng/ml) with 25(OH)D of 20.2±5.9 ng/ml. In univariate analysis, higher serum 25[OH]D levels were significantly associated with lower serum IL17 levels (p=0.004) in this group. This association persisted in multivariate analysis after adjusting for known confounders, including age, body mass index (BMI), gender, race/ethnicity and seasonal variation (p=0.02). In the subset of patients (n=25, 28.7%) who were vitamin D deficient (25[OH]D levels <20 ng/ml), with 25[OH]D of 14.4±3.4ng/ml, univariate analysis revealed that higher serum 25(OH)D levels were significantly associated with higher microvascular function, as assessed by RHI (p=0.04). This association persisted in multivariate analysis after adjusting for known confounders, including age, BMI, gender, and race/ethnicity (p=0.04).

Conclusion: Vitamin D deficiency in RA patients may affect Th17 responses and contribute to microvascular dysfunction. These results indicate that maintaining normal serum levels of vitamin D in patients with RA may protect against IL17 mediated inflammatory responses and provide a protective effect against vascular damage that afflicts patients with this disease.

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Asymptomatic Carotid Plaques in Rheumatoid Arthritis Results in Inadequate Treatment to Lipid Targets in Cardiovascular Prevention. Anne Grete Semb[1], Inge Olsen C[2], Sella Provan[1], Terje R. Pedersen[3], Einar Stranden[4], Désirée van der Heijde[5], Jonny Hisdal[4] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Smerud Medical Research, Oslo, Norway, [3]Oslo University Hospital-Ullevaal, Oslo, Norway, [4]Uslo University Hospital-Aker, Oslo, Norway, [5]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: One of the cornerstones in cardiovascular (CV) prevention is lipid lowering (LL), which is divided into primary (no CV disease) and secondary (known CV disease) prevention. The prevalence of asymptomatic carotid plaque (a-CP) is 2–3 times higher in rheumatoid arthritis (RA) patients compared to the general population. Patients with a-CP, which is equivalent of CV disease, should receive secondary CV preventive treatment, with intensive LL. Carotid ultrasound is not commonly used and the a-CP will therefore not commonly be taken into account in the CV risk stratification. There is therefore a high risk of treatment misclassification concerning LL in RA patients in that they wrongly will be categorized into either no preventive treatment or primary prevention instead of secondary preventive LL treatment. Our aim was to calculate the risk for preventive treatment misclassification by SCORE when a-CP was present.

Methods: We performed CV risk stratification by using SCORE in 86 RA patients and 56 controls without known CV disease. B-Mode ultrasound of the carotid arteries was performed. Cross- tabulations and Chi^2 were used for calculation of risk for treatment misclassification in patients with and without CP when SCORE < or > 5%.

Results: There were no differences between RA patients and controls concerning age (56.2±9.2 vs. 54.5±9.4 years), but slightly more females in the RA group (79 vs. 63%, p=0.05). Presence of CV risk factors, including lipids, was similar in the two groups, but a-CP was significantly more frequent in RA patients [n=39 (45.3%)] than in controls [15 (26.8%)] (p=0.003). In the RA group 75 patients had a SCORE<5% indicating no need for primary LL prevention. However, 30 (40.0%) of these patients had a-CP and should receive intensive LL treatment. In the RA group with SCORE >5% (n=11), indicating a need for primary prevention, 9 (81.8%) patients had a-CP and should therefore be categorized to more intensive LL treatment, as in secondary prevention. Of the 49 controls with SCORE<5%, indicating no need for LL therapy, 10 (20.4%) had a-CP and should have been categorized to secondary preventive LL treatment. Whilst of the 7 controls with SCORE >5%, 5 (71.4%) of those had a-CP and should have more intensive LL treatment as in secondary instead of primary preventive therapy. Thus, the risk for treatment misclassification (i.e. LL under treatment) in RA when SCORE <5% and >5% was 40.0% and 81.8% respectively.

Conclusion: RA patients with a-CP should receive intensive LL preventive treatment. There is also a high risk of a-CP when SCORE > 5%. Consequently, recommending more intensive LL treatment, as in secondary instead of primary preventive treatment may be preferable, when ultrasound of the carotid arteries is not feasible in cardiovascular risk stratification. Confirmation of these data is warranted in larger studies.

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Cardiac Involvement in Patients with secondary Amyloidosis Due to Rheumatoid Arthritis. Daisuke Kobayashi[1], Yoko Wada[1], Shuichi Murakami[1], Takeshi Kuroda[2], Masaaki Nakano[3] and Ichiei Narita[1]. [1]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Niigata University, Niigata, Japan, [3]Niigata University School of Medicine, Niigata, Japan

Background/Purpose: Rheumatoid arthritis (RA) is one of the major causes of amyloid A (AA) amyloidosis, the major organs affected being the kidneys and gastrointestinal tract. Although cardiac amyloidosis is the principal cause of death in patients with amyloid L (AL) amyloidosis, significant cardiac involvement in AA amyloidosis is thought to be rare. On the other hand, the survival rate of hemodialysis patients with AA amyloidosis associated with RA has been shown to be low, and our previous study revealed that cardiac failure accounted for more than half of all deaths in these patients. We examined the cardiac features of patients with RA associated with AA amyloidosis.

Methods: Twenty-one RA patients (2 males, 19 females) with AA amyloidosis who were followed up at our hospital between 2001 and 2010 were enrolled. Each patient fulfilled the 1987 American Rheumatism Association criteria for RA. All the patients had undergone GI tract (n=17), myocardium (n=2), or abdominal fat (n=2) biopsies, and had been confirmed to have reactive AA amyloidosis by histopathological examination. The patients' background data and echocardiographic features were analyzed retrospectively. Additionally, 14 patients whose left ventricular (LV) wall thickness exceeded 12 mm were assigned to a LV hypertrophy (LVH) group, and their clinical features were compared with a normal group (n=6).

Results: The mean period between the onset of RA and echocardiographic examination was 21.1 ± 9.9 years (range, 7 to 39 years), and the mean period between the onset of AA amyloidosis and echocardiographic examination was 3.7 ± 5.7 years (range, 0 to 16.2 years). Among the 21 patients, 19 were asymptomatic, and only 2 showed cardiac failure at the time of evaluation. Echocardiography demonstrated mild LVH, a low E/A ratio, and a normal ejection fraction (LV posterior wall thickness: 11.0 ± 2.1 mm, Interventricular septal thickness: 1.20 ± 0.25 mm, Ejection fraction: 66.8 ± 9.86%, E/A ratio: 0.80 ± 0.24). Patients in the LVH group had a significantly longer history of RA (24.3 ± 7.84 years vs. 14.8 ± 11.2 years, p=0.037), a lower estimated glomerular filtration rate (eGFR) (36.4 ± 18.3 ml/min vs. 54.2 ± 36.4 ml/min), and more severe poteinuria, than those in the normal group. Furthermore, we found a negative correlation between eGFR and LV wall thickness (R^2 =0.6647, p<0.001) and interventricular septal thickness (R^2 =0.40, p=0.006), but not the E/A ratio.

Conclusion: Thickening of the LV wall and myocardial diastolic dysfunction are the major cardiac features of patients with AA amyloidosis. Although cardiac involvement is said to be rare in AA amyloidosis, subclinical LV dysfunction may show insidious progression.

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Detection of Left Ventricular Regional Dysfunction by Using Cardiac Magnetic Resonance Imaging in Rheumatoid Arthritis Patients without Cardiac Symptoms; Comparison Between Non-Biologic DMARDs and Biologics Groups. Hitomi Kobayashi[1], Isamu Yokoe[1], Hiroshi Sato[1] and Yasuyuki Kobayashi[2]. [1]Itabashi Chuo Medical Center, Tokyo, Japan, [2]St Marianna Univ Sch of Med, Kawasaki, Japan

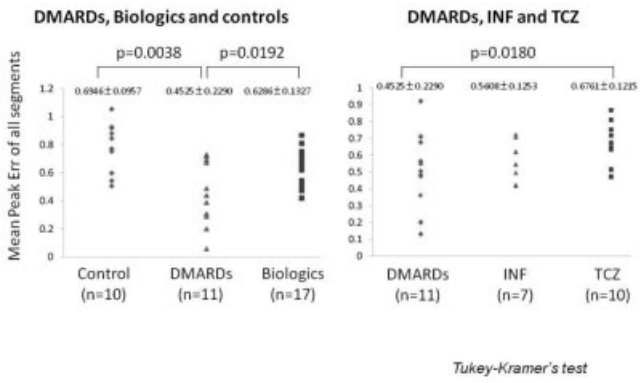
Background/Purpose: In patients with rheumatoid arthritis (RA), cardiac involvement is common and can contribute to worsening of patient outcome. Regional left ventricular (LV) dysfunction reflects myocardial abnormalities. Regional LV function in RA has not been systematically studied by cardiac

magnetic resonance imaging (CMR). We sought to detect LV regional dysfunction by using CMR in RA patients without cardiac symptoms.

Methods: Consecutive patients with RA and healthy control subjects were enrolled. RA patients received either non-biologic DMARDs or biologics. All subjects with no history and/or clinical findings of hypertension, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, dyslipidemia, or echocardiographic abnormalities underwent non-contrast CMR on a 1.5 T scanner. Peak systolic regional radial strain (Err, %) was calculated by feature tracking of cine MRI in six segments of the mid-slice of LV. We explored the associations of peak Err between the control and RA groups. Comparisons of peak Err between the DMARDs and the biologics groups, and the association of peak Err with disease activity and severity measures were determined.

Results: We compared 28 RA patients (92.9 % female; mean age 58.0±12.6 years) with 10 non-RA controls (100% female; mean age 55.7±4.6 years). RA patients received either DMARDs or infliximab (IFX; 3 mg/kg) or tocilizumab (TCZ; 8 mg/kg). DAS28-ESR was higher in the DMARDs group than in the biologics group, but not significantly different (4.08±1.12 vs. 2.09±1.60; p=0.06). Modified Health Assessment Questionnaire (mHAQ) scores were significantly higher in the DMARDs group than in the biologics group (0.61±0.25 vs. 0.18±0.22; p =0.01). Mean peak Err of all segments was lower in RA patients than in normal subjects but not significantly different (0.69±0.09 vs. 0.55±0.19; p=0.07). Peak Err in both the anterolateral and inferior wall was significantly lower in RA patients than in controls (p=0.01, p=0.01, respectively). In the DMARDs group, mean peak Err was significantly lower than in the biologics group (p=0.02). Mean peak Err was higher in the TCZ group than in the DMARDs group (0.67±0.12 vs. 0.45±0.22; p=0.01) [Fig1]. Abnormal peak Err in RA patients was associated with higher mHAQ scores (R^2=0.31).

Fig.1 Mean peak Err of all segments determined by MRI in patients with DMARDs, INF, TCZ and controls



Conclusion: Our findings suggested sub-clinical LV regional dysfunction in RA patients without cardiac symptoms. Evaluation of regional LV function by CMR appears useful for detecting subclinical myocardial involvement in RA patients. Higher mHAQ scores might be an independent risk factor for myocardial involvement in RA. Our results indicated that TCZ might affect the normalization of LV regional function compared with non-biologic DMARDs.

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Effect of Disease Activity on Lipoproteins Levels in Patients with Early Arthritis. Silvia Pérez-Esteban, Ana M. Ortiz, Ana M. Fernández-Ortiz, Santos Castañeda and Isidoro González-Alvaro. Hospital Universitario de La Princesa. IIS Princesa, Madrid, Spain

Background/Purpose: Persistent inflammatory activity in patients with rheumatoid arthritis (RA) is associated with an increased risk for cardiovascular complications. Risk factors for these complications include smoking, elevated C-reactive protein and dyslipidaemia. The two former risk factors are clearly related to the development or activity of RA. However, the relationship between lipoproteins levels and RA remains controversial. The objective of this work was to analyse the relation between total cholesterol (TCh) and its fractions, including oxidized LDL (oxLDL) and different variables in early arthritis (EA) patients.

Methods: We analysed data from 220 patients of our EA register: 76% women, age at onset: 53.6 [42–67] years (median [p25-p75]) and disease duration at entry: 5.9 [3.8 –8.6] months; 70% met RA 1987 criteria at two years of follow-up. Rheumatoid factor was positive in 46.4% of patients and anti-citrullinated peptide antibodies in 44%. The follow-up of patients ranged from 2 to 5 years with a total of 540 visits with lipid measurements available (mean 2.5 visits by patient). Demographic and disease related variables, as well as treatments prescribed were systematically recorded. TCh, LDL, HDL, VLDL and triglyceride (TG) levels were obtained from the routine laboratory results. oxLDL levels were assessed using a commercial ELISA kit (Mercodia AB, Uppsala, Sweden) in 157 patients. To determine the effect of independent variables on levels of TCh, its fractions HDL, LDL, VLDL and oxLDL and TG, we fitted population-averaged by generalized linear models, nested by patient and visit, using the *xtgee* command of Stata 10.1 for Windows (StataCorp LP, College Station, TX, USA).

Results: The table below shows the beta coefficients of the variables significant or nearly significant but relevant to the multivariate analysis models for each of the dependent variables.

	TCh	LDL	HDL	VLDL	TG
	βCoeff/p	βCoeff/p	βCoeff/p	βCoeff/p	βCoeff/p
Female	13.3 ± 5.6/0.017	—	13 ± 2.7/0.000	0.1 ± 0.05/0.008	—
Age (by year)	0.9 ± 0.1/0.000	0.3 ± 0.1/0.055	0.2 ± 0.1/0.025	—	0.7 ± 0.3/0.003
Smoking	11.1 ± 5.4/0.039	10.8 ± 5.6/0.054	—	—	—
Statin use	−26.8 ± 6/0.000	−25.9 ± 5.8/0.000	—	6.04 ± 2.2/0.007	—
BMI	1.5 ± 0.5/0.003	1.3 ± 0.5/0.018	—	0.70 ± 0.2/0.002	5.4 ± 1.3/0.000
HAQ	4.7 ± 3.3/0.16	—	−3.1 ± 1.8/0.095	—	28.7 ± 9.7/0.003
DAS28CRP	−5.5 ± 1.5/0.000	—	−1.9 ± 0.9/0.029	—	−16.3 ± 4.3/0.000
DMARDs					
Leflunomide	0.9 ± 0.3/0.000	0.6 ± 0.3/0.057	—	0.30 ± 0.1/0.019	—
Methotrexate	—	0.6 ± 0.2/0.005	—	—	−1.07 ± 0.6/0.07
Antimalarials	—	−0.04 ± 0.02/0.06	—	—	—

In addition, oxLDL levels were also analysed and were associated with female gender (beta coeff = −25 ± 9.3; p = 0.007), frozen time (−0.24 ± 0.02; p < 0.001), LDL level (0.38 ± 0.11; p = 0.001) and DAS28CRP (9.5 ± 3.3; p = 0.004).

Conclusion: TCh levels decrease significantly with increasing degree of arthritis activity. This finding was mainly due to the HDL fraction. Conversely, oxLDL levels significantly increased when the disease activity was greater. Higher HAQ values are related with increased lipid serum levels. These observations could contribute to the increased cardiovascular morbidity in RA.

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Vascular Calcification On Hand and Wrist Radiographs Are Associated with Comorbidity and Overall Mortality In Rheumatoid Arthritis. Zachary Pruhs[1], Kaleb D. Michaud[2], Alan R. Erickson[3], Harlan Sayles[4], Gail S. Kerr[5], Angelo L. Gaffo[6], Liron Caplan[7], Grant W. Cannon[8], Deana M. Lazaro[9], Andreas M. Reimold[10], Dannette S. Johnson[11], Bogdan Cherascu[12], Pascale Schwab[13], Nasim A. Khan[14] and Ted R. Mikuls[15]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Univ of Nebraska Med Ctr & National Data Bank for Rheumatic Diseases, Omaha, NE, [3]UNMC Physicians - Brentwood, LaVista, NE, [4]University of Nebraska Medical School, Omaha, NE, [5]Washington DC VA and Georgetown University, Washington, DC, [6]Birmingham VA Medical Ctr, Birmingham, AL, [7]Denver VA and University of Colorado, Aurora, CO, [8]Salt Lake City VA and University of Utah, Salt Lake City, UT, [9]Brooklyn VA, Brooklyn, NY, [10]Dallas VA and University of Texas Southwestern, Dallas, TX, [11]University of Mississippi Med Center, Jackson, MS, [12]Iowa City VA and University of Iowa, Iowa City, IA, [13]Portland VA and Oregon Health & Science University, Portland, OR, [14]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, [15]Omaha VA and University of Nebraska, Omaha, NE

Background/Purpose: There is an established relationship between the presence of vascular calcification (VC) on plain radiography and cardiovascular disease (CVD) in select patient populations without rheumatoid arthritis (RA). VC may be found incidentally in RA patients on hand and wrist radiographs obtained for diagnostic purposes or as an assessment of disease severity. This study was undertaken to determine the frequency of VC on hand and wrist radiographs and to examine the relationship of VC with CVD risk factors and all-cause mortality in RA patients.

Methods: Hand and wrist radiographs from 756 patients enrolled in the Veterans Affairs RA (VARA) registry were examined. The radiographs were read by an investigator and scored as either "positive" or "negative" for VC. A second investigator read a sample of the radiographs (n = 40) to confirm scoring accuracy. Inter-observer agreement was strong with a kappa coefficient = 0.7.

Patients with and without VC were compared in regards to demographics and the presence of CVD risk factors using the Student's t-test for continuous variables and chi-square test for categorical variables. The association of patient characteristics with VC were examined using backwards stepwise multivariable logistic regression. The association of VC with mortality was examined using multivariable Cox proportional hazards regression.

Results: VC was observed in hand and wrist radiographs in 88 (11%) patients. Patient characteristics for those with and without VC are shown:

	VC positive (n = 88)	VC negative (n = 668)	P-value
Age (years)	72 ± 8	63 ± 10	<0.001
Men	97%	90%	0.051
RA duration (years)	16 ± 14	13 ± 11	0.006
Anti-CCP positive	77%	78%	0.891
RF positive	81%	82%	0.818
Nodules	45%	45%	0.944
Diabetes	38%	15%	<0.001
Hyperlipidemia	43%	42%	0.780
Ever smoking	63%	83%	<0.001
Prevalent CVD	40%	21%	<0.001
Prednisone use	56%	42%	0.017

In multivariable analyses, factors independently associated with VC included diabetes (OR = 2.6; 95% CI 1.7 to 4.2; p<0.001), prevalent CVD (OR = 1.6; 95% CI 1.2 to 2.2; p=0.001), and patient global well-being (OR = 1.01; 95% CI 1.01 to 1.02; p<0.001). Compared to never smokers, former (OR = 0.3; 95% CI 0.2 to 0.6; p<0.001) and current smokers (OR = 0.2; 95% CI 0.1 to 0.3; p<0.001) were less likely to have VC. There was a non-significant trend toward an association of prednisone use (OR = 1.8; 95% CI 1.0 to 3.2, p = 0.065) with the presence of VC. Adjusting for age and gender, VC was associated with future all-cause mortality (HR = 1.4; 95% CI 1.0 to 1.9, p = 0.038). The association of VC with all-cause mortality is attenuated and no longer significant after adjusting for comorbidities and RA related measures.

Conclusion: The incidental finding of VC on hand and wrist radiographs may be informative as a means of CVD risk assessment in patients with RA. In addition to associations with higher overall mortality, VC is strongly and positively associated with established predictors of future cardiovascular events including prevalent CVD and diabetes. The inverse association of VC with ever smoking was not expected and could relate to 'left censoring', statistical chance, or other undefined biologic effects.

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Cardiovascular Risk Models and Carotid Intima-Media Thickness Predict Cardiovascular Disease Events in Rheumatoid Arthritis. Inge A.M. van den Oever[1], Alper M. van Sijl[1], Hennie G. Raterman[2], Maarten Boers[3], Mike J.L. Peters[2], Yvo M. Smulders[2], Alexandre E. Voskuyl[3] and Michael T. Nurmohamed[4]. [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]VU University medical center, Amsterdam, Netherlands, [3]VU University Medical Center, Amsterdam, Netherlands, [4]Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease with an increased cardiovascular (CV) risk. Carotid intima-media thickness (cIMT) independently predicts CV events in the general population, and hence, is used as a non-invasive screening tool to identify patients at high CV risk. In RA, it is still unclear whether estimated 10-year CV risk models, such as the Systematic Coronary Risk Evaluation (SCORE) and Framingham accurately predict CV disease incidence and whether cIMT measurement can improve the risk classification. Objective of this study is to investigate the predictive value of SCORE- and Framingham risk models and cIMT for future CV events in RA.

Methods: CARRÉ is an ongoing cohort study of CV disease in RA. In a subpopulation (n=141) we measured cIMT at baseline; 120 had no prior CV disease. In these 120 patients SCORE- and Framingham risk models calculated 10-year risk of fatal and nonfatal CV disease; we compared these calculations with actual CV events recorded in a mean follow-up of 9 years. Univariate logistic regression analyses investigated the extent to which individual CV risk factors, SCORE-, Framingham and cIMT predicted CV disease incidence.

Table 1. Baseline characteristics

	All patients (n = 120)	Patients with CV events (n = 13)	Patients without CV events (n = 107)
Demographic characteristics			
Age, in years	63 ± 7	67 ± 8	63 ± 7*
Males, %	34	54	31
CV-risk factors			
Systolic BP, in mmHg	143 ± 19	152 ± 20	141 ± 19
Hypertension, %	61	77	59
Current smoking, %	27	23	26
Total cholesterol, in mmol/L	5.74 ± 1.06	5.55 ± 0.82	5.77 ± 1.09
HDL-cholesterol, in mmol/L	1.48 ± 0.50	1.19 + 0.39	1.51 + 0.51*
LDL-cholesterol, in mmol/L	3.67 + 1.04	3.64 ± 0.79	3.68 ± 1.08
Atherogenic index	4.27 ± 1.52	5.22 ± 2.23	4.16 ± 1.38*
cIMT, in mm	0.82 ± 0.14	0.89 ± 0.13	0.81 ± 0.14
10-year CVD risk			
SCORE (mortality), %	6 (3–11)	9 (6–16)	5 (3–10)*
Modified SCORE (according to EULAR), %	7 (4–12)	11 (6–24)	7 (3–11)*
Framingham (morbidity and mortality), %	11 (7–15)	18 (10–27)	11 (7–15)*

* significant difference between patients with and without CV events p≤0,05

Results: Thirteen patients (incidence rate: 13.5 %, 95% CI: 7.8–23.2) developed a CV event, four of these events were fatal (incidence rate: 4.2 %, 95% CI: 1.6–11.1). Considering the 9-year follow up, SCORE- and Framingham predictions were very close to actual mortality and morbidity and consequently significantly predicted (fatal) CV events. cIMT also showed a trend in prediction of CV disease.

Table 2. Univariate logistic regression of CV disease incidence with CV risk factors, CV risk models and cIMT

	OR (95%-CI)	Standardized OR (95%-CI)	p
Age, 10-year increment	1.09 (1.00–1.18)*	1.80 (1.00–3.23)*	0.048
Male sex	2.37 (0.74–7.57)	—	0.15
Systolic BP, 1 mmHg increment	1.03 (0.99–1.06)	1.64 (0.94–2.86)	0.08
Hypertension, %	2.28 (0.59–8.75)	—	0.23
Atherogenic index, 1 point increment	1.47 (1.04–2.06)*	1.79 (1.06–3.01)*	0.03
Current smoking, %	1.11 (0.48–2.53)	—	0.81
IMT, 100 micrometer increment	1.44 (0.98–2.11)	1.67 (0.97–2.85)	0.06
10-year Framingham CV-risk (FRS), 1% increment	1.07 (1.01–1.13)*	1.82 (1.12–2.96)*	0.02
10-year SCORE CV-risk, 1% increment	1.08 (1.02–1.14)*	1.83 (1.17–2.88)*	0.009

* significant result p<0,05

Conclusion: This long term follow up study underscores the value of SCORE and Framingham in prediction of CV disease incidence, also in RA. In this study of RA patients the evidence for cIMT, a surrogate marker of CV disease in the general population, was inconclusive.

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Insulin Resistance, a Non-Traditional Cardiovascular Risk Factor Influenced Both by Disease Activity and Adiposity in Rheumatoid Arthritis. Ronan H. Mullan[1], Susan Vankerkamp[1], Owen Sullivan[1], Oliver M. FitzGerald[2], Ursula Fearon[3] and Douglas J. Veale[3]. [1]St Vincent's University Hospital, Dublin, Ireland, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]Translation Rheumatology Research Group, Dublin, Ireland

Background: Rheumatoid Arthritis (RA) is associated with an increased cardiovascular (CV) mortality not fully explained by traditional cardiovascular risk factors. Insulin resistance (IR), which as a component of the metabolic syndrome is associated with central adiposity and cardiovascular disease, is also increased in RA. Adiponectin is an adipokine which is elevated and associated with radiographic progression in RA but which is suppressed in the metabolic syndrome. **Purpose.** To examine the associations of adiposity, disease activity and serum adiponectin levels with IR in RA.

Methods: Ninety-three RA patients were assessed at a single timepoint for CV risk factors, BMI and RA disease activity measures. Percentage Body fat and Android/Gynoid Fat ratio distribution was measured using Whole Body Dual X-Ray Absorptiometry. Fasting blood samples were taken for quantification of fasting lipoproteins, insulin and glucose. Paired sera were collected and stored at −80°C. Adiponectin was measured in serum by ELISA. IR was defined as Homeostasis Model Assessment (HOMA-IR)

measurement >1. Associations between IR with measures of obesity, adiponectin and disease activity were assessed. Spearman Rank Correlations and Mann Whitney U were used for univariate analysis. Statistical associations to HOMA-IR on univariate analysis were tested for independent associations by linear regression analysis using SPSS v11 software.

Results: IR was present in 84% patients (2.1 + 1.6 HOMA-IR, mean + SD). Obese patients (BMI > 30) when compared to patients with BMI 20–30 had higher levels of IR (3.4 + 2.2 vs 1.5 + 0.7 HOMA-IR, $P < 0.001$), CRP (12.0 + 15.9 v 6.0 + 10.9mg/dl, $P = 0.003$) and DAS28 (4.0 + 1.7 vs 3.2 + 1.3, $P = 0.06$) but lower levels of adiponectin (0.46 + 0.3 vs 0.73 + 0.5ng/ml, $P = 0.032$). IR was positively correlated with BMI ($r = 0.651$, $P < 0.001$), Android/Gynoid ratio ($r = 0.531$, $P < 0.001$), and percentage body fat ($r = 0.316$, $p = 0.04$) and negatively correlated with adiponectin ($r = -0.278$, $P < 0.04$). Using linear regression modelling controlling for age, gender, disease duration, RF status, pack year smoking history, and serum cholesterol, only BMI ($P = 0.012$) and SJC28 component of DAS28 ($P = 0.027$) were independently associated with IR.

Conclusion: Insulin Resistance (IR) is a highly prevalent and under-recognized cardiovascular risk factor associated both with increased disease activity and increased BMI in RA. Reduction of IR both through suppression of disease activity and weight loss may improve long-term cardiovascular outcomes in RA.

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Prevalence and Correlates of Metabolic Syndrome in Patients with Rheumatoid Arthritis. Maria Haye Salinas[1], Ana M. Bertoli[2], Francisco Caeiro[3], Luis Lema[4], Veronica Bellomio[5], Santiago Aguero[6], Federico Ceccato[7], Carla Saucedo[8], Javier Rosa[8], R. Quintana[9], Marcela Schmid[10], Walter Spindler[11], Natalia Tamborenea[12], Sergio Paira[7], Bernardo Pons Estel[13], Alberto J. Spindler[14], Enrique R. Soriano[8], Alejandro J. Alvarellos[15] and Veronica Saurit[16]. [1]Hospital Privado, Córdoba, Argentina, [2]Instituto Reumatológico Strusberg, Cordoba, Cordoba, Argentina, [3]Hospital Privado de Cordoba, Cordoba, Argentina, [4]Instituto Modelo de Cardiologia, Cordoba, Argentina, [5]Consultorio, Tucuman, Argentina, [6]Centro de Rehabilitación II, Catamarca, Argentina, [7]Hospital Jose Maria Cullen, Santa Fe, Argentina, [8]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [9]Hospital Provincial, Rosario, Argentina, [10]Hospital Cullen, Santa Fe, Argentina, [11]Centro Medico Privado, Tucuman, Argentina, [12]Consultorio, Buenos Aires, Argentina, [13]Sanatorio Parque, Rosario, Argentina, [14]Universidad Nacional Tucumán, Yerba Buena Tucuman, Argentina, [15]Hospital Privado, Cordoba, Argentina, [16]Hospital Privado Córdoba, Córdoba, Argentina

Background/Purpose: Patients with Rheumatoid Arthritis (RA) have increased morbidity and mortality due to cardiovascular (CV) disease. The screening of CV risk factors, metabolic syndrome (MS) among them, is therefore mandatory. The purpose of this study is to determine and compare the frequency of MS in patients with RA and a control group, and to assess the factors associated with MS.

Methods: This is a cross-sectional study involving 1033 (409 RA and 624 age and gender matched controls) patients, that were being followed at nine different medical institutions from Argentina. MS was defined according to the Adult Treatment Panel III (ATPIII) and International Diabetes Federation (IDF). The relationship between demographic variables (age, gender), clinical data (disease duration, disease activity as per the DAS28, presence of RF and/or ACCP antibody, presence of extra-articular manifestations), pharmacological treatment and MS was examined by descriptive statistics (the chi-square test for categorical variables and the Mann-Whitney test for continuous variables). Variables with $p \leq 0.10$ in these analyses were then examined by logistic regression.

Results: The frequency of MS in RA patients and the control group was 30% Vs 39%; $p = 0.002$ when defined with the ATPIII, and 35% vs 40%; $p = 0.1$ when defined with the IDF. When both definitions of MS were applied, patients with RA and MS tended to be older (60.6±10.9 age vs 54.3±13.7 age; $p<0.001$), to display higher values of erythrocyte sedimentation rate (22 mm/hr vs 18 mm/hr; $p=0.005$), to be positive for RF and/or ACCP antibody (92% vs 86%; $p=0.057$), to have extra-articular manifestations (35% vs 27%; $p=0.06$) and to use hydroxychoroquine (11% vs 18%; $p=0.03$). Other variables, such as gender, disease duration and activity and the use of methotrexate and biologic therapies did not differ between patients with and without MS. Variables independently associated with MS in RA patients were age (OR=1.03, 95%CI 1.01–1.06; $p=0.01$ for ATPIII- OR=1.03, 95%CI 1.01–1.05; $p<0.001$ for IDF), presence of RF and/or ACCP antibody (OR=2.91, 95%CI 1.11–7.61; $p=0.02$ for ATP III- OR=2.37, 95%CI 1.09–5.16; $p=0.02$ for IDF) and the use of hydroxychloroquine (OR=0.48, 95%CI 0.23–0.97; $p= 0.04$).

Conclusion: In this study, we were not able to demonstrate a higher frequency of MS in RA patients. However, among RA those older patients who also display features of a more severe disease such as a positive serology and extra- articular manifestations seem to be at a higher risk for the development of MS; while those on hydroxichloroquine seem to be at lower risk, probably reflecting the use of this drug in cases with a less severe disease.

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Rate of Progression of Subclinical Atherosclerosis in Femoral Versus Carotid Arteries in Patients with Rheumatoid Arthritis Over 3 Years. E. Zampeli[1], A. Protogerou[1], K. Stamatelopoulos[2], K. Fragiadaki[1], C. Katsiari[1], K. Kyrkou[2], C. Papamichael[2], M. Mavrikakis[2], G. D. Kitas[3] and P. P. Sfikakis[1]. [1]First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [2]Vascular Laboratory, Department of Clinical Therapeutics, Alexandra Hospital, Athens University Medical School, Athens, Greece, [3]The Dudley Group of Hospitals NHS Foundation Trust, Dudley, and Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA) is associated with coronary artery disease (CAD). Subclinical femoral atherosclerosis has been suggested to be linked to the presence of CAD in the general population. We assessed prospectively subclinical atherosclerosis, as indicated by plaque presence and formation, in femoral and carotid arteries in RA patients to detect whether in these 2 arterial beds there are differences: (a) in the rate of atherosclerosis progression; (b) in the factors contributing to this.

Methods: Femoral and carotid plaques were identified by ultrasonography at baseline (2006–2007) and follow-up end (2009–2010), separated by an average of 3.6±0.2 years, in 64 non-diabetic RA patients without concomitant cardiovascular (CV) disease (53 women, aged 59.2±12 years; disease duration 7.8±6.2 years at baseline). Clinical evaluation and laboratory tests were performed every 3–6 months.

Results: At baseline, femoral plaques were significantly less frequent than carotid plaques (20.6% *vs* 46.9%, $p<0.001$). Sixteen patients (25%) developed at least one new femoral plaque and 19 (29.7%) at least one new carotid plaque during follow-up. Only 6 patients were common in these two subgroups (kappa test, $p=0.430$). Those having developed only carotid plaque(s) (n=13) were significantly older (70.6±6.7 years *vs* 61.8±4.6 years, $p=0.006$) than those who developed only femoral plaque(s) (n=10). No other significant differences were observed between the subgroups regarding classical CV risk factors and RA-related parameters. Binary logistic regression analysis revealed that of the classical CV risk factors only smoking associated independently with new femoral plaque formation, while for carotid atherosclerosis progression additionally age and duration of low-dose corticosteroid use were independent predictors. Disease related parameters (RA duration, stage, functional class, hs-CRP, ESR) did not predict either carotid or femoral plaque formation.

Conclusion: Despite baseline differences suggesting more advanced changes in the carotid rather than femoral arteries, the rate of new plaque formation in these two arterial beds was similar at follow-up, and predicted by different classical CV, but not RA-related risk factors.

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Rheumatoid Arthritis Patients Are Not At Increased Risk for 30-Day Cardiovascular Events or Infections Following Total Joint Arthoplasty. Kaleb Michaud[1], Edward Fehringer[2], Kevin Garvin[2], James R. O'Dell[3] and Ted R. Mikuls[3]. [1]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Omaha VA and University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Although serious infection and cardiovascular disease are increased in patients with rheumatoid arthritis (RA), it is not known whether RA impacts the risk for these complications following total joint arthroplasty (TJA). We examined whether RA was associated with the occurrence of 30-day postoperative complications in a large population of patients undergoing TJA.

Methods: Analyses included data from the Veterans Affairs (VA) Surgical Quality Improvement Program (VASQIP) for fiscal years 1999–2006. ICD9 codes and medication dispensing data were obtained from the VA Pharmacy Benefits Management (PBM) database. RA was defined for those with a corresponding ICD9 (714.0) plus receipt of at least one DMARD

within 1 year before TJA. All other patients had an ICD9 (715.x) corresponding to osteoarthritis (OA). 30-day complications (major cardiovascular event, infection, and return to the operating room) were compared by diagnosis (RA vs. OA) using multivariate regression. Post-operative infections included systemic sepsis, pneumonia, urinary tract infection, superficial and deep wound surgical site infections. Cardiovascular events included cardiac arrest, myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis. All analyses were adjusted for age, sex, and clustering by site (n = 104 sites). Additional covariates included sociodemographics, comorbidities, health behaviors, and well defined operative risk factors (up to 44 covariates examined).

Results: There were 37,103 patients (n = 888 with RA) undergoing TJA, with total knee arthroplasty being most common (64%), followed by hip (33%), shoulder (2%), and elbow (0.2%). Patients were predominantly men (96%) with a mean (SD) age of 64 (11) years. Among RA patients, the most frequently used DMARDs included methotrexate (59%), hydroxychloroquine (40%) and sulfasalazine (23%) while 41% were taking glucocorticoids and 24% biologic DMARDs. The frequency of select complications based on diagnosis is summarized in the table below. Compared to OA patients, those with RA were significantly more likely to require a return to the operating room but had similar rates of postoperative infection and cardiovascular events.

Table. The frequency of select complications following TJA in patients with RA and OA

	RA (n = 888)	OA (n = 36,215)	RA OR (95% CI)
Infection	4.17%	4.12%	1.02 (0.72, 1.47)
Cardiovascular event	1.24%	1.98%	0.69 (0.37, 1.28)
Return to operating room	4.50%	3.01%	1.45 (1.08, 1.94)

Conclusion: RA patients are not at an increased risk for short-term infectious complications or cardiovascular events following TJA. RA patients did have an increased rate of return to the operating room. Reasons for this difference and strategies to address it require further study.

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High-Density Lipoprotein Subfractions HDL2 and HDL3 Are Reduced in Female Patients with Rheumatoid Arthritis and Do Not Appear to Be Affected by Disease Activity. Elke.E.A. Arts, Jaap Fransen, Heidi Lemmers, Leo A.B. Joosten, Piet L.C.M. Van Riel and Calin Popa. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: High-density lipoprotein cholesterol (HDL) is associated with anti-atherogenic properties. Higher levels of HDL subfractions HDL3 and particularly HDL2 protect for cardiovascular disease (CVD). Inflammation reduces HDL concentration and possibly impairs its anti-atherogenic effect. HDL composition and the impact of inflammation/disease activity on HDL subfractions in RA is still unknown. The objective of this study was to assess HDL2 and HDL3 concentrations in RA patients and their association with the level of disease activity.

Methods: Non-fasting blood samples were collected from 45 RA patients and 45 healthy controls, who did not suffer from inflammatory conditions (13 men and 32 women in both groups). None of the participants had a history of CVD or diabetes, or used lipid-lowering drugs. HDL2 and HDL3 concentrations were obtained by ultracentrifugation. Between-group comparisons were done using independent-sample t-tests, HDL2 concentration was compared between RA patients and healthy controls using analysis of covariance (ANCOVA) with exposure to RA (patients or controls) as independent variable, gender and age as covariates. The effect of disease activity on HDL2:HDL3 ratio was also analyzed in RA patients using ANCOVA, with age, gender, rheumatoid factor and disease duration as covariates.

Results: HDL2 and HDL3 were significantly lower in RA patients compared to healthy controls (p=0.01 and p=0.005, respectively). Mean±SD concentrations of HDL2 were 0.5±0.3 mmol/L in RA patients, compared to 0.7±0.4 mmol/L in the control group, a mean difference of 0.2 (95%CI 0.05–0.34). HDL3 levels were 0.8±0.2 mmol/L in the RA group and 0.9±0.2 mmol/L in the control group a mean difference of 0.1 (95%CI 0.04–0.19). The HDL2:HDL3 ratio was significantly lower in the patient group (0.5±0.3 mmol/L) compared to the control group (0.7±0.4 mmol/L) with a mean difference of 0.2 (95%CI 0.01–0.31) (p=0.04). Female gender was an effect modifier, HDL2 and HDL3 levels were primarily altered in women (fig.1). The HDL2:HDL3 ratio was only significantly different between groups in females, with a mean difference of 0.2 (95%CI 0.04–0.40, p=0.02) compared to a mean difference of 0.01 (95%CI −0.2–0.1, p=0.9) in males. HDL2 and HDL3 concentrations were similar for all categories of the DAS28 (low <3.2, medium 3.2–5.1, and high >5.1). Only after correcting for confounders; age and disease duration, was the effect of disease activity on HDL2 significant (p=0.04).

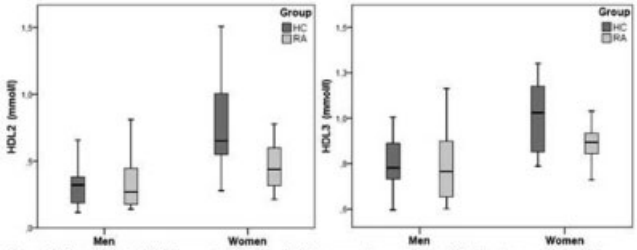

Figure 1. Mean HDL2 and HDL3 concentrations (mmol/L) for men and women in the RA patient group (RA) and the healthy control group (HC).

Conclusion: HDL2:HDL3 ratio is reduced in RA women, primarily due to lower HDL2 concentrations. This may contribute to accelerated atherosclerosis and CVD reported in RA. Height of disease activity does not appear to contribute to these modifications. Our results suggest that including HDL2:HDL3 ratio in CV risk assessment of RA patients may be of great importance. http://acr.confex.com/data/abstract/acr/2011/Paper_21969_abstract_16456_0.jpg

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Association of Medicaons and Rheumatoid Arthritis Susceptibility Polymorphism with Lipid Profiles in Patients with Rheumatoid Arthritis. Lisa A. Davis[1], Lauren M. Pointer[2], Roger K. Wolff[3], Andreas M. Reimold[4], Gail S. Kerr[5], Ted R. Mikuls[6], Grant W. Cannon[7] and Liron Caplan[8]. [1]Univ of Colorado School of Med, Aurora, CO, [2]Denver Veterans Affairs Medical Center, Denver, CO, [3]University of Utah, Salt Lake City, UT, [4]Dallas VA and University of Texas Southwestern, Dallas, TX, [5]Washington DC VA and Georgetown University, Washington, DC, [6]Omaha VA and University of Nebraska, Omaha, NE, [7]Salt Lake City VA and University of Utah, Salt Lake City, UT, [8]Denver VA and University of Colorado, Aurora, CO

Background/Purpose: Rheumatoid arthritis (RA) patients have an increased risk of cardiovascular disease (CVD), and though the mechanism is unknown, there are independent associations with RA-related factors (del Rincon I *Arth Rheum* 2005; Wolfe F, *Arth Rheum* 2008; Goodson *Arth Rheum* 2002). We examined whether single nucleotide polymorphisms (SNPs) linked with RA susceptibility and treatment are associated with low density lipoprotein (LDL) and triglyceride (TG) levels in subjects with RA.

Methods: Patients (n=1362) enrolled in the prospective Veterans Affairs RA (VARA) registry were genotyped for multiple SNPs with DNA samples derived from whole blood. Genes and associated SNPs included: REL (rs10203477, rs842647, rs13031237, rs9309331); DDAH2 (rs15574), interleukin-10 (rs3024493, rs1800872, rs1800896); methylenetetrahydrofolate reductase (rs1801131, rs1801133); tumor necrosis factor/ lymphotoxin A (rs3093662, rs1800629, rs3093668); and tumor necrosis factor receptor associated factor 1 (rs1014529, rs1014530). Covariates included: patient characteristics (age, ethnicity, gender, body mass index [BMI], diabetes, smoking status, education); RA severity markers (anti-CCP and rheumatoid factor status, C reactive protein level); lipid-lowering agent use (statin, fibrate, bile acid sequestrant); and lipid profile data. Multivariate linear regression was performed to determine factors associated with TG and LDLs. A p-value <0.01 was deemed significant in the final model.

Results: Factors associated with lower LDL level were age, diabetes, statin use, and the REL-related SNP (rs9309331), where the presence of CC conferred a 13 point lower LDL value compared to GG (see Table). The distribution of TG values required a lognormal transformation of the data, and results are interpretable as percentages relative to subjects without the described trait. For example, subjects using fibrates still demonstrated TG values 87% higher than subjects not taking fibrates, despite use of these agents. Factors associated with higher TG levels were Caucasian race, BMI, diabetes, smoking status, and fibrate use. There was an interaction term between diabetes and fibrate use that was associated with a decreased TG level.

Table. Predictors of LDL and TG levels in patients with rheumatoid arthritis

Variable		Parameter estimate	SE	Transformed percentage	p-value
Low density lipoprotein (LDL) model					
Age		−0.32	0.09	—	<0.001
Presence of diabetes		−7.25	2.42	—	0.003
rs9309331	*CC*	−12.92	4.89	—	0.008
	GC	−4.33	2.16	—	0.045
	GG	referent		—	—
Statin Use		−15.65	3.20	—	<.0001
Triglyceride (TG) model					
Caucasian		0.24	0.04	27.29%	<.0001
Body mass index		0.02	0.00	1.84%	<.0001
Presence of diabetes		0.17	0.04	18.04%	<.0001
Smoking status	*current*	0.15	0.05	16.59%	0.001
	former	0.08	0.04	8.87%	0.037
	never	referent			
Fibrate use		0.62	0.15	86.66%	<.0001
Diabetes fibrate interaction term*		−0.70	0.25	−49.50%	0.005

Conclusion: RA subjects on statins demonstrate lower LDL compared to RA subjects not receiving statins, but this was not found for fibrate use and TGs (unless the subject was also diabetic). A possible connection between rs9309331 and LDL levels should be further investigated.

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Urine Albumin Excretion Is Associated Differently with Cardiometabolic Risk Factors and Subclinical Atherosclerosis in Rheumatoid Arthritis (RA) Compared with Controls. Amanda Sammut[1], Joan M. Bathon[1], Roger Blumenthal[2], Moyses Szklo[3], Steven Shea[1], Joseph Polak[4], Russell Tracy[5] and Jon T. Giles[1]. [1]Columbia University Medical Center, New York, NY, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [4]Tufts University School of Medicine, Boston, MA, [5]University of Vermont, Colchester, VT

Background/Purpose: Albuminuria is a marker for subclinical cardiovascular disease (CVD) in the non-RA population. However, the associations of urine albumin excretion with measures of atherosclerosis have not been explored in RA, a population with increased atherosclerosis and CVD events.

Methods: Urine albumin excretion from a spot morning-collected urine sample was measured and the ratio of urine albumin to creatinine (UACR) calculated for men and women with RA and non-RA controls (frequency matched to the RA group on age, gender, and ethnicity) enrolled in a study of subclinical atherosclerosis, the Multi Ethnic Study of Atherosclerosis (MESA). Elevated UACR was defined as ≥ 25mg/g for women and ≥ 17mg/g for men. The associations of UACR with CVD risk factors [i.e. hypertension, diabetes, smoking, lipid parameters, insulin resistance assessed with the homeostatic model assessment (HOMA-IR)] and measures of atherosclerosis [coronary arterial calcification (CAC) quantified using 64-slice multidetector row computed tomography (MDCT) and maximal intima-medial thickness (IMT) of the common (CCA) and internal (ICA) carotid arteries, and presence of focal plaques in the ICA, assessed with bilateral B-mode ultrasonography] were compared cross-sectionally between the RA and control groups.

Results: A total of 196 RA patients [40% male, mean age 59±9 years, median RA duration 9 years, mean DAS28 3.7±1.1] were compared with 271 demographically matched non-RA controls. Median UACR did not differ between the RA and control groups (4.48 vs. 4.54 mg/g, respectively; p=0.40) and 21% in each group were found to have elevated UACR. In both the RA and control groups, higher age, waist circumference, hsCRP, IL-6, and the presence of diabetes, were associated with higher UACR. In contrast, hypertension and higher levels of HOMA-IR and homocysteine were significantly associated with higher UACR only in the control group (see Table). In both the RA and control groups, higher UACR levels were associated with a higher prevalence of any CAC (OR=1.25 per log unit increase in UACR, p=0.028). In contrast, UACR was associated with carotid measures only in the control group (see Table). Within both groups, adjustment for CVD risk factors reduced the magnitude and significance of the associations of UACR with CAC and carotid outcomes.

Table. Association of log UAC (log mg/g) with Cardiometabolic Risk Factors and Measures of Carotid Atherosclerosis, According to RA Status

Outcome	RA Group (n = 196) β	RA Group (n = 196) 95% CI	Controls (n = 271) β	Controls (n = 271) 95% CI	p-value for interaction by RA status
Hypertension*	1.37	(0.99, 1.90)	2.08	(1.52, 2.83)	0.040
log HOMA-IR**	−0.026	(−0.13, 0.075)	0.176	(0.096, 0.26)	0.002
log Homocysteine**	−0.011	(−0.055, 0.031)	0.039	(0.004, 0.073)	0.042
log CCA-IMT**	0.013	(−0.012, 0.039)	0.052	(0.025, 0.079)	0.025
log ICA-IMT**	0.016	(−0.043, 0.075)	0.098	(0.036, 0.16)	0.036
Carotid plaque (ICA/bulb)*	1.07	(0.75, 1.54)	1.65	(1.07, 2.55)	0.087

* β coefficients represent the average difference in the odds of the dichotomous outcome per each one unit higher log UACR (*modeled using ordinary logistic regression*)
** β coefficients represent the average difference in the continuous outcome per each one unit higher log UACR (*modeled using linear regression*)

Conclusion: Although the association of UACR with measures of subclinical coronary atherosclerosis was similar between RA and non-RA groups, we observed no association in the RA group of UACR with measures of carotid atherosclerosis, nor with several key cardiometabolic risk factors. This could suggest differing mechanisms linking urinary albumin excretion with cardiometabolic risk factors and atherosclerosis in RA compared to non-RA controls, and a lower utility for UACR as an indicator of subclinical CVD in RA.

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Atrial Fibrillation Is Not More Common in Patients with Rheumatoid Arthritis. A. Kirstin Bacani, Sherine E. Gabriel, Cynthia S. Crowson and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Patients with rheumatoid arthritis (RA) suffer from an excess burden of cardiovascular disease, but little is known about the incidence of arrhythmia in patients with RA. It has recently been suggested that the incidence of atrial fibrillation in increased in RA. The purpose of our study was to examine the incidence of atrial fibrillation among patients with RA and to compare the incidence to that in a non-RA cohort.

Methods: A population-based inception cohort of patients with RA who fulfilled 1987 ACR criteria for RA between 1/1/1980 and 12/31/2007 and a cohort of non-RA subjects from the same underlying population were assembled and followed until death, migration, or 12/31/2008. The occurrence of atrial fibrillation was ascertained from review of the medical record, defined as the first date of documented atrial fibrillation on electrocardiogram. Cumulative incidence of atrial fibrillation adjusted for the competing risk of death was estimated.

Results: The study included 813 RA patients (mean age [SD] 55.9 [15.7] years, 68% women). The average length of follow-up was 9.6 years [SD 6.9], and in 66% the rheumatoid factor was positive. There was no difference in the prevalence of atrial fibrillation among patients with RA diagnosed in 1995–2007 compared to non-RA subjects at RA incidence/index date (number, %) (n=20, 4% vs n=22, 5%), p=0.75, or in the incidence of atrial fibrillation during followup (n=47, 15% vs n=47, 12%), p=0.67; percentages are cumulative incidence at 10 years of follow-up. There was no change in the prevalence of atrial fibrillation among patients with RA diagnosed in 1980–1994 (n=13, 4%) compared to 1995–2007 (n=20, 4%) at RA incidence; p=0.68, or in the incidence of atrial fibrillation during followup (n=71, 13%) vs n=47, 15%), p=0.59. There was no statistically significant difference in development of atrial fibrillation in patients with RA and non-RA subjects without underlying coronary artery disease (p=0.83). Atrial fibrillation was associated with mortality equally in both patients with RA and non-RA subjects (interaction p=0.31).

Conclusion: The incidence and prevalence of atrial fibrillation are not increased in patients with RA diagnosed in 1995–2007 compared to non-RA subjects. The incidence and prevalence of atrial fibrillation in patients with RA has remained unchanged over the 30 year observation period. Arial fibrillation is not more strongly associated with mortality in patients with RA than in patients without RA.

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Hypothyroidism In Rheumatoid Arthritis and the Development of Cardiovascular Disease. Sara McCoy[1], Cynthia S. Crowson[2], Sherine E. Gabriel[2] and Eric L. Matteson[2]. [1]Mayo Clinic College of Medicine, Rochester, MN, [2]Mayo Clinic, Rochester, MN

Background/Purpose: To elucidate the association between rheumatoid arthritis (RA) and hypothyroidism in the development of cardiovascular disease.

Methods: A retrospective medical record review was performed using all incident cases of adult onset RA from a defined geographic population base that fulfilled criteria for RA in 1988–2007. A comparison cohort of patients without RA of similar age and sex was also examined. Cardiovascular disease (CVD) was defined as myocardial infarction, revascularization procedures, angina, or heart failure. Medical record and laboratory information regarding thyroid dysfunction were reviewed. The cumulative incidence of hypothyroid disease was estimated adjusting for the competing risk of death. Cox proportional hazards models were used to compare development of hypothyroid disease and CVD as well as associated risk factors.

Results: A cohort of 650 patients with RA and an age and sex matched comparison cohort of 650 patients without RA was assembled (both cohorts mean age 55.8; 69% female). There was no significant difference between cohorts in the presence of hypothyroid disease or subclinical hypothyroidism at time of RA diagnosis. Of patients with RA, 107 (16%) had hypothyroidism at RA incidence date. Of the cohort without RA, 88 (14%) of patients had hypothyroidism at the RA incidence/index date. No significant difference was found in the cumulative incidence of hypothyroid disease between the two cohorts. The cumulative incidence (%) of hypothyroidism among patients with RA was 7.7 ± 1.4 and in non-RA patients it was 6.7 ± 1.3 at 10 years after RA incidence/index date. Hypothyroid disease was found to be significantly associated with CVD in patients with RA (hazard ratio of 2; confidence interval 1.1,3.6). This difference remained significant after adjustment for traditional cardiovascular risk factors.

Conclusion: No significant difference was found in either incidence or prevalence of hypothyroidism between patients with or without RA. Hypothyroid disease was significantly associated with CVD in patients with RA, even after adjustment for cardiovascular risk factors.

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The Burden of Autoimmunity and Risk for Coronary Artery Disease in Rheumatoid Arthritis. Katherine P. Liao[1], Fina Kurreeman[1], Raul N. Guzman P.[2], Jun Zhang[3], Tianxi Cai[3], Gang Li[1], Grant Duclos[1], Namrata Gupta[4], Sergey Goryachev[5], Vivian Gainer[2], Shawn N. Murphy[5], Susanne Churchill[5], Isaac Kohane[1], Elizabeth W. Karlson[6] and Robert M. Plenge[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Information Systems, Boston, MA, [3]Harvard School of Public Health, Boston, MA, [4]The Broad Institute, Cambridge, [5]Partners Healthcare Systems, Boston, MA, [6]Brigham and Womens Hospital, Boston, MA

Background/Purpose: RA patients are at a 2-fold risk of coronary artery disease (CAD) compared with the general population. Immune dysregulation is thought to contribute to this elevated risk of CAD, but the precise mechanisms are unknown. We hypothesized that the burden of autoimmunity, represented by the presence of autoantibodies, or autoimmune risk alleles are associated with increased risk of CAD in RA. We tested this hypothesis in RA and 2 diseases with pathognomonic autoantibodies and published genetic risk alleles, systemic lupus erythematosus (SLE) and celiac sprue. Both SLE and celiac also share genetic risk alleles with RA.

Methods: This study was conducted in a cohort of 1335 RA subjects identified from the electronic medical records of a large academic institution using our published algorithm. We identified RA subjects with prevalent CAD through medical record review. Subjects were identified with CAD if they had a CAD diagnosis by their treating physician and documentation of CAD after cardiac catheterization, stress test, EKG or if they underwent angioplasty, stent placement, or a coronary artery bypass graft.

We measured anti-nuclear antibodies (ANA), antibodies to tissue transglutaminase (tTG), and antibodies to cyclic citrullinated peptide (CCP) in all RA cases using commercial ELISA kits. We genotyped subjects for 34 SLE, 17 celiac, 29 RA validated risk alleles based on GWAS and meta-analyses, and 182 ancestry informative markers (AIMs). We conducted our analysis in European American (EU) subjects to minimize population stratification. We calculated a SLE, celiac, and RA count genetic risk score (GRS) by adding the number of disease specific risk alleles for each individual. We tested the association between ANA, tTG, CCP titers and CAD outcome using logistic regression in 3 separate models. The association between CAD outcome and disease-specific GRS was conducted using a student's t-test separately for SLE, celiac and RA.

Results: Among 1335 RA cases, 81% were female, 70% were CCP positive, 76% had bone erosions, and 8% (n=111) had CAD; 84% (n=1124) were EU by AIMs of which 9% (n=100) had CAD. In EU RA cases we observed an association between the celiac GRS and CAD outcome (p=0.03). There was a suggestive trend of higher tTG titers associated with increased risk of CAD (p=0.06). No association was observed between the SLE and RA GRS and CAD outcome. Similarly we found no association between ANA and CCP titers and CAD outcome in RA cases.

Conclusion: The unexplained risk for CAD in RA patients may be partially explained by the burden of autoimmunity, in particular genetic predisposition for celiac disease.

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Treatment to Lipid Targets in a Preventiv Cardio-Rheuma Clinic. Anne Grete Semb[1], Silvia Rollefstad[1], Terje R. Pedersen[2], Ingar Holme[2] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Oslo University Hospital-Ullevaal, Oslo, Norway

Background/Purpose: Even if cardiovascular prevention is established for the general population, only about 40% of individuals treated with lipid lowering (LL) agents reach recommended lipid targets.(1) Patients with inflammatory joint disease (IJD) have increased risk of cardiovascular (CV) disease. EULAR recommendations for CV primary prevention in patients with IJD (2) were published last year, but there is an unmet need of CV treatment results in this high risk patient population. Our objective was to perform cardiovascular risk stratification in patients with IJD and treat them with lipid lowering agents to lipid targets according to recommendations.(2)

Methods: Of the 239 patients with IJD referred to a preventive CV-rheumatologic clinique, 72 (30.1%) patients were not in the target group for treatment with statins (SCORE<5%). The rest, [167/239(69.9%)], were categorized to either primary or secondary LL preventive therapy with simvastatin, atorvastatin or rosuvastatin.

Results: At this reporting time, 55/167 (32.9%) of these patients are still under LL titration, whereas112 patients with rheumatoid arthritis (RA): n= 72, ankylosing spondylitis (AS): n= 27, and psoriatic arthritis (PsA): n=13) were treated to the nearest possible level of the lipid targets. Number of patient consultations needed to reach lipid goals vs. number of consultations used in patients still titrating LL treatment was (mean+SD) 2.96+1.19 vs. 1.19+0.59. There was no difference in age, blood pressure, smoking, inflammatory biomarkers (SR/CRP) and lipid levels between patients with RA/AS/PsA who reached lipid targets. A substantial number of the patients who were treated to lipid targets had known CVD (RA 43.1%, AS 25.9%, PsA 61.5%). In addition, asymptomatic carotid artery plaques were present in 42/72 (58.3%)/17/27 (63.0%)/ 6/13 (46.2%) among RA/AS/PsA respectively. Lipid changes in IJD patients from start to final consultation were significant; total cholesterol: 1.54 mmol/L (95%CI: 1.27, 1.80; p<0.0001), LDL: 1.32 (1.08, 1.56; p<0.0001), HDL: 0.07 (0.01, 0.14; p=0.02), TG: 0.34 (0.11, 0.57;p=0.004). The proportion of patients reaching at least 2 lipid goals was for RA/AS/PsA: 90.3/92.6/84.6% respectively. No serious adverse events were observed.

Conclusion: Patients with IJD referred to CV risk stratification have a high probability for the need of CV prevention. Treatment to lipid target goals was successful in almost 90% of patients with IJD. This experience supports the importance and relevance of establishing cardiovascular-rheumatologic prevention clinics.

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Incidence and Time Trends of Herpes Zoster in Rheumatoid Arthritis: A Population Based Cohort Study. Bharath Manu Akkara Veetil, Eric L. Matteson, Sherine E. Gabriel and Cynthia S. Crowson. Mayo Clinic, Rochester, MN

Background/Purpose: To determine the risk factors, incidence, time trends and severity of herpes zoster (HZ) in a population based incidence cohort of patients with rheumatoid arthritis (RA) compared to a group of individuals without RA from the same population.

Methods: A population-based inception cohort of patients with RA who fulfilled 1987 American College of Rheumatology criteria for RA between 1/1/1980 and 12/31/2007 and a cohort of non-RA subjects from the same population base were assembled and followed until death, migration, or 12/31/2008. Incidence, risk factors and outcome data were collected by a retrospective chart review. The cumulative incidence of HZ adjusted for the competing risk of death was estimated. Cox proportional hazards models were used to compare the rate of development of HZ between patients with RA and the non-RA comparison cohort and to assess the association of risk factors on the development of HZ among patients with RA. Time-dependent covariates were used to model risk factors that developed over time.

Results: The study population consisted of 813 RA and 813 non-RA subjects. There was no difference in the presence of HZ prior to RA incidence/ index date between cohorts (p=0.85). Among patients who did not have HZ prior to incidence/index date, 84 RA patients and 46 non-RA subjects developed HZ during follow-up. The rate of development of HZ was 12.1 per 1000 person-years (95% CI: 9.6, 14.9) in RA patients and 5.6 per 1000 person-years (95% CI: 4.1, 7.5) in non-RA subjects. Thus, patients with RA were more likely to develop HZ during follow-up (hazard ratio [HR]: 2.3; 95% confidence interval [CI]: 1.6, 3.3). Patients diagnosed with RA in 1995–2007 had a higher likelihood of developing HZ than patients with RA diagnosed in 1980–1994 (HR: 1.9; 95% CI: 1.1, 3.2; p=0.013). Among patients with HZ, 13 (16%) patients with RA and 7 (15%) non-RA subjects were diagnosed with post-herpetic neuralgia (p=0.95). Hospitalization was required in 11 (13%) of RA patients and 1 (2%) of non-RA subject (p=0.055). Erosive disease, previous joint surgery, use of hydroxychloroquine and corticosteroids were significantly associated with the development of HZ in patients with RA. There was no significant association between the use of methotrexate or biologic response modifiers and the development of HZ.

Conclusion: The incidence of HZ is increased in RA and has risen in recent years. The increasing incidence of HZ in more recent years reflects the increase noted in the general population and does not appear to be associated with biologic use.

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Validation of An Infection Risk Score in Rheumatoid Arthritis. Cynthia S. Crowson, Deana D. Hoganson, Patrick Fitz-Gibbon and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Patients with rheumatoid arthritis (RA) have increased susceptibility for infections, which contributes to increased mortality. We previously developed a score to predict risk of serious infection in patients with RA in the pre-biologic era (1955–1994). The purpose of this study was to examine the performance of this infection risk score in patients more recently diagnosed with RA.

Methods: A population-based inception cohort of RA subjects who fulfilled 1987 ACR criteria for RA in 1995–2007 was assembled and followed through their complete medical records until death, migration, or 12/31/2008. The outcome measures included all serious infections (requiring hospitalization or IV antibiotics). Data were collected on use of biologic response modifiers and components of the risk score, which included age, sex, leukopenia, comorbidities (alcoholism, diabetes mellitus, chronic lung disease, cardiovascular disease), RA disease characteristics (extra-articular manifestations, rheumatoid factor, erythrocyte sedimentation rate) and glucocorticoid use. Calibration (i.e., ability to accurately predict the absolute risk level) of observed risk to predicted risk from our risk score was assessed using standardized incidence ratios (SIR; ratio of observed to predicted risk) and discrimination (i.e., accurately ranking risk from low to high) was assessed using the concordance (c-statistic).

Results: Among the 410 RA patients (mean age 55 years; 69% female; mean followup 5.6 years; 2,292 total person-years [py]), 79 had ≥1 serious infection (206 total serious infections). The rate of serious infections in these patients (9.0 per 100 py) was similar to the 1955–1994 time period (9.1 per 100 py). The infection risk score demonstrated very good discrimination for predicting serious infection in these patients (c-statistic=0.87). However, the predicted risk significantly underestimated the observed risk (SIR: 1.2; 95% confidence interval [CI]: 1.01, 1.3; p=0.037) indicating poor calibration. Biologics were used in 83 (20%) patients. The predicted risk of infections was higher among biologics users (p<0.001), but biologic use was not a significant predictor of serious infections (p=0.33 adjusted for the risk score). Among biologic users, the risk score showed good discrimination (c-statistic=0.91) and calibration (SIR: 1.02, 95% CI: 0.7, 1.4; p=0.90).

Conclusion: The risk score demonstrated good discrimination for serious infections among patients with RA. Re-calibration could improve accuracy of the risk predictions. Inclusion of biologic use in the risk score is unlikely to improve risk prediction. This risk score may alert clinicians to the potential occurrence of infection in their patients with RA.

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Risk for Herpes Zoster in Patients with Rheumatoid and Psoriatic Arthritis. Dimitrios A. Pappas[1], George Reed[2], Michele M. Hooper[3], Ying Shan[2], Bojena Bitman[4], Jeffrey D. Greenberg[5], Deborah Wenkert[3], Jie Zhang[6], Joel M. Kremer[7] and Jeffrey R. Curtis[6]. [1]Columbia University, College of Physicians & Surge, New York, NY, [2]UMass Medical School, Worcester, MA, [3]Amgen, Thousand Oaks, CA, [4]Amgen Inc., Thousand Oaks, CA, [5]New York University School of Medicine, New York, NY, [6]University of Alabama at Birmingham, Birmingham, AL, [7]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: Opportunistic infections, including herpes zoster (HZ), occur more frequently in Rheumatoid Arthritis (RA) patients (pts) than in the general population. There is limited data on herpes zoster susceptibility in other inflammatory arthritides, such as psoriatic arthritis (PsA), despite an overlap in cellular and biochemical dysregulation underlying these diseases. It is also unclear, if the extent of immune dysfunction, as reflected by RA severity, also underlies the extent of vulnerability to opportunistic infections. We therefore investigated the incidence of HZ in PsA pts and, in RA pts, the disease severity, and other potential risk factors for HZ among pts participating in the Consortium of Rheumatology Researchers of North America (CORRONA) registry.

Methods: The CORRONA registry is a network of US private and academic rheumatology practices with data regarding ~ 25,000 RA and ~ 3500 PsA pts. We compared the incidence rate (IR) of physician-reported HZ in pts with RA and PsA. For RA pts, we investigated HZ risk vs. RA related factors (CDAI, mHAQ, RA duration, prednisone treatment), pt characteristics (age) and comorbidities including diabetes mellitus (DM), malignancy and cardiovascular disease (CVD). Baseline CDAIs were evaluated by category: remission (CDAI <=2.8), low (2.8–10) moderate (10–22), and high (CDAI >22). Analyses were adjusted for prevalent use of biologic and non-biologic DMARDs. Cox regression estimated hazardratios (HR) for incident HZ cases.

Results: 22,306 RA pts and 3,325 PsA pts had at least one follow up visit in the CORRONA registry and were included in the analysis. Age adjusted incidence rates (IR) of HZ were 6.8/1000 person-years (95% CI: 6.0–7.6) for pts with RA, and 5.3 (95% CI 3.8–6.8) for PsA, (crude IR were 8.1 and 5.3 respectively). In univariate models of RA pts, significant predictors of incident HZ were age (HR: 1.02, 95% CI 1.01–1.02), use of prednisone (HR: 1.28 95% CI 1.01–1.64), use of ≥2 prior biologics (HR: 1.43, 95% CI 1.02–2.01) and diabetes (HR: 1.54, 95% CI 1.03–2.30). In adjusted Cox models, each 5 year increase in age was associated with a HR of 1.11 (95% CI 1.06–1.17). Baseline CDAI categories yielded HR of: CDAI remission (HR=1), low (HR: 1.42, 95% CI 1.02–1.99) moderate (HR:1.17, 95% CI 0.80–1.70) and high (HR: 1.20, 95% CI 0.78–1.86). Prior use of > one biologic yielded a HR of 2.02 (95% CI:1.25, 3.26) for the development of HZ. Comorbidities and prednisone use were not significant in adjusted models.

Conclusion: HZ IR were high in both RA and PsA pts with a tendency towards higher IR in our RA study population. Among RA pts, HZ was associated with increasing age in our RA pts as is seen in the general population. A trend towards increased risk for pts with higher disease activity was observed. Greater use of prior biologics, perhaps reflecting more refractory disease, was also associated with increased risk. Ongoing analyses are evaluating drug-specific effects on the risk of developing HZ.

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Combining Tuberculin Skin Test and Interferon Gamma Release Assays for Latent Tuberculosis Infection Screening May Be Necessary for the Exclusion of Latent Tuberculosis in a High Risk Individuals with Rheumatoid Arthritis. Bella Mehta[1], Bret Sohn[2] and Petros V. Efthimiou[3]. [1]Lincoln Medical and Mental Health Center, New York, NY, [2]Lenox Hill Hospital,NY, New York, NY, [3]LM&MHC/Weill Cornell MC, New York, NY

Background/Purpose: Latent TB reactivation has emerged as a significant complication in patients with RA, especially with the increasing therapeutic use of biologic medications. RA patients were estimated to have a 4-fold increased risk for TB reactivation when compared to the general population. Current guidelines strongly recommend LTBI screening and treatment of positives with anti-tuberculous agents prior to biologics use. Interferon Gamma Release Assays (IGRAs) such as the Quantiferon-TB Gold test (QFT-G) have recently been introduced in clinical practice for LTBI screening. There is still limited evidence of their comparative efficacy in RA.

Methods: A retrospective, chart review, study was conducted in RA patients followed at the rheumatology outpatient clinic of an urban teaching hospital, serving an inner city, largely immigrant population. 116 RA patients who had both TST and QFT-G testing performed during their initial evaluation were included. QFT-G could be interpreted as positive, negative or indeterminate. All TST testing was performed and interpreted consistently by 2 qualified evaluators and defined as positive if >5mm induration was present. Patients were diagnosed with LTBI if TST and/or QFT-G were positive and were treated with 9 months of Isoniazid/B6 after active TB was ruled out by chest radiography. Additional LTBI screening tests, performed yearly, were recorded for a mean period of 2.54 (sd–1.35) years following the initial negative screen.

Results: Out of 116 patients studied, 88(77%) were classified as Hispanic, reflecting the community demographics served by the hospital.

Two patients had indeterminate QFT-G and negative TST and were excluded from our analysis. 45(39%) patients were diagnosed with LTBI with either a positive TST 37(32%) and/or QFT-G 21(18%). 13(11%) were positive and 69 (61%) were negative for both tests. The agreement between TST and QFT-G was 72 % (κappa =0.279, CI-95% 0.106–0.452, p=0.087). Disagreement between TST and QFT-G was 32(28%) which included both positive TST with negative QFT-G 24(21%) and negative TST with positive QFT-G 8(7%). In 69 patients with negative TST and QFT-G, 14 did not have subsequent TST and/or QFT-G. Of the remaining 55 patients, there were no TST conversions, whereas 3 patients experienced sero-conversions to QFT-G positive. None of the patients developed active TB, including one patient on TNF-inhibitor who converted to QTF-G positive.

Screening Test	TST (positive)	TST (negative)	Total
QFT-G(positive)	13	8	21
QFT-G(negative)	24	69	93
Total	37	77	114

Conclusion: There was low moderate agreement between TST and QFT-G in our high risk RA population. QFT-G identified 7% of patients that TST did not detect while TST identified 21% of patients that QFT- G didn't. In the absence of clearly defined gold standard and limitations associated with both tests, early screening with both tests and treatment of all identified cases, regardless of the test, may be an effective and safe approach with the aim to minimize the risk of LTBI reactivation.

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Cytomegalovirus (CMV) and Rheumatoid Arthritis (RA)—a Critical Role of CMV Specific T Cells? Kathrin Rothe[1], Dagmar Quandt[1], Matthias Pierer[2], Anett Schulz[1], Undine Meusch[1], Manuela Rossol[3], Roger Scholz[2], Christoph G. Baerwald[4] and Ulf Wagner[4]. [1]University of Leipzig, Leipzig, Germany, [2]Haertelstrasse 16–18, Leipzig, Germany, [3]Translationszentrum für Regenerative Medizin (TRM), University of Leipzig, Leipzig, Germany, [4]University Hospital, Leipzig, Germany

Background/Purpose: Herpes virus infections, such as cytomegalovirus infections are very common, affecting roughly about 50% of the European population. Initial CMV infections are typically asymptomatic but usually lead to a life-long virus persistence. Virus specific CD8 as well as CD4 memory T cell responses are found in infected persons with an extremely high frequency, described as the inflationary memory. In an inflammatory setting such as in rheumatoid arthritis, the changes in the overall reactivity of the T cell compartment maybe also affects the CMV reactivity and in turn this can contribute to the disease outcome.

Methods: We investigated whether a latent CMV infection is associated with the pathophysiology of RA patients. On the one hand retrospective analyses on clinical parameters were performed. In additiion, in vitro cell culture assays with PBMC derived from blood of CMV+ RA patients and CMV+ healthy donor (HD) were performed.

Results: First we were interested in the overall rate of CMV infections in RA patients as compared to healthy donor (HD). We found no difference in the number of CMV seropositive subjects in a retrospective analyses of 202 RA patients and 272 healthy donor (HD). Interestingly, more advanced joint destruction and increased surgical joint procedures could be detected in 102 CMV+ RA as compared to 78 CMV- RA patients by radiography.

CMV specific proliferation was analyzed on a single cell level with the use of a CFDA-SE proliferation assay. The results show a comparable level of proliferating CMV specific CD4 as well as CD8 T cells in CMV+ RA patients (mean CD4: 6.4%, mean CD8: 9.7%; n= 10) compared to CMV+ HD (mean: CD4 6.8%, mean CD8: 11.2%; n= 7). Additionally, activation markers like CD71 and CD25 correlated very well with the proliferative response of the T cells. In order to control the virus, IFNg production by T cells is very important. Using an IFNg secretion assay we found an increased frequency of CMV specific CD3+CD4+ IFNg producers with 2.1 % (n=4) in CMV+ RA patients as compared to 0.24% (n=6) IFNg producers among CD3+CD4+ T cells in CMV+ HD after CMV (pp65) peptide specific short time restimulation in vitro.

Conclusion: In conclusion, latent CMV infection amplifies joint damage in RA, in part due to an increased CMV specific effector function in the CD4+ T cell compartment.

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Outcome of Pulmonary NTM Disease in Patients with Underlying Rheumatic Disease:A Retrospective Observational Study. Jung Won Noh[1], Jiwon Hwang[1], Jaejoon Lee[1], Joong Kyong Ahn[2], Chan Hong Jeon[3], Jinseok Kim[4], Won-Jung Koh[1], Eun-Mi Koh[1] and Hoon-Suk Cha[1]. [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Soonchunhyang University College of Medicine, Bucheon, South Korea, [4]Jeju National University Hospital, Jeju, South Korea

Background/Purpose: The existing data suggest that the incidence and prevalence of pulmonary nontuberculous mycobacteria (NTM) infections are increasing. However, the effect of rheumatic disease itself and immunosuppressive therapy on the clinical significance and the outcome of NTM pulmonary disease are unknown. This study was undertaken to evaluate the clinical significance and the outcome of pulmonary NTM disease in patients with underlying rheumatic disease.

Methods: We performed a retrospective analysis using medical records at a single tertiary hospital from January 2002 to January 2011. The patients with pulmonary NTM disease with underlying rheumatic disease were identified. The demographic data, underlying rheumatic diseases, immunosuppressive regimen, isolated NTM organism, treatment regimen for NTM disease, and culture negative conversion rate of NTM were analyzed.

Results: A total of 24 patients with underlying rheumatic diseases who satisfied the criteria for pulmonary NTM disease as recommended by the American Thoracic Society were identified. Mean age was 60.9 ± 12.3 years and mean duration of follow up was 4.1 ± 3.2 years. The most common rheumatic disease was rheumatoid arthritis (58.3%), followed by systemic lupus erythematosus (8.3%), Sjogren's syndrome (8.3%), relapsing polychondritis (8.3%), ankylosing spondylitis (4.2%), mixed connective tissue disease (4.2%) and microscopic polyangiitis (4.2%). Immunosuppressive regimen included prednisolone (66.7%), methotrexate (33.3%), leflunomide (16.7%), cyclosporin (12.5%), azathioprine (8.3%), and TNF-α inhibitors (4.2%). The most commonly isolated NTM organism was mycobacterium avium complex (83.4%), followed by mycobacterium abscessus (12.5%) and mycobacterium fortuitum (4.2%). Seventeen patients (70.8%) required treatment for pulmonary NTM disease. Of these, 12 patients (70.6%) achieved culture negative conversion. The culture negative conversion rate in patients with rheumatic diseases was comparable to those without underlying rheumatic diseases from our institution. Furthermore, various immunosuppressive agents did not influence the rate of culture negative conversion. Dissemination or progression of pulmonary NTM disease was not observed.

Conclusion: Our study demonstrates that pulmonary NTM disease in patients with underlying rheumatic diseases may not have worse clinical consequences compared to those without. With proper treatment, the outcome of pulmonary NTM disease as assessed by culture negative conversion rate is comparable to those without rheumatic diseases despite the use of various immunosuppressive drugs.

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Serodiagnosis of *Mycobacterium Avium*-Complex Pulmonary Disease with An Enzyme Immunoassay Kit That Detects Anti-Glycopeptidolipid Core Antigen IgA Antibodies In Patients with Rheumatoid Arthritis. Shogo Banno[1], Maiko Watanabe[2], Kanesige Sasaki[2], Taio Naniwa[2] and Yoshihito Hayami[2]. [1]Aichi Medical University, Aichi-prefecture, Japan, [2]Nagoya City University, Nagoya city, Japan

Background/Purpose: Rheumatoid arthritis (RA) has many pulmonary manifestations including bronchial abnormalities that can develop into *Mycobacterium avium*-complex (MAC)-pulmonary disease (PD). MAC-PD can be lethal in patients receiving tumor necrosis factor alpha-blockers despite the administration of antibiotics. Diagnosis of MAC-PD is often difficult because MAC is an environmental organism. In this study, we investigated the usefulness of the serodiagnosis of MAC-PD in RA patients by using an enzyme immunoassay (EIA) kit that detects anti-glycopeptidolipid (GPL) core antigen IgA antibodies.

Methods: Antibody levels were measured in 63 patients with RA; 14 with MAC-PD plus 3 cultured nontuberculous mycobacteria (NTM) other than MAC; and 16 with pulmonary abnormalities characterizing NTM but undetected in sputum culture; 30 control subjects.

Results: RA patients with MAC-PD showed significantly higher antibody levels than the controls ($p=0.02$). The cutoff point was set at 0.7 IU/l, making the sensitivity and specificity of the antibody in MAC-PD and control patients 43% and 100%, respectively.

Conclusion: The EIA kit is useful for the diagnosis of MAC-PD in RA patients because of its high specificity. This test is an easier and less invasive form of examination and could therefore replace bronchoscopy as the main diagnostic procedure for RA patients with MAC-PD.

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High Expression of Haptoglobin in the Peripheral Blood Mononuclear Cells From Methotrexate-Resistant Rheuamatoid Arthritis Patients. Wenfeng Tan, Fang Wang, Dunming Guo, Xiaoming Zhu, Yao Ke and Miaojia Zhang. the First Affiliated Hospital of Nanjing Medical University, Nanjing, CHINA., Nanjing, China

Background/Purpose: Starting with methotrexate (MTX) monotherapy is cost-effective in early Rheuamatoid arthritis (RA) patients. However, only 30–40% of the patients will experience a good response to MTX alone. Thus, it is important to identify the biomarker to predict MTX therapy response. Here, we investigate the gene expression profiles in peripheral blood mononuclear cell (PBMC) from methotrexate-resistant Rheuamatoid arthritis patients.

Methods: Baseline active RA patients treatment with MTX alone and RA disease activity was evaluated every 4 weeks until week 12 using a joint disease activity score (DAS28). Remission and treatment response were categorised using European League Against Rheumatism (EULAR) definitions. Gene expression profiles in PBMC from 10 MTX-resistant RA (MRR) and 5 MTX good-response (MGR) RA were analyzed by IIIumina microarray. Targeted gene mRNA expression levels in PBMC from 30 MRR, 20 MGR RA patients and 30 healthy controls (HC) were further analyzed using Real-time PCR.

Results: Multiple genes were up-regulated in PBMC from MRR RA patients compared to those in MGR patients. Differentially expressed genes involved in several overlapping pathways including immune responses (19%), signaling pathways (27%), transcription/translation regulators (26%), and metabolic functions (15%). Among those, Haptoglobin expression signal was 5.1 fold increased in MRR RA patients compared to those in MGR patients. Real-time PCR further indicated that Haptoglobin mRNA was higher in PBMC from MRR RA patients than those in MGR RA and HC. When stratifying RA patients into remission, low, moderate and high disease activity subgroup based on DAS28 score, the high disease activity subgroup displayed higher levels o Haptoglobin levels than those in the remission, low or moderate disease active subgroup as well as HC ($p<0.05$, respectively).

Conclusion: High expression of Haptoglobin in PBMC might predict MTX therapy response and could provide a new pathway invovled in RA pathogensies.

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Histological Analyses of Surgically Resected Synovial Tissues In Patients with Rheumatoid Arthritis Treated with/without Biological Agents. Yuichi Mochida[1], Katsushi Ishii[1], Kengo Harigane[1], Naoto Mitsugi[1] and Tomoyuki Saito[2]. [1]Yokohama City University Medical Center, Yokohama, Japan, [2]Yokohama City University School of Medicine, Yokohama, Japan

Background/Purpose: Recent treatment of rheumatoid arthritis (RA) was dramatically improved after introducing biological agents. Although there are several reports with small numbers of cases that analyzed the effect of biological agents from the view point of histopathology, the significance of biological agents on histological changes of joint synovium is remained uncertain. The purpose of this study was to compare the histopathological findings of surgically resected synovium in patients with RA between 2 groups with and without use of the biological agents.

Methods: Between January 2006 and December 2010, 59 biopsy specimens of synovium were obtained during joint surgery from 52 cases of RA. The obtained specimens were fixed in 10% neutral buffered formalin and routinely embedded in paraffin. Microscope slides were prepared, stained with hematoxylin and eosin, and reviewed. The histopathological findings of synovium in each specimen were evaluated and scored for detailed findings such as synoviocyte hyperplasia, fibrosis, proliferating blood vessels, perivascular infiltrates of lymphocytes, focal aggregates of lymphocytes, and diffuse infiltrates of lymphocytes using the histological score of the synovium by Rooney et al. The cases were divided into 2 groups. The group with the use of biological agents (Group A) included 25 cases with 32 joint specimens (24 female and 1 male). Seven cases underwent another joint surgery in different surgeries. In Group A, 10 cases (12 joints) used etanercept, 10 cases (12 joints) used infliximab, 3 cases (5 joints) used tocilizumab, and 2 cases (3 joints) used adalimumab at the time of surgery. The variations of surgery were total knee arthroplasty (TKA) in 17 cases, total hip arthroplasty (THA) in 4 cases, total elbow arthroplasty (TEA) in 4 cases, and others in 7 cases. The group without use of biological agents (Group B) included 7 cases with 27 joint specimens (25 female and 2 male). These cases underwent surgery during same study period as Group A. In Group B, the variations of surgery were TKA in 16 cases, THA in 2 cases, TEA in 3 cases, and others in 6 cases. The background data such as age, averaged duration of disease, CRP, DAS-28 score, and mean dose of methotrexate (MTX) and prednisolone (PSL) were not different between 2 groups.

Results: Group A showed significantly decreased scores in synovial hyperplasia, perivascular infiltrates of lymphocytes, focal aggregates of lymphocytes, diffuse infiltrates of lymphocytes and also total score than in the Group B. The scores of fibrosis and proliferating blood vessels did not show difference between 2 groups. No correlation between total Rooney's score and age, Larsen's classification, Steinblocker's classification, or the mean dose of MTX or PSL was found in each group. In Group A, no difference of total Rooney's score was found by variety of biologics, additionally, there was no correlation between total Rooney's score and the duration of disease or the duration of administration of biologics. In Group B, there was positive correlation between total Rooney's score and the duration of disease.

Conclusion: Based on these results, biological agents for RA clearly showed significant effects on histological findings of joint synovium.

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Induced Abortions in Women with Rheumatoid Arthritis on Methotrexate. Evelyne Vinet[1], Christian A. Pineau[2], Bindee Kuriya[3], Ann E. Clarke[1], Robert Platt[4] and Sasha Bernatsky[5]. [1]McGill University Health Centre, Montreal, QC, [2]McGill Univ Health Center, Montreal, QC, [3]University of Toronto, Toronto, ON, [4]McGill University, Montreal, QC, [5]McGill UHC/RVH, Montreal, QC

Background/Purpose: Statistics from North America and the United Kingdom suggest that up to half of pregnancies are unplanned; almost half of unintended pregnancies are terminated. In women with RA with unplanned pregnancies, those exposed to teratogenic drugs, such as methotrexate (MTX), may be more likely to undergo an induced abortion. Since there are few data examining these issues, we aimed to determine the rate of induced abortion in women with RA exposed to MTX compared to women with RA unexposed to this medication.

Methods: We performed a nested case-control study using Quebec's physician billing and hospitalizations databases (from 01/01/2000 to 31/12/2008), which cover all healthcare beneficiaries (~7.5 million). All women with RA, aged between 15–45 years, were identified based on ≥1 hospitalization with either a primary or secondary diagnosis of RA, or ≥2 physicians' claims for RA within any 2-year period (provided they were at least 8 weeks apart). Women who had an intra-uterine device, any procedures leading to sterilization, and/or any conditions causing infertility were excluded. Cases were defined as women having an induced abortion, based either on one procedure code and/or diagnostic code for induced abortion. Each case was matched to ≥1 controls for age, calendar time, and cohort entry. Exposure was defined as having filled at least one prescription of MTX in the 16 weeks prior to the index date. We performed a multivariate conditional logistic regression, including other potential predictors of induced abortion (i.e. exposure to anti-tumor necrosis factor (anti-TNF) agents in the previous 16 weeks, prednisone use, disease severity as indicated by extra-articular manifestations, and disease duration).

Results: We identified 112 cases of induced abortion in women with RA and 5855 corresponding RA controls. Exposure to MTX occurred in 10.7% of cases and in 21.7% of controls. Women exposed to MTX had a lower rate of induced abortion compared to unexposed women (adjusted rate ratio (RR) 0.47; 95% CI 0.25, 0.89). In multivariate analysis, there was a trend for an increased rate of induced abortions among women exposed to anti-TNF agents (RR 2.07; 95% CI 0.81, 5.27) and those with extra-articular manifestations (RR 2.17; 0.51; 9.35). We did not establish an independent effect of prednisone use (RR 0.78; 95% CI 0.41, 1.49) and disease duration on induced abortions.

Conclusion: Our findings suggest that women with RA exposed to MTX may be less likely to have an induced abortion compared to unexposed women. There are many potential reasons for this, such as more careful pregnancy counseling in these women, or possibly less sexual activity.

However, women with severe disease (i.e. on anti-TNF agents and/or with extra-articular manifestations) are potentially at increased risk for induced abortion, presumably for unplanned pregnancies. These results should prompt further research on contraceptive counseling and practices in women with RA.

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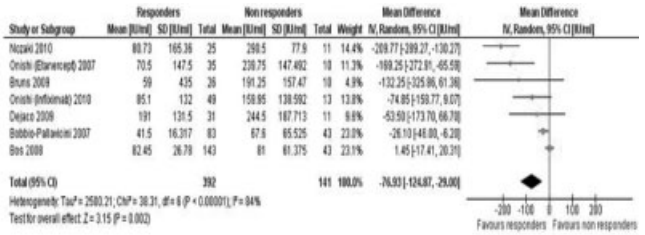
Influence of Baseline Rheumatoid Factor on the Response to Tumor Necrosis Factor Antagonists of Rheumatoid Arthritis Patients: A Systematic Review and Meta-Analysis. Eva Salgado, Jose Ramon Maneiro, Loreto Carmona and Juan J. Gomez-Reino. Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain

Background/Purpose: To explore whether baseline titer or positivity of rheumatoid factor (RF) are predictors of the response of rheumatoid arthritis (RA) patients to tumor necrosis factor (TNF) antagonists.

Methods: A systematic review and meta-analysis using combined synonyms of the terms "rheumatoid arthritis", "Tumor Necrosis Factor-alpha/antagonists or inhibitors", "rheumatoid factor", and "response" (as MeSH terms and free-text)were conducted. Medline, Embase, Cochrane, and abstracts from the ACR and EULAR meetings were searched (up to June 2011). The search was limited to longitudinal observational studies in humans written in English, French, Spanish, Portuguese or Italian. Two independent reviewers did the selection by titer and abstract. All studies on association between baseline RF (titer and/or status) and response to any TNF antagonists, or with enough data to estimate this association were included.. Risk of bias was assessed using an adaptation of Quality Assessment for Prognostic Studies checklist. Qualitative data analysis by outcome and test was performed Meta-analysis with random effects models was run if sufficient homogeneity was present.

Results: The search produced 4163 hits. After selection by title and abstract, 18 articles were included for detailed analysis. Sixty-six associations between some measure of response and RF were tested: 44 on IgM RF (28 on RF titer, 16 on positivity), 10 on IgG RF (7 on titer, 3 on positivity) and 12 on IgA RF (8 on titer, 4 on positivity). Differences in time and method to assess response made some comparisons difficult. The majority of studies were of moderate to high quality. Six comparable studies with small sample sizes reported mean differences in baseline FR IgM titer between responders (EULAR good or moderate response) and non-responders at 14–48 weeks (see figure). Baseline RF IgM tends to be higher in the non-responder group (mean difference (responders- non responders) −76.93 [95%CI −124.87, −29.00]). Heterogeneity was very high (I^2=84%) in the studies showing this association. Comparison of other measures of outcomes in association with IgG RF and IgA RF tests showed contradictory results.



Conclusion: Studies that analyze the association between RF and response to treatment in RA are heterogeneous and show conflicting results. A positive association of IgM RF and response to treatment with TNF antagonists is hampered by the high heterogeneity of the studies.

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Factors Affecting Glucocorticoid Use in Early Rheumatoid Arthritis. Results from an Early Arthritis Cohort. Pooneh S.Akhavan[1], Glen S. Hazlewood[1], Ye Sun[2], Edward C. Keystone[3], Gilles Boire[4], Janet E. Pope[5], Carol A. Hitchon[6], Boulos Haraoui[7], Diane S. Ferland[8], V. Bykerk[9] and CATCH Investigators[10]. [1]University of Toronto, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Mount Sinai Hospital, Toronto, ON, [4]CHUS - Sherbrooke University, Sherbrooke, QC, [5]St. Joseph's Health Care, University of Western Ontario, London, ON, [6]University of Manitoba, Winnipeg, MB, [7]Institut de Rhumatologie, Montreal, QC, [8]LaSalle, QC, [9]Brigham & Women's Hospital, Boston, MA, [10]Toronto, ON

Background/Purpose: Recent guidelines recommend early, short-term use of Glucocorticoids (GC) in patients with recently diagnosed active RA. Concerns over side effects, however have limited the use of these therapeutic agents. The pattern of GC therapy in real world setting may vary based on patients' clinical status, availability of other therapeutic agents, physician and patient preference. The objective was to determine the prevalence of GC use in patients with early RA and to identify the effect of baseline characteristics of patients and treatment center on GC use.

Methods: Patients with early RA were studied in the Canadian Early Arthritis Cohort (CATCH), a prospective cohort where data was collected according to a standardized protocol from 19 participating centers. For the present analysis we included any patient who had at least 3 months follow up. The primary outcome was any form of systemic GC (oral or parenteral) use during the first 3 months. Disease activity, using DAS28, was assessed at baseline and then every 3 months in each group. Univariate analysis compared baseline characteristics in two groups and a multivariable logistic regression analysis was used to model the use of GCs.

Results: 455 patients were included in the analysis who had at least 3 month follow up and were not treated prior to enrolment. 74% were women with a mean age of 52 (SD)(15) years, DAS28 5.5(1.4) and disease duration of 183(270) days. Rheumatoid factor (RF) was positive in 61%. 92 patients (20%) had received systemic GC (PO or IM) during the first 3 months. In univariate analysis two groups were not significantly different in their baseline DAS28 or HAQ. Steroid users were older (p=0.00018), had higher ESR (p=0.0006), CRP (p=0.0003) and erosion (p=0.045) but lower rheumatoid factor +ve (p=0.004). Multivariate regression analysis showed that patients' higher age and treatment center were associated with steroid use.

Conclusion: Despite recent guidelines recommending short-term use of GCs as part of initial management in patients with active recently diagnosed RA, most of these patients did not receive GC in this real word clinical setting. GC use was strongly influenced by the treating center. Younger patients were less likely to receive GC.The heterogeneity in practice patterns may represent a potential role for clinical practice guidelines to inform treatment decision making.

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No Evidence of Increased Mortality in Rheumatoid Arthritis Patients Treated with Biologics: Results From a Multicenter Cohort in Japan. Ayako Nakajima[1], Toshihisa Kojima[2], Wataru Fukuda[3], Taku Yoshio[4], Eisuke Inoue[1], Koichi Amano[5], Seiji Minota[4], Kazuyoshi Saito[6], Shigeki Momohara[1], Naoki Ishiguro[2], Yoshiya Tanaka[7], Tsutomu Takeuchi[8] and Hisashi Yamanaka[1]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Nagoya University, Nagoya, Japan, [3]Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan, [4]Jichi Medical University, Tochigi, Japan, [5]Saitama Medical University, Saitama Medical Center, Saitama, Japan, [6]University of Occupational & Environmental Health, Kitakyushu, Fukuoka, Japan, [7]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [8]Keio University School of Medicine, Tokyo, Japan

Background/Purpose: To investigate the association between treatment with biologics and mortality in patients with rheumatoid arthritis in a multicenter cohort in Japan.

Methods: All patients with rheumatoid arthritis (RA) who received at least one dose of any biologic agent targeting tumor necrosis factor (TNF), interleukin 6 (IL-6) or others at six large rheumatology institutes in Japan (Biologics cohort) were included and monitored until May 15, 2010 or death, whichever occurred first. Death information about the date and cause was received from affiliated hospitals. Active monitoring by phone or mail was conducted for patients who stopped clinic visits. Mortality of the Biologics cohort was compared to the general Japanese population and to a practical RA cohort (the IORRA cohort), using standardized mortality ratio (SMR) determination. To evaluate the effect of lost to follow-up, sensitivity analyses were conducted. Factors associated with mortality were assessed by Cox model, in which age, sex, disease duration, DAS28, and doses of methotrexate (MTX) and corticosteroids were evaluated.

Results: Overall, 2,697 patients with RA were registered into the Biologics cohort; the median [IQD] age was 58.0 [47.2–66.1] years, 84.0% were women, and the median disease duration was 6.9 [2.3–14.8] years. Baseline disease activity indicated by dis DAS28 was 5.6 [4.8–6.4] and disability indicated by Japanese version of Health Association Questionnaire (J-HAQ) was 1.00 [0.50–1.75]. Biologics included infliximab (n=1,112), etanercept (n=1,053), adalimumab (n=345), and tocilizumab (n=173).

MTX and corticosteroids were prescribed in 77.7% and 54.2% of patients, respectively. Thirty-eight deaths were recorded among 6,940.9 patient-years of follow-up in the Biologics cohort, and 540 patients (20.0%) were lost to follow-up. With weighting for patients lost to follow-up, the weighted SMR in this Biologics cohort was 1.08 (95% confidence interval [95%CI], 0.77–1.47) compared to the Japanese general population, and 0.93 (95%CI, 0.66–1.28) compared to the practical RA cohort. The main cause of death was respiratory diseases, including pneumonia and interstitial lung diseases (Table). Risk factors for mortality included male gender (hazard ratio [HR], 3.01 [95%CI, 1.24–6.25]), older age (HR, 1.07 [95%CI, 1.03–1.11]), and corticosteroid dose (HR, 1.08 [95%CI, 1.01–1.17]).

Table. Underlying causes of death classified according to WHO International Classification of Disease (ICD)-10 chapter number

Chapter	Blocks	Chapter title	Deaths n = 38 (%)
I	A00-B99	Certain infections and parasitic diseases	6 (15.8)
II	C00-D48	Neoplasm	5 (13.2)
IV	E00-E90	Endocrine, nutritional and metabolic diseases	1 (2.6)
IX	I00-I99	Diseases of circulatory system	5 (13.2)
	I20-I25	Ischemic heart diseases	1
	I60-I69	Cerebrovascular diseases	3
X	J00-J99	Disease of respiratory system	18 (47.4)
	J10-J18	Influenza and pneumonia	7
XVIII	R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	3 (7.9)

Conclusion: Biologics treatment in RA patients was not associated with increased mortality in a multicenter registry in Japan.

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Generalizability of Patients with Rheumatoid Arthritis in Biologic Clinical Trials. Priyanka Vashisht[1], Harlan Sayles[2], Grant W. Cannon[3], Gail S. Kerr[4], Pascale Schwab[5], Deana M. Lazaro[6], Andreas M. Reimold[7], Nasim A. Khan[8], Bogdan Cherascu[9], Angelo L. Gaffo[10], Dannette S. Johnson[11], Ted R. Mikuls[12] and Kaleb Michaud[13]. [1]Creighton University Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Salt Lake City VA and University of Utah, Salt Lake City, UT, [4]Washington DC VA and Georgetown University, Washington, DC, [5]Portland VA and Oregon Health & Science University, Portland, OR, [6]Brooklyn VA, Brooklyn, NY, [7]Dallas VA and University of Texas Southwestern, Dallas, TX, [8]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, [9]Iowa City VA and University of Iowa, Iowa City, IA, [10]Birmingham VA Medical Ctr, Birmingham, AL, [11]Jackson VA and University of Mississippi Medical Center, Jackson, MS, [12]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [13]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Biologic response modifiers for the treatment of rheumatoid arthritis (RA) are efficacious and cost effective as determined by randomized clinical trials (RCTs), yet observational studies rarely show similar efficacy. RCTs have many criteria for participation which may limit the generalizability of their results. Our objective is to identify the proportion of clinical RA patients who would meet entry criteria for all RCTs of biological agents.

Methods: A nation-wide clinical cohort of 1522 patients in the Veterans Affairs RA registry who had met the 1987 ACR criteria for RA was evaluated at a random clinic visit. We reviewed 24 primary phase-III clinical trials for the 9 FDA-approved biologic treatments for RA and recorded all trial inclusion and exclusion criteria. Each participating patient was assessed for overall trial inclusion as well as four domains of inclusion: demographics, disease activity, medication exposure and comorbidities. For items not measured in the clinic as well as for all "wash-out" periods, we assumed a conservative 100% inclusion.

Results: Based on the review of criteria for 9 biologics in 24 RCTs, the mean percentage of patients meeting inclusion was 10.4 (SD 8.7). The domain most responsible for exclusion was disease activity, specifically joint count criteria which excluded patients on average 65.1% for tender and 63.2% for swollen joint counts. In comparison, biomarker criteria were much less restrictive as ESR excluded 22.2% and CRP excluded 5.5% patients. Disease duration was the most important factor of the demographic domain excluding 17.7% of patients. Previous treatment with methotrexate excluded about 52% patients for 6 trials and prior treatment with tumor necrosis factor inhibitor (TNFi) excluded 27% for 8 trials. Previous cancer history led to exclusion of about 35% patients for 3 trials. Comparing the non-TNFi and TNFi biologic agents, the RCTs for non-TNFi biologics were more restrictive than RCTs for TNFi (6.9% vs. 11.8% inclusion, $p=0.07$). There was no statistical trend in inclusion in RCTs by date published or date the drug was approved.

Conclusion: On average, 90% of our RA study patients did not meet criteria for inclusion for a given biologic RCT. Most trials require the patient to have moderate to severe disease activity, levels often associated with flares. While RCTs have shown these therapies to have high efficacy, it is possible that similar results are not seen in observational studies as those patients who are RCT eligible represent a small portion of those seen in the clinic.

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Predictors, Features and Effects of First Biologic Switch in Rheumatoid Arthritis within GISEA register: Italian 10-Year Experience. Bernd Raffeiner[1], Costantino Botsios[1], Paolo Sfriso[1], Antonio Carletto[2], Domenico Biasi[2], Elisa Gremese[3], Gianfranco Ferraccioli[4], Clodoveo Ferri[5], Mauro Galeazzi[6], Roberto Gerli[7], Paola Cipriani[8], Roberto Giacomelli[8], Tamara Ziglioli[9], Roberto Gorla[9], Marcello Govoni[10], Antonio Marchesoni[11], Fausto Salaffi[12], Walter Grassi[13], Fabiola Atzeni[14], Piercarlo Sarzi-Puttini[15], AnnaRita Giardina[16], Giovanni Triolo[16], Florenzo Iannone[17], Giovanni Lapadula[17] and Leonardo Punzi[1]. [1]Rheumatology Unit, University of Padova, Padova, Italy, [2]Rheumatology Unit, University of Verona, Verona, Italy, [3]Rheumatology Unit, Catholic University, Roma, Italy, [4]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [5]Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy, [6]Rheumatology Unit, University of Siena, Siena, Italy, [7]Rheumatology Unit, University of Perugia, Perugia, Italy, [8]Rheumatology Unit, University of Aquila, L'Aquila, Italy, [9]Rheumatology Unit, University of Brescia, Brescia, Italy, [10]Rheumatology Unit, University of Ferrara, Ferrara, Italy, [11]Rheumatology Unit, Ospedale G Pini, Milano, Italy, [12]Rheumatology Unit, Polytechnic University of the Marche, Jesi, Italy, [13]Università Politecnica delle Marche, Jesi, Italy, [14]Rheumatology Unit, L Sacco University Hospital, MiIano, Italy, [15]Rheumatology Unit, L Sacco University Hospital, Milano, Italy, [16]Rheumatology Unit, University of Palermo, Palermo, Italy, [17]Rheumatology Unit, University of Bari, Bari, Italy

Background/Purpose: To identify predictors for first switch of biologic agents in real-life treatment of moderate to severe rheumatoid arthritis (RA) in Italy. To illustrate switch strategies adopted and to analyze results obtained this way.

Methods: Retrospective observational study was performed on RA patients who started biologic agents from 1999 to 2010 because of unresponsive moderate to severe RA within *GISEA* ("Gruppo italiano per lo studio dell'early arthritis") register including 14 tertiary rheumatology centers of Italy. Baseline parameters of patients maintaining and patients discontinuing first biologic agent were compared, and stepwise logistic regression model was calculated to find baseline parameters predictive for first switch. Switch strategies between biologics, time to and reason of first switch were analyzed. Efficacy of first switch was determined by EULAR response achieved at 6 and 12 months, and by rate of failure occurring with second line biologic divided for type of agent used and reason of switch. For statistical analysis the Kruskal-Wallis and chi-squared test were used as appropriate. $P < 0.05$ was considered statistically significant.

Results: 3,702 RA patients starting biologic treatment were included. Patients continuing first biologic had better EULAR responses at 6 and 12 months after starting biologic agent than those switching later on. Predictors for first switch were disease activity, glucocorticoids, lower age and disease duration, whereas concomitant DMARDS and the use of adalimumab and etanercept instead of infliximab resulted protective. Switching to second TNFα blocker was the strategy most applied, and showed greatest EULAR responses at 6 and 12 months. Etanercept performed better for response and failure rate than adalimumab and infliximab. As second line agents biologics with novel mechanisms of action presented lowest discontinuation rates, but were not significantly different from anakinra and etanercept. Switch because of inefficacy resulted in worse response and higher probability to fail again due to inefficacy.

Conclusion: Behavior in managing biologics is changing because more agents are available including those working on alternative pathways. Nevertheless, TNFα blockers confirmed their efficacy in first and second line, but possible superiority of new agents in long-term disease control has to be considered in further studies.

1202

Sleep Disturbances and IL-6 Receptor Inhibition in Rheumatoid Arthritis. K. Fragiadaki[1], MG Tektonidou[1], M. Konsta[1], GP Chrousos[2] and PP Sfikakis[1]. [1]Laikon Hospital, Athens University Medical School, Athens, Greece, [2]First Department of Pediatrics, Athens University Medical School, Athens, Greece

Background/Purpose: Sleep quality has been recognized as a central component of health-related quality of life in patients with rheumatoid arthritis (RA) and sleep disturbances have been correlated with disease activity, pain and psychological distress. Indirect support for a possible link with the abundance of proinflammatory cytokines stems from sleep quality studies reporting an association between sleep problems and increased concentrations of TNF and IL-6 in healthy subjects. In this pilot 6-month study we examined whether administration of the IL-6 receptor antagonist tocilizumab affects sleep disturbances in RA.

Methods: Patients with documented sleep disturbances at baseline received monthly infusions of tocilizumab (8 mg/kg) for moderately or severely active RA. Sleep quality, by Pittsburgh Sleep Quality Index (PSQI) and daytime sleepiness, by Epworth Sleepiness Scale were evaluated at baseline, first, second, third and sixth month of treatment in 15 patients (13 women). RA disease activity, by DAS28 (ESR), functional status and disability, by Health Assessement Questionaire (HAQDi) and fatigue, by FACIT-Fatigue Scale (FFS) were evaluated in parallel. Medications used before enrollment, remained unchanged during follow-up.

Results: Sleep quality improved and daytime sleepiness decreased significantly at first-month assessment comparing to baseline, and these changes became more evident through 6 months ($p<0.00001$ and $p<0.004$ respectively, by repeated measures analysis). Moreover, disease activity decreased, fatigue decreased and functional status improved significantly. Further analysis revealed that individual changes in PSQI score over time were not associated with the corresponding individual changes in DAS28 ($r=0.37$, $p=0.17$) but correlated significantly with HAQDi changes ($r=0.60$, $p=0.02$) and marginally with changes in FSS scores ($r = -0.46$, $p = 0.08$)

Conclusion: Improvement of sleep quality after tocilizumab treatment in patients with RA does not appear to directly result from decreased disease activity, further suggesting that aberrant IL-6 regulation associates with sleep disturbances.

1203

Fatigue in Patients with Rheumatoid Arthritis: Examination of Contributory Factors Post Tumour Necrosing Factor Inhibitor Treatment. Patricia Minnock[1], Gabrielle McKee[2], Barry Bresnihan[3], Oliver M. FitzGerald[4] and Douglas J. Veale[5]. [1]Our Lady's Hospice & Care Services, Dublin, Ireland, [2]Trinity College Dublin, Dublin, Ireland, [3]St. Vincent's University Hospital, Dublin, Ireland, [4]St. Vincent's Univ Hospital, Dublin, Ireland, [5]Dublin Academic Medical Centre, University College Dublin, Dublin, Ireland

Background/Purpose: The nature of fatigue in patients with rheumatoid arthritis (RA) is poorly understood. The purpose was to determine contributory factors to persistent fatigue despite good disease outcome following six months of tumour necrosing factor inhibitor (TNFi) therapy.

Methods: Selection criteria included patients with RA assessed at baseline and six months post initiation of TNFi therapy, demonstrating a moderate / good disease response using the EULAR response criteria (ERC). This group was divided into two subgroups i) with poor fatigue outcome and, ii) with good fatigue outcome. The good fatigue outcome subgroup, selected to serve as a basis for comparison, were stratified to match gender, age range, disease duration, and functional status. Through postal survey, validated questionnaires: Short Form McGill pain questionnaire; Pittsburgh Sleep Quality Index; Profile of Mood States, Beck Depression Inventory and Beck Hopelessness Scale; Arthritis Self-Efficacy Scales, were used to capture information on possible contributory factors to persistent post treatment fatigue. Statistical analysis used chi-square test for nominal data (Rheumatoid Factor), parametric independent sample t-test for group means on the normally distributed scale variables, (HAQ-disability index, self-efficacy for pain), and the non-parametric Mann-Whitney *U* test for data which deviated from the normal (two-tailed).

Results: Twenty–eight patients with *Poor Fatigue Outcome*, despite demonstrating a moderate to good improvement in disease status (ERC$>0.6>1.2$) following six months of TNFi therapy, were identified for comparative study with 28 patients with *Good Fatigue Outcome*. The majority (80%) of the patients were female. The poor fatigue outcome subgroup differed significantly from the good fatigue outcome subgroup in the following parameters: RF positive 15 (54%), versus 5 (14%), $\chi^2 = 36.8$; exact $p\leq 0.001$; Ever failed synthetic DMARDS; 18 (64%) versus 24 (86%), $U = 285$; $Z=-2.331$, exact $p = 0.036$; Early morning stiffness duration (range) 0–180 minutes versus 0–30 minutes, $U = 0$ 85; Z –3.14; exact $p = 0.00$, Mean DAS28 ± SD (range), 3.3± 1.1 (1.7–5.8), and 2.4 ± 0.7 (1.2–4.4), $U=0$ 99; Z –3.051; exact p= 0.002, mean ± SD (range). The HAQ-disability index was higher in the poor fatigue outcome group 1.11 ± 0.6 (0–3) versus 0.76 ± 0.5 (1–3), this difference of 0.35 between groups which exceeds the known MCID of 0.22 was not statistically significant (t= 0.18; exact p= 0.07). Patients with *Poor Fatigue Outcome* experienced more pain (p=0.02–0.009), low arthritis self-efficacy for 'other symptoms' (p=0.022), and better sleep quality (p=0.014).

Conclusion: Despite demonstrating a moderate/good disease response patients with *Poor Fatigue Outcome* had a higher DAS28, more pain, less self-efficacy in relation to fatigue, more than symptoms related to pain and functioning; they also reported better sleep quality and lower mood than those with good fatigue outcome.

1204

Pregnancy and the Risk of Rheumatoid Arthritis In a High Risk North American Native Population. Christine A. Peschken[1], David B. Robinson[1], Irene Smolik[1], Carol A. Hitchon[1], Donna M. Hart[2], Charles N. Bernstein[1] and Hani El-Gabalawy[1]. [1]University of Manitoba, Winnipeg, MB, [2]Health Sciences Centre, Winnipeg, MB

Background/Purpose: Previous studies have examined rheumatoid arthritis (RA) risk and pregnancy history, with conflicting results. North American Natives (NAN) have a high birth rate, a high risk of RA, and develop RA at a younger age. We examined reproductive history and RA risk in this highly predisposed population with unique fertility characteristics.

Methods: We examined pregnancy history and RA risk using results from females enrolled in 2 studies: a study of RA in NAN RA patients (n=141) and their unaffected 1st degree relatives (n=197); and NAN RA patients (n=27) and unrelated healthy NAN controls (n=203) enrolled in a study of autoimmunity in NAN populations. All participants were interviewed using identical questionnaires detailing reproductive history. RA patients with onset before menarche were excluded. Only those pregnancies occurring prior to the diagnosis of RA were included. Age was defined as age at RA onset for RA patients, and age at study enrolment for controls.

Results: RA patients (n=168) and controls (n=400) were overall similar in age (37±12 vs. 36±12 years), high school completion (37% vs. 35%), frequency of shared epitope (one or more copies 78% vs. 81%) number of pregnancies (3.7 ±2.6 vs. 3.6± 2.7)and age at first pregnancy (19 ± 4.2 vs. 20 ± 4.1 years). Both groups had similarly high rates of smoking (81% vs. 77%), and low rates of breastfeeding (Duration 0–3 months; 65% vs. 67%). In multivariate analysis, for women who had 6 or more births the OR for developing RA was 0.43(95%CI 0.21–0.87) compared to women with 1–2 births *(p for trend = 0.046);* for women who gave birth for the first time after age 20 the OR for developing RA was 0.33 (95%CI 0.16–0.66) compared to women whose first birth occurred at age 17 or younger *(p for trend=0.001).* Most striking was the high risk of developing RA in the 1st postpartum year (OR 3.8; 95%CI 1.45–9.93) compared to subsequent years *(p for trend =0.004).*

Conclusion: We found a significantly lower risk of RA in multiparous women compared to those with only 1–2 pregnancies; however an early age at first birth strongly increased the risk of RA. In addition, our clinical impression of the postpartum period as very high risk for the development of RA in this population was also confirmed. The explanation for these findings is not known, but may relate to the protective effect of repeated exposure to the ameliorating hormonal levels of multiple pregnancies balanced against the effect of early exposure to postpartum hormonal changes.

1205

A Significant Proporcion of Patients with Palindromic Rheumatism and Positive Anti-Citrulinated Protein Antibodies Do Not evolve to Rheumatoid Arthritis after a Long Term Follow-up. S. Cabrera[1], J. A. Gomez-Puerta[1], M. V. Hernandez[1], V. Ruiz-Esquide[1], Georgina Salvador[2], M.E. Gomez-Caballero[1], J. Ramirez[1], J. D. Cañete[1] and R. Sanmarti[1]. [1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]Hospital Mutua de Terrassa. Barcelona, Barcelona, Spain

Background/Purpose: A significant proportion of patients with palindromic rheumatism (PR) develop rheumatoid arthritis (RA) during follow-up.

Positive anti-citrullinated protein antibodies (ACPA) are frequently found in PR and have been suggested as a biomarker for the development of RA. However, in clinical practice, we have observed some patients with PR and positive ACPA, who do not evolve to chronic rheumatic disease after a long term follow-up.

Objectives: To analyze the long-term clinical evolution of patients diagnosed with pure PR according to the ACPA status at the time of the first serum measurement.

Methods: All patients with a diagnosis of PR according to the criteria of *Guerne et al* seen by our arthritis unit were analyzed; only patients with pure PR, defined as no evidence of associated rheumatic disease at the time of the first serum measurement of ACPA, were included. Some of these patients were analyzed in our previous study which was the first to describe positive ACPA in patients with PR*. Demographic characteristics, duration of PR until serum ACPA measurement and total follow-up time were recorded. ACPA in sera were measured using the CCP1 test until 2002 and the CCP2 test thereafter. All patients were followed until December 2010 in order to evaluate the development of chronic rheumatic disease. In some patients, serial ACPA determinations were made.

Results: We included 71 patients (27 from our original study) with pure PR (52 F/ 19 M) with a mean age at the time of the first ACPA serum measurement of 52.4 ±12.6 years and a duration of symptoms of 53.9 ± 9 months. Serum ACPA were positive in 37 patients (52.1%) with mean serum levels of 704.7 ± 592.5 UI. After a mean follow-up of 90.9 month ± 56.6 (range 1–213), 24 patients (33.8%) evolved to chronic rheumatic or systemic disease: RA 16 patients (22%), SLE 4 p (5.6%), other diseases: 4 p (5.6%) psoriatic arthritis, undifferentiated spondyloarthropathy, autoimmune hepatitis and familial Mediterranean fever. Development of RA during the follow-up was more frequently seen in ACPA positive than in ACPA negative patients, although the difference was not statistically significant, probably due to the small sample size (29.7% vs 14.7% p= 0.109). RA was diagnosed after a mean follow-up of 44.2 m ± 58.3 (44.2 ± 66.4 month in ACPA+ patients and 44.2 ± 41.9 month in ACPA- patients, p >0.05). No evidence of RA or other rheumatic disease was observed in 26 out of the 37 ACPA+ patients (70.3%) during the follow-up. ACPA serum levels of these patients were not significantly different from those of patients who evolved to RA (628.4±547.4 vs 736.9±618.1 p>0.05). Serial ACPA measurements were performed in 57 patients and in only two patients (one of them evolving to RA) a seroconversion from negative ACPA to positive ACPA was observed during the follow-up; the same serological status was demonstrated in the remaining patients

Conclusion: ACPA are frequently found in the sera of PR patients and may be considered as a biomarker for RA in these patients. However, a significant proportion of patients with PR and serum positive ACPA, even those with high titers, do not develop RA after a long term follow-up.

* Salvador et al. Rheumatology (Oxford) 2003; 42:972–75

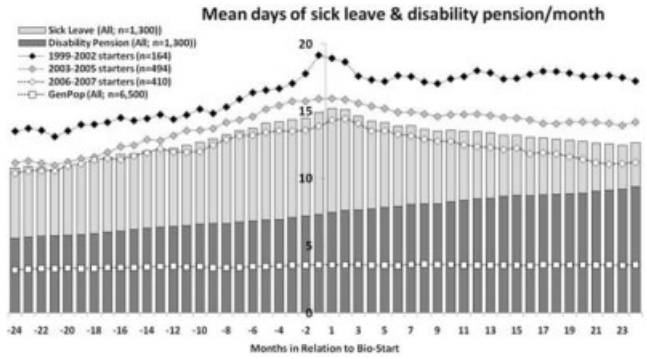
1206

Sick Leave and Disability Pension Before and After Initiation of Biologics in Psoriatic Arthritis Patients: Four-Year Nationwide Cohort Study. Martin Neovius[1], Jonas Eriksson[2], Julia F. Simard[2], Johan Askling[1] and ARTIS Study Group[3]. [1]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Solna, Sweden, [2]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Sweden

Background/Purpose: Productivity losses and biologic drugs are considered the major cost drivers in psoriatic arthritis (PsA), but long-term productivity data from PsA patients treated with biologics remain scarce. The aim of this study was to investigate changes in sick leave and disability pension in relation to start of biologic treatment in PsA patients.

Methods: PsA patients aged 19–60y initiating their first biologic (n=1,300; mean age 45y; 52% men) were identified in the Swedish Biologics Register ARTIS between 1999 and 2008. Five general population comparators per patient were sampled using age, sex, education and start year as matching factors. Sick leave and disability pension data (1997–2010) were retrieved from the Swedish Social Insurance Agency from two years before to two years after the day of biologic treatment start.

Results: Mean monthly days on disability pension increased monotonically from −24 months to +24 months after bio-start (5.6 to 9.4; p<0.001; **Figure**) with 25% and 39% on disability pension at the respective time points. The difference compared to the general population was large and increased from a mean of 3.6 to 6.7 days/month (Δmean 3.1; p<0.001), while the disability pension prevalence ratio increased from 3.5 to 4.0. Mean monthly sick leave days increased from 5.2 at −24 months to 7.7 at bio-start, but then decreased to 3.3 at +24 months. Mean total days of sick leave and disability pension was 14.9 at bio-start, significantly higher than at both −24 and +24 months (10.8 and 12.7 days, respectively; both p<0.001). The medians at −24, bio-start and +24 months were 0, 16 and 8 days/month, respectively. At bio-start the mean difference versus the general population was 11.6 total days/month (compared to 7.6 at −24 and 9.1 at +24 months). The distribution of days of sick leave and disability pension was skewed: 21% of patients accounted for >50% of total days at +24 months. Calendar period differences also existed with higher levels of sick leave and disability pension in the earlier compared to the later bio-start cohorts (Figure).



Conclusion: Mean and median monthly sick leave and disability pension days increased before bio-start. After bio-start, productivity improved but did not fully rebound to the −24 month level and remained significantly elevated compared to the general population. A small number of patients accounted for the bulk of the productivity losses.

ACR/ARHP Poster Session B
Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy II
Monday, November 7, 2011, 9:00 AM–6:00 PM

1207

Treating to Target Matrix Metalloproteinase 3 Normalisation Together with Disease Activity Score Below 2.6 Yields Better Effects Than Each Alone In Rheumatoid Arthritis Patients: Treating to Twin Targets; T-4 Study. Yukitomo Urata[1], Ryoko Uesato[1], Dai Tanaka[1], Yoshihide Nakamura[2] and Shigeru Motomura[2]. [1]Seihoku Chuo Hospital, Gosyogawara, Japan, [2]Hirosaki University Graduate School of Medicine, Hirosaki, Japan

Background/Purpose: To assess whether therapy to achieve both disease activity score in 28 joints (DAS28) <2.6 and matrix metalloproteinase (MMP)-3 normalisation offers better outcomes than either target alone in early rheumatoid arthritis at 56 weeks; Treating to twine targets; T-4 study.

Methods: A total of 243 early RA patients were randomly allocated to one of four strategy groups: routine care (R group; n=62); DAS28-driven therapy (D group; n=60); MMP-3-driven therapy (M group; n=60); or both DAS28- and MMP-3-driven therapy group (Twin; T group; n=61). Specifically, medication was started with sulfasalazine (1 g/day) in all intervention groups. Targets were DAS28 <2.6 for D group, MMP-3 normalisation for M group, and both DAS28 <2.6 and MMP-3 normalisation for T group. If the value in question did not fall below the previously measured level, we intensified medication including methotrexate, other disease-modifying anti-rheumatic drugs and biologic agents. Primary, secondary, tertiary and quaternary outcome measures consisted

of the proportions of patients in clinical remission (DAS28 <2.6), showing radiographic nonprogression (Dmodified total Sharp score ≤0.5), showing normal physical function (modified Health Assessment Questionnaire score=0), and comprehensive disease remission defined as the combination of clinical remission, radiographic nonprogression, and structural normal physical function.

Results: Comprehensive disease remission at 56 weeks was achieved by more patients in T group (34%) than in R group ($p<0.001$), D group ($p<0.05$), or M group ($p<0.001$).

Conclusion: Results of the T-4 study revealed that comprehensive disease remission is an achievable goal in early RA with more aggressive therapy.

1208

Risk of Infections In Rheumatoid Arthritis Patients Treated with Tocilizumab—a Retrospective Data-Analysis. Veronika Lang[1], Matthias Englbrecht[1], Jürgen Rech[1], Bernhard Manger[2], Georg Schett[3] and Jochen Zwerina[4]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Medical School Erlangen, Erlangen, Germany, [3]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [4]University of Erlangen-Nuremberg, Germany, Erlangen, Germany

Background/Purpose: The human anti- interleukin 6 receptor (IL-6R) antibody tocilizumab is approved for the treatment of rheumatoid arthritis (RA) in patients who inadequately respond or are intolerant to therapy with DMARDs or TNF-alpha inhibitors. Infections are the most common adverse event during tocilizumab therapy. Therefore, we investigated the occurrence and risk factors for infections in rheumatoid arthritis (RA) patients treated with tocilizumab in clinical practice.

Methods: A cohort of all RA patients (N = 112) receiving tocilizumab therapy between October 2008 and March 2010 in Northern Bavaria, Germany, was assessed for the incidence of infections. Mild/moderate and severe infections were recorded. Multivariate logistic regression analysis was used to analyze risk factors for infection.

Results: In total, 26 patients developed infections (23.2%, 58.0/100py), 18 of them experienced mild to moderate infections (16.1%, 40.1/100py) and 8 faced severe infections (7.1%, 17.9/100py). One patient died. Concomitant use of leflunomide and prednisone, high disease activity and previous therapy with rituximab were associated with the occurrence of mild/moderate infections. Severe infections were related to age, longer disease duration, exposure to more than 3 previous DMARDs and concomitant therapy with proton pump inhibitors (PPI).

Conclusion: The rate of infection in RA patients treated with tocilizumab in clinical practice is higher compared with the populations in clinical trials. Increased awareness should especially be given to patients with higher age and longer disease duration, those concomitantly using leflunomide, prednisone or PPI as well as those with a previous exposure to rituximab.

1209

Bone Resorption, OsteoClastogenesis and Adalimumab. A Study On the Impact of Anti-Tumor Necrosis Factor Therapy On Osteoclastogenesis In Patients with Rheumatoid Arthritis. Sabrina Guay-Belanger[1] and Arthur J. Fernandes[2]. [1]Universite de Sherbrooke, Sherbrooke, QC, [2]Universite de Sherbrooke, Sherbrooke

Background/Purpose: Osteoclastic bone resorption depends on the capacity to generate osteoclasts (OCs) and on their individual activity. Our objective was to study the effect of anti-TNF therapy on the number of OC precursors in the peripheral blood of patients with RA, on *in vitro* osteoclastogenesis and on OCs activity before and during the treatment of patients with Adalimumab.

Methods: 25 patients with active RA diagnosed according to the ACR criteria and willing to sign an informed consent were recruited from the outpatient clinics at the Centre Hospitalier Universitaire de Sherbrooke. Adalimumab 40 mg sub-cutaneous was administered every two weeks. Primary outcomes were 1) the number of OC precursor (CD14+) cells in the peripheral blood, 2) the number of OCs generated *in vitro, and* 3) the amount of bone resorption *in vitro* before administration of Adalimumab and 3 and 6 months into the treatment. Secondary outcomes were disease *activity* defined as a DAS28 scoreand change in functional status by the M-HAQ. PBMCs were isolated from 50 ml of blood by Ficoll-Hypaque gradient and the number of CD14+ cells was determined by FACS. The whole population of PBMCs was plated in 48-well tissue culture plates and the cells were allowed to differentiate for 21 days in the presence of recombinant RANKL (75 ng/ml) and M-CSF (10 ng/ml). The cells were then stained for TRAP activity. The number of TRAP+ cells containing 3 or more nuclei was counted in each well. For bone resorption assays, cells differentiated for 30 days on bone slices were stained for 0.2% toluidine blue. Resorption surface was quantified using the image analysis program Simple PCI.

Results: Treatment with Adalimumab had no impact on the number of OC precursors in peripheral blood in any of the points studied. For the number of OCs generated *in vitro*, the medians with (25^{th} centile, 75^{th} centile) at first, 3 months and 6 months visits were 220.0 (109.5, 396.5), 201.0 (38.0, 387.0) and 58.0 (19.0, 386.5) OCs/well; these differences were not statistically significant. For the resorption assays, the medians with (25^{th} centile, 75^{th} centile) at first, 3 months and 6 months visits were 21466.0 (0.0, 855844.1), 0.0 (0.0, 411915.0) and 0.0 (0.0, 0.0) μm^2. Although there was a strong trend towards a decrease in the resorption area in visits 3 and 6 months, none of these results reached statistically significant difference when compared to the first visit (p = 0,057). Adalimumab induced a significant decrease in the DAS28 score and in the M-HAQ. For the DAS28 score, the difference between the medians was statistically significant for the first and 3 months visits (p = 0.0008) and for the first and 6 months visits (p = 0.0017). For the M-HAQ, the difference was statistically significant for the first and 6 months visits (p = 0,006).

Conclusion: Treatment with Adalimumab up to 6 months had no statistically significant impact on the number of OC precursors, osteoclastogenesis and resorption *in vitro* even if we can observe a trend toward a decrease in the number of OCs and bone resorption with treatment. For the clinical results, Adalimumab had a statistically significant impact in DAS28 and M-HAQ, decreasing both.

1210

Golimumab's Efficacy in Patients with Very Active Disease in Methotrexate-naïve Rheumatoid Arthritis. Paul Emery[1], R. M. Fleischmann[2], Elizabeth C. Hsia[3], Stephen Xu[4], Weichun Xu[5] and Daniel G. Baker[6]. [1]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [2]University of Texas Southwestern Medical Center and Metroplex Clinical Research Center, Dallas, TX, [3]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA, [4]Centocor R & D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, [5]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, [6]Centocor R & D, a division of Johnson & Johnson Pharmaceutical Research and Development, LLC, Malvern, PA

Background/Purpose: To assess golimumab (GLM) treatment effect in patients with rheumatoid arthritis (RA) naïve to methotrexate (MTX) therapy with severe, active and progressive disease.

Methods: The GO-BEFORE trial studied GLM 50mg and 100mg + MTX in MTX-naïve patients. In the overall GO-BEFORE study population, patients exhibited lower disease activity (baseline ACR components and DAS28) than was observed in previous studies of biologic agents in MTX-naive patients[1]. This is a retrospective analysis of GO-BEFORE wk 52 data which compares efficacy outcomes in subsets of RA patients with severe, active disease to the overall study population. 637 MTX-naïve pts were randomized to PBO+MTX (Grp 1), GLM 100mg+PBO (Grp 2), GLM 50mg+MTX (Grp 3), or GLM 100mg+MTX (Grp 4). GLM/PBO received injections q4wks. Pts with <20% improvement in TJC/SJC at wk28 in Grps 1, 2, and 3 entered early escape to GLM 50mg+MTX, GLM 100mg+MTX, and GLM 100mg+MTX, respectively.(Grp4 had no change). The following baseline disease characteristics were used to define subsets of patients with severe, active, and progressive disease: SJC≥20 and TJC ≥12, EULAR DAS28 CRP >5.1, and CRP ≥3 mg/dL. Treatment effect for each subset and the overall population was defined as the differences between GLM 50mg or 100mg +MTX and MTX-alone in ACR50, DAS28 (CRP) remission, change in HAQ ≥ 0.25 and total vdHS score ≤0. Differences in the treatment effect between each subset of severe, active and progressive RA and the overall population was examined.

Results: Greater proportions of patients achieved the efficacy endpoints in the GLM+MTX groups versus MTX-alone and the difference between the treatment groups (tx effect) was generally larger in the severe, active and progressive subsets compared with the overall population (Table).

Table. Treatment effect between golimumab + MTX and MTX-alone at Wk 52

	Grp 1* MTX Alone N = 160	Grp 3** GLM 50mg + MTX N = 159	Tx effect Grp 3 vs Grp 1	Grp 4 GLM 100mg + MTX N = 159	Tx effect Grp 4 vs Grp 1
ACR50 % (n/N)					
All pts	35.6 (57/160)	42.1 (67/159)	6.5	48.4 (77/159)	12.8
CRP ≥3	29.3 (12/41)	52.4 (22/42)	23.1	48.8 (21/43)	19.5
SJC ≥20 and TJC ≥12	31.4 (11/35)	47.7 (21/44)	16.3	44.2 (19/43)	12.8
DAS28 CRP >5.1	33.9 (37/109)	45.6 (52/114)	11.7	43.6 (48/110)	9.7
EULAR DAS28 CRP remission %(n/N)					
All pts	26.3 (42/160)	35.8 (57/159)	9.5	39.6 (63/159)	13.3
CRP ≥3	14.6 (6/41)	35.7 (15/42)	21.1	30.2 (13/43)	15.6
SJC ≥20 and TJC ≥12	11.4 (4/35)	27.3 (12/44)	15.9	34.9 (15/43)	23.5
DAS28 CRP >5.1	18.3 (20/109)	33.3 (38/114)	15.0	30.9 (34/110)	12.6
HAQ ≥0.25 % (n/N)					
All pts	62.5 (100/160)	65.4 (104/159)	2.9	70.4 (112/159)	7.9
CRP ≥3	78.0 (32/41)	85.7 (36/42)	7.7	86.0 (37/43)	8.0
SJC ≥20 and TJC ≥12	68.6 (24/35)	75.0 (33/44)	6.4	88.4 (38/43)	19.8
DAS28 CRP >5.1	71.6 (78/109)	78.1 (89/114)	6.5	82.7 (91/110)	11.1
X-ray vdHS ≤0 % (n/N)					
All pts	53.9 (76/141)	71.4 (100/140)	17.5	61.2 (85/139)	7.3
CRP ≥3	34.1 (14/41)	64.3 (27/42)	30.2	51.2 (22/43)	17.1
SJC ≥20 and TJC ≥12	34.3 (12/35)	68.2 (30/44)	33.9	65.1 (28/43)	30.8
DAS28 CRP >5.1	52.3 (57/109)	72.8 (83/114)	20.5	60.0 (66/110)	7.7

*Includes pts who early escape at wk28 to GLM 50 mg + MTX; **Includes pts who early escape at wk28 to GLM 100 mg + MTX; For early escape pts, wk28 value carried forward to wk 52; Last observation carried forward for missing data, and treatment failure rules applied.

Conclusion: Overall, treatment effect in the efficacy parameters between GLM 50mg +MTX and GLM 100mg +MTX versus MTX-alone was greater for the severe, active and progressive subsets versus the overall population.

References:

1 Emery et al. *Arthritis&Rheumatism.* 2009; 60(8); 2272–2283

1211

Impact of Rituximab On the Quality of Life and Physical Function of Patients with Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register. Moetaza M. Soliman[1], Kimme L. Hyrich[2], Mark Lunt[2], Kath D. Watson[2], Deborah PM Symmons[2] and Darren M. Ashcroft[1]. [1]School of Pharmacy and Pharmaceutical sciences, University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom

Background/Purpose: Improvements in the quality of life and physical function of rheumatoid arthritis (RA) patients receiving rituximab (RTX) have been shown in clinical trials. This study aimed to assess quality of life and physical function of RA patients six months after receiving RTX in routine clinical practice in the UK, and to identify factors that were associated with improvements in physical function.

Methods: The study included 448 RA patients registered with the British Society for Rheumatology Biologics Register, a national prospective cohort study, who were starting RTX and provided Health Assessment Questionnaire (HAQ) at baseline and six months after starting RTX. Changes in the HAQ scores and European Quality of life 5 Dimensions (EQ5D) ratings were used to evaluate improvements in physical function and quality of life. Multivariate regression models were used to identify factors that were associated with improvements in HAQ scores in patients receiving RTX who had failed at least one anti-tumour necrosis factor therapy. The models examined baseline demographic and disease characteristics, baseline physical function, concomitant drug therapies and previous biologic and non-biologic therapies.

Results: Six months after starting RTX, the mean HAQ, EQ5D utility, and EQ5D visual analogue scores had significantly improved (table 1). Over one third of patients (36%) achieved the minimal clinically important difference (MCID) in HAQ (improvement of 0.22 units at least). The multivariate analysis found that high baseline HAQ score was significantly associated with an improvement in HAQ (table 2). Patients receiving concurrent steroids were significantly less likely to show an improvement in HAQ. Older patients, females, and current smokers were also significantly less likely to show either HAQ improvements or achieving MCID in HAQ.

Table 1. Six months improvements

Outcome	Baseline	Six months
Mean HAQ (95% CI)*	1.96 (1.91, 2.02)	1.84 (1.78 to 1.90)
Mean EQ VAS (95% CI)†	45.6 (43.5, 47.7)	53.0 (51.1 to 54.9)
Mean EQ5D utility score (95% CI)§	0.29 (0.26, 0.32)	0.39 (0.36 to 0.42)

*HAQ range is 0 to 3, †EQ VAS range is 0 to 100, § utility score range is −0.59 to 1.00

Table 2. Significant predictors of HAQ improvements

Baseline factor	Linear Change in HAQ (Coefficient (95% CI))	Achieving MCID in HAQ (Odds ratio (95% CI))
Age (10 years)	0.07 (0.03 to 0.11)*	0.72 (0.55 to 0.93)*
Gender	0.14 (0.04 to 0.25)*	0.47 (0.25 to 0.91) *
Baseline HAQ	−0.13 (−0.20 to −0.06)*	1.49 (0.92 to 2.41)
Concurrent steroids	0.09 (0.01 to 0.18)*	0.63 (0.37 to 1.07)
Current smoking	0.13 (0.02 to 0.24)*	0.45 (0.21 to 0.96)*

*$P < 0.05$

Conclusion: In routine clinical practice, RTX was found to be effective in improving the quality of life and physical function of RA patients. Factors that influenced the degree of improvement in physical function included: baseline disability, smoking, concurrent use of steroids, age, and gender.

1212

Mortality and Cause of Death In Young Rheumatoid Arthritis Patients Treated with Anti-TNF Therapy: Results From the British Society for Rheumatology Biologics Register. Malack Alachkar, Kath D. Watson, Kimme L. Hyrich and Deborah PM Symmons. Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased mortality, with cardiovascular disease (CVD) being the leading cause of mortality and premature death. Any deaths observed in young RA patients are likely premature and possibly related to the underlying RA. In this study, we examined the cause of death in young RA patients aged 50 years or less who were treated with anti-TNF therapy.

Methods: The patients were selected from the British Society for Rheumatology Biologics Register (BSRBR), a UK national prospective cohort study to monitor the long-term safety of biologic therapy. The analysis included subjects with RA aged 50 years or less at registration with the BSRBR. Patients were followed either from the start of anti-TNF (adalimumab, etanercept or infliximab) therapy or from registration into the non-biologic disease modifying antirheumatic drug (nbDMARD) comparison cohort until 10/31/2009 or death, whichever came first. All patients were flagged with the UK national death register who provided copies of death certificates. We used student's t or chi-square (χ^2) tests to compare the baseline demographic characteristics and comorbidites between the two cohorts. Mortality rate per 1000 patient-years of observation (pyrs) with 95% confidence interval (95% CI) was estimated in each group and the two rates were compared. However, it was not possible to do baseline adjustment in the analysis because the numbers of death were too small.

Results: In total, 4883 young RA patients were recruited to this study; 4089 anti-TNF (21380 pyrs) and 794 nbDMARD (3206 pyrs) treated patients. Compared to the nbDMARD treated patients, anti-TNF treated patients were younger at RA onset, had longer RA duration and higher disease activity, and were more likely to be rheumatoid factor (RF) positive and to be receiving steroids (Table). Subjects in the biologic group were more likely to have hypertension (15% vs. 10.5%, p=0.003) but less likely to have chronic obstructive pulmonary disease (1.8% vs. 3.7%, p=0.0009) and a history of asthma (10% vs. 14%, p=0.0017). During the time of observation, 36 patients died in the anti-TNF cohort compared to 3 patients in the nbDMARD cohort (Table).

Table. Patient baseline characteristics, number of deaths and mortality rate.

Number of Patients	nbDMARD cohort n=794	Anti-TNF cohort n=4089
Patient-years of observation	3206*	21380*
Age at onset of RA years, mean (SD)	35.4 (8.9)*	30.7 (9.4)*
Age at registration years, mean (SD)	41.8 (7)	41.2 (7.3)
Disease duration years, mean (SD)	6.7 (6.1)*	15 (8)*
Female%	76%	79%
Steroid use, no (%)	64 (15.8)*	2042 (66.9)*
RF status positive, no (%)	429 (54.2)*	2472 (61.4)*
Baseline DAS28 mean (SD)	5.1 (1.1)*	6.4 (0.8)*
Baseline HAQ mean (SD)	1.5 (0.6)*	2.1 (0.5)*
Number of deaths	3	36
Mortality rate/1000 pyrs (95% CI)	0.94** (0.19–2.7)	1.68** (1.2–2.3)

*p value <0.001, **p value = 0.32 Causes of death in the anti-TNF group were infection (n=11), malignant neoplasms (n=7), CVD (n=6), interstitial lung disease (ILD) (n=4) and other (n=8). The causes of the death in the nbDMARD group were malignant neoplasm (n=1), CVD (n=1) and an intestinal vascular event (n=1).

Conclusion: There was no significant difference in mortality rate in this young cohort between those treated with anti-TNF and nbDMARD therapy. It is possible that the deaths due to infection and ILD may be attributable to the underlying RA or its treatment. RA may also have contributed to the CVD deaths.

1213

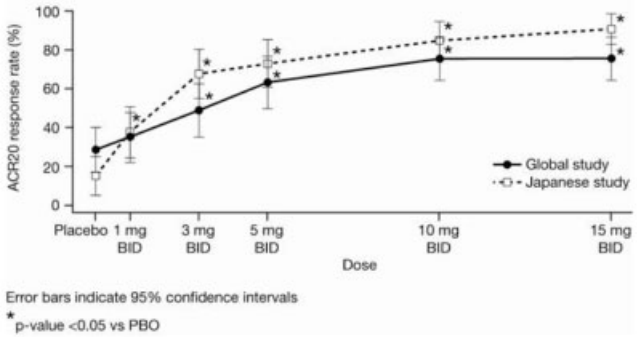
Tofacitinib (CP-690,550), An Oral Janus Kinase Inhibitor, As Monotherapy in Patients with Active Rheumatoid Arthritis: A Comparison Between Japanese and Global Populations Over 12 Weeks of Dosing in Phase 2b Studies. T. Takeuchi[1], Y. Tanaka[2], H. Yamanaka[3], M. Suzuki[4], H. Nakamura[4], K. Yazawa[4], S. Toyoizumi[4], J. D. Bradley[5] and S. H. Zwillich[5]. [1]Keio University School of Medicine, Tokyo, Japan, [2]University of Occupational & Environmental Health, Kitakyushu, Fukuoka, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [4]Pfizer Inc., Tokyo, Japan, [5]Pfizer Inc., Groton, CT

Background/Purpose: To compare the efficacy, safety, and tolerability of tofacitinib monotherapy for the treatment of rheumatoid arthritis (RA) in Japanese (J) and global (G) pts with an inadequate response to DMARDs.

Methods: This was a planned comparison of J and G Phase 2 studies of tofacitinib monotherapy. The J study randomized 318 pts; the G study was conducted outside Japan and randomized 384 pts. Both were randomized, double-blind, placebo (PBO) controlled studies of tofacitinib 1, 3, 5, 10, and 15 mg twice daily (BID) enrolling pts with active RA (≥6 tender and swollen joints at baseline). The G study also included an active comparator arm and ran for 24 weeks (wks) in total. Inclusion and exclusion criteria and primary endpoints (ACR20 response rates at Wk 12) were matched to permit comparison. For the primary endpoint, a pair-wise Chi-Square Test with a 2-sided significance level of 0.05 was used to compare tofacitinib 1, 3, 5, 10, and 15 mg BID with PBO; type 1 error was protected using a step-down procedure in each study.

Results: In both studies the mean ages and durations of RA were similar. In contrast, the range of mean body weight was lower for J (52.9 to 57.4 kg) than G pts (65.7 to 75.7 kg). There were differences in baseline (pre-treatment) number of tender joints (J: 13.6–18.6 vs G: 24.1–27.1) but there was no major difference in DAS28-4(ESR) (J: 5.87–6.42 vs G: 6.30–6.57).

ACR20, ACR50, and AC70 response rates were dose-dependent in both studies and the dose response was similar across studies, although absolute response rates were higher in Japan (Figure).



The incidence of adverse events (AEs) was 44.2% (PBO), 55.5% (5 mg BID), 60.4% (10 mg BID), and 51.9% (15 mg BID) in the J study and 40.7% (PBO), 49.0% (5 mg BID), 50.8% (10 mg BID), and 52.6% (15 mg BID) in the G study. Categories of AEs occurring at an incidence of ≥10% were gastrointestinal disorders, infections and infestations, investigations, metabolism and nutritional disorders, nervous system disorders, skin and subcutaneous tissue disorders; the incidence rates of AEs were similar between the studies. Serious AEs were infrequent and had no apparent relationship to tofacitinib dose (Table).

Table. Summary of safety at 12 wk in the J and G studies

	NCT00687193 (J study) Tofacitinib						NCT00550446 (G study) Tofacitinib					
	1 mg BID N=53	3 mg BID N=53	5 mg BID N=52	10 mg BID N=53	15 mg BID N=54	PBO N = 52	1 mg BID N=54	3 mg BID N=51	5 mg BID N=49	10 mg BID N=61	15 mg BID N=57	PBO N = 59
Incidence of AEs (%)	21 (39.6)	23 (43.4)	29 (55.8)	32 (60.4)	28 (51.9)	23 (44.2)	19 (35.2)	19 (37.3)	24 (49.0)	31 (50.8)	30 (52.6)	24 (40.7)
Incidence of SAEs (%)	0	3 (5.7)	2 (3.8)	2 (3.8)	1 (1.9)	1 (1.9)	0	1 (2.0)	0	0	1 (1.8)	1 (1.7)
Incidence of severe AEs (%)	0	2 (3.8)	1 (1.9)	1 (1.9)	0	0	0	1 (2.0)	0	0	2 (3.5)	1 (1.7)
Incidence of discontinuation due to AEs (%)	0	1 (1.9)	2 (3.8)	3 (5.7)	0	2 (3.8)	2 (3.7)	2 (3.9)	0	1 (1.6)	2 (3.5)	1 (1.7)
Incidence of temporary discontinuation due to AEs (%)	1 (1.9)	3 (5.7)	2 (3.8)	2 (3.8)	4 (7.4)	3 (5.8)	1 (1.9)	2 (3.9)	1 (2.0)	2 (3.3)	3 (5.3)	0
Neutrophil ($\times 10^2/\mu L$)	0.06	−0.98	−1.44	−2.10	−1.66	0.47	0.04	−0.69	−1.00	−1.49	−1.59	−0.74
Serum creatinine (mg/dL)	0.01	0.02	0.04	0.05	0.06	−0.01	0.02	0.01	0.03	0.04	0.05	−0.01
HDL (mg/dL)	5.04	10.81	17.73	21.94	21.11	−0.94	4.06	5.86	7.98	9.7	9.12	0.84
LDL (mg/dL)	3.21	11.77	16.43	21.45	24.69	−0.24	4.28	12.27	16.78	24.64	28.3	−2.91

HDL, high density lipoprotein; LDL, low density lipoprotein

Dose-dependent decreases in neutrophil counts, dose-dependent increases in total, high and low density lipoprotein cholesterol and small increases in serum creatinine were observed in both studies (Table). Overall, the safety profiles in the two studies were similar.

Conclusion: The efficacy dose-response and safety of tofacitinib monotherapy at 12 wks was similar in J and G pts.

1214

Early Aggressive Intervention for Rheumatoid Arthritis Increases Rate of Remission Defined Using a Boolean Approach in Clinical Practice with Tocilizumab. Toshihisa Kojima[1], Atsushi Kaneko[2], Yuji Hirano[3], Hisato Ishikawa[4], Yuichiro Yabe[5], Hideki Takagi[6], Masatoshi Hayashi[1], Koji Funahashi[1], Daizo Kato[1], Hiroyuki Matsubara[7], Naoki Ishiguro[8] and TBCR Study Group[7]. [1]Nagoya Univeristy, School of Medicine, Nagoya, Japan, [2]Nagoya Medical Center, Nagoya, Japan, [3]Toyohashi Municipal Hospital, Toyohashi, Japan, [4]Nagano Red Cross Hospital, Nagano, Japan, [5]Tokyo Kosei Hospital, Tokyo, Japan, [6]Nagoya Kyoritsu Hospital, Nagoya, Japan, [7]Nagoya, Japan, [8]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan

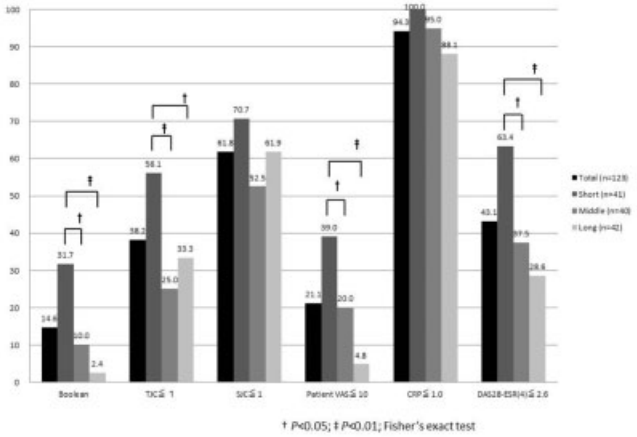
Background/Purpose: The goal of treating rheumatoid arthritis(RA) should be remission, for which a new definition was proposed in 2011. The efficacy of Tocilizumab for RA, a humanized monoclonal antibody that binds to and inhibits the interleukin-6 (IL-6) receptor, was demonstrated in several clinical trials, and its effectiveness in clinical practice is currently under investigation. To determine which patients can achieve the new Boolean-based definition of remission in clinical practice, we analysed factors associated with remission in 123 patients who received tocilizumab for 52 weeks.

Methods: All RA patients (n=134) who underwent tocilizumab treatment between May 2008 and September 2009 at Nagoya University Hospital and 12 other institutes (Tsurumai Biologics Communication Study Group) were enrolled in this study. Demographic data at the initiation of treatment (baseline) and the following parameters of disease activity (tender joint count (TJC) on 28 joints, swollen joint count (SJC) on 28 joints, patient global assessment of disease activity, erythrocyte sedimentation rate (ESR), and serum CRP levels) at baseline and 52 weeks later. We evaluated remission at 52 weeks using the 2011 definition of remission developed for use in RA clinical trials (Boolean approach). We analysed differences of baseline characteristics with disease duration and factors to determine those associated with remission using logistic regression analysis.

Results: Mean (SD) of age, disease duration and DAS28-ESR were 57 (13) years old, 10.5 (8.5) years and 5.8 (1.4). 52% of the patients had history of previous TNF-failure.

We found that patients with short disease duration (<4.8 years) had a significantly higher rate of remission (31.7%) than those with longer disease duration, and patient global assessment was the most important factor for achieving remission (Fig.1). Multivariate analysis revealed the following predictors of remission: short disease duration (<4.8 years; odds ratio [OR] 2.5, 95% confidence interval [CI] 1.4–4.7) and lower disease activity (DAS28-ESR<5.23; OR 2.5, 95% CI 1.2–5.1).

Figure 1 Boolean core measure set of patients categorized by disease duration at 52 weeks.



† $P<0.05$; ‡ $P<0.01$; Fisher's exact test

Conclusion: In this study, we showed that remission, as newly defined using a Boolean approach, is a realistic goal for patients with short disease duration in real-world clinical practice with tocilizumab.

1215

Tofacitinib (CP-690,550), An Oral Janus Kinase Inhibitor, As Monotherapy or with Background Methotrexate in Japanese Patients with Rheumatoid Arthritis: A Phase 2/3 Long-Term Extension Study.

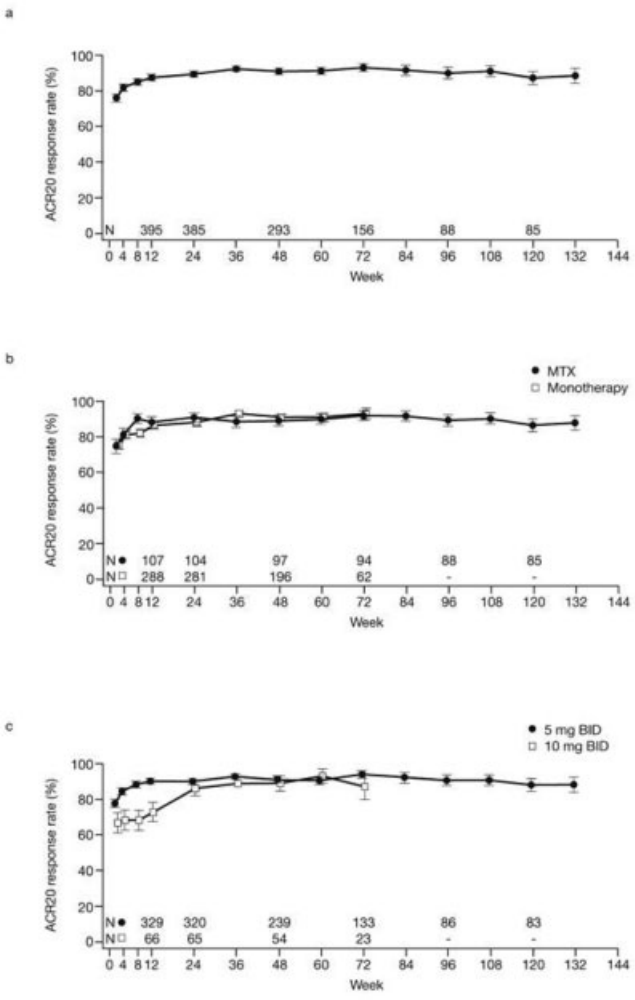
H. Yamanaka[1], Y. Tanaka[2], T. Takeuchi[3], M. Suzuki[4], H. Nakamura[4], Y. Komuro[4], S. Toyoizumi[4], J. D. Bradley[5] and S. H. Zwillich[5]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]University of Occupational & Environmental Health, Kitakyushu, Fukuoka, Japan, [3]Keio University School of Medicine, Tokyo, Japan, [4]Pfizer Inc., Tokyo, Japan, [5]Pfizer Inc., Groton, CT

Background/Purpose: Tofacitinib has previously shown efficacy and a manageable safety profile in 12-week (wk) randomized Phase 2 (P2) studies for the treatment of rheumatoid arthritis (RA) in Japan. Here we compare the safety and efficacy of tofacitinib in a long-term extension (LTE) study for Japanese pts with RA who received tofacitinib either as monotherapy or with background methotrexate (bkMTX).

Methods: This LTE study (NCT00661661) recruited pts completing P2 studies of tofacitinib either as monotherapy (NCT00687193) or with bkMTX (NCT00603512). LTE pts received tofacitinib 5 mg twice daily (BID) and could change or stop background DMARDs including MTX; inadequate responders could increase to tofacitinib 10 mg BID. For the purposes of this analysis pt groups were defined as follows: pts entering LTE on bk'MTX' (N=113) or 'monotherapy' (N=291); pts receiving tofacitinib '10 mg BID' for >12 wks (N=66), or all others, i.e. receiving tofacitinib '5 mg BID' (N=338).

Results: Results are presented for 404 pts whose tofacitinib exposure ranged from 8 months (mo) through 3 years (y). Efficacy was maintained over the long term in all pts (Figure 1a). Treatment with tofacitinib monotherapy for 1–2 y and with bkMTX for 2–3 y provided similar long-term efficacy. In both populations, the ACR20 response rate was maintained (Figure 1b). In total, 16% (66/404) pts received tofacitinib 10 mg BID for at least 12 wks. An increase in ACR20 response rate was apparent in those pts (Figure 1c).

Figure 1. Maintenance of efficacy (ACR20 +/-SE) during long-term treatment: a) all pts; b) monotherapy and MTX pts; c) tofacitinib 5 and 10 mg BID pts



There was no relationship between length of participation in the study and incidence of adverse events (AEs). Rates of discontinuation (DC) for AEs, DC for serious AEs (SAEs) and DC for serious infections (SIEs) also appeared stable over time (Table).

Table. Summary of safety during each time period in the Japanese LTE study

	Time (mo)				
	0 ≈ 6 N=404	7 ≈ 12 N=373	13 ≈ 18 N=224	19 ≈ 24 N=92	25 ≈ N=86
Incidence of AEs, n (%)	336 (83.2)	222 (59.5)	89 (39.7)	63 (68.5)	55 (64.0)
Incidence of DC due to AEs, n (%)	24 (5.9)	13 (3.5)	8 (3.6)	1 (1.1)	4 (4.7)
Incidence of DC due to SAEs, n (%)	10 (2.5)	14 (3.8)	5 (2.2)	3 (3.3)	1 (1.2)
Incidence of DC due to SIEs, n (%)	4 (1.0)	8 (2.1)	2 (0.9)	1 (1.1)	1 (1.2)

The most common AEs were infections such as nasopharyngitis (42.8%) and herpes zoster (9.9%). The most common AEs leading to DC were herpes zoster (1.5%), pneumonia (1.0%), and elevations in aspartate aminotransferase (0.5%) and alanine aminotransferase (1.0%) for which the protocol defined 3-fold elevation over the normal range as mandating treatment DC. SIEs were the category of SAEs most frequently leading to DC; the most common SIE was herpes zoster (1.5%).

Conclusion: Tofacitinib demonstrated sustained efficacy in the treatment of Japanese pts with RA when administered as monotherapy for 1–2 y or with bkMTX for 2–3 y. ACR response rates were similar in pts receiving tofacitinib as monotherapy or with bkMTX. The safety profile of tofacitinib, with or without bkMTX, was generally tolerable and consistent with that from P2 studies.

1216

Baseline Predictors of Remission with Combination Etanercept-Methotrexate Therapy in Moderately Active Rheumatoid Arthritis: Interim Results of the PRESERVE Trial. Josef Smolen[1], Annette Szumski[2], Lisa Marshall[2] and Andrew S. Koenig[2]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]Pfizer Inc., Collegeville, PA

Background/Purpose: Clinical remission is the aim of rheumatoid arthritis (RA) treatment [1] and baseline disease characteristics that predict an increased likelihood of reaching remission are of interest to clinicians. Patients with moderately active RA make up the majority of patients in the clinic [2] and achieve far better outcomes than patients with severe disease [3] but receive far less attention in clinical trials. The objective of this study was to analyze baseline characteristics that may predict remission in patients with moderately active RA (disease activity score in 28 joints [DAS28] >3.2 and ≤5.1) treated with combination etanercept (ETN) 50 mg once weekly (QW) + methotrexate (MTX) at Week 36 (Period 1) of the PRESERVE trial [4].

Methods: Patients with DAS28 >3.2 and ≤5.1, despite stable doses of oral MTX for ≥8 weeks, received open-label ETN 50 mg QW + MTX for 36 weeks. Remission was defined as DAS28 <2.6, simplified disease activity index (SDAI) ≤3.3, and clinical disease activity index (CDAI) ≤2.8. Predictors of remission were analyzed using logistic models and adjusted for geographic region and baseline DAS28, SDAI, or CDAI. Statistical tests were not adjusted for multiplicity.

Results: At Week 36, 67%, 25%, and 27% of patients achieved DAS28, SDAI, and CDAI remission, respectively. Younger age of patient (≤40 vs. >40) and lower health assessment questionnaire (HAQ) score (≤0.5 vs. >1.5) at baseline were significantly more predictive of SDAI, CDAI, and DAS28 remission (P<0.05 for all, Table). A lower HAQ score of ≤0.5 vs. 1.0–1.5 was predictive of CDAI and DAS28 remission (P<0.05 for both) and male gender was significantly predictive of SDAI and DAS28 remission (P<0.05 for both). Levels of rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) levels at baseline were not predictive of remission response at Week 36 (P>0.10). Results for the continuous versions of these baseline predictors support the dichotomous results presented here. The only continuous baseline characteristic from DAS28, CDAI, and SDAI that was significantly predictive of all 3 remission measurement tools, after adjusting for baseline measurements, was DAS28 (P<0.05). However, baseline CDAI and SDAI were significantly predictive of CDAI and SDAI remission, respectively (P<0.05 for both).

Table. Baseline predictors of Week 36 remission in patients with moderately active RA

		DAS28 <2.6		SDAI ≤3.3		CDAI ≤2.8	
Baseline characteristic	N* (categ.1, categ.2)	Adjusted odds ratio (95% CI)†	P-value†	Adjusted odds ratio (95% CI)†	P-value†	Adjusted odds ratio (95% CI)†	P-value†
Age (>40 vs. ≤40)	563, 200	0.6 (0.4, 0.9)	0.011	0.6 (0.4, 0.9)	0.014	0.6 (0.4, 0.9)	0.010
Anti-CCP (>3x ULN vs. ≤3x ULN)	550, 208	1.3 (0.9, 1.8)	0.173	0.8 (0.5, 1.2)	0.218	0.8 (0.6, 1.2)	0.336
Anti-CCP (POS vs. NEG)	590, 166	1.3 (0.9, 1.9)	0.183	0.8 (0.5, 1.2)	0.243	0.8 (0.5, 1.2)	0.264
CRP (>ULN vs. ≤ULN)	279, 482	0.9 (0.7, 1.3)	0.739	0.9 (0.6, 1.2)	0.396	0.9 (0.7, 1.3)	0.727
Disease duration (6–12 vs. <=6 months)	90, 33	0.5 (0.2, 1.3)	0.174	1.0 (0.4, 2.7)	0.999	0.9 (0.3, 2.3)	0.775
Disease duration (12–24 vs <=6 months)	86, 33	0.8 (0.3, 2.1)	0.696	1.0 (0.1, 2.9)	0.941	0.9 (0.3, 2.5)	0.877
Disease duration >24 vs. <=6 months)	552, 33	0.9 (0.4, 2.0)	0.7954	0.9 (0.4, 2.1)	0.817	0.8 (0.4, 1.9)	0.692
ESR (>ULN vs. <=ULN)	300, 463	0.9 (0.7, 1.3)	0.601	1.2 (0.8, 1.7)	0.367	1.1 (0.8, 1.6)	0.486
Gender (M vs. F)	132, 631	1.7 (1.1, 2.7)	0.016	1.6 (1.0, 2.5)	0.046	1.5 (0.9, 2.3)	0.085
HAQ (0.5–1.0 vs. <=0.5)	215, 136	0.6 (0.4, 1.1)	0.082	0.9 (0.6, 1.6)	0.832	0.8 (0.5, 1.4)	0.481
HAQ (1.0–1.5 vs. <=0.5)	233, 136	0.5 (0.3, 0.8)	0.005	0.6 (0.4, 1.1)	0.080	0.6 (0.4, 1.0)	0.040
HAQ (>1.5 vs. <=0.5)	174, 136	0.4 (0.2, 0.7)	0.001	0.5 (0.3, 0.9)	0.026	0.5 (0.3, 0.9)	0.019
Prior or current smoker (Y vs. N)	141, 622	0.9 (0.6, 1.3)	0.530	1.0 (0.6, 1.5)	0.955	1.0 (0.7, 1.6)	0.916
RF (> vs. <=median of 52)	385, 374	0.9 (0.6, 1.2)	0.442	1.0 (0.7, 1.5)	0.822	1.1 (0.8, 1.5)	0.750
RF (>3x ULN vs. <=3x ULN)	440, 319	0.9 (0.6, 1.2)	0.401	1.1 (0.8, 1.5)	0.642	1.1 (0.8, 1.5)	0.667
RF (POS vs. NEG)	552, 207	1.1 (0.8, 1.5)	0.705	1.2 (0.8, 1.7)	0.458	1.1 (0.8, 1.6)	0.605

* N values are based on DAS28 endpoints, the N values for SDAI and CDAI were similar. †Statistics from logistic regression model of Week 36 DAS2/SDAI/CDAI remission with baseline predictor, baseline DAS28/SDAI/CDAI and geographic region. Categ=category; CRP=C-reactive protein; ULN=upper limit of normal; M=male; F=female; ESR=erythrocyte sedimentation rate; Y=yes; N=no; POS=positive; NEG=negative.

Conclusions: Younger age, lower HAQ and lower DAS28 at baseline may be significantly predictive of SDAI, CDAI, and DAS28 remission in patients with moderately active RA on combined ETN-MTX therapy. Baseline RF and anti-CCP levels were not predictive of remission. These data may help clinicians manage patients according to the current treatment guidelines and more effectively treat patients to remission.

References:

1. Smolen JS, et al. *Ann Rheum Dis* 2010;69:631.**2.** Pincus T, et al. *Arthritis Rheum* 2005;52:1009.**3.** Mader R, et al. *J Rheumatol Suppl* 2007;80:16.**4.** Smolen J, et al. Presented at *Excellence in Rheumatology*, 2011, Istanbul, Turkey.

1217

Is Long-Term Etanercept Monotherapy Ever An Option in a Patient with Moderate to Severe Rheumatoid Arthritis (RA)? Roy M. Fleischmann[1], Michael H. Schiff[2], Deborah Wenkert[3], Bojena Bitman[4], Sandeep Chaudhari[5], Jie Liu[6], Grace S. Park[7] and Debra J. Zack[8]. [1]University of Texas Southwestern Medical Center and Metroplex Clinical Research Center, Dallas, TX, [2]Rheumatology Division, University of Colorado, Denver, CO, [3]Amgen, Thousand Oaks, CA, [4]Amgen Inc., South San Francisco, CA, [5]KForce Clinical Research, Tampa, FL, [6]SimulStat Incorporated, San Diego, CA, [7]Amgen Inc., Thousand Oaks, CA, [8]Amgen Inc, Thousand Oaks, CA

Background/Purpose: Methotrexate is recommended as first-line therapy in patients with early RA. An improvement in efficacy has been demonstrated for all currently available tumor necrosis factor (TNF) inhibitors when used in combination with methotrexate. For the TNF inhibitors infliximab and adalimumab, methotrexate not only increases the response rate to the agent, but also appears to play a role in its continued efficacy by suppressing the formation of anti-drug antibodies. There are patients, however, for whom methotrexate is not an option. Since neutralizing anti-drug antibodies have not been seen with etanercept treatment, we examined long-term efficacy data in patients with moderate to severe early RA on the subset of patients who chose to remain on etanercept monotherapy.

Methods: We analyzed data from the Early Rheumatoid Arthritis (ERA) clinical trial of etanercept and up to 9 years of its subsequent long-term open-label extension. In the ERA study, patients were randomized to receive etanercept 10 mg or 25 mg twice weekly (BID) or methotrexate; after 1 year, patients continued on treatment unblinded. The current analysis examined patients who received and continued on etanercept 25 mg BID. Outcome measures included rates of remission and low disease activity based on disease activity scores using the 28-jount count with C-reactive protein as the indicator of inflammation (DAS28) and Simple Disease Activity Index (SDAI) scores, and Health Assessment Questionnaire Disability Index (HAQ-DI) scores.

Results: Of 114 patients receiving etanercept monotherapy, 61 patients had chosen to continue etanercept monotherapy through year 9. No discernable baseline characteristics (age, sex, race, rheumatoid factor status, disease severity) distinguished the 61 patients for whom 9-year data regarding etanercept monotherapy was available from the 114 patients originally placed on etanercept monotherapy. Low disease activity was achieved by 1 year in 64.9% and 62.5% of patients by DAS28 and SDAI, respectively, with 45.6% and 14.3% in DAS28 and SDAI remission. At year 9, 67.3% and 61.8% had low disease activity by DAS28 and SDAI with 54.5% and 32.7% in remission, respectively. Although SDAI scores varied widely from visit to visit for individual patients, most patients in SDAI remission at year 9 had been in SDAI low disease activity or better at each time point starting from year 1 or 2. HAQ-DI scores improved from mean (standard deviation [SD]) score of 1.41 (0.70) at baseline to 0.65 (0.74) at 6 months. HAQ-DI scores had improved to scores associated with the general population (score ≤ 0.5) in 54.1% of patients at year 1 and in 55.7% of patients at year 9.

Conclusion: Although combination therapy is the treatment of choice, some patients with moderate to severe RA can derive persistent, significant clinical benefit for at least 9 years from etanercept monotherapy.

1218

Efficacy and Safety of Certolizumab Pegol Plus Methotrexate in Japanese Rheumatoid Arthritis Patients with An Inadequate Response to Methotrexate. Kazuhiko Yamamoto[1], Tsutomu Takeuchi[2], Hisashi Yamanaka[3], Naoki Ishiguro[4], Yoshiya Tanaka[5], Katsumi Eguchi[6], Akira Watanabe[7], Hideki Origasa[8], Toshiharu Shoji[9], Yoshiharu Sakamaki[10], Nobuyuki Miyasaka[11] and Takao Koike[12]. [1]Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan, [2]Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan, [4]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan, [5]University of Occupational & Environmental Health, Kitakyushu, Fukuoka, Japan, [6]Sasebo City General Hospital, Sasebo, Nagasaki, Japan, [7]Institute of Development, Aging and Cancer, Tohoku University, Sendai, Miyagi, Japan, [8]University of Toyama School of Medicine, Toyama, Toyama, Japan, [9]Otsuka Pharmaceutical Co., Ltd, Shinagawa-ku, Tokyo, Japan, [10]UCB Inc, Chiyoda, Tokyo, Japan, [11]Graduate School of Medicine and Dentistry, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan, [12]Sapporo Medical Center NTT EC, Sapporo, Japan

Background/Purpose: Certolizumab pegol (CZP) as add-on therapy to methotrexate (MTX) provided rapid and sustained efficacy in RA patients (pts) in multiple international clinical trials.[1,2] The objective of

this study was to investigate the efficacy and safety of CZP + MTX in Japanese pts with active RA and an inadequate response to MTX.

Methods: In this 24-week (wk), Phase II/III, multicenter, double-blind, randomized, placebo-controlled, study (NCT00791999), Japanese pts with active RA and an inadequate response to MTX were randomized (1:1:1:1) to 1 of 4 treatment groups: CZP 100, 200, or 400 mg or placebo (PBO) + MTX every 2 wks (Q2W). Per study design, pts in the CZP groups received induction dosing with 200 mg (100 mg group) or 400 mg (200 and 400 mg groups) at Wks 0, 2, and 4. Pts who did not achieve an ACR20 response at Wks 12 and 14 were withdrawn from the study at Wk 16 and were eligible to enter an open-label extension study, as were pts completing the study. Primary efficacy end point was ACR20 response at Wk 12.

Results: A total of 316 pts were randomized. Demographic and baseline (BL) characteristics were similar between treatment groups: RA disease duration ranged from 5.6 to 6.0 years, DAS28(ESR) from 6.19 to 6.46, HAQ-DI from 1.12 to 1.19, and MTX dose from 7.4 to 7.6 mg/wk across groups. The primary end point was met; ACR20 and ACR50 response rates were significantly higher in each CZP group compared with PBO at Wks 12 and 24 (Table). Differences in CZP ACR20 response rates vs PBO were significant as early as Wk 1 and sustained to Wk 24. At Wk 24, mean radiographic progression from BL was reduced, and more pts were mTSS non-progressors in the CZP-treated groups vs PBO; differences seen with the 100 mg Q2W dose were not significant vs PBO. Improvements in all ACR core set of disease activity measures, including physical function, were observed as early as Wk 1 and were sustained to Wk 24 at all CZP doses. CZP was well tolerated and no new safety signals were identified. SAEs ranged from 4.2% to 5.9% in the CZP groups (with 4 pts developing serious infections or infestations) vs 1.3% in the PBO group. There were no cases of TB or deaths.

Table. Efficacy of CZP + MTX at Wks 12 and 24 in Japanese RA pts

	CZP 100 mg n=72	CZP 200 mg n=82	CZP 400 mg n=85	PBO n=77
Wk 12				
ACR20,% responders[a]	62.5*	76.8*	77.6*	28.6
ACR50,% responders[a]	34.7*	41.5*	51.8*	7.8
ACR70,% responders[a]	13.9	20.7	25.9	0.0[c]
DAS28(ESR), LS mean change from BL (SE)[b]	−1.89 (0.14)*	−2.23 (0.13)*	−2.33 (0.13)*	−0.56 (0.13)
HAQ-DI, LS mean change from BL (SE)[b]	−0.42 (0.05)*	−0.47 (0.05)*	−0.51 (0.05)*	−0.16 (0.05)
Pain VAS, LS mean change from BL (0–100 mm) (SE)[b]	−23.8 (2.5)*	−25.6 (2.3)*	−28.7 (2.3)*	−8.9 (2.4)
DAS28(ESR) remission rate[b],%	8.3	16.0	11.8	0.0[c]
Moderate or good EULAR response[b],%	76.4	86.4	90.6	36.4[c]
Wk 24				
ACR20,% responders[a]	61.1*	73.2*	71.8*	24.7
ACR50,% responders[a]	44.4*	54.9*	54.1*	16.9
ACR70,% responders[a]	26.4*	29.3*	30.6*	1.3
DAS28(ESR), LS mean change from BL (SE)[b]	−2.11 (0.16)*	−2.46 (0.15)*	−2.69 (0.14)*	−0.63 (0.15)
HAQ-DI, LS mean change from BL (SE)[b]	−0.43 (0.06)**	−0.55 (0.05)**	−0.57 (0.05)**	−0.18 (0.06)
Pain VAS, LS mean change from DL (0–100 mm) (SE)[b]	−26.9 (2.6)*	−27.9 (2.5)*	−31.9 (2.4)*	−10.6 (2.6)
DAS28(ESR) remission rate[b],%	20.8	17.1	25.9	0.0[c]
Moderate or good EULAR response[b],%	77.8	85.4	89.4	29.9[c]
mTSS, LS mean change from BL (SE)[d,e]	1.04 (0.41)[g]	0.21 (0.38)**	0.65 (0.37)**	2.78 (0.39)
mTSS,% non-progressors[d,e,f]	62.9[g]	74.1**	70.2**	47.4

[a] NRI. [b]LOCF. [c]p Value not calculated. [d]The actual number of subjects in the summaries varies slightly from n=316 due to nonimputable missing data for each parameter. [e]Lin ext. [f]mTSS non-progressor: mTSS change from BL score at WK 24 <0.5. [g]Not significant compared with PBO. LS = least square.
* p<0.001, **p<0.01 each CZP group vs PBO. ACR response, DAS28(ESR) remission rate, mTSS non-progressors and EULAR response was assessed by logistic regression. DAS28(ESR), HAQ-DI, pain VAS and mTSS LS mean change from BL were assessed by analysis of covariance (ANCOVA).

Conclusion: Treatment with CZP + MTX resulted in a rapid and sustained reduction in RA signs and symptoms, inhibited progression of structural joint damage, and improved physical function in Japanese RA pts with an inadequate response to MTX. The 200 mg Q2W maintenance dose showed numerically greater clinical efficacy and better inhibition of radiographic progression compared with the 100 mg Q2W dose. No additional benefit was observed with the 400 mg Q2W dose vs the 200 mg Q2W dose. These results confirm the findings of the RAPID studies[1, 2] and substantiate 200 mg Q2W as the optimal maintenance dosing for CZP.

References

1. Keystone E, et al. Arthritis Rheum 2008;58:3319–3329.
2. Smolen J, et al. Ann Rheum Dis 2009;68:797–804.

1219

Integrated Safety Summary of Modified-Release Prednisone and Immediate-Release Prednisone Comparing Doses ≤5mg/Day Versus >5mg/Day.

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Background/Purpose: Glucocorticoid (GC) chronotherapy with a modified-release (MR) prednisone tablet enables programmed delivery of prednisone during the night to target the circadian pattern of inflammatory mediators. This therapeutic approach has demonstrated both clinically relevant reduction of morning stiffness compared to conventional, immediate-release (IR) prednisone, as well as improvement in ACR response criteria (Buttgereit *et al Lancet* 2008, Buttgereit *et al Ann Rheum Dis* 2010, Alten *et al J Rheumatol* 2010). Adverse effects related to GCs increase with dose and duration of treatment (Da Silva *et al Ann Rheum Dis* 2006). The data here describe the integrated safety summary for low-dose glucocorticoid therapy in patients from two phase 3 clinical studies.

Methods: The CAPRA studies investigated safety and efficacy of MR prednisone in patients with RA, not adequately controlled by disease-modifying antirheumatic drug (DMARD) therapy. The CAPRA-1 study compared MR prednisone (3–10 mg/d, average of 6.8 mg/d) to conventional IR prednisone over 12 weeks in 288 patients, the CAPRA-2 study compared 5 mg/d MR prednisone + DMARD to placebo (PBO) + DMARD over 12 weeks in 350 patients. MR prednisone or PBO was administered once daily in the evening; IR prednisone or PBO once daily in the morning. An open-label extension of CAPRA-1 provided safety data for up to 12 months. All Adverse Events (AEs) were collected in a standardized manner and categorized according to the dose of prednisone received during the study (≤5 mg/d or >5mg/d).

Results: Overall, 41.9% of MR prednisone patients, 39.6% of IR prednisone patients, and 48.7% of PBO patients reported a treatment emergent adverse event (TEAE) during the 12 week blinded period showing comparable safety of the different formulations. In the MR prednisone group, discontinuations due to any TEAE were higher for the >5 mg/d dose, with 9.7% of patients discontinuing compared to 2.2% of patients receiving ≤5 mg/d. In the IR prednisone group, 5.3% of patients receiving ≤5 mg/d discontinued due to any TEAE compared to 4.4% of patients receiving >5 mg/d. The incidence of TEAEs in descending frequency are shown in Table 1. Safety data for the open label phase were consistent and similar (not shown).

		MR Prednisone			IR Prednisone		
	PBO (N=119)	≤5 mg/d (N=313)	>5 mg/d (N=62)	Total (N=375)	≤5 mg/d (N=76)	>5 mg/d (N=68)	Total (N=144)
Mean Daily Dose (mg ± SD)	NA	4.86 ± 0.37	8.45 ± 1.49	5.46 ± 1.50	4.93 ± 0.34	8.59 ± 1.48	6.66 ± 2.11
Any Adverse Event	48.7%	43.1%	35.5%	41.9%	42.1%	36.8%	39.6%
Frequency by Severity							
Mild	29.4%	20.4%	8.1%	18.4%	18.4%	16.2%	17.4%
Moderate	15.1%	20.8%	22.6%	21.1%	19.7%	19.1%	19.4%
Severe	4.2%	1.9%	4.8%	2.4%	3.9%	1.5%	2.8%
Preferred Term							
Rheumatoid arthritis flare	26.1%*	14.4%	4.8%	12.8%	11.8%	7.4%	9.7%
Nasopharyngitis	3.4%	4.8%	1.6%	4.3%	6.6%	4.4%	5.6%
Abdominal pain upper	1.7%	1.6%	1.6%	1.6%	7.9%	2.9%	5.6%
Headache	4.2%	4.5%	1.6%	4.0%	3.9%	2.9%	3.5%
Vertigo	0%	1.3%	0%	1.1%	3.9%	2.9%	3.5%

*p=0.0137 PBO versus MR prednisone; all other comparisons are nonsignificant; NA = not applicable, SD = standard deviation

Conclusion: Safety findings from the 12 week blinded period were similar between MR prednisone and PBO or IR prednisone, demonstrating that the MR formulation does not adversely impact the known safety profile of the active ingredient. MR Prednisone has been shown to be more effective than IR prednisone and PBO with regard to standard RA outcome parameters. Taken together, these data support that MR prednisone may improve the benefit/risk ratio of long-term low-dose GC treatment in patients with RA on standard DMARD therapy.

1220

Efficacy and Safety of Certolizumab Pegol without Methotrexate Co-Administration in Japanese Patients with Active Rheumatoid Arthritis. Kazuhiko Yamamoto[1], Tsutomu Takeuchi[2], Hisashi Yamanaka[3], Naoki Ishiguro[4], Yoshiya Tanaka[5], Katsumi Eguchi[6], Akira Watanabe[7], Hideki Origasa[8], Koichi Iwai[9], Yoshiharu Sakamaki[10], Nobuyuki Miyasaka[11] and Takao Koike[12]. [1]Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [4]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan, [5]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [6]Sasebo City General Hospital, Sasebo, Nagasaki, Japan, [7]Institute of Development, Aging and Cancer, Tohoku University, Sendai, Miyagi, Japan, [8]University of Toyama School of Medicine, Toyama, Toyama, Japan, [9]Otsuka Pharmaceutical Co., Ltd, Shinagawa-ku, Tokyo, Japan, [10]UCB Inc, Chiyoda, Tokyo, Japan, [11]Tokyo Medical and Dental University, Tokyo, Japan, [12]Sapporo Medical Center NTT EC, Sapporo, Japan

Background/Purpose: Certolizumab pegol (CZP) as monotherapy or as add-on to methotrexate (MTX) provided rapid and sustained efficacy in RA patients (pts) in international clinical trials.[1–3] The objective of this study was to investigate efficacy and safety of CZP in Japanese pts with active RA in whom MTX could not be administered.

Methods: In this 24-week (wk), Phase III, double-blind, randomized, placebo-controlled study (NCT00791921), pts were randomized to CZP 200 mg (following induction dosing of 400 mg at Wks 0, 2, and 4) or placebo (PBO) every 2 wks. Pts not achieving ACR20 at Wks 12 and 14 withdrew at Wk 16 and were eligible to enter an open-label extension, as were pts completing the study. Primary efficacy endpoint was ACR20 at Wk 12. ACR20 response rates and radiographic progression were also investigated in subgroups of pts receiving CZP monotherapy or concomitant DMARDs.

Results: Demographic and baseline (BL) characteristics of the 230 randomized pts were similar between CZP and PBO groups: mean RA disease duration 5.4 and 5.8 y, mean HAQ-DI 1.05 and 1.21, mean DAS28(ESR) 6.09 and 6.30, respectively. At BL, 53.4% of CZP pts (vs 57% PBO pts) received concomitant DMARDs and 46.6% received CZP monotherapy. The primary endpoint was met; ACR20 and ACR50 responses were significantly higher in all CZP groups vs PBO at Wks 12 and 24 (Table). Significant differences in ACR20 responses were seen as early as Wk 1 and sustained to Wk 24. At Wk 24, mean radiographic progression from BL was reduced and more pts were mTSS non-progressors in the CZP group (Table). At Wk 12, ACR20 responses were higher in CZP pts either on monotherapy or with concomitant DMARDs, with similar treatment differences of 51.1 points and 54.2 points, respectively (CZP vs PBO: monotherapy, 59.3% vs 8.2%; concomitant DMARDs, 74.2% vs 20.0%). Preliminary post-hoc analyses showed that at Wk 24, CZP significantly inhibited radiographic progression when administered as monotherapy (mTSS mean change from BL: 3.65 PBO vs 0.68 CZP, p=0.0087) or with concomitant DMARDs (mTSS mean change from BL: 1.61 PBO and CZP 0.24, p=0.001). CZP was well tolerated with no new safety signals. 11.2% of CZP pts experienced SAEs vs 2.6% in PBO (with 4 and 1 pts developing serious infections or infestations, respectively). There was 1 death in the CZP group and no cases of TB.

Table. Efficacy of CZP at Wks 12 and 24 in Japanese RA pts

	CZP 200 mg n=116	PBO n=114
Wk 12		
ACR20,% responders[a]	67.2*	14.9
ACR50,% responders[a]	37.9*	6.1
ACR70,% responders[a]	19.0[c]	0.0
DAS28, LS mean change from BL (SE)[b]	−2.01 (0.10)*	−0.29 (0.10)
HAQ-DI, LS mean change from BL (SE)[b]	−0.47 (0.05)*	0.03 (0.05)
Pain VAS, LS mean change from BL (0–100 mm) (SE)[b]	−26.4 (1.9)*	−1.9 (2.0)
DAS28 (ESR) remission rate[b],%	13.8**	0.9
Moderate or good EULAR response[b],%	82.7[c]	28.1
Wk 24		
ACR20,% responders[a]	63.8*	11.4
ACR50,% responders[a]	46.6*	6.1
ACR70,% responders[a]	25.9*	0.9
DAS28, LS mean change from BL (SE)[b]	−2.06 (0.12)*	−0.21 (0.12)
HAQ-DI, LS mean change from BL (SE)[b]	−0.48 (0.05)*	0.12 (0.05)
Pain VAS, LS mean change from BL (0–100 mm) (SE)[b]	−27.5 (2.1)*	−1.2 (2.1)
DAS28(ESR) remission rate[b],%	16.4**	0.9
Moderate or good EULAR response[b],%	77.6[c]	22.0
mTSS, LS mean change from BL (SE)[d,e]	0.48 (0.38)*	2.45 (0.38)
mTSS non-progressors,% responders[d,e,f]	76.3*	45.6

[a] NRI. [b]LOCF. [c]p Value not calculated. [d]The actual number of subjects in the summaries varies slightly from n=316 due to nonimputable missing data for each parameter. [e]Lin ext. [f]mTSS non-progressor: mTSS change from BL score at Wk 24 ≤0.5. LS = least square.
* p<0.001, **p<0.01, CZP vs PBO.
ACR response, DAS28(ESR) remission rate, mTSS non-progressors and EULAR response were assessed by logistic regression. DAS28(ESR), HAQ-DI, Pain VAS, and mTSS LS mean change from BL were assessed by analysis of covariance.

Conclusion: Treatment with CZP in Japanese RA pts in whom MTX could not be administered resulted in rapid and sustained improvement of RAsigns and symptoms, inhibited progression of structural joint damage, and ameliorated physical function. Efficacy and radiographic results were consistent regardless of use of concomitant DMARDs; notably, CZP showed significant inhibition of radiographic progression when used as monotherapy.

References

1. Fleischmann R, et al. Ann Rheum Dis 2009;68:805–811.
2. Keystone E, et al. Arthritis Rheum 2008;58:3319–3329.
3. Smolen J, et al. Ann Rheum Dis 2009;68:797–804.

1221

Dose Escalation Among Rheumatoid Arthritis Patients Treated with Infliximab or Abatacept: Comparison in Claims Data. Theodore Darkow[1], Benjamin Chastek[2], Lisa Rosenblatt[1], Digisha Trivedi[1], Tony Hebden[1], Henry Henk[2] and Fang Liu[2]. [1]Bristol-Myers Squibb, Plainsboro, NJ, [2]Innovus, an Optum Insight Company, Eden Prairie, MN

Background/Purpose: Published studies have documented dose escalation of infliximab in rheumatoid arthritis (RA) patients. We have previously demonstrated that abatacept-treated patients were significantly less likely to experience dose escalation than patients on infliximab[1].

Objectives: To determine whether previous findings of dose escalation with infliximab versus abatacept were reproducible in claims data using a larger sample size and longer follow-up.

Methods: Claims-based analysis of commercial enrollees of a large, US-managed care plan was conducted to examine treatment patterns among adult patients with RA. The identification period was January 1, 2006 through August 31, 2010. Patients newly initiated on infliximab or abatacept who had at least five infusions were included. Patients with evidence of other indications for biologic treatment (e.g. psoriasis) were excluded. Continuous plan enrollment for 6 months before initiation through the fifth infusion was required. Patients were followed until plan disenrollment, treatment termination, or August 31, 2010. Dose escalation was defined as two or more increases in either dose amount or frequency following the third infusion.

Results: A total of 1198 patients initiating infliximab and 799 patients initiating abatacept were identified, with a mean follow-up time of 477 and 275 days, respectively. The average increase in number of infused vials between the first and last infusion was 1.30 for the infliximab cohort and 0.12 for the abatacept cohort (p<0.001). The proportion of infliximab patients who experienced dose escalation during the follow-up period was 70.7%, with 56.6% having an increase in dose amount and 51.9% having an increase in frequency. In contrast, only 11.3% of the abatacept cohortexperienced escalation, with 10.5% having an increase in dose amount and 1.1% having an increase in frequency (p<0.001 for all comparisons). On average, time to first dose escalation did not differ between the two treatment groups (143.4 vs 149.0 days; p=0.68). Risk of escalation remained substantially lower for abatacept patients after controlling for patients' demographic and clinical characteristics in a multivariate survival model (hazard ratio=0.115; p<0.001).

Conclusion: The majority of patients treated with infliximab experienced dose escalation, whereas significantly fewer patients treated with abatacept had evidence of escalation. Furthermore, the escalation in dose seen with abatacept was relatively minor compared with that observed with infliximab and was consistent with previous analyses[1].

1. Darkow T, et al. Comparison of Dose Escalation among Rheumatoid Arthritis Patients Treated with Infliximab or Abatacept. AMCP 2010 Educational Conference, Oct. 13–15, 2010, St. Louis, MO.

1222

The Effectiveness of Abatacept in a Large Rheumatoid Arthritis Real World Practice: Changes in the HAQ Over Time and Durability of Response. Janet E. Pope[1], Emmanouil Rampakakis[2], John S. Sampalis[2] and Olivier Desjardins[3]. [1]St. Joseph's Health Care, University of Western Ontario, London, ON, [2]McGill University & JSS Medical Research, Montreal, QC, [3]Bristol Myers Squibb Canada, St. Laurent, QC

Background/Purpose: A large Canadian database was used to determine effectiveness of abatacept in real world RA patients by examining changes in health assessment questionnaire (HAQ), and the proportion of patients continuing abatacept over time.

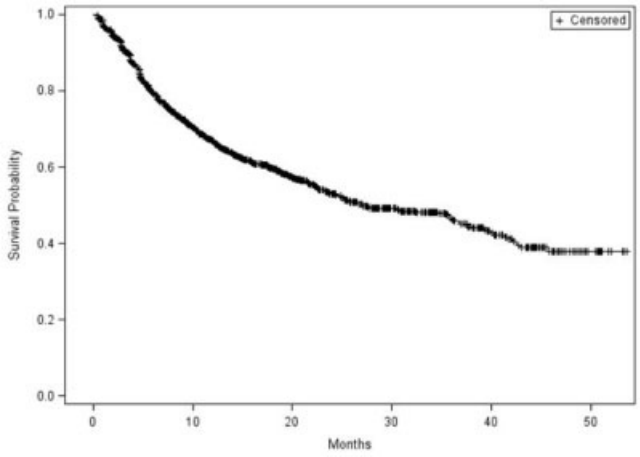
Methods: RA patients administered abatacept in routine practice via the Orencia Response Program network, between Aug. 2006 and Feb. 2011 who

received clinic or home infusions and had at least one follow-up evaluation were included. The number needed to treat (NNT) to improve HAQ by at least the minimally important difference (MID ≥ 0.22) and abatacept survival until last follow up were calculated overall, and for those post DMARD and post TNFi.

Results: Among the 2,929 patients enrolled, 1,771 (60.5%) were eligible for the study (mean age 57.6 years; disease duration 16.5 years (SD 11.0), 77% female, 79.2% had past TNFi) with a mean (SD) follow up of 13.8 (12.3) months. Mean (SE) durability of treatment was 26.8 (0.53) months; where 66% were still on abatacept at 12 and 53% at 24 months (Figure 1). The survival was longer where abatacept was the first biologic vs. post TNFi (P=0.0001) (Figure 1). In abatacept as 1st biologic, 70% achieved MID in HAQ vs. 71% if post TNFi (P=0.65) with NNT=1.4 in each group and there were also no differences in% achieving MID comparing no past biologic to 2, 3 or 4 pervious biologics. For those staying on abatacept, the mean improvement in HAQ increased over time; changing at 6,12, 18 and 24 months by −0.29, −0.41, −0.45 and −0.51 respectively with no difference between abatacept as first biologic vs. post TNFi (Table 1). Increased baseline HAQ (OR 2.13 (1.89, 2.39)) and less years of RA (OR 0.98 (0.97, 0.99)) were significant predictors of achieving the MID for HAQ.

Table 1. Characteristics and Patient Disposition

Parameter		Post DMARD N=369	Post TNFi N=1,402	Total Cohort N=1,771	P-Value	
Mean (SD) Age (years)			58.80 (13.65)	57.28 (13.10)	57.60 (13.23)	0.0496
Mean (SD) Time Since Diagnosis (years)			13.25 (10.83)	17.36 (10.92)	16.53 (11.02)	<0.001
Female Gender: n (%)			260 (70.46)	1,107 (78.96)	1,367 (77.19)	<0.001
Disease Severity: n (%)	Mild		1 (0.27)	4 (0.29)	5 (0.28)	0.736
	Moderate		22 (5.96)	104 (7.42)	126 (7.11)	
	Severe		346 (93.77)	1,291 (92.08)	1,637 (92.43)	
	NA		0 (0.00)	3 (0.21)	3 (0.17)	
Baseline HAQ			1.45 (0.71)	1.72 (0.69)	1.66 (0.70)	<0.001
	12 Months		−0.34 (0.66)	−0.43 (0.67)	−0.41 (0.67)	0.207
	24 Months		−0.48 (0.70)	−0.52 (0.70)	−0.51 (0.70)	0.786
	36 Months		−0.36 (0.69)	−0.60 (0.71)	−0.58 (0.71)	0.297
Mean (SD) Durability of Treatment			26.12 (0.86)	25.75 (0.58)	26.79 (0.53)	<0.001
% on Abatacept (Survival Estimate)	12 Months		74	64	66	
	24 Months		65	50	53	
	36 Months		56	43	46	



Parameter	Value
Total N	1,771
N (%) Failed	672 (37.94)
N (%) Censored	1,099 (62.06)
Mean (SE) Durability of Treatment (months)	26.79 (0.53)

Figure 1. Overall Durability of Abatacept

Conclusion: The results demonstrate that abatacept is effective in improving function in RA despite long disease duration. For those still on abatacept, HAQ continued to improve over the first 2 years. The real world durability of abatacept is better as first biologic; however the overall survival in this large study seems similar to other biologics despite 79% having previous TNFi exposure.

1223

Drug Survival and Long-Term Dose Comparison of Etanercept and Infliximab in Rheumatoid Arthritis Patients. Brian D. Hanna[1] and Alpesh Shah[2]. [1]McMaster University, Ontario, Kitchener, ON, [2]Community Rheumatology Clinic, Etobicoke, ON

Background/Purpose: Reports from observational studies show that anti-TNF drug adherence rates in rheumatoid arthritis are higher for etanercept compared with infliximab. Clinical practice shows that not all rheumatoid arthritis patients respond to the 3 mg/kg dose of infliximab, leading some rheumatologists to use higher doses and/or reduce the dosing interval for infliximab. The purposes of this study are: 1) to compare dosing patterns and drug survival rates of etanercept and infliximab, and 2) to compare the initial dose with the optimal, any escalated and the last dose administered for infliximab in rheumatoid arthritis patients in a community based practice.

Methods: This study is a retrospective analysis of rheumatoid arthritis patients treated between June 2000 and December 2010 at community rheumatology clinic, starting treatment with either infliximab or etanercept, as a first biologic agent. Information was collected on age, sex, diagnosis, disease duration, previous and ongoing DMARDs, biologic dose, treatment start and termination dates as well as cause of withdrawal. Treatment groups were compared by baseline characteristics, dosing patterns and drug survival. The overall drug survival was compared using survival data with Kaplan-Meier plots. An optimal dose for infliximab was identified as the dose raised in mg/kg or a decrease in dosing interval by six months of treatment to achieve adequate response.

Results: A total of 116 patients (etanercept: 79 and infliximab: 37) were included in the analysis. All etanercept-treated patients were maintained with 50 mg per week therapy. Mean optimal dose of infliximab was 4.23 ± 1.29 mg/kg and majority of them given at every 8 week interval. Subsequently, 51.4% patients in the infliximab group required dose escalation to 4.51 ± 1.14 mg/kg. Of these, majority (73.8%) patients required infliximab at every 6 week intervals. Median drug survival time for the etanercept group was 58 months, for the infliximab group at optimal doses was 27 months and for the optimal plus escalated doses was 88 months.

Conclusion: In this study of real-world patients half of the patients in the infliximab group required dose escalation. Drug survival rate was higher with etanercept and the escalated infliximab groups compared with infliximab at initial and optimal doses over ten years of follow-up.

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Remission According to Different Composite Disease Activity Indices in Biologic-naïve Patients with Rheumatoid Arthritis Treated with Abatacept or Infliximab Plus Methotrexate. Josef S. Smolen[1], Maxime Dougados[2], Corine Gaillez[3], Coralie Poncet[4], Manuela Le Bars[3], Monica Mody[5] and Michael H. Schiff[6]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]Hôpital Cochin, Paris, France, [3]Bristol-Myers Squibb, Rueil Malmaison, France, [4]Docs International, Sévres, France, [5]Bristol-Myers Squibb, Princeton, NJ, [6]University of Colorado, Denver, CO

Background/Purpose: Levels of acute phase reactants correlate with clinical disease activity in rheumatoid arthritis (RA)[1], and are weighted differently—or not included—in the calculation of disease activity indices such as SDAI, CDAI and DAS28. Biologics with different mechanisms of action (TNF blockers, anti-IL6 agent, T-cell costimulation modulator) may impact both acute phase reactants and disease activity measures differently[2]. We evaluated remission using the new definition of remission according to ACR/EULAR[3] versus DAS28-defined remission in RA patients (pts) treated with abatacept, infliximab or placebo plus MTX in the ATTEST trial, and investigated the contributions of the different core components.

Methods: In ATTEST, biologic-naïve pts with RA and an inadequate response to MTX were randomized to abatacept (~10 mg/kg every 4 wks), infliximab (3 mg/kg every 8 wks), or placebo (every 4 wks), plus MTX[4]. Remission according to DAS28 (CRP), SDAI and CDAI at Month 6 were evaluated for abatacept- infliximab- and placebo-treated pts, with missing data imputed by LOCF; SDAI and CDAI were evaluated post-hoc. Cut-offs for remission were <2.6 for DAS28; ≤3.3 for SDAI; and ≤2.8 for CDAI. Mean scores (with SD) from baseline at Month 6 in individual disease activity measures were assessed for pts in remission at Month 6.

Results: Baseline demographics and clinical characteristics were comparable between groups[4]. Mean (SD) DAS28, SDAI and CDAI scores, respectively, were 6.4 (0.9), 48.8 (13.2) and 45.7 (12.2) for abatacept, 6.4 (0.9), 48.4 (13.1) and 45.1 (12.3) for infliximab, and 6.3 (0.8), 48.3 (12.0) and 45.6 (11.2) for placebo. At Month 6, similar treatment effects for remission were observed for abatacept and infliximab, independent of indices used (Table). Among abatacept-treated pts in DAS28 remission, 46.7 and 56.7% also achieved SDAI and CDAI remission, respectively, compared with 43.6 and 43.6% of infliximab-treated pts. In patients reaching remission at Month 6, mean scores for core components, including ESR and CRP, were generally similar between the two active treatment arms (Table), although numerically lower SJC were seen with abatacept versus infliximab for patients in DAS28 remission.

	Abatacept, n=156			Infliximab, n=165			Placebo, n=110		
	DAS28	SDAI	CDAI	DAS28	SDAI	CDAI	DAS28	SDAI	CDAI
Remission at Month 6, n (%)*	30 (19.2)	14 (9.0)	18 (11.5)	39 (23.8)	17 (10.4)	20 (12.2)	6 (5.5)	4 (3.6)	5 (4.5)
95% CI	13.0–25.4	4.5–13.5	6.5–16.6	17.3–30.3	5.7–15.0	7.2–17.2	1.2–9.7	1.0–9.0	0.7–8.4
Mean (SD) scores at Month 6 for patients in remission									
SJC	0.3 (0.6)	0.2 (0.6)	0.2 (0.6)	1.0 (1.4)	0.2 (0.6)	0.2 (0.4)	1.7 (2.3)	0.3 (0.5)	0.2 (0.5)
TJC	0.2 (0.4)	0.1 (0.4)	0.2 (0.4)	0.3 (0.7)	0.1 (0.2)	0.2 (0.4)	0.0 (0.0)	0.3 (0.5)	0.4 (0.6)
PGA	12.4 (12.5)	5.0 (5.8)	6.4 (7.2)	13.6 (12.3)	6.5 (4.7)	7.3 (6.2)	9.2 (5.5)	7.0 (7.4)	6.6 (6.4)
EGA	8.3 (8.0)	3.2 (2.7)	3.5 (3.0)	8.7 (9.9)	3.8 (2.4)	3.4 (2.1)	10.7 (8.2)	5.0 (6.7)	4.8 (5.8)
ESR	21.2 (9.9)	17.9 (10.4)	19.6 (11.2)	26.6 (19.7)	27.5 (24.0)	30.8 (22.2)	33.3 (30.4)	41.0 (36.1)	51.2 (38.7)
CRP	7.9 (6.6)	6.8 (7.7)	14.4 (26.8)	5.3 (4.6)	4.9 (3.4)	9.2 (12.0)	9.2 (3.9)	9.8 (1.5)	12.3 (5.8)

CI=confidence intervals; SD=standard deviation; DAS28=Disease Activity Score 28; SDAI=simplified disease activity index; CDAI=clinical disease activity index; SJC=swollen joint count; TJC=tender joint count; PGA=patient global assessment; EGA=evaluator global assessment; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein

Conclusion: Remission rates at Month 6 were similar for abatacept and infliximab, irrespective of the type of composite measure used. This remained true when more stringent remission criteria, such as SDAI, were applied. Furthermore, mean TJC and SJC for abatacept-treated patients in DAS28 remission were similar to patients in SDAI and CDAI remission, suggesting that these patients are not experiencing residual disease activity as has been seen for patients in DAS28 remission treated with other biologics[2].

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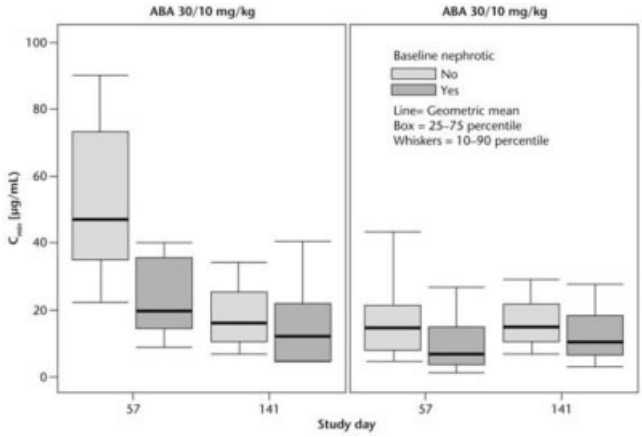
1225

Pharmacokinetics of IV Abatacept in Systemic Lupus Erythematosus Patients with Active Proliferative Glomerulonephritis. Michael Tagen[1], Blisse Vakkalagadda[1], Neelima Thanneer[1], Stephanie Meadows-Shropshire[1], Martin Ullmann[1], Robert Wong[1], Richard Aranda[2] and Bindu Murthy[1]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb [at time of study], Princeton, NJ

Background/Purpose: Results from a dose-ranging study of abatacept (ABA) in systemic lupus erythematosus (SLE) patients (pts) with active proliferative glomerulonephritis (PGN) showed a larger reduction in urinary protein:creatinine ratio (UPCR) in nephrotic pts treated with ABA versus placebo[1]. Limited studies have shown differences in exposure to biologics due to renal damage in non-lupus pts[2,3]; therefore, the relationship between proteinuria and ABA systemic exposure was examined. We describe the pharmacokinetics of IV ABA in pts with active PGN due to SLE and evaluate the association with baseline nephrotic status (UPCR >339 mg/mmoL).

Methods: In Study IM101075, lupus nephritis pts with active PGN (UPCR ≥50 mg/mmoL) were randomized to receive placebo (n=100) or one of two IV ABA regimens: either 3 mths of ABA 30 mg/kg followed by ABA ~10 mg/kg for 9 mths (30/10; n= 99), or ~10 mg/kg for the entire 12 mths (10/10; n= 99). Mean (standard deviation [SD]) glomerular filtration rates at screening were 85 ± 36, 92 ± 36, and 88 ± 31 mL/min and mean (SD) UPCR values were 446 ± 381, 483 ± 954, and 403 ± 329, for the ABA 30/10, ABA 10/10, and placebo groups. A validated enzyme-linked immunosorbant assay (ELISA) was used to determine serum ABA concentrations. Measures of systemic exposure to ABA (maximum observed concentration [C_{max}], area under the concentration–time curve [AUC], and trough concentration [C_{min}]) were derived by model-independent analysis.

Results: Systemic exposure to ABA was 3-fold higher for the first 3 mths in the 30/10 regimen group compared with the 10/10 regimen group, demonstrating linear pharmacokinetics. After transitioning from 30 mg/kg to 10 mg/kg on Day 57, systemic exposure in the 30/10 group was comparable to that of the 10/10 regimen group by Day 141. Pts who were nephrotic at baseline (34% of ABA-treated pts) had 2.2-fold lower geometric mean C_{min} values at Day 57 (Figure) and 1.2-fold lower geometric mean AUC values than pts who were not nephrotic at baseline, suggesting that nephrotic pts clear ABA more rapidly. C_{max} values were similar in nephrotic and non-nephrotic pts, suggesting that distribution volume was not affected by renal damage. Pts who were nephrotic at baseline, but had improvement in proteinuria, had corresponding increases in ABA C_{min} values.



Conclusion: ABA systemic exposure is lower in nephrotic pts due to increased clearance secondary to active PGN. Nephrotic pts showed better improvement in UPCR compared with non-nephrotic pts despite having lower ABA exposure. Although these results were unexpected, they suggest that clinical response may be related to other factors besides ABA exposure in SLE pts with active PGN. Further investigation is needed to understand if this observation is due to different therapeutic trough levels or other factors.

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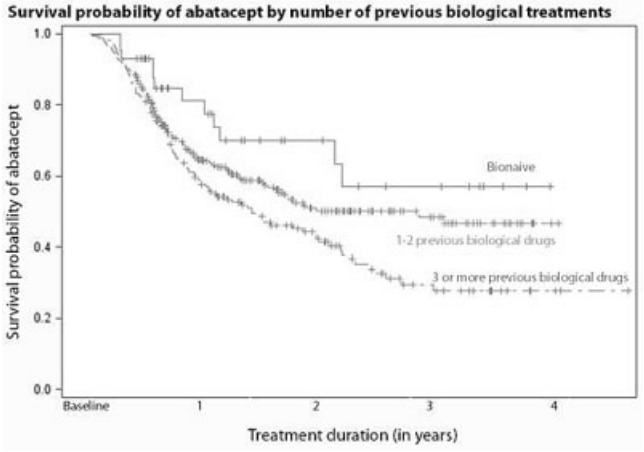
Clinical Effect of Abatacept in Patients with Rheumatoid Arthritis, Data From the Swedish Rheumatology Quality Registry. Ralph Nisell[1], Leszek Stawiarz[2] and Staffan Lindblad[1]. [1]Karolinska University Hospital, Stockholm, Sweden, [2]Karolinska Institutet and Carmona AB, Stockholm/Halmstad, Sweden

Background/Purpose: Abatacept is a biological T-cell modulation therapy used in RA. Data on diagnosis, preceding treatment as well as the reason for the discontinuation of the preceding treatment was derived from the Swedish Rheumatology Quality Registry.

Methods: Observational data from the Swedish Rheumatology Quality Registry was collected for the period from April 2006 to May 2011. Survival analysis (Kaplan Meier curves) with right censoring and log-rank test of equality across strata was performed. Comparisons between all pairs of curves (all strata) with Tukey-Kramer multiple-comparison adjustments were made.

Results: There were 606 patients started abatacept treatment from Apr 2006 to Dec 2010. Regarding the 473 RA patients (367 females or 78%), median and interquartile range of age at start of abatacept was 60 years (52–66) and median disease duration was 11 years (6–19). Median time since first given biological treatment to abatacept start was 3.3 years (1.3–6.3).

Abatacept was given as first biological treatment in 44 patients (9%), after one or two previous biological treatments in 263 (55%) patients, after three or more biological treatments in 167 (36%). Survival probability of abatacept in these groups is shown in Figure 1. After 1, 2 and 3 years drug survival was 78%, 70% and 57% respectively in bio-naïve patients, 64%, 50% and 49% in patients with 1–2 previous biological treatment and 57%, 41% and 29% in patients with 3 or more previous biological treatments. Bio-naïve patients had significantly longer drug survival time than patients with 3 or more previous treatments (p=0.0065), and patients with 1–2 previous biological treatments had longer drug survival time than patients with 3 or more previous treatments.



DAS28 was measured before treatment and after 3, 6 and 12 months of treatment. A per-protocol analysis was used. There was significant reduction of DAS28 at all time points compared with baseline. Median DAS28 at baseline was 5.5, at 3 months 4.5, at 6 months 4.3 and at 12 months 3.9. The effect of abatacept expressed in DAS28 was significantly better in men than in women at all time points except for 6 months. There was a significant tendency towards a longer drug survival in men compared to women (p=0.05). At 1, 2 and 3 years respectively drug survival was 69%, 57%, 52% in men and 61%, 46%, 37% in women.

Conclusion: In this cohort of 473 RA patients starting abatacept treatment during a time period of four years, drug survival time was longer for bio-naïve patients compared to patients treated with previous biological drugs. There was seen a gender difference in abatacept treatment outcome in favour of men.

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Sustained Clinical Response with Golimumab Administered Subcutaneously Every 4 Weeks in Ankylosing Spondylitis: 104-Week Results of a Randomized, Placebo-Controlled Study. Jürgen Braun[1], Desiree van der Heijde[2], Atul Deodhar[3], Anna Beutler[4], Michael Mack[4], Benjamin Hsu[5] and Robert D. Inman[6]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Oregon Health & Science University, Portland, OR, [4]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA, [5]Centocor R&D, a division of J&J Pharmaceutical R& D, LLC/Univ. of Pennsylvania, Malvern/Philadelphia, PA, [6]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: The results through wk24 of the GO-RAISE study indicated that golimumab (GLM) significantly improved the signs and symptoms of ankylosing spondylitis (AS) vs. placebo (PBO). The purpose of this study was to assess the long-term clinical efficacy of GLM over 104 wks in pts with active AS who did and did not exhibit clinical improvement at wk24.

Methods: Pts (n=356) were randomly assigned (1:1.8:1.8) to subcutaneous injections of PBO, GLM 50 mg, or GLM 100 mg q4wks. At wk16, pts in the PBO or 50-mg groups with <20% improvement in both total back pain and morning stiffness entered early escape (EE) to GLM 50 or 100 mg, respectively. At wk24, patients still receiving PBO crossed over (CO) to GLM 50 mg. Among the subgroups of pts defined by clinical efficacy observed at wk24 (Yes vs. No for the individual variables, see Table), the proportions of pts achieving Assessment of SpondyloArthritis International Society (ASAS) partial remission (value < 2 on each of four 0- to 10-cm ASAS domains), AS Disease Activity Score based on C-reactive protein (ASDAS-CRP) remission (score <1.3), ASDAS-CRP major responder (decrease ≥2 from baseline), and ≥50% improvement from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50) were determined at wk104.

Results: After wk24 all pts were receiving GLM 50 or 100 mg. Among pts who demonstrated clinical improvement at wk24, the vast majority maintained their response to GLM through week 104, i.e., 88% of wk24 responders for ASAS partial remission, 91% of pts for ASDAS-CRP remission, 86% of pts for ASDAS-CRP major response, and 89% of pts for BASDAI50 response. No differences in wk104 response were observed among the randomized treatment groups (Table). Among pts who had not achieved clinical improvement at wk24, 22%, 29%, 27% and 44% of pts achieved ASAS partial remission, ASDAS-CRP remission, ASDAS-CRP major response, and BASDAI50 response, respectively at wk104. Among these wk24 nonresponders, the highest wk104 response rates were observed in pts who initially received PBO but EE/CO to GLM at wk16/24 (Table).

Table. Clinical response at wk104 by wk24 response status.

Responder at wk24	PBO	GLM 50&100 mg combined	All patients
ASAS partial remission (n=77)	88.9% (8/9)	88.2% (60/68)	88.3% (68/77)
ASDAS-CRP remission (n=106)	93.3% (14/15)	90.1% (82/91)	90.6% (96/106)
ASDAS-CRP major response (n=72)	85.7% (6/7)	86.2% (56/65)	86.1% (62/72)
BASDAI50 response (n=149)	86.4% (19/22)	89.8% (114/127)	89.3% (133/149)
Nonresponder at wk24			
ASAS partial remission (n=208)	30.8% (16/52)	18.6% (29/156)	21.6% (45/208)
ASDAS-CRP remission (n=158)	52.4% (22/42)	19.8% (23/116)	28.5% (45/158)
ASDAS-CRP major response (n=203)	40.4% (21/52)	21.9% (33/151)	26.6% (54/203)
BASDAI50 response (n=139)	65.9% (27/41)	34.7% (34/98)	43.9% (61/139)

Conclusion: Clinical response that was achieved by patients receiving golimumab through 24wks was sustained through wk104. In addition 22–35%of patients who had not yet responded well by week 24 to golimumab treatment acquired benefit later in the course of treatment.

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Fatigue and Morning Stiffness Are Correlated in Early Arthritis and Both Are Substantially Improved by Glucocorticoids. Gisela Westhoff[1], Angela Zink[2] and Frank Buttgereit[3]. [1]German Rheumatism Research Center Berlin, Berlin, Germany, [2]Deutsches Rheumaforschungszentrum and Charité University Medicine, Berlin, Germany, [3]Charité University Medicine, Berlin, Germany

Background/Purpose: Morning stiffness (MS) in rheumatoid arthritis (RA) is considered to be causally related to the circadian rhythms of pro-inflammatory factors and is ameliorated by glucocorticoids (GC). In contrast, the pathophysiology of fatigue, a similarly frequent and debilitating RA symptom, is still not well understood. We therefore investigated the association between MS and fatigue in patients with early arthritis and delineated the effects of GC on both manifestations.

Methods: Baseline data of 516 patients of an early arthritis inception cohort (disease duration <26 weeks, μ 13 ±8) were used. Morning stiffness was measured as duration (minutes) and severity (NRS 0–10). Dimensions of fatigue were assessed by the PROFAD items 'need rest', 'poor starting', 'low stamina', 'weak muscles' and 'poor concentration' (NRS 0–10). The patients with no GC, GC to be started and GC ≥1 week were compared with respect to the severity of MS and fatigue. The effects were adjusted for serological and immunological parameters, tender and swollen joint counts (0–28) and the duration under DMARDs (just started vs. ≥1 week).

Results: All patients were clinically diagnosed with either RA or undifferentiated arthritis (definite RA 56.1%, probable RA 36.1%, uA 7.8%) and 69.1% were classified as RA by the new ACR/EULAR RA classification criteria. 62% had just started a DMARD therapy with only 4% taking DMARDs for a week or more. 22% had oral GC (μ 16 mg/d, median 10) for at least one week (μ 2.7 ±3 weeks) and another 44% were designated to start GC. The patient-reported fatigue score (0–50) was significantly correlated with the physician-reported duration of MS (r = 0.246; P <0.001) and patient-reported severity of MS (r = 0.514, P <0.001) but was at the utmost weakly correlated with acute phase reactants and joint counts. Patients without GC yet and those designated to start GC were comparable in all measures considered, whereas patients taking GC for a week or more reported substantially less severe MS and fatigue, particularly less severe problems with "it is being hard to get going, things taking an effort or are a battle". Multivariate logistic regression analysis with below average-fatigue (PROFAD score ≤12) as target variable revealed that patients with GC for at least one week reported twice as likely low fatigue severity (adjusted OR 2.10, 95% CI 1.30–3.40; P = 0.002). Age, sex, diagnoses, blood parameters, joint counts and duration under DMARDs were not associated with the binary fatigue severity score.

Morning stiffness and fatigue by glucocorticoid therapy at baseline

	n	MS duration minutes	MS severity 0–10 phys.	MS severity 0–10 pts.	Need rest	Poor starting	Low stamina	Weak muscles	Poor concentration
No GC	174	58	4.1	5.2	3.6	3.6	2.9	3.4	2.4
GC to be started	226	77	4.8	6.1	3.9	4.2	3.0	3.6	2.5
GC >1 week	116	66	3.9	4.0	2.5	2.5	2.1	2.5	1.8
Total	516	68	4.4	5.3	3.5	3.6	2.9	3.3	2.3
P		0.011	0.007	<0.001	<0.001	0.002	0.003	0.075	

Conclusion: Our data indicate an association between MS and several dimensions of patient-reported fatigue. Since both RA manifestations are inter-correlated and ameliorated by GC, a common pathophysiology is suggested that may contribute to the understanding and treatment of fatigue in inflammatory arthritis.

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Different Remission Definitions Capture Different Proportions of Patients with Rheumatoid Arthritis Treated in Clinical Practice. Till Uhlig[1], Elisabeth Lie[1], Cecillie Kaufmann[2], Erik Rodevand[3], Knut Mikkelsen[4], Synnøve Kalstad[5] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Buskerud Central Hospital, Drammen, Norway, [3]St. Olav Hospital, Trondheim, Norway, [4]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [5]University Hospital in Northern Norway, Tromsø, Norway

Background/Purpose: Clinical remission is the treatment target in rheumatoid arthritis (RA) and several composite indices are available for evaluation of remission states, including the newly formulated ACR/EULAR definition. These definitions have not been applied in real life daily clinical practice.

The purpose of this study was to examine how often clinical remission is achieved in clinical practice using existing definitions, and to test how well patients in remission preserve physical function.

Methods: Data for this study were provided by the NOR-DMARD register in all 5788 patients with RA started with a synthetic (n=3875) or biological DMARD (n=1913). Age was mean (SD) 55.3 (29.9) yrs, disease duration was 8.2 (9.6) yrs, 73.3% of patients were females.

Applied definitions for clinical remission included the Disease Activity Score based on 28 joint counts (DAS28) <2.6, the Simplified Disease Activity Index (SDAI) ≤3.3, the Clinical Disease Activity Index (CDAI) ≤2.8, Routine Assessment of Patient Index Data (RAPID3, range 0–10) ≤1, and the preliminary ACR/EULAR remission definition where in the Boolean (BOOL) application tender joint count, swollen joint count, patient global assessment (scale 0–10), and CRP (mg/dL) all must be ≤1. ACR/EULAR remission is warranted if either ACR/EULAR BOOL is satisfied or SDAI ≤3.3. We also explored a practical definition of ACR/EULAR BOOL without CRP (ACR/EULAR PRAC). Data after 3 and 6 months of treatment were used for assessment of remission. Then patients with remission at 3 months were examined for deterioration of physical function (measured by the modified Health Assessment Questionnaire [MHAQ]) between months 3 and 12, likewise remission at month 6 for deterioration between months 6 and 12.

Results: The table shows percentages of patients in remission after 3 months and 6 months, and further among these patients with remission at 3 and 6 months percentages of patients with no deterioration in MHAQ until 12 months. SDAI, CDAI and the new ACR/EULAR definition for remission are most stringent and classify 7–8% as in remission after 3 months of DMARD treatment, and 9–11% after 6 months. DAS28 and RAPID3 classify most patients as in remission. All remission definitions performed similar in identifying patients with preserved physical function.

	DAS28	SDAI	CDAI	RAPID3	ACR/EULAR BOOL	ACR/EULAR	ACR/EULAR PRAC
3 mts	19.1	7.6	8.1	17.0	6.9	9.3	8.1
MHAQ non progr. 3–12 mts	65.7	63.9	64.9	65.2	64.2	63.6	65.6
6 mts	24.7	10.5	11.3	19.8	9.0	12.3	11.0
MHAQ non-progr. 6–12 mts	69.6	73.5	73.6	69.8	74.9	72.6	73.7

Conclusion: Definitions of remission differ regarding the proportion of patients classified as in remission after 3 and 6 months of DMARD treatment in clinical practice. However, no individual definition seems superior in identifying patients who preserve physical function until 12 months.

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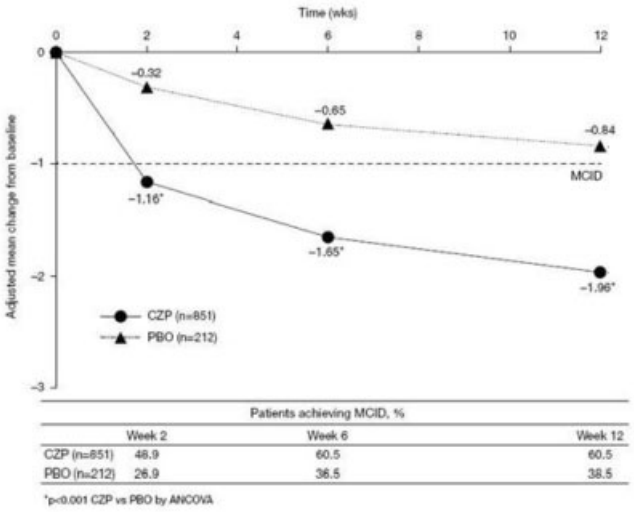
Patient-Reported Disease Activity Including Joint Assessment: A Comparison of RADAI (Rheumatoid Arthritis Disease Activity Index) and RAPID3 (Routine Assessment of Patient Index Data 3) in Patients Treated with Certolizumab Pegol Over 12 Weeks. Michael E. Weinblatt[1], Janet E. Pope[2], Roy M. Fleischmann[3], Clifton O. Bingham[4], Geoffroy Coteur[5] and Maxime Dougados[6]. [1]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]St. Joseph's Health Care, University of Western Ontario, London, ON, [3]MCRC, University of Texas, Dallas, TX, [4]Johns Hopkins University, Baltimore, MD, [5]UCB, Brussels, Belgium, [6]Paris-Descartes University, Cochin Hospital, Paris, France

Background/Purpose: Self-reported disease activity (DA) indices such as RAPID3 (**R**outine **A**ssessment of **P**atient [pt] **I**ndex **D**ata 3) and RADAI (**R**heumatoid **A**rthritis [RA] **DA** **I**ndex)[1] offer a pt-focused approach to clinical management. RAPID3 is an index without formal joint counts, whereas RADAI includes a self-assessment of tenderness in 16 joint areas. This post hoc analysis of the REALISTIC (**RA** **E**v**AL**uation **I**n **S**ubjects receiving **T**NF **I**nhibitor **C**ertolizumab pegol [CZP]) study[2] assessed the performance of RAPID3 and RADAI to measure impact of treatment with CZP in a broad population of RA pts closely resembling routine clinical practice.

Methods: During the 12-week (wk), double-blind phase of REALISTIC (NCT00717236) 1063 pts with inadequate response to ≥1 DMARD were randomized 4:1 to CZP 400 mg at Wks 0, 2, and 4, followed by 200 mg at Wks 6, 8, and 10, or placebo (PBO), added to their current treatment. 75% pts were from North America. The RADAI (summarized as a joint tenderness score [JS] or the total score [TS], both ranging 0–10, with 10 indicating highest DA) was administered at 0, 2, 6, and 12 wks. Mean change from baseline (BL) in RADAI-TS was assessed using ANCOVA applying LOCF (CZP vs PBO). The% of pts achieving a minimum clinically important difference (MCID) for the RADAI-TS was evaluated (defined as a 1-point decrease). Correlations between RADAI-TS, RADAI-JS, RAPID3, and clinical DA measures (including DAS28[ESR] and total and swollen joint counts [TJC, SJC]) were examined using Pearson coefficients.



Patients achieving MCID, %

	Week 2	Week 6	Week 12
CZP (n=851)	48.9	60.5	60.5
PBO (n=212)	26.9	36.5	38.5

*p<0.001 CZP vs PBO by ANCOVA

Results: Mean BL RAPID3 and RADAI-TS were similar between groups (CZP vs PBO: RAPID3 14.75 vs 15.50, RADAI-TS 5.56 vs 5.68). Statistically significant improvements in RAPID3 and RADAI-TS were reported with CZP vs PBO from as early as Wk 2 up to Wk 12 (Figure). Significantly more CZP pts had improvements ≥MCID in RADAI and achieved RAPID3 low DA or remission from Wk 2 onward. Correlations between RADAI (TS and JS) or RAPID3 and DAS28(ESR) were high, while correlations between RADAI-TS and RAPID3 were very high (Table). Pt-reported scoring of the joint for tenderness in the RADAI highly correlated with physician-reported TJC and moderately with SJC. Responsiveness of RADAI and RAPID3 was good, especially in pts with moderate or high number of affected joints at BL.

Conclusion: Rapid and significant improvements in RAPID3 and RADAI were observed within the first 3 months of CZP treatment in a broad population of RA pts. RADAI and RAPID3 may represent reliable pt-reported measures of DA in RA pts.

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Initial Combination Therapy with Adalimumab Plus Methotrexate Leads to Better Long-Term Outcomes Than with Either Monotherapy in Patients with Early Rheumatoid Arthritis: 8-Year Results of An Open-Label Extension of a Phase 3 Trial. Ferdinand C. Breedveld[1], Edward Keystone[2], Désirée van der Heijde[3], Robert Landewe[4], Josef Smolen[5], Benoit Guerette[6], Melissa McIlraith[6], Hartmut Kupper[7], Shufang Liu[8], Benjamin Wolfe[8] and Arthur Kavanaugh[9]. [1]Leiden Univ Medical Ctr, Leiden, Netherlands, [2]University of Toronto, Toronto, ON, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Academic Medical Center, Amsterdam, Netherlands, [5]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [6]Abbott, Rungis, France, [7]Abbott GmbH & Co KG, Ludwigshafen, Germany, [8]Abbott, Abbott Park, IL, [9]University of California San Diego, San Diego, CA

Background/Purpose: PREMIER was a phase 3, randomized, controlled trial (RCT) in MTX-naïve patients (pts) with early RA who received MTX, adalimumab (ADA), or ADA+MTX for 2 years (yrs) of blinded treatment. The RCT demonstrated the radiographic, clinical, and functional superiority of initial combination therapy over the individual monotherapies[1]; results were extended through an additional 3 yrs of open-label (OL) treatment in a 5-yr report[2]. This analysis aimed to evaluate long-term radiographic, clinical, and functional outcomes in pts treated with ADA, with and without MTX, for up to 8 yrs (i.e. 6 yrs beyond the 2-yr RCT).

Methods: Pts completing the RCT were eligible to receive OL ADA for a total of 10 yrs of treatment (this trial is ongoing); MTX could be added at the investigator's discretion during the OL extension. This post hoc analysis evaluated the 8-yr completers cohort with radiographic data available at baseline (BL) and yr 8; results are summarized overall and by initial treatment arms. Radiographic damage [mTSS, representing the sum of joint (jt) erosion (JE) and jt space narrowing (JSN)] was assessed at BL and yrs 2, 6, and 8; progressors were defined as a change (Δ) in mTSS from BL >0.5. Differences in ΔmTSS were assessed using a longitudinal ANCOVA following adjustment for BL damage. Clinical outcomes were assessed using the DAS28, and swollen (66 jts assessed) and tender (68 jts assessed) jt counts. Physical function was assessed using the HAQ-DI.

Results: A total of 299 (37.4%; 103, 96, and 100 from the initial ADA+MTX, MTX, and ADA arms, respectively) of the 799 pts initially randomized received OL ADA±MTX through yr 8. Following up to 8 yrs of ADA±MTX therapy, pts continued to demonstrate inhibition of radiographic progression and effective disease control (mean ΔmTSS=8.6; mean DAS28=2.6; mean HAQ-DI=0.6). Further, approximately half of pts experienced an absence of swollen (52.5%) and tender (47.9%) jts. Pts initially randomized to ADA+MTX demonstrated lower mean ΔmTSS, ΔJE, and ΔJSN at yr 8 (3.8, 1.4, 2.4) when compared with pts initially randomized to either MTX (11.4, 6.1, 5.2) or ADA (10.8, 5.6, 5.3) monotherapy (P <.001 for both mTSS comparisons) and were associated with fewer radiographic progressors (56.3% versus 72.9% and 73.0% for MTX and ADA monotherapy, respectively). OL ADA±MTX treatment inhibited radiographic progression in pts initially randomized to MTX or ADA monotherapy to levels that were comparable with those observed during OL treatment of pts from the initial ADA+MTX arm. Initial randomization to combination therapy also was associated with greater proportions of pts achieving high levels of disease control and normal physical function at yr 8 (DAS28 <2.6: 71.3%, 58.4%, 49.5%, and HAQ-DI <0.5: 60.2%, 55.9%, 47.4%, for ADA+MTX, MTX, ADA, respectively).

Conclusion: Following up to 8 yrs of treatment with ADA±MTX, pts with early, aggressive RA maintained effective disease control. Pts who initially received combination therapy with ADA+MTX demonstrated better long-term outcomes than those initially receiving either monotherapy.

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Association Between Leptin, Adiponectin and TNF-α and Response to Treatment in Patients with Rheumatoid Arthritis. Daniel X. Xibille Friedmann[1], Sara Eugenia Hernandez Gongora[2], Carolina Bustos Bahena[3], Liliana Dominguez Hernandez[3], Ivan Martinez Rivera[3], Marisol Sandoval Rios[3], Jorge Eduardo Ortiz Panozo[4] and Jose Luis Montiel Hernandez[5]. [1]Hospital General de Cuernavaca, Cuernavaca Morelos, Mexico, [2]Postgraduate Research Coordination, School of Medicine, Universidad Latinoamericana, Cuernavaca, México, [3]Cytokines and Autoimmunity Laboratory, Faculty of Pharmacy, Universidad Autónoma del Estado de Morelos, Cuernavaca, México, Cuernavaca, Mexico, [4]Center for Population Health Research. Instituto Nacional de Salud Pública, Cuernavaca, México, [5]Cytokines and Autoimmunity Laboratory, Faculty of Pharmacy, Universidad Autónoma del Estado de Morelos, Cuernavaca, México

Background/Purpose: Response to treatment in Rheumatoid Arthritis (RA) determines the functional prognosis in affected patients. The development of predictors of response to therapy is essential in order to adequately treat patients with RA. Leptin and Adiponectin are white fat cell derived hormones that play an immunomodulatory role in RA and their levels have been associated with clinical activity in RA.Our objective was to determine whether baseline levels of leptin, adiponectin and TNF-α predict response to treatment in patients with RA at 6 months, 1, 2, 3 and 4 years of follow-up.

Methods: Patients were followed at the Rheumatology outpatient clinic of the Hospital General de Cuernavaca. Patients had been diagnosed with established RA by a Rheumatologist and fulfilled the 1987 ACR classification criteria. All patients were receiving treatment with steroids and/or DMARDs, both in combination or as monotherapy, and visited the clinic every three months where physical examination and routine lab testing was performed, which included RF (nephelometry), CRP (qualitative) and ESR (Westerngren). A blood sample was taken at a baseline visit between March 2006 and December 2008 in order to determine plasma anti-CCP, leptin, adiponectin and TNF-α levels (measured using ELISA). Patient follow-up occurred on visits at 6 months and every year afterward. Descriptive statistics were employed for demographic data while linear regression and ANOVA were employed in order to determine predictors of response to treatment. Response to treatment was assessed by a change in the DAS28 score from baseline to each time point. A p-value of <0.05 was considered as statistically significant.

Results: 147 patients were included of which 99 completed at least 6 months of follow up, 75 were followed for one year, 52 two years, 35 three years and 16 completed four years of follow up. All patients but 5 were women (94.9%). Mean age was 45.8 years (18–70) and mean time since onset of disease was 7.7 years (0–36). Mean body mass index was 26.95 (15–43). 92.5% of patients were RF positive and 79.7% were anti-CCP positive. Most patients received combination therapy at baseline, which included at least 2 DMARD (84.8%), the most common being methotrexate, 9.1% received methotrexate monotherapy and 6.1% received only prednisone and/or NSAIDs. No patients undergoing biologic therapy were included. Mean plasma levels for leptin were 0.27±0.8 ng/ml, for adiponectin 174.4±88.2 ng/ml, and for TNF-a 6.05±7.7 ng/ml. Higher baseline leptin levels predicted a good response to treatment at 6 months and one year (p=0.036 and 0.035, respectively), as did higher baseline TNF-α levels at one year (p=0.05). Neither leptin nor TNF-α were statistically significant predictors for long-term response to treatment (2 years and over). Higher baseline TNF-a and adiponectin levels, although not reaching statistical significance, did show a tendency to predict a poor response to treatment after 2 years (p=0.087) and 4 years (p=0.077) of follow-up, respectively.

Conclusion: Baseline levels of leptin and TNF-a predict a good response to treatment in RA patients at one year, but not in the longer term.

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Safety and Efficacy of Etanercept Over Five Years in a Large, UK Observational Cohort. C. D. Poole[1], Paul Emery[2], Adam Young[3], Duncan Porter[4], C. L. Morgan[1], H. Walker[5], C. J. Currie[6] and A. Reynolds[7]. [1]Pharmatelligence, Cardiff, United Kingdom, [2]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [3]City Hospital, St Albans, United Kingdom, [4]Gartnavel General Hosp, Glasgow, United Kingdom, [5]Pfizer UK Ltd, Tadworth, United Kingdom, [6]Cardiff University, Cardiff, United Kingdom, [7]Reynolds Clinical Sciences Ltd, Eastleigh, United Kingdom

Background/Purpose: Prospective observational registries have been established to monitor the long-term safety of TNF inhibitors and standard disease modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA). The purpose of this study was to evaluate relative safety of etanercept (ETN) when compared with a DMARD

reference cohort and the efficacy of ETN over 5 years using data from a UK registry.

Methods: The British Society of Rheumatology Biologics Register (BSRBR) provided anonymised raw data on ETN and DMARD cohorts. No further data was provided if a patient switched to a non-ETN biologic. At baseline, patients underwent detailed clinical assessment by a rheumatologist. Follow-up questionnaires were completed every six months for three years by consultants and patients, then annually by consultants only for two more years. Health Assessment Questionnaire (HAQ) data were characterized for the first three years.

Patients with a potential for five years follow-up, a maximum window of ±90 days between RA treatment initiation and baseline registration were included. HAQ changes and DAS28 remission rates were calculated. Survival rates for serious adverse events were examined using Kaplan-Meier survival models and risk differences compared using the multivariate Cox proportional hazards model. These models were specified using a forward manual inclusion method for parameters where $P<0.05$. Subjects were followed to the date of last follow-up or death.

Results: ETN n=3,470, DMARDs n=1,365. Mean (median) follow-up 4.1 (4.9) years in both groups. Adjusted hazard ratios (aHR) for ETN vs. DMARDs and efficacy outcomes for ETN are detailed in Table 1. There were statistically significant differences in aHRs for malignancy and cardiovascular events. Of note was a significant reduction in mortality observed when deaths were restricted to on drug+90days with ETN aHR = 0.512 (95% CI 0.380–0.690, $p<0.001$), although this was not significant over the full observation period. Concomitant methotrexate therapy was associated with an increased likelihood of remission vs. ETN monotherapy (odds ratio [OR] = 1.69 (95%CI 1.32–2.14, $p<0.001$) at one year, and OR = 1.47 (95%CI 1.12–1.93, $p=0.006$) at five years). Subjects treated with ETN showed a significant improvement in HAQ compared with those receiving DMARDs at each timepoint during the first three years: −0.283 vs. −0.013 at 1yr; −0.305 vs. +0.008 at 2yrs, −0.272 vs. +0.101 at 3yrs (all $p<0.001$).

Table 1. aHR ETN vs DMARDs for safety outcomes

Safety parameters	aHR	95% CI	p-value		
Serious infection	1.01	0.81–1.26	0.943		
Malignancy	0.74	0.58–0.96	0.023		
Lymphoproliferative malignancy	0.64	0.30–1.40	0.266		
Cardiovascular events	0.64	0.49–0.85	0.002		
Death	0.80	0.62–1.04	0.096		
Efficacy outcomes for ETN					
Year	1	**2**	**3**	**4**	**5**
% patients remaining on ETN	71	61	54	49	40
% patients in remission (DAS28<2.6)	16	18	18	19	19

Conclusion: This evaluation at 5 years showed that ETN therapy was effective, whilst not associated with any increased risk of serious infection, malignancy, cardiovascular events or death when compared to a DMARD reference group; some risks may be reduced. While residual confounding may exist, this real-world data showed treatment with ETN was effective and as safe as treatment with DMARDs in patients with RA.

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Response with Combination Therapy—Methotrexate, Sulfasalazine, and Hydroxychloroquine—Appears Similar to the Response to Methotrexate and Anti-Tumor Necrosis Factor in US Veterans in the Veterans Affairs Rheumatoid Arthritis Registry. Grant W. Cannon[1], Brian C. Sauer[1], Candace L. Hayden[1], Stephen G. Pickard[1], Gail S. Kerr[2], J. Steuart Richards[2], Dannette S. Johnson[3], Liron Caplan[4], Ted R. Mikuls[5] and Andreas M. Reimold[6]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Washington DC VA and Georgetown University, Washington, DC, [3]Jackson VA and University of Mississippi Medical Center, Jackson, MS, [4]Denver VA and University of Colorado, Aurora, CO, [5]Omaha VA and University of Nebraska, Omaha, NE, [6]Dallas VA and University of Texas Southwestern, Dallas, TX

Background/Purpose: The linkage of pharmacy databases with objective clinical outcome measures provides an opportunity to compare the effectiveness and safety of rheumatoid arthritis (RA) therapies in real world clinical settings. Merging information from the Veterans Affairs RA (VARA) registry initiated in 2003 with assessment of disease activity and the VA Pharmacy Benefits Management (PBM) database with data from 1998 allows comparison of patients receiving combination therapy with methotrexate, sulfasalazine and hydroxychloroquine (MTX/SH) to patients receiving the combination of methotrexate and anti-tumor necrosis factor (TNF) therapy (MTX/TNF).

Methods: VARA routinely collects disease activity score (DAS28) on RA patients in this longitudinal prospective observational cohort study. For each prescription, PBM data was used to ascertain duration of the prescription, total dose dispensed, and anticipated date for refill of medication was recorded. Individual prescription courses were consolidated to determine regimens of combination therapy with MTX/SH and MTX/TNF. Regimens were defined as time from the initiation of the combination therapy regimen until the expected refill date for the last treatment before a 90 day gap or discontinuation. The average DAS28 and average ESR during each regimen of greater than 90 days was calculated during the observation period from 90 days after initial prescription to the end of the regimen.

Results: Of the 1382 patients in the VARA cohort, 443 (32%) received combination therapy with either MTX/SH or MTX/TNF; approximately half of these (n = 259) receiving treatment during observation. Of these 443 combination treated patients, 131 (30%) received only MTX/SH, 254 (57%) received only MTX/TNF and 58 (13%) received both combinations. A comparison of patients receiving only MTX/SH to MTX/TNF showed that patient treated with only MTX/SH were more frequently men and older than patients receiving only MTX/TNF. Among those with available DAS28 during VARA observation, measures of disease activity were similar across treatment groups (Table).

Characteristics of VARA patients receiving combination therapy with only MTX/SH, only MTX/TNF, and both MTX/SH and MTX/TNF for all patients and the subset of patients who had a treatment course ≥90 days and DAS28 measured - listed as DAS28 in the table below.

	Only MTX/SH		**Only MTX/TNF**		**MTX/SH & MTX/TNF**	
	All patients (n=131)	**DAS28 (n=56)**	**All patients (n=254)**	**DAS28 (n=163)**	**All patients (n=58)**	**DAS28 (n=40)**
Gender (% Male)	94%*	100%*	85%*	85%*	91%	93%
Age at diagnosis of RA	52 ± 11*	55 ± 10*	48 ± 16*	49 ± 13*	59 ± 12	52 ± 12
Age at enrollment	63 ± 11*	64 ± 8*	59 ± 12*	60 ± 10*	63 ± 11	64 ± 9
Age at 1st treatment (Rx)	62 ± 11*	63 ± 10*	59 ± 12*	59 ± 10*	60 ± 11	64 ± 9
Disease duration at 1st Rx	11 ± 10	8 ± 8	11 ± 14	10 ± 10	10 ± 10	9 ± 10
Nodules	43%	23%*	45%	48%	45%	42%
RF (+)	81%	82%	82%	86%	85%	84%
ACCP (+)	74%	77%	78%	77%	79%	73%
Erosion on hand X-ray	42%	36%	38%	32%	44%	47%
DAS28	—	3.5 ± 1.6	—	3.7 ± 1.4	—	3.9 ± 1.3
ESR	—	21 ± 16	—	21 ± 18	—	24 ± 20

* = $p<0.05$ for comparison between MTX/SH and MTX/TNF

Conclusion: Among U.S. veterans with RA, approximately half have received combination therapies with MTX/SH and/or MTX/TNF. In patients receiving these treatments, the combination of non-biologic DMARDs appears to be used more commonly than MTX/TNF in men and among older individuals. These differences may be related to channeling bias that could not be detected by the analysis for confounders. In this observational study, these treatment combinations do not appear to result in meaningful differences in disease activity over follow-up.

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Greater Physical Dysfunction Is a Negative Predictor for Achieving Boolean-Based Remission in Patients with Rheumatoid Arthritis Treated with Tocilizumab. Daisuke Hoshi, Kumi Shidara, Yohei Seto, Eiichi Tanaka, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: A new, Boolean-based definition of remission in the treatment of rheumatoid arthritis (RA) was proposed by the ACR/EULAR in 2010. Tocilizumab (TCZ) directly influences the function of IL-6 resulting in suppression of serum inflammatory markers, so it is necessary to evaluate the efficacy of TCZ by using the new remission criteria.

Methods: We analyzed the efficacy of TCZ treatment in 80 RA patients at 24 weeks after initial treatment with TCZ by using "DAS28 remission" defined to be DAS28-ESR < 2.6 and "Boolean remission" defined to be all criteria in the Boolean definition ≤ 1. We stratified the 80 RA patients by previous use of biologics, by concomitant use of methotrexate (MTX), by age

over or under 65 years, by disease duration and by physical dysfunction as measured by the Japanese version of the Health Assessment Questionnaire (J-HAQ). We compared the achievement of "DAS28 remission" by chi-square test and "Boolean remission" by Fisher's exact test. We further analyzed the predictive factors that influenced the achievement of "Boolean remission" at 24 weeks after initial treatment of TCZ by using stepwise multiple logistic regression analysis.

Results: Among the 80 RA patients, 88.8% were women. The median [25%, 75%] age was 60.0 [48.2, 65.0] years and disease duration was 100 [49, 176] months. MTX was used in 70% of patients and corticosteroid was in 77.5%. The number (percentage) achieving "DAS28 remission" and "Boolean remission" at week 24 were 40 (50.0%) and 10 (12.5%), respectively. There was no difference in reaching remission either defined by "DAS28 remission" or "Boolean remission" when patients were stratified by previous biologics use, concomitant MTX use, or age over or under 65 years. There were significant differences in achieving "Boolean remission", but not "DAS28 remission", when patients were stratified by disease duration ($p = 0.0368$) or by J-HAQ ($p = 0.0444$) in tertile. The predictive factor for not achieving "Boolean remission" at 24 weeks was a worse baseline J-HAQ score (odds ratio: 3.66, 95% confidence interval: 1.17–14.48).

Table. Risk factors at baseline for not satisfying "Boolean remission" at 24 weeks

	odds ratio	95% confidence interval	*P* value
Disease duration (month)	1.007	0.099–1.021	0.235
J-HAQ	3.655	1.174–14.475	0.039
ESR (mm/h)	0.98	0.954–1.005	0.121
Corticosteroid use (%)	2.952	0.617–14.085	0.163

Conclusion: This study showed that the achievement of "Boolean remission" was 12.5% and "DAS28 remission" was 50% in patients treated with TCZ. Greater physical dysfunction is a negative predictor for achieving "Boolean remission".

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Direct Comparison of Four Biologics in Biologic-naïve Rheumatoid Arthritis Patients. Yukio Yonemoto[1], Kimihiko Takeuchi[2], Koichi Okamura[1], Masatoshi Matsushita[2], Tsutomu Kobayashi[1], Tetsuo Aramaki[2], Tetsuya Kaneko[1] and Kenji Takagishi[1]. [1]Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [2]Isesaki Fukushima Hospital, Isesaki, Gunma, Japan

Background/Purpose: The treatment of rheumatoid arthritis (RA) has been transformed in recent years by the appearance of novel agents centered on biologics. The idea of "treat to target" has emerged, and the significance of remission has increased dramatically. However, few papers have compared different biologics under the same conditions at the same time, and no consistent view has emerged regarding the choice of agent. We compared treatment response to four biologics, infliximab (IFX), etanercept (ETN), tocilizumab (TCZ) and *adalimumab* (ADA), in biologic-naïve RA patients who had been started on treatment in the same period in the real clinical setting.

Methods: One hundred and forty-two biologic-naïve RA patients were started on a biologics (IFX 37, ETN 39, TCZ 27, ADA 39) from July 2008 onwards. Baseline and six months later, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), the swollen and tender joint counts, the Disease Activity Score in 28 joints using ESR (DAS28-ESR) and the European League Against Rheumatism (EULAR) remission criteria (DAS28-ESR$<$2.6) were examined. The drug survival rate on each agent was also surveyed.

Results: After 6 months, ESR, CRP, MMP-3, the swollen and tender joint counts and DAS28-ESR had fallen significantly from baseline with all four agents. Comparing the individual products, DAS28-ESR and MMP-3 fell significantly more with TCZ than with IFX and ETN. No significant difference was identified at 6 months in the DAS28-ESR remission rates (DAS28-ESR$<$2.6) and drug survival rate for each biologics.

Conclusion: In this study, DAS28-ESR was used whereas remission standards including clinical disease activity index (CDAI), simplified disease activity index (SDAI) and Boolean definition have been proposed at present. It has been reported that TCZ, which directly inhibits acute-phase reactant, can lead to an overestimation of the response to treatment. Another paper sets out a correlation between DAS28-ESR and CDAI, SDAI, and states that evaluation based on DAS28 is valid. The present study indicated a larger fall in MMP-3 with TCZ than with the other two agents, and suggested that TCZ may provide therapeutic efficacy at least comparable to TNF inhibitors in biologic-naïve RA patients.

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Impact of Tocilizumab Therapy for Remission Quartet in Rheumatoid Arthritis—the Result of 104 Weeks Follow up Data of REACTION study. Yoshiya Tanaka[1], Tsutomu Takeuchi[2], Koichi Amano[3], Eri Sato[4], Masao Nawata[5], Hayato Nagasawa[6], Daisuke Hoshi[7], Kazuyoshi Saito[8], Shunsuke Fukuyo[5], Kentaro Hanami[8], Hideto Kameda[2], Takahiko Kurasawa[6], Yuko Kaneko[9] and Hisashi Yamanaka[4]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Saitama Medical Center, Saitama Medical University, Saitama, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [5]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [6]Saitama Medical Ctr, Kawagoe, Japan, [7]Tokyo Women's Medical University, Tokyo, Japan, [8]University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, [9]Keio Univ School of Medicine, Shinjuku-ku, Japan

Background/Purpose: Biologics have changed dramatically the management of patients with rheumatoid arthritis (RA). Four levels of remission based on the concept of "treating to target" have been required, which is to achieve clinical, structural, and functional remission as well as to sustain remission over the long term. We evaluated those remissions and their sustainment in the REACTION Study, an observational study on tocilizumab (TCZ) in daily clinical practice.

Methods: The 229 patients were treated with TCZ 8 mg/kg every 4 weeks. The clinical remission (the disease activity score using the 28 joint count (DAS)28-ESR$<$2.6 and clinical disease activity index (CDAI)$\leq$2.8), structural remission (the estimated yearly progression of modified total Sharp score (ΔmTSS) $\leq$0.5), and functional remission (health assessment questionnaire (HAQ)$\leq$0.5) were evaluated. Sustained remission was defined as the remission sustainment rate at week 104 in patients who achieved remission at 52 weeks.

Results: Treatment with TCZ was continued for 2 years in 127 patients (55%). The patient characteristics who continued 2 years TCZ treatment were as follows. Mean age: 57.9 years; mean disease duration: 11.3 years; prior treatment with TNF inhibitor: 80 patients (63.0%); concomitant methotrexate (MTX): 80 patients (63.0%). The remission rates represented by DAS28$<$2.6 and CDAI$\leq$2.8 (measures of clinical remission) and HAQ$\leq$0.5 (measure of functional remission) tended to increase over time. At Week 104, 71.2% had achieved DAS28$<$2.6, 37.4% had achieved CDAI$\leq$2.8, and 38.2% had achieved HAQ$\leq$0.5. The main reason for discontinuation of TCZ was adverse drug reactions (47/229, 20.5%). In adverse drug reactions, pneumonia was 9 cases. Analysis of mTSS in 112 patients out of the 127 patients revealed ΔmTSS to be 20.1 at baseline, 1.1 at Week 52, and 0.6 at Week 104, indicating 97% inhibition compared to baseline. ΔmTSS$\leq$0.5 was about the same at Weeks 52 and 104, with ΔmTSS$\leq$0.5 at Week 104 in 52.9% (Table). Sustained remission: DAS28$<$2.6 in 85.5%, CDAI$\leq$2.8 in 70.0%, ΔmTSS$\leq$0.5 in 64.9%, and HAQ$\leq$0.5 in 83.3%. Multivariate analysis revealed predictive factors affecting total remission of DAS28, CDAI, TSS and HAQ at week 104 were disease duration (P=0.03) and CDAI (P=0.04) at baseline.

	0w	24w	52w	104w
DAS28-ESR$<$2.6	0 (0%)	67 (54%)	69 (59%)	89 (71%)
CDAI$\leq$2.8	0 (0%)	18 (15%)	30 (22%)	46 (37%)
ΔTSS$\leq$0.5	–	–	57(56%)	54(53%)
HAQ$\leq$0.5	16 (13%)	36 (29%)	38 (31%)	47 (38%)

Conclusion: Patients who could continue treatment with tocilizumab for 2 years were achieved significant remission of CDAI, which includes no measures for assessing inflammatory markers such as CRP. Moreover, structural remission and functional remission were both maintained over the long term in a high percentage of patients.

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Clinical Response At Months 1–6 Can Predict Likelihood of Achieving Remission in Abatacept Plus Methotrexate-Treated Patients with Early Rheumatoid Arthritis. Yusuf Yazici[1], Jurgen Wollenhaupt[2], Patrick Durez[3], Juan J. Gomez-Reino[4], Walter Grassi[5], Manuela Le Bars[6], Corine Gaillez[7], Coralie Poncet[8], Ayanbola Elegbe[9] and Rene Westhovens[10]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Schoen-Klinik Hamburg-Eilbek, Hamburg, Germany, [3]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, [4]Hospital Clinico Universitario, Santiago de Compostela, Spain, [5]Università Politecnica delle Marche, Ancona, Italy, [6]Bristol-Myers Squibb, Rueil-Malmaison, France, [7]Bristol-Myers Squibb, Rueil Malmaison, France, [8]Docs International, Issy les Moulineaux, France, [9]Bristol-Myers Squibb, Princeton, NJ, [10]UZ Gasthuisburg, Leuven, Belgium

Background/Purpose: ACR/EULAR treat-to-target recommendations define remission as the goal for patients (pts) with early rheumatoid arthritis (RA), with appropriate therapeutic adaptation every 3–6 mths dependent on response[1]. In the AGREE study, a large proportion of methotrexate (MTX)-naïve pts with early RA achieved DAS28 remission over 1 yr; 41 (95% CI: 35–47) vs 23% (18–29) for pts treated with abatacept (ABA) + MTX vs MTX alone ($p<0.001$)[2]. Applying a threshold of a change from baseline (BL) in DAS28 of >0.6 (DAS28 response) or ≥1.2 (clinically meaningful DAS28 response) during the first few mths of therapy may help identify pts more likely to reach Low Disease Activity State (LDAS) or remission at a later time-point. We present *post-hoc* analyses examining if a DAS28 response or a clinically meaningful DAS28 response at Mths 1–6 can predict likelihood of achieving remission or LDAS at Yr 1, in pts treated with ABA + MTX.

Methods: In the 1-yr double-blind (DB) period of AGREE, MTX-naïve pts with early (≤2 yrs) RA, poor prognostic factors and high disease activity, as evidenced by tender (≥12) and swollen (≥10) joint counts, were randomized 1:1 to ABA + MTX or placebo + MTX (MTX alone)[2]. All pts completing the DB period entered the open-label (OL) period to receive ABA + MTX. Remission was defined as DAS28-CRP <2.6 and LDAS as ≤3.2. Likelihood of achieving remission at Yr 1 was evaluated for pts with a DAS28 response (change from BL >0.6) or a clinically meaningful DAS28 response (change from BL ≥1.2) at Mths 1–6. Data are as observed for pts treated with ≥1 dose of ABA in the OL period.

Results: Analyses included 459 pts; 232 treated with ABA + MTX and 227 with MTX alone. BL characteristics were similar between groups[1]; mean (SD) DAS28-CRP was 6.3 (1.0) in each group. Over 90% of ABA + MTX-treated pts experienced a DAS28 response (change from BL >0.6) from Mths 2 through 6, compared with ~73–88% of MTX-alone treated pts (Table). For pts with DAS28 response at Mths 2 through 6, approximately 50% of ABA + MTX-treated pts achieved remission at Yr 1, vs ~30% of MTX-alone treated pts (Table); for these pts, >60% of the ABA + MTX group vs 44–48% of the MTX alone group achieved LDAS at Yr 1 (data not shown). Through Mths 2 to 6, 76–88% of ABA + MTX-treated pts achieved a clinically meaningful DAS28 response (change from BL ≥1.2) vs 50–76% of MTX alone-treated pts (Table). Among these pts, ~50% of the ABA + MTX-treated group achieved remission at Yr 1 vs ~30% of MTX-alone treated group (Table); ~70% and 50–54% from each group, respectively, achieved LDAS (data not shown).

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
DAS28 response (change from baseline >0.6), % (n/N)						
ABA + MTX	77.2 (173/224)	90.8 (208/229)	92.1 (211/229)	93.9 (215/229)	95.2 (216/227)	95.1 (213/224)
MTX alone	53.4 (119/223)	72.6 (162/223)	76.6 (170/222)	86.7 (195/225)	88.1 (192/218)	87.6 (191/218)
DAS28 remission at Year 1,% (n/N), according to achievement of DAS28 response each month						
ABA + MTX	49.1 (85/173)	48.1 (100/208)	47.9 (101/211)	47.4 (102/215)	46.8 (101/216)	47.9 (102/213)
MTX alone	32.8 (39/119)	30.2 (49/162)	27.6 (47/170)	27.7. (54/195)	29.2 (56/192)	29.8 (57/191)
Clinically meaningful DAS28 response (change from baseline ≥1.2),% (n/N)						
ABA + MTX	54.0 (121/224)	75.5 (173/229)	79.0 (181/229)	84.7 (194/229)	85.9 (195/227)	88.8 (199/224)
MTX alone	31.4 (70/223)	49.8 (111/223)	58.6 (130/222)	68.9 (155/225)	74.8 (163/218)	76.1 (166/218)
DAS28 remission at Year 1,% (n/N), according to achievement of clinically meaningful DAS28 response each month						
ABA + MTX	54.5 (66/121)	53.2 (92/173)	52.5 (95/181)	52.6 (102/194)	51.3 (100/195)	50.8 (101/199)
MTX alone	38.6 (27/70)	34.2 (38/111)	33.1 (43/130)	31.6 (49/155)	31.3 (51/163)	31.9 (53/166)

DAS28=Disease Activity Score 28; ABA=abatacept; MTX=methotrexate;

Conclusion: ABA + MTX-treated pts who achieve a DAS28 response (change from BL >0.6), or a clinically meaningful DAS28 response(change from BL ≥1.2), during the first 6 mths of therapy have a higher likelihood (~50%) of achieving remission at Yr 1 vs MTX-alone treated pts (~30%). These data support the concept of treating-to-target[1] with ABA + MTX in pts with early RA.

1 Smolen J, et al. *ARD* 2010;**69**:631–7
2 Westhovens R, et al. *ARD* 2009;**68**:1870–7

1239

Impact of Tocilizumab Therapy After Switching From Tumor Necrosis Factor (TNF) inhibitors – Prevention of Joint Damage by Tocilizumab in Patients with Inadequate Response to Anti-TNF Therapies. Yoshiya Tanaka[1], Tsutomu Takeuchi[2], Koichi Amano[3], Eri Sato[4], Masao Nawata[5], Hayato Nagasawa[6], Daisuke Hoshi[7], Kazuyoshi Saito[8], Shunsuke Fukuyo[5], Kentaro Hanami[8], Hideto Kameda[2], Takahiko Kurasawa[6], Yuko Kaneko[9] and Hisashi Yamanaka[4]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Saitama Medical Center, Saitama Medical University, Saitama, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [5]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [6]Saitama Medical Ctr, Kawagoe, Japan, [7]Tokyo Women's Medical University, Tokyo, Japan, [8]University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, [9]Keio Univ School of Medicine, Shinjuku-ku, Japan

Background/Purpose: Anti-TNF agents are highly effective, but clinical remission is achieved in only about 40% of patients. In this study, we evaluated the efficacy of tocilizumab (TCZ) for preventing the joint damage as well as clinical and functional improvement in patients with inadequate response to anti-TNF agents by comparing the efficacy achieved during anti-TNF therapy one year prior to TCZ treatment.

Methods: Baseline characterisitics, efficacy as measured by disease activity score using the 28 joint count (DAS)28-ESR, clinical disease activity index (CDAI), health assessment questionnaire-disability index (HAQ-DI), and modified total Sharp score (mTSS) were assessed.

Results: In total, 145 patients with inadequate response to the anti-TNF therapies were analyzed. At baseline, mean age was 56.6±14.6 years (median [min-max]: 61.0 [15–88]), mean duration of disease was 12.4±10.5 years (median [min-max]: 10.0 [0.1–56.2]), methotrexate (MTX) was concomitantly used in 64.1%. The mean DAS28-ESR, CDAI and HAQ score was improved from 5.71±1.25 at baseline to 2.84±1.53 (% of <2.6=48.5) at week 52, from 26.7±13.1 to, 9.84±9.12 (% of ≤2.8=22.4), and 1.54±0.74 to 1.19±0.81 (% of ≤0.5=26.9), respectively..Analysis of 95 patients with available mTSS revealed the estimated yearly progression (ΔTSS) at baseline to be 16.7, but this had improved to 1.1 at 52 weeks, indicating 93.4% inhibition of joint destruction. Structural remission (ΔTSS≤0.5) was achieved in 53 patients (55.8%). The incidence of the patients who reached DAS28-ESR<2.6, CDAI≤2.8, and ΔTSS≤0.5 were improved significantly after switching from anti-TNF agents to tocilizumab (Table). Especially, Estimated ΔTSS after TCZ treatment (1.37) was significant improved from the EYP during one year anti-TNF treatment.

	−52w	0w	52w
Mean DAS28-ESR (% of <2.6)	5.24 (0%)	5.85 (0%)	2.87 (50%)
Mean CDAI (% of ≤2.8)	21.1 (0%)	27.4 (0%)	11.1 (18.9%)
Mean HAQ (% of ≤0.5)	1.24 (16.2%)	1.46 (7.9%)	1.12 (15.8%)
ΔTSS (% of ≤0.5)	3.55 (42.1%)	1.37 (63.2%)	

Conclusion: The clinical response and the efficacy in prevention of joint damage were significantly improved compared to pretreatment by switchin to tocilizumab from TNF-inhibitors in RA patients with inadequate response to TNF-inhibitors.

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Comparative Efficacy and Tolerability of Biologic Therapies in Early Rheumatoid Arthritis Utilizing a Bayesian Approach. Yusuf Yazici[1], Christopher Swearingen[2], Anagha Nadkarni[3] and Lisa Rosenblatt[3]. [1]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY, [2]University of Arkansas, Little Rock, AR, [3]Bristol-Myers Squibb, Plainsboro, NJ

Background/Purpose: Currently, five biologic disease-modifying antirheumatic drug (DMARD) therapies are used in MTX-naïve, early rheumatoid arthritis (RA). In the absence of head to head studies, indirect approaches are required in order to gain insight into the comparative efficacy and tolerability of these agents.

Objectives: To determine the relative efficacy and tolerability of biologic agents approved for the treatment of MTX-naïve early RA patients using mixed treatment comparison (MTC) methodology.

Methods: A systematic literature review was performed to identify RCTs published between January 1, 1990 and June 16, 2010 that measured efficacy and safety endpoints in an MTX-naïve, early RA population. Those RCTs that included any one of the approved biologics abatacept (ABA), adalimumab (ADA), etanercept (ETN), golimumab (GOL), and infliximab (INF), were included in the MTC that compared the following outcomes at 1 year: American College of Rheumatology (ACR) 20/50/70, Disease Activity Score 28 (DAS 28) remission, severe adverse events (AEs), serious infections and withdrawals due to an AE or due to any reason.

Results: No difference in the odds of achieving ACR 50 or ACR 70 scores was seen between the biologics, although both INF (odds ratio [OR]=0.48, 95% CI=0.27–0.82) and ADA (OR=0.53, 95% CI=0.29–0.94) had significantly lower odds of achieving ACR20 compared with ETN. The odds of achieving DAS28 remission was also found to be similar between all biologic therapies with the exception of INF which had significantly lower odds (OR=0.54, 95% CI=0.30–0.97) compared with ADA. Tolerability to the biologic agents was not significantly different with the exception of INF and GOL, as the former had significantly higher odds of experiencing serious infections compared with ETN (OR=5.12, 95% CI=1.20–24.80) and significantly higher odds of discontinuing treatment due to AEs compared with ABA (OR=4.80, 95% CI=1.45–17.08) and ETN (OR=4.28, 95% CI=1.75–11.35), while GOL had higher odds of discontinuing treatment due to AEs compared with those receiving ETN (OR=3.43, 95% CI=1.07–12.67).

Conclusion: In general, all biologic agents used in MTX-naïve early RA demonstrated similar efficacy and tolerability, except for INF which appeared to have less favorable efficacy and tolerability. For specific outcomes studied, ETN and ABA were not significantly different from each other and were the only biologics that did not demonstrate a significantly decreased likelihood of efficacy or tolerability compared with any of the other agents.

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Differences in Gene Expression Profiles in Rheumatoid Arthritis Peripheral Blood Mononuclear Cells Suggest Apoptosis As Relevant Mechanism for Response to Methotrexate Monotherapy. RD Oliveira[1], V. Fontana, C. Macedo, CM Junta, Eduardo A. Donadi[3], GA Passos and Paulo Louzada-Junior[1]. [1]School of Medicine of Ribeirao Preto - University of Sao Paulo, Ribeirao Preto, Brazil, [2]Faculty Med of Ribeirao Preto, Ribeirao Preto, Brazil

Background/Purpose: Methotrexate (MTX) remains the standard therapy for rheumatoid arthritis (RA), although about 30% of RA patients do not respond to MTX monotherapy. A better understanding of the mechanisms of MTX action may be useful in identifying those RA patients who are most likely to have benefit from MTX treatment. The aim of the study was to evaluate the gene expression profile in peripheral blood mononuclear cells (PBMC) in RA patients who did not respond to MTX monotherapy.

Methods: We evaluated 17 MTX-non-responders (MTX-NR) RA patients using MTX monotherapy (15–25 mg/week). As a control group, we also evaluated eight MTX-responders (MTX-R) RA patients, also under MTX monotherapy (15–25 mg/week). All patients were using stable dose of prednisone (5 mg/day). The classification in responders and non-responders to MTX fulfilled the EULAR response criteria for RA. Total blood was collected and RNA was extracted from peripheral blood mononuclear cells (PBMC) and the complementary DNA microarray was performed. We selected the genes presented at least in 80% of the microarray hybridizations.

Results: Clinical and laboratorial characteristics of the RA patients are shown in Table 1. Microarray analysis showed 535 differentially expressed genes when we compared MTX-NR with MTX-R and the hierarchical clustering analysis showed an unambiguous distinction. To identify general mechanisms of action, we selected genes whose magnitude of difference (fold change) in the gene expression between MTX-NR and MTX-R were higher than 1.3 or lower than 0.7. For the MTX-NR group, we observed four down-regulated genes involved in apoptosis induction, four up-regulated genes involved in apoptosis inhibition, and one up-regulated gene involved with immune response and inflammation (Table 2).

Table 1. Clinical and laboratorial characteristics of the RA patients.

Features	MTX-R (n=8)	MTX-NR (n=17)	p
Age, mean years (range)	54.7 (37–71)	51 (29–67)	Ns[a]
Female/Male	4/1	3/1	Ns[b]
Time of disease (years)	6.6	5.4	Ns[a]
Smoking (%)	38	53	Ns[b]
+ RF (%)	88	65	Ns[b]
+ ACPA (%)	75	82	Ns[b]
+ HLA-SE(%)	75.0	70	Ns[b]
DAS28 (mean ± SD)	1.87+0.76	6.47+1.1	<0.0001[a]

MTX-R: responders to methotrexate; MTX-NR: non-responders to methotrexate; +RF: positive rheumatoid Factor; +ACPA: positive antibodies to citrullinated protein antigen; + HLA-SE: presence of shared epitope of Human Leukocyte Antigen; DAS28: disease activity index including a 28-joint count; Ns= not significant.
Statistical tests: [a]two-sample t test,[b]exact Fisher test

Table 2. Differentially regulated genes in MTX non-responder group when compared with MTX responder group

Gene Symbol	Gene Name	Process involved	Fold change (MTX-NR vs MTX-R)
Apoptosis			
HTRA2	HtrA serine peptidase 2	Induction of apoptosis	0.69
CAV1	Caveolin 1	Induction of apoptosis	0.65
CASP8AP2	Caspase 8 associated protein 2	Induction of apoptosis	0.54
PRKDC	Protein kinase, DNA-activated, catalytic polypeptide	Induction of apoptosis	0.49
BCL2A1	BCL2-related protein A1	Inhibition of apoptosis	1.62
MXD1	MAX dimerization protein 1	Inhibition of apoptosis	1.43
TNIP1	TNFAIP3 interacting protein 1	Inhibition of apoptosis	1.35
BTG2	BTG family, member 2	Inhibition of apoptosis	1.32
Immune response			
CCL4	Chemokine (C-C motif) ligand 4	Inflammatory response	1.89

Conclusion: Using analysis of the gene expression profile from PBMC, we observed a unique distinction between MTX-NR and MTX-R patients. These results suggest apoptosis as relevant mechanism involved in the non-response to MTX, providing new gene insights in the pharmacological actions of MTX in the treatment of RA.

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Comorbidity and Cost Burden of Patients Prior to Initiating Abatacept or Infliximab As First Line Biologic Therapy for the Treatment of Rheumatoid Arthritis. Theodore Darkow, Digisha Trivedi, Brian Meissner, Lisa Rosenblatt and Tony Hebden. Bristol-Myers Squibb, Plainsboro, NJ

Background/Purpose: Patients with rheumatoid arthritis (RA) typically have significant comorbidity which, along with underlying RA severity, may impact both choice and response to treatment. Prior research has shown that, compared with patients initiating subcutaneous biologic therapy, patients who receive an intravenous (IV) biologic have higher baseline RA-related costs, suggesting more severe disease. However, a description of the characteristics of patients initiating IV biologic therapy has not been done.

Objectives: Characterize baseline healthcare costs and degree of comorbidity and disease severity in RA patients, prior to initiating first-line treatment with the IV administered biologic agents abatacept or infliximab.

Methods: Utilizing a large, managed care plan claims database, an analysis was conducted in adult RA patients during the 6 months prior to initiating first-line biologic treatment with abatacept or infliximab. The identification period was January 1, 2006 through August 31, 2010. Severity of overall comorbidity was described using Charlson Comorbidity Index (CCI) and all-cause health care costs, while RA-related healthcare costs were used as a proxy measure for severity of RA.

Results: A total of 1623 RA patients were identified who initiated abatacept or infliximab as first-line biologic therapy. Baseline RA-related healthcare costs for abatacept treated patients (n=411) were approximately twice those of patients treated with infliximab (n=1212). Baseline total all-cause health care costs and CCI were also significantly higher for abatacept treated patients (Table).

	Abatacept Mean (SD)	Infliximab Mean (SD)	p-value
Baseline Charlson Comorbidity Index	1.64 (1.17)	1.44 (0.92)	0.001
Baseline RA-related health care costs	$3,145 ($10,774)	$1,506 ($4,406)	0.003
Baseline all-cause health care costs	$7,491 ($16,886)	$4,548 ($8,529)	<0.001

Conclusion: In a commercially insured population, those patients initiating first-line abatacept appeared to demonstrate greater baseline severity of RA, as well as more comorbidity than those who received first-line infliximab. Further research is required to better understand how pre-existing conditions and severity of RA impact selection of intravenous biologic therapy and subsequent response in this patient population.

1243

Fatigue in Patients with Rheumatoid Arthritis Treated with Tocilizumab (Actemra®) in Real Life: Clinically Relevant Improvement in 62% of Patients At 4 Months and Rapid Onset of Action. the PEPS Study. Laure Gossec[1], Stephanie Rouanet[2], Ghislaine Steinberg[3] and Bernard G. Combe[4]. [1]Cochin Hospital, Paris, France, [2]Roche, Neuilly sur Seine, France, [3]Roche, Neuilly Sur Seine, France, [4]Hopital Lapeyronie, Montpellier, France

Background/Purpose: Fatigue is an important domain of health in rheumatoid arthritis (RA). Biologics and in particular Tocilizumab (TCZ) have demonstrated their efficacy on fatigue [1]. However, there is a lack of data in real life on the effects of TCZ on fatigue and its rapidity of appearance. The main objective was to describe TCZ real life effect on fatigue over the first 4 months of treatment in RA patients.

Methods: PEPS is a multicenter non-interventional study assessing fatigue in real life in patients starting TCZ. *Patients:* RA patients requiring TCZ according to their physician. *Treatment:* TCZ as prescribed in real life. The first 5 infusions (4 months) were assessed. *Primary endpoint*: percentage of patients with variation of fatigue (FACIT-fatigue scale, 0–52, higher results indicate less fatigue) from inclusion to 4 months, above the minimal clinically important difference (MCID: 4 points) [2]. *Secondary endpoints:* VAS fatigue, SF-36 vitality, HAQ, patient global, sleep, anxiety and depression by HADS, pain, DAS28, haemoglobin and tolerance. *Analysis*: patients with at least one TCZ infusion and FACIT score available at inclusion and at least once under TCZ were analysed. Last observation carried forward (LOCF) method was used to handle missing data on the primary criterion and DAS28. Survival analysis was performed to quantify the onset of action on fatigue. Univariate then multivariate logistic regressions were conducted to explain improvement of fatigue.

Results: 719 pts were included; 610 had analysable data: mean age 56±13 yrs, disease duration 12±10 yrs, 490 (81%) women, 463 (81%) rheumatoid factor or ACPA positive, 84% biologic IR. Mean (±SD) baseline DAS28 and FACIT-fatigue were respectively 5.3±1.1 and 24±10. At 4 months, TCZ reduced disease activity: mean DAS28 was 2.9±1.3, and improved fatigue: mean FACIT-fatigue was 33±11; 62% (n=378) patients reached MCID improvement for fatigue. Less fatigue was already observed at 2 weeks after treatment initiation. The mean percentage reduction of fatigue assessed by the FACIT score versus baseline was respectively 26% at week 2, and 37%, 52%, 61% and 59% at 1, 2, 3 and 4 months. The median time to reach FACIT-fatigue improvement >MCID with maintenance afterwards was 3 months.

In multivariate analysis, the only determinants of improvement of fatigue above MCID were high baseline level of fatigue (OR 3.2; 95% CI 2.0–5.1) and CRP (OR 1.01, 95% CI 1.00–1.03). When excluding baseline fatigue from the analysis, the significant determinants were baseline high levels of CRP (OR 1.01, 95% CI 1.00–1.03), of pain (OR 1.6, 95% CI 1.0–2.6) and baseline low SF36 vitality score (OR 2.0, 95% CI 1.2–3.2).

Safety profile was consistent with phase III results.

Conclusion: In these long-standing active RA patients, TCZ was efficacious on fatigue with rapid reduction seen as early as 2 weeks after the first infusion. Improvement in fatigue was mainly linked to high baseline fatigue, CRP and pain. In patients with disabling fatigue, TCZ may be a useful therapeutic option.

References:

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1244

Treatment Satisfaction and Adherence of Patients on Biologic Monotherapy. Jörg Kaufmann[1], Anne-Eve Roske[2], Adrian Kielhorn[2], Eugen Feist[3] and Wolfgang A. Schmidt[4]. [1]Rheumatologist, Ludwigsfelde, Germany, [2]Roche Pharma AG, Grenzach-Wyhlen, Germany, [3]Charité Medical School, Berlin, Germany, [4]Med Ctr Rheumatol Berlin Buch, Berlin, Germany

Background/Purpose: The combination of a biologic DMARD (bDMARD) with methotrexate (MTX) is regarded as the gold standard for patients having not adequately responded to a conventional DMARD (cDMARD) therapy. Nevertheless, up to 40% of patients are receiving bDMARD monotherapy.

The aim is to compare treatment satisfaction and adherence in patients with rheumatoid arthritis on either TNF inhibitors or tocilizumab, both given as monotherapy.

Methods: Data from 254 patients treated with bDMARD monotherapy (TNF inhibitor or tocilizumab) between February and June 2010 were analyzed retrospectively in 23 centers across Germany. Analysis included drug adherence over a period of six months as well as patients and physicians global assessment on a 100 mm analogue scale. Selection criteria were confirmed diagnosis of RA; age > 18 years, and treatment initiation between February and June 2010. Patients had to be on their first or second bDMARD.

Results: Eighty-four percent of the patients were female; the mean age was 58 years (SD=18) and the mean weight was 70kg (SD 15.8). The mean time since diagnosis was 8.7 (SD 7.7) years. The tocilizumab and TNF inhibitor cohorts consisted of 126 and 128 patients, respectively.

Category	Tocilizumab (SD)	TNF inhibitors (SD)	All
Percentage still on treatment after 6 months (adherence)	90% (n=113)	76% (n=97)	83% (n= 210)
Patients global assessment after 6 months	75.3 (23.0)	66.8 (23.6)	71.0 (23.6)
Physicians global assessment after 6 months	74.9 (22.8)	67.1 (23.5)	70.9 (23.5)
General Health (VAS, change from baseline)	−32.0 (23.0)	−15.3 (30.5)	−25.2 (27.4)

*0= not satisfied, 100= satisfied, SD = standard deviation

Conclusion: Biologic DMARD mono-therapy is well tolerated by patients as expressed by the high adherence rate of 83%. The adherence rate of 90% shows tocilizumab to be an attractive treatment option in these patients.

1245

Baseline Tender Joint Count Scores Predict Long-Term Household Productivity in Patients with Rheumatoid Arthritis Treated with Certolizumab Pegol Plus Methotrexate. Arthur Kavanaugh[1], Oana Purcaru[2], Josef Smolen[3], Paul Emery[4], Vibeke Strand[5], Edward Keystone[6] and Ronald F. van Vollenhoven[7]. [1]University of California San Diego, San Diego, CA, [2]UCB, Brussels, Belgium, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [4]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [5]Stanford University, Palo Alto, CA, [6]University of Toronto, Toronto, ON, [7]Karolinska Institute, Stockholm, Sweden

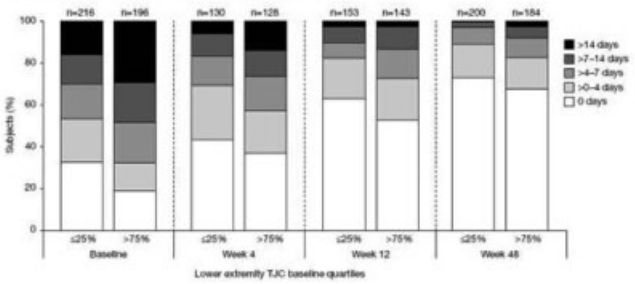
Background/Purpose: The impact of disease activity on household productivity has not been studied in detail. This analysis evaluated if baseline (BL) tender/swollen joint counts (TJC/SJC) are associated with and predict household productivity in patients (pts) with active rheumatoid arthritis (RA) receiving certolizumab pegol (CZP) plus methotrexate (MTX).

Methods: Pooled data at 1 year for CZP 200 and 400 mg completers from RAPID 1 (NCT00152386) and RAPID 2 and its open-label extension (NCT00160602/NCT00160641) were used. Household productivity (missed days of household work, days with reduced household productivity, days with outside help hired, missed days of family/social/leisure activities) was assessed using the Work Productivity Survey (WPS-RA).[1] Frequency distribution of WPS-RA scores over time was summarized by TJC/SJC BL 25% and 75% quartiles. Hand, large upper extremity (shoulder, elbow, hand), large lower extremity (hip [tender-

ness], knee, ankle), or total JC were assessed. Analyses were conducted on observed data (no imputation of missing data).

Results: At BL higher disease activity was associated with higher impairment in household duties and social activities (Table). Pts receiving CZP had rapid, sustained improvements in household productivity over time in all TJC/SJC quartiles. Over 1 year, fewer days of household work were missed per month in pts with lower (≤25% quartile) vs higher (>75% quartile) TJC BL scores in large lower extremity joints: by Week 4 (Wk) 69.2% vs 57.0% of pts missed ≤4 days of household work per month, increasing to 82.4% vs 72.7% by Wk 12 and by Wk 48, to 89.0% vs 82.6% (Figure). Although improvements in household productivity were reported by pts with higher BL TJC scores in the lower extremities, these were consistently smaller vs pts with lower BL TJC scores. Similarly pts with lower TJC BL scores in large lower extremity joints had greater reductions in days with reduced productivity and in days with outside help hired vs pts with higher BL scores. Fewer days of family/social/leisure activities were missed per month in pts with lower vs higher hand/total TJC BL scores. Pts with higher vs lower SJC BL scores had similar improvements in household productivity over time; there were no differences between the 2 groups at Wk 48.

Figure. Number of days with no household work per month (frequency distribution) in CZP patients, by large lower extremity TJC baseline scores (≤25% and >75% quartiles)



Conclusion: At BL higher TJC/SJC scores were associated with increased impairment in household productivity. Improvements in household productivity were seen with CZP treatment in both pts with lower vs higher BL TJC scores, with greater improvements in pts with lowest BL TJC scores.

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Osterhaus J, et al. Arthritis Res Ther 2009;11:R73.

1246

Improvement & Maintenance of Hemoglobin Levels Among Rheumatoid Arthritis, Psoriatic Arthritis&Ankylosing Spondylitis Patients with Anemia of Inflammation After Treatment with Golimumab:3 Year Pooled Analysis.

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Background/Purpose: Previous analyses have shown that treatment with golimumab (GLM) for 6 months resulted in significant improvements in hemoglobin (Hgb) levels among patients with anemia at baseline, particularly for patients with anemia of inflammation. The purpose of this analysis was to determine the long-term effects of GLM on anemia of inflammation in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Methods: Data through 3 yrs were pooled from 5 studies in the GLM rheumatology clinical program including: 3 RA studies (GO-BEFORE, GO-FORWARD, GO-AFTER), 1 PsA study (GO-REVEAL), and 1 AS study (GO-RAISE). Subcutaneous (SC) placebo (PBO) or GLM (50mg or 100mg) was administered q4wks in the randomized portions of the ongoing Phase3 trials. At 6 months/1 yr, pts remaining in the studies entered long term extensions (LTE) and received GLM 50mg or 100mg q4wks in an unblinded fashion. Dose escalation from 50mg to 100mg was allowed; no dose reduction was permitted. Primary endpoints for the studies compared patients treated with GLM±MTX with patients receiving placebo (PBO±MTX). Patients were defined as anemic if their Hgb were below the age- and sex-specific normal range of the central laboratory (Quintiles Laboratories, Smyrna, GA, United States). The normal Hgb range for the central laboratory was 11.6 to 16.2 g/dL for women aged ≤65 yrs, 11.0 to 16.1 g/dL for women aged ≥66 yrs, 13.0 to 17.5 g/dL for men aged ≤65 yrs, and 12.6 to 17.7 g/dL for men aged ≥66 yrs. A subset of patients with anemia of inflammation (anemic and ferritin ≥ 60 ng/mL), at baseline (BL) was analyzed for normalization and improvement of Hgb levels at 6 months; the long-term maintenance of these improvements were also analyzed at yrs 1, 2, and 3.

Results: At 6 months, among patients who had anemia of inflammation at baseline, patients treated with GLM±MTX showed greater Hgb improvements than patients treated with PBO±MTX (median improvement: 1.45 g/dL vs. 0.55 g/dL, $p < 0.001$) at 6 months. More GLM±MTX-treated patients achieved normal Hgb (67.9% vs. 42.3%, $p = 0.020$). Table 1 shows that 93.0% to 96.7% of these patients maintained normal Hgb at 1-, 2- and 3 years.

Table 1. Pooled Analysis of Data From GLM Rheumatology Clinical Trials-Maintenance of Normalized Hgb /Improvement From 6 Months to Years 1, 2, and 3 Among Pts With Anemia of Inflammation at BL

	Anemia of Inflammation at BL	Anemia of Inflammation at BL; Median Hgb improvement (g/dL)
Normalized Hgb at 6 months		
PBO	11/27 (40.7%)	0.55
GLM±MTX	55/84 (65.5%)	1.45
Maintenance of normalized Hgb*		
Year 1	58/62 (93.6%)	1.9
Year 2	59/61 (96.7%)	1.8
Year 3	53/57 (93.0%)	2.0

At 6 months all patients were receiving GLM (except in GO-BEFORE where all patients were receiving GLM at 1 year)
* Of all patients (including PBO- and GLM-treated patients) who had anemia of inflammation at BL and improved at 6 months

Conclusion: Among patients with RA, PsA and AS with anemia of inflammation at BL, patients treated with GLM±MTX achieved greater median improvements in Hgb and greater proportions had normalized Hgb levels at 6 months. Patients who achieved normal levels at 6 months and continued treatment with GLM, maintained the normal Hgb levels through 3 yrs. These improvements in anemia of inflammation support the hypothesis that anemia of inflammation responds to suppression of inflammation with GLM.

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Rheumatologists' Benefit-Risk Preferences for Biologic Treatments for Rheumatoid Arthritis.

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Background/Purpose: Little data exists on how physicians weigh benefit-risk tradeoffs of drugs, despite the impact on prescribing decisions. Biologic rheumatoid arthritis (RA) treatments can yield substantial benefits for patients, but can be associated with potentially serious, life-threatening risks. The aim of this study was to examine rheumatologists' preferences when weighing potential benefits and potential risks of biologic RA therapies.

Methods: US rheumatologists treating 10 or more RA patients monthly completed a web-enabled survey with a series of treatment-choice questions. These questions required choosing between two hypothetical RA treatments with differing levels of efficacy (defined as reduction in difficulty doing activities of daily living) and five potential treatment-related risks: annual risks of pneumonia, pneumocystis and progressive multifocal leukoencephalopathy (PML); 5-year risk of lymphoma; and risk of post-injection/-infusion anaphylaxis. An index of the importance of each treatment attribute was estimated using a mixed-logit choice model. The results of the model were used to calculate the

maximum level of each risk rheumatologists considered acceptable to achieve different improvements in patients' functioning.

Results: 190 rheumatologists completed the survey. The majority (77%) was male and in private practice (84%). Most (70%) had been in practice for at least 10 years.

Rheumatologists were willing to accept increases in treatment-related risks to improve a patients' ability to do daily activities. The most important risk was annual PML, followed in order of decreasing importance by 5-year risk of lymphoma, risk of post-injection/-infusion anaphylaxis, annual risk of pneumocystis, and annual risk of pneumonia. The maximum level of treatment-related risks that rheumatologists would accept for reduced limitations on daily activities from moderate to mild or from mild to none are presented in Table 1. Rheumatologists were consistently more willing to accept greater risks for greater benefits (improving RA from moderate to mild). Serious but rare risks such as PML, lymphoma and anaphylaxis were much less tolerated than more common risks with significant morbidity and mortality.

Table 1. Maximum percentage-point treatment-related risk rheumatologists would accept for different improvements in limitations on daily activities.

Treatment-Related Risk	Maximum Acceptable Risk for an Improvement in daily limitations from Moderate to Mild	Mild to None
Annual risk of PML	0.48% (0.36,0.60)	0.25% (0.15,0.34)
5-year risk of lymphoma	0.96% (0.57,1.35)	0.49% (0.28,0.70)
Risk of anaphylaxis after each injection or infusion	1.08% (0.71,1.45)	0.55% (0.32,0.79)
Annual risk of pneumocystis	2.23% (0.46,4.00)	1.14% (0.22,2.06)
Annual risk of pneumonia	3.78% (2.76,4.81)	1.94% (1.18,2.69)

Conclusion: Rheumatologists do not place uniform importance on different potential treatment-related risks. In order to reduce the impact of RA on patients' ability to conduct daily activities, rheumatologists appear willing to accept levels of treatment-related greater than those levels reported in the literature. PML was more unacceptable than we anticipated relative to risks such as lymphoma and pneumocystis that are associated with substantial morbidity, mortality and much greater frequency.

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Assessment of Immune Responses to Pneumococcal and Influenza Vaccines in Patients with Rheumatoid Arthritis Receiving Certolizumab Pegol. A. Kivitz[1], Joy Schechtman[2], Michele Texter[3], Andreas Fichtner[4] and Elliot Chartash*[3]. [1]Altoona Center for Clinical Research, Duncansville, PA, [2]SunValley Arthritis Center, Peoria, AZ, [3]UCB, Smyrna, GA, [4]UCB Biosciences GmbH, Monheim, Germany

Background/Purpose: The extent of antibody response to influenza and pneumococcal vaccination was evaluated in adult patients (pts) with rheumatoid arthritis (RA) receiving certolizumab pegol (CZP) or placebo (PBO).

Methods: This was a 6-week (wk) randomized, single-blind, PBO-controlled, phase IV trial followed by a 6-month open-label phase (NCT00993668). In the 6-wk phase, pts were randomized 1:1 and stratified by concomitant (MTX) use to receive CZP 400 mg or PBO at Wks 0, 2, and 4. All pts received commercially available 23-valent pneumococcal and 2009–10 trivalent subvirion influenza virus vaccines at Wk 2, prior to dosing with CZP. The co-primary endpoints (assessed independently) were the percentage of pts, in the per protocol set (PPS, included only those pts without protective titers at baseline [BL]) with a satisfactory humoral response defined as a ≥2-fold titer increase in ≥3 of 6 pneumococcal antigens (6B, 9V, 14, 18C, 19F, and 23F) and a ≥4-fold increase for each of 3 influenza antigens (H1N1 [nonpandemic], H3N2, and B), at Wk 6 (4 wks post-vaccination). Differences in proportions between groups were presented with a 95% confidence interval (CI). The results from 6-wk phase are reported.

Results: Of 224 randomized pts (CZP = 110; PBO = 114), 217 (96.9%) completed the 6-wk single-blind phase. BL demographics were similar between groups; 65.5% (72/100) of CZP and 68.4% (78/114) of PBO pts had concomitant MTX use (mean dose,16.6 mg/wk) at BL. In the PPS, following pneumococcal vaccination 53.3% of CZP pts (48/90) and 62.2% (56/90) of PBO pts achieved humoral response, at Wk 6 (–8.9; 95% CI: –23.3; 5.5). Following influenza vaccination, 54.0% (47/87) of CZP pts and 61.9% (52/84) of PBO pts achieved humoral response, at Wk 6 (–7.9; 95% CI: –22.7; 6.9). There was a >2-fold increase from BL to Wk 6 in titers in both treatment groups for each of the antigens tested in all pts including those with protective titers at BL (full analysis set, FAS). Following vaccination, 62.6% (67/107) of CZP and 65.5% (72/110) of PBO pts and 71.0% (76/107) of CZP and 77.1% (84/109) of PBO pts in the FAS developed protective pneumococcal and influenza antibody titers, respectively. Responses to pneumococcal and influenza antigens were reduced in both CZP and PBO pts who received concomitant MTX vs those who did not (CZP vs PBO: pneumococcal antigens, with concomitant MTX = 45.2% [28/62] vs 49.2% [30/61], without concomitant MTX = 71.4% [20/28] vs 89.7% [26/29]; influenza antigens, with concomitant MTX = 47.4% [27/57] vs 50.9% [29/57], without concomitant MTX = 66.7% [20/30] vs 85.2% [23/27]). Incidence of adverse events was comparable in CZP and PBO; most events were mild to moderate in intensity. There was 1 death in CZP group (bladder cancer diagnosed during study; unrelated to study drug) and none in the PBO group.

Conclusion: Humoral responses to pneumococcal and influenza vaccines were comparable in RA pts receiving treatment with CZP and PBO. Vaccine responses were reduced in both treatment groups with concomitant MTX therapy. These results indicate that RA pts receiving CZP can be effectively immunized with pneumococcal and influenza vaccines.

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Number of Cardiovascular Risk Factors May be Associated with Higher Disease Activity Severity. Exploratory Analysis of Baseline Data from the Canadian Methotrexate and Etanercept Outcome Study: A Randomized Trial of Etanercept and Methotrexate vs Etanercept Alone in Rheumatoid Arthritis. Janet Pope[1], Edward Keystone[2], Boulos Haraoui[3], J. Carter Thorne[4] and Melanie Poulin-Costello[5]. [1]Univ of Western Ontario, London, ON, [2]University of Toronto, Toronto, ON, [3]Institut de Rhumatologie, Montreal, QC, [4]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [5]Amgen Canada Inc., Mississauga, ON

Background/Purpose: We designed a real-world rheumatoid arthritis (RA) non-inferiority trial to compare the proportion of patients with low disease activity while on etanercept (ETN) monotherapy vs ETN + methotrexate (MTX). The trial is still ongoing. Baseline data were explored to determine if cardiovascular (CV) risk factors such as hypertension (HTN), diabetes mellitus (DM), hypercholesterolemia, prior myocardial infarction (MI), and high body mass index (BMI) correlate with higher baseline disease activity. Two studies suggest increased erosions in those with low BMI in early RA.[1,2]

Methods: Baseline characteristics of established RA patients who, despite MTX therapy, had active disease (≥ 3 swollen joints), DAS28 ≥ 3.2, and were TNF inhibitor naïve were studied. A post-hoc exploratory analysis of baseline data examined the impact of CV risks on baseline DAS, adjusting for sex, age, prior RA medications, and duration of disease, using analysis of variance (ANOVA). Model selection was done by backwards elimination for $p < 0.1$.

Results: 258 patients with active RA (76% female; mean age, 54.7 ± 12.5 yrs; DAS28, 5.4 ± 1.1; duration of RA, 8.9 ± 8.4 yrs) were enrolled. Mean baseline health assessment questionnaire (HAQ) score was 1.38 ± 0.61. Mean duration of MTX treatment was 4.9 ± 4.7 yrs (mean dose, 20.5 ± 4.1 mg/wk). Higher baseline disease activity was statistically correlated with an increased number of CV risk factors ($p < 0.0001$), although each CV risk was not significant. No other factors had a significant statistical correlation with DAS28. In addition, BMI and DAS were not related statistically.

Limitations: Data on smoking and family history of CV events were not collected, and CV risk was determined from patient medical history. Only patients with active disease were selected for the study; which could bias the results compared to a prevalent RA population. Our study size is small and this was a post-hoc analysis, however numerically (but not statistically) it appears that many CV risk factors were associated with higher DAS.

Table 1. Cardiovascular Comorbidities and Disease Activity at Baseline

Comorbidity	Total Population (N = 258)	
	n	Mean DAS28 (95% CI)
Number of CV risk factors*, p = 0.0002[a]		
0	116	5.1 (4.9, 5.3)
1	75	5.6 (5.3, 5.8)
2	41	5.7 (5.4, 6.0)
≥ 3	26	6.0 (5.6, 6.4)
Gender, p = 0.0678		
Female	197	5.5 (5.3, 5.6)
Male	61	5.2 (4.9, 5.5)
Diabetes Mellitus, p = 0.2481		
Yes	18	5.7 (4.9, 6.5)
No	239	5.4 (5.3, 5.5)
Hypertension, p = 0.1417		
Yes	81	5.8 (5.6, 6.0)
No	154	5.2 (5.0, 5.4)
Hypercholesterolemia†, p = 0.9254		
Yes	43	5.7 (5.4, 6.0)
No	215	5.4 (5.2, 5.5)
Myocardial infarction, p = 0.7403		
Yes	11	5.9 (4.9, 6.8)
No	247	5.4 (5.3, 5.5)
BMI, kg/m^2, p = 0.3057[b]		
< 18.5	5	5.9 (5.4, 6.4)
≥ 18.5 to < 25	59	5.3 (5.0, 5.6)
≥ 25 to < 30	74	5.3 (5.1, 5.5)
≥ 30	63	5.8 (5.5, 6.1)
Other CV medical history, p = 0.5820		
Yes‡	27	5.6 (5.2, 6.0)
No	231	5.4 (5.3, 5.5)
Elevated CRP[c]		
≥ 3 mg/L	173	5.6 (5.4, 5.8)
< 3 mg/L	51	4.7 (4.5, 4.9)

[a] p-values from the multivariate ANOVA backwards elimination results. Age, duration of disease, and duration of methotrexate were also included in the model (p > 0.10) but are not shown here.
[b] BMI was a continuous variable in the ANOVA
[c] Not included in the ANOVA
* CV risk factors: hypertension, hypercholesterolemia, diabetes, prior MI, BMI ≥ 30
† Hypercholesterolemia includes dyslipidemia and high cholesterol
‡ 27 subjects had 46 cardiac-related medical histories including: angina attack, angina pectoris, angioplasty, cardiac catheterization, cardiovascular disease, carotid artery stenosis, carotid endarterectomy, coronary artery bypass graft, coronary arterial stent insertion, dyslipidemia (resolved at time of study start), hypertension (resolved at time of study start), ischemia, myocardial infarction, stent placement
Abbreviations: ANOVA = analysis of variance; BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; CV = cardiovascular; MI = myocardial infarction

Conclusion: There is a statistical suggestion from this baseline data that an increase in the number of CV risks were associated with worse baseline DAS28 scores in this clinical trial of patients with active RA.

References:
1. Velpula U, et al. J Rheumatol. 2011;38(3):434–8. Epub 2010 Nov 15.
2. Kaufmann J, et al. J Rheumatol. 2003;30(11):2350–5.

Trial Registration: ClinicalTrials.gov, number: NCT00654368
Role of the Study Sponsor: Amgen Canada Inc. oversaw the design, conduct, collection of data in the study and assisted in the analysis and interpretation of data
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Effect on rheumatoid factor and anti-Cyclic Citrullinated Peptide Antibodies Levels of treatment with Infliximab and Adalimumab in patients with Rheumatoid Arthritis. Selene Baos, Chamaida Plasencia, Susana Ramiro, Rosario Moral, Jesús Díez, E. Martin-Mola, Alejandro Balsa and Dora Pascual-Salcedo. La Paz University Hospital, Madrid, Spain

Background/Purpose: Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) have been demonstrated to be useful in the diagnosis of rheumatoid arthritis (RA). Therapeutical monoclonal antibodies that inhibit tumour necrosis factor (TNF) activity, like infliximab (IFX) and adalimumab (ADA), have a demonstrated effect in the improvement of RA disease activity. IFX and ADA can induce the development of anti-drug antibodies (Abs) and this has been associated with a poor clinical response. Our aim was to study the effect of anti-TNF therapy (with IFX or ADA) on the variation of RF and ACPA levels in RA patients with a long-term treatment and if the formation of anti-drug Abs, concomitant treatment with MTX and the clinical response have any influence on RF and ACPA titers

Methods: We studied 83 patients with active RA treated with a TNF inhibitor (50 patients with IFX,and 33 with ADA), for a median of 4.3 (± 2.6) years. Clinical characteristics, serum trough drug levels and the presence of anti-drug Abs were evaluated. Clinical activity was measured by Disease Activity Score 28 (DAS28) and clinical response was evaluated by EULAR criteria. ACPA were measured by second generation ELISA, RF by nephelometry and the presence of anti-drug Abs by a bridging ELISA (1). Three time points (6 months, 1 year and 2–4 years) were chosen for the study. For the purpose of this study only patients with positive RF and/or ACPA were considered.

Results: RF was positive in 79 (95.2%) patients and ACPA in 76 (91.6%) patients. Both drug group (IFX and ADA) were analyzed together because no differences were seen in the decrease of RF (p=0.108) and ACPA (p=0.888) levels between groups. At baseline, there was no association between clinical activity and ACPA and RF levels (Pearson correlation (PC)=0.21 and PC=0.25, respectively). At 6 months RF but not ACPA, showed a significant decrease (320.66±393.53 at baseline vs 181.26±239.60 at 6 months, p<0.001 in RF and 1537.82±1263.87 at baseline vs 1428.59±1278.33 at 6 months, p=0.239 in ACPA). At 1 year and 2–4 years, both RF and ACPA titers had a significant decrease (p<0.05).The relative change (%) was significantly higher for RF than for ACPA during all the study (p<0.0001). More patients became negative in RF than in ACPA levels along the study [7 out of 79 (8.8%) vs 5 out of 76 (6.5%) at 6 months (p=0.4), 19 out of 79 (24%) vs 4 out of 76 (5.2%) at 1 year (p=0.001), 21 out of 79 (26.5%) vs 4 out of 76 (5.2%) at 2–4 years (p=0.0001), respectively]. EULAR clinical response was not associated by the lost of positivity of RF and ACPA at any studied point (p>0.1). RF and ACPA levels were not affected by the development of anti-drug Abs (p=0.2 and p=0.62, respectively), concomitant MTX therapy (p=0.858 and p=0.588, respectively) and clinical EULAR response at 4 years (p=0.165 and p=0.537, respectively).

Conclusion: The anti-TNF therapy has an influence on RF and ACPA levels. in RA patients in a long term treatment, being RF decrease more pronounced than the reduction of ACPA levels. The change in the RF and ACPA titers was not associated with a improvement in the clinical response.

(1) Pascual-Salcedo et al. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. Epub 22 March 2011

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Does Single Nucleotide Polymorphism in Folate Metabolic Pathway Contribute to Methotrexate Efficacy in Indian (Asian) Patients with Rheumatoid Arthritis? Yogita Ghodke[1], Arvind Chopra[2], Amrutesh S. Puranik[1], Pooja Shintre[3], Anjali Radkar[4], Kalpana Joshi[5] and Bhushan Patwardhan[5]. [1]University of Minnesota, Minneapolis, MN, [2]Centre for Rheumatic Diseases, Pune 411001, India, [3]Sinhgad College of Engineering, Pune, India, [4]Gokhale Institute of Politics and Economics, Pune, India, [5]Symbiosis International University, Pune - 411042, India

Background/Purpose: Folate antagonist MTX is preferred because of its cost and long term experience. However, ~50% patients experience good clinical response. Inconsistent non genetic prediction (treatment response) variables, significant variability in MTX response and expensive alternative biologic DMARDs demand better predictive markers for MTX response. We investigated SNPs in folate metabolic pathway in Indian (Asian) RA patients treated with MTX. We hypothesized that these SNP would affect MTX pharmacokinetics (PK) and MTX treatment outcome.

Methods: A total of 336 ACR classified RA patients (Female 85%, RF 79%) undergoing supervised MTX therapy for > 3 months were randomly selected from a community rheumatology clinic; 217 patients were analyzed; maximum (usually limited by tolerability) MTX dose 3.75–20 mg, median 17.5mg. We retrospectively analyzed standard CRF but recalled several patients to confirm events. Responders were classified as patients having ACR 50 at 12 months plus ACR 20 response at 6 months; ACR improvement response as per ACR. 12 SNPs in 9 genes of

folate-MTX metabolism (including transporters) were genotyped using PCR-RFLP and Real-time Taqman allelic discrimination that also included 144 healthy controls (HC). To evaluate the effect of SNPs on MTX PK; PK analysis was performed on 94 patients (weekly dose ranging 3.75 mg – 20 mg). Plasma MTX and its metabolite 7-OH MTX levels were determined at 0, 2 and 8 hr. by HPLC post column photoxidation-fluorescence detection and plasma homocysteine was estimated at 0 hr.

Results: (1) *MTHFR* A1298C 'C' allele (OR =2.6, 95% CI 1.9– 3.5, P<0.0001) and *RFC*1 G80A 'G' allele (OR=2.0, 95% CI, 1.5– 2.7, P<0.0001) were significantly associated with RA when compared to HC. (2) The table shows frequency distribution of genotypes associated with ACR 50 response. At 12 months patients with *MTHFR* 1298 CC genotype and *RFC*1 80 GG genotype were more likely to have poor MTX efficacy relative to *MTHFR* 1298 AA-AC (OR= 3.3, 95% CI 1.3–8.5, P=0.01) and *RFC*1 80 AA-GA (OR= 2.2, 95% CI 1.0–4.9, P=0.04) respectively. None of the other SNPs in folate-MTX pathway were associated with MTX efficacy in our RA population. (3) PK analysis revealed no significant difference in the plasma concentration of MTX, 7OH MTX and Hcy at 0hr, 2hr and 8 hrs between responders and non responders. However patients having 1298 CC genotype showed higher 7 OH MTX levels at 8 hrs.

Polymorphism	ACR 50 response	
	Responders (n=49)	Non responders (n=168)
***MTHFR* A1298C** AA + AC CC	0.840.16	0.680.32*
***RFC*1 G80A** AA + GA GG	0.730.27	0.600.40*

Conclusion: Patients with *MTHFR* 1298 CC and *RFC*1 80 GG showed poor clinical improvement with MTX. PK study show some associations with genetic polymorphisms but need to be further validated. SNPs in folate pathway may contribute to MTX efficacy in Indian RA patients. Large sample size validation cohort would be required to confirm our observations with an attempted higher dose to treat.

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Association of ACR Clinical Responses with CDAI (Clinical Disease Activity Index) and RAPID3 (Routine Assessment of Patient Index Data 3) Indices of Disease Activity in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol Plus Methotrexate. Michael H. Schiff[1], Kristel Luijtens[2], Owen Davies[2] and Yusuf Yazici[3]. [1]Rheumatology Division, University of Colorado, Denver, CO, [2]UCB, Brussels, Belgium, [3]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: CDAI (clinical disease activity index) and RAPID3 (routine assessment of patient index data 3) cut points defining responses that best match ACR20/50/70 response in rheumatoid arthritis (RA) patients (pts), are unknown. This study evaluates these cut points in a large study population treated with certolizumab pegol (CZP) plus methotrexate (MTX)[1].

Methods: ACR responders through Week (Wk) 12 from 393 pts treated with CZP (initial dose of 400 mg at Wks 0, 2 and 4 followed by 200 mg every 2 wks) plus MTX in RAPID 1 trial (NCT00152386) were categorized by proposed response cut points in CDAI (change from baseline CFB ≥6.7, ≥10.0, ≥13.9 and RAPID3 CFB ≥1.8, ≥3.6). ACR20/50/70 responses were compared with these proposed categorizations using cross-tabulations and kappa statistics. CART[2] (classification and regression trees) modeling was used to identify CDAI and RAPID3 cut points most closely associated with ACR20/50/70 responses.

Results: At Wk 12, almost all (93–100%) ACR20/50/70 responders achieved CFB in CDAI (≥6.7, ≥10.0, ≥13.9); however fewer pts (73–80%) with CFB in CDAI (≥6.7, ≥10.0, ≥13.9) achieved an ACR20 response (Table 1). CFB in CDAI≥13.9 was most closely associated with ACR20 response (κ=0.57). Association between proposed categorizations and ACR50/70 was weak (κ range: 0.05–0.29). Nearly all (90–100%) ACR20/50/70 responders achieved CFB in RAPID3 (≥1.8, ≥3.6); fewer pts (75–80%) with a CFB in RAPID3 (≥1.8, ≥3.6) also achieved an ACR20 response (Table 2). CFB in RAPID3≥3.6 was most closely associated with ACR20 response (κ=0.55); association between proposed categorizations and ACR50/70 was weak (κ range: 0.08–0.30). CART modeling identified CFB in CDAI ≥13.80, ≥20.15 and CFB in RAPID3 ≥5.46, ≥7.28 as the categorizations most closely associated with ACR50/70 responses. There was better association between ACR50 response and CART-defined CDAI of CFB ≥20.15 (κ=0.43) compared with proposed categorizations (κ range: 0.14–0.29) (Table 1) and better association with ACR70. CART-defined RAPID3 categorizations were more closely associated with ACR20/50/70 responses; with better association between ACR50 and CART-defined RAPID3 categorizations (κ=0.45) than with proposed categorizations (κ range: 0.21–0.30) (Table 2).

Table 1.

	ACR responders at Week 12 who also achieved CDAI CFB in patients[a] according to proposed cutpoints (Patients%) *Patients[a] (%) with CFB in CDAI who also achieved an ACR response at Wk 12* (kappa coefficient)			ACR responders at Wk 12 who also achieved CDAI CFB in patients[a] according to cutpoints defined by CART modelling (patients%) *Patients[a] (%) with CFB in CDAI who also achieved an ACR response at Wk 12* (kappa coefficient)	
	CDAI ≥6.7	CDAI ≥10.0	CDAI ≥13.9	CDAI ≥13.80	CDAI ≥20.15
ACR20	99.6	98.0	93.1	93.1	
	73.3 (0.41)	*75.7* (0.48)	*80.5* (0.57)	*80.5* (0.57)	
ACR50	100.0	100.0	99.2		95.3
	38.0 (0.14)	*39.9* (0.19)	*44.3* (0.29)		*51.9* (0.43)
ACR70	100.0	100.0	100.0		96.6
	17.5 (0.05)	*18.4* (0.07)	*20.6* (0.12)		*24.3* (0.19)

Table 2.

	ACR responders at Week 12 who also achieved CFB in proposed RAPID3, Patients[a] (%) *Patients[a] (%) with CFB in RAPID3 who also achieved an ACR response at Wk 12* (kappa coefficient)		ACR responders at Week 12 who also achieved CFB in CART-defined RAPID3, Patients[a] (%) *Patients[a] (%) with CFB in RAPID3 who also achieved an ACR response at Wk 12* (kappa coefficient)		
	RAPID3 ≥1.8	RAPID3 ≥3.6	RAPID3 ≥5.46	RAPID3 ≥5.53	RAPID3 ≥7.28
ACR	96.4	90.3	79.4		
	75.8 (0.47)	*80.8* (0.55)	*86.3* (0.55)		
ACR50	100.0	96.9			79.7
	40.8 (0.21)	*44.9* (0.30)			*56.4* (0.45)
ACR70	100.0	98.31		94.9	
	18.8 (0.08)	*21.0* (0.13)		*24.8* (0.20)	

CFB, change from baseline; CDAI, clinical disease activity index; RAPID3, routine assessment of patient index data 3; CART, classification and regression trees
[a] Patients who received an initial dose of CZP 400 mg Wks 0, 2 and 4 followed by 200 mg every 2 wks plus MTX

Conclusion: Thresholds for CDAI and RAPID3 CFB were identified that defined the closest associations with ACR responses in pts with inadequate response to MTX and high disease activity at baseline (mean DAS28 6.9). Responses based on cut points closely associated with ACR20 were identified, but association with ACR50 and ACR70 was not as strong. Further studies are needed to analyze different pt populations, including those with lower disease activity at baseline.

Reference:
1 Keystone E, et al. Arthritis Rheum 2008; 58(11):3319–29.
2 Classification And Regression Trees (CART) software, Salford Systems, CA, USA

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Efficacy and Safety of Certolizumab Pegol in a Broad Population of Patients with Active Rheumatoid Arthritis: Week 28 Results From a Phase IIIb Randomized Controlled Study. Michael Weinblatt[1], Roy M. Fleischmann[2], Ronald F. van Vollenhoven[3], Paul Emery[4], T.W.J. Huizinga[5], Maurizio Cutolo[6], Ruth Goldermann[7], Benjamin Duncan[8], Owen Davies[9] and Maxime Dougados[10]. [1]Brigham & Women's Hospital, Boston, MA, [2]MCRC, University of Texas, Dallas, TX, [3]Karolinska Institute, Stockholm, Sweden, [4]University of Leeds, Leeds, United Kingdom, [5]Leiden University Medical Centre, Leiden, Netherlands, [6]Research Laboratory and Academic Unit of Clinical Rheumatology, University of Genova, Genova, Italy, [7]UCB, Monheim, Germany, [8]UCB, Raleigh, NC, [9]UCB, Brussels, Belgium, [10]Rene Descartes University, Paris, France

Background/Purpose: In the 12-week (wk) REALISTIC (**R**A **E**v**AL**uation **I**n **S**ubjects receiving **T**NF **I**nhibitor **C**ertolizumab pegol) (NCT00717236) Phase IIIb trial, certolizumab pegol (CZP) was associated with rapid and consistent clinical responses, reduced disease activity, and improved physical function in a diverse group of rheumatoid arthritis (RA) patients (pts) irrespective of concomitant or prior therapy or disease duration.[1,2] We evaluated clinical responses in pts who completed the 12-wk double-blind (DB) phase and entered the open-label extension (OLE), up to Wk 28.

Methods: Following the 12-wk DB phase (CZP 400 mg/placebo [PBO] at Wks 0, 2, 4, then CZP 200 mg/PBO at Wks 6, 8, 10 plus current treatment) pts received open-label CZP 200 mg every other week

for ≥16 Wks. ACR responses, change from baseline (BL) in DAS28(CRP) and HAQ-DI, and DAS28(ESR) remission (DAS28 <2.6) at Wk 28 are shown in CZP and PBO Wk 12 completers receiving at least 1 dose of OL CZP at Wk 12 (OLE population). Pts who withdrew from the OLE for any reason had data imputed from that time point onward. For ACR responses, NRI and LOCF (from OLE visits only) were used for pts who withdrew due to AEs/lack or loss of efficacy and other reasons, respectively. Mixed model repeated measures (MMRM) was used for DAS28 and HAQ-DI. Safety data in DB phase and up to Wk 28 in OLE are presented.

Results: Of 851 CZP and 212 PBO pts in the ITT population, 771 (90.6%) and 184 (86.8%) completed the 12-wk DB phase and entered the OLE, respectively. BL disease characteristics and prior and concomitant therapy at randomization (Wk 0) were similar between CZP and PBO completers (Table). Percentage of pts with prior TNF inhibitor use was similar in OLE and DB phase (37.4% vs 37.6%, respectively). Clinical responses and improvements in DAS28 and HAQ-DI were comparable in CZP (28 wks CZP) and PBO (16 wks CZP) completers (Table). At Wk 28, DAS28(ESR) remission (DAS28<2.6) was achieved in 15.2% and 11.4% of CZP and PBO completers, respectively. CZP safety profile was similar to previous CZP trials. In the DB phase, incidence of AEs and serious AEs in CZP vs PBO groups was 522.05 and 26.68 vs 483.20 and 25.83 cases/100 pt-years, respectively; there were 2 deaths (1 case each of sigmoid diverticulitis and necrotizing pneumonia). In the OLE, incidence of AEs and serious AEs in CZP vs PBO completers was 239.12 and 13.03 vs 328.85 and 20.61 cases/100 pt-years, respectively; 2 deaths (1 case each of myocardial infarction and small-cell lung cancer) and 1 case of disseminated tuberculosis were reported.

Table. Disease characteristics at baseline and efficacy outcomes at Wk 28 for patients originally randomized to double-blind CZP or PBO for 12 weeks (CZP or PBO completers) followed by open-label CZP

Disease characteristics and prior and concomitant therapy in the OLE population at randomization (Wk 0)	Patients originally receiving CZP in the double-blind phase (CZP completers [28 wk CZP treatment]) n=770[a]	Patients originally receiving PBO in the double-blind phase (PBO completers [16 wk CZP treatment]) n=184
DAS28(CRP), mean (SD)	5.69 (0.90)	5.72 (0.84)
DAS28(ESR), mean (SD)	6.36 (0.94)	6.44 (0.85)
HAQ-DI, mean (SD)	1.48 (0.64)	1.60 (0.59)
Disease duration (years)		
Mean (SD)	8.53 (8.67)	8.85 (9.04)
Median (interquartile range)	5.30 (2.14–12.00)	6.43 (2.00–12.94)
Disease duration ≥2 years, n (%)	566 (76.1)	139 (75.5)
Prior TNF inhibitor use, n (%)	286 (37.1)	71 (38.6)
Concomitant MTX use, n (%)	533 (69.2)	128 (69.6)
Clinical assessment in the OLE population at Wk 26		
ACR20 responders,%	59.7	53.3
ACR50 responders,%	36.0	31.0
ACR70 responders,%	18.1	14.7
LS mean change from BL in DAS28(CRP)	−1.97	−1.82
LS mean change from BL in DAS28(ESR)	−2.18	−2.00
LS mean change from BL in HAQ-DI	−0.47	−0.40

NRI, non-responder imputation; LS, least square; DAS, disease activity score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire-disability index. [a]The number varies from n=771 CZP Wk 12 completers entering the OLE due to 1 CZP completer who discontinued the OLE after Wk 12 due to an AE, did not receive any study medication in the OLE, and was not included in the OLE analysis set.

Conclusion: In a diverse group of pts with RA, treatment with CZP was associated with rapid efficacy and improvements in disease activity and physical function up to 28 weeks, irrespective of concomitant DMARDs, prior TNF inhibitor therapy, or duration of disease.

References

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1254

No Change in Arterial Stiffness After 6 Months of Abatacept Treatment in Rheumatoid Arthritis. Sylvain Mathieu[1], Bruno Pereira[2], Emilie Rabois[1], Anne Tournadre[1], Jean Jacques Dubost[1] and Martin Soubrier[2]. [1]CHU Gabriel Montpied, Clermont-Ferrand, France, [2]CHU CLERMONT-FERRAND, Clermont-Ferrand, France

Background/Purpose: The excess cardiac risk found in rheumatoid arthritis (RA) has been attributed to biological inflammation. Effective control of inflammation and disease activity may be of benefit in reducing cardiovascular risk in RA patients.

Methods: and Objectives: To investigate the effects of 24 weeks of abatacept treatment in active RA on arterial stiffness measured by augmentation index (AIx) and pulse wave velocity (PWV) and on traditional cardiovascular risk factors (lipid profile, blood pressure).

Results: Twenty-one patients, of whom 17 (81.0%) were female; with a mean age of 65.2 ± 13.7 years and a mean disease duration of 21.5 ± 10.0 years, were included. Of the 21 RA patients, 10 (47.6%) had positive rheumatoid factors, 16 (76.2%) had positive anti-CCP antibody, and 90.5% (n=19) were erosive. Sixteen patients (76.2%) were non-responders to anti-TNF alpha treatments.

After 6 months of abatacept treatment, no change was observed in PWV and AIx (PWV: 8.5 ± 3.8 m/s at baseline, 9.3 ± 3.0 at 6 months; p=0.07 and AIx: 31.4 ± 10.7% at baseline, 31.6 ± 9.1 at 6 months; p=0.97). A significant increase in levels of HDL cholesterol (1.64 ± 0.45 mmol/l at baseline, 1.93 ± 0.62 at 6 months; p=0.01) and a decrease in atherogenic index (total cholesterol/HDL cholesterol), but not to a level of significance (3.14 ± 0.79 at baseline, 2.89 ± 0.96 at 6 months, 3.37 ± 1.03 at one year; p=0.14), were obtained. We found no modification in levels of total cholesterol (4.91 ± 0.99 mmol/l at baseline, 5.22 ± 0.86 at 6 months; p=0.33), LDL cholesterol (2.65 ± 0.65 mmol/l at baseline, 2.70 ± 0.63 at 6 months; p=1.0) or triglycerides (1.17 ± 0.53 mmol/l at baseline, 1.31 ± 0.73; p=0.72). No change was found in levels of blood pressure. DAS28 ESR (5.1 ± 1.0 at baseline, 3.5 ± 1.3 at 6 months; p<0.001) and DAS28 CRP (4.8 ± 0.9 at baseline, 3.4 ± 1.2 at 6 months; p<0.001) were significantly improved. We found a significant decrease in parameters of biological inflammation, significant for ESR (35.7 ± 38.9 mm/h at baseline, 26.6 ± 28.1 at 6 months; p=0.04) but not for CRP (21.5 ± 36.1 mg/l at baseline, 11.8 ± 15.1 at 6 months; p=0.61).

Conclusion: This study shows that arterial stiffness was not improved after 6 months of abatacept therapy. This lack of improvement might be due to insufficient decrease in biological inflammation in these 21 RA patients. However, the treatment did have a beneficial effect on lipid profile and so it would be interesting to have an assessment over a longer period.

Disclosure: S. Mathieu, None; **B. Pereira**, None; **E. Rabois**, None; **A. Tournadre**, None; **J. J. Dubost**, None; **M. Soubrier**, None.

1255

Folate Metabolic Pathway Single Nucleotide Polymorphisms a Predictive Pharmacogenetic Marker of Methotrexate Related Adverse Events in Indian (Asian) Patients with Rheumatoid Arthritis. Yogita Ghodke[1], Arvind Chopra[2], Amrutesh S. Puranik[1], Pooja Shintre[3], Anjali Radkar[4], Kalpana Joshi[5] and Bhushan Patwardhan[5]. [1]University of Minnesota, Minneapolis, MN, [2]Centre for Rheumatic Diseases, Pune, India, [3]Sinhgad College of Engineering, Pune, India, [4]Gokhale Institute of Politics and Economics, Pune, India, [5]Symbiosis International University, Pune - 411042, India

Background/Purpose: Methotrexate (MTX) is a folate analogue and the best tolerated DMARD but is limited by major interpatient variability in clinical response and unpredictable toxicity. Though the increasingly recognized association of single nucleotide polymorphisms (SNPs) of the folate metabolic pathway is published little is known about Indian population. We present the results of a pharmacogenetic study in Indian RA patients on MTX. We hypothesized the role of SNPs in MTX pharmacokinetics (PK) and MTX related adverse events (AE).

Methods: 322 RA patients (Female 86%, RF 79%) undergoing supervised MTX therapy for > 3 months; were randomly selected from a community rheumatology clinic; maximum (usually limited by tolerability) MTX dose 3.75–20 mg, median 17.5mg. We retrospectively analyzed standard CRF but recalled several patients to confirm events. Hepatic, gastrointestinal (nausea, vomiting, gastritis, diarrhea), pain in abdomen, bone marrow, skin rash/aggravated nodules, mucositis, hair-loss and central nervous system related were identified as significant AE. Any one or combinations of above events were noted as "overall AE". 12 SNPs in 9 genes of folate metabolism (including transporters) were genotyped using PCR-RFLP and Real-time Taqman allelic discrimination. Toxicogenetic index was calculated as the sum of homozygous variant genotypes carried by an individual (Arthritis Rheum 2006; 54(2):607–12). The genotypes which showed significant association (P<0.05) in the binary logistic regression analysis were taken into consideration for calculating toxicogenetic index. The presence of the 4 genotypes was summed as a composite index to constitute a toxicogenetic index for each patient (index range 0–4). PK analysis was performed on 94 patients by determining plasma MTX and metabolite 7-OH MTX levels at 0, 2 and 8 hr by HPLC and plasma Hcy at 0hr.

Results: (1) The table shows occurrence of AE by risk genotype (Values are odds ratio (95% confidence interval: *P < 0.05). The toxicogenetic index

ranged from 0 to 4. An index of 4 was associated with ~3 fold higher likelihood of side effect compared with an index of 0 ($P = 0.0001$). (2) Pharmacokinetic analysis shows that the patients with risk genotype have significantly high plasma concentration of MTX at 2hr (*TS* 5UTR *2R/2R), 8hr (*TS* 6bp/6bp) and its active metabolite 7-OH MTX at 8 hr. (*SHMT*1 CC).

	No of patients	Hepatic	Bone marrow	Pain in abdomen	Overall AE
TS 5UTR 2R/2R vs. 3R/3R and 2R/3R	57 vs. 259	1.3 (0.6–2.8)	4.9 (1.7–13.6)*	0.8 (0.2–3)	1.5 (0.8–2.9)
TS 3 UTR 6bp/6bp vs. 6bp/6bp and 0bp/0bp	65 vs. 257	1.4 (0.7–3)	0.1 (0.3–3)	1.1 (0.3–4)	2.8 (1.4–5.6)*
GGH C401T TT vs. CC and CT	124 vs. 198	2.3 (1.3–4.1)*	1.1 (0.4–2.9)	1.0 (0.3–3)	1.7 (1.0–2.8)*
SHMT1 C1420T CC vs. CT and TT	8 vs. 304	0.7 (0.1–4.1)	1.3 (0.1–4.7)	6.9 (1.1–46.1)*	1.7 (0.3–9.7)

Conclusion: Our findings revealed newer risk association with MTX related AE in Indian (Asian) RA cohort. Pharmacokinetic studies do show some associations with genetic polymorphisms but need to be further validated. Our observations propose that a toxicogenetic index can provide a means of profiling patients who develop AE to MTX and may be useful in establishing the likelihood of occurrence of AE to MTX. However, prospective studies with large no of patients will be necessary to reveal the predictive value of this pharmacogenetic marker.

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Design of a High Potency CTLA4-Ig with Extended Half-Life for Improved Dosing Convenience. Matthew J. Bernett, Seung Y. Chu, Holly M. Horton, Erik Pong, Irene Leung, Gregory L. Moore, Umesh S. Muchhal, Greg A. Lazar, David E. Szymkowski and John R. Desjarlais. Xencor, Inc., Monrovia, CA

Background/Purpose: Biologics consisting of CTLA4 fused to the Fc domain of IgG (CTLA4-Ig), marketed as abatacept and belatacept, are immunosuppressive therapies approved for treatment of rheumatoid arthritis (RA) and kidney transplant, respectively. These biologics function by selectively modulating the CD80/CD86:CD28 costimulatory signal needed for full T-cell activation. CTLA4-Ig is significantly less potent at inhibiting CD86-dependent costimulation as opposed to CD80-dependent costimulation, due to CTLA4 binding with much higher avidity to CD80 than CD86. Abatacept is administered by a monthly IV infusion, which is less convenient than the subcutaneous self-injections of competing anti-TNF biologics. We have therefore developed a new optimized CTLA4-Ig with an engineered CTLA4 domain that binds preferentially and with higher affinity to CD86. In addition, by increasing affinity of the CTLA4-Ig Fc domain for the antibody salvage receptor FcRn, we generated a biologic with significantly longer half-life (Zalevsky et al. Nat. Biotech. 2010; 28:157). This biologic has the potential to increase efficacy, reduce dosing frequency, and enable more convenient subcutaneous dosing.

Methods: XENP9523 is a CTLA4-Ig with optimized affinity for CD86 and containing an extended half-life Ig domain. Using rational structure-based engineering, 21 positions in the extracellular domain of CTLA4 were identified as targets for mutagenesis. A total of 149 variants were constructed at these positions during two rounds of affinity optimization. After each round, CD80 and CD86 affinity was measured using SPR, and variants with higher CD86 affinity were identified. For mixed lymphocyte reaction (MLR) assays, PBMC at 1.2×10^6 per well from two different donors were mixed with CTLA4-Igs and incubated for 6 days, followed by measurement of IL2 release by ELISA. For PK studies, same-sex mice transgenic for human FcRn ($mFcRn^{-/-}$ hFcRn Tg 276 heterozygote on a B6 background) were obtained from The Jackson Laboratory and a single IV dose of CTLA4-Ig at 10 mg/kg given, followed by regular blood collection. PK parameters were determined for individual mice with a non-compartmental model using WinNonlin.

Results: CTLA4-Ig variants with 20-fold increased binding to CD86 were identified and variant XENP9523 was chosen based on favorable CD80/CD86 binding (improvement in CD86 >> CD80). This variant showed a 4-fold improvement in IC50 for the ability to inhibit IL2 production in MLR assays compared to abatacept. Variant XENP9523 when fused to our extended half-life Fc domain showed a 2-fold improvement in half-life and similar exposure compared to abatacept in a PK study using huFcRn transgenic mice.

Conclusion: We show that CTLA4-Ig engineered for enhanced binding to CD86 via its CTLA4 domain, and for extended half-life via its Ig domain, is a potent suppressor of T-cell activation in vitro. Our results demonstrate the importance of high affinity binding to CD86 for modulating the CD80/CD86:CD28 costimulatory signal. The combination of increased potency and extended in vivo half-life suggests that XENP9523 has potential clinical advantages compared to abatacept and belatacept, while simultaneously enabling the convenience of subcutaneous dosing.

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Campylobacter Fetus Infection In Three Patients Treated with Rituximab for Rheumatoid Arthritis. Alain Meyer[1], Arnaud Theulin[2], Emmanuel Chatelus[3], Christelle Sordet[2], Rose-Marie Javier[2], Helene Chifflot[4], Jacques-Eric Gottenberg[5] and Jean Sibilia[6]. [1]Hautepierre Strasbourg university, Strasbourg, France, [2]Hautepierre Strasbourg Hospital University, Strasbourg, France, [3]Hopital Hautepierre, Strasbourg, France, [4]Hautepierre Strasbourg Hospital University, 67000, France, [5]Strasbourg University Hospital, Strasbourg, France, [6]Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, Strasbourg, France

Background/Purpose: *Campylobacter fetus (C fetus)* is a rare microaerophilic pathogen in humans that usually causes prolonged or recurrent bacteraemia. Osteoarticular, prosthetic material infection or cellulitis have been more rarely described, mainly in immunocompromised patients.

Methods: We report three RA patients treated with RTX who developed osteoarticular and cutaneous infection due to *C fetus*.

Results: Age of the patients was 71, 53 and 80 years respectively with a median RA duration of 24, 13 and 19 years. All patients had history of diabetes mellitus. Patient n°2 also suffered of COPD and patient n°3 of BOOP and hypertensive cardiomyopathy. All patients were co-treated with corticosteroids, with a dosage of 10mg/D and DMARDs. Patients had received respectively 4, 1 and 2 RTX cycle before *C fetus* infection. Gamma globulin amount before the last RTX infusion was 5, 5.8 and 6.9 g/L. *C fetus* infection occurred within a delay of 4 month [0.75–36] before the last RTX infusion. Patient n°1 developed left knee prosthesis infection, patient n°2 cellulitis of the right leg, and patient n°3 arthritis of the right elbow. Only one patient had fever. CRP amount was 16.5, 2 and 50mg/dl and median WBC was 13 200, 15 400 and 13 200. All patients had severe B lymphopenia (respectively 0, 2 and 7 CD19+ B lymphocyte /mm3) and hypogammaglubulinemia (respectively 5, 5.8 and 3.2 g/L of gammaglobulin) at the onset of infection. Evolution was good in all patients after antibiotic therapy and discontinuation of RTX treatment (Table 1).

Table. Characteristics of the three RA patients treated with RTX with C fetus infection

Case	Age/ sex	Comorbidity	RA duration (years)	Biotherapy before RTX treatment	Treatment concomitant to RTX	N° of RTX cycle prior to C fetus infection	Gammaglobulin prior to RTX treatment (mg/L)	Delay between last RTX infusion and the beginning of infection	Nature of infection	Fever	CRP (mg/dL)	WBC count (/mm3)	CD19+ amount at the time of infection (/mm3)	Gammaglobulin amount at the onset of infection (g/L)	Site of isolation of C fetus	Antibiotic treatment	Evolution
N°1	71/F	diabetes mellitus, left total knee arthroplasty	24	infliximab	CS (10mg/D), MTX (15mg/W)	4	5	4 months	Left knee prothesis infection	No	16.5	13 000	0	5	Left knee arthrocentesis	clindamycin, doxycyclin	good
N°2	53/M	diabetes mellitus, COPD	13	No	CS (10mg/D), MTX (20mg/W)	1	5.8	3 weeks	Cellulitis of the right leg	No	2	15 400	2	5.8	Hemoculture	amoxicillin, ciprofloxacin	good
N°3	80/F	diabetes mellitus, hypertensive cardiomyopathy, BOOP	19	No	CS (10mg/D), leflunomid	2	6.9	3 years	Arthritis of the right elbow	yes	50	13 200	7	3.22	Right elbow artrocentesis	amoxicillin, clavulanic acid, levofloxacin	good

Conclusion: This represents the first report of a series of *C. fetus* infections in RA patients treated with RTX. Our observations highlight a crucial role of B cell in C fetus infection.

Interestingly, the 3 patients were treated with corticosteroids with a dosage of 10mg/d and had hypogammaglobulinemia, both before RTX infusion and when infection occurred which have been recently shown to be risk factors of severe infections in RA patients treated with RTX (1). The three patients had also diabetes mellitus that has probably promote the infection.

C fetus infections are certainly under diagnosed, mainly because this germ growth requires microaerophylic culture conditions (2). Our observations show that clinicians should be aware of the possibility of *C fetus* infection in RA patient treated with RTX and should ask for specific research of microaerophilic organism in case of "culture negative" monoartritis and/or cellulitis, especially when risk factors of severe infections such as hypogammaglobulinemia or diabetes mellitus are present.

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1258

Short- and Long-Term Effect of Unguided, Intra-Articular Injections with Betamethasone In Early Rheumatoid Arthritis. Impact of Joint Area, Repeated Injections, MRI Findings, Anti-CCP, IgM-RF and CRP. Merete L. Hetland[1], Mikkel Østergaard[2], Bo J. Ejbjerg[3], Søren Jacobsen[4], Kristian Stengaard-Pedersen[5], Peter Junker[6], Tine Lottenburger[6], Ib Hansen[7], Lis Smedegaard Andersen[8], Ulrik Tarp[9], Anders Svendsen[10], Jens Kristian Pedersen[6], Henrik Skjødt[11], Torkell Ellingsen[12], Hanne M. Lindegaard[6] and Kim Hørslev-Petersen[13]. [1]Copenhagen University Hospital at Glostrup, on behalf of DANBIO, Copenhagen, Denmark, [2]Copenhagen University Hospital in Glostrup, Glostrup, Denmark, [3]Hospital at Slagelse, Slagelse, Denmark, [4]Rigshospitalet - 4242, Copenhagen, Denmark, [5]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [6]Odense University Hospital, Odense C, Denmark, [7]Viborg Hospital, Viborg, Denmark, [8]Denmark, [9]Aarhus University Hospital, Aarhus, Denmark, [10]Odense, Denmark, [11]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [12]University Hospital, Silkeborg, Denmark, [13]University of Southern Denmark, Graasten, Denmark

Background/Purpose: To investigate in rheumatoid arthritis (RA) patients the short- and long-term efficacy of unguided intra-articularly injections with betamethasone, and the impact of joint area, repeated injections, magnetic resonance imaging (MRI) pathology, anti-cyclic citrullinated peptides (anti-CCP) and IgM-rheumatoid factor (RF) status on long-term efficacy.

Methods: 160 patients with early RA (<6 months' duration) received intra-articular betamethasone in all (max 4) swollen joints at each visit (2 week intervals for 8 wks, then every 4 wks) in combination with step-up DMARDs during 2 years. This was part of the CIMESTRA trial (1–2).

Short-term efficacy was assessed by EULAR good-response. Long-term efficacy by Kaplan-Meier plots of the joint-injection-survival (i.e. the time-span between injection and renewed synovitis).

Potential predictors of joint-injection-survival were tested.

Results: 1373 joints (wrists, knees, MCP, shoulders, ankles, PIP, elbows, MTP) were injected. Of these, 531 were 2nd injections in a previously injected joint, and 262 were 3rd. At baseline, the median DAS28 was 5.5 (IQR: 4.6–6.2), and the numbers of injections/dose of betamethasone given were: 4(3–4)/4 (3–4), declining to 0(0–2)/0 (0–1.5) at the following visits. At week 2, 4 and 6, respectively, 50.0%, 58.1% and 61.7% had achieved a good EULAR response.

After 1 and 2 years, respectively, 62.3%(95% C.I. 58.1–66.9%) and 55.5%(51.1–60.3%) of the joints injected at baseline had *not* relapsed. All joint areas had good 2-years' joint-injection-survival, longest for the PIP-joints (73.7%(79.4–95.3%), p<0.01.

2-year joint survival was higher for 1st injections 56.6%(53.7–59.8%) than for 2nd 43.4%(38.4–49.0%) and 3rd injections 31.3%(25.0–39.3%), p<0.0001.

The cumulated dose of betamethasone after 2 years was: 11ml (IQR 7–17ml). The median intraarticular betamethasone dose during the first 2 years corresponded to less than 1 mg prednisolone per day.

Adverse events were mild and transient. High MRI synovitis score of MCP joints and anti-CCP were associated with poorer joint-injection-survival, whereas CRP and IgM-RF were not.

Conclusion: In early RA, intra-articular unguided injections of betamethasone in small and large peripheral joints together with DMARD treatment resulted in very rapid, effective and long-lasting inflammatory control. The cumulative dose of betamethasone was low, and the injections were well tolerated.

References:

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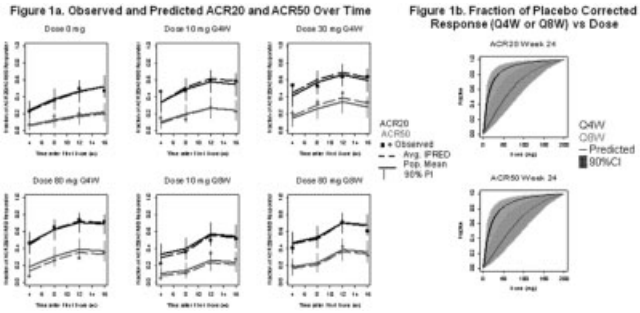
1259

Pharmacokinetic-Pharmacodynamic Modeling of Ozoralizumab (ATN-103), a Novel Humanized Nanobody Tumor Necrosis Factor Inhibitor for Rheumatoid Arthritis. Chandrasekhar Udata[1], Arnab Mukherjee[2], Matt Hutmacher[3], Mark Peterson[1], Kai-Hsin Liao[1], Tina Checchio[2], Kathy Shields[4], Xu Meng[1] and Gail Comer[4]. [1]Pfizer, San Diego, CA, [2]Pfizer, Groton, CT, [3]A2PG, Ann Arbor, MI, [4]Pfizer, Collegeville, PA

Background/Purpose: Ozoralizumab (ATN-103), a novel tumor necrosis factor inhibitor (TNFi), is a humanized, trivalent, bi-specific nanobody containing two human TNF-binding domains linked to a human serum albumin-binding domain. Pharmacokinetic-pharmacodynamic (PK-PD) modeling of data from a seamless phase 1/2 study in subject with active rheumatoid arthritis (RA) was performed to understand the relationship of ATN-103 exposure to clinical efficacy measures ACR20 and ACR50, and to predict clinical responses at other doses and dose regimens.

Methods: In this seamless phase 1/2 study, subjects (253) received total 4 subcutaneous injections of placebo or ATN-103 doses of 10 mg, 30 mg, or 80 mg every 4 weeks (Q4W) or 10 mg or 80 mg every 8 weeks (Q8W) for 16 weeks. A total of 1988 serum ATN-103 samples, intensive first and last dosing cycle with troughs at other event, were analyzed using NONMEM. Longitudinal models of ACR20 and ACR50, data up to week 16, as ordered categorical were tested using published latent variable approach with direct, indirect, and effect-compartment PK-PD models. Simulations were performed to predict possible ACR responses at other doses, regimens, and for longer treatment durations.

Results: A 2-compartment open population PK model with first-order absorption and elimination adequately described the observed concentration-time data. For a typical patient weighing 70 kg, ATN-103 PK parameter estimates were: clearance = 0.325 L/d, central volume = 1.14 L, inter-compartmental clearance = 0.642 L/day, peripheral volume = 2.65 L and the absorption rate constant = 0.152 1/d. Between-subject variability was 38% and 33% for clearance and central volume, respectively. Body weight was identified as a significant covariate on clearance and central volume of distribution and included allometrically. Higher trough ATN-103 concentrations were associated with higher ACR responses, suggesting that exposure may be predictive of clinical response. Observed ACR responses over time were best described by the effect-compartment PK-PD model at all dose/regimens (Figure 1a). Week 16 ACR20 and ACR50 responses at 80 mg Q4W were estimated to be similar to that of other anti-TNFi. For a Q8W regimen, clinical response similar to that of TNFi was predicted at a 160 mg dose (Figure 1 b).



Conclusion: A longitudinal effect-compartment PK-PD model utilizing a latent variable approach was used to describe the ACR20 and ACR50 responses across a range of doses investigated and subsequently used for simulations of other desired treatment regimens. Analysis results suggest that a 160 mg Q8W regimen is likely to be as efficacious as the 80 mg Q4W regimen in terms of ACR20 and ACR50 responses.

1260

Correlation of CDAI and SDAI with DAS in a Large Real-Life Cohort of Rheumatoid Arthritis Patients Treated with Infliximab. Denis Choquette[1], William G. Bensen[2], Milton F. Baker[3], Sophie Elise Michaud[4] and Hayssam Khalil[5]. [1]University of Montreal, Notre-dame Hospital, Montreal, QC, [2]McMaster University, Hamilton, ON, Hamilton, ON, [3]VIHA, Victoria, BC, [4]Merck Canada Inc, Montreal, QC, [5]Merck Canada Inc, Kirkland, QC

Background/Purpose: In recent years, the efficacy of anti-TNF-alpha in the management of RA has been demonstrated in numerous controlled clinical trials. The Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) have been recently designed as simplified disease activity scores. The purpose of this analysis is to evaluate the correlation between these simplified disease activity scores and routine clinical practice scores.

Methods: The data for this analysis were obtained from an observational study of adult RA patients initiated on treatment with infliximab and followed prospectively as per routine care since 2002. The majority of patients enrolled were biologic naïve.

Results: A total of 440 patients were included in this analysis. Mean (SD) age was 56.4 (13.6) years and mean (SD) disease duration at baseline was 11.0 (10.2) years. Mean SDAI, CDAI, DAS28-CRP and HAQ scores decreased significantly over 48 months (p< 0.001, for all parameters). A statistically significant strong positive correlation was observed between the DAS28-CRP and the SDAI (r=0.82; p< 0.001) or CDAI (r=0.94; p< 0.001). Differences in the proportion

of patients achieving low disease activity (LDA) and remission were observed between DAS28-CRP, SDAI and CDAI.

Parameter	Month 6 %	Month 12 %	Month 24 %	Month 36 %	Month 48 %
LDA (DAS 28 <3.2)	39.2	37.6	39.7	47.2	54.1
LDA (SDAI <11)	21.2	26.0	37.6	40.5	50.0
LDA (CDAI <10)	36.1	43.5	53.7	59.6	70.8
Remission (DAS 28 <2.6)	24.2	24.0	29.8	34.0	40.0
Remission (SDAI <3.3)	3.2	2.0	10.4	13.1	18.1
Remission (CDAI <2.8)	9.3	11.1	20.1	19.2	30.3

Conclusion: The results of this real-life observational study demonstrate that over four years of treatment infliximab is effective in reducing symptom severity and improving outcomes in patients with Rheumatoid Arthritis using different scores. Also, the data from this registry confirmed the validity of the SDAI and CDAI as disease activity measures in a real-life RA cohort.

1261

Development of a Whole Blood Assay to Determine Rituximab Mediated Complement Dependent Cytotoxicity of B Lymphocytes. Jonathan D. Jones[1], B. JoNell Hamilton[2], Whitney Hilton[3] and William F. C. Rigby[4]. [1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [2]Dartmouth College, Lebanon, NH, [3]Dartmouth Hitchcock Med Ctr, Lebanon, NH, [4]Dartmouth-Hitchcock Med Ctr, Lebanon, NH

Background/Purpose: Rituximab (RTX) is a monoclonal antibody targeting CD20, a marker found exclusively on B lymphocytes. RTX has shown efficacy in treating rheumatoid arthritis (RA). Although RTX depletes circulating B cells in all patients, less than half of RA patients achieve a high level of response. Moreover, the clinical response to RTX trails peripheral blood B cell depletion by weeks, if not months. Studies have suggested that synovial B cell depletion is important for clinical response, but the mechanism of B cell depletion in this compartment is not clear, particularly for non-circulating, resident synovial B cells. One possibility is that for clinical responses to occur, RTX must mediate synovial depletion of resident B cells via complement-dependent cytotoxicity (CDC) of B lymphocytes. By extension of this, non-responders fail to deplete synovial B cells by CDC. We report our development of a novel whole blood assay of RTX-CDC using hirudin anticoagulation and measurement of variable activity in normal volunteer donors.

Methods: Peripheral blood was drawn from healthy donors using hirudin, heparin or EDTA as an anticoagulant. Optimum hirudin concentration was found to be 50 μg/ml. Rituximab was added at varying concentrations and for various times and the percentage of CD19+ B cells as a function of all CD45+ cells determined by flow cytometry (FACScalibur, BD Biosciences).

Results: Using hirudin as an anticoagulant, we observed a rapid (15 minute) reduction in CD19 B cells with RTX concentrations as low as 0.01 μg/ml. No depletion was seen with RTX treatment when heparin or EDTA was employed as an anticoagulant, suggesting complement dependence. The role of complement activation was confirmed as B cell depletion was blocked by the addition of compstatin, which prevents the cleavage of C3 (Figure 1). The average percentage of B cell depletion was 35%, with an inter-donor variability of 11% to 60%. Only a portion of B cells deplete in this assay, and there is marked inter-donor heterogeneity of B cell depletion, findings which we are continuing to explore. These findings likely underlie the variability seen in RA response to rituximab.

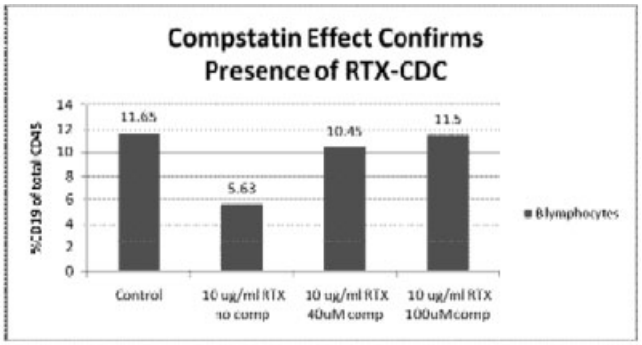


Figure 1. Addition of compstatin, a C3 inhibitor, blocked the reduction in CD19+ B cells following RTX addition, confirming the role of complement activation in the observed B lymphocyte depletion.

Conclusion: We have developed an assay that measures RTX mediated CDC of B cells. This assay presents a novel approach to assess the heterogeneity of RTX response, and will allow for increased understanding of the mechanisms of RTX effect. This may account for the variable success of RTX in various rheumatologic diseases, and has the potential to lead to a model to predict *a priori* RTX response. Additionally, these studies may provide insight into the success of other monoclonal antibodies currently in development.

1262

A Profile of Rheumatoid Arthritis Patients Treated with Tocilizumab in a United States Registry Population. Dimitrios A. Pappas[1], Alan Rathbun[2], George Reed[3], Joel M. Kremer[4], Isidro Villanueva[5], Jenny Devenport[6], Sarika Ogale[6], Ani John[6] and Jeffrey D. Greenberg[7]. [1]Columbia University, College of Physicians & Surge, New York, NY, [2]UMASS Medical School, Worcester, MA, [3]UMass Medical School, Worcester, MA, [4]Albany Medical College and The Center for Rheumatology, Albany, NY, [5]Viregen Macarena Hospital, Sevilla, Spain, [6]Genentech, South San Francisco, CA, [7]New York University School of Medicine, New York, NY

Background/Purpose: Tocilizumab (TCZ), a humanized anti-IL-6 receptor monoclonal antibody has demonstrated safety and efficacy in the treatment of RA across numerous randomized clinical trials (RCTs). The purpose of this abstract is to describe characteristics of patients initiating TCZ in usual care settings using the US CORRONA registry and to assess treatment response.

Methods: The CORRONA registry is a network of more than 100 private and academic rheumatology practices across the U.S., with data on approximately 27,000 RA patients. Descriptive analysis of baseline characteristics was summarized for all patients initiating TCZ. Response to TCZ treatment (change from baseline to 6 months) was summarized for the subset of patients who had data available at baseline and continued treatment for 6 months.

Results: In the CORRONA registry from August 23 2009 to May 2010, out of 2583 biologic initiations, 197 (7.6%) were treated with TCZ. Patients were predominately female, median age was 58 yrs (IQR 49–65), with median disease duration of 11 yrs (IQR 7–18) and baseline CDAI of 20.0 (IQR 12.1, 32.2). Some commonly reported baseline comorbidities were Cardiovascular Disease 13 (6.6%), Hypertension 61 (31.0%), Diabetes 13 (6.6%), Liver Disorder 15 (8.7%), Peptic Ulcer disease 24 (12.2%), Cancer 21 (10.7%), and hospitalized infection in last 12 months 1 (0.5%). 77% of the patients starting TCZ had discontinued their previous therapy for efficacy reasons and 8.8% for safety reasons. Almost all TCZ patients reported prior biologic use; 62 (31.5%) had 1 previous TNF exposure, 60 (30.5%) had 2 previous TNF exposure, 66 (33.5%) had ≥ 3 previous TNF exposure and 6 (3.0%) reported no previous biologic exposure.

At Baseline, most patients (62.4%) were initiated on TCZ at 4 mg, 35% of them were treated as monotherapy. In the subset of patients with available data for change from baseline up to 6 months of TCZ treatment (77 patients); median CDAI scores improved from 20.3 (IQR: 13, 32) at BL to 14.5 (IQR: 9.5, 27) [Table 1]; Swollen Joint Count (28) improved from 6 (IQR: 2, 10) to 4 (IQR: 1, 10) and Tender Joint Count (28) from 6 (IQR: 3, 10) to 3.5 (IQR: 1, 10).

Table 1. Response to Tocilizumab Treatment from Baseline to 6 month follow-up (N=77)

CDAI Disease Activity	Baseline Median (IQR) 20.3(13, 32)	6 month Follow Up Median (IQR) 4.5 (9.5, 27)
Remission	n = 2 2.6%	n = 8 10.4%
Low	n = 11 14.3%	n = 15 19.5%
Moderate	n = 28 36.4%	n = 28 36.4%
Severe	n = 36 46.2%	n = 26 33.8%

Conclusion: During the analysis period of 9 month, TCZ comprised 7.6% of all biologic initiations in the CORRONA registry. TCZ was mostly used in patients with long standing disease duration, with moderate to severe disease and for patients who had failed to respond to one or more prior TNF treatment. The majority of TCZ initiators were on combination therapy; with most on 4 mg/kg dose and for a one-third of these patients TCZ was used as monotherapy. In this real-world setting, patients treated with TCZ for 6 months showed a decrease in RA disease activity.

1263

SNP Algorithms for Prediction of Efficacy and Adverse Events of Abatacept. Tsukasa Matsubara[1], Satoru Koyano[2], Keiko Funahashi[2], Takafumi Hagiwara[1], Takako Miura[1], Kosuke Okuda[1], Takeshi Nakamura[1], Mitsuyoshi Iwahashi[3], Tomomi Tsuru[4], Shoichi Uchimura[5] and Shigeru Honjo[6]. [1]Matsubara Mayflower Hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]Higashi-Hiroshima Memorial Hospital, Higashi-hiroshima, Japan, [4]PS Clinic, Fukuoka, Japan, [5]Kanzaki Municipal General Hospital, Kanzaki, Japan, [6]Honjo Rheumatism Clinic, Takaoka, Japan

Background/Purpose: Abatacept (ABT), a CTLA4-Ig fusion protein agent targeted to T-cells, is a relatively new biological agent for RA treatment in Japan. However, there is no method for prediction of responders, non-responders, or adverse events which can occur during treatment. We established SNP algorithms for prediction of responders or non-responders, and adverse events in ABT-treated patients.

Patients and Methods: Forty-six RA patients treated with ABT were included in this study. Efficacy was assessed by DAS28 (CRP) at 48 weeks after the initial treatment. Any adverse events that may have been related to ABT administration and observed at 48 weeks of this long-term administration and during phase II were considered to be side effects. Genome-wide SNP genotyping was performed by Illumina Human610-Quad chip technology. Case-control analyses between 598,821 SNPs and responsiveness, remission or occurrence of adverse events were examined by Fisher's exact test. We selected 10 SNPs associated with ABT-responsiveness, remission, and adverse events ($p < 0.0001$). We scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in responders: +1 point, hetero allele: 0 points, and homo allele in the majority of non-responders: −1 point), and then examined relationships between responders and non-responders, remission and non-remission, and occurrence of adverse events, plus or minus, and the total score.

Results: Accuracy ((true positive+true negative)/total), specificity (true negative/(false positive+true negative)), and sensitivity (true positive/(true positive+false negative)) of the algorithm for responsiveness of abatacept ranged from 90–96%. For remission, accuracy, specificity and sensitivity of the algorithm ranged from 91–97%. For adverse events, accuracy, specificity and sensitivity of the algorithm ranged from 95–100%. It is therefore suggested that the SNP algorithms can predict responders and adverse events prior to the initiation of treatment with abatacept.

Conclusion: These highly accurate algorithms using SNP analysis may be useful in the prediction of responsiveness and adverse events before treatment with abatacept, and in this way can contribute to future tailor-made treatment with biologic agents.

1264

Low Persistence of Methotrexate Monotherapy in the Veterans Affairs Rheumatoid Arthritis (VARA) Registry. Grant W. Cannon[1], Brian C. Sauer[1], Katherine L. Martin[1], Candace L. Hayden[1], Andreas M. Reimold[2], Liron Caplan[3], J. Steuart Richards[4], Gail S. Kerr[4], Dannette S. Johnson[5] and Ted R. Mikuls[6]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Dallas VA and University of Texas Southwestern, Dallas, TX, [3]Denver VA and University of Colorado, Aurora, CO, [4]Washington DC VA and Georgetown University, Washington, DC, [5]Jackson VA and University of Mississippi Medical Center, Jackson, MS, [6]Omaha VA and University of Nebraska, Omaha, NE

Background/Purpose: Several studies initiating disease modifying anti-rheumatic drugs (DMARDs) in DMARD naïve patients have suggested that a significant portion of rheumatoid arthritis (RA) patients will experience and sustain a significant clinical response to methotrexate (MTX) monotherapy (MTX-MON). Little information is available about the long term persistence of MTX-Mon in clinical practice.

Methods: A cross sectional analysis of RA patients in the Veterans Affairs Rheumatoid Arthritis (VARA) registry recorded DMARD history in the VA computerized patient record system (CPRS) and VA pharmacy records. Patients with RA of greater than 3 years duration who were currently receiving MTX-MON were identified and compared to VARA patients who had received MTX but had either discontinued the drug and/or received other DMARDs in addition to MTX.

Results: Of the 1039 RA patient reviewed, 912 (88%) had an RA disease duration >3years. Of these patients 832 (91%) had received MTX and 439 (48%) were continuing to receive MTX. Of the 832 patients treated with MTX-MON, 38 (5%) had continued MTX and not received other DMARDs over the duration of their disease (16 +11 years). An additional 98 (11%) patients had received other DMARDs alone or in combination with MTX in the past, but were currently only receiving MTX-MON at the time of the review. Many patients received MTX in combination with traditional DMARDs, anti-TNF drugs (TNF), or other biologic (OB) agents. A comparison of MTX-MON patients to other patients with >3 years of RA history treated with MTX did not identify any baseline factors associated with MTX-MON persistence, including patient demographics, serologic data for rheumatoid factor and anti-CCP, and shared epitope (SE). Pain score reported on a 10 point range at clinic visits and a cumulative composite measure of DAS28 over time calculated as DAS28 area under the curve (DAS28 AUC) were statistically significantly lower in MTX-MON patients naïve to other DMARDs in comparison to all other groups and all MTX currently on MTX alone in comparison to patient currently on DMARD combinations ($p<0.001$). A comparison of all patient currently on MTX to all patient currently on MTX in combinations with other DMARDs showed an older age at RA onset (54±14 versus 49±13, $p<0.001$) and age at evaluation (69±11 versus 64±11, $p<0.005$), but no other statistically significant differences.

History of RA greater than three years duration n = 912

Never Received MTX n=80 (9%) | History of MTX exposure n = 832 (91%)

MTX Stopped N=394 (45%) | Current MTX treatment n=438 (48%)

MTX alone n = 136 (15%) | MTX in Combination n = 302 (33%)

Prior non-MTX DMARD | MTX+DMARD n=143 (16%) | MTX+TNF n=149 (16%) | MTX+OB n=10 (1%)

			No n=38 (5%)	Yes n=98 (11%)			
Male Gender	74 (93%)	357 (91%)	37 (97%)	89 (91%)	132 (93%)	132 (88%)	10 (100%)
Age (years)	66 (11)	67 (10)	67 (10)	70 (11)	66 (11)	64 (12)	60 (8)
Age at RA onset	52 (15)	51 (13)	54 (14)	51 (14)	52 (12)	49 (14)	44 (11)
Disease Duration	16±12	17±11	13±12	18±12	18±10	15±10	15±11
RF-Positive (%)	59/60 (96%)	641/670 (96%)	24/25 (96%)	73/78 (94%)	109/115 (95%)	117/125 (94%)	9/9 (100%)
Anti-CCP Positive (%)	54/77 (70%)	289/366 (79%)	21/31 (68%)	81/90 (79%)	94/126 (75%)	118/148 (80%)	7/7 (100%)
Erosions Present	29 (39%)	152 (42%)	13 (37%)	42 (44%)	55 (40%)	53 (36%)	5 (50%)
SE-negative	25%	24%	30%	33%	32%	23%	0%
SE-1 allele	60%	49%	55%	48%	51%	51%	63%
SE-2 alleles	15%	27%	15%	19%	17%	26%	37%
Pain Score**	2.7 (3.2)	2.3 (3.1)	1.8 (2.4)	2.9 (3.4)	2.6 (3.1)	3.1 (2.9)	6.4 (2.2)
DAS28 AUC**	3.3 (1.2)	3.7 (1.2)	3.1 (1.1)	3.8 (1.2)	3.3 (1.1)	3.8 (1.1)	4.6 (0.7)
#DMARDs by Hx	2.4 (1.2)	4.5 (1.9)	1.0 (0)	3.5 (1.9)	3.1 (1.2)	4.4 (1.5)	6.5 (2.3)
Current DMARDs	1.3 (0.7)	1.2 (0.8)	1.0 (0)	1.0 (1)	2.3 (0.5)	2.3 (0.5)	2.1 (0.3)

** P < 0.001 for MTX-MON alone. #DMARDs by Hx = Total number of DMARDs taken over patient's RA course.

Conclusion: Long term persistence with MTX therapy alone is very uncommon with the majority of patients currently receiving MTX alone having a history of receiving other DMARDs during their past management. There were no baseline disease characteristics associated with long term persistent MTX-MON. While almost half of the patients with RA in our cohort continue to receive MTX, the vast majority of patients will receive additional DMARD therapy and/or discontinue MTX during the course of their disease.

1265

Effects of TNF-Alpha Inhibitors on Lipid Profile and on Sub-Clinical Atherosclerosis in Rheumatoid Arthritis. Systematic Review and Meta-Analysis. Sylvain Mathieu[1], Sarah Payet[1], Bruno Pereira[2], Eric Bruckert[3] and Martin Soubrier[2]. [1]CHU Gabriel Montpied, Clermont-Ferrand, France, [2]CHU CLERMONT-FERRAND, Clermont-Ferrand, France, [3]CHU Pitié-Salpêtrière, AP–HP, Paris

Background/Purpose: Rheumatoid arthritis is associated with an increased cardiovascular risk that has been recently reported to be decreased by anti-TNF alpha, whose mechanisms remain uncertain.

Methods: MEDLINE, EMBASE, the Cochrane Collaboration and congress abstracts were searched to identify all reports of interest published up to May 2010. All observational and case/controls studies assessing the short- (4 weeks), medium- (16 weeks) and long-term (52 weeks) effects of TNF alpha blockade (infliximab, adalimumab, etanercept) on lipid profile or intima-media thickness (IMT) or endothelial dysfunction in RA patients were included.

Results: Thirty publications and abstracts were included, which represented 1135 RA patients. We found no significant change in lipid profile, in both the short, medium and long term of treatment (Table 1). Anti-TNF alpha caused no significant change in the flow-mediated dilation and Augmentation Index, nor significant modification of IMT over time (0.73[0.68–0.79] mm at baseline, 0.68[0.54–0.82] after 16 weeks and 0.88[0.34–1.41] after one year; $p=0.83$). Anti-TNF alpha improved disease activity and systemic inflammation.

Table 1. Differences in parameters of lipid profile after TNF blockade treatment

	Baseline	4 weeks	16 weeks	52 weeks	p-value
TC, mmol/l	n=20	n=11	n=10	n=2	p=0.52
	5.10 [4.92–5.29]	5.31 [5.11–5.50]	5.19 [5.04–5.35]	5.17 [4.88–5.47]	
LDL, mmol/l	n=11	n=5	n=6	n=2	p=0.88
	3.21 [3.00–3.41]	3.24 [2.80–3.69]	3.15 [3.02–3.27]	3.07 [2.96–3.18]	
HDL, mmol/l	n=18	n=11	n=9	n=3	
	1.39 [1.30–1.48]	1.45 [1.35–1.55]	1.52 [1.35–1.70]	1.53 [1.45–1.62]	p=0.47
TG, mmol/l	n=14	n=8	n=5	n=1	p=0.48
	1.31 [1.15–1.46]	1.34 [1.14–1.55]	1.28 [1.05–1.50]	0.94 [0.82–1.06]	
Atherogenic index	n=11	n=6	n=5	n=2	p=0.34
	3.86 [3.64–4.08]	4.18 [3.57–4.79]	3.49 [3.14–3.83]	3.48 [2.93–4.04]	

n=number of included studies. TC=total cholesterol; LDL=low density lipoprotein cholesterol; HDL=high density lipoprotein cholesterol; TG= triglycerides.

Conclusion: Despite a significant decrease in biological inflammation, anti-TNF alpha caused no change in intima-media thickness, endothelial dysfunction or lipid profile in RA patients.

1266

Evaluation of A Novel Homogeneous Mobility Shift Assay for the Measurement of Human Antibodies-to-Infliximab and Infliximab Levels in Patient Serum. Shui Long Wang, Linda Ohrmund, Scott Hauenstein, Jared Salbato, Rukmini Reddy, Patrick Monk, Steven Lockton, Nicholas Ling and Sharat Singh. Prometheus Laboratories, San Diego, CA

Background/Purpose: The list of antibody-based drugs available for the treatment of autoimmune disease, such as rheumatoid arthritis, is steadily increasing. However, certain patients will generate anti-drug antibodies (ADA) that causes many consequences, including loss of drug efficacy and adverse reactions. Monitoring of patients for drug and ADA levels is not only required by the FDA, but also very important for patient management. Current methods for the assessment of ADA and drug levels include bridge ELISA, radioimmunoassay and SPR, which have many disadvantages such as low drug tolerance in the sample. We have developed a non-radio labeled homogeneous mobility shift assay to measure the antibodies-to-infliximab (ATI) and drug levels in serum from patients treated with infliximab (IFX). This method overcomes many of the limitations of the current methods.

Methods: To perform the mobility shift ATI assay, Alexa488 labeled IFX with Alexa488 internal control is incubated with ATI positive serum. After equilibration, the free Alexa488 IFX and bound IFX are resolved by size exclusion HPLC and the intensity of the fluorescence in each peak is measured by a fluorescent detector. The changes in the ratio of the internal control to the free IFX peak are proportional to the amount of ATI. The amount of ATI in the sample is calculated from a standard curve generated with different dilutions of ATI positive serum. Similar methodology and analysis are used to measure the IFX level in the serum. We have performed a full method validation on both ATI and IFX assays, and compared the clinical sample test results with those obtained from ELISA methods.

Results: Validation of the mobility shift ATI assay revealed a lower limit of quantitation of 35.4ng/mL in serum, lower than the industry requirement of 250–500ng/mL. The linear range of quantitation is 35.4–790ng/mL. The intra- and inter-assay precision is less than 15% of CV, and the accuracy of the assay is within 20%. IFX drug tolerance in the assay is 100μg/mL in the serum. Sera from 100 healthy subjects were tested to set up the cutoff point of 35.4ng/mL. ATI positive samples analyzed by bridge ELISA from 120 patients were also evaluated by the new method and the results showed a strong correlation between the two methods. However, the new method identified 23 false positive samples from the bridge ELISA. Similar results were obtained from the validation of the mobility shift IFX assay.

Conclusion: Results from this study demonstrated the superiority of the mobility shift assay in measuring ATI and IFX in patient serum. This method can also be applied to detect other antibody drugs and ADA in patient serum such as those treated with adalimumab.

1267

Tofacitinib Reduces Interferon-γ and Interleukin-17 Production From CD4+ T Cells in Patients with Rheumatoid Arthritis. Satoshi Kubo, Kunihiro Yamaoka, Koshiro Sonomoto, Keisuke Maeshima, Shintaro Hirata, Kazuhisa Nakano, Norifumi Sawamukai, Masao Nawata, Shigeru Iwata, Kazuyoshi Saito and Yoshiya Tanaka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Background/Purpose: Tofacitinib, a Janus kinase (JAK) inhibitor, has gathered attention in treatment of rheumatoid arthritis (RA), revealing the prompt clinical effects in randomized clinical trials. However, its mode of action remains uncertain, particularly when administered to RA patients. Therefore, we collected CD4+ T cells from RA patients treated with tofacitinib, and investigated the cytokine prolife from T cells in vitro and its relevance to clinical efficacy.

Methods: Patients who met the ACR criteria for RA and participated in the tofacitinib clinical trials and continued medication up to 52 weeks in our department were eligible. After the double blind period (12- or 24-weeks), during which patients were randomized to receive different doses of tofacitinib or placebo, all patients were treated with tofacitinib 5 mg or 10 mg BID open-label. CD4+ T cells from blood were collected by magnetic selection at 0 and 52-weeks and cultured under the stimulation with anti-CD3 and anti-CD28 antibodies for 3 days. Serum levels of IFN-γ and IL-17 in collected supernatants were measured by ELISA.

Results: (1) Patient background: 30 patients were assigned, mean age; 53.8 years, mean disease duration; 82.2 months, methotrexate was administered in 23 patients and the median dose was 9.2 mg/week, oral corticosteroids were administered in 7 patients and the median dose was 6.0 mg/day. At baseline, patients had a high degree of disease activity: -SDAI 37.6, DAS28 (ESR) 6.3, HAQ 1.8, CRP 20.3 mg/l, ESR 50.7 mm/h, MMP-3 229.4ng/ml, RF 208.0U/ml.

(2) The mean disease activity score was SDAI=7.7 and DAS28=3.1 at 52-weeks, which was significantly lower than that at baseline ($P<0.05$) and 73% achieved low disease activity (SDAI $<$ 11). HAQ was 0.7 at 52-weeks and 46% achieved HAQ-remission (HAQ$<=$0.5).

(3) Production of IFN-γ from CD4+ T cells at 52-weeks (1124.8 pg/ml) was significantly reduced, compared to that at baseline (1563.8 pg/ml) ($P<0.05$). Similar findings were noted in IL-17 production. IL-17 production at 52-weeks (1021.2 pg/ml) significantly decreased from that at baseline (1820.5 pg/ml) ($P<0.05$).

(4) There was no statistically significant correlation between the reduction of IFN-γ and IL-17 production from CD4+ T cells and improvement of clinical disease features including SDAI, CRP, ESR, MMP-3 and RF.

Conclusion: Tofacitinib acts on CD4+ T cells and suppress production of IFN-γ and IL-17 after 52 weeks of administration in patients with RA, suggesting the inhibitory effect on Th1 and Th17 differentiation. However, the reduction of cytokine production did not correlate with the clinical efficacy suggesting that tofacitinib acts not only on CD4+ T cells but also on other immune cells (such as dendritic cells, synovial fibroblast, and B cells) which may have direct or indirect connection with clinical efficacy.

1268

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Multiple, Intravenous, Ascending-Dose Study of Sirukumab in Patients with Cutaneous or Systemic Lupus Erythematosus. Jacek C. Szepietowski[1], Surasak Nilganuwong[2], Anna Wozniacka[3], Annegret Kuhn[4], Filippa Nyberg[5], Jacek Szechinski[1], Ronald F. van Vollenhoven[6], Anders Bengtsson[7], Adam Reich[1], Dick de Vries[8], Bart van Hartingsveldt[8], Bei Zhou[9] and Benjamin Hsu[10]. [1]Wroclaw Medical University, Wroclaw, Poland, [2]Siriraj Hospital, Bangkok, Thailand, [3]Medical University of Lodz, Lodz, Poland, [4]University of Münster, Münster, Germany, [5]Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden, [6]Karolinska Institute, Stockholm, Sweden, [7]Department of Rheumatology, Lund University Hospital, Sweden, [8]Janssen Biologics B.V., Leiden, Netherlands, [9]Centocor Research & Development, a Division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA, [10]Centocor R&D, a division of J&J Pharmaceutical R& D, LLC/Univ. of Pennsylvania, Malvern/Philadelphia, PA

Background/Purpose: Interleukin-6 may play a key role in the pathogenesis of cutaneous lupus erythematosus (CLE) and/or systemic lupus erythematosus (SLE).

Methods: This is a 2-part, phase 1, double blind, placebo controlled study to evaluate the safety and PK of multiple IV infusions of sirukumab, a human anti-interleukin-6 mAb in CLE/SLE pts. In Part A, pts with histologically-confirmed CLE were randomized to receive a total of 4 IV infusions of placebo or sirukumab 1, 4, or 10 mg/kg q2w. In Part B, pts with SLE diagnosed by ACR criteria and a SELENA-SLEDAI score of 5 to 12 were randomized to receive a total of 4 IV infusions of placebo or the highest well tolerated sirukumab dose in Part A (10 mg/kg) q2w. Primary evaluations were safety and PK. Secondary evaluations were PD, immune response, and preliminary clinical responses

Results: In Part A, 33 CLE pts were randomized (64% F; 31 Caucasian, 2 Asian; age 29–69; weight 49–100 kg), and 31 were treated. In Part B, 15 SLE pts were randomized and treated (87% F; 9 Caucasian, 6 Asian; age 19–58; weight 46–81 kg). More AEs were reported with sirukumab than placebo (Part A: 21/23 [91%] vs 5/8 [63%], Part B: 9/10 [90%] vs 4/5 [80%]). Sirukumab led to sustained, dose-independent decreases in WBC, ANC (neutropenia), platelets (thrombocytopenia); and minor elevations in total cholesterol. More skin-related AEs occurred with sirukumab 1 and 4 mg/kg than placebo; none occurred with 10 mg/kg. The majority of infectious AEs were mild upper respiratory infections reported similarly between groups in Part A but more often with sirukumab in Part B. More SAEs occurred with sirukumab than placebo (Part A: 3/23 [13%] vs 0/8 [0%], Part B: 2/10 [20%] vs 1/5 [20%]). SAEs reported with sirukumab were Horner's syndrome, epistaxis followed by iatrogenic wound infection and lung cancer, cholelithiasis, and pneumonia; none were possibly related to study drug except pneumonia. One pt on placebo had an unrelated myocardial infarction. One death occurred from a car accident. Sirukumab showed linear PK at IV doses of 1 to 10 mg/kg in CLE pts. Systemic exposure (Cmax and AUC[day 0–14]) and half-life were comparable between CLE and SLE pts. Sirukumab was not detected in urine samples from SLE pts. CRP and SAA decreased to low median levels by wk 1 and remained low through wk 14 with sirukumab in all pts. Complement C3 and C4 decreased with sirukumab in all pts without associated clinical disease flare. Of 32 pts with evaluable samples, none developed anti-sirukumab antibodies. Decreases in titers of ANA and anti-dsDNA and no other autoantibody changes occurred with sirukumab. No clinical improvement was detected by CLASI, overall BILAG global score, or SELENA-SLEDAI scores. In SLE pts, those treated with sirukumab improved in SF-36 physical scores and had stable DLQI scores while those treated with placebo had stable SF-36 and worsening DLQI.

Conclusion: Treatment with IV infusions of sirukumab was generally safe and well tolerated in both CLE and SLE pts. Sirukumab showed linear PK over the IV dose range of 1 to 10 mg/kg. Systemic exposure and half-life were comparable in CLE and SLE pts. Future studies in pts with more severe disease are needed to clarify the safety profile and efficacy potential of sirukumab.

1269

Meta-Analysis Suggests Intensive Non-Biologic Combination Therapy with Step-Down Prednisolone May Also 'Disconnect' Disease Activity and Damage in Rheumatoid Arthritis. Maarten Boers[1], Lilian H.D. van Tuyl[1], Marianne van den Broek[2], Piet J. Kostense[1] and Cornelia F. Allaart[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: In rheumatoid arthritis (RA) treatment with TNF inhibitors changes the relationship between disease activity and progression of radiological joint damage (the so-called 'disconnect' that allows arrest of damage progression even at moderate disease activity levels). In early RA intensive combination therapy of methotrexate and sulfasalazine with step-down prednisolone (COBRA schedule) has been shown to be equivalent to high-dose methotrexate and infliximab in suppression of damage progression (BeSt trial).[1] We investigated whether COBRA treatment also results in a 'disconnect' between disease activity and damage.

Methods: In a meta-analysis we combined the data of the COBRA trial[2] (COBRA v sulfasalazine monotherapy) with that of two arms of the BeSt trial (COBRA v sequential monotherapy). For each trial, 1-year progression of damage (Sharp van der Heijde score) was the dependent variable in a linear regression formula with the variables disease activity, treatment strategy (COBRA or control) and their interaction as independent factors. As estimates of disease activity we used the 1-year time-averaged Disease Activity Score (DAS44) and C-reactive protein (CRP) in separate analyses. The focus was on the interaction between disease activity and treatment strategy as proof of the existence of a 'disconnect'. Therefore we pooled the interaction terms of the two analyses, weighting by their inverse variance according to standard technique. Because of the directionality of the hypothesis and the relative insensitivity of regression for the detection of interaction, we used one-sided significance tests.

Results: For these analyses between 60 and 100% of original trial patients had complete data. In both trials analysed separately time-averaged DAS44 and CRP, respectively, were the only (strongly) significant independent factors related to damage progression. In the models that included disease activity, neither treatment group nor the interaction between treatment and disease activity entered as significant factors. However, pooling resulted in a (weakly) significant test for interaction:

Time-averaged-DAS44 × treatment interaction: one-sided $p = 0{,}027$.

Time averaged CRP × treatment interaction: one-sided $p = 0{,}044$.

Conclusion: This analysis has limitations inherent in metaanalysis, and a generic lack of power to detect interactions, especially in the context of low damage progression overall in a skewed distribution. Nevertheless, it gives some support to the suggestion that changes in the relationship between disease activity and damage progression are not limited to anti-TNF treatment, but a property of early, rapid and deep suppression of joint inflammation.

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1270

Clinical Response and B Cell Analysis by High-Sensitive Flowcytometry After the Second Course of Rituximab. Hans-Peter Brezinschek[1], Franz Rainer[2], Kerstin Brickmann[1], Raimund Lunzer[2] and Winfried B. Graninger[1]. [1]Medical University Graz, Graz, Austria, [2]Hospital Barmherzige Brueder, Graz- Eggenberg, Austria

Background/Purpose: Recently, we have shown that in an Austrian rituximab-registry RA-patients did not have a better clinical response when they completely depleted B cells 15 days after the first infusion. In addition, our results suggested that RA patients with a low number of transitional 1 B cells and/or low percentage of CD95+ post switch cells will benefit more profoundly from a B cell depleting therapy. The purpose of this study was to correlate the effect of a second course of rituximab (RTX) with the number of B cells after 15 days as well as B cell subsets.

Methods: Patients in the Austrian B Cell surveillance (ABS)-register were included in the study when they had a second course of RTX. DAS28 was determined before, 2 and 24 weeks after rituximab application. Peripheral blood mononuclear cells were isolated at the same time points and cells were stained with monoclonal antibodies directed towards CD19, CD24, CD27, CD38, CD45 and IgD. To exclude T cells and monocytes CD3 and CD14 were utilized. Five hundred thousand cells were acquired and analyzed using a seven-channel flow cytometry (BD Canto II cytometer, Software FACS-Diva). According to their surface staining B cells were divided in naive (CD19+, IgD+, CD27-); IgD memory (CD19+, IgD+, CD27+), post switch (CD19+, IgD-, CD27+) and double negative (CD19+, IgD-, CD27-) cells. In addition, B cells were further characterized using CD95 and CD80. Complete depletion was defined as 0,002%, i.e. 10 events or less in 500.000 CD45+ cells.

Results: Until now, 105 RA patients have been included in the ABS registry and 13 patients have undergone the week 24-analysis of a second course of RTX. There was a significant reduction in the DAS28 (mean ± SE) before the first and the second therapy course (5,92 ± 0.25 versus 4.23 ± 0.25, $p < 0.0001$). Interestingly, patients who did not respond to RTX after the 1st course still had a reduction in DAS28 after the second treatment, but it was smaller compared to 1st cycle responders (−0.8 ± 0.8 versus −1.9 ± 0.4; respectively). Similar to the results from the 1st cycle, no correlation between the EULAR response and complete depletion at day 15 was found. Thus, there was no significant difference in the mean number of B cells (mean ± SE) in responders and non-responders (33.0 ± 22.6 versus 19.5 ± 4.6, respectively). Interestingly, 2 out of four non-responder had an improvement of their DAS28 after the second cycle. Non-responder had an elevated frequency of post switch B cells compared to responders (29.8% 5.9 versus 15.0% ± 7.6; respectively). No significant differences were found for CD80 or CD95 expression on B cell subsets for responders and non-responders. Furthermore, in responders the numbers of transitional (T1) B cells were lower compared to non-responders or healthy controls (45 ± 23, 67 ± 40 and 384 83, respectively), but this was not significant.

Conclusion: Our preliminary results suggest again that the enumeration of B cells on day 15 will not help to discriminate Rituximab-responders from non-responders. Furthermore, a second cycle of RTX is warranted in RA-patient with an inappropriate response to the first therapy-course.

1271

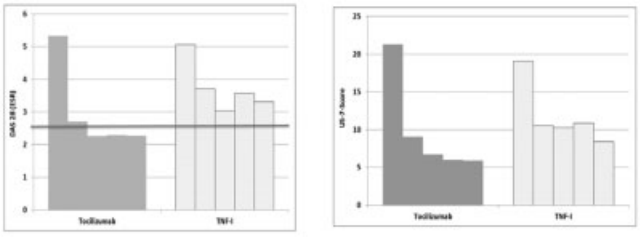
Comparison of Tocilizumab and TNF Inhibitor Therapy in Rheumatoid Arthritis. Jörg Kaufmann[1], Susanne Seel[2] and Anne-Eve Roske[3]. [1]Rheumatologist, Ludwigsfelde, Germany, [2]Ambulant Centres f. Rheumatology, Ludwigsfelde, Germany, [3]Roche Pharma AG, Grenzach-Wyhlen, Germany

Background/Purpose: The combination of a biologic DMARD (bDMARD) with methotrexate (MTX) is regarded as the gold standard for patients having not adequately responded to a conventional DMARD (cDMARD) therapy. There are no results from randomized controlled studies comparing different bDMARDs. Aim is to compare the effectiveness of TNF inhibitors with Tocilizumab with respect to clinical and sonographic parameters.

Methods: Data from 98 patients in whom bDMARD (TNF inhibitor or Tocilizumab) therapy had been initiated between September 2009 and September 2010 were retrospectively analysed. Selection criteria included confirmed diagnosis of RA and age >18 years. Patients had to be on their first bDMARD. Patients were examined sonographically at baseline and every 3 months using the US-7 score. The DAS28 score was recorded every 3 months.

Results: The Tocilizumab and TNF inhibitor cohorts consisted of 40 and 48 patients, respectively. Both groups were comparable in age, disease duration and gender distribution.

The following table shows the mean values for the DAS28 baseline and after 3, 6, 9 and 12 months compared to the biologics, which differ in their mode of action. The horizontal line marks the DAS28 remission threshold at 2.6.



Conclusion: Tocilizumab shows in the groups both clinically and sonographically significantly better effectiveness compared to TNF inhibitors. Prospective randomized controlled studies have been initiated to confirm these results.

1272

Efficacy Evaluation of Tocilizumab with the New ACR/EULAR Remission Criteria and DAS28-ESR. Tomonori Ishii[1], Yasuhiko Hirabayashi[2] and Michinoku Tocilizumab Study Group[3]. [1]Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan, [2]Hikarigaoka Spellman Hospital, Sendai, Japan, [3]Senndai

Background/Purpose: New classification/remission criteria have been proposed to ensure the early diagnosis of rheumatoid arthritis (RA) and achieve remission or low disease activity according to strict criteria. As tocilizumab (TCZ) decreases the levels of acute phase proteins (e.g., CRP and ESR), it has been questioned whether it is appropriate to evaluate disease activity in patients on TCZ based on levels of acute phase proteins. In Japan, TCZ was approved in April 2008 as the third biological agent for the treatment of RA. The Michinoku Tocilizumab Study Group (MTSG) has registered RA patients receiving TCZ in 34 institutions in 6 prefectures in Tohoku area to analyze their clinical data. The usefulness of the new ACR/EULAR RA remission criteria (i.e., tender or swollen joint count (SJC/TJC) <1, patient global assessment <1, and CRP of <1 mg/dL; referred to as Criteria A) and Criteria A without CRP (Criteria B) was evaluated in patients receiving TCZ. Also, the association between these criteria and the conventional remission criteria (DAS28-ESR <2.6) was evaluated.

Methods: Patients with RA who were registered by the MTSG from May 2008 to November 2009 and received TCZ for 12 months were evaluated. Patients were assessed every 3 months by Criteria A and B and DAS-ESR, and the percentages of patients with remission at month 12 were obtained. The ROC analysis was performed to obtain cut-off values of DAS28-ESR score to achieve remissions according to the new criteria. Data were analyzed using the LOCF method.

Results: TCZ treatment was continued for 12 months in 81.8% of the patients registered by the MTSG. The data of 285 patients were analyzed in this study. The mean age at baseline was 59.6 years; 225 patients (79%) were female and the mean duration of RA was 10.2 years. Other biological agents had been used in 140 patients (49.1%), and methotrexate was used with TCZ in 145 patients (50.9%). At month 12, 71 (24.9%) and 72 (25.3%) patients achieved remission with Criteria A and B, respectively, and no significant difference was observed in the criteria with and without CRP (P=0.9230). Remission with DAS28-ESR was achieved in 164 patients (57.5%). RCO analysis revealed that the cut-off value to expect the achievement of remission with Criteria A was a DAS2-ESR score of <1.54 with sensitivity, specificity, positive predictive value and negative predictive value of 88.7, 85.5%, 67.0% and 95.8%, respectively. However, patients having RA for ^{3}10 years and patients in Stage 4 tended not to achieve remission even if the DAS2-ESR was <1.54.

Conclusion: In the clinical setting, the new remission criteria could confirm the remission with TCZ treatment without being affected by CRP level. The fact that the cut-off value to expect the remission according to the new criteria was DAS28-ESR <1.54 indicated that more stringent remission than the conventional criteria may be required for the new criteria in patients receiving TCZ.

Expectation of achievement of the new criteria of remission with a cut-off level of DAS28-ESR<1.54

Sensitivity	88.7%
Specificity	85.5%
Positive predictive rate	67.0%
Negative predictive rate	95.8%

1273

High Levels of Serum IL-6 but Not CRP or TNF-α During Tocilizumab Treatment Induces Myalgia Among the Patients with Rheumatoid Arthritis. Osamu Saiki[1] and Hiroshi Uda[2]. [1]Shiraishi Hospital, Imabari, Japan, [2]Keiseikai Hospital, Higashiosaka, Japan

Background/Purpose: Many biologics has been developed in recent years. Tocilizumab, IL-6 receptor antagonist, is one of essential biologics to treat RA patients. Several adverse reactions have been reported after tocilizumab injection, but occurrence of myalgia has rarely been discussed. We experienced RA patients who complained myalgia after tocilizumab treatment, so we conducted this study to examine the mechanism how the pain appears.

Methods: RA patients who had inadequate response to MTX and/or TNF inhibitor were treated by 8mg/kg of tocilizumab every 4 weeks. Serum IL-6 and CRP levels and DAS28 score of them were examined at baseline and every 4 weeks at tocilizumab injection. Patient's myalgia was evaluated everyday by themselves using 0 to 100 mm visual analog scales (VAS). The serum levels of creatine kinase (CK), aldolase, and TNF-α were also examined in addition to regular blood tests.

Results: Seventy-six RA patients were treated with tocilizumab every 4 weeks. Of these patients, 28 complained myalgia which started one or two days after receiving tocilizumab injection and decreased gradually, but the myalgia recurred by further tocilizumab injections. They suffered from severe myalgia of upper body such as neck, shoulder, and back muscles, but these pains were quite different from those of fibromyalgia nor polymyalgia rheumatica. When the patients complained myalgia, the levels of CRP had decreased to basal levels (less than 3 mg/L) and their activities of rheumatoid arthritis such as the number of swelling joints were rather decreased. RA patients with high disease activity at initial tocilizumab treatment developed myalgia more frequently than those with low disease activity. In the patients experienced myalgia, the serum IL-6 levels were significantly higher (107 $\pm$ 56 pg/L) than those in patients without myalgia (31 $\pm$ 18 pg/L) at 28 days after initial tocilizumab treatment. But the serum levels of high sensitive TNF-α and CRP were decreased to within normal limits, and the levels of CK or aldolase were within normal range. After initial tocilizumab treatment, the magnitude of myalgia decreased well paralleled with serum IL-6 levels.

Conclusion: During tocilizumab treatment, RA patients with high disease activities frequently experienced myalgia in spite of decreasing the disease activities. In the patients who complained myalgia, the levels of IL-6 but not CRP or TNF-α were selectively high. However, before tocilizumab treatment, the patients did not complain myalgia, when both IL-6 and CRP levels were high, suggesting the myalgia supposed due to interaction of IL-6 and tocilizumab.

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Development of a Novel Recombinant Biotherapeutic with Applications in Targeted Therapy of Human Arthritis. Panagiotis Kamperidis[1], Tahereh Kamalati[1], Mathieu Ferrari[1], Lewis Lee[1], Rita Jones[1], Toby Garrood[1], Malcolm D. Smith[2], Soraya Diez-Posada[1], Chris Hughes[1], Ciara Finucane[1], Stephen Mather[1], Ahuva Nissim[1], Andrew J. T. George[1] and Costantino Pitzalis[3]. [1]London, United Kingdom, [2]Adelaide, Australia, [3]Centre for Experimental Medicine and Rheumatology, QMUL, London, United Kingdom

Background/Purpose: To isolate recombinant antibodies with specificity for human arthritic synovium and to develop targeting reagents with joint specific delivery capacity for therapeutics and/or diagnostic applications.

Methods: *In vivo* single chain antibody (scFv) Phage Display screening using a human synovial xenograft model was used to isolate antibodies specific to the microvasculature of human arthritic synovium. scFv antibody tissue specific reactivity was assessed by immunostaining of: (i) synovial tissues from normal controls, RA and OA patients, (ii) normal human tissues arrays and (iii) tissues from other inflammatory diseases displaying neovasculogenesis. *In vivo* scFv antibody tissue specific targeting capacity was examined in the human synovial xenograft model using both ^{125}I labeled and biotinylated antibody.

Results: We have isolated a novel human, recombinant antibody, scFv A7, with specificity for the microvasculature of human arthritic synovium. We show that *in vivo*, this antibody can efficiently target human synovial microvasculature in SCID mice transplanted with human arthritic synovial xenografts. Our results demonstrate that scFv A7 antibody has no reactivity with the microvasculature or, other cellular components, found in a comprehensive range of normal human tissues including normal human synovium. Further, we show that the reactivity of the scFv A7 antibody is not a common feature of neovasculagenesis associated with chronic inflammatory conditions.

Conclusion: Here we report for the first time the identification of a scFv antibody, A7, that specifically recognizes an epitope expressed in the microvasculature of human arthritic synovium and has the potential to be developed as a joint specific pharmaceutical.

1275

Gene Expression Profiling of Folate Pathway Related Genes in Methotrexate naïve- and Methotrexate-Treated Rheumatoid Arthritis Patients. Marjolein Blits[1], Gerrit Jansen[1], Yehuda G. Assaraf[2] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Technion, Haifa, Israel

Background/Purpose: The folate antagonist methotrexate (MTX) is an anchor drug in the treatment of rheumatoid arthritis (RA). Many attempts have been undertaken to predict response to MTX treatment, in particular by evaluating possible correlations with polymorphic variations of methotrexate/folate-related genes. Thus far, however, many of these studies were not elusive in providing robust predictive markers. The aim of this study was to explore whether analysis of expression of methotrexate/folate-related genes could provide information on the mechanism underlying (non)responsiveness of RA patients for MTX therapy.

Methods: Large-scale expression profiling by cDNA Stanford microarrays, containing 43000 elements, was performed on peripheral blood from 35 RA patients and 15 healthy individuals (van der Pouw Kraan, et al., Ann Rheum Dis 2007). The RA patient group included 25 patients treated with methotrexate (MTX^+ group) and 10 patients untreated for methotrexate (MTX^- group). As a control, a group of healthy, age and sex-matched, individuals (n=15) were arrayed. The array data was filtered and normalized in the Stanford microarray database. Subanalysis on this dataset was preformed for a set of genes involved in the methotrexate/folate pathway (van der Heijden, et al., Nat Clin Pract Rheumatol. 2007), in particular those involved in the cellular uptake (FR's) and efflux (MRP1–5, BCRP and P-gP) of MTX, as well as the metabolism and intracellular targeting of MTX (FPGS, GGH, DHFR, TYMS, and GART). Statistical analysis was performed using Student's *t* test or Mann-Whitney *U* test, p-values of ≤ 0.05 were considered to be statistically significant.

Results: Several folate/MTX-related genes were markedly and significantly altered between the three study groups. Interestingly, the metabolic enzymes FPGS and GGH were significantly up-regulated in the MTX^- RA group compared to the healthy control group (HC group), whereas GART expression was markedly down-regulated. Following MTX treatment, these alterations in expression levels were normalized to those observed in the HC group. Furthermore, the MTX-efflux transporters multidrug resistance protein-2 (MRP2) and MRP3 showed an increased expression in the MTX^+ group compared to the MTX^- group and the HC group, suggesting that cellular extrusion may contribute to a diminished MTX response in the MTX^+ group.

Conclusion: Collectively, these results indicate that, under inflammatory conditions basal folate metabolism is altered in blood cells of RA patients vs HC. Treatment with MTX restores expression of these genes to the levels within the range of the HC group. Finally, our results provide the first indication that multidrug resistance protein efflux transporters could contribute to an attenuated MTX response in MTX-based RA treatment.

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Retrospective Analysis of the Efficacy of Tacrolimus in Rheumatoid Arthritis: Suggestive Synergistic Effects with Methotrexate. Kenta Hoshi, Sumiaki Tanaka, Tatsuhiko Wada, Junichi Tanaka, Tatsuo Nagai and Shunsei Hirohata. Kitasato University School of Medicine, Sagamihara, Japan

Background/Purpose: Tacrolimus (TAC) is an immunosuppressant with a calcineurin inhibitory effect and has been shown to be beneficial in treating rheumatoid arthritis (RA). It's well known that the effects of biologics for treating RA are better in patients receiving biologics with methotrexate (MTX) than those in patient receiving biologics alone. It's therefore likely that MTX may enhance the effects of TAC for treating RA. To clarify the efficacy of combination therapy with TAC and MTX, we performed a retrospective cohort study of RA patients, who received TAC.

Methods: We selected all RA patients treated with TAC from 2006 to 2010 in our hospital and corrected clinical data from their medical records. To compare improvement of disease activity score of 28 joints (DAS28) during 12 months between MTX+TAC group (patients treated with TAC and MTX) and TAC group (patients treated with TAC with or without Disease-modifying antirheumatic drugs), we adjusted DAS28 for sex, age, dosage of prednisolone, and analysed using multivariate analysis of variance (MANOVA).

Results: 142 patients were treated with TAC for RA between 2006 and 2010 (Figure 1). Thirty-six patients were discontinued due to the lack of efficacy within 12 months, and 22 patients were discontinued due to adverse events including infection (4 patients), renal dysfunction(5) or hyperglycemia (2). 53 patients (TAC+MTX group: 21 patients, TAC group: 32 patients) were continued to receive TAC therapy over 12 months. As shown in Table, TAC significantly improved DAS28 during 12 months. Adjusted DAS28 before TAC and after 12months were summarized in Figure 2. MANOVA showed that the improvement adjusted DAS28 in 12 months was significantly greater in TAC+MTX group than in TAC group (p=0.0017).

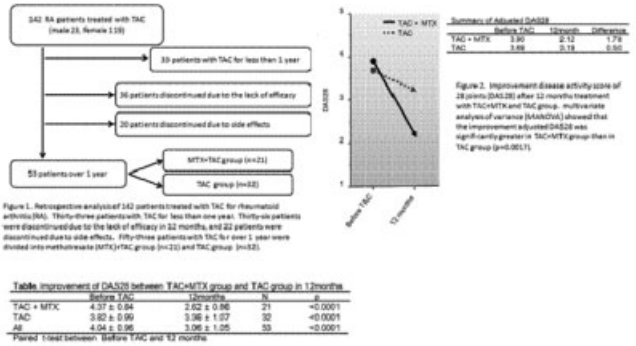

Figure 1. Retrospective analysis of 142 patients treated with TAC for rheumatoid arthritis (RA). Thirty-three patients with TAC for less than one year. Thirty-six patients were discontinued due to the lack of efficacy in 12 months, and 22 patients were discontinued due to side effects. Fifty-three patients with TAC for over 1 year were divided into methotrexate (MTX)+TAC group (n=21) and TAC group (n=32).

Summary of Adjusted DAS28

	Before TAC	12month	Difference
TAC + MTX	3.90	2.12	1.78
TAC	3.66	3.18	0.50

Figure 2. Improvement disease activity score of 28 joints (DAS28) after 12 months treatment with TAC+MTX and TAC group. multivariate analysis of variance (MANOVA) showed that the improvement adjusted DAS28 was significantly greater in TAC+MTX group than in TAC group (p=0.0017).

Table. Improvement of DAS28 between TAC+MTX group and TAC group in 12months

	Before TAC	12months	N	p
TAC + MTX	4.37 ± 0.84	2.62 ± 0.86	21	<0.0001
TAC	3.82 ± 0.99	3.96 ± 1.07	32	<0.0001
All	4.04 ± 0.96	3.06 ± 1.05	53	<0.0001

Paired t-test between Before TAC and 12 months

Conclusion: The results confirm that TAC has beneficial effects in treatment of RA. More importantly, the data demonstrate that combination therapy with TAC and MTX is more effective than TAC therapy.

1277

Anti-CCP Titers Are Predictive of the Response to Biological Agents in Patients with Rheumatoid Arthritis. Ryo Takahashi[1], Ryo Yanai[1], Hidekazu Furuya[1], Kuninobu Wakabayashi[1], Tsuyoshi Odai[1], Takeo Isozaki[2], Nobuyuki Yajima[1], Yusuke Miwa[3] and Tsuyoshi Kasama[1]. [1]Showa University School of Med, Shinagawa-ku Tokyo, Japan, [2]University of Michigan Medical School, Ann Arbor, MI, [3]Division of Rheumatology, Tokto, Japan

Background/Purpose: Biological agents have changed the therapy of rheumatoid arthritis (RA) dramatically last few years. But in some cases,

the effect is scarce, and there is also the risk to cause a serious infectious disease. Anti-cyclic citrullinated protein antibody (anti-CCP) is known as an important indicator for diagnosis of early RA and the positivity of anti-CCP is thought as one of the poor prognosis factors. To examine the relation between serum anti-CCP titer and patient responsiveness to biological agents in RA patients.

Methods: Anti-CCP was measured by ELISA. Disease activity and its clinical improvement were assessed using Disease Activity Scores [DAS28; erythrocyte sedimentation rate (ESR) 4] with European League Against Rheumatism (EULAR) response criteria.

Results: In the present study, 64 patients with RA treated with biological agents (infliximab; 30, etanercept; 19, tocilizumab; 7, adalimumab; 8) were included. The mean age was 36.0±18.0 yrs, mean disease duration was 7.8±4.1 yrs, and mean baseline DAS28 was 5.42±1.47. Among the 64 RA patients, 55 patients (85.9%) were positive for anti-CCP, and the mean antibody titer was 293.1±733.4 U/ml. After 14 weeks of treatment, 26 patients showed good responses and 30 moderate responses to biologic agents based on EULAR response criteria, while 8 showed no clinical improvement.

The anti-CCP titer was 73.7±112.1 U/ml in the good responders and 230.3±261.5 U/ml in the moderate responders, which were significantly lower than in the non-responders (1335±1791.5 U/ml). In addition, 100% of patients with low (<100 U/ml) basal anti-CCP titers showed moderate-good response, and 88.0% of those with moderate (100–499 U/ml) titers also showed a moderate-good response. Among those with higher (≥500 pg/ml) basal anti-CCP titers, 50% showed a moderate response and 50% no response. In addition, the anti-CCP titer was 85.9±879.1 U/ml in the group with remission at 14weeks, although significant higher titers of anti-CCP (396.8±129.2 U/ml) were seen in those had no remission.

Conclusion: The result suggests that anti-CCP titer might to be one of significant predictors of the efficacy of the biological agents in patients with RA.

1278

Abatacept Reduces N-Terminal Pro Brain Natriuretic Peptide Levels in Patients with Rheumatoid Arthritis: Results From a Prospective Cohort Study. Inge A.M. van den Oever[1] and Michael T. Nurmohamed[2]. [1]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands, [2]Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) patients are at increased risk of heart failure (HF). The chronic inflammatory state in RA is associated with increased levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a clinical biomarker for HF. Recently a study has shown that NT-proBNP levels in RA patients decrease under TN-blocking therapy. It is not know whether this is also observed in biologics with another mode of action. Therefore, we investigated the association between EULAR response and change of NT-proBNP during abatacept treatment.

Methods: Of twenty-eight RA patients, treated with abatacept (10mg/kg) every 4 weeks and included in an observational cohort study, disease activity parameters and serum samples were collected at baseline and after 12 and 24 weeks of therapy. Clinical response to abatacept was assessed after 24 weeks of therapy using EULAR response criteria. Responding patients comprised both good and moderate EULAR responders. NT-proBNP levels were measured by the Elecsys 2010 electrochemiluminescence method (Roche diagnostics).

Results: Table 1 shows the baseline characteristics of the 28 RA patients. These characteristics did not differ significantly between EULAR responders and non responders. In all patients, NT-proBNP levels decreased (p= 0.09) after 12 weeks of therapy and decreased significantly (p=0.04) after 24 weeks of abatacept therapy (table 2). Out of 28, 19(68%) patients were EULAR responders after 24 weeks of therapy. At baseline NT-proBNP levels were higher in responding patients compared to non-responding patients. After 12 weeks of treatment more decrease in NT-proBNP levels was observed in responding patients compared to non-responders.(table 1). The same tendency was found after 24 weeks of therapy. Univariate analysis demonstrated a significant association between EULAR response and NT-proBNP levels (regression coefficient 1.18, 95%CI 2.18 to 0.19; p=0.022).

Table 1. Baseline characteristics of 28 patients with RA

Demographic variables	
Age (years)	53 (16)
Women	86%
RA-related variables	
RA duration (years)	16 (4–23)
IgM-RF ≥ 30 IU/ml	68%
erosions on radiographs	68%
nodules	29%
current methotrexate usage	39%
current prednison usage	41%
current usage of other DMARDs	25%
cardiovascular risk factors	
prior cardiovascular disease	18%
systolic blood pressure (mm Hg)	134 (17)
diastolic blood pressure (mm Hg)	85 (9)
body mass index (kg/m2)	26 (5)
diabetes mellitus type 2	11%
current smoker	21%
current usage of antihypertensives	36%
current usage of statins	14%

Values are mean (SD), median (IQR) or percentage

Table 2. changes in NT-proBNP levels

	baseline	12 weeks	24 weeks
all patients	9.3 (4.4 – 25.5)	10 (3.8 – 22.2)	9.0 (3.8 – 21.0)*
EULAR responders	22.0 (6.9 – 63.6)	13.3 (5.3 – 34.5)*	17.2 (6.0 – 39.5)*
EULAR non-responders	8.15 (3.5 – 9.7)	4.8 (3.0 – 17.9)*	5.9 (2.1 – 9.3)*

P<0.05

Conclusion: Decrease in NT-proBNP levels was more prominent in patients responding to abatacept therapy compared to non-responding patients. These findings underscore the importance of tight control of systemic inflammation in RA patients in order to decrease CV risk.

1279

Do Impared Memory, Cognitive Dysfonction and Distress Play a Role In Methotrexate-Related Pancytopenia In Rheumatoid Arthritis Patients? Salim Donmez[1], Yavuz Pehlivan[2], Omer Nuri Pamuk[1], Bunyamin Kisacik[2], Gulsum Emel Pamuk[1], Ahmet Mesut Onat[2], Mehmet Sayarlioglu[3] and Gözde Yildirim Çetin[3]. [1]Edirne, Turkey, [2]Gaziantep, Turkey, [3]Kahramanmaras, Turkey

Background/Purpose: Studies which investigate the risk factors for methotrexate (MTX)-related pancytopenia in rheumatoid arthritis (RA) patients conclude that the most important factors are age, the dose of methotrexate and genetic factors. In this study, we investigated the role of impaired memory and distress on the development of methotrexate-related hematological toxicity

Methods: Twentyfive RA patients (14 females, 11 males) who were being followed up at 2 centers and who developed pancytopenia and/or febrile neutropenia were included into the study. The control group included 3 RA patients whose hospital registration numbers were immediately after the RA patient of interest (72 cases; 61 females, 11 males). Patients' baseline clinical and sociodemographic features were recorded down from hospital files. RA patients who developed methotrexate toxicity were administered the mini mental test (MMT) and hospital anxiety and depression scale (HADS) one month after discharge from hospital. The controls were also administered the above-mentioned tests.

Results: Three of the patients (12%) with MTX toxicity died. Eight patients (32%) had concurrent hepatotoxicity, the ALT levels were 2–3 times higher than normal only in 2 patients. RA patients with MTX-related pancytopenia were more frequently males (56% vs. 15.3%, p<0.001), did not know how to read and write (52.4% vs. 16.2%, p=0.004), were more frequently living alone /24% vs. 7%, p=0.03), and higher creatinine levels (1.22+0.7 vs. 1.02+0.8, p=0.035) when compared to controls. The groups were similar in age, RF, anti-CCP positivity, HAQ scores, and annual income (all p values >0.05). When the questionnaires were interpreted, it was seen that MMT scores were significantly lower in the MTX toxicity group (22.6±4.3 vs. 26.08±4.8, p=0.002); HADS-A (10.4±4.7 vs. 7.5±3.8, p=0.016) and HADS-D (10.5±4.5 vs. 5.5±4.2, p=0.001scores were significantly higher.

Conclusion: The risk factors for the development of MTX-related pancytopenia in our study were male sex, high creatinine levels, having a low educational level, living alone and visual impairment. In addition, we observed that the presence of impaired memory, depression and anxiety played important roles for the development of methotrexate toxicity. As a result, we conclude that the administration of the MMT to RA patients with low education level, living alone and who are planning to be given MTX, might prove useful to decrease toxicity.

1280

Acute Pain Relief by a Proprietary, Nano-Formulated Lower-Dose Oral Indomethacin. Roy D. Altman[1], Stephen Daniels[2] and Garen Manvelian[3]. [1]UCLA, Los Angeles, CA, [2]Premier Research Group, Austin, TX, [3]Iroko Pharmaceuticals, Poway, CA

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, are commonly prescribed for the relief of arthritic, musculoskeletal, and postoperative pain. Because there is a direct relation between dose of NSAID and adverse effects (AEs), there is a need to develop a formulation which safely provides fast onset of acute pain relief at a reduced dose of medication while decreasing the potential gastrointestinal AEs. This study evaluated the time to onset of analgesia of an investigational, proprietary, lower dose nano-formulated, oral indomethacin (nano-formulated indomethacin) compared with placebo, as well as a loading dose of celecoxib, in subjects with acute dental pain.

Methods: This was a Phase 2, multicenter, randomized, double-blind, single-dose, parallel-group, placebo-controlled study. In total, 203 subjects were enrolled who were 18–50 years of age, had extraction of ≥2 third molars (at least 1 of which had to be a fully or partially impacted mandibular third molar), and experienced moderate to severe pain intensity (a score of ≥50 mm on a 100 mm Visual Analogue Scale [VAS]) ≤6 hours after surgery. Subjects assessed their baseline pain intensity (VAS) at Time 0 before receiving either nano-formulated indomethacin 20 mg or 40 mg, celecoxib 400 mg, or placebo. Efficacy variables included time to onset of analgesia and total pain relief. The Kaplan-Meier method was used to evaluate the treatment effect for each time to event endpoint. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) was based on data collected using the 2-stopwatch method.

Results: Data from the intent-to-treat population were included in the analysis. There was a statistically significant improvement in mean time to meaningful pain relief and mean time to peak pain relief for lower-dose nano-formulated indomethacin when compared with placebo (**Table**).

Parameter	Nano-formulated Indomethacin 20 mg Mean±SE (N=50)	Nano-formulated Indomethacin 40 mg Mean±SE (N=51)	Celecoxib 400 mg Mean±SD (N=51)	Placebo Mean±SE (N=51)
Mean Time to Meaningful Pain Relief (h)	2.4 ± 0.25[b]	1.8 ± 0.21[a]	2.6 ± 0.40[a]	3.4 ± 0.50
Mean Time to Peak Pain Relief (h)	3.4 ± 0.39	2.6 ± 0.30[c]	3.3 ± 0.36	4.4 ± 0.53

[a] $P<0.001$ compared with placebo
[b] $P=0.08$ compared with placebo
[c] $P<0.05$ compared with placebo
SE=standard error

Total pain relief over 8 hours (primary endpoint) for nano-formulated indomethacin was significantly ($P<0.001$) better compared with placebo (mean; 95% CI): 20mg (10.79; 2.66); 40mg (12.56; 2.64); placebo (3.02; 2.64). Tolerability data were comparable and there were no differences in treatment emergent adverse events between nano-formulated indomethacin 20 mg (38%; 19/50) or 40 mg (51%; 26/51), celecoxib (37.3%; 19/51), and placebo (56.9%; 29/51).

Conclusion: A lower dose, nano-formulated indomethacin demonstrated improved pain relief compared with placebo in this Phase 2 clinical trial, suggesting that use of this NSAID formulation may provide clinical benefit in the relief of acute arthritic/rheumatic and postoperative pain as a means of reducing AEs. Utilizing a lower dose, while maintaining efficacy, could result in an improved tolerability and safety profile and is in line with the FDA directive to use the lowest effective dose.

1281

A Phase 2 Study Evaluating the Acute Pain Relief of a Nano-Formulated Oral Naproxen. Garen Manvelian[1], Stephen Daniels[2], Allan Gibofsky[3] and Vibeke Strand[4]. [1]Iroko Pharmaceuticals, Poway, CA, [2]Premier Research Group, Austin, TX, [3]Hospital for Special Surgery, New York, NY, [4]Stanford University, Palo Alto, CA

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the relief of a variety of painful rheumatologic and musculoskeletal conditions, despite concerns about the safety and tolerability of this class of drugs. The purpose of this randomized controlled trial was to evaluate the efficacy and safety of an investigational, nano-formulated, oral naproxen when compared with naproxen and placebo in a validated and standardized model of acute pain.

Methods: This was a Phase 2, multicenter, randomized, single-dose, active- and placebo-controlled trial. In total, 253 subjects 18–50 years of age were enrolled following extraction of ≥2 third molars (≥1 of which was a fully or partially impacted mandibular third molar) who experienced moderate to severe pain (a score of ≥50 mm on a 100 mm Visual Analogue Scale [VAS]) ≤6 hours after surgery) within 6 hours after surgery. Subjects received nano-formulated naproxen 200 mg or 400 mg, standard naproxen 250 mg or 500 mg, or placebo. The primary efficacy endpoint was the sum of total pain relief (TOTPAR) over 0–12 hours (TOTPAR-12). TOTPAR-8 and TOTPAR-4, secondary efficacy endpoints, were also evaluated along with VAS pain intensity difference (VASSPID).

Results: Nano-formulated naproxen 400 mg and 200 mg was significantly ($P<0.001$) better than placebo for TOTPAR-12 (**Table**).

	Nano-formulated naproxen 400 mg[a] N=51	Standard Naproxen 500 mg[a] N=51	Nano-formulated naproxen 200 mg[a] N=50	Standard Naproxen 250 mg[a] N=50	Placebo N=51
TOTPAR-12, mean; SD	31.9; 12.4	28.3; 13.0	25.7; 16.1	24.6; 15.3	9.6; 13.6
TOTPAR-8, mean; SD	21.5; 7.6	19.8; 8.1	17.3; 9.8	16.9; 9.8	6.8; 8.8
TOTPAR-4, mean; SD	10.1; 3.5	9.5; 3.8	8.2; 4.3	8.0; 4.5	3.5; 3.9

[a] $P<0.001$ compared with placebo
SD=standard deviation

Similarly, TOTPAR-4 and TOTPAR-8 values for nano-formulated naproxen 400 mg and 200 mg also demonstrated statistical significance in favor of the active treatments compared with placebo (**Table**). Additionally, VASSPID values over 4, 8, and 12 hours for each treatment group were significantly ($P<0.001$) better than placebo. Adverse events were reported in 13 subjects (5.1%): nano-formulated naproxen 400 mg (1, 2%); nano-formulated naproxen 200 mg (0), standard naproxen 500 mg (2, 3.9%), standard naproxen 250 mg (3, 6%), and placebo (7, 13.7%).

Conclusion: An investigational nano-formulated, lower dose, oral naproxen demonstrated efficacy and was well-tolerated in an acute pain model. These Phase 2 study results suggest that use of this nano-formulation could offer treatment of acute pain at a lower dose.

1282

Application of Nanotechnology to Improve Non-Steroidal Anti-Inflammatory Drugs. Garen Manvelian[1], Roy D. Altman[2] and Vibeke Strand[3]. [1]Iroko Pharmaceuticals, Poway, CA, [2]UCLA, Los Angeles, CA, [3]Stanford University, Palo Alto, CA

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for various conditions involving both acute and long-term pain. However, concerns exist about the safety and tolerability associated with NSAIDs. We have completed 3 Phase 2 clinical trials in acute pain models to assess the analgesic efficacy and safety of investigational, nano-formulated, oral NSAIDs: diclofenac, indomethacin, and naproxen.

Methods: All 3 Phase 2 trials were multi-center, randomized, double-blind, single-dose, parallel-group, active- and placebo-controlled studies. More than 200 subjects (N=202 [diclofenac], N=203 [indomethacin], and N=253 [naproxen]) were enrolled for each trial. Subjects were 18–50 years of age, had extraction of ≥2 third molars (at least one of which had to be a fully or partially impacted mandibular third molar), and experienced moderate to severe pain intensity within 6 hours after surgery.

Subjects received nano-formulated diclofenac, indomethacin, or naproxen, an active comparator (parent compound or celecoxib), or placebo. The sum of total pain relief (TOTPAR) was assessed at 4, 8, and 12 hours. The primary efficacy endpoints were TOTPAR 0 to 12 hours (diclofenac and naproxen) and 0 to 8 hours (indomethacin). Higher scores indicated better pain relief.

Results: All active treatments resulted in significantly ($P<0.001$) better TOTPAR values compared with placebo (**Table**).

	TOTPAR-12 Mean; SD	TOTPAR-8 Mean; SD	TOTPAR-4 Mean; SD
Nano-formulated Diclofenac 18 mg, N=49	17.8; 13.8[a]	14.3; 9.4[a]	8.2; 4.2[a]
Nano-formulated Diclofenac 35 mg, N=51	16.8; 12.8[a]	13.9; 8.8[a]	7.9; 4.3[a]
Celecoxib 400 mg, N=51	14.6; 15.1[a]	11.2; 10.5[a]	5.7; 5.0[a]
Placebo, N=51	5.7; 11.5	3.9; 7.2	2.1; 3.3
Nano-formulated Naproxen 400 mg, N=51	31.9; 12.4[a]	21.5; 7.6[a]	10.1; 3.5[a]
Standard Naproxen 500 mg, N=51	28.3; 13.0[a]	19.8; 8.1[a]	9.5; 3.8[a]
Nano-formulated Naproxen 200 mg, N=50	25.7; 16.2[a]	17.3; 9.8[a]	8.2; 4.3[a]
Standard Naproxen 250 mg, N=50	24.6; 15.3[a]	16.9; 9.8[a]	8.0; 4.5[a]
Placebo, N=51	9.6; 13.6	6.8; 8.8	3.5; 3.9
Nano-formulated Indomethacin 20 mg, N=50	Not assessed	10.8; 10.5[a]	5.5; 4.6[a]
Nano-formulated Indomethacin 40 mg, N=51	Not assessed	12.6; 10.7[a]	6.2; 4.8[a]
Celecoxib 400 mg, N=51	Not assessed	14.9; 9.9[a]	7.2; 4.2[a]
Placebo, N=51	Not assessed	3.0; 6.6	1.6; 2.8

[a]$P<0.001$ compared with placebo
SD=standard deviation

TOTPAR values for nano-formulated diclofenac and nano-formulated naproxen were numerically better than the active comparators, although the studies were not powered to assess this statistically. Additionally, visual analog scale pain intensity difference values for each treatment group were all significantly ($P<0.001$) better than placebo.

Conclusion: Investigational, nano-formulated, oral NSAIDs demonstrated efficacy in an acute pain model. These Phase 2 data indicate that nano-formulated diclofenac, indomethacin, and naproxen may offer efficacy at a lower dose and deserve further investigation in Phase 3 clinical trials. The aforementioned results are in line with the FDA directive to use the lowest effective NSAID dose.

1283

Demonstration of the Symptomatic and Structural Effect of Methotrexate in Daily Practice As the First RA-DMARD Despite Its Sub-Optimal Use: Results From the ESPOIR Early Synovitis Cohort. Cécile Gaujoux-Viala[1], Simon Paternotte[2], Bernard G. Combe[3] and Maxime Dougados[4]. [1]Paris 6 – Pierre et Marie Curie University; Rheumatology, Pitié-Salpêtrière Hospital, Paris, France, [2]Hopital Cochin, Paris, France, [3]Hopital Lapeyronie, Montpellier, France, [4]Paris-Descartes University, Paris, France

Background/Purpose: Methotrexate (MTX) is recommended the first DMARD in rheumatoid arthritis (RA). Despite its widespread use and more than two decades of experience, considerable variations exist among rheumatologists in prescribing MTX, including its dose and its concomittent folic acid supplementation. Objective: To describe the use of MTX in early arthritis in daily clinical practice and to evaluate short-term (6 months) symptomatic efficacy and 12 months structural efficacy.

Methods: Patients: including in the French nationwide cohort of early arthritis (ESPOIR). Patients had to present with inflammatory arthritis lasting for 6 weeks up to 6 months, involving more than 2 joints and diagnosed by the referring physician as RA or RA-like (i.e. a high suspicion of RA).

- Data collected: at baseline patients characteristics and every 6 months symptomatic variables (DAS28,HAQ) and Xrays at baseline and 1 year.

- Analysis: a) Comparison of the patients characteristics with regard to the MTX intake (yes/no); b) The evaluation of the symptomatic and structural efficacy has been performed by generalized linear regression after adjustement on propensity score (by modelling the start of MTX by disease specific- and demographic variables obtained at baseline, using logistic regression analysis) in the group of patients receiving MTX versus the ones receiving any treatment except leflunomide or sulfazalasine or TNF inhibitors.

Results: Within the first 6 months of follow-up of 777 RA patients, 59% received a DMARD which was MTX in 68% (N=313). The mean dose of MTX was 12.7±3.8 mg/week. The folic acid supplementation was given in only 53.7% of the patients. MTX was initiated in patients with more active and severe disease (DAS28: 5.39±1.22 vs 4.83±1.30; HAQ: 1.11±0.68 vs 0.85±0.65; ACPA +: 50% vs 28%; erosion: 64.5% vs 53%; all $p<0.002$). After adjustment on the propensity score, MTX was found to be more efficient in terms of both symptomatic and structural end point than control group: change in DAS28 −1.81±1.50 vs −1.54±1.47, p=0.009; change in HAQ −0.51±0.65 vs −0.31±0.62,$p<0.0001$; radiographic progression score 0.88±0.23 vs. 1.60±0.22 units, p=0.031, respectively.

Conclusion: This study confirms the symptomatic and structural efficacy of MTX in early arthritis in daily practice.These data have been observed despite the non-optimal use of MTX including low doses and low frequency of folic acid supplementation.

ACR/ARHP Poster Session B
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment II
Monday, November 7, 2011, 9:00 AM–6:00 PM

1284

Impact of Etanercept Therapy on Glycemic Control in a Cohort of Psoriatic Patients: The PRISTINE Trial. Andrew S. Koenig, Annette Szumski, Ronald Pedersen and Debbie H. Robertson. Pfizer Inc., Collegeville, PA

Background/Purpose: Psoriasis patients have an increased risk of systemic comorbidities, including cardiovascular disease and diabetes.[1] The mechanisms underlying these associations and the impact of systemic psoriasis therapy have not been well studied. In the PRISTINE trial (NCT00663052), a post hoc analysis was conducted of the effects of etanercept therapy on cardiometabolic biomarkers in subjects with psoriasis based on diabetes status.

Methods: Subjects ≥18 years with moderate-to-severe plaque psoriasis were randomised to receive either etanercept 50 mg once or twice weekly double blind for 12 weeks. Diabetes status was determined at baseline by patient history; subjects who were non-diabetic, pre-diabetic, and diabetic were also identified based on American Diabetes Association (ADA) diagnostic criteria (non-diabetic=glycosylated hemoglobin A1C [HbA1c] <5.7 with no medical history or diabetes medication; pre-diabetic=HbA1c 5.7–6.4%; diabetic=HbA1c >6.4% or medical history or diabetes medication). Median changes in cardiometabolic biomarkers were analysed based on diabetes status in subjects with both baseline and Week-12 visits for both treatment groups combined.

Results: At baseline, subjects (N=273) were 70% male, with mean age of 44 y, mean BMI of 28.3 kg/m^2 (males)/29.6 kg/m^2 (females), mean PASI of 21, and mean psoriasis duration of 17 y; 31% had a history of psoriatic arthritis (mean duration, 8 y). Overall 10% had a history of diabetes at baseline; 45% were identified as either pre-diabetic (32%) or diabetic (13%) based on ADA diagnostic criteria. In the non-diabetic, pre-diabetic, and diabetic subgroups, median changes in C-reactive protein from baseline to week 12 were −0.1*, −0.2*, −0.3* mg/dL, respectively (median baseline values: 0.3, 0.3, and 0.4 mg/dL; *$P<0.05$, change from baseline to Week 12); median changes in the apolipoprotein B/apolipoprotein A ratio were 0*, −0.1*, and 0 (median baseline values: 0.7, 0.8, 0.7; *$P<0.05$, change from baseline to Week 12). After-treatment changes in glycemic control markers are shown (table).

Effects of etanercept therapy on markers of glycemic control in subjects with psoriasis by diabetes status

	HbA1c* (%)		Plasma insulin† (mcU/mL)		Plasma glucose† (mg/dL)		HOMA-A*	
Subjects	Baseline	Change at Wk 12	Baseline	Change at Wk 12	Baseline	Change at Wk 12	Baseline	Change at Wk 12
Non-diabetic (n=152)	5.4	0‡	12.5	2.0‡	91.8	0.0	2.9	0.6‡
Pre-diabetic (n=86)	5.8	−0.1‡	14.0	2.0	95.4	2.7	3.6	0.4
Diabetic (n=35)	7.0	−0.3	14.0	3.0‡	122.4	1.8	5.3	1.1‡

All values shown are medians.
* Non-fasting; †fasting; ‡$P<0.05$, change from baseline to Week 12 (Wilcoxon Signed Rank Test)

Conclusion: Approximately 10% of subjects in the PRISTINE trial had a history of diabetes at baseline, whereas 45% were identified as being pre-diabetic or diabetic according to current diagnostic guidelines. Those with pre-diabetes or diabetes showed no overall worsening in glycemic control (HbA1c) and had slight increases in plasma insulin and the insulin-resistance measure HOMA-A. These findings suggest that etanercept therapy does not worsen glycemic control in these at-risk populations.

Reference:
1. Davidovici BB, et al. *J Invest Dermatol.* 2010;130:1785–96.

1285

Long Term Results of a Remission Induction Approach to Early Axial Spondyloarthritis: Still Looking for the Window of Opportunity. Zoe R. Ash[1], Nick Barkham[1], Dennis McGonagle[1], Elizabeth Hensor[2], Paul Emery[1] and Helena Marzo-Ortega[1]. [1]University of Leeds, Leeds, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom

Background/Purpose: We have previously reported on an RCT assessing the efficacy of infliximab in very early axial SpA. Importantly, the clinical improvements correlated with resolution of MRI inflammatory spinal lesions. However, the key question is whether this early suppression of inflammatory activity translates into arrest of new bone formation, the hallmark of AS. We now report on the long term outcome of these patients, followed up at five years.

Methods: In the initial study patients received infliximab or placebo for 16 weeks. Subjects were then observed up to week 40 and were eligible for open-label treatment with infliximab on disease flare (BASDAI≥4). In the current phase subjects underwent a clinical assessment and laboratory investigations. Current imaging included whole spine and SIJ MRI to assess for ongoing disease activity and radiographs of the SIJs, lumbar and cervical spine to assess for disease progression including fulfilment of the modified New York criteria (mNYC).

Results: So far, 64% (25/39) of the patients who completed the original study have been assessed, 80% (20 patients) of whom are currently receiving an anti-TNF agent (8 adalimumab, 9 etanercept, 3 infliximab) and 52% are taking NSAIDs. The majority of patients have well controlled disease, with a median disease activity (BASDAI) of 0.65, median BASFI of 0.50. CRP is <5 mg/L in 88% (22/25) of the patients.

No substantive differences were seen in current disease activity or radiographic progression between patients who received infliximab in the initial randomised phase and those who received placebo. However, only 58% (7/12) of those who initially received infliximab are still on an anti-TNF agent, in comparison to 100% (13/13) of those who received placebo. Of those not on an anti-TNF agent, four remain well with minimal or no symptoms, one patient has active disease (BASDAI 4.52) but has defaulted from treatment.

Complete radiographic data was available for 15 patients (radiographs at baseline and follow up). Three patients fulfilled the mNYC for AS at baseline. The remaining 12 patients all have evidence of radiographic progression in the SIJs, with 8 patients now meeting the mNYC for AS. The median mSASSS score was low at 3.7, suggesting little progression within the spine. No patients have progressed to complete spinal ankylosis. Current MRI scans show very little active disease. No substantive differences were found in baseline disease activity scores or MRI findings between patients who now fulfil radiographic criteria for AS and those who do not. However a higher percentage of those with AS than those with non-radiographic axial SpA are now receiving NSAIDs (67% vs. 30%) and anti-TNF (92% vs. 70%).

Conclusion: A third of axial SpA patients treated early with a 3 month course of infliximab remain well and off treatment after 5 years, while all patients initially randomised to placebo continue to require anti-TNF treatment. Despite patients reporting a good clinical status with overall low disease activity and good function, it appears that there is ongoing SIJ radiographic progression in a significant proportion of patients. However this is a small study and these findings require confirmation in larger cohorts.

1286

High Prevalence of Coronary Heart Disease and Its Risk Factors In Veterans with Spondyloarthritides. Suhail Kumar, Trayton Mains and Vikas Majithia. University of Mississippi Medical Center, Jackson, MS

Background/Purpose: An increased prevalence of cardiovascular disease (CVD) and coronary heart disease (CHD) has been reported in patients with spondyloarthritides. This study investigated the prevalence of CVD risk factors, CVD including CHD and stroke in veterans at Jackson VAMC with spondyloarthritides (SpA) including PsA, ankylosing spondylitis (AS), and reactive arthritis (ReA).

Methods: A retrospective chart review, using ICD-9 codes for PsA, AS, and ReA was performed at Jackson, VAMC. Data including age, race, gender, medications, ESR, CRP, lipid panel, HbA1c, 25-OH vitamin D level, hypertension (HTN), smoking, statin use, and CVD events were tabulated. Comparisons of CHD, stroke, and CVD risk factors were made to a matched population from the American Heart Association data. Risk factors included smoking, dyslipidemia (DLD), HTN, and diabetes mellitus (DM). Prevalence ratio and odds ratio were calculated by standard method. Statistical significance (alpha<0.05) was calculated using Chi-square and Fisher's exact test.

Results: See Table. There were 81 patients, 79 male and 2 female, with mean age of patients with PsA, AS, and ReA being 61.8, 60.4, and 56, respectively. There was significant increase in the prevalence of CHD and the risk factors in the SpA, PsA and AS patients. There was an insufficient number of black patients in the cohort to assess effect of ethnicity.

	Control (%)	SpA (%)	PsA (%)	AS (%)	ReA (%)
CHD	9.1	23.46	25.00	26.09	14.29
PR		2.58	2.75	2.86	NS
OR		3.06	3.33	3.52	NS
p-value		*≤0.001*	*0.01*	*<0.05*	*NS*
CVA	2.5	3.70	6.82	0	0
PR		1.48 (NS)	2.73 (NS)		
DM	7.6	24.69	22.73	26.09	28.57
PR		3.25	2.99	3.43	3.76
HTN	34.4	74.07	77.27	73.91	64.29
PR		2.15	2.25	2.15	1.87
DLD	45.2	82.72	88.64	73.91	78.57
PR		1.83	1.96	1.64	1.74
Smoking	23.1	33.33	36.36	26.09	35.71
PR		1.44	1.57	1.13	1.55

PR, prevalence ratio; OR, odds ratio; NS, not significant

Conclusion: Our results further confirm that patients with SpA have an increased risk of developing CHD as well its risk factors. Our study is unique as increased risk and its quantification have not been previously reported in the U.S. veteran population. The increased CHD risk attributable to the increased prevalence of risk factors cannot be determined in this study but has been suggested to be over and above in previous studies.

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Clinical and Radiological Evaluation of Sacroiliac Joints (SIJ) Compared with Ultrasound (US) Examination in Early Spondiloarthritis. Francesca Bandinelli[1], Daniela Melchiorre[1], Francesco Scazzariello[1], Antonio Candelieri[2], Leonardo Giovannini[1], Giuliana Salvadorini[1], Francesco Porta[1] and Marco Matucci-Cerinic[1]. [1]University of Florence, Florence, Italy, [2]University of Calabria, Cosenza, Italy

Background/Purpose: BACKGROUND: The sacroiliac joint (SIJ) inflammation is the hallmark of all Spondiloartropathies (SpA) because it often takes several years before that the radiological damage can be demonstrated. The recent ASAS criteria for SpA have included Magnetic resonance (MRI) for early diagnosis, but other new imaging techniques, cheaper and more accessible, as SIJ ultrasonography (US), were not sufficiently investigated until now. In fact, US might have a promising role in detecting enthesitis and effusion of SIJ (1) in the next future. OBJECTIVE: To compare US with clinical examination and traditional radiography (XR) findings of SIJ in early SpA patients.

Methods: In 23 early SpA patients (42 [2,1] mean age, 4 male and 19 female, 11 Psoriatic Arthritis, 7 associated with inflammatory bowel disease and 10 undifferentiated SpA) diagnosed according to ASAS criteria (2), with active sacroileitis (bone oedema at MRI) and duration of disease lower than 3 years,

were investigated: disease activity (BASFI, BASDAI, pain VAS) scores, clinical examination (sacral sulcus tenderness), New York XR score for SIJ. Patients and 11 healthy controls (negative for axial symptoms, SIJ clinical examination and questionnaires) were examined with My Lab70 US 7–18 MHHz (Esaote, Genoa, Italy) the presence of effusion of SIJ and enthesopathy (thickness) of posterior sacroiliac and sacro-tuberosus ligaments.

Results: SIJC distension (right 2.2 ± 0.6 and left 2.3 ± 0.7 in SpA *vs* 1.7 ± 0.2 and 1.8 ± 0.2 in healthy controls, respectively) and ST thickness (right 3.9 ± 1.3 and left 3.4 ± 1.0 *vs* 1.9 ± 0.1 and 1.8 ± 0.1, respectively) were higher in SpA patients than in controls ($p<0,001$ and $p<0,05$ respectively). PS thickness was similar in patients and controls. Only ST thickness correlated with SIJ tenderness (15/23 patients painful at clinical examination [65,2%], $p<0,01$), pain VAS (21/23 with VAS>0 [91,3%], mean 6,5 [2,9], $p<0,001$), BASFI (18/23 with BASFI>0 [78,2%], mean 1,9 [1,6], $p<0,05$). XR SIJ evaluation (14/23 [60,8%] with New York score>1, mean [right] 0,86 [0,62] and [left] 0,65 [0,71]) did not correlate with US results

Conclusion: Our data confirm that SIJC distension and ST thickness were higher in early SpA but that only ST correlated with clinics. US is a promising imaging technique for SIJ more sensitive than clinical examination and XR.

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Early Treatment of Psoriatic Arthritis Is Associated with Improved Outcomes: Findings From the Etanercept (Enbrel ®) PRESTA Trial.
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Background/Purpose: Early detection of rheumatoid arthritis (RA) and a rapid therapeutic intervention reduces the risk of clinical progression, joint damage and subsequent irreversible loss of function. However, this has not been well investigated in patients with psoriatic arthritis (PsA). Importantly, the role of biologic agents in early PsA management is still unclear. The objective of this study was to explore the relationship between duration of PsA disease and improvement in health outcomes in patients treated with etanercept enrolled in the PRESTA trial.

Methods: Patients with both moderate/severe psoriasis and PsA who participated in the PRESTA trial and received etanercept 50 mg once weekly were included in the analysis. Subjects in this analysis had to be dosed at least once and have a post-baseline value. Change in baseline values of efficacy measures and Patient Reported Outcomes (PROs) at 24 weeks of treatment of patients with disease duration <2 years (defined as early treatment arm) was compared to change in patients with disease duration ≥2 years. Measures included the Health Assessment Questionnaire of physical function (HAQ), EQ-5D quality of life, Hospital Anxiety and Depression Scale (HADS), Psoriasis Activity and Severity Index (PASI), a Physician Global Assessment (PGA) of arthritis, swollen joint count, joint pain, patient-reported arthritis activity, duration of morning stiffness, and missed workdays. For each of the 12 efficacy variables and PROs, a linear regression of change on its baseline and PsA duration was performed. Age and gender were added as covariates.

Results: A total of 372 patients (103 with disease duration <2 years, 269 with disease duration ≥2 years) were studied. In both groups all outcomes measures at week 24 improved significantly from baseline and the change was similar in the two groups, however linear regression showed that early PsA disease was strongly associated with improvement in EQ-5D, PGA of arthritis, joint pain, and arthritis activity responses (Table). Improvement in EQ-5D, PGA of arthritis, joint pain, and arthritis activity was also associated with being younger, while quality of life and arthritis activity responses were also associated with being female. Improvement in HAQ, anxiety, depression, PASI, and morning stiffness was not associated with early treatment.

Table. The effect of disease duration, age, and sex on efficacy and PROs at Week 24 in patients with PsA

Variable	N	Disease duration <2 P value*	Age P value*	Female P value*
HAQ	371	0.5647	<.0001	0.5542
EQ5D	371	0.0457	<.0001	0.0006
EQ5D-VAS	368	0.0402	0.0002	0.5404
HAD anxiety	369	0.5977	0.0251	0.034
HAD depression	370	0.9493	0.0101	0.3317
PASI	370	0.5586	0.5676	0.2511
PGA arthritis	346	0.0269	0.002	0.3902
Swollen joint count	357	0.3086	0.2559	0.0864
Joint pain	367	0.0072	<.0001	0.0951
Arthritis activity	367	0.0148	<.0001	0.0527
Morning stiffness	360	0.6718	0.3673	0.3446
Sick days	207	0.8985	0.0787	0.9131

*Calculated using linear regression

Conclusion: Although PsA patients with early disease and with longer-duration disease both responded to etanercept treatment, PsA patients with early disease had better responses in several measures.

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Efficacy of a Shorter 6-Month Isoniazid treatment in Patients At High Risk for Tubercolosis Treated with Etanercept.
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Background/Purpose: Treatment with tumor necrosis factor (TNF) antagonists is associated with reactivation of latent tubercolosis infection (LTBI). Health authorities worldwide have proposed recommendations for screening of LTBI with purified protein derivative (PPD) and for the initiation of isoniazid (INH) therapy before starting anti-TNF therapy. Our objective was to evaluate the risk of developing active TB in PPD-positive patients on etanercept (ETN) therapy treated with shorter (6 instead of 9-month) course INH chemoprophylaxis.

Methods: All patients with a positive PPD test and candidate to anti-TNF treatment for rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) were treated with ETN (50 mg/week) and INH (300 mg/die for 6 months). LTBI therapy was scheduled to be started 1 month prior to the initiation of ETN therapy. Patients were carefully followed to reveal any active TB infection either while taking or after the 6 months discontinuating ETN treatment.

Results: From January 2006 to June 2010, 578 patients were evaluated for starting an anti-TNF treatment. Thirty-nine (6.75%) of these had a positive PPD and were enrolled in the present prospective study. The study cohort (24 men, 15 women; mean age 49.9 ± 9.0 years) included 10 patients with RA, 12 with PsA and 17 with AS. The mean follow-up after initiation of ETN was 43 months (median 47; range 5 to 73 mo). All but 4 patients completed the 6-month INH prophylaxis. Reasons for discontinuation of INH included abnormal liver enzymes in 2, peripheral neuropathy in 1, and rash in 1. All the discontinuating patients completed chemoprophylaxis with a 4-month rifampicin course. None of the studied patients experienced a LTBI reactivation.

Conclusion: A shorter 6-month INH chemoprophylaxis seems to be efficacious in preventing LTBI reactivation in a cohort of high-risk PPD-positive patients treated with ETN.

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Change in Back Pain Over Time As a Function of C-Reactive Protein Across Studies of Ankylosing Spondylitis.
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Background/Purpose: C-reactive protein (CRP) levels rise in response to inflammation and are often used to measure disease progress or effectiveness of treatment [1]. Ankylosing spondylitis (AS) is a chronic rheumatic disease that largely affects the spine leading to inflammatory back pain, physical disability, and a reduced quality of life [2]. The objective of this analysis was to investigate the relationship between CRP levels and change in back pain in patients with AS.

Methods: Data were pooled from four controlled clinical trials (placebo or sulfasalazine versus etanercept) [3–6]. Patients with at least one treatment dose, baseline data, and Week 12 data were analyzed. Subject nocturnal and total back pain was measured on the pain visual analogue scale (0–100). Each model was adjusted for baseline nocturnal back pain or baseline total back pain to control for any differences across studies. Pearson correlation coefficients for baseline and

Week 12 were calculated and linear regression controlling for study, treatment, geographic region, and Human Leukocyte Antigen (HLA)-B27 status was performed.

Results: Strong correlations were observed (Table) between nocturnal back pain and total back pain baseline values (r=0.7403, P<0.0001), Week 12 (r=0.9267, P<0.0001), and change from baseline at Week 12 values (r=0.8364, P<0.001). Correlations were very weak between CRP and nocturnal back pain baseline values (r=0.0190, P=0.5105), and weak for Week 12 (r=0.2319, P<0.0001) and change from baseline at Week 12 values (r=0.1852, P<0.0001); similar results were observed for the relationship between CRP and total back pain (Table). Based on the linear regression analysis results, CRP change was a statistically significant predictor of both nocturnal and total back pain change, even after adjusting for HLA-B27 status (both P < 0.0001), however, the contribution of CRP to the regression model was limited.

Table. Pearson correlation coefficients for nocturnal back pain, total back pain, and CRP at baseline, Week 12, and change from baseline

	Nocturnal back pain baseline	Total back pain baseline	CRP baseline
Nocturnal back pain baseline	1	0.7403	0.0190
		P<0.0001	P=0.5105
Total back pain baseline	0.7403	1	0.0107
	P<0.0001		P=0.7106
CRP baseline	0.0190	0.0107	1
	P=0.5105	P=0.7106	
	Nocturnal back pain Wk 12	Total back pain Wk 12	CRP Wk 12
Nocturnal back pain Wk 12	1	0.9267	0.2319
		P<0.0001	P<0.0001
Total back pain Wk 12	0.9267	1	0.2119
	P<0.0001		P<0.0001
CRP Wk 12	0.2319	0.2119	1
	P<0.0001	P<0.0001	
	Nocturnal back pain change	Total back change	CRP change
Nocturnal back pain change	1	0.8364	0.1852
		P<0.0001	P<0.0001
Total back pain change	0.8364	1	0.1889
	P<0.0001		P<0.0001
CRP change	0.1852	0.1889	1
	P<0.0001	P<0.0001	

Wk=Week; CRP=C-reactive protein.

Conclusion: These data show CRP levels alone may not be indicative of back pain levels in patients with AS. Focusing on CRP levels exclusively could be misleading; clinicians also need to ask patients about changes in nocturnal and/or total back pain to get a complete clinical picture of change with treatment.

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PASE Tool for Early Screening of Psoriatic Arthritis: Association with Disease Biomarkers and Score Cutoffs. M. Elaine Husni[1], Abrar A. Qureshi[2], Ronald Pedersen[3], Andrew S. Koenig[3] and Debbie H. Robertson[3]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Brigham and Women's Hospital, Boston, MA, [3]Pfizer Inc., Collegeville, PA

Background/Purpose: Psoriatic arthritis (PsA) can lead to irreversible joint damage. The Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire is a validated tool to screen for active PsA among individuals with psoriasis at the earliest possible stage. We assessed the association of PASE cutoff scores and the relationship with PsA disease biomarkers.

Methods: The PRISTINE trial (NCT0066305) evaluated the efficacy and safety of 2 etanercept doses for the treatment of psoriasis. Participants were randomized to receive etanercept 50 mg once or twice weekly for 12 weeks. At study entry, participants self-reported prior physician-diagnosed PsA and assessed their global joint pain (scale 1–5). The PASE questionnaire was administered at baseline. Receiver operating characteristics (ROC) analyses were performed on PASE scores based on prior diagnoses of PsA to determine optimal cutoff scores for best specificity and sensitivity. Logistic regression was used to examine the association of PASE total scores and subscores with serum CRP levels, Subject Global Assessment of joint pain (SGA-Joint), and the history of PsA diagnosis. PASE scores were examined for all patients and associations assessed for a sub-group that excluded patients treated with concomitant methotrexate. (PASE scores are sensitive-to-change with methotrexate).

Results: Of 273 participants at baseline, 30% (n=83) self-reported a physician-diagnosis of PsA. The mean PASE total score for these patients was 47.78 (standard deviation [SD] = 14.14), whereas patients without a diagnosis of PsA had a mean score of 28.26 (SD = 11.93). ROC analyses of baseline PASE total scores indicated that the optimal PASE total cutoff score for >50% probability of the presence of PsA is ≥47 (Table). SGA-Joint scores had a borderline strong correlation with PsA diagnosis (Pearson correlation coefficients 0.69 to 0.74). Interestingly, serum CRP levels showed low correlation with an historical diagnosis of PsA, PASE scores, or the SGA-Joint scores (coefficients ≤0.37 for all). The association results held for both the total population and the sub-group that was not treated with methotrexate.

Table. ROC analyses of baseline PASE scores based on prior diagnosis of PsA

		Characteristics of best scores		Possible PASE cutoff scores with best characteristics		
PASE Scale or subscale	ROC AUC	Proportion correct	Specificity/ Sensitivity*	Percent correct†	Specificity/ Sensitivity‡	>50% probability of PsA presence§
Total score	0.8447	83.92%	78.51	50	41	47
Symptom subscale score	0.8426	85.52%	77.71	23	23	23
Function subscale score	0.8235	82.52%	77.00	25	25	25

* 1/2 (sensitivity + specificity), maximum possible value = 100; †PASE scores that distinguish patient-reported PsA diagnoses from lack of diagnoses; ‡PASE scores that represent high specificity and sensitivity; §PASE scores that screen for a high probability of PsA, PASE, Psoriatic Arthritis Screening and Evaluation; PsA, psoriatic arthritis; ROC, receiver operating characteristic; AUC, area under the curve.

Conclusion: These findings confirm earlier work that the PASE tool is useful for screening for PsA symptoms early.[1] In this analysis, we compared PASE scores to patient-reported diagnoses of PsA in a clinical trial setting. The results support PASE as an informative tool, alerting physicians to the potential need for a rheumatologist's diagnosis for PsA.

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Impact of Ankylosing Spondylitis on Sick Leave, Presenteeism and Work Satisfaction in Turkish People. Emel Ozcan[1], Ekin Sen[1], Sina Esmaeilzadeh[1], Aylin Rezvani[2], Tugba Baysak[1], Ayse Karan[1] and Annelies Boonen[3]. [1]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Vakif Gureba University Hospital, Istanbul, Turkey, [3]Rheumatology-Medicine, Maastricht, Netherlands

Background/Purpose: The aim of this study is to evaluate the influence of Ankylosing Spondylitis (AS) on sick leave, presenteeism and work satisfaction and to explore the relationships between these outcomes and disease activity as well as physical function in Turkish patients.

Methods: A total of 68 consecutive and unselected patients with AS who were referred to the Rheumatologic Rehabilitation Units in the Departments of Physical Medicine and Rehabilitation in Istanbul University, Istanbul Faculty of Medicine and Vakif Gureba University Hospital between January and May 2011 were included in this study. Patients completed a self-reported questionnaire on socio-demographic characteristics and several patients reported outcomes among which Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Work Productivity and Activity Impairment Questionnaire (WPAI). The Turkish adaptation and test-retest reliability of the questionnaires was carried out successfully before beginning the study. The impact of AS on presenteeism, work satisfaction were examined with Visual Analogue Scale (VAS) and compared according to workload. Disease activity and physical function were assessed with the BASDAI and the BASFI, respectively. The relationships between BASDAI/BASFI scores and work outcomes as well as workload in paid work patients were analyzed by Spearman's correlation and Kruskal Wallis tests.

Results: The mean age of the patients was 37.7±7.3 (21–55) years, 94.1% (n=64) of the patients were male, 86.8% (n=59) of the patients had paid work. In patients with paid work 20.3% (n=12) had physical, 22.0% (n=13) had mental and 57.6% (n=34) had both physical and mental demanding works. There was not found any significant differences between patients with three types of work load and sick leave, presenteeism as well as work satisfaction (p>0.05). 13.6% (n=8) of patients with paid work had sick leave due to AS, average score of presenteeism was 3.1±2.9 and work satisfaction 6.2±2.9. There was a positive correlation between sick leave related to AS and BASDAI (r=0.287, p=0.028), and BASFI scores (r=0.269, p=0.040). There was a positive correlation between presenteeism and BASDAI (r=0.547, p<0.001), also between presenteeism and BASFI (r=0.584, p<0.001) scores. There was a negative correlation between work satisfaction and BASDAI (r=−0.280, p=0.032), and BASFI (r= −0.349,

p=0.007) scores. There was a positive correlation between difficulty in performing unpaid tasks in the last week and BASDAI (r=0.622, p<0.001), and BASFI (r=0.708, p<0.001) scores in paid work patients.

Conclusion: These findings suggest that disease activity and limitations in physical functioning are strongly associated with productivity, presenteeism and satisfaction in workplace. Also, patients with AS not only have substantial sick leave but also experience restrictions while being at work. Finally, in conjunction with treatment protocols, emphasis on the impact of AS on work status and productivity also any attempts to improve the working conditions in patients with AS will increase the efficacy of medical care and rehabilitation programs.

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Cardiovascular Outcome and High Dose Statin Treatment in Patients with Inflammatory Joint Disease. Anne Grete Semb[1], Tore K. Kvien[1], Rana Fayyad[2], David A. DeMicco[2], John LaRosa[3], John Betteridge[4], Terje R. Pedersen[5] and Ingar Holme[5]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Pfizer Inc, New York, [3]State University of New York health Science Centre, New York, [4]Middelsex Hospital, London, United Kingdom, [5]Oslo University Hospital-Ullevaal, Oslo, Norway

Background/Purpose: We examined the effect of intensive lipid lowering (LL) in patients with inflammatory joint disease (IJD): rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) on a composite cardiovascular mortality and morbidity (CVMM) endpoint by a pooled analysis of TNT, IDEAL, and CARDS trials.

Methods: IDEAL (n=8888) compared atorvastatin 80 mg and simvastatin 20–40 mg in post-myocardial infarction patients with 4.8-year follow-up. TNT randomized 10001 CHD patients to double-blind 10 or 80 mg atorvastatin and followed for 4.9 years. CARDS (n=2838) assessed atorvastatin 10 mg versus placebo in patients with type 2 diabetes and no CVD; follow-up was 3.9 years. Of the 21727 patients, 222 had RA, 50 AS, and 36 PsA.

Results: Demographic data were similar between RA/AS/PsA and other participants (non IJD), except that those with IJD were older and more frequently females. Patients with AS had lower atherogenic lipids and apolipoprotein B (Table1) compared to non IJD. LL by statins was comparable in patients with and without IJD. Intensive lipid reduction reduced the rate of CVMM in patients with and without IJD; the lowest rate of CVMM was in AS (Table 2).

	Total cholesterol, mmol/L	LDL, mmol/L	ApoB, g/L
Patients with AS			
Mean ± SD	4.7 ± 0.9	2.8 ± 0.7	1.1 ± 0.3
LSMeans ± SE*	4.7 ± 0.1	2.7 ± 0.1	1.1 ± 0.04
p-value†	p=0.0186	p=0.0290	p=0.0600
Non IJD			
Mean ± SD	4.9 ± 0.9	2.8 ± 0.8	1.2 ± 0.3
LSMeans ± SE*	5.0 ± 0.008	2.9 ± 0.005	1.2 ± 0.002

*adjusted for age, gender, and study
†p-value versus non IJD

	Atorvastatin 80mg	Atorva10/ Simva40/ placebo	Interaction by treatment
RA (n=222)			
Incidence of CVMM	29/107 (27.10%)	25/115 (21.74%)	
HR (95% CI)	1.04 (0.60, 1.80)	-----	p=0.30
	p=0.90		
AS (n=50)			
Incidence of CVMM	4/31 (12.90%)	9/19 (47.37%)	
HR (95% CI)	0.26 (0.07, 0.91)	-----	p=0.02
	p=0.04		
PsA (n=36)			
Incidence of CVMM	4/18 (22.22%)	4/18 (22.22%)	
HR (95% CI)	0.81 (0.18, 3.55)	-----	p=0.97
	p=0.78		
Non IJD (n=21419)			
Incidence of CVMM	2043/9278 (22.02%)	2695/12141 (22.20%)	
HR (95% CI)	0.80 (0.76, 0.85)		
	p<0.0001		

Conclusion: Patients with IJD had comparable lipid lowering and a similarly reduced risk of CVMM after treatment with statins as those without IJD. Intensive LL with atorvastatin was most effective in reducing CVMM in AS, despite their lower levels of atherogenic lipids at baseline.

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Epidemiologic Results of Early Rheumatologic Evaluations in a Cohort of Psoriatic Patients Complaining of Musculo-Skeletal Symptoms. Gabriele De Marco[1], Angelo Cattaneo[2], Carlo Carrera[2], Simona Tavecchio[3], Massimo Ricci[4], Claudio Fracchiolla[5] and Antonio Marchesoni[6]. [1]Istituto Ortopedico Gaetano Pini, Milano, Italy, [2]Fondazione I. R. C. C. S. Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, [3]Universita' delgli Studi di Milano, Milano, Italy, [4]Universita' degli Studi di Milano, Milano, Italy, [5]A. S. L. Desenzano del Garda, Desenzano del Garda, Italy, [6]Rheumatology Unit, Ospedale G Pini, Milano, Italy

Background/Purpose: Psoriatic arthritis (PsA) is a chronic rheumatism estimated to affect about 20% of psoriatic subjects. Initiatives such as rheumatologic consultations performed at dermatologic clinics are believed to be the key for PsA diagnostic latency reduction. PURPOSES: Describe the epidemiologic result of the rheumatologic evaluations performed in a dermatologic clinic dedicated to diagnosis and care of Psoriasis.

Methods: Between September 2008 and December 2010 the psoriatic subjects followed up at dermatologic clinic of the IRCCS Policlinico di Milano received a thorough rheumatologic evaluation, if they reported: a) muscolo-skeletal painful symptoms and/or b) articular swelling. The rheumatologic parameters evaluated encompass joint counts (tender, swollen, damaged), entheses counts and others as suggested in the GRAPPA international guidelines. The patients also underwent radiographic evaluation of the painful joints. Patient who were known for established PsA were evaluated only in case of active articular disease despite of appropriate treatment.

Results: Overall, among about 1200 subjects followed up at our center, 211 consecutive patients were evaluated (among these, 92 males). The mean age was 56.3 years (standard deviation 12.8 years; median 59, range 22–81), 73.5% suffered from plaque psoriasis (12.8% had nail disease). Only 18% of patients reported a previous diagnosis of PsA (documented by a rheumatologist or a dermatologist). In our cohort we diagnosed 80 PsA (37.9% of the sample, 57.5% of them were males). Sixty-two percent of PsA patients received the diagnosis for the first time and 25% reported the onset of inflammation within 2 years or less. PsA was classified in 66.2% of cases as peripheral arthritis, 28.7% of patients had dactylitis and 16.2% showed axial disease. Radiographic damage due to PsA was present in 36.2% of cases. In regard of age at the moment of evaluation, we did not notice differences between PsA subjects (mean 53.5 years) and the other members of the cohort (mean 57.9 years), as well as for the prevalence of nail disease (13.7%). Il 9.4% of the subjects in our cohort did not show signs or symptoms frankly attributable to inflammatory articular/entheseal disease, nor further investigations helped in diagnostic process. Therefore, these were not classified as PsA. One hundred and sixteen patients (55% of the cohort) were classified as Osteoarthritis, of whom 11 only (9.4%) suffered from PsA contemporarily.

Conclusion: We report that PsA is frequent (37.9%) among psoriatic subjects who complain of musculo-skeletal symptoms. The early rheumatologic consultation allowed us to identify mostly PsA in pre-radiographic stage, in 25% of cases with the onset of articular disease within 2 years.

Disclosure: G. De Marco, None; **A. Cattaneo**, None; **C. Carrera**, None; **S. Tavecchio**, None; **M. Ricci**, None; **C. Fracchiolla**, None; **A. Marchesoni**, None.

1295

Proposal for An Adaptation of the Berlin Algorithm for Diagnosing Spa: Results of the SPondyloArthritis Caught Early (SPACE)-Cohort. R. van den Berg, M. Reijnierse, T.W.J. Huizinga and D.M.F.M. van der Heijde. Leiden University Medical Center, Leiden, Netherlands

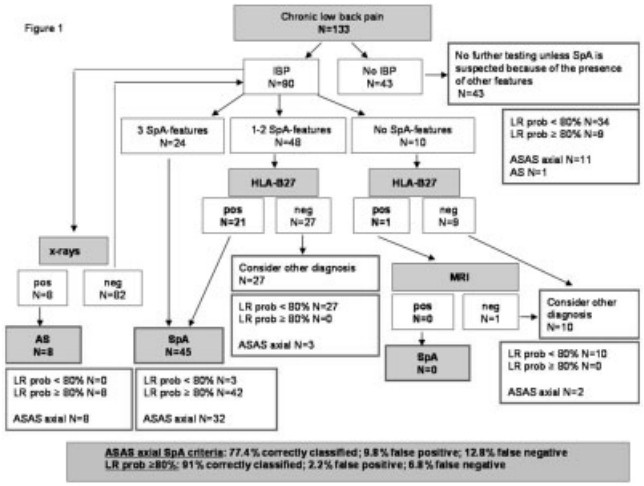
Background/Purpose: The recently developed Berlin algorithm is meant to assist clinicians in diagnosing early axial SpA. Inflammatory back pain (IBP) plays a dominant role. However, IBP is not a very specific symptom and might lead to misclassification. The goal is to validate the Berlin algorithm in the SPondyloArthritis Caught Early (SPACE)-cohort.

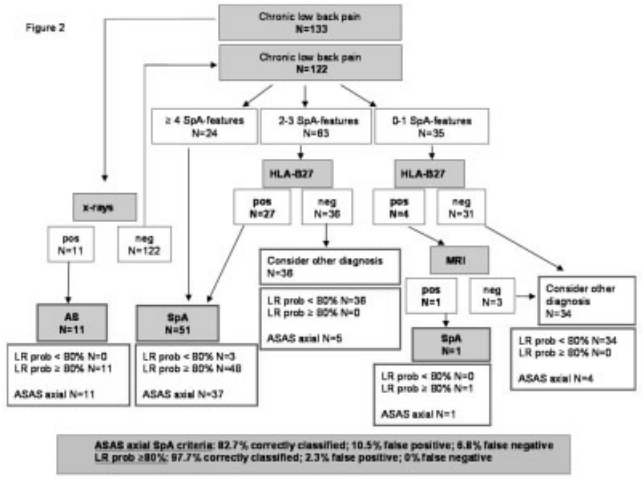
Methods: The SPACE-cohort is set-up in the Leiden University Medical Center (LUMC) to diagnose and treat axial spondyloarthritis (SpA)-patients early. All patients with back pain (>3 months, but <2 years; onset <45 years) were included and underwent a diagnostic work-up; MRI and X-rays of the SI-joints and laboratory assessments. All patients were classified according to the Berlin algorithm and to the ASAS axial SpA classification criteria. The LR-product was calculated based on

the present SpA-features; the cut-off ≥80% probability was used. Second, all patients were classified according to a modified algorithm, excluding IBP as entry criterion.

Results: In 6/133 patients no MRI is made, and in 1 patient also no X-ray is performed. These patients are analyzed as MRI- and X-ray-. 4/6 are diagnosed with axial SpA according to the algorithm. 40/53 (75.5%) patients diagnosed as axial SpA according to the algorithm fulfilled the ASAS axial SpA criteria and 50 (94.4%) had ≥80% probability of having SpA. The 3 remaining patients had a probability of 79.5% and 77.7% respectively. 17/80 (21.3%) patients not diagnosed as axial SpA fulfilled the ASAS axial SpA criteria and 9 (11.3%) had ≥80% probability of having axial SpA (figure 1).

The modified algorithm has IBP not as entry criterion but as additional SpA-feature. According to this modified algorithm, 63 patients (47.4%) could be diagnosed as axial SpA, of which 49 (77.8%) fulfilled the ASAS axial SpA criteria and 57 (95.2%) had ≥80% probability of having axial SpA. Again, these 3 additional patients had a probability close to 80%. 9/70 (12.9%) patients not diagnosed as SpA fulfilled the ASAS axial SpA criteria (figure 2).





The modified algorithm could classify 10 additional patients as axial SpA and no single patient with a probability >80% was excluded; the number of false classified patients is decreased. Some HLA-B27- patients are classified false negative by excluding them from the algorithm although they had MRI+ and other present SpA-features. Thus, in HLA-B27- patients with a high suspicion of SpA, we would advice to perform MRI as well.

Conclusion: We propose a slightly modified algorithm excluding IBP as an entry criterion that is better in accordance with the ASAS axial SpA criteria and the LR-product probability ≥80%, especially by reducing false negative classification.

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1296

Patient-Perceived Impact of Psoriatic Arthritis Is Due to Pain and Fatigue, but Also to Psychological Aspects - the Psa Impact of Disease Study. Laure Gossec[1], Maarten de Wit[2], Andra Balanescu[3], Peter V. Balint[4], Gabor Békés[4], Juergen Braun[5], Juan D. Canete[6], Laurence Carton[7], Alina Dinte[3], Kurt L. De Vlam[8], Turid Heiberg[9], Philip Helliwell[10], Umut Kalyoncu[11], Uta Kiltz[12], Thomas Luger[13], Mara Maccarone[14], Ronan H. Mullan[15], Dennis O'Sullivan[15], Kati Otsa[16], Andrew Parkinson[17], Anselm Sanchez Lombarte[6], Rossana Scrivo[18], Josef Smolen[19], Tanja A. Stamm[20] and Tore K. Kvien[21]. [1]Cochin Hospital, Paris, France, [2]Dutch Arthritis Patient League, Amersfoort, Netherlands, [3]"Sf. Maria" Hospital, Bucharest, Romania, [4]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [5]Ruhr-University Bochum, Herne, Germany, [6]Hospital Clinic, Barcelona, Spain, [7]Cochin Hospital and Association Française de Lutte Anti-Rhumatismale, Paris, France, [8]University Hospital, Leuven, Belgium, [9]Ullevaal Univ Hospital, Oslo, Norway, [10]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [11]Hacettepe University Faculty of Medicine, Ankara, Turkey, [12]Rheumazentrum Ruhrgebiet, Herne, Germany, [13]University Hospital Münster, Münster, Germany, [14]Associazione per la Difesa degli Psoriasici, Rome, Italy, [15]St Vincent's University Hospital, Dublin, Ireland, [16]Tallinn Central Hospital, Tallinn, Estonia, [17]University of Leeds, Leeds, United Kingdom, [18]Reumatologia - Sapienza Università di Roma, Rome, Italy, [19]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [20]Medical University of Vienna, Vienna, Austria, [21]Diakonhjemmet Hospital, Oslo, Norway

Background/Purpose: There is a relative lack of qualitative studies in Psoriatic Arthritis (PsA). Such studies would help, to increase the knowledge of the patient's perspective in this disease.

The PsA impact of disease (PsAID) project is a EULAR initiative to elaborate a composite index reflecting the impact of PsA based on the patients' perception. The objective of this first step was to identify areas of health (domains) perceived most important for patients, that would be candidates for inclusion in such a composite index.

Methods: Eleven patient research partners (6 men, 5 women) from 11 European countries identified during a 1-day focus group meeting, 16 domains or areas of health important for the patient. In a subsequent survey, 139 patients from 13 countries ranked by decreasing importance the 16 domains of health and gave a priority rating to those domains they found to be a priority.

Results Were analysed as (a) mean rank of each domain, (b) percentage patients giving priority to each domain, and (c) percentage patients giving a high rank (within the first half of ranks i.e. rank 1–8) to each domain (Table).

Table. domains of health with ranks and priorities (lower mean ranks indicate greater importance)

		Mean rank	Priority	In top 8 ranks
1	Pain	2.56	84.4%	94.7%
2	Skin problems	6.23	52.7%	64.8%
3	Fatigue	6.43	43.4%	74.1%
4	Ability to work and/or to do leisure activities	6.67	50.4%	66.9%
5	Disability	7.23	45.7%	64.0%
6	Feeling of discomfort	7.58	25.6%	64.0%
7	Sleep disturbance	7.96	36.4%	56.1%
8	Anxiety, fear and uncertainty	8.42	33.3%	50.4%
9	Coping	8.45	34.9%	53.2%
10	Embarrassment and/or shame due to appearance	9.74	24.0%	39.6%
11	Social participation	10.01	23.2%	33.1%
12	Depression	10.06	24.0%	38.9%
13	Relationship with family	10.51	30.2%	34.5%
14	Concentration difficulties	10.61	18.6%	31.7%
15	Rejection and discrimination due to appearance	11.60	12.4%	22.3%
16	Sexual life	11.61	14.7%	25.1%

Results: The 16 domains selected by patients and reflecting the impact of PsA are in the Table and comprise physical domains (N=4), psychological domains (N=7), social/societal domains (N=2) and mixed/other domains (N=3). In the ranking survey, physical domains were rated as important; pain was by far the first domain in terms of impact; skin was considered the second domain; fatigue was also important since it was

rated as a priority by 43.4% of the participants. Psychological aspects were also considered important; foremost were anxiety and coping. Among social aspects, work and leisure activities obtained high priority. Discrimination and sexual life were considered the least important domains in this study.

Conclusion: This study gives insights into the patient's perspective in PsA and brings to light the importance of fatigue, but also of several previously under-estimated psychological aspects in PsA. This will form the basis of the development of a composite patient-reported outcome measure to better assess the patient's perspective in PsA.

1297

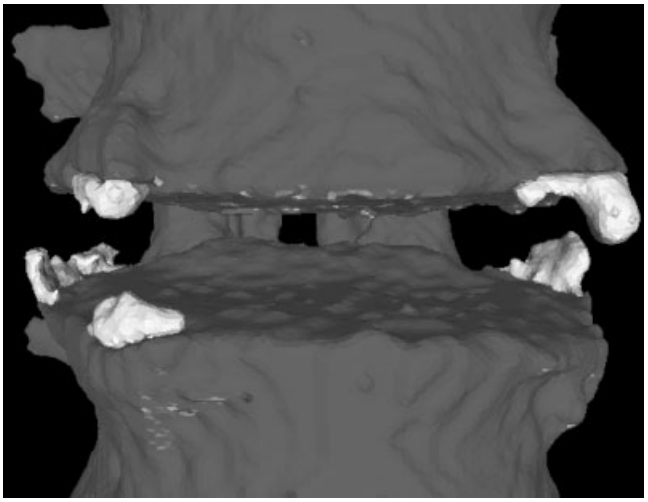
Fully Quantitative Syndesmophyte Measurement in Ankylosing Spondylitis Using Computed Tomography: Reliability of Volume and Height Measures.

Sovira Tan[1], Jianhua Yao[1], John A. Flynn[2], Lawrence Yao[1] and Michael M. Ward[3]. [1]NIH, Bethesda, MD, [2]Johns Hopkins University, Baltimore, MD, [3]NIAMS/NIH, Bethesda, MD

Background/Purpose: Syndesmophyte progression at the margins of intervertebral disk spaces (IDS) is the hallmark of structural damage in ankylosing spondylitis (AS). Syndesmophyte growth is currently typically monitored by visual inspection of radiographs. The limitations inherent to the modality (2D projection of a 3D object) and rater (qualitative human judgment) entail a possibly important loss in sensitivity. We developed a 3D computer algorithm to measure syndesmophyte volumes and heights from computed tomography (CT) scans of the spine. In anticipation of longitudinal studies, we investigated the precision of this method using scans from 7 patients.

Methods: 7 patients with AS (6 men, 1 woman, mean age of 61 years) were scanned twice consecutively within minutes. Scans were done of the thoracolumbar junction (T10 to L4), providing 4 IDS for analysis. The algorithm segments the vertebral bodies from the scans, detects the 2 opposite end plates of each IDS and identifies as syndesmophyte the bone between those end plates. Syndesmophytes can then be quantified in terms of volume and height. The figure shows an example of IDS with segmented syndesmophytes. In each IDS, we calculated total syndesmophyte volume and height of the tallest syndesmophyte, and compared results of paired scans within patients. We evaluated reliability using the intraclass correlation coefficient (ICC). We examined the 95% limits of agreement using Bland-Altman analysis. For syndesmophyte volume, because the magnitude of the paired differences increased with the mean volume, the limits of agreement were evaluated on log transformed variables and converted back to the original scale.

Results: The 7 patients had IDS syndesmophyte volumes ranging from 0 to 1514 mm^3, and heights ranging from 0 to 8.14 mm (table). Differences between paired measures were very small, and ICCs for syndesmophyte volume and height measures were both 0.99. The limits of agreement for syndesmophyte volume were [$-0.04 \times$ volume, $0.04 \times$ volume] mm^3. For heights, the limits of agreement were independent of the mean and were [−0.2, 0.22] mm. Based on these results, a longitudinal increase in volume of more than 0.04 times the baseline volume, or an increase in height of more than 0.22 mm, represents changes beyond those expected by chance.



	VOLUME (mm3)			HEIGHT (mm)		
	1st Scan	2nd Scan	Differences (absolute value)	1st Scan	2nd Scan	Differences (absolute value)
Min	0	0	0	0	0	0
Max	1488	1514	27.3	8.02	8.14	0.42
Median	192.9	192.4	2.55	4.27	4.09	0.075
ICC	0.99			0.99		
95% limit of agreement	$-0.04 \times$ volume, $0.04 \times$ volume			−0.2, 0.22		

Conclusion: Based on analysis of 28 IDSs from the repeat CT scans of 7 patients, this computerized method that fully quantifies syndesmophytes in 3D space has excellent reliability and precision. The narrow limits of agreement are promising for application to longitudinal clinical studies of changes in syndesmophyte. None.

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Fully Quantitative Syndesmophyte Measurement in Ankylosing Spondylitis Using Computed Tomography: Validity of Volume and Height Measures.

Sovira Tan[1], Jianhua Yao[1], John A. Flynn[2], Lawrence Yao[1] and Michael M. Ward[3]. [1]NIH, Bethesda, MD, [2]Johns Hopkins University, Baltimore, MD, [3]NIAMS/NIH, Bethesda, MD

Background/Purpose: A sensitive method to monitor syndesmophyte growth is desirable for the clinical studies of drug efficacy against structural damage in ankylosing spondylitis (AS). The current standard, the scoring of radiographs, is limited by problems of poor visualization, use of 2D images to assess 3D structures and qualitative scoring system. To address these limitations we developed a computer algorithm that fully quantifies syndesmophytes in the 3D space of CT scans. We tested the validity of this method by comparing its measures to the readings of a physician on the scans of 36 patients.

Methods: Each patient had a CT scan of the thoracolumbar junction (T10 to L4), providing 4 intervertebral disk spaces (IDS) for analysis. The algorithm segments the vertebral bodies, detects the 2 end plates of each IDS and identifies as syndesmophyte the bone between the end plates. For each IDS, the algorithm computes the total syndesmophyte volume and height of the tallest syndesmophyte divided by the local IDS width.

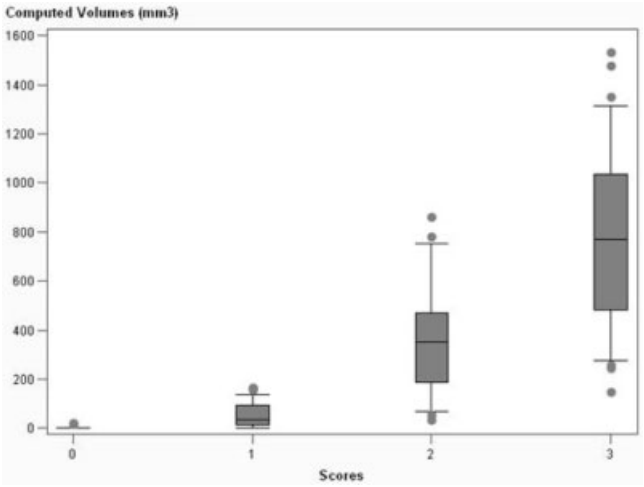
The IDS were scored for volume and height by visual ratings of the CT scans by a physician blinded to the algorithm results, using a 4 point scale. Scores for volume ratings were:

0 = no syndesmophyte
1 = non bridging syndesmophyte involving less than ¼ of vertebral rim
2 = syndesmophyte involving more than ¼ of vertebral rim or local bridging
3 = bridging involving more than ¼ of vertebral rim

The scores for heights were:

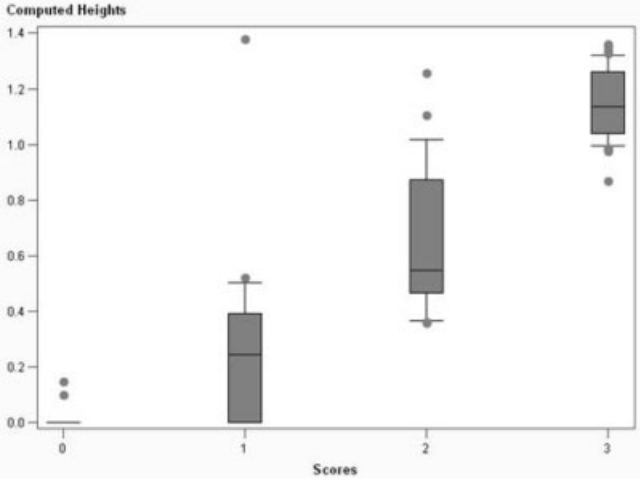
0 = no syndesmophyte
1 = syndesmophyte less than ½ IDS width
2 = syndesmophyte involving more than ½ IDS width
3 = bridging

We used the Kruskal-Wallis test to compare computed volumes and heights across the rating scores.



Results: We studied 36 patients with AS (30 men, 6 women; mean (SD) age 45.9 (11.5); mean duration of AS 20.5 (12.0) years). Among all patients, 144 IDS were scored. For volume, physician ratings of 0, 1, 2, and 3 were present in 32%, 26%, 20%, and 22% of IDS. Measured volumes by the algorithm increased with physician ratings (figure) ($p < .0001$), with little overlap in measured volumes between scores. The collapsed box at score 0 shows that the algorithm generated

few false positives. For height, ratings of 0, 1, 2, and 3 were present in 32%, 19%, 19%, and 30% of IDS. Measured heights also increased progressively with physician ratings (figure) (p <.0001).



Conclusion: An algorithm based on CT scans that fully quantifies syndesmophytes in 3D space accurately detected differences in syndesmophyte volume and height that were rated as different by visual ratings of a physician. Volume and height measures were higher in more severely involved disk spaces and the overlap between grades was small.

1299

Impact of Tumor Necrosis Factor α, Infliximab, and Antibodies Toward Infliximab in Ankylosing Spondylitis Activities: Data From a Monocentric Crossectional Study. Elodie Constant[1], Florence Chopin[1], Béatrice Pallot-Prades[1], Thierry Thomas[1], Stéphane Paul[2] and Hubert Marotte[1]. [1]Inserm U1059, Saint-Etienne, France, [2]GIMAP, EA3064, University Hospital, Saint-Etienne, France

Background/Purpose: Infliximab is a chimaeric monoclonal antibody targeting tumour necrosis factor alpha (TNFα) indicated in ankylosing spondylitis (AS). We analyze association TNFα, infliximab, or antibodies toward infliximab (ATI) blood level with AS activity.

Methods: In a monocentric crossectional study, 30 AS patients treated with infliximab were collected. AS patients are the main characteristic of AS with 66% men, with a mean age of 44.4 years old (from 17 to 63) treated with infliximab since 37.4 months (from 0.5 to 106.4). Only 3 patients were treated with MTX and 2 with prednisone. AS activity was assessed by Ankylosing Spondylitis Disease Activity Score (ASDAS). TNFα, infliximab, and ATI serum concentrations were measured in the blood collected before the next infliximab infusion by enzyme-linked immunosorbent assay (LisaTracker, BMD, France). Data were analyzed using the Kruskall–Wallis one-way analysis of variance (ANOVA) test, followed by Dunnett's multiple comparison post hoc tests with $P<0.05$ chosen as the level of significance. Non-parametrict correlations were performed with Spearman test.

Results: We observe heterogeneity in TNFα concentration according to AS activity ($P < 0.001$). A dose TNFα effect was observed according to an increased AS activity assessed by ASDAS. Similarly, infliximab concentrations were heterogenous in the 30 AS patients ($P < 0.02$). Except for inactive AS, we observed an opposite dose effect between infliximab concentration and ASDAS ($P < 005$). Significant level of ATI were observed in 4 AS patients. One had a moderate activity and 3 had a very active disease. In this population, we also observed a positive correlation between TNFα concentration and ASDAS (Spearman correlation coefficient = 0.48, $P < 0.01$). Furthermore, a negative correlation between infliximab concentration and ATI was also observed (Spearman correlation coefficient = −0.47, $P < 0.01$).

Conclusion: Our study suggested that remaining circulating TNFα is associated with AS disease activity assessed by ASDAS. These confirm interest of a personal monitoring in arthritic patients treated by TNFα blockers. Furthermore studies including interventional approaches need to confirm impact of monitoring in the daily practice.

1300

Ultrasound Assessment of Enthesis Thickening in Psoriatic Arthritis Patients Treated with Adalimumab Compared to Methotrexate. Irena Litinsky[1], Jonathan Wollman[2], Alexandra Balbir-Gurman[3], Uri Arad[2], Daphna Paran[4], Dan Caspi[2] and Ori Elkayam[2]. [1]Department of Rheumatology, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine Tel Aviv University, Tel Aviv, Israel, [2]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Rambam Health Care Campus, Haifa, Israel, [4]Tel Aviv Souraski Medical Ctr, Tel Aviv, Israel

Background/Purpose: Enthesitis –inflammation of the origin and insertion of ligaments, tendons and aponeuroses is widely accepted clinical and imaging feature of Psoriatic arthritis (PsA). Clinical assessment of enthesitis by eliciting tenderness at the enthesis is inaccurate. Musculoskeletal ultrasound (MSUS) has become the gold standard for examination of tendons and has already been proved to be helpful in monitoring synovitis in RA patients treated with TNF-α antagonists. Evidence for the effect of TNF-α antagonists on ultrasonic features of inflamed enthesis and tendon is still limited. We aimed to assess the effect of adalimumab (ADA) compared to methotrexate (MTX) on the thickness of tendons and enthesis in PsA patients.

Methods: Thirty two PsA patients with active PsA were included. Group1: 21 PsA patients starting treatment with ADA: 14 women (66.6%), 7 men (33.4%), mean age 51.9+9.5 years. Group 2: 11 PsA patients beginning MTX: 5 (45.5%) women, 6(54.5%) men, mean age 45.1+14.3 years. The ultrasound (US) assessment and thickness measurement of the extensor (ET) and flexor tendons (FT) of the 2nd and 3rd finger of both hands, plantar aponeurosis (PA) and Achilles tendon (AT) bilaterally were performed on the day of initiating the therapy, 6 and 12 weeks after. Disease activity was assessed by the number of tender (TJ) and swollen joints (SJ), the number of inflamed enthesitis (IE), pain assessment (PA), patient (PDA) and physician (PGDAI) disease activity evaluation by VAS.

Results: Within each Group: In group 1, all disease activity parameters were improved at visit 3 and reached statistically significant for the number of TJ (10.38 vs 6.06 (P=0.0071)), SJ (8.19 vs 4.94 (P=0.04)), PA (71.52 vs 43.44(p=0.006)) and PGDAI (70.45 vs 40.95(p=0.0014)). Decreased thickness was observed for Achilles tendons bilaterally and was significant for the left side (Rt:0.35cm vs 0.33 (p=0.7) and lt: 0.38 vs 0.33 (p=0.02)), and for left plantar aponeurosis (0.13 vs. 0.1 (p=0.01))), while no significant changes were observed for the thickness of flexor and extensor hands tendons.A statistically significant positive correlation was found between the decrease of thickness of the extensor tendons and the number of TJ,number of IE, PGAD, PGA (3rd lt Et –PGA; 3rd rt ET-TJ, IE, PGA;2nd ET –TJ).In group 2, the disease activity parameters of IE (p=0.04), PA (p=0.0079), PGA (p=0.017) and PGDA (p=0.05) decreased significantly, while the number of TJ and SJ did not changed during the follow up period of 3 months. No change was observed in the thickness of both Achilles tendons and plantar aponeurosis, flexor and extensor tendons of hands after 12 weeks. **Comparison within groups:** Six weeks after initiating treatment with ADA, thickness of left Achilles tendon,2nd rt FT and the number of TJ, SJ, PA, PGA were significantly decreased in comparison to the MTX group (p=0.007;p=0.05 p=0.032; p=0.001;p=0.034 and p=0.003 respectively).

Conclusion: In patients with PsA, treatment with ADA, compared to MTX, significantly improved signs of diseases activity as well as several ultrasonic parameters of enthesis. The US assessment of enthesis is an additional useful tool in the monitoring of psoriatic enthesopathy.

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Characterization of a Colombian Cohort of Patientes with Reactive Arthritis. Wilson Bautista-Molano[1], John Londoño[1], Consuelo Romero-Sanchez[1], Paola Peña[1], Ana Santos[2] and Rafael Valle-Oñate[1]. [1]Spondyloarthritis Group. Rheumatology Division. Hospital Militar Central/Universidad de La Sabana., Bogotá, Colombia, [2]Facultad de Ciencias. Universidad de los Andes, Bogotá, Colombia

Background/Purpose: Reactive Arthritis (ReA) shares some clinical characteristics with others members of the Spondyloarthritis group of disorders, such as Ankylosing Spondylitis and Psoriatic Arthritis. It occurs after a preceding infection of the urogenital tract or the gout. It is associated with human leukocyte antigen HLA-B27 and patients present with asymmetric lower limb arthritis, enthesitis, dactylitis or inflammatory back pain. The mean disease duration has been reported to be between 3 and 6 months; however, a chronic course occurs in up to 20% of patients. Literature review do not report any study in our population to define if the characteristics are

similar to other regions. Given genetic susceptibility, environmental and socio cultural characteristics in our region, the clinical manifestations are different. Our objective is to describe clinical, demographic and laboratory findings of a cohort of patients with ReA in our country.

Methods: Data was collected from a Spondylarthritis Database of Rheumatology Service; which includes the information related to the disease. The patients were evaluated following the ASAS recommendations. Patient demographics, disease duration, family and personal history, clinical pattern, and HLA tipping were recorded. Questionnaires were administered for functional status (BASDAI- BASFI). All analyses were performed using SPSS software.

Results: 58 patients with ReA were identified. 46 were man (79.3%) and 12 woman (20.7%) with a mean age of 29 years and mean age at disease onset of 26.1 years. We found history of arthritis in 52 patients (89.7%), enthesopathy 44 (75.9%), back pain 34 (58.6%), buttock pain 15 (25.9%) and dactylitis 13 (22.4%). The duration of first episode was 3.79 months (0.5 – 12). Initial symptoms were: arthritis 26 (44.8%), several initial symptoms 23 (39.7%), back pain 4 (6.9%), enthesitis 3 (5.2%), buttock pain 1 (1.7), and uveitis 1 (1.7%). Taking into account the onset of disease, 32 patients (55.2%) had peripheral onset, 15 (25.9%) had mixed onset and 11 (19%) had axial involvement. There was history of infection in 57 (98.3%) mainly gastrointestinal. HLA typing was performed in 52 patients, of whom 32 were negative (61.6%) and 20 were positive (38.4%). 8 patients were B15 positive. At time of examination the main BASDAI score was 5.02 and main BASFI score was 4.92.

Conclusion: In our population we found predominantly young people, peripheral involvement and the pattern of asymmetric arthritis as initial symptom (similar than reported in the literature). The mean disease duration are also similar and enthesitis was found in higher frequency. However, the presence of HLA*B27 allele is less than reported in other papers and almost all of the patients had history of infection. This is remarkable, given not only by genetic susceptibility but also by environmental and socio cultural conditions in our region. This features influence the manifestation of the disease and the clinical pattern of presentation. Enrollment continues to increase the cohort and best characterize the population according to serological, microbiological and genetic tests.

Ref:

Carter JD, Hudson AP. Reactive Arthritis: clinical aspects and medical management. Rheum Dis Clin North Am 2009;35:21–44

1302

Anti-TNFα Efficacy Against Spondyloarthropathy without Associated Imaging Signs. Aurélia Bisson-Vaivre[1], Jean-François Menard[1], Didier Alcaix[2], Olivier Vittecoq[1], Xavier X. Le Loet[1], Charles Zarnitsky[2] and Vincent Goeb[1]. [1]Rouen University Hospital, Rouen, France, [2]Le Havre General Hospital, Le Havre, France

Background/Purpose: Some clinical presentations satisfy spondyloarthropathy (SpA)-diagnosis criteria without any detected imaging signs, sometimes posing the question of when early biotherapy should be started. Objective: To evaluate anti-TNFα efficacy in patients with clinical but not imaging (radiographic, computed-tomography scan, MRI) signs of SpA.

Methods: This retrospective study concerned patients with axial SpA followed in 2 hospitals, treated, according to EULAR recommendations, with anti-TNFα after failure of conventional therapies. Therapeutic responses, assessed according to BASDAI50 and ASAS20 or −40 definitions, were evaluated after 6 and 12 months. Factors associated with those responses were also sought.

Results: Among 385 patients included, 257 with imaging signs had significantly more frequent therapeutic responses and partial remissions ($p=0.0005$ and 0.03, respectively). The response rate of *HLA-B27* carriers with initial imaging sign(s) was significantly higher ($p=0.028$). Responders were younger at biotherapy onset, with lower BASFI and pain visual analog scale score, and higher CRP, compared to nonresponders. About 40% of the SpA patients without imaging sign(s) responded to anti-TNFα.

Conclusion: The initial presence of SpA imaging sign(s) seems to be a factor prognostic of the response to anti-TNFα, especially in *HLA-B27* carriers. However, the percentage of patients with exclusively clinical SpA signs and responding to anti-TNFα was far from negligible, thereby reinforcing the pertinence of ASAS criteria.

1303

Continuance of Non-Steroidal Anti-Inflammatory Drugs May Reduce Radiographic Progression in Ankylosing Spondylitis Patients on Biological Therapy. Nigil Haroon[1], Hua Shen[2], Adele Carty[3], Ammepa Anton[3], Richard J. Cook[2] and Robert D. Inman[1]. [1]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [2]University of Waterloo, Waterloo, ON, [3]Toronto Western Hospital, Toronto, ON

Background/Purpose: Anti-TNF therapy has brought significant improvement in symptoms and quality of life of patients with ankylosing spondylitis (AS). However a reduction in the rate of progression of radiographic damage has not been clearly demonstrated. The only therapy that has been shown to affect radiographic damage is the continuous use of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are commonly discontinued once symptoms are well controlled with biologics. We aimed to study the effect of continuous NSAID therapy in patients with AS who are already on biologics.

Methods: In this study 20 patients with AS (modified New York criteria) on anti-TNF therapy who continued their NSAIDS (B+N), were followed with X-rays at 2 years and clinical evaluation annually. For comparison, 20 AS patients on biological therapy (B) in whom NSAIDs had been discontinued were assessed. All patients were assessed on a regular basis on a longitudinal protocol. Disease activity was assessed by BASDAI, CRP and ESR. BASFI, BASG and BASMI were recorded. X-rays were obtained at baseline and follow up and scored using the mSASSS method. Absolute change in mSASSS and rate of change (change per year) were calculated and used as dependant variables. Mann-Whitney test and Fisher's exact test were used where appropriate.

Results: The mean (SD) age of onset of AS for B was 21 (9.1) years and for B+N 18.9 (8.5) years. There was no significant difference in the age of onset or diagnosis of AS between the two groups. There were three females in both groups. HLA B27 was positive in 12 and 15 patients respectively in the B and B+N groups. The baseline mSASSS scores were comparable (B: 12.35 ± 16.9; B+N:13.4 ± 18.5). The baseline BASMI, CRP and ESR were comparable in the two groups. The baseline BASDAI was higher in the B+N group (3.93 ± 2.1 vs 2.6 ± 2.2; $p=0.05$). There was a trend at baseline towards higher BASFI (3.5 ± 2.7 vs 2.1 ± 2.1) and BASG (4.1 ± 2.5 vs 2.6 ± 2.3) in the B+N group. The mean change in mSASSS over 2 yr was 3.05 ± 6.2 in group B compared to only 0.2 ± 3.4 units in group B+N ($p=0.08$). The rate of change in mSASSS also was similarly different with 2.508 ± 5.9 units change per year seen in group B compared to much lower progression at 0.05 ± 2.1 units per year in group B+T ($p=0.09$). There was no difference in the prevalence of extra-articular manifestations in the two groups.

Conclusion: The results point towards a trend reflecting less radiographic progression when NSAIDs are continued after the institution of biologic therapy in AS. Larger studies are needed to confirm this observation.

1304

Anti-TNF Therapy and Malignancy in Spondyloarthropathy-the Leuven Arthritis Biologics Register. Ine Westhovens, Rik Lories, Rene Westhovens, Patrick Verschueren and Kurt L. De Vlam. University Hospitals KULeuven, Leuven, Belgium

Background/Purpose: Tumor necrosis factor alpha (TNF-alpha) is a key member of a large family of cytokines and receptors that are crucial to cellular organization. The use of TNF-alpha antagonists has opened new perspectives for the treatment of patients with spondyloarthropathy (SpA), but concerns are rising about the occurrence of malignancy as a possible adverse event with this kind of therapy.

To report the malignancy incidence in a large single center cohort of patients with SpA treated with one or more anti-TNF therapies and to compare the results with the malignancy incidence in the Belgian population.

Methods: From September 2000 until March 2010, all SpA patients starting treatment with one or more anti-TNF therapies were included in this single center retrospective cohort study: 231 patients with a mean age of 47.86 were included for a total of 1020.74 patient years treatment and 1199.83 patient years follow-up after treatment start. The primary outcome of this study was the incidence of malignancy after starting anti-TNF treatment. Incidence rates were compared with the incidence rates of malignancy in Belgium in 2006 for the 45–50 year old population, registered by the Belgian Cancer Registry.

Results: In our study population, 6 out of 231 patients (2,6%) developed a malignancy after the start of anti-TNF treatment. The overall incidence rate of malignancy is 500,1 per 100000 patient years. The incidence rate for malignancy in female SpA patients is more than twice as high as in males (770.1/100000 versus 370.2/100000 patient years respectively), but standard-

ized incidence ratios are in the same range for male and female patients (156.1 for females and 147.8 for males) and indicate a higher incidence of malignancy in our study population compared to the Belgian population.

Conclusion: We see a tendency towards a higher incidence of malignancy in SpA patients treated with anti-TNF therapy. It is still not clear whether this increased risk is disease-related or treatment-related.

1305

Serum Biomarkers to Predict Clinical Response in Proof-of-Concept Trials in Spondyloarthritis. Maureen C. Turina, Nataliya Yeremenko, Jacqueline Paramarta, Bernard Vandooren, Paul-Peter Tak, Leen E. De Rycke and Dominique L. Baeten. Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: With the availability of TNF blockers for the treatment of spondyloarthritis (SpA), the clinical evaluation of new drugs requires quick "go/no go" signal in small scale, short term proof-of-concept (PoC) trials. The inclusion of a set of biomarkers complementing the clinical evaluations may help to reduce the length and size of these PoC. Therefore, we aimed to identify and validate serum biomarkers to predict clinical response at the group level in small-scale, short term, PoC trials in SpA.

Methods: Matrix metalloproteinase-3 (MMP-3), Pentraxin-3 (PTX-3), high sensitive C-reactive protein (hs-CRP), calprotectin, Interleukin-6 (IL-6), Vascular Endothelial Growth Factor (VEGF), and alpha-2 macroglobulin (alpha-2-MG) were selected as candidate biomarkers based on previous studies in SpA. Serum levels were determined by ELISA in healthy controls (n=20) as well as at week 0 and week 2 in SpA patients treated with either infliximab (5 mg/kg at week 0, 2, and 6) (n=18) or placebo (n=19). Clinical outcome parameters (patient and physician global assessment of disease activity and BASDAI) were evaluated at week 0 and 12.

Results: Whereas the baseline clinical parameters were similar in both SpA cohorts, treatment with infliximab but not with placebo induced a significant decrease in all clinical parameters at week 12 after initiation of treatment ($p<0.005$). Analysis of the baseline serum samples revealed similar levels of the selected biomarkers in the two SpA cohorts. In comparison with the healthy controls, however, levels of PTX-3 ($p<0.001$), hs-CRP ($p<0.001$), calprotectin ($p<0.001$) and VEGF ($p<0.001$) were significantly increased in SpA whereas IL-6 and alpha-2-MG were not elevated. Additionally, PTX-3 ($p<0.01$) was slightly increased in axial versus peripheral disease with a similar trend for hs-CRP ($p=0.08$).

In the placebo group, the levels of these biomarkers remained stable over 2 weeks. In contrast, infliximab induced a significant decrease of hs-CRP ($p<0.0001$), calprotectin ($p<0.001$), and IL-6 ($p=0.04$) with a similar trend for MMP-3 ($p=0.063$). VEGF and alpha-2-MG levels were not significantly modulated. The Standardized Response Mean (SRM), which reflects the ability to detect changes over time at the group level, was high for calprotectin (SRM 1.259) and good for hs-CRP (SRM 0.746) and MMP-3 (SRM 0.521). The SRM was low for the other biomarkers in the treated group and for all biomarkers in the placebo group. In contrast to the findings at the group level, linear regression to determine the biomarker value at the individual level revealed some significant but low correlations of changes in hs-CRP (r^2 between 0.24 and 0.36) and calprotectin (r^2 between 0.08 and 0.19) at week 2 with clinical outcome parameters at week 12.

Conclusion: Early changes in serum calprotectin, hs-CRP, and MMP-3 showed a good ability to predict longer term clinical response at the group level but have no predictive value at the individual level in SpA. These candidate biomarkers are currently validated in other small-scale, short term, PoC trials in SpA.

1306

Inflammation May Be Associated with An Unfavorable Lipid Profile in Psoriatic Arthritis Patients in the CORRONA Registry. Asena Bahce-Altuntas[1], Julie S. Schwartzman-Morris[1], Nicole Jordan[1], Jeffrey D. Greenberg[2], Chaim Putterman[1], George Reed[3] and Anna R. Broder[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]New York University School of Medicine, New York, NY, [3]UMass Medical School, Worcester, MA

Background/Purpose: Although TNF-α is pro-atherogenic (1), the long-term effects of TNF-α inhibition on lipid patterns are still unclear. Only a few small studies in Psoriatic Arthritis (PsA) have evaluated the relationship between TNF-α inhibitor (anti-TNF) use and the lipid profile, a major cardiovascular (CV) risk factor, with mixed results (2).

Methods: We performed a cross-sectional analysis of the relationship between anti-TNF and the lipid profile of PsA patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. We included PsA patients who had at least one CORRONA visit with all lipid values available. The following cut-offs were used for the components of the lipid profile: (1) high Total Cholesterol, TC>200 mg/dl (5.17 mmol/L), (2) low High Density Lipids, males HDL<40 mg/dl (1.03 mmol/L), females HDL<50 mg/dl (1.29 mmol/L), (3) elevated Low Density Lipid, LDL>100 mg/dl (2.59 mmol/L) and LDL>130 mg/dl (3.36 mmol/L), and (4) high Triglycerides, TG>150 mg/dl (1.69 mmol/L), using previously established definitions for CV risk (3).

Results: Of the 4,015 PsA CORRONA patients, 274 met inclusion criteria, 157 anti-TNF-α users (anti-TNF+) and 117 non-anti-TNF-α users (anti-TNF-). Anti-TNF+ were younger than anti-TNF- [53.9 $\pm$ 10.5 years old vs. 58.7 $\pm$ 12.4 year old, $p=0.001$], included more males [62% vs. 46%, $p=0.01$], and had longer disease duration [13.2 $\pm$ 11.13 years vs. 8.9 $\pm$ 8.8 years, $p=0.001$]. Anti-TNF- had significantly more disease activity compared with anti-TNF+, as measured by CDAI [8.86 $\pm$ 8.1 vs. 6.54 $\pm$ 8.1, $p=0.02$]; log ESR [2.35 $\pm$ 1.2 vs. 1.89 $\pm$ 1.1, $p=0.05$]; log CRP [-0.39 ± 1.4 vs. -1.05 ± 1.3, $p=0.03$]; MD Skin Assessment [32.65 $\pm$ 33.4 vs. 23.93 $\pm$ 29.0, $p=0.03$]; and the presence of enthesitis or sausage digits [31% vs. 19%, $p=0.03$]. Statin use was similar in the two groups [32% vs. 24%, $p=0.17$]. There was no statistically significant difference in any lipid outcomes based on TNF use in the bivariate or in the multivariate analysis, adjusting for potential confounders such as demographics, disease activity markers and medications. Disease activity markers were associated with unfavorable lipid outcomes in the bivariate analysis. Low HDL associated with log ESR, OR 1.69 [95%CI: 1.14–2.52, $p=0.01$]; log CRP, OR 1.44 [95%CI: 1.04–1.99, $p=0.03$]; and CDAI, OR 1.04 [95%CI: 1.04–1.07, $p=0.03$]. Log CRP was also associated with both HDL levels $\beta-2.50$ [95%CI: -4.83–-0.17, $p=0.04$] and log TC/HDL ratio $\beta0.05$ [95%CI: 0.00–0.10, $p=0.04$]. There was a significant association between the presence of enthesitis or sausage digits with TG>150 mg/dl, OR 1.97 [95%CI: 1.13–3.46, $p=0.02$]. Limitations include the cross-sectional nature of the study.

Conclusion: We did not find an association between anti-TNF-α use and various lipid parameters in the CORRONA PsA study population. However, an unfavorable lipid profile may be associated with higher disease activity such as CDAI, ESR, CRP and presence of enthesitis or sausage digits. Further longitudinal studies are warranted to study whether controlling disease activity can improve the lipid profile of PsA patients.

References:

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1307

Comparison of Screening Instruments for Psoriatic Arthritis in Patients with Psoriasis. Jessica Walsh[1], Daniel O. Clegg[2] and Kristina Callis Duffin[3]. [1]University of Utah Hospital, Salt Lake City, UT, [2]University of Utah Medical Ctr, Salt Lake City, UT, [3]University of Utah, Salt Lake City, UT

Background/Purpose: To compare the abilities of screening instruments to accurately predict a diagnosis of psoriatic arthritis (PsA) in patients with psoriasis.

Methods: Psoriasis Epidemiology Screening ProjecT (PEST), Toronto Psoriatic Arthritis Screen (ToPAS), and Psoriatic Arthritis Screening and Evaluation (PASE) instruments were assembled in random order into packets and distributed to 1194 participants of the Utah Psoriasis Initiative. Responding participants were evaluated by the principal investigator (PI). Previously established cutoff scores were used to designate positive and negative results for each screening tool. The sensitivities and specificities of the instruments were determined by comparing the results to the PI's diagnostic assessment.

Results: Evaluations were completed in 197 participants. Exclusions were made for unclear diagnoses (n = 22) and missing data (n = 17). Of the remaining 158 participants, 114 were diagnosed with PsA. The PI's diagnosis was corroborated by ClASsification of Psoriatic Arthritis (CASPAR) criteria in 90% of all participants and in 93% of participants with available laboratory and radiographic data relevant to CASPAR criteria. 44% of participants were on $\geq$1 disease modifying antirheumatic drug (DMARD) at the time of

evaluation. PEST and ToPAS were more sensitive and specific for the diagnosis of PsA than PASE (Table 1.) 37 participants had false negative scores on ≥ 1 instrument. Among these participants, 31 had synovitis documented by a rheumatologist, 16 had erosive peripheral arthritis, 3 had predominantly axial disease, and 2 had arthritis mutilans. Among the 23 participants with false positive scores on ≥ 1 instrument, 13 had osteoarthritis, 5 had fibromyalgia, 3 had crystal arthritis, and 2 had unclear alternative diagnoses.

Table 1

	Sensitivity	Specificity	PPV	NPV
PEST	0.89	0.64	0.86	0.71
ToPAS	0.93	0.64	0.87	0.78
PASE	0.68	0.49	0.78	0.36

PPV = positive predictive value NPV = negative predictive value

Conclusion: PEST and ToPAS performed better than PASE with higher sensitivities and specificities. Participants in this population may have had fewer active symptoms than patients in other psoriasis populations because of frequent DMARD use. PEST and ToPAS are theoretically more sensitive than PASE in patients with less active disease, because they include questions about current and past symptoms, whereas PASE questions pertain to current symptoms only. The high prevalence of PsA may be explained by histories of more burdensome musculoskeletal symptoms in patients motivated to enroll and/or by encouragement to participate from referring providers in patients with suspected PsA diagnoses. The specificities of the instruments were likely lowered by patients reporting that they participated in order to gain access to a rheumatologist, even when alternative diagnoses were suspected. Despite these limitations, ToPAS and PEST were useful in this population and may be better than PASE at predicting PsA in patients with less active symptoms at the time of evaluation.

1308

Burden of Delay to Diagnosis of Ankylosing Spondylitis. Sarah E. Grigg, Belinda J. Martin, Russell R. Buchanan and Lionel Schachna. Austin Health, Melbourne, Australia

Background/Purpose: Few studies have addressed the psychological, economic and health-related quality of life effects of the distinctively prolonged delay in diagnosis of ankylosing spondylitis (AS).

Methods: Based on the results of a pilot study, a structured self-administered questionnaire was designed to examine the global impact of delay to diagnosis among patients with AS. The questionnaire was completed by 127 of 219 patients attending an AS referral center and treated with a tumor necrosis factor (TNF) inhibitor.

Results: Mean ± SD age at symptom onset was 23.9 ± 9.3 and delay to diagnosis was 10.0 ± 8.9 years. The first symptom was axial in 76.4%, peripheral articular in 18.1%, and extra-articular in 5.5%. Over one-third (34.6%) delayed consulting a health care professional for more than 12 months after onset of symptoms, 70.9% assuming that their symptoms would resolve. The diagnosis of AS was established by a rheumatologist in 67.7%, family physician in 18.1%, and orthopedist in 5.5%. Prior to diagnosis, 68.2% consulted a physical therapist (15.8%, 3 or more), 43.6% a chiropractor (8.7%, 3 or more), and 27% an osteopath (3.2%, 3 or more). The diagnosis of spondyloarthritis was, however, suspected by an allied health professional among only 2 patients (1.7%). The first proposed musculoskeletal diagnosis was non-specific back pain in 55.1% and degenerative disc disease in 26.0%, while AS or a spondyloarthritis was the first presumptive diagnosis in only 21.3%. Estimated costs of treatment prior to diagnosis was greater than US3000 in 25.6% of AS patients with delay to diagnosis less than 5 years compared with 44.4% between 5 and 10 years (p=0.08), and 67.4% for greater than 10 years (p=0.002). Among these strata, employability was affected in 66.7% compared with 75.6% (p=0.37) and 90.7% (p=003), respectively. Eighty percent of respondents thought that physicians could devote more time to try to establish an AS diagnosis and 70.1% that their diagnosis could have been established earlier. Once a diagnosis was established, emotional relief was experienced by 69.3%, positive shift in perception of symptoms by 75.6%, and optimistic outlook for the future by 66.1%. Delay in diagnosis was not associated with long-term depressed mood as evidenced by current Beck Depression Inventory scores.

Conclusion: Delay in diagnosis of AS is associated with significant psychological and economic burden. Allied health professionals are an important target group for educational strategies, given early and often repeated contact with AS patients.

1309

Serum IL-23 Does Not Correlate with Disease Activity in Spondyloarthritis. Hanna Przepiera-Bedzak, Iwona Brzosko, Katarzyna Fischer and Marek Brzosko. Pomeranian Medical University, Szczecin, Poland

Background/Purpose: There are some data that IL-23 play an important role in pathogenesis of spondyloarthritis.

The aim of the study was to assess the association between serum concentrations of IL-23 and disease activity in spondyloarthritis (SpA).

Methods: We studied 184 SpA patients: 82 psoriatic arthritis (PsA) patients, 80 ankylosing spondylitis (AS) patients, 22 SAPHO syndrome patients and 20 healthy persons. We recorded: age, sex, disease duration. We assessed: BASFI, BASDAI, BASG, BASMI, VAS, SF-36, PASI scores. Blood was collected for analysis of IL-23, EGF, FGFb and FGFc by ELISA method. We assessed also CRP, ESR, WBC.

Results: Mean age of patients was: 52,8 years in PsA group, 48,0 years in AS group and 54,8 years in SAPHO group. Mean disease duration was 8,6 years in PsA group, 13,7 years in AS group and 6 years in SAPHO group. Mean serum IL-23 levels were: 4,1 pg/ml In PsA group, 2,6 pg/ml in AS group and 3,5 pg/ml in SAPHO group. There was no correlation between IL-23 and disease activity assessed by CRP and ESR in SpA patients. There was no correlation between IL-23 and disease activity assessed by BASMI, BASDAI, BASFI and BASG in SpA. There was no correlation between IL-23 and EGF and FGF in SpA. There was negative correlation between VAS score and IL-23 in SAPHO group (R = −0,46; p = 0,04). There was positive correlation between SF-36 and IL-23 in PsA group (R = 0,42; p = 0,003).

Conclusion: There is no association of serum concentrations of IL-23 with disease activity in SpA.

1310

Effect of Weight, Body Mass Index and Weight-Based Dosing on Persistency of Anti-TNFs in Psoriatic Arthritis. Jeffrey D. Greenberg[1], Rebecca Bolce[2], Ying Shan[3], Katherine C. Saunders[4], George Reed[3], Joel M. Kremer[5] and Dennis Decktor[2]. [1]New York University School of Medicine, New York, NY, [2]Janssen Services, LLC, Horsham, PA, [3]UMass Medical School, Worcester, MA, [4]CORRONA, Inc., Southborough, MA, [5]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: Among approved anti-TNF agents for PsA, both fixed and weight-based dosing biologics are commonly prescribed. Despite the well-described higher body mass index (BMI) in PsA patients, there are few studies addressing whether patient weight and/or BMI influences patient outcomes on anti-TNFs. The effect of weight, BMI and weight-based dosing on persistency of treatment in anti-TNF biologic therapy among PsA patients was evaluated.

Methods: Patients with a diagnosis of PsA who were biologic naïve, initiated an anti-TNF biologic, and had at least one follow-up visit after this initiation were identified. Fixed dosing anti-TNFs (adalimumab and etanercept) versus weight-based (infliximab) dosing anti-TNFs were compared. Patients were considered persistent on treatment if they remained on the same drug therapy and did not switch or discontinue. Cox regression models adjusted for site clustering were used to estimate risk of discontinuation. Weight, BMI, and weight-based dosing were evaluated using Cox regression models and Kaplan-Meier survival analysis.

Results: Using data from CORRONA from 2/02–03/11, patients with a diagnosis of PsA (N=4,495) who were biologic naïve and initiated an anti-TNF biologic (N=428) and had at least one follow-up visit after this initiation (N=392) were identified. Obesity (BMI≥30) was significantly associated with a higher risk of discontinuation (unadjusted HR=1.8 [1.3, 2.5]; persistency 80% vs 63% at 18 months). PsA patients on fixed dosing anti-TNFs showed estimated higher risk of discontinuation compared to weight based dosing TNFi (unadjusted HR=1.3 [0.9, 2.0]; persistency 75% vs 70% at 18 months). Factors that were also associated with persistency were adjusted for—patient pain, gender, being disabled, duration of disease, history of CVD and year of initiation—BMI and fixed dosing anti-TNFs continued to show increased risk (Table 1). In separate models, weight showed similar effects on persistency as BMI.

Table 1. Multivariate Cox regression model for risk of discontinuation+.

	Hazard Ratio	95% CI	p-value
Fixed dosing (vs weight-based) anti-TNF	1.38	0.90,2.11	0.140
BMI (≥30) vs BMI <30	1.52	1.08,2.14	0.017
Pt. Pain (≥4 vs <4)	1.48	1.05,2.10	0.026
Female vs Male	1.64	1.17,2.29	0.004
Disabled	1.78	1.00,3.16	0.050
History of CVD	2.68	1.31,5.49	0.007
Duration of PsA	0.98	0.96,1.00	0.064

+ also adjusted for year of initiation

Conclusion: Increased BMI and weight were both significantly associated with risk of discontinuation of anti-TNFs in PsA patients. Infliximab, a weight-based dosing anti-TNF, was associated with a lower risk estimate of discontinuation than fixed dosing anti-TNFs although this did not reach statistical significance. Other determinants of risk of drug discontinuation included baseline patient pain level, gender, prior disability and CV comorbidity.

1311

Correlation Biomarkers of Cartilage and Bone Turnover with Disease Activity, Function, Quality of Life, Radiology and Magnetic Resonance Imaging in Patients with Early Spondiloarthritis. Raquel Almodovar[1], Valeria Ríos[2], Sara Ocaña[1], Milena Gobbo[3], Marisa Casas[1], Pedro Zarco[4] and Xavier Juanola-Roura[5]. [1]Hospital Universitario Fundación Alcorcón, Alcorcon. Madrid, Spain, [2]Hospital universitario Belvitge,, Barcelona, Spain, [3]Spanish Society of Rheumatology, Madrid, Spain, [4]Fundación Hopsital Alcorcon, Alcorcon, Madrid, Spain, [5]Hospital Universitario de Bellvitge, Barcelona, Spain

Background/Purpose: To analyse the influence of sex, HLA B27, psoriasis, osteitis in MRI and involvement pattern on biomarkers **of cartilage and bone turnover** [matrix metalloproteinase-3(MMP-3), high sensitivity C-reactive protein (hsCRP), C Telopéptide (CTX) and D-Pyridoline] in early spondiloarthritis (SpA) To determine the relationship between the biomarkers and activity, functional capacity, quality of life and radiology in early SpA.

Methods: A cross-sectional study of baseline visits from 60 patients included in Esperanza program was performed. Patients analyzed were under 45 years old, with onset symptoms within the range of 3 to 24 months. All patients included met the following criteria: a) inflammatory back pain, or b) symmetric arthritis, or c) back pain /articular pain, in addition to at least one of the following: a) psoriasis, b) inflammatory bowel disease (IBD), c) anterior uveitis (AU), d) radiographic sacroiliitis, e) family history of spondylitis, psoriasis, IBD, or AU, f) HLA-B27 positive. Data collected: social/demographic, ESR, CRP, HLA-B27, BASDAI, BASFI, total BASRI and ASQol. MRI of sacroiliac joints (SIJs) was performed on 23 patients and activity was defined according to the ASAS Group definitions for active lesions on MRI. Serum MMP-3 (ELISA), CTX (Cromatogrphic), hsCRP (Nefelometric) and urinary D-pyridoline (QLIA) were measured in all patients. Analysis: Chi square was used to compare rates and U de Mann-Whitney to analyze continuous variables. Pearson correlation coefficient analysis was performed to examine the contribution of differents biomarkers.

Results: At baseline, a total of 60 patients diagnosed of **early SpA** were included: 26 male (43%) and 34 female (56.6%), with age 32.3± 6.6 years and disease duration of 12.4± 6.7 moths. Eight percent of patients had axial affectation, 23% peripheral, 2% mixed and 3% enthesitic pattern. The HLA B27 was positive in 26.6% patients. Thirteen percent had psoriasis. Six patients (26%) had active sacroiliitis by MRI. The values (mean ± SD) were: nocturnal pain (cm) 4.5± 2.6; BASDAI (cm) 4.2 ± 2.4; ESR (ml/h)15± 14; CRP (mg/L) 5.3± 9.4; BASFI (cm) 2.7± 2.4; total BASRI 0.38 ±1 and ASQol 6.7± 5. Biomarkers showed no significant differences between HLA-B27 positive or negative patients, with or without psoriasis patients, with or without osteitis in MRI and type of involvement pattern. CTX **(0.53 mgr/L vs. 0.24mgr/L; p=0.001)** and MMP-3 **(0.53 mgr/L vs. 0.24mgr/L; p=0.001)** were significantly higher in male **than in female** with early **SpA.** Of the biomarkers examined, only the **h**igh sensitivity C-reactive protein (hsCRP) showed a significant correlation with the ESR level (r=0.3, p=0.04). MMP-3 and urinary D-pyridoline demonstrated a trend toward a positive correlation with ESR (r=0.2, p=0.08) and (r=0.3, p=0.08), respectively. hsCRP showed a trend toward a positive correlation with total BASRI (r=0.3, p=0.05).

Conclusion: In our study, the male sex is associated with higher levels of CTX and MMP-3 in early SpA, which may indicate higher radiographic damage in men. HLAB27, psoriasis and osteitis in MRI had no influence on any biomarkers. We found only a significant correlation between hsCRP and ESR.

1312

Effect of Adalimumab on Function, Health-Related Quality of Life, Work Productivity, and Daily Activities in Patients with Non-Radiographic Axial Spondyloarthritis. Walter P. Maksymowych[1], Philip J. Mease[2], Sumati Rao[3], Aileen Pangan[3], L. Steven Brown[3], Vipin Arora[3] and Mary A. Cifaldi[3]. [1]University of Alberta, Edmonton, AB, [2]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [3]Abbott Laboratories, Abbott Park, IL

Background/Purpose: To evaluate the effect of the anti–tumor necrosis factor agent adalimumab (ADA) on physical function and health-related quality of life (HRQOL) and productivity in patients with non-radiographic axial spondyloarthritis (SpA).

Methods: Biologic-naïve patients with non-radiographic axial SpA, excluding those meeting the modified New York criteria for AS, and inadequate response to or intolerance of ≥1 nonsteroidal anti-inflammatory drug were randomized to ADA 40 mg every other week (eow) or placebo for 12 weeks of double-blind treatment (Ability 1 trial). The blinded phase was followed by a 92-week open-label phase. Function was assessed using the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S) and HRQOL using the Short Form 36 Health Survey (SF-36) Physical Component Summary (PCS) score. Productivity was assessed using the 4 components of the Work Productivity and Activity Impairment Questionnaire (WPAI). Changes from baseline to Week 12 were compared between groups using ANCOVA with adjustment for baseline scores and treatment as a factor.

Results: Analyses were conducted on the full-analysis set, a subset of the intent-to-treat population (N=91 for adalimumab; N=94 for placebo). Mean age was 38 years, 55% were women, and duration of SpA symptoms averaged 10 years. Baseline HAQ-S scores were similar between ADA- and placebo-treated patients (0.99 and 1.05, respectively) and indicated moderate impairment. For both groups, baseline SF-36 PCS scores were lower than the general US population average of 49.1 (33.9 for ADA, 33.1 for placebo). Baseline WPAI scores indicated substantial total work productivity impairment (TWPI; 46% average reduction for ADA, 49% for placebo) and total activity impairment (TAI; 57% average reduction for both ADA and placebo) due to axial SpA. ADA therapy was associated with statistically significant improvements in HAQ-S, SF-36 PCS, absenteeism, and daily nonwork activity impairment scores (TAI) compared with placebo; presenteeism and TWPI showed no significant treatment group differences (table). Improvement in SF-36 PCS met the minimum clinically important difference of 3.0.

Mean Changes From Baseline to Week 12 in Function, HRQOL, and WPAI Scores in Patients With Non-Radiographic Axial SpA

	Placebo (N=94)	ADA 40 mg EOW (N=91)	P-Value
Physical Function			
HAQ-S	−0.1	−0.3	0.027[a]
HRQOL			
SF-36 PCS	2.0	5.5	0.001[b]
WPAI			
Absenteeism	2.3	−7.2	0.005[b]
Presenteeism	−5.8	−12.3	0.07[b]
TWPI	−5.7	−12.1	0.122[b]
TAI	−3.6	−14.9	0.002[b]

[a]Last observation carried forward.
[b]As observed.

Conclusion: Patients with non-radiographic axial SpA had substantial impairment of function, HRQOL, work productivity, and nonwork activities at baseline. After 12 weeks of therapy, the ADA group experienced clinically and statistically significant improvements in function and HRQOL and significantly less absenteeism from work and less impairment in daily nonwork activities compared with placebo.

1313

Are High Titers of Anti-CCP Antibodies in Psoriatic Arthritis Patients a Biomarker of Erosive Disease? Ignacio Garcia-Valladares[1], Raquel Cuchacovich[1], Antonio A. Iglesias-Gamarra[2] and Luis R. Espinoza[1]. [1]Louisiana State University, New Orleans, LA, [2]Universidad Nacional, Bogota, Colombia

Background/Purpose: The presence of positive anti-CCP antibodies (anti-CCP), especially at high titers, is characteristic of rheumatoid arthritis (RA) and predictive of the development of erosive disease. In contrast, anti-CCP antibodies may be present in PsA in less than <15% and usually at low titers.

The aim of this study was to compare the clinical, serological and radiologic characteristics of PsA patients with and without anti-CCP antibodies.

Methods: Serum anti-CCP antibodies were measured in 80 patients with PsA. Age, gender, family history, means disease duration, pattern of joint involvement, nail and skin involvement, and treatment were obtained. CASPAR criteria were used.

Results: Of the 80 patients with PsA, 38 were women and 42 men. The mean age 45.7-yrs (39–72), and the mean disease duration was 9.4-yrs (2–14). Anti-CCP antibodies were present in 10 patients, mean titer 174.9 IU. Most patients were female (9/1), had polyarticular involvement, and erosive disease. In contrast to anti-CCP negative PsA patients, PsA patients with positive CCP antibodies were older 53.2 –yrs vs 47.7-yrs, exhibited more RA-like polyarthritis, 8/10 (80%) vs 12/65 (18.4%), less nail involvement 4/10 (40%) vs 57/65 (87.6%), and less psoriatic spondyloarthropathy 0/10 vs 5/65 (7.7%). Anti-CCP negative PsA patients had predominant oligoarticular involvement 44/65 (67.7%) vs 2/10 (20%). Presence of enthesitis/dactylitis and PASI scores were similar in both groups. Rheumatoid factor was present in higher frequency in anti-CCP positive PsA patients, 4/10 (40%) vs 4/70 (5.7%), and anti-TNF-μ was given to 5/10 (50%) of anti-CCP antibodies positive patients as compared to 28.5% in negative anti-CCP antibodies PsA patients.

Conclusion: The clinical distinction between RA and PsA is often difficult to establish. Positivity for RF and anti-CCP antibodies is highly sensitive and to certain extent specific markers and can pre-date the onset of RA. Others and we however, have described the presence, albeit in low frequency (5–15%), of anti-CCP antibodies in patients with PsA but not in psoriasis.

These findings clearly demonstrate that a subset of PsA patients with positivity for anti-CCP is highly associated with RA-like polyarticular involvement, erosive changes and possibly a more severe progression of disease, and also higher use of anti-TNF-μ therapy; which lend support to the notion that anti-CCP antibodies should be considered a marker of disease severity in patients with PsA. Further studies, however, in larger number of patients are needed to define the role of these antibodies in PsA.

1314

Does the Change in Season Affect Disease Outcomes in Patients with Psoriatic Arthritis? Zahi Touma[1], Arane Thavaneswaran[2], Vinod Chandran[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Studies have shown a trend for worsening of psoriasis (Ps) in the winter and improvement in the summer. Patients with psoriatic arthritis (PsA) tend to report more joint pain during the winter time. We aimed to determine whether there is seasonal variation in disease activity of patients with PsA.

Methods: This retrospective study was conducted on all patients enrolled in a prospective longitudinal PsA cohort. Patients undergo a complete history, physical examination and laboratory evaluation at 6–12 month intervals. We defined the seasons as follows: June 22 to September 21 is summer, and December 22 to March 21 is winter. We identified the first available set of consecutive summer and winter visits on every patient. Comparisons between these repeated summer and winter visits from 1978 until 2011 for the same identified patients was conducted for the following outcomes: demographic, clinical data, inflammatory markers (ESR and CRP), treatment and Patient' Global Assessment (PGA).

We further categorized PsA disease activity into mild-moderate/severe for Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and mild/moderate/severe for active joints and Psoriasis Area and Severity Index (PASI) scores. Univariate and multivariate analyses using generalized estimating equations were conducted to account for repeated summer and winter visits per patient that included demographic/lifestyle and clinical variables.

Results: 253 patients with first available summer and winter visit were identified. Among these patients 1789 observations were analyzed. There was no statistically significant difference in patients' demographics, active and damaged joints, categorized joints disease severity, psoriasis (PASI) and categorized psoriasis severity, and treatment between summer and winter visits (Table 1–2).

Table 1. Patient's demographics and drug information for 253 patients in 1789 observations by season

Variable	Frequency (%) of Mean (sd) Summer N=917 visits	Winter N=872 visits	P-value
Sex: M/F	517 (59.0%)/360 (41.1%)	338 (39.1%)/527 (60.9%)	0.4095
Race:	—	—	0.5960
White:	779 (88.8%)	773 (89.4%)	
South Asian:	39 (4.5%)	29 (3.4%)	
Hispanic:	2 (0.2%)	2 (0.2%)	
Black:	—	—	
Chinese:	22 (2.5%)	23 (2.7%)	
Southeast Asian:	2 (0.2%)	3 (0.4%)	
Korean:	3 (0.3%)	3 (0.4%)	
Filipino:	5 (0.6%)	6 (0.7%)	
Aboriginal:	5 (0.6%))	4 (0.5%)	
Other:	20 (2.3%)	22 (2.5%)	
Age at visits	48.2 (12.7%)	47.4 (12.8%)	0.1185
Age at Diagnosis of Ps	27.8 (14.6)	27.4 (14.4)	0.6940
Age at Diagnosis of PsA	36.8 (12.5)	36.6 (12.3)	0.5358
Duration of Ps	20.3 (13.6)	19.9 (13.3)	0.1111
Duration of PsA	11.4 (9.8)	10.9 (9.3)	0.1276
Active Joints	629 (72.3%)	620 (71.7%)	0.5870
Active Joint Count	9.1 (9.8)	8.8 (9.6)	0.9677
Damage Joints	478 (54.6%)	465 (53.9%)	0.8096
Damaged Joint Count	10.9 (12.0)	11.5 (12.3)	0.0573
Medications			
NSAIDs	538 (85.9%)	541 (84.7%)	0.7851
DMARDs	576 (82.5%)	554 (81.0%)	0.1570
Biologic	146 (39.7%)	157 (42.4%)	0.4518
UVT	50 (7.8%)	43 (6.8%)	0.3272

Table 2. Measures of Disease Activity

Measures of Disease Activity			
BASDAI severity	—	—	0.0469
Mild-Moderate:	82 (56.6%)	70 (67.3%)	
Severe:	63 (43.4%)	34 (32.7%)	
BASDAI score			0.8012
Joint Severity	—	—	0.2131
Remission-Minimal:	375 (43.1%)	373 (43.1%)	
Mild-Moderate:	272 (31.3%)	296 (34.2%)	
Severe:	223 (25.6%)	196 (22.7%)	
PASI Severity	—	—	0.7209
Remission-Minimal:	327 (43.9%)	324 (45.1%)	
Mild-Moderate:	316 (42.4%)	294 (40.9%)	
Severe:	102 (13.7%)	101 (14.0%)	
PASI	4.5 (6.2)	4.7 (7.4)	0.1499
Patient Global	—	—	0.0462
Assessment	—	—	
Very good:	61 (15.6%)	48 (12.0%)	
Good:	175 (44.8%)	178 (44.5%)	
Fair:	118 (30.2%)	126 (31.5%)	
Poor:	30 (7.7%)	38 (9.5%)	
Very Poor:	7 (1.8%)	10 (2.5%)	
Inflammatory markers			
CRP	10.3 (18.0)	13.8 (20.4)	0.1803
ESR	17.5 (17.2)	17.8 (17.3)	0.6430

Although BASDAI scores were greater in summer visits as compared to winter visits in the univariate analysis, this difference did not hold in the multivariate analysis (OR=0.85, CI 0.34–2.13 p=0.73). Patients graded their disease worse in winter as compared to summer and this was statistically significant in the univariate analysis (p=0.04) but not in the multivariate analysis (OR=1.39; CI 0.99–1.94 =0.56).

Conclusion: The change in season doesn't affect PsA disease activity. Patients' disease activity as determined by active joints, inflammatory back pain, psoriasis and patients perspective of their disease doesn't change significantly between summer and winter.

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Changes in Psychological Status in Patients with Chronic Spondyloarthropathy Treated with Infliximab. Rosa M. Morlà[1], Hector Corominas[2], M. V. Hernandez[3], Mireia Moreno[4], Miquel Sala[5], Vera Ortiz-Santamaria[6], Patricia Reyner[6], Vicente Torrente-Segarra Jr.[7], Agusti Sellas Fernandez[8], Georgina Salvador[9], Elena Sirvent[10], Cristina Masuet[11] and Xavier Juanola-Roura[12]. [1]Hospital Sta Tecla, Tarragona, Spain, [2]Hospital Moises Broggi, Barcelona, [3]Hospital Clinic of Barcelona, Barcelona, Spain, [4]Servei de Reumatologia, Sabadell, Spain, [5]Rheumatology Unit, Figueres, Spain, [6]Unitat de Reumatologia, Spain, [7]Hospital General de Hospitalet, Barcelona, Spain, [8]Senior Consultant, Barcelon, Spain, [9]Hospital Mutua de Terrassa. Barcelona, Barcelona, Spain, [10]Hospital de Sant Boi, [11]Hospital de Bellvitge, Hospitalet de LLobregat, Spain, [12]Hospital Universitario de Bellvitge, Barcelona, Spain

Background/Purpose: Patients with chronic inflammatory rheumatic disease are known to present frequently associated psychological disorders. Several studies have reported the benefit of biological therapies in spondyloarthropathies (SpA), but there are few data regarding its impact on psychological symptoms and well-being.

To analyze the influence of infliximab as a anti-TNF therapy on self-reported indices of anxiety and depression in patients with chronic spondyloarthropathy, and their relation to the main disease activity parameters.

Methods: 62 patients with SpA according to the European Spondyloarthropathy Study Group (48 anchylosing spondilytis, 14 undifferentiated SpA) fulfilling Spanish Rheumatology Society criteria for biological therapy were enrolled in a prospective multicentric observational study. They received 5 mg/Kg infliximab iv infussion at 0,2,6 and every 8 weeks thereafter. At baseline and at 22 weeks patients were assessed for demographic variables, number of affected joints (NAJ), analytical parameters (ESR and C reactive protein), metrological indices (Schöber test and finger-floor distance), BASDAI (disease activity) and BASFI (functional status) questionnaires, visual analogic numeric scales for night and day pain and global self-reported pain. Patients were also assessed for self-reported anxiety (STAI-R and STAI-S questionnaires) and psychological disorder (HADS, with cutpoint at 12 points) and its subscales for anxiety (HADA, cutpoint at 8 points) and depression (HADD, cutpoint at 5 points). Continuous variables at baseline and 22 weeks were compared with Student or Wilcoxon tests, while categorical variables were compared with McNemar's or Wilcoxon's tests. A multivariate Binary Logistic Regression analysis was performed taking a $>$ 3 points decrease in the HADS score as the dependent variable.

Results: HADS score decreased significantly at 22 weeks. The median (interquartilic range) went from 16 (10–22) at baseline to 9 (3–15), $p<0.001$. The HADS anxiety and depression subscale scores decreased from 8 (5–12) to 6 (3–10), $p<$ 0,001, and from 8 (5–12) to 5 (3–10), $p<$ 0,001 respectively. Also a reduction was observed in the proportion of patients with psychological disorder (HADS $>=$ 12), from 71.2% to 48.1%, $p=0,029$, and with definite depression (HADD score $>=$ 5) from 59.7% to 44.6%, $p=0.01$. Other parameters improved significantly as expected, including NAJ, finger-floor distance, ESR, CRP, self-reported numeric scale of pain (at day, night and global), and disease activity (BASDAI) and functionality (BASFI) indices. In the multivariate analysis, only ESR (OR: 0.908 – 0.996) and BASFI (OR: 0,422–0,990) were found to contribute significantly to the variance of HADS. Low baseline values of both parameters were related to higher probability of psychological improvement.

Conclusion: Patients with chronic spondyloarthropathies receiving infliximab therapy presented a high incidence of psychological disorders that improved after 22 weeks of therapy, as assessed by the HADS validated self-reported test. Low values of VSG and BASFI were significant predictors of such improvement.

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Antibody Response to the Standard Hepatitis B Vaccination in Patients with Rheumatoid Arthritis and Ankylosign Spondylitis Treated with Infliximab. María Montoro Álvarez Sr.[1], Carlos Gonzalez Fernandez Sr.[2] and Ainhoa Gonzalez Expósito Sr.[2]. [1]Gregorio Marañón Hospital, Madrid, Spain, [2]Gregorio Maranon Hospital, Madrid, Spain

Background/Purpose: Measurement of antibody response to standar hepatitis B vaccination in patients with infliximab. Patients treated with infliximab are at an increased risk of infections, including many that are vaccine-preventable. Risk increases with the use of immunosuppressive medications, including corticosteroids and immunomodulators. It is important to assess vaccination status early on in the clinical care of patients who will have a possibility to receive infliximab as the best chance for administering all the indicated vaccines, and having the best chance of antibody response, is prior to the initiation of immunosuppressive medications. The viral hepatitis vaccines, hepatitis A and hepatitis B, are indicated in patients under infliximab therapy. There have been reports of HBV reactivation, and acute liver failure, in at-risk patients who receive anti-TNF therapy. Anti-TNF therapy are able to decrease immunogenic response to hepatitis B vaccine.

Methods: All rheumatoid arthritis (RA) and ankylosis spondylitis (Asp) patients receiving infliximab theraphy ($>$ 6 months), at rheumatology day care unit, with antiHBs negative were advice to received standar vaccination. Standar vaccination is given by receiving 3 intramuscular injections of the standard dose (20 μg) of recombinant HBV vaccine at weeks 0, 4, and 24. Percentage of responders at week 28, defined as patients with hepatitis B surface antibody (anti-HBs) of more than 10 mIU/mL who received at least 2 dose of vaccine. Patients with missing anti-HBs titer measurement at the final follow-up visit at week 28 were considered to be nonresponders. Post-vaccination titers should be obtained to confirm antibody response.

Results: Complete vaccination was administered in 52 patients (27 ASp, 25 RA). Titer of antiHBs $>$10 was achieved for 1 patient with RA and 3 patients with Asp. Nonresponders were 89% (24/27) in SpA and 96% (24/25) in RA. No serious adverse event possibly related to vaccine were reported.We observe in our patients on infliximab TNF treatment a decreased antibody response to HBV vaccination. It was measured by titers of anti-HBs antibody 28 week after first dosage of vaccine.

Conclusion: Antibody titer that define protection is not well know. Addressing HBV status, and vaccinating at-risk patients, should be a priority in patients who may require anti-TNF therapy. It is important to educate both physicians and patients regarding vaccination recommendations. Addressing these issues early on, gives more options in terms of ensuring optimal antibody response to the vaccination. Alternative schedules more immunogenic than the standard hepatitis B vaccine regimen are needed in patients under infliximab therapy

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Clinical and Radiological Manifestations of Ankylosing Spondylitis: Gender Differences. Fernando Pimentel-Santos[1], Ana F. Mourão[2], Célia Ribeiro[1], José Costa[3], Helena Santos[4], Anabela Barcelos[5], Patricia Pinto[6], Fátima Godinho[7], Margarida Cruz[8], Elsa Vieira-Sousa[9], Jorge Félix[10], J. E. Fonseca[11], Henrique Guedes-Pinto[12] and Jaime C. Branco[1]. [1]Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal, [2]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Ocidental, EPE, Hospital Egas Moniz, Lisbon, Portugal, [3]Centro Hospitalar do Alto Minho, Hospital de Ponte de Lima, Ponte de Lima, Portugal, [4]Instituto Português de Reumatologia, Lisboa, Portugal, [5]Hospital Infante D. Pedro, [6]Centro Hospitalar de Vila Nova de Gaia/Espinho EPE, [7]Hospital Garcia de Orta, [8]Centro Hospitalar Oeste Norte, Centro Hospitalar das Caldas da Rainha, [9]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [10]EXIGO Consultores, [11]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisboa, Portugal, [12]Universidade de Trás-os-Montes e Alto Douro

Background/Purpose: Ankylosing Spondylitis (AS) is a systemic inflammatory disorder with a men:women ratio of 2–3:1. There are evidence for differences in the expression of AS between the genders. To examine the clinical and radiographic features in men and women in the CORPOREA cohort, a large cross-sectional study of patients with AS, in order to understand the influence of gender in determining the severity of the disease.

Methods: Ankylosing Spondylitis (AS) is a systemic inflammatory disorder with a men:women ratio of 2–3:1. There are evidence for differences in the expression of AS between the genders. To examine the clinical and radiographic features in men and women in the CORPOREA cohort, a large cross-sectional study of patients with AS, in order to understand the influence of gender in determining the severity of the disease.

Results: A total of 369 patients were included, (62.3% men and 37.1% women), with a mean age of 45.4$\pm$13.2 years (range 20 – 79 years). Table 1 summarize the results for whole group and by gender. The mean delay between onset of symptoms and diagnosis was 7.6 $\pm$ 9.0 years. Compared with men, the mean BASDAI in women was 1.2 points higher (4.9 *vs* 3.7, $p<0.001$) and the mean BASFI was 0.7 points higher (4.5 *vs* 3.8, $p=0.01$),

but the mean BASMI was 0.8 points lower (3.5 *vs* 4.3, p=0.006) and the mean mSASSS was 17.6 points lower (10.2 *vs* 27, p<0.001).

Table 1. Characteristics of the overall cohort and analysis by gender.

	Total (n=369)	Male (n=232)	Female (n=137)	*p-value**
Gender	100%	62.8%	37.1%	—
Age (years)	45.4 ± 13.2	45.7 ± 13.5	44.9 ± 13.9	0.52
Age at onset (years)	26.5 ± 10.8	25.8 ± 10.8	27.5 ± 10.8	0.185
Age at diagnosis (years)	34.1 ± 13.4	33.0 ± 12.3	35.8 ± 12.4	0.040
Disease duration (years)	11.4 ± 10.5	12.6 ± 11.0	9.5 ± 9.3	0.022
Diagnosis delay (years)	7.6 ± 9.0	7.1 ± 9.0	8.3 ± 9.0	0.081
BASDAI	4.2 ± 2.3	3.7 ± 2.2	4.9 ± 2.3	<0.001
BASFI	4.1 ± 2.7	3.8 ± 2.6	4.5 ± 2.7	0.010
BASMI	4.0 ± 2.5	4.3 ± 2.6	3.5 ± 2.2	0.006
mSASSS	20.9 ± 23.1	27.4 ± 24.6	9.8 ± 14.7	<0.001
ESR (mm/h)	21.7 ± 17.7	20.1 ± 17.4	24.3 ± 18.2	0.012
HLA-B27 positivity	70.7%	73.5%	67.2%	—

Conclusion: The average age at symptom onset and the diagnostic delay were similar in both genders. However females reported greater disease activity (BASDAI) and functional impairment (BASFI), but had better metrology (BASMI) and better radiological evaluation (mSASSS). All of these findings suggest that the phenotype of AS differs between the genders, raising the question about the mechanisms underlying clinical manifestations of the disease.

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Anti-TNF Agents May Accelerate the Remodeling of Hip Cartilage in Ankylosing Spondylitis. Sang-Hoon Lee[1], Jaeho Choi[1], Somi Kim[2], Ran Song[1], Yeon-Ah Lee[2], Seung-Jae Hong[2] and Hyung-In Yang[3]. [1]Medical Center at Gangdong, School of Medicine, Kyung Hee University, Seoul, South Korea, [2]Kyung Hee University, Seoul, South Korea, [3]Kyung Hee University Hospital at KANGDONG, Kyung Hee University, Seoul, South Korea

Background/Purpose: Anti-TNF agents have been used for patients with ankylosing spondylitis (AS) that don't respond to anti-inflammatory drugs and DMARDs. Recently, it has been known that anti-TNF agents can prevent bone erosion but also delay the cartilage loss in rheumatoid arthritis patients. Therefore, we reviewed the effect of anti-TNF agents on hip joint cartilage, which is frequently involved in ankylosing spondylitis.

Methods: Through retrospective chart review, we investigated AS patients who were diagnosed according to the modified New York criteria and treated with anti-TNF agents. Patients are included who treated with TNF-alpha blockers during more than 12 months.We confirmed hip joint space changes before and after drug treatment by comparing the changes in simple X-ray, pelvis AP or CT scans.

Results: A total of 100 patients were enrolled. 86 out of 100 patients had no interval changes in hip joint space. The hip joint space of 4 patients decreased and 10 patients' hip joint space increased before and after anti-TNF agents. We analyze that the factors may influence changes of hip joint space such as the changes of BASDAI, ASDAS, CRP, ESR, IgA, anti-TNF agents with age, sex, and disease duration.

Factors that influence hip joint's Interval narrowing were not statistically significant because the number of patients was too small. 3 out of 4 patients were intermittently treated with anti-TNF agents though they were not in remission, and the hip joint space decreased. 1 patient used all three kinds of anti-TNF agents, but the effect was not enough. ESR, CRP, and BASDAI of the patient were consistently high and his symptoms were continued. 9 out of 10 patients have recently received the ongoing treatment regardless of their symptoms, and the hip joint space has significantly increased.1 patient treated only with medication such as NSAIDs and DMARDs reached remission after anti-TNF treatment of a year.

Conclusion: There have been no reports of anti-TNF agent that inhibits cartilage loss in hip joint until now. This study suggests anti-TNF agents have the protective effect of cartilage in AS. Although it is known that cartilage is not regenerated, some cases show actually the increase of hip joint space in this study. We suggest an additional large prospective case-control study will need anti-TNF agent's hip joint protective effect.

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Evaluation of Circulating Endothelial and Platelet Microparticles In Men with Ankylosing Spondylitis. Ismail Sari[1], Giray Bozkaya[2], Halil Kirbiyik[2], Ahmet Alacacioglu[2], Halil Ates[1], Gulten SOP[2], Gercek Sen[3], Ali Taylan[4], Ozden Piskin[1], Yasar Yildiz[2] and Nurullah Akkoc[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Izmir Bozyaka Training and Research Hospital, Izmir, Turkey, [3]Izmir Ataturk Training and Research Hospital, Izmir, Turkey, [4]Izmir Tepecik Training and Research Hospital, Izmir, Turkey

Background/Purpose: Microparticles (MPs) are molecules that are released from the various cells, most notably from platelets and endothelial cells, during the activation or apoptosis. MPs are involved in a wide range of physiological and pathological processes. MPs may modulate endothelial function by stimulating cytokine release, intervening in the production of nitric oxide and prostacyclin by endothelial cells as well as monocyte chemotaxis and adherence to the endothelium. Endothelial dysfunction has increasingly been studied in patients with ankylosing spondylitis (AS) with yet no clear mechanism to explain. In the present study, we aimed to evaluate the endothelial microparticle (EMP) and platelet microparticle (PMP) profiles in men with AS and healthy subjects to test whether PMPs and EMPs are altered in AS. We also aimed to determine whether the concentrations of MPs correlate with disease activity (BASDAI), function (BASFI), and spinal mobility (BASMI).

Methods: This descriptive, cross-sectional study comprised 82 men with AS according to the modified New York criteria and 53 healthy controls. Subjects with a history of chronic diseases including coronary artery disease, hypertension, diabetes mellitus, and dyslipidemia were excluded. MPs were isolated from plasma by ultracentrifugation. Following the isolation, MPs were stained with monoclonal antibodies against platelets, and endothelial cells, and quantified by using flow cytometry. MPs which are positive for both (CD31+/CD42+) and total CD42(+) are identified as PMPs; and MPs consisting (CD31+/CD42−), and total CD144(+) are considered as EMPs.

Results: Age, waist circumference, smoking status, fasting glucose and serum lipids were similar between the patient and control groups (p>0.05, Table 1). Mean disease duration was 13.2±8.9 years. There were no differences in regard with the concentration of EMPs and PMPs between the AS patients and healthy controls (p>0.05, Table 1). The comparison of active (BASDAI≥4) and inactive disease state AS patients showed that the concentration of EMPs and PMPs were not different between the groups (p>0.05). Correlation analysis revealed no correlation with BASDAI, BASFI or BASMI. However, that CRP, and HDL were significantly correlated with total CD42(+) PMPs (r=0.5, and −0.3), CD42(+)CD31(+) PMPs (r=0.4, and −0.3), and CD42(−)CD31(+) EMPs (r=0.3, and −0.2). Total CD144(+) EMPs showed significant correlations with fasting glucose and triglycerides (r=0.3 and 0.3).

Table 1. Clinical and laboratory results of the study group

	AS Patient (N=82)	Healthy Subjects (N=53)	P Value
Age (years)	39 (17–63)	35 (24–60)	0.7
Waist circumference (cm)	89 (64–10)	92 (62–112)	0.6
Fasting glucose (mg/dL)	88 (65–120)	87 (50–123)	0.2
LDL cholesterol (mg/dL)	106 (34–157)	116 (54–155)	0.07
Systolic blood pressure (mmHg)	110 (100–140)	115 (100–140)	0.6
Smoking status (%)	40.4	50.6	0.3
Platelet microparticles (*particle/μL*)			
Total CD42(+)	7371 (938–230565)	8472 (364–22552)	0.5
CD42(+)CD31(+)	5896 (390–21947)	6571 (158–21824)	0.7
Endothelial microparticles (*particle/μL*)			
CD42(−)CD31(+)	959 (107–3259)	1006 (72–3107)	0.07
Total CD144(+)	1125 (341–6912)	1391 (489–4038)	0.07

Conclusion: Circulating EMPs and PMPs, one of the indicators and mediators of vascular injury, are not significantly altered in male AS patients who do not have classical cardiovascular risk factors.

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Diagnostic Utility of Sacroiliac Joint MRI in Non-Radiographic Spondyloarthritis: Validation of Three Assessment Methods in Two Inception Cohorts. Ulrich Weber[1], Veronika Zubler[2], Susanne Juhl Pedersen[3], Stanley Chan[1], Kaspar Rufibach[4], Robert GW Lambert[1] and Walter P. Maksymowych[1]. [1]University of Alberta, Edmonton, AB, [2]Balgrist University Hospital, Zurich, Switzerland, [3]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [4]University of Zurich, Zurich, Switzerland

Background/Purpose: A systematic evaluation of sacroiliac joint (SIJ) MRI based on both active and structural lesions (global evaluation) has shown high diagnostic utility in axial spondyloarthritis (SpA) [1]. The incorporation of

erosions (ER) with bone marrow edema (BME) as defined by ASAS improved diagnostic utility compared to BME alone.

Objectives: To validate global and lesion-based (BME, BME plus ER) approaches to evaluation of SIJ by MRI in two inception cohorts of consecutive patients with back pain suspected of having SpA.

Methods: Cohort A comprised 88 consecutive patients, age ≤50, with acute anterior uveitis (AAU) and back pain referred by an ophthalmology centre. Cohort B comprised 69 consecutive patients ≤50 years referred by practising rheumatologists and primary care physicians to a tertiary care center for further assessment of suspected inflammatory back pain. They were classified according to clinical, laboratory and imaging evaluation as having non-radiographic SpA (nrSpA) (n=20; 65% HLAB27 positive, 55% male), ankylosing spondylitis (AS) by the modified New York criteria (mNYc) (n=10), and non-specific back pain (NSBP) (n=39). Scans from 20 local healthy controls (HC) were also assessed. SIJ MRI were scored independently in random order by 4 readers blinded to patient identifiers.

Results: The assessment of ER in addition to BME enhanced diagnostic utility in both cohorts despite differences in the prevalence of SpA. For the AAU cohort, AS by mNYc was diagnosed in 28/88 (31.8%) and 16/88 (18.2%) were diagnosed with NSBP. Of 44/88 (50%) that had suspected SpA (68% HLAB27 positive, 52% male), sensitivity/specificity of MRI according to 2 readers was 32%/100% by global assessment, 27%/100% for BME alone, and 36%/100% for BME plus ER, compared to NSBP. Similar data was noted in cohort B. Sensitivity/specificity (mean of 4 readers) of SIJ MRI for nrSpA compared to NSBP was 75%/96% by global assessment, 72%/85% for BME alone, and 81%/83% for BME plus ER. In cohort B, ER was detected in 75% of nrSpA patients. ER was not recorded in NSBP patients and HC, but both groups showed BME (NSBP in 23%, HC in 20%).

Table 1. Cohort B, nrSpA versus NSBP

Assessment method	Sens	Spec	LR+	LR-
Global	0.75	0.96	20.2	0.3
BME alone	0.72	0.85	4.3	0.3
BME + ER	0.81	0.83	7.0	0.2

Conclusion: In two unselected cohorts of consecutive patients we show that ER detected by MRI is highly specific for nrSpA and contributes to diagnostic utility beyond assessment of BME alone.

[1] Arthritis Rheum 2010;62:3048

1321

Multifocal Inflammatory Lesions in Ankylosing Spondylitis Patients Depicted by Whole Body MRI (WBMRI) Improve by a One Year Therapy with Etanercept. Martina Karpitschka[1], Daniel Theisen[1], Annie Horng[1], Christian Glaser[1], Maximilian Reiser[1], Sabine Weckbach[1] and Herbert Kellner[2]. [1]Munich, Germany, [2]Centre for Inflammatory Joint Diseases, Munich, Germany

Background/Purpose: In ankylosing spondylitis (AS) multifocal inflammatory manifestations of the musculoskeletal system are common. Whole-body magnetic resonance imaging (WBMRI) is known to detect widespread inflammatory lesions. Anti-tumor necrosis factor (TNF) therapy is highly effective in AS, however, expensive. Therefore, accurate assessment of therapy response is of clinical relevance. The purpose of this study was to evaluate WBMRI compared to clinical exam alone in patients during etanercept therapy.

Methods: 6 patients with AS underwent a 12 months therapy with etanercept (Enbrel ® 50 mg / week). Patients were examined by an established WBMRI protocol (1.5 T scanner, STIR and T1-w unenhanced and contrast-enhanced sequences) at 3 different points of time (0, 12 and 52 weeks) after application of the first dose of etanercept. WBMRI was evaluated in consensus by 2 experienced radiologists (blinded to clinical exam) for inflammatory lesions (e.g. spondylitis, sacroileitis, bursitis, enthesitis and synovitis). The lesions were counted and graded on a grading system (severe, moderate, mild, minimal). Simultaneously, clinical examination was performed by an experienced rheumatologist, including collecting data from BASDAI, BASFI and CRP. WBMRI and clinical scores were correlated.

Results: During etanercept therapy, symptomatic therapy with NSAID could significantly be reduced, (3.0±0.4 down to 1.5±0.2 (50%, $p<0.05$). The clinical examination scores showed significant improvement under therapy, e.g. the BASDAI-index decreased from 5.6±0.7 (week 0) to 1.6±0.5 (weeks 12, $p<0.05$) and to 1.4±0.6 (week 52, $p<0.05$). The patients' estimation of AS activity at week 0 averaged 6.8±1.1, physician assessment was 7.0+0.3 respectively. At week 12, the AS-activity averaged 1.2±0.5 by patients ($p<0.05$) and 2.0±0.3 ($p<0.05$) by the physician. The amount of pain diminished during therapy from 7.2±0.7 (BASDAI, week 0) to 1.3±1.0 (BASDAI, week 52).The morning stiffness significantly decreased from 72,0±18.0 (week 0) to 12.0±8.7 (week 52). In addition, clinical values improved under therapy, e.g. CRP averaged 15.9±4.7 at week 0 and declined to 2.1±21 at week 52 ($p=0.055$). In WBMRI, the sum of all lesions showed a significant decrease from week 0 (30.6±12.4) to week 12 (14.2±7.5), equivalent to a 59.2±13.8% reduction of lesions. Especially for spondylitis anterior and sacroileitis, there was a significant decline of inflammatory lesion, e.g. 9.5±2.6 in week 0 to 1.0±1.0 in week 52 for spondylitis anterior (reduction about 92.7±7.3, $p<0.05$) or 5.5±1.0 in week 0 to 0.0±0.0 in week 52 for sacroileitis (reduction of 100%, $p<0.05$). WBMRI detected significantly more areas of synovialitis and enthesitis than clinical examination ($p<0.05$).

Conclusion: Under etanercept therapy the activity of AS significanty decreased, which was proven by clinical examination, CRP and quality of life questionnaires (BASDAI) as well as by WBMRI. WB-MRI detected significantly more inflammatory lesions than clinical exam alone. The results suggest that WB-MRI improves the detection of inflammatory changes and the assessment of their course under therapy.

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Improvement in Ankylosing Spondylitis Disease Activity Score in Patients with Ankylosing Spondylitis Treated with Tumor Necrosis Factor-Alpha Blocking Therapy. Suzanne Arends[1], Eveline van der Veer[1], Pieternella M. Houtman[2], Martha K. Leijsma[1], Cees G.M. Kallenberg[1], Elisabeth Brouwer[1] and Anneke Spoorenberg[2]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]Medical Center Leeuwarden, Leeuwarden, Netherlands

Background/Purpose: The Ankylosing Spondylitis Disease Activity Score (ASDAS) has been developed to assess the full concept of disease activity with aspects of both subjective and objective nature. Recently, the cut-off values for ASDAS improvement were defined. Our aim was to assess the percentage of AS patients achieving ASDAS improvement, in comparison to ASAS and BASDAI response, after tumor necrosis factor-alpha (TNF-α) blocking therapy in daily clinical practice.

Methods: Between November 2004 and April 2010, 217 consecutive AS outpatients from the MCL and UMCG who started TNF-α blocking therapy because of active disease were included in the GLAS study, a prospective longitudinal observational cohort study. All patients fulfilled the modified New York criteria for AS or **the** ASAS criteria for axial spondyloarthritis. Infliximab (n=31) (5mg/kg) was administered intravenously at 0, 2, and 6 weeks and then every 8 weeks; etanercept (n=135) (50mg once a week or 25mg twice a week) and adalimumab (n=51) (40mg on alternate weeks) were given subcutaneously. After 3 and 6 months, response to treatment was defined using ASDAS clinically important improvement (≥1.1 improvement in ASDAS-CRP), ASDAS major improvement (≥2.0 improvement), ASAS20 (≥20% and ≥1 unit improvement in ≥3 of the 4 domains physical function, pain, patient's global disease activity, and inflammation, with no worsening ≥20% in the remaining domain), ASAS40 (≥40% and ≥2 units improvement in ≥3 of 4 domains, with no worsening in remaining domain), and BASDAI50 (≥50% improvement in BASDAI).

Results: Mean age of the 217 AS patients was 42.9 years (SD±11.9), median disease duration was 15 years (range 1–53), and 69% were male. Mean ASDAS was 3.8 (SD±0.8) at baseline, 2.1 (SD±0.9) after 3 months ($p=0.000$), and 2.0 (SD±0.8) after 6 months ($p=0.000$) of treatment. After 3 months, 67% and 35% of patients achieved ASDAS clinically important and major improvement, respectively. After 6 months, these percentages were 66% and 38%, respectively. For ASAS and BASDAI response see Table 1.

Table 1. Percentage of AS patients achieving response after 3 and 6 months of TNF-α blocking therapy (n=217)

	3 months	6 months
Missing data	6 (3%)	12 (6%)
ΔASDAS ≥1.1	142 (67%)	135 (66%)
ΔASDAS ≥2.0	74 (35%)	78 (38%)
ASAS20	142 (67%)	129 (63%)
ASAS40	101 (48%)	94 (46%)
BASDAI50	102 (48%)	101 (49%)

Conclusion: Approximately two-third of the AS patients achieved ASDAS clinically important improvement and approximately one-third ASDAS major improvement after 3 and 6 months of TNF-α blocking therapy. These data indicate that the response rate for ASDAS clinically important improvement is comparable to ASAS20 response, while ASDAS major improvement seems to reflect response in fewer patients than ASAS40 and BASDAI50 response.

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European SCORE May Underestimate the Cardiovascular Risk in Psoriatic Arthritis: Comparison of Two Indexes and Related Variables. César Magro-Checa, José L. Rosales-Alexander, Juan Salvatierra Sr., Jesús Cantero-Hinojosa, Jose Gonzalez-Dominguez and Enrique Raya-Alvarez. University Hospital San Cecilio, Granada, Spain

Background/Purpose: EULAR task force recommendations in the cardiovascular (CV) risk have been recently published. In contrast to RA, in patients (pts) with Psoriatic Arthritis (PsA) the the Systematic Coronary Risk Evaluation (SCORE) is not adapted by introducing a 1.5 multiplication factor. EULAR recommends the use of the SCORE when no local guidelines are available. In our country the SCORE table has been calibrated by the National Cardiology Society. The objective was to assess the CV risk in PsA pts using the SCORE for low risk European countries (eSCORE) and compare it with the calibrated SCORE (cSCORE) according to our local guidelines. Furthermore, we analyzed the correlation of several clinical and serological variables with these SCOREs indexes and the percentage of pts that received adequate therapy for the management of CV risk.

Methods: This cross-sectional study included 125 consecutive pts who fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR criteria) followed in our outpatient clinics. Patients with a previous CV event were excluded. The following data were recorded for analysis: sex, age, body mass index, duration in months since diagnose, clinical pattern of the disease, classic CV risk factors, lipid profile, treatment and inflammatory markers. Both the eSCORE function model calculated on the basis of atherogenic index and the cSCORE on the basis of total cholesterol, were compared. According to our national guidelines, a high CV risk has been defined by a SCORE $\geq$ 5%, the cutoff point recommended to start treatment.

Results: Based on the classic CV risk factors, the eSCORE was 1,21 $\pm$ 1,62% (mean $\pm$ standard deviation) and 4 pts (3.2%) were above the threshold of high or very high CV risk ($\geq$5%). After applying the cSCORE, the values were 2 $\pm$ 2,55% which meant a change in the eSCORE in almost 70% of the pts. Therefore, 17 pts (13,6%) were reclassified above the threshold of high and very high CV risk. Regression coefficient analysis showed that the average increased in the Spanish SCORE can be obtained by multiplying the SCORE function for low risk countries by 1.5 ($p < 0.000$). Multivariate regression analysis showed that the most important prognostic factor for predicting the SCORE was the age (Total R-square 68%, standardized beta 0,65; $p = 0,000$) followed by systolic blood pressure and smoking. Of notice, the ESR was also a prognostic factor of the SCORE. Analyzing the percentage of pts that received adequate therapy for the management of CV risk, according to the eSCORE 100% and 50% of high and very high risk pts respectively were treated adequately, but when pts were reclassified with cSCORE, this percentage decreases to 64,7% and 35,3% respectively.

Conclusion: Assessment of the CV risk in PsA pts applying the eSCORE leads to an underestimation of the risk in comparison with the application of the cSCORE, which may have an impact on the correct management of these pts. According to EULAR, it seems that PsA is not considered by itself as a CV risk factor, in contrast to RA, when using the eSCORE. Variable analysis showed that ESR, but not CRP, was a prognostic factor of the SCORE what suggests that sustained inflammation could play a role in the increase of CV risk.

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The Relation Between Daily Physical Activity Measured with the Accelerometer and Clinical Assessments in Patients with Ankylosing Spondylitis. Suzanne Arends[1], Marianne Hofman[1], Yvo P.T. Kamsma[1], Eveline van der Veer[1], Martha K. Leijsma[1], Pieternella M. Houtman[2], Cees G.M. Kallenberg[1], Anneke Spoorenberg[2] and Elisabeth Brouwer[1]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]Medical Center Leeuwarden, Leeuwarden, Netherlands

Background/Purpose: Intervention studies concerning exercise programs and physical therapy in Ankylosing Spondylitis (AS) have revealed positive effects on clinical assessments of disease activity, physical function, and spinal mobility. Until now, data concerning the amount of daily physical activity (i.e. household, work, transport, and leisure time activities) in relation to these clinical assessments are lacking. The aim of the present study was to investigate the relation between daily physical activity and clinical assessments of disease activity, physical function, and spinal mobility in patients with AS.

Methods: Fifty-five Dutch AS outpatients were included. All patients were over 18 years of age and fulfilled the modified New York criteria for AS or **the** ASAS criteria for axial spondyloarthritis. Clinical assessments of disease activity (BASDAI, CRP, ESR, and ASDAS), physical function (BASFI), and spinal mobility (occiput-to-wall distance, chest expansion, modified Schober test, lateral spinal flexion, and cervical rotation) were administered at the outpatient clinic. In succession, daily physical activity was assessed using the ActiGraph accelerometer during 7 consecutive days. The outcome of the accelerometer was expressed in average kilo counts per day (kcounts/day). Pearson and Spearman correlations were calculated between accelerometer outcome and clinical assessments.

Results: Mean age of the 55 AS patients was 44 years (SD$\pm$13), median disease duration was 17 years (range 2–54), and 62% were male. Median BASDAI was 3.2 (range 0.4–8.6), mean ASDAS was 2.2 (SD$\pm$1.0), and mean BASFI was 3.4 (SD$\pm$2.3), indicating mild disease activity and functional impairment. Daily physical activity, measured with the accelerometer, was negatively correlated with ESR ($\rho = -0.460$, $p<0.001$) and CRP ($\rho = -0.279$, $p<0.05$) and there was a trend suggesting a negative correlation with ASDAS ($r = -0.257$, $p=0.061$). Furthermore, daily physical activity negatively correlated with BASFI ($r = -0.274$, $p<0.05$) and positively correlated with the modified Schober test ($\rho=0.338$, $p<0.05$), lateral spinal flexion (left: $r=0.344$, $p<0.05$ and right: $r=0.385$, $p<0.01$), and cervical rotation (left: $\rho=0.358$, $p<0.01$ and right: $\rho=0.285$, $p<0.05$). No significant correlations were found between accelerometer outcome and BASDAI, occiput-to-wall distance, and chest expansion and accelerometer.

Conclusion: The present study indicates that higher daily physical activity, measured with the accelerometer, is related to lower disease activity, better physical function, and better spinal mobility in AS patients. Further studies are needed to investigate this relation.

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The Effectiveness of Leflunomide in Psoriatic Arthritis. Alhussain Asiri[1], Arane Thavaneswaran[2], Vinod Chandran[1], Gideon Kalman-Lamb[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: While the short term efficacy and safety of Leflunomide in psoriatic arthritis (PsA) was documented in a short term randomized controlled trial, its longterm effect and safety in "real life" clinical situation is not known. This study aimed to evaluate the effectiveness of Leflunomide alone and in combination with methotrexate in "real life" situation as well as their adverse effects.

Methods: At the PsA Clinic patients have been followed prospectively and are evaluated according to a standard protocol which includes a detailed clinical history including drug therapy, physical examination, laboratory and radiological assessments at regular intervals. All information is tracked on an oracle database. Leflunomide became available in 2002. PsA patients who received leflunomide alone and in combination with methotrexate were identified from the PsA clinic database. Effectiveness was defined by persistence on the medication, a $\geq$ 40% reduction in actively inflamed joint a $\geq$ 40% reduction in swollen joint count, and PASI50 and PASI75 response following treatment with leflunomide. Univariate and multivariate logistic regression analyses with stepwise selection were used for data analysis.

Results: 84 patients were identified in our cohort. 43 patients (50.6%) were on Leflunomide alone and 42 (49.4%) patients were on Leflunomide in combination with methotrexate. There were 38 females and 47 males with a mean age of 51.6 (12.6) and mean disease duration of 12.3 (9.1). The mean number (sd) of actively inflamed joints count was 16(12.9), swollen joint count was 5.4(5.8), damaged joint count was 12.3 (13.0) and the mean PASI score was 4.7(6.5). 30 patients discontinued leflunomide, 16 in the leflunomide alone group and 14 in those taking leflunomide and MTX. The main reasons for discontinuing the drug were toxicity, including diarrhea, alopecia, and renal toxicity. Of the 54 patients who continued the drug, 38% achieved a $\geq$ 40% reduction of actively inflamed joint count at 3 months, 48% at 6 months and 56% at 12 months. PASI50 was achieved by 27%, 28% and 38% at 3, 6 and 12 months, whereas PASI75 was achieved by 19% at 3 and 6 months and 32% at 12 months. No predictors were identified for the improvement in actively inflamed joint count. However, duration of PsA (OR 1.09 95% CI 1.00, 1.18, $p=0.03$) and the number of swollen joints (OR 1.35, 95% CI 1.00, 1.83, $p=0.003$) at baseline were predictive for improvement of the swollen joint count at 3 months. The number of swollen joints at baseline was also predictive for improvement at 12 months (OR 2.01 95% CI 1.23, 3.27, $p=0.005$). The use of concomitant MTX was predictive for achieving a PASI50 (OR 6.19 95% CI 1.20, 31.97) at 12 months.

Conclusion: Leflunomide eventually led to ≥ 40% reduction in tender and swollen joint counts in almost 50% of the patients by 1 year. Those also taking MTX were more likely to achieve a PASI50 response. There was no significant difference in side effects between the Leflunomide group and Leflunomide and Methotrexate group.

1326

Validation of the Patient Acceptable Work State: Establishing Thresholds for Patient-Reported Outcomes in a Longitudinal, Observational Study in Patients with Ankylosing Spondylitis. Walter P. Maksymowych[1], Sumati Rao[2], Annelies Boonen[3], Naijun Chen[4] and Mary A. Cifaldi[2]. [1]University of Alberta, Edmonton, AB, [2]Abbott Laboratories, Abbott Park, IL, [3]University Hospital Maastricht, Maastricht, Netherlands, [4]Abbott Laboratories, Abbott Park, Illinois, Abbott Park, IL

Background/Purpose: Restrictions in paid and unpaid work are a feature of ankylosing spondylitis (AS) and are measured using several instruments that score impairment on a continuous scale, although the significance of these scores is unclear. It may be helpful to define work performance on a dichotomous basis as either satisfactory or not satisfactory using the concept of patient acceptable work state (PAWS). This approach would help to more easily identify patients with problems while at work and at risk for sick leave and work disability. In this study, we validated 3 questions that assess PAWS in relation to patient-reported outcomes.

Methods: Data were obtained from the Patient-Reported Outcomes in Employment Study (PROSE), a longitudinal, observational study of AS and work productivity. Patients with AS completed questions on work status and disease characteristics (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] and Bath Ankylosing Spondylitis Functional Index [BASFI]) at baseline, 3 months, 6 months, 9 months, and 12 months (5 time points). Patients also answered the 3 PAWS questions (yes/no): "Considering all the different ways your disease is affecting you, if you would stay in this state for the next few months, do you consider that: 1) your ability to perform your current job is satisfactory?; 2) you will continue to work in your present job?; and 3) you may need to stop working and go on sick leave or disability leave?" PAWS was considered present (PAWS+) if patients answered "yes" to Questions 1 and 2 and "no" to Question 3. We calculated thresholds for the BASDAI, BASFI, and Work Productivity and Activity Impairment Questionnaire (WPAI) domains according to the 75th percentile of scores in PAWS+ patients and assessed the stability of these thresholds over time.

Results: Of 226 surveys obtained, 172 (76.1%) were from AS patients employed at baseline. At baseline, 143 (83.1%) patients indicated they would be satisfied with their current job in the next few months, given their current disease state; 158 (91.9%) indicated they would continue working in their present job; and 149 (86.6%) indicated they would not stop working, given their disease state. Results remained consistent at Months 3, 6, and 12**.** The number of patients considered PAWS+ was 135 (78.5%) at baseline and this remained stable over time (80.0%–89.4%). WPAI threshold scores were stable over the 5 time points, especially WPAI presenteeism (20%), overall work impairment (25%–30%), and activity impairment (30%). Although threshold scores were relatively stable for the BASFI (3.3–4.1), stability was less apparent for the BASDAI (3.6–5.0) (table).

75th Percentile (95% Confidence Interval) of WPAI Domain Scores, BASDAI, and BASFI for PAWS Responders (Employed Patients Only)

	WPAI Presenteeism	WPAI Overall Work Impairment	WPAI Overall Activity Impairment	BASDAI	BASFI
Baseline (N=135)	20 (20, 30)	30 (20, 30)	30 (30, 40)	5.0 (4.3, 5.6)	4.1 (3.1, 4.8)
Month 3 (N=110)	20 (20, 20)	20 (20, 30)	30 (30, 40)	4.2 (3.7, 4.9)	3.6 (2.8, 4.4)
Month 6 (N=101)	20 (20, 30)	20 (20, 30)	30 (30, 40)	4.2 (3.4, 4.8)	3.8 (3.3, 4.7)
Month 9 (N=93)	20 (20, 30)	20 (20, 30)	30 (20, 40)	4.2 (3.3, 4.5)	3.3 (2.9, 4.3)
Month 12 (N=76)	20 (20, 30)	25 (20, 33)	30 (20, 30)	3.6 (3.3, 4.4)	3.6 (2.6, 4.5)

Conclusion: The relationship between PAWS and work impairment and function remained stable over time in patients with AS. There was a less stable association with BASDAI, suggesting that factors other than disease activity may influence satisfaction at work.

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The Predictors of Infection in Psoriatic Arthritis—Results From a Longitudinal Observational Cohort. Amir Haddad[1], Arane Thavaneswaran[2], Vinod Chandran[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Many patients with psoriatic arthritis are treated with immunosuppressives and biologic agents. Infection is a reported adverse event. The purpose of this study is to identify factors that could predict infection in patients with psoriatic arthritis (PsA) in contrast to a control group of patients with psoriasis without arthritis.

Methods: The PsA cohort was initiated in 1978. Patients fulfil the CASPAR criteria and are followed at 6–12 month intervals according to a standard protocol. In 2006 a cohort of patients with psoriasis without arthritis (PsC) was initiated. Patients with psoriasis were all assessed by a rheumatologist to exclude the presence of inflammatory arthritis, and are followed at yearly intervals according to a standard protocol. Data are tracked in a computerized database. From these observational cohorts data on infection and disease characteristic variables were collected prospectively in the respective databases. Multivariate analysis using generalized estimating equations was used to relate the probability of infection to potential predictor variables such as age, sex, PASI score, functional comorbidity index, actively inflamed joint count and treatment with NSAIDs, DMARDs, Biologics and phototherapy. Survival analysis was used to distinguish individual contribution of these predictors to infection.

Results: The PsA cohort included 695 patients with 607 reported infections, the most prevalent infection was pneumonia at 19.2%. The incidence rate of infection was 0.33 (95% CI 0.31–0.36) per patient-year but was higher among patients treated with biologic agents (0.44 (95% CI 0.39–0.50)). Patients with infections were less likely to be males (OR=0.42 95% CI 0.31–0.55) and more likely to be treated with biologics (OR=1.43 95% CI 1.07–1.91). Patients with pneumonia were more likely to be older (OR=1.73 95%CI 1.02–2.96). Patients with serious infections (that required antibiotics or hospitalization) were more likely to have a higher PASI score (OR=1.1 95% CI 1.04–1.16). Older age at visit and treatment with biologics predicted more infections in the PsA cohort with an estimate of 0.05 (95% CI 0.065–0.036) and 1.42 (95% CI −0.006–2.85) respectively. The PsC cohort included 511 patients with a total of 176 observed infections, the most commonly reported infection affected the skin at 12.1%, the incidence rate of infection was 0.29 (95% CI 0.25–0.30) per patient-year and was higher (0.66 (95% CI 0.39–1.04)) in patients on biologics. Patients with all infections were more likely to be younger at visit (OR=0.97 95% CI 0.94–0.99), less likely to be males (OR=0.58 95% CI 0.36–0.93) and had a Higher FCI (1.33 95% CI 1.1–1.6), no predictor was found to be associated with skin infections.

Conclusion: The positive predictors for infection in patients with PsA are female gender and treatment with biologics. These data prove the association between infection and biologic treatment in PsA.

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A Retrospective Analysis of Anti-TNF Treatment of 146 Ankylosing Spondylitis Patients According to Gender. Yasemin Yalcinkaya, Özlem Pehlivan, Ahmet Omma, Bahar Artim-Esen, Burak Erer, Nihat Hüseyinsinoglu, Sevil Kamali, Murat Inanc, Orhan Aral, Ahmet Gul and Lale Ocal. Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

Background/Purpose: To investigate disease characteristics according to gender differences in patients with ankylosing spondylitis (AS) receiving anti-TNF therapy.

Methods: This report evaluated retrospectively data of 146 patients with AS fulfilling modified New York criteria followed between 2001 and 2010, including demographics, symptoms, physical examinations, laboratory findings, complications and treatment details. Student's *t* test was used for comparison.

Results: The mean age of patients was 40.1 and 70% were males. Age at symptom onset, delay in diagnosis, disease duration(year) were 24.4, 5.8 and 15.8 respectively. The mean age at symptom onset(year) was significantly low in males (22.7 vs 28.3, $p<0.01$). The time interval between the onset of symptoms and anti-TNF therapy was >10 years in 89(61%), 5–10 years in 32(22%) and <5 years in 25(17%) patients. Females receiving anti-TNF therapy within 5 years were significantly high (23 vs 12%).

The mean duration of treatment (month) was 23.2 for infliximab(IFX)(n: 79), 21.4 for etanercept(ETN)(n:85) and 19.8 for adalimumab(ADA)(n:20). Switching to a second anti-TNF agent was 18%(n:26) and to a third agent 3%(n:5) for inefficacy (n:27), infusion reaction (n:5), uveitis (n:2), pulmonary tuberculosis(n:1) and psoriasis (n:1). Sixteen% of females and 19% of males required a second, 5% of females and 3% of males required a third agent (Table-1).

Initiation of anti-TNF agent due to axial involvement and high acute phase response were similar in females and males (96 vs 99% and 48 vs 52%). Peripheral arthritis and uveitis were more frequent in females (66 vs 37% and 4.5 vs 2%) whereas proteinuria/amyloidosis were more frequent in males(4 vs 2%).

In 12 patients (Table 1), dose reduction and cessation of anti-TNF therapy due to remission waspossible. Dose reduction was higher in males (7/102, 7% vs 1/44, 2%) and cessation was higher in females (3/44, 7% vs 1/102, 1%). The mean duration of treatment (month) in this group was 21 for infliximab(n:5) and 25.3 for etanercept (n:7); the time interval between the onset of symptoms and anti-TNF therapy was >10 years in 7(58%)(5 male), 5–10 years in 1(8%)(male) and <5 years in 4(33%)(2 male) patients. Termination due to complications (3 infusion reactions, 1 pulmonary tuberculosis, 1 hepatotoxicity, 1 pneumonia, 1 psoriasis) was significantly higher in males (n:6, 5.9% vs n:1, 2.3%).

Table 1. Details of anti-TNF treatment

	Females (n:44)	Males (n:102)
Dose reduction of anti-TNF therapy		
Satisfactory response	1 (2%)	7 (7%)
Cessation of anti-TNF therapy		
Remission	3 (7%)	1 (1%)
Complications	1 (2.3%)	6 (5.9%)
Switching to a second agent (n:26)	7 (16%)	19 (19%)
IFX → ETN (n:13)	3	10
ETN → IFX (n:6)	2	4
IFX → ADA (n:3)	–	3
ADA → IFX (n:2)	1	1
ETN → ADA (n:1)	1	–
ADA → ETN (n:1)	–	1
Switching to a third agent (n:5)	2 (5%)	3 (3%)
ETN → IFX→ ADA (n:3)	1	2
IFX → ADA→ ETA (n:1	–	1
IFX → ETA→ ADA (n:1)	1	–

Conclusion: In AS patients receiving anti TNF therapy, males were younger and had dominantly axial involvement. The mean duration of anti-TNF treatment was 27,8 months and similar for each agent (ETN /ADA / IFX). Females received anti-TNF therapy earlier but both male and female patients had satisfactory responses to anti TNF treatment. Switching between anti TNF agents was similar in males and females. Complications related with treatment were frequent in males.

1329

Differences in Clinical and Inflammation Outcomes in Patients with Axial Spondyloarthritis of Shorter and Longer Disease Duration After One Year Treatment with Etanercept. Anja Weiβ[1], In-Ho Song[2], Kay-Geert Hermann[3], Christian Althoff[3], Bruce Freundlich[4], Martin Rudwaleit[5], Joachim Listing[1] and Joachim Sieper[6]. [1]German Rheumatism Research Centre, Berlin, Germany, [2]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [3]Charite Medical School, Berlin, Germany, [4]University of Pennsylvania, Philadelphia, PA, [5]Ev. Krankenhaus Hagen-Haspe, Hagen, Germany, [6]Charité – Campus Benjamin Franklin, Berlin, Germany

Background/Purpose: To investigate the influence of the disease duration on the outcome in patients with axial spondylarthritis (SPA)

Methods: 62 patients with axial SpA with a symptom duration of less than 5 years were treated with Etanercept (ETA) for one year, either with ETA until week 48 (n=40) or they were switched from sulfasalazine treatment in the first year to ETA in the second year from week 48 until week 108 (n=26), as part of the ESTHER trial (1). 52% of these patients had a diagnosis of radiographic axial SpA and 48% had radiographic sacroiliitis. The patients were stratified into two groups: less than 3 years and more than 3 years of symptom duration before inclusion into the trial. These two groups were compared for clinical, CRP and magnetic resonance imaging (MRI)-outcome parameters using analysis of covariance (ANCOVA) with baseline status as covariable. Spearman correlation coefficients are calculated to analyse the relationship between two variables.

Results: Clinical parameters such as Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis functional index (BASFI) and Bath ankylosing spondylitis metrology index (BASMI) showed significantly better improvement for short vs longer diseased patients (Table 1). The results for improvement of MRI inflammation score for sacroiliac joints (SIJ) and spine and for CRP showed no significant differences between the two groups (Table 1). In patients with SIJ score at baseline > 0 the change in BASDAI showed a correlation with the change in SIJ score in patients with a short disease duration (rho=0.4, p=0.05) and longer disease duration (rho=0.4, p=0.06). The correlation between spine score and BASDAI was weaker. Significant correlation between BASDAI and CRP was found for short diseased patients (rho=0.6, p=0.002) but not for longer diseased patients (rho=0.3, p=0.14). Interestingly, patients fulfilling the New York criteria for radiographic sacroiliitis did not differ from patients not fulfilling the criteria regarding change in BASDAI (p=0.97), BASFI (p=0.7), BASMI (p=0.21), CRP (p=0.93), MRI spine score (p=0.74) and MRI SIJ score (p=0.66).

Table 1. Mean outcome parameters at baseline, adjusted means under treatment with etanercept and adjusted mean changes from baseline. Adjustment was made for baseline status (95% confidence intervals (CI) were given).

	Means at baseline		Adjusted means under ETA therapy		Adjusted mean change (95% CI)		
Parameter	< 3 years n=32	>=3 years n=34	< 3 years n=32	>=3 years n=34	< 3 years n=32	>= 3 years n=34	p-value
BASDAI	5.0	5.4	2.5	3.4	2.7 (2.1, 3.3)	1.8 (1.2, 2.3)	0.028
BASFI	3.9	4.2	1.8	2.9	2.2 (1.7, 2.8)	1.2 (0.7, 1.7)	0.004
BASMI	1.9	2.1	1.4	1.9	0.6 (0.3, 0.9)	0.1 (−0.2, 0.4)	0.012
CRP	10.8	8.1	5.5	4.7	4.4 (1.6, 7.1)	5.3 (2.5, 7.8)	0.690
MRI spine score	1.3	2.2	0.99	0.7	0.9 (0.3, 1.4)	1.2 (0.6, 1.7)	0.470
MRI SIJ score	5.9	6.0	1.5	2.3	4.4 (3.7, 5.1)	3.6 (2.9, 4.3)	0.090

Conclusion: In patients with early axial SpA treated with ETA for one year short diseased patients showed a better improvement in all clinical parameters such as BASDAI, BASFI and BASMI than longer diseased patients, but such a difference was not present for objective parameters of inflammation such as MRI inflammation and CRP. These data indicate that patients with longer symptom duration respond less well to TNF-blockade for reasons which go beyond structural damage.

[1] Song I.-H. et al. 2011. Ann Rheum Dis. 2011 Apr;70(4):590–6.

1330

Profiling NSAID Responders in Ankylosing Spondylitis. Khalid A. Alnaqbi[1], Nigil Haroon[2], Hua Shen[3], Richard J. Cook[3], Adele Carty[2] and R. D. Inman[4]. [1]Toronto Western Hospital-EW 1–420, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON, [3]University of Waterloo, Waterloo, ON, [4]The Arthritis Program, Toronto Western Hospital and Division of Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: There is a substantial subset of ankylosing spondylitis (AS) patients in whom symptoms are well controlled with NSAID therapy alone. This is an important domain, since failure to achieve symptomatic control with NSAIDS is the operational prerequisite for biologic therapy in AS. The current study was undertaken to characterize that subset of AS patients who are responsive to NSAID therapy.

Methods: The longitudinal prospective database of an AS cohort (patients was analyzed on the basis of response to NSAIDs. NSAID-responders (NS-R) were defined as having a BASDAI<4 on the last clinic visit while be treated only with NSAIDs. NSAID-nonresponders (NS-NR) were defined as having a BASDAI>4 on the last clinic visit while be treated only with NSAIDs **OR** as having required biologic treatment. AS patients met the modified New York criteria for AS and demographic, clinical and radiographic variables including BASDAI, BASFI, BASG, metrology, CRP, ESR, extra- articular manifestations, and mSASSS scores were compared to see if NS-R and NS-NR could be differentiated.

Results: In the cohort of 524 AS patients there were 136 NS-R and 388 NS-NR.

Clinical assessment **(Table)** indicated that NS-R patients had milder disease as reflected in: (i) better spinal mobility (ii) lower BASFI scores (iii) absence of peripheral joint involvement. However, this was *not* reflected in differences in mSASSS scores.

Comparative Features of NSAID-responders vs NSAID-nonresponders

Variable (mean ±SD)	NS-R	NS-NR	p
Occiput to wall, cm	2.7 (5.5)	4.9 (7.8)	<0.001
Lateral spine flexion, cm	16.8 (5.6)	12.8 (6.1)	<0.001
Chest expansion, cm	5.1 (2.4)	4.1 (2.2)	<0.001
BASFI	1.9 (1.8)	4.6 (2.8)	<0.001
BASDAI	2.6 (1.6)	5.7 (2.2)	<0.001
mSASSS	16.9 (23.4)	15.9 (21.9)	0.8
CRP	10.9 (12.5)	13.2 (21.6)	0.2
ESR	13.1 (14.5)	15.5 (15.6)	0.2
Disease duration, yr	7.5 (9.5)	9.3 (10.1)	0.06
Age, yr	39.3 (14.0)	39.7 (12.8)	0.8

The following parameters examined failed to identify differentiating features between NS-R and NS-NR: age, gender, HLA-B27 status, use of methotrexate or sulfasalazine, concomitant uveitis or psoriasis or IBD, CRP or ESR. There was a trend toward shorter disease duration but this was not statistically significant.

Conclusion: In our AS cohort, 26% of patients were NS-R, achieving a satisfactory symptomatic state with NSAID therapy alone. Of interest, the radiographic severity was no different in NS-R vs NS-NR, suggesting a disconnect between symptoms and radiographic damage. While NS-R patients manifested a milder disease profile, there was no clinical feature which predicted response to NSAID, raising the possibility that genetic factors may dictate this difference.

1331

Serum Kallikreins As Biomarkers in Psoriatic Disease. Azza Eissa[1], Dafna D. Gladman[2], Arane Thavaneswaran[2], Fawnda Pellett[3], Eleftherios Diamandis[1] and Vinod Chandran[3]. [1]Mount Sinai Hospital, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON, [3]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: There is high prevalence of PsA in patients with psoriasis seen in dermatology clinics. Biomarkers may be helpful in screening psoriasis patients for PsA. Kallikrein-related peptidases (KLKs) constitute a single family of 15 highly conserved trypsin- or chymotrypsin-like serine proteases that regulate important pathobiological processes such as skin desquamation, remodelling of extracellular matrix and innate immunity. Our purpose was to investigate serum KLKs as biomarkers of psoriatic disease and PsA.

Methods: In phase 1, 52 patients with psoriasis and 26 healthy controls were recruited. Psoriasis was diagnosed by a dermatologist. 26 of these patients had PsA satisfying CASPAR classification criteria, and in the remaining 26 (PsC), PsA was excluded by a rheumatologist. Patients with PsC and PsA were group matched for age, sex and psoriasis duration, while controls were matched for age and sex. Blood samples were drawn at the time of assessment and serum levels of KLK5, KLK6, KLK7, KLK8, KLK10, KLK11 and KLK13 was determined using Immunofluorometric ELISA. In phase 2, KLKs that showed promise were investigated in an independent cohort of 100 patients with severe psoriasis, 50 of who had PsA. Statistical methods used included logistic regression and correlation analysis.

Results: The 52 patients with psoriatic disease had a mean age of 46 years and psoriasis duration of 17 years. Compared to controls, only increased serum levels of KLK8 [Odds ratio per unit increase (OR) 2.56, 95% CI (1.08, 6.12) p = 0.03] independently associated with psoriatic disease in a multivariate reduced model. Polychotomous logistic regression analysis to identify biomarkers that have differential association between the three subject groups (PsC, PsA and controls) showed that increased levels of KLK8 have significantly different effects when modelling PsC and PsA separately, controlling for age, sex and the other KLKs. However, logistic regression analysis comparing PsC with PsA did not show a significant difference in the serum KLK8 levels between PsC and PsA. Since KLK8 was identified as a marker for psoriasis, KLK8 levels were further investigated in patients with severe psoriasis defined as PASI score >8 (with or without PsA). KLK8 levels were significantly elevated in patients with both PsA and PsC when compared to controls. There was no difference in KLK8 levels between PsA and PsC (p=0.21). KLK8 levels significantly correlated with PASI score in all 100 patients (r= 0.52, P = <0.0001) as well as when patients with PsC (r= 0.43, P = 0.002) and PsA (r=0.60, P <0.0001) were considered separately. Logistic regression analysis adjusting for age, sex and duration of psoriasis showed that KLK8 levels do not discriminate between patients with PsA and PsC. In patients with PsA KLK8 did not correlate with actively inflamed joint count (p=0.35) or swollen joint count (0.12).

Conclusion: Serum KLK8 is a soluble biomarker for psoriatic disease and psoriasis severity, but does not differentiate between PsA and PsC.

1332

Comparison Between Psoriasis and Psoriatic Arthritis in An International Cohort. Dafna D. Gladman[1], Renise Ayearst[2], Vinod Chandran[2], Jan P. Dutz[3], John T. Elder[4], Christopher Ritchlin[5], Cheryl Rosen[2] and Proton Rahman[6]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Univ of BC, Vancouver, BC, [4]University of Michigan, Ann Arbor, [5]University of Rochester, Rochester, NY, [6]St. Claires Mercy Hospital, St. Johns, NF

Background/Purpose: Genetic and longitudinal data on psoriasis and psoriatic arthritis patients will provide essential information regarding pathogenesis, risk factors and disease outcomes in these relatively prevelant and related disorders. We therefore established collaboration among several groups from Canada and the United States with the support of a New Emerging Team (NET) grant from the Canadian Institutes of Health Research (CIHR) in 2008. The overall goal of this research network is to improve outcomes for patients with psoriasis and PsA. A central aim of the initiative is to compare the clinical features in patients with psoriasis without arthritis (PsC) and patients with psoriatic arthritis (PsA) included in the database.

Methods: A central component of the NET is that aRheumatologists collaborates with a dermatologist at each site. Five sites formed the core group, including 3 sites in Canada and 2 in the USA, and subsequently 3 other Canadian sites, and sites in Australia and Argentina were added. A web-based database was developed that includes a physician, patient and an investigation component. The physician component includes a complete history, general physical examination and detailed musculoskeletal and skin examinations. All investigators and assessors were trained with proper assessments tools as well as database structure. The patient component includes 8 instruments including the HAQ, SF-36, DLQI, fatigue severity scale, FACIT-fatigue, ASQoL, BASDAI, BASFI and a patient global assessment of disease activity (PGA). Laboratory information includes routine tests, rheumatoid factor, antinuclear factor and radiographs. PsC as well as PsA pts are recruited in each site. Descriptive statistics, t tests and chi square tests were used to analyze the data.

Results: To date, the IPART database has accumulated 2649 patients of whom 1847 have PsA and 802 have psoriasis without arthritis. A comparison between patients with PsA and patients with psoriasis uncomplicated by arthritis demonstrated that patients with psoriasis had longer disease duration compared to PsA (17 vs 15 years p=0.03) while patients with PsA had higher PASI scores (6.4 vs 5.7, p=0.02) and more frequent nail involvement (68.4% vs 48.2% p<0.001). While hyperlipidemia was more common among patients with psoriasis (19.1% vs 14.5%, p<0.001), hypertension was more common among patients with PsA (30.1% vs 24.1%, p<0.001). Depression was slightly more prevalent among patients with psoriasis than those with PsA. No statistically significant differences in the prevalence of diabetes, cardiovascular morbidity, or cancer was noted between the two groups.

Conclusion: An international web based database has been established to follow patients with psoriasis and PsA. Several demographic and disease related differences between patients with psoriasis and those with PsA were observed. This program will allow for the identification of patients with PsA early stages, and will provide detailed skin and joint phenotypes, outcome data and essential ascertainment data for genetic and biomarker studies.

1333

Prevalence of Autoimmune Diseases and Other Comorbidities in Patients with Psoriatic Arthritis in the United States. Frank Zhang[1], Annie Guerin[2], Genevieve Gauthier[2], Robert Day[1] and Zeba Khan[1]. [1]Celgene Corporation, Summit,, NJ, [2]Analysis Group, Inc., Montreal, QC

Background/Purpose: Psoriatic arthritis (PsA) is an immune mediated disease involving skin manifestations (psoriasis) and joint disease. Limited information has been published on the comorbidity profile of patients with PsA. This retrospective study aimed to estimate the comorbidity burden of patients with PsA, with a particular focus on autoimmune diseases.

Methods: In a large US representative administrative claims database (2004–2008), we identified adult patients with ≥2 PsA diagnoses (ICD-9 code: 696.0). PsA-free patients (i.e., patients without any reported psoriasis (ICD-9 code: 696.1) or PsA diagnosis from 2004 to 2008) were selected and matched to PsA patients in a 1:1 ratio by age and gender. Proportions of patients with mild PsA (i.e., patients who were either not treated, used

non-steroidal anti-inflammatory drugs or corticosteroids) or moderate-to-severe PsA (i.e., patients receiving disease-modifying anti-rheumatic drugs, including biologics) were reported. Patient demographic characteristics and comorbidity profile information, including the Charlson comorbidity index (CCI) score, the prevalence of autoimmune diseases, and an exhaustive list of other physical and mental comorbidities were compared between PsA and PsA-free patients using Wilcoxon signed-rank tests for continuous variables or McNemar tests for discrete variables.

Results: Among the 21,332 selected matched pairs, 53% were female and the mean age was 52 years (SD=12 years). In the PsA population, 35% had mild PsA and 65% had moderate-to–severe PsA. PsA patients had a higher mean CCI score compared to PsA-free patients (1.47 vs. 0.71; p<.01). Compared to PsA-free patients, PsA patients had a significantly higher prevalence of autoimmune diseases, including rheumatoid arthritis (49.1% vs. 3.1%), ankylosing spondylitis (7.0% vs. 0.8%), ulcerative colitis (1.3 vs. 0.6%), Crohn's disease (1.2% vs. 0.5%), and Sjogren's syndrome (1.1% vs. 0.1%) (all p<.01). PsA patients also had higher prevalence of other comorbidities, including hypertension (46.3% vs. 35.3%), chronic pulmonary diseases (18.9% vs. 12.2%), diabetes (18.8% vs. 12.5%), hypothyroidism (15.0% vs. 9.7%), deficiency anemias (13.3% vs. 7.1%), depression (9.4% vs. 5.8%), valvular diseases (8.6% vs. 5.4%), psychoses (8.0% vs. 4.7%), fluid electrolyte disorders (7.7% vs. 4.4%), solid tumor without metastases (6.4% vs. 5.5%), and peripheral vascular disease (6.2% vs. 3.7%) when compared to PsA-free patients (all p<.01).

Conclusion: PsA was associated with a substantial comorbidity burden, including a significantly higher prevalence of autoimmune diseases and other physical and mental comorbidities.

1334

Does Clinical Examination Underestimate Joint Inflammation In Patients with Psoriatic Arthritis? Dafna D. Gladman[1], Richard J. Cook[2], Lihi Eder[1], Anupam Wakhlu[3], Claire Riddell[4], Mikkel Ostergaard[5], Arane Thavaneswaran[1] and Vinod Chandran[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]University of Waterloo, Waterloo, ON, [3]CSM Medical University, Lucknow, India, [4]Antrim Area Hospital, Northern Health and Social Care Trust, Antrim BT41 2RL, Northern Ireland, Ireland, [5]Copenhagen University Hospital at Glostrup, Glostrup, Denmark

Background/Purpose: We aimed to determine the correlation between clinical examination, magnetic resonance imaging (MRI) and ultrasound (US) evaluation of actively inflamed joints in psoriatic arthritis (PsA). We hypothesized that MRI and US will detect inflammation in the peripheral joints in PsA more often than clinical examination, and that MRI will detect inflammation more often than ultrasound.

Methods: PsA patients with variable degrees of inflammation and damage were identified from the PsA clinic. Each patient was reviewed clinically by 4 rheumatologists, who agreed for each joint of the wrists, MCPs 1–5 and MTPs 1–5 whether it was tender, swollen, both tender and swollen, and/or damaged (defined as limitation of range of movement >20% of the range not related to the presence of joint effusion, the presence of joint deformities, subluxation, flail joints or ankylosis). US examination of the same joints was performed by an expert ultrasonographer, for the presence of synovial hypertrophy; joint effusion and power Doppler signal which were considered evidence of inflammation. Each patient underwent an MRI examination of the most affected area – either hand/wrist, or foot. MRI images were reviewed by an expert reader for inflammation (bone marrow edema, synovitis, or periarticular inflammation). The sensitivity and specificity of MRI and US, respectively, were calculated with the clinical consensus as the "gold standard". The sensitivity/specificity of US with MRI as gold standard was also calculated.

Results: 13 patients (6M, 7F) participated in the study with mean age of 51.3 yr (SD9.9), PsA disease duration of 9.8 yr (7.7), 10.8 (9.0) actively inflamed joints, and 14.3 (15.2) damaged joints. Inflammation was detected in 13/26 wrists by clinical examination of which 10 were also detected by US. However, US detected inflammation in 6 additional wrists not considered inflamed by clinical examination. In MCP joints, US and MRI consistently identified more inflamed joints than did clinical examination. However, in the MTP joints, (except for the 1st MTP) clinical examination identified more inflamed joints than US and MRI. MRI identified the 8 wrist joints detected by clinical examination, but also an additional 3 wrists. While MRI detected more inflamed wrists than did US, both detected the same *inflamed* MCP joints; whereas MRI detected more inflamed MTPs than did US. The sensitivity/specificity is depicted in the table.

Modality - Site	Sensitivity	Specificity
US vs clinical		
Overall	0.91 (0.84, 0.95)	0.28 (0.21, 0.35)
Wrists	0.77 (0.46, 0.94)	0.54 (0.26, 0.80)
MCPs	1.00 (0.89, 1.00)	0.12 (0.06, 0.21)
MTPs	0.89 (0.78, 0.95)	0.44 (0.32, 0.57)
MRI vs Clinical		
Overall	0.60 (0.47, 0.72)	0.53 (0.42, 0.65)
Wrists	1.00 (0.60, 1.00)	0.25 (0.01, 0.78)
MCPs	0.64 (0.41, 0.82)	0.53 (0.36, 0.69)
MTPs	0.47 (0.29, 0.65)	0.57 (0.40, 0.73)
US vs MRI		
Overall	0.87 (0.74, 0.92)	0.25 (0.15, 0.37)
Wrists	0.64 (0.32, 0.88)	1.00 (0.06, 1.00)
MCPs	1.00 (0.87, 1.00)	0.00 (0.00, 0.15)
MTPs	0.76 (0.56, 0.89)	0.42 (0.26, 0.59)

Conclusion: US and MRI identified more inflamed joints than were detected on clinical examination. However, many joints considered inflamed on clinical examination did not appear inflamed by imaging. Further work is required to determine whether joints labelled 'inflamed' clinically but "uninflamed" by imaging are actually inflamed, and whether inflammation identified by imaging but not by clinical examination, has clinically significant consequences.

1335

The Natural Course of Radiographic Progression in Ankylosing Spondylitis – Differences Between Genders and Appearance of Characteristic Radiographic Features. Xenofon Baraliakos[1], Joachim Listing[2], Anna von der Recke[1] and Juergen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]German Rheumatism Research Centre, Berlin, Germany

Background/Purpose: Although male patients are believed to suffer more by clinical and radiographic signs in ankylosing spondylitis (AS), only a few studies with limited numbers of patients tried to assess differences between genders in this disease. We here systematically analyze the radiographic progression of AS patients, based on gender differences but also on different progression velocities over time in a large cohort of patients.

Methods: Overall, 146 AS patients were retrospectively blindly analysed in at least two time-points within 6 years by using the mSASSS. Radiographic progression between time points was compared by multivariat analysis, after adjustment for baseline radiographic status and symptom duration. The Mann-Whitney-U test was used to compare the data between subgroups at single time points. Moderate radiographic progression was defined as two new syndesmophytes, slow progression as not more than one new syndesmophyte and fast progression as more than 2 syndesmophytes every 2 years of follow-up (FU).

Results: 114 patients (78%) were male. Overall, this cohort was similar to other cohorts with patients with established AS but included patients with more advanced disease: the time since first symptoms was 23.6±11.2 years (range 5 – 58 years) and the mean time since diagnosis was 22.6±12.1 years (range 2 – 55 years). The mean FU time was 3.8±1.7 years (range 1–6 years), and the mean number of consecutive FU visits with x-rays was 2.7 (range 2–6). The mean mSASSS was 19.7±18.6 units at baseline (BL) and 25.8±20.9 units at FU (p<0.001). The mean mSASSS progression was similar between males (6.4±8.8) and females (5.4±6.6), p=0.670. However, females showed a trend for higher progression in the cervical spine (3.4±5.6 mSASSS units vs. 2.9±5.2 in males, p=0.374) and males in the lumbar spine (3.5±6.4 vs. 1.9±3.2 in females, p=0.154). More females (53.1%) vs. males (33.3%) (p=0.035) showed new cervical syndesmophytes and more males (40.4%) vs. female (25%) (p=0.111) showed new lumbar syndesmophytes. More females (38%) than males (13%) showed moderate radiographic progression and more males (14%) than females (3%) showed fast radiographic progression, while slow and no progression was similar for both genders.

Conclusion: Radiographic progression in AS is similar between male and female patients but female AS patients show more cervical structural lesions, while males show overall more rapid progress.

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Comparative Analysis of Outcomes in Ankylosing Spondylitis: 6 Year Data From the DISTILLER Biologic Registry. Leonard C. Harty, Ciara A. Murray, Conor Fearon, Mairead Dockery, Ursula Fearon and Douglas J. Veale. Translation Rheumatology Research Group, Dublin, Ireland

Background/Purpose: To examine the clinical and serological features of Ankylosing Spondylitis (AS) patients treated with TNF inhibitors (TNFi).

Methods: Data was prospectively collected on 147 consecutive, unse-

lected AS patients treated with TNFi's, from 2004–2011. Patients also received physiotherapy and were reviewed 3 monthly for the first year of therapy and then annually. BASMI, BASDI and BASFI, chest expansion, HAQ, ESR & CRP scores were assessed. Kruskal Wallis and Mann-Whitney U tests were used to compare non parametric categorical and continuous data. Results are given as the mean unless otherwise specified.

Results: 147 AS patients were registered commencing TNFi therapy with a mean age of 45 (IQR 15) and mean disease duration of 11 years (IQR 13). 72% were male. 61% were current or ex-smokers. 42% were in employment. 35% were treated with adalimumab, 50% with etanercept, 14% with infliximab, 1% with golimumab. Mean first recorded BASDI for the whole cohort was 4.7 (IQR 3), BASFI 4.3 (3.8), BASMI 3.7 (2.6). There was no difference between the TNFi's either in speed of response or outcomes measured. Current smokers presented with significantly more spinal pain than never / ex-smokers ($p=0.045$). Women had significantly lower BASMI scores (2.9 v 4, $p=0.012$) at baseline yet had worse patient global health (6.7 v 5.5, $p=0.033$). Post-TNFi therapy women had higher BASDI (3.7 v 2.7, $p<0.001$) and BASFI (3 v 2.4, $p=0.032$) scores compared to men. In addition, women had higher scores for HAQ (.6 v.2, $p<0.001$), ESR (21 v 9, $p<0.001$), CRP (8 v 6, $p=0.047$) and patient global (5 v 3, $p<0.001$).

Conclusion: Female AS patients present with higher pain and disability despite better mobility, following TNFi therapy they continue to have higher disease activity and functional scores compared to male AS patients. AS patients who smoke have more pain at baseline.

ACR/ARHP Poster Session B
Spondylarthropathies and Psoriatic Arthritis - Pathogenesis, Etiology
Monday, November 7, 2011, 9:00 AM–6:00 PM

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Association of Platelet Endothelial Cell Adhesion Molecule-1 and β1 Integrin Gene Polymorphisms with Uveitis Development in Ankylosing Spondylitis. Seung Cheol Shim, Donghyuk Sheen, Mi-Kyoung Lim, Jiyoung Kim, Soyoung Lee and Sangkwang Lee. Eulji University Hospital, Daejeon, South Korea

Background/Purpose: Genetic factors provide over 90% of the overall susceptibility to ankylosing spondylitis (AS) and recent studies have focused on non-major histocompatibility complex genes. The etiology of uveitis in AS has been suggested to involve two adhesion molecules including intercellular adhesion molecule (ICAM)-1 and leukocyte functional antigen (LFA)-1.

Platelet-endothelial cell adhesion molecule 1 (PECAM1) is a member of the immunoglobulin superfamily which is expressed on endothelial cells. There is emerging evidence to suggest that PECAM1 may be an important regulator of antigen induced cell activation of lymphocytes. The β1 integrin (ITGB1) can associate with different membrane proteins and cause signal transduction by interactions in the extracellular and trans-membrane domain. Therefore, we examined the association of PECAM1 and ITGB1 gene polymorphisms with development of uveitis in patients with AS.

Methods: We conducted a case–control study where 223 AS patients who met the Modified New York criteria and 239 ethnically matched controls were genotyped for 9 single nucleotide polymorphisms (SNPs) in the PECAM-1 promoter and gene. Genomic DNA was isolated from peripheral blood leukocytes by a standard phenol–chloroform method and a GoldenGate assay (Illumina, http://www.illumina.com) was used for genotyping.

Results: Conditional logistic regression was used to evaluate the association between the PECAM1 or ITGB1 SNPs with susceptibility to AS, and no significant association was found on both genes. However, in the subgroup analyses between AS patients with uveitis and those without, seven SNPs in PECAM1 gene were associated with the presence of uveitis, including rs1050382 (dominant model (DM), $p=0.022$), rs2812 (recessive model (RM), $p=0.013$), rs4968721 (DM, $p=0.016$), rs6808 (DM, $p=0.011$), rs6809 (DM, $p=0.013$), rs9899806 (DM, $p=0.013$) and rs9913080 (DM, $p=0.019$) (Table 1). In addition, seven polymorphisms in ITGB1 gene including rs11009147 (DM, $p=0.012$; co-dominant model (CDM), $p=0.034$), rs17468 (DM, $p=0.012$; CDM, $p=0.019$), rs2153875 (CDM, $p=0.030$), rs2230396 (DM, $p=0.012$; CDM, $p=0.034$), rs2488330 (DM, $p=0.004$; CDM, $p=0.017$), rs3780871 (DM, $p=0.031$) and rs7079624 (RM, $p=0.004$; CDM, $p=0.017$) were associated with uveitis development (Table 2).

Table 1.

rs No.	Dominant Model Odds (95% CI)	Dominant Model P. Value (adj.P.)	Recessive Model Odds (95% CI)	Recessive Model P. Value (adj.P.)	Co-dominant Model Odds (95% CI)	Co-dominant Model P. Value (adj.P.)
rs1050382	2.170 (1.116–4.219)	0.022 (0.027)	0.456 (0.129–1.611)	0.223 (0.262)	1.314 (0.824–2.095)	0.250 (0.294)
rs11079538	1.623 (0.745–3.537)	0.222 (0.261)	1.289 (0.568–2.924)	0.543 (0.571)	1.345 (0.821–2.02)	0.238 (0.297)
rs2812	2.190 (0.620–7.736)	0.223 (0.247)	0.424 (0.215–0.837)	0.013 (0.024)	0.732 (0.457–1.173)	0.195 (0.300)
rs4968721	2.302 (1.167–4.541)	0.016 (0.022)	0.412 (0.117–1.446)	0.166 (0.237)	1.304 (0.820–2.075)	0.261 (0.290)
rs6808	2.406 (1.220–4.743)	0.011 (0.020)	0.456 (0.129–1.611)	0.223 (0.278)	1.379 (0.862–2.205)	0.178 (0.298)
rs6809	2.354 (1.193–4.641)	0.013 (0.020)	0.456 (0.129–1.611)	0.223 (0.297)	1.364 (0.852–2.184)	0.195 (0.279)
rs8065316	1.124 (0.490–2.578)	0.781 (0.822)	1.774 (0.908–3.468)	0.093 (0.155)	1.360 (0.848–2.180)	0.201 (0.268)
rs9899806	2.354 (1.193–4.641)	0.013 (0.022)	0.509 (0.143–1.813)	0.297 (0.330)	1.414 (0.876–2.283)	0.155 (0.282)
rs9913080	2.252 (1.141–4.443)	0.019 (0.025)	0.392 (0.112–1.373)	0.143 (0.220)	1.270 (0.800–2.016)	0.310 (0.326)

Table 2.

rs number	Dominant Model Odds (95% CI)	Dominant Model P. Value (adj.P.)	Recessive Model Odds (95% CI)	Recessive Model P. Value (adj.P.)	Co-dominant Model Odds (95% CI)	Co-dominant Model P. Value (adj.P.)
rs11009147	0.436 (0.226–0.839)	0.012 (0.021)	0.712 (0.273–1.858)	0.488 (0.596)	0.582 (0.353–0.960)	0.034 (0.046)
rs1187078	0.873 (0.261–2.921)	0.826 (0.865)	0.919 (0.486–1.737)	0.796 (0.834)	0.926 (0.560–1.531)	0.767 (0.804)
rs17468	0.436 (0.226–0.839)	0.012 (0.019)	0.563 (0.249–1.272)	0.167 (0.245)	0.589 (0.377–0.918)	0.019 (0.030)
rs2153875	0.527 (0.249–1.117)	0.094 (0.122)	0.465 (0.202–1.071)	0.072 (0.113)	0.582 (0.356–0.949)	0.030 (0.044)
rs2230396	0.436 (0.226–0.839)	0.012 (0.020)	0.712 (0.273–1.858)	0.488 (0.565)	0.582 (0.353–0.960)	0.034 (0.044)
rs2298141	1.340 (0.702–2.559)	0.374 (0.457)	3.718 (1.126–12.28)	0.031 (0.052)	1.508 (0.906–2.511)	0.113 (0.131)
rs2488330	0.390 (0.203–0.748)	0.004 (0.008)	0.712 (0.273–1.858)	0.488 (0.631)	0.546 (0.330–0.901)	0.017 (0.032)
rs2503997	1.278 (0.659–2.477)	0.466 (0.540)	1.308 (0.586–2.920)	0.511 (0.562)	1.205 (0.778–1.865)	0.401 (0.441)
rs3780871	0.268 (0.081–0.888)	0.031 (0.042)	0.745 (0.390–1.424)	0.374 (0.514)	0.662 (0.398–1.103)	0.113 (0.139)
rs7079624	1.403 (0.538–3.662)	0.488 (0.536)	2.560 (1.335–4.909)	0.004 (0.008)	1.830 (1.109–3.021)	0.017 (0.030)

Conclusion: This is the first analysis of the PECAM1 and ITGB1 gene polymorphisms in AS, demonstrating a clear association with uveitis in AS. Given the functional role of PECAM-1 and ITGB1 variants in the immune system, larger studies are now warranted to elucidate the association of PECAM-1 and ITGB1 in the pathogenesis of uveitis in AS.

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Predictive and Protective Value of Biomarkers in Patients with Ankylosing Spondylitis Who Are At High Risk of Radiographic Spinal Progression. Denis Poddubnyy[1], Kristina Conrad[2], Gisela Ruiz-Heiland[3], Uta Syrbe[2], Hildrun Haibel[2], Heiner Appel[2], Martin Rudwaleit[4], Georg Schett[3] and Joachim Sieper[2]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Charité – Campus Benjamin Franklin, Berlin, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]Ev. Krankenhaus Hagen-Haspe, Hagen, Germany

Background/Purpose: In the recent years several biomarkers have been found to be associated with radiographic spinal progression/syndesmophyte formation in ankylosing spondylitis (AS): matrix metalloproteinase 3 (MMP-3) and C-reactive protein (C-RP) (positive association), sclerostin (SOST), Dickkopf 1 (DKK1), and periostin, (negative association). However, it is not clear, whether these biomarkers are also able to predict new bone formation in AS patients who are at high risk of radiographic progression due to a presence of syndesmophytes at baseline. The objective of the study was to to investigate the association of biomarkers with radiographic progression (new syndesmophytes formation or growth of the existing syndesmophytes) in patients with AS with and without radiographic damage at baseline.

Methods: Altogether 97 patients with AS from the German Spondyloarthritis Inception Cohort (GESPIC) were included in this analysis. Radiographs of the lumbar and cervical spine performed at baseline and after 2 years of follow-up were scored independently by two trained readers according to the mSASSS scoring system. Three groups of patients were defined according to the scoring results:

Group I (n=26): patients with syndesmophytes at baseline and new syndesmophyte or syndesmophytes growth after 2 years;

Group II (n=38): patients with syndesmophytes at baseline but without radiographic progression after 2 years;

Group III (n=33): patients without radiographic spinal damage at baseline and after 2 years.

Serum levels of the following biomarkers were examined: MMP-3, CRP, SOST, DKK1, periostin, C-terminal cross-linked telopeptide of type II collagen (CTX-II), bone alkaline phosphatase, sRANKL, osteoprotegerin, N-terminal telopeptide of type I collagen, procollagen type I and II N-propeptide (PINP and PIINP), bone sialoprotein and cartilage oligomeric matrix protein.

Results: There was a statistically significant difference between Group I and Group II in the serum levels of MMP3, CRP and PIINP (table), indicating that higher serum levels of these biomarkers might be associated with active progression of spinal structural changes in the patients who are at high risk of

such a progression. At the same time, higher levels of SOST, DKK-1, periostin, and CTX-II might be protective regarding radiographic spinal progression in AS since the highest level of these markers were found in patients without syndesmophytes neither at baseline nor after two years despite high levels of CRP, MMP3 and PIINP (table). None of the other investigated biomarkers showed an association with radiographic spinal progression.

Table. Baseline serum levels of biomarkers in three groups of patients AS defined according to the presence of syndesmophytes and their progression over 2 years.

Biomarkers	Group I: baseline syndesmophytes, progression	Group II: baseline syndesmophytes, no progression	Group III: no syndesmophytes, no progression	p (Kruskall-Wallis test)
MMP-3, ng/ml	30.3 ± 25.9*	14.4 ± 19.7	25.5 ± 34.2	0.020
CRP, mg/l	17.1 ± 17.1*	8.7 ± 9.9	11.7 ± 22.8	0.152
PIINP, ng/ml	175.4 ± 81.6*	133.5 ± 82.5	233.3 ± 237.7	0.099
CTX-II, ng/ml	1259 ± 1082	2464 ± 3078	7170 ± 11097*§	0.002
SOST, ng/ml	0.15 ± 0.4	0.8 ± 2.4	3.5 ± 6.3*§	0.002
DKK-1, ng/ml	4.7 ± 2.1	5.4 ± 5.3	9.8 ± 6.9*§	0.038
Periostin, ng/ml	46.3 ± 78.5	106.8 ± 151.8	243.7 ± 201.2*§	<0.001

* $p < 0.05$ vs. Group II; §$p < 0.05$ vs.Group I.

Conclusion: Higher levels of MMP-3, CRP and PINP may predict further radiographic spinal progression/new bone formation in patients with AS already having syndesmophytes, while higher levels of SOST, DKK-1, periostin and CTX-II might play a protective role.

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Increased T Cell Receptor Clonotype Sharing Among Ankylosing Spondylitis Patients Revealed by Deep Repertoire Sequence Analysis. Malek Faham[1], Victoria Carlton[1], Martin Moorhead[1], Jianbiao Zheng[1], Tom Asbury[1] and R. D. Inman[2]. [1]Sequenta, Inc., San Francisco, CA, [2]The Arthritis Program, Toronto Western Hospital and Division of Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: Of all rheumatic diseases, ankylosing spondylitis (AS) exhibits the strongest HLA association, with over 90% of AS patients carrying the class I MHC allele HLA B27. Since the canonical role for class I MHC is peptide presentation to T cells, the HLA-B27 relationship in AS has implicated a T cell response restricted by this antigen presentation function. By implication, this has also suggested that a specific antigen is important in the pathogenesis of the disease. This hypothesis would predict that specific T Cell Receptor (TCR) sequences would be shared among different AS patients.

Methods: We have developed a technology for large scale sequencing of TCRβ to assess the repertoire profile in individual samples. All TCRβ sequences are amplified from peripheral blood samples and >1 million TCRβ sequences are obtained to generate a comprehensive profile of the blood TCR repertoire at that time point. We have applied this new technology to determine whether AS patients have excess sharing of TCR sequences.

Results: We assessed TCRβ repertoire data obtained from blood samples of 16 individual AS patients, all of whom met the modified New York criteria for AS. This profile was compared with 16 patients with systemic lupus erythematosus (SLE), representative of another autoimmune disease with much lower HLA association. We counted clonotypes that are shared among each patient set (present in >7/16 patients) and found a significantly higher number of shared clonotypes among AS patients ($p = 5 = 10^{-4}$). Many of the shared clonotypes can be anticipated to be shared by chance, due to the small number of added bases in these clonotypes during the recombination to form the specific TCRβ sequence. Therefore we used a TCRβ repertoire data from 50 blood samples from 21 healthy individuals to filter out clonotypes that seem to be present in an appreciable number of these samples. We filtered clonotypes present in more than 3 of the normal samples to identify a shared specific clonotypes for each of the SLE and AS patients. We observed a significantly higher number of shared non-generic clonotypes among AS when compared to lupus patients ($p = 1.0 = 10^{-4}$). A number of these clones, present in 9/16 AS patients, seem highly specific as they were not present in another set of 50 unrelated individuals.

Conclusion: Using a novel deep repertoire sequence analysis, we provide evidence that there is a distinctive set of shared clonotypes in the T cell repertoire in AS patients. This sheds light on the immunological role of HLA B27 in AS, and lays the groundwork for defining the antigenic stimulus for this T cell response, as well as the application of TCR profiling in the diagnosis and clinical assessment of AS.

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Family-Based Association Study of SPA3, a New Susceptibility Locus for Spondyloarthritis on 6p11-q11. Félicie Costantino[1], Brigitte Izac[1], Gilles Chiocchia[2], Roula Said-Nahal[3], Ariane Leboime[3], Elena Zinovieva[1], Diana Zelenika[4], Maxime A. Breban[3] and Henri-Jean Garchon[1]. [1]Institut Cochin, Paris, France, [2]Institut Cochin, 75014 Paris, France, [3]Ambroise Paré Hospital, Boulogne-Billancourt, France, [4]Centre National de Génotypage, Evry

Background/Purpose: Spondyloarthritis (SPA) is a highly heritable disease with a major genetic susceptibility factor, the HLA-B27 allele. Genome-wide association studies have revealed an involvement of other genes such as IL23R or ERAP1. Nonetheless, a significant fraction of the genetic predisposition to SpA remains to be explained. One major interest of linkage studies is their potential to capture loci with low-prevalence disease susceptibility alleles. However, to date, such studies have identified few non-MHC loci in SpA. Only one of these, called SPA2, could be replicated. More recently, in a new whole-genome linkage study, we mapped three novel loci on 6p11-q11, 13q13 and Xqter (LOD score of 5.21, 4.06 and 5.94 respectively; *Arthritis Rheum* 2009,60:S436). The aim of the present study was to investigate the 6p11-q11 region by means of association analyses.

Methods: The discovery cohort was the same as that used in the whole-genome linkage study and comprised 904 subjects from 154 families with multiples cases of SPA. A replication cohort comprised 136 independent trios. Demographic and disease characteristics were comparable between the 2 cohorts. Genotyping was performed using Affymetrix® 250K single-nucleotide polymorphisms (SNP) arrays in the discovery cohort and using Taqman® assays in the replication cohort. Family-based association analyses of the 6p11-q11 region were done using UNPHASED. In the discovery cohort, 1,494 SNPs located between 50Mb and 70Mb from the p-telomere were tested. Bonferroni correction was used to adjust for multiple comparisons (significance threshold: 3.3×10^{-5}).

Results: No SNP reached the significance threshold in the single-locus association analysis in the discovery cohort. We therefore re-analysed a subset of 87 trios drawn from the 53 families of the discovery cohort showing strongest linkage to 6p11-q11 (pLOD > 0.15). We identified a group of 4 SNPs (rs283552, rs9349565, rs6921803 and rs2273120) forming 2 significantly associated haplotypes, one predisposing (GTCC) and the other protective (GTTT). We confirmed these associations in the replication cohort (Table). The 4 SNPs were not in linkage disequilibrium with HLA-B27 that is 20 Mb away ($r^2<0.05$). They encompass the IL17A and F genes and other loci relevant for SpA pathogenesis. Fine mapping of the region covered by the 4 SNPs is underway.

	Linked families (87 trios) Global p = 8.7×10^{-8}			Replication cohort (136 trios) Global p = 0.05			Combined (223 trios) Global p = 2.4×10^{-5}		
Haplotype	T	U	p	T	U	p	T	U	p
GTCC	0.28	0.12	8.9×10^{-5}	0.16	0.07	0.005	0.21	0.10	2.4×10^{-5}
GTTT	0.005	0.10	0.004	0.06	0.10	0.06	0.04	0.11	6.0×10^{-4}

Conclusion: We identified 2 haplotypes associated with SPA in the recently linked 6p11-q11 region. These data extend the linkage findings and altogether, these provide evidence for a new SPA locus called SPA3. Our study emphasizes the interest of family-based studies to uncover new genetic factors in SPA.

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Highly Expressed HLA-B27 Accumulate in Subcellular Vesicular Compartments and Form Oligomers That Behave Differently From HLA-B7. Cindy Jeanty[1], Adèle Sourisce[1], Aurore Wielgosik[1], Maxime A. Breban[2] and Claudine André[1]. [1]Institut Cochin, 75014 Paris, France, [2]Hopital Ambroise Pare, Boulogne, France

Background/Purpose: The HLA-B27 molecule is strongly associated with spondyloarthritis (SpA). This association has been largely studied, but mechanisms of pathology remain unclear. The HLA-B27 has an enhanced propensity to misfold and form aberrant disulfide linked heavy chain dimers in the endoplasmic reticulum (ER). Animal studies have helped to go deeper understanding the mechanisms in which HLA-B27 exerts its effects. Indeed, development of a spontaneous inflammatory disease resembling human SpA in transgenic rats is specific of HLA-B27 and correlates with high levels of expression of this

molecule. Our goal was to determine if and to what extent B27 homodimers are involved in this requirement of overexpression. We therefore monitored the intracellular trafficking of HLA-B27 focusing on its overexpression level.

Methods: To perform these studies, HeLa cells transfected with HLA-B*2702, −05 and −06 proteins fused at their C-ter to Renilla Luciferase (RLuc) or YFP were used. These allowed applying the Bioluminescence Resonance Energy Transfer (BRET) technique to study HLA-B27/HLA-B27 interactions *in situ*. Further aspects of the HLA-B27 processing (e.g. subcellular distribution, folding state, relative abundance of mono- and homodimers) were studied using classical techniques, including immunoblot, microscopy and flow cytometry. Cells transfected with HLA-B*0702 fusion proteins were used as control.

Results: Monitoring the subcellular distribution of the HLA-B-YFP fusion proteins evidenced that misfolded HLA-B27 and -B7 proteins tend to accumulate in ERGIC-type (Endoplasmic Reticulum Golgi Intermediate Compartment) intracellular vesicles. This phenomenon correlated with an increased expression of the HLA-B proteins. For both, HLA-B7 and HLA-B27, BRET signals increased rapidly in HeLa cells cotransfected with HLA-B-YFP and -RLuc proteins due to heavy chain homodimerisation. Interestingly, at high levels of vesicle formation, BRET signals for HLA-B*2702 and −05 remained steady, whereas those for HLA-B*0702 and HLA-B*2706, a subtype weakly associated with SpA, strongly decreased in these high expression conditions.

Conclusion: Our results reveal that at a high expression levels, differences appear in the oligomerisation state between strongly SpA-associated HLA-B27 subtypes (B*2702, B*2705) and weakly or non-associated HLA-B alleles (B*2706, B*0702). The mechanisms underlying this differential behavior, possibly implying cellular responses such as UPR, autophagy or protein degradation, remain as yet unknown and are currently under investigation. These findings open new perspectives in understanding the pathogenicity of HLA-B27 proteins.

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Exacerbated Uveitis in the Context of IFN-Gamma Deficiency Is Ameliorated by Blockade of the Th17 Response in a murine model of Proteoglycan-Induced Arthritis and Spondylitis. Holly L. Rosenzweig[1], Jelena M. Kezic[1], Michael P. Davey[2], Stephen R. Planck[1], Tibor T. Glant[3] and James T. Rosenbaum[1]. [1]Oregon Health & Science University, Portland, OR, [2]Veterans Affairs Medical Center, Portland, OR, [3]Rush University Medical Center, Chicago, IL

Background/Purpose: Uveitis, or intra-ocular inflammatory disease, frequently occurs in patients with spondyloarthropathies such as ankylosing spondylitis. Despite the co-occurrence of uveitis and arthritis very little is understood of how the eye is predisposed to disease. Our prior data demonstrated discordant mechanisms of disease in the eye versus joints with respect to IFN-gamma in a murine spondyloarthropathy model of cartilage proteoglycan (PG) aggrecan induced arthritis and spondylitis. Here, we sought to elucidate the extent to which the Th17-related cytokines contribute to uveitis in the absence of IFN-gamma.

Methods: Female BALB/c IFN-gamma knockout (KO) mice also transgenic for the T cell receptor specific for a dominant epitope of the G1 domain of PG (TCR-Tg mice) were immunized with PG. Mice received weekly intraperitoneal injections of blocking antibodies to IL-17, IL-23p19 (unique chain for IL-23), or IL-23p40 (common chain for IL-12/IL-23) or isotype control antibodies (n=8–10 mice/group). Uveitis was analyzed by intravital videomicroscopy and histology at 3 weeks following immunization (peak occurrence of uveitis). The corresponding effects on the severity of arthritis were examined by clinical scoring and histology. Splenocytes from naïve, IFN-gamma KO/TCR-Tg or TCR-Tg mice were stimulated with 20 μg/ml recombinant G1 domain of PG, and cytokines were measured by multiplex ELISA 48h later.

Results: Cytokine analysis of supernatants from G1 domain-stimulated splenocytes revealed a significant increase in IL-17 production in the absence of IFN-gamma compared to wild-type counterparts, implicating a Th17 skewed response. Assessment of the contribution of Th17-related cytokines to uveitis in IFN-gamma KO mice revealed that blockade of any of the 3 cytokines (IL-17, IL-23p19, or IL-23p40) significantly reduced the leukocyte rolling, adherence and infiltration within the iris vasculature and tissue as assessed by intravital videomicroscopy. Histological analysis confirmed the diminished uveitis. Somewhat surprisingly retinal phototoxicity from the anti-IL-17 antibody treatment was noted, in that the photoreceptors were obliterated in ~50% of these mice. The incidence of phototoxicity was less in mice treated with either of the anti-IL-23 antibodies (~10%), and was never observed in mice injected with isotype-matched control antibodies. Akin to uveitis, the remaining arthritis in IFN-gamma KO mice was diminished as a consequence of treatment with any of the 3 blocking antibodies.

Conclusion: The data here reveal a critical regulatory role for IFNg in suppression of a Th17 response in the eye. In contrast to arthritis, IFN-gamma deficiency worsens uveitis and inhibition of Th17-related cytokines ameliorated eye disease. However, retinal phototoxicity was observed with anti-IL-17 therapy but to a lesser extent with anti-IL-23 targeted antibodies.

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Identification of Immunogenic HLA-B*27:05 Restricted Peptides of Salmonella Outer Membrane Protein (OMP) in Patients with Reactive Arthritis and Undifferentiated Spondyloarthropathy. Ramnath Misra[1], Amit Singh[1] and Amita Aggarwal[2]. [1]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]Additional Professor Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Lucknow, India

Background/Purpose: We have earlier reported that Salmonella OMPs are major immunogenic targets of synovial fluid lymphocytes of patients with *Salmonella* induced ReA/uSpA[1]. Since these group of patients have genetic predisposition to HLA-B*27 and its subtype HLA-B*27:05, we sought to identify HLA-B*27:05 binding Salmonella OMP peptides which are immunogenic in patients with ReA/uSpA.

Methods: Crude lysates of E coli, Salmonella typhimurium, Shigella flexneri, Y enterocolitica and OMP of S typthimurium were prepared. 125 HLA-B*27:05 binding Salmonella OMP peptides identified using Propred1 software were synthesized and grouped in 23 pools. These panel of antigens (5 and 10 μg/ml) and peptide pools (10 μg/ml) were cultured with 1×10^5 synovial fluid or peripheral blood mononuclear cells (SF/PBMC) from 23 patients with ReA/uSpA, 10 patients with RA and PBMC of 10 healthy individuals (controls) for 5 days in 96 well culture plate. Lymphocyte proliferation was assayed by tritiated thymidine uptake and IFN-γ levels in culture supernatant. A stimulation index (SI) of >2.5 was considered significant. Individual peptides from pools having significant response were retested against cryopreserved SFMC/PBMC to identify immunogenic peptides. HLA-B*27 and its subtypes were done by PCR using allele specific primers. A BLASTp program was used to search for similar peptides from protein bank of arthritogenic bacteria and human.

Results: SFMC of 19/23 patients with ReA/uSpA showed a significant proliferative response to Salmonella OMP but there was minimal response in PBMC (1/10) of ReA/uSpA, SFMC of RA (1/10) or PBMC from control (1/10). Nine Salmonella OMP peptides QRAEMLPTL, SRSGLNIAL, LRFLYAKSL, RLEGTWVKL, ARCIAPYAL, KLFLTTAAL, YRNSDFFGL, QRPAVRVKL and YRVGPGDVL showed significant response (Table 1). Response to QRAEMLPTL was mainly restricted to HLA-B*27:05 positive (6/7) patients. All immunogenic peptides had sequence similarity with peptides derived from arthritogenic bacterial proteins while 5 immunogenic peptides had similarity with peptides from evolutionary conserved human proteins.

Table 1. Sequence of individual immunogenic peptides, its protein and number of patients SFMC responded

Peptide No.	Pool No.	Sequence	Protein Details	No. of Patients responded
100	13, 9	QRAEMLPTL	outer membrane efflux-like protein, OprM (53 kDa) (485 aa) NP-459345	7
47	5, 19	SRSGLNIAL	putative outer membrane protein (205 kDa) (1869 aa) NP-461450	3
43	5, 15	LRFLYAKSL	outer membrane usher protein, FimD, (95 kDa) (870 aa) NP-459541	3
33	13, 2	ARCIAPYAL	outer membrane usher protein, FimD, (95 kDa) (870 aa) NP-459541	3
55	13, 6	LRLEGTWVK	putative outer membrane protein (51 kDa) (468 aa) NP-459672	2
108	9, 20	QRPAVRVKL	multidrug efflux system subunit MdtB (1040 aa) NP-461072	2
110	9, 22	KLFLTTAAL	putative outer membrane protein (11 kDa) (94 aa) NP_459160	2
121	19, 10	YRNSDFFGL	outer membrane protein F (40 kDa) (368 aa) NP_459974	2
125	22, 2	YRVGPGDVL	putative outer membrane polysaccharide export protein (41 kDa) (379 aa) NP461063	2

Conclusion: A set of 9 novel HLA-B*27:05 binding peptides of Salmonella OMP were immunogenic to SFMC of patients with ReA/uSpA. Immune response to these peptide targets could be useful for diagnosis in undifferentiated spondyloarthropathy.

References:

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Endoplasmic Reticulum Aminopeptidase 1 Interaction with Human Leukocyte Antigen B27 Influences the Unfolded Protein Response. Nigil Haroon[1], Aifeng Lin[2], Ali Akram[1] and Robert D. Inman[1]. [1]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [2]Toronto Western Research Institute and University Health Network, Toronto, ON

Background/Purpose: Endoplasmic reticulum aminopeptidase 1 (ERAP1) is second only to HLA B27 in the strength of genetic association with ankylosing spondylitis. We have reported a functional interaction of ERAP1 with alteration in MHC-I free heavy chain and HLA-B27-peptide presentation. An aberrant UPR response has previously been reported in B27-positive cells, but the influence of ERAP1 on that response has not been resolved. Here we report the influence of ERAP1 on unfolded protein response (UPR) genes in HLA B27 transgenic mice.

Methods: HLA-B27 transgenic mice (B27tg) were developed on a MHC double knock out (DKO) strain which lacked endogenous murine class I MHC. These mice were crossed with ERAP1 −/− mice to generate the HLA-B27-ERAP-KO mice (B27tgE-). ERAP1 is known to have variation in tissue level of expression with high levels in the liver. Mesenteric lymph nodes (MLN), spleen and liver were obtained from age-matched B27tg and B27tgE- before and 5 days after intra-gastric Yersinia infection. Yersinia enterocolitica 0:8 was delivered to the mice by intragastric tube at a dose of 10^7 organisms. RNA was extracted from tissues and subjected to quantitative PCR with primers specific for the following markers of UPR: Bip, CHOP, XBP-1 and GADD45. β-actin expression was used a control.

Results: There was consistent expression of all 4 genes of UPR in the tissues tested except for GADD45 expression in the spleen. In the liver which has the highest expression of ERAP1, the UPR genes were expressed at significantly higher levels in the B27tgE- compared to B27tg. The fold expression of the respective genes in the B27tg *vs* B27tgE- were: Bip (15.4 *vs* 30.2), CHOP (3.05 *vs* 4.9), XBP-1 (19.9 *vs* 53.9) and GADD45 (7.6 *vs* 12.2). The fold expression of UPR genes in the spleen were comparable between B27tg and B27tgE-: BiP (1.84 *vs* 1.70); CHOP (2.41 vs 2.20), XBP-1 (3.79 vs 3.52). MLN demonstrated higher expression of UPR genes in B27tg compared to B27tgE-: Bip (2.07 *vs* 1.21), CHOP: (1.96 *vs* 1.52), XBP-1 (2.78 *vs* 1.22), GADD45 (3.20 *vs* 1.27).

Following Yersinia infection, there was a downregulation of the UPR response genes, seen in both strains. In MLN and spleen, the degree of downregulation of UPR genes was comparable. However, in the liver the decrease in CHOP and XBP-1 following infection was significantly more pronounced in the B27tgE- (CHOP: 2.20 to 1.55 and XBP-1: 3.52 to 2.16) than in the B27tg (CHOP: 2.41 to 2.04 and XBP-1: 3.79 to 3.02).

Conclusion: ERAP1 variations and interaction with HLA-B27 results in functionally significant alteration of the UPR and show differential effects after gastrointestinal infection. The effects seen may be especially prominent in those tissue with higher endogenous ERAP1 expression.

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Phenotype of Resting and Activated Monocyte-Derived Dendritic Cells Grown From Peripheral Blood of Patients with Ankylosing Spondylitis. Gleb Slobodin[1], Aharon Kessel[1], Natalia Kofman[2], Elias Toubi[1], Itzhak A. Rosner[1] and Majed Odeh[1]. [1]Bnai Zion Medical Center, Haifa, Israel, [2]Technion, Haifa, Israel

Background/Purpose: Decreased levels of class II MHC expression and impaired formation of immunological synapse by dendritic cells (DCs) of HLA-B27 transgenic rats have been recently demonstrated. The resulting dysfunction of DCs may be implicated in the pathogenesis of the HLA-B27-related disease in transgenic animals. The phenotype of DCs in patients with ankylosing spondylitis (AS) has not been evaluated.

Methods: Monocyte-derived DCs (MDDCs) were grown from 5 HLA-B27 positive patients with active AS (mean BASDAI score 6.9, range 6.6–7.5) and 8 age-matched healthy volunteers. Surface expression of HLA-DR, co-stimulation molecules CD80, CD86 and CD40, as well as CD83 was assessed by flow cytometry and compared between the groups under 3 conditions: in resting state, after stimulation by lipopolysaccharide (LPS) and after stimulation by LPS in the presence of etanercept, a soluble receptor of tumor necrosis factor a.

Results: Lower baseline expression of class II MHC molecules (HLA-DR) was observed by MDDCs grown from AS patients, as compared to healthy subjects ($p=0.04$). A major increase in HLA-DR expression was observed in both AS and control groups upon LPS-induced activation ($p<0.01$ for both groups). However, the MDDCs grown from AS patients demonstrated higher rates of HLA-DR expression growth ($31.1\pm13.9\%$ vs $21.9\pm15.4\%$ growth in the control group), which minimized the difference between two groups as to the final levels of triggered HLA-DR expression. When added, etanercept decreased the rate of LPS-induced HLA-DR growth similarly in both groups ($8.7\pm6.3\%$ for AS and $7.5\pm4.7\%$ for control group). No difference between groups in the levels of expression of co-stimulation molecules and CD83 was observed.

Conclusion: Lower basic expression of class II MHC by the MDDCs grown from patients with AS may be associated with impaired regulation of their activity. Functional studies on DCs from patients with AS are needed to evaluate the integrity of their antigen-presenting function.

1346

Chondrocalcin, C-Terminal Propeptide of Type II Collagen, Can Be Found in Sclerotic Lesions of Spine and Its Gene Expression Is Significantly Increased in Patients with Ankylosing Spondylitis. Yong-Jin Kwon, Tae-Yeon Kim, Sang-Won Lee, Yong-Beom Park, Soo Kon Lee and Min-Chan Park. Yonse University College of Medicine, Seoul, South Korea

Background/Purpose: It has been suggested that chondrocalcin, C-terminal propeptide of type II collagen encoded by *COL2A1* gene, shows calcium-binding capacity and induces calcification of cartilage matrix. It can be found in great concentration in calcifying cartilage, such as hypertrophic zone of growth plate and deep articular cartilage, and acts as a nucleation core by binding to proteoglycan aggregates and initiating calcification. Abnormal calcification and pathologic new bone formation are the hallmark of ankylosing spondylitis (AS), but the role of chondrocalcin in syndesmophytosis of AS has never been investigated. The purposes of this study were to detect the production of chondrocalcin at the sites of enthesial inflammation and syndesmophytosis in patients with AS, and to investigate whether the expression of chondrocalcin mRNA is elevated in patients with AS.

Methods: Fragments of vertebral bodies of lower cervical spines were obtained from patients with long-standing AS during decompressive cervical laminectomy and facetetctomy and control vertebral fragments were obtained from patients with spondylolytic spondylolisthesis who underwent total facetectomy. The production and localization of chondrocalcin in the vertebral fragments from patients with AS was assessed by H&E staining and immunohistochemical staining using anti-chondrocalcin antibody and compared to those in control vertebral bony fragments. Peripheral blood mononuclear cells (PBMCs) were harvested and isolated from 46 patients with AS. The mRNA expression of chondrocalcin from PBMCs was measured by real-time quantitative RT-PCR, and then compared to those from patients with rheumatoid arthritis (RA) and healthy controls.

Results: The histological evaluation of the bony fragments of vertebral bodies from patients with AS revealed signs of severe enthesitis and sclerosis. Immunohistochemical analysis showed remarkably increased chondrocalcin deposition in inflamed and sclerotic areas of their vertebral bodies, compared to control vertebrae from patients with degenerative spondylosis. Real-time PCR analysis exhibited that the mRNA expression of chondrocalcin was significantly increased in patients with AS, compared to those from patients with RA and healthy controls.

Conclusion: In this study, we found that chondrocalcin was detected at the sites of inflammation and sclerosis of vertebral bony fragments and that chondrocalcin gene expression was significantly increased in PBMCs from patients with AS. These findings suggest that chondrocalcin can have a certain role in the process of syndesmophytosis in AS.

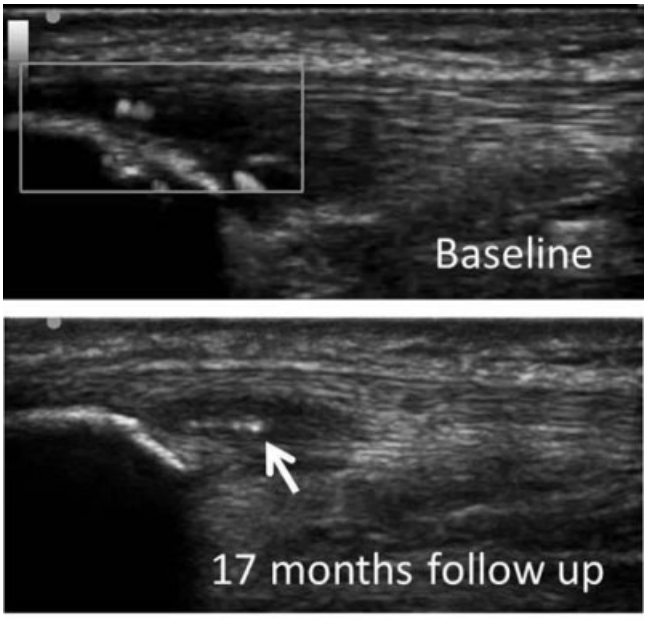
1347

Serial Ultrasonography Documents New Bone Formation At Entheses in Spondyloarthritis. Ralf G. Thiele[1], Bethany A. Marston[1], Darren Tabechian[2], Allen P. Anandarajah[3] and Christopher Ritchlin[1]. [1]University of Rochester, Rochester, NY, [2]Univ of Rochester Schl of Med, Rochester, NY, [3]Univ of Rochester Medical Ctr, Rochester, NY

Background/Purpose: Entheseal inflammation is a hallmark feature of spondyloarthritis (SpA). New bone formation is thought to be part of the pathogenesis of joint damage and ankylosis in SpA. A progression from enthesitis to new bone formation and joint damage has been postulated but is difficult to assess as a process in vivo. Conventional radiography cannot visualize tendons, and MRI may be less sensitive in detecting small calcifications than ultrasound (US). The aim of this study was to assess development of enthesitis in vivo using serial high resolution US.

Methods: 144 images and video clips of 8 clinically symptomatic and sonographically abnormal entheses in 7 patients with SpA (psoriatic arthritis, n=4; reactive arthritis, n=2; ankylosing spondylitis (AS), n=1) were obtained over 2 years (long and short axis views in gray scale and power Doppler, and video clips to document pulsatile flow). The 8 entheses included: origin of patellar ligament: n=3; insertion of Achilles tendon, n=4; insertion of medial collateral ligament of first metatarsophalangeal joint, n=1. US criteria for enthesitis were: 1) cortical irregularity at interface of ligament or tendon and bone; 2) pulse synchronous Doppler signal at interface and within body of tendon or ligament; 3) loss of densely packed fibrillar pattern with decrease of hyperechogenicity and increased thickness of tendon or ligament at insertion or origin (edema). Criterion for entheseal new bone formation was: hyperechoic material within body of tendon or ligament that was not seen on prior studies. All studies were performed by a rheumatologist certified in musculoskeletal ultrasound, with 20 years' experience. Transducer frequencies of 10–18 MHz were used. All patients underwent treatment: NSAIDs alone, n=1; methotrexate and NSAIDs, n=1, methotrexate and TNF-inhibitor, n=5.

Results: Inflammatory changes by US criteria decreased in all 8 entheses followed after 15–24 months: No more Doppler signal was seen at the entheses, hypoechogenicity and thickness had decreased in all at the time of the last study. CRP and ESR levels had remained within normal limits in all patients throughout the observation period, and were not suitable as markers of entheseal inflammation in our patients. Clinical entheseal pain was present in all at study entry and none at the time of the last US study. Newly formed hyperechoic material was eventually seen in all entheses (mean time to development 17 months). This calcific appearing material was present at the site of previously seen Doppler signal in all cases (Figure). In the case of AS, enthesitis led to calcification of a collateral ligament.



Conclusion: Within entheses, sites of deposition of calcified material correlate with sites of prior hyperemia. In AS, enthesitis preceded collateral ligament calcification in our study. Serial US can document disease development from enthesitis to new bone formation.

1348

Syndesmophyte Formation Is Associated with Low-Grade Spine Inflammation and Disconnected From Peripheral Arthritis in Mice Immunized with Recombinant Human Aggrecan G1 Domain. Mohamed Ramez, Toni S. Forde, Elena Kudryavtseva and Vyacheslav A. Adarichev. Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: The balance between inflammation-driven cartilage and bone erosion and new bone formation is set at different levels in rheumatoid arthritis and ankylosing spondylitis. Inflammation and tissue damage usually prepare the stage for the later repair process of new tissue formation like syndesmophytes and bone fusions in AS. To understand mechanisms of bone remodeling in inflammatory conditions, we developed a murine model of spondylitis induced with aggrecan immunizations.

Methods: Human aggrecan G1 domain (1–235 aa of ACAN-201) tagged with 6xHis was cloned using a baculovirus system, and the fusion protein was overexpressed in insect cells. Secreted rhAG1 protein was isolated using Ni-NTA resin. Protein identity and purity was characterized with SDS-PAGE and immunodetection. BALB/c females were immunized intraperitoneally with rhAG1 emulsified either in Complete Freund's adjuvant (CFA) or in dimethyldioctadecylammonium bromide (DDA) adjuvant or DDA alone. Mice were scored for visual signs of peripheral arthritis. Histopathology sections of paws and thoracic-caudal spines were stained with hematoxylin & eosin and alcian blue and examined for inflammation and intervertebral disk (IVD) afflictions.

Results: Mice immunized with rhAG1-DDA showed slightly higher arthritis severity than rhAG1-CFA group. Slowly progressive arthritis reached maximum after four immunizations. Histopathological examination of paw sections confirmed the presence of inflammatory cells, but severity of arthritis was rather mild. Despite the slow peripheral inflammation, histopathological assessment of spine sections revealed massive ventral chondroplasia of fibrocartilaginous annulus fibrosus-like cells that had been displacing anterior longitudinal ligament. Ventral aspects of enthesis, annulus fibrosus, and growth plate were mainly affected. Chondrophyte/syndesmophyte sizes reached up to 50% of the size of IVD. One to three syndesmophytes per every spine were observed in 20% of examined mice. The most affected regions were the junction of sacrum with lumbar and caudal parts of axial skeleton: S1-L6 and S4-Ca1. We observed consistent but low grade inflammation around afflicted skeletal regions that strongly correlated with spine chondrophytosis, r=0.81. Correlation between peripheral joints inflammation and syndesmophyte formation was much weaker, r=0.29.

Conclusion: A new murine model for syndesmophyte formation with disconnect between otherwise weak peripheral joints inflammation is developed. The balance between peripheral inflammation, spondylitis and chondrophytosis seems to be dependent on the source, biochemical properties and immunogenicity of the immunizing aggrecan antigen.

1349

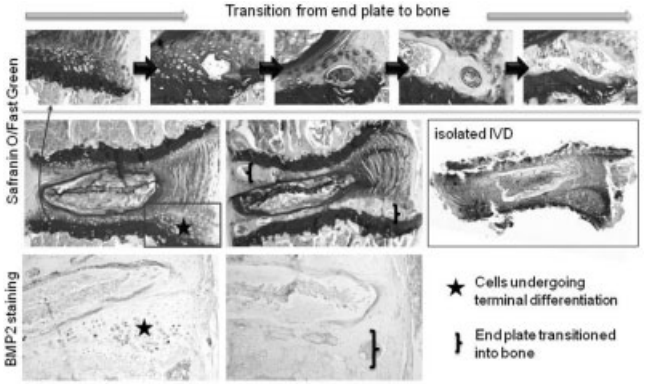
Transition From a Cartilage Phenotype Into Bone in the Intervertebral Disc End Plate in Ageing Mice: Role for Bone Morphogenetic Protein 2. Esmeralda N. Blaney Davidson[1], Elly Vitters[2], Wim B. van den Berg[1] and Peter M. van der Kraan[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands

Background/Purpose: Degeneration of the intervertebral disc (IVD) is considered an important source of back pain and affects 80% of the ageing population. The mechanisms underlying this age-related degeneration remain to be elucidated. Our present study is designed to study age-related changes in gene expression in IVD and to find clues whether changes in gene expression can explain age-related disc degeneration. We show that with age the end plate of murine lumbar spine undergo terminal differentiation followed by bone formation and accompanied by high mRNA expression of osteocalcin and intense BMP2 staining.

Methods: We isolated lumbar IVD of C57Bl/6 mice aged 4, 8, 12 and 20 months for RNA isolation and subsequent Q-PCR or whole spines for histology. A Q-PCR was performed evaluating the expression of aggrecan, collagen type I, collagen type II, collagen type X and osteocalcin and Id1. Values were corrected for GAPDH and calculated as a fold increase compared to 4 months of age. Paraffin sections were made from the whole spines and stained with Safranin O and Fast Green or immunohistochemistry was performed for BMP2.

Results: IVD used for RNA isolation partially contained the growth plate, the entire end plate, annulus fibrosus and nucleus pulposus (see figure). In these IVD aggrecan RNA decreased up to 1.9-fold by 20 months when compared to 4 months of age. Collagen type II increased 3.7 fold by 12 months of age and remained stable thereafter. Collagen type I also increased up to 4.5 fold by 12 months of age and reduced to 3.3 fold increase compared to 4 months of age. The most striking change was an increase in osteocalcin of 3.2 fold by 8 months, 5.4 fold by 12 months and even 6.1-fold by 20 months of age, indicated bone formation having its onset before 8 months of age.

To investigate the cause of this osteocalcin increase, we turned to histology and found hypertrophic differentiation in 6 month old end plate followed by replaced by bone eventually covering the entire growth plate (figure, middle part). As BMP2 is a major bone inducer we stained for BMP2 and found increased staining with age especially intense in the terminally differentiating end plate chondrocytes that are eventually replaced by bone (figure bottom left). On RNA level we found that Id-1 expression increased 1.4 fold at 8 months and 2.8 fold by 12 months of age and was stable after that when compared to 4 months of age.



Conclusion: We show age-related terminal differentiation in end plate chondrocytes which are eventually replaced by bone. This is accompanied by intense BMP2 staining in the hypertrophic cells and a sustained increase in osteocalcin and Id1 expression with age in the IVD. Our data strongly suggesting a role for BMP2 in bone formation in the IVD end plate with age. This phenomenon will contribute to age-related degeneration of the IVD.

1350

Simultaneous but Spatially Distinct Occurrence of Inflammation, Tissue Destruction and Osteoproliferation in the HLA-B27/Human beta2 Microglobulin Transgenic Rat Model of Spondyloarthritis. Leonie M. van Duivenvoorde[1], Martha L. Dorris[2], Nimman Satumtira[2], Paul P. Tak[1], Joel D. Taurog[2] and Dominique L. Baeten[1]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]UT Southwestern Medical Center, Dallas, TX

Background/Purpose: Spondyloarthritis (SpA) is characterized by inflammation as well as osteoproliferation of axial and peripheral joints. Clinical observations that TNF blockade halts inflammation and destruction but does not show a major impact on osteoproliferation raises the question of the exact relationship between these processes.

The objective of this study aimed to analyze the spatial and temporal relationship between inflammation, destruction and osteoproliferation in experimental SpA.

Methods: Histological samples were obtained from different stages of spontaneous tail spondylitis (n=10) and peripheral arthritis (n=9) in B27/hB2m tg rats[1]. Samples were formalin fixed and decalcified in EDTA. Paraffin sections were stained with H&E or toluidine blue and evaluated by two independent observers.

Results: In spondylitis, the first signs of mild inflammation were consistently found in loose connective tissue located at the junction of the annulus fibrosus with the vertebral bone. The inflammatory infiltrate contained numerous polymorphonuclear cells (PMNs). In moderately affected vertebral joints, inflamed tissue started to erode the bony endplate with appearance of multinucleated giant cells resembling active osteoclasts. In severe inflammation, this process gradually affected the cartilage growth plate and invaded the underlying bone marrow. Also here, numerous PMNs and multinucleated giant cells were observed. End-stage disease was characterized by an almost complete destruction of the intervertebral disc and the vertebral body, with persistence of inflammatory infiltration as well as osteoclastic bone resorption. Hypertrophic chondrocytes and new bone formation appeared at the stage of moderate inflammation and persisted at the stages of severe inflammation and end-stage destruction. Of interest, osteoproliferation was consistently found at the edge of the vertebral body, at a distance from the inflammatory and destructive process.

Peripheral arthritis was characterized by infiltration of synovial tissue with a similar predominance of PMNs. The inflamed pannus gradually invaded cartilage and bone and could also extend along the tendons, even though clear enthesitis was not observed. In contrast to the axial skeletal findings, pronounced infiltration of the bone marrow (osteitis) in the absence of synovitis was found in some cases. Both synovitis and osteitis contained multinucleated giant cells eroding the bone surfaces. Periosteal new bone formation was observed at different stages of inflammation.

Conclusion: Spontaneous spondyloarthritis in B27/hB2m tg rats is characterized by a destructive synovitis with PMNs and multinucleated giant cells rather than by enthesitis or osteitis. The simultaneous but spatially distinct appearance of inflammation and destruction versus osteoproliferation argues against the concept of reparative osteoproliferation after resolution of inflammation.

Reference:
Tran TM et al., Arthritis Rheum. 2006; 54(4):1317–27

1351

Inhibition of IL-17 by Antibody Administration Improves Onset of Tarsal Ankylosis In a Murine Model. Shin Ebihara and Masao Ono. Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan

Background/Purpose: Ankylosis is a major joint pathology of spondyloarthropathy (SpA). Therapeutic intervention against spontaneous progression of ankylosis has been investigated. There is recent accumulating evidence that IL-17 is involved in the pathogenesis of SpA. The aim of this study is to evaluate efficacy of anti-IL-17 therapy on a spontaneous tarsal ankylosis in mice.

Methods: The onset of tarsal ankylosis observed in male DBA/1 mice was assessed on footpad swelling and, in part, histopathological examination. Serum IL-17 concentration was determined by enzyme-linked immunosorbent assay. The periodic administration of anti-IL-17 antibody to male DBA/1 mice started before or after the ankylosis onset and weekly continued until experimental end point. Pathological changes and mRNA expressions were assessed for joints and skins obtained at experimental end point.

Results: Footpad swelling of male DBA/1 was frequently observed as previously reported and histopathologically characterized by entheseal arthropathy. These mice developed psoriasis-like dermatitis with ankylosis. Circulating IL-17 was found to increase with the onset of ankylosis. Prophylactic administration of anti-IL-17 antibody significantly prevented the development of both the ankylosis and dermatitis. On the other hand, its administration after the onset of diseases has partial effect only on the ankylosis but not dermatitis.

Conclusion: Tarsal ankylosis of male DBA/1 mice occurs and develops in an IL-17-dependent manner. IL-17 is a potential therapeutic target of ankylosing arthropathy in human.

1352

HLA Associations Reveal Genetic Heterogeneity in Psoriatic Arthritis and in the Psoriasis Phenotype. Robert Winchester[1], Gregory Minevich[1], Valeria Steshenko[1], Brian Kirby[2], David Kane[3], David A. Greenberg[4] and Oliver M. FitzGerald[2]. [1]Columbia University, New York, NY, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]Adelaide, Meath hospital Dublin (incorporating the National Children's hospital), Dublin 24, Ireland, [4]Mailman School of Public Health Columbia University, New York City, NY

Background/Purpose: Susceptibility to psoriasis (Ps) is clearly associated with *C*06:02,* but in psoriatic arthritis (PsA) the results of different studies on the role of HLA are quite disparate. Factors, contributing to the divergence in HLA allele frequencies in PSA include using serologic methods; the potential for case-control stratification and incomplete haplotype delineation in more admixed populations; and perhaps most importantly, the lack of proper case definition. We compared rigorously ascertained psoriatic arthritis cases presenting to a rheumatology unit with Ps cases without musculoskeletal features from a dermatology unit to address: (1) the extent to which the MHC contribution to PsA susceptibility resembles that of Ps; and (2) whether MHC genes determine quantitative traits within the PsA phenotype.

Methods: Separate discovery and validation cohorts for Ps (n=102 and 122) and PsA (n=197 and 162) recruited from the relatively homogeneous Irish population were studied by sequence-based HLA typing, comparing *HLA-B* and *HLA-C* allele and haplotype frequencies. In the Ps group musculoskeletal involvement was excluded by a rheumatology examination. Control cohorts included Irish blood donors, n=1000, and a local cohort (n=119) without family history of Ps. A significant association present in both discovery and validation cohort was considered definite, while an association in only one cohort was termed "preliminary".

Results: In PsA the frequency of *C*06:02* was lower, 28.7%, than in the Ps cohort, 57.5%, p=9.9exp-12. Three haplotypes containing *B*27:05* or *B*39:01* were significantly increased in frequency in PsA, but not in the psoriasis cohort allowing rejection of the hypothesis that the psoriasis phenotype is genetically homogeneous. Interestingly, the structurally related *B*39:06* allele was not increased. *B*27* was associated with an interval of 0.98 years between skin and musculoskeletal disease, p=2.05exp-6, versus 10.14 years for *C*06*. Preliminary evidence suggested *B*38:01* and *B*08* may be associated with susceptibility and that allotypes, including *B*40:01* and *B44:02*, but not *B*44:03*, encoding P2 pockets binding side chains opposite in charge from those encoded by *B*27* and *B*39* molecules exert a protective role.

Conclusion: The data suggest the psoriasis phenotype results from at least two patterns of MHC effect. The first involves the classic Ps susceptibility gene *C*06*, characterized by more penetrant skin disease with less prevalent and more time dependent musculoskeletal phenotype development. The second, appears mediated by HLA-B alleles, notably *B*27*, and includes temporally more coincident musculoskeletal involvement that is nearly equivalent in penetrance to skin disease.

1353

Differential Human Leukocyte Allele Association Between Psoriasis and Psoriatic Arthritis—A Family-Based Association Study. Lihi Eder[1], Fawnda Pellett[2], Vinod Chandran[2], Sutharshini Shanmugarajah[2], Shelley Bull[3] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Mount Sinai Hospital, Toronto, ON

Background/Purpose: Our recent population based study has identified several HLA alleles as conferring an independent risk for PsA among patients with psoriasis. We aimed to validate these results using a family based association study.

Methods: PsA probands, psoriasis probands and their 1st degree family members (parents and siblings) were included in this study. The PsA probands were part of the University of Toronto PsA cohort and satisfied the CASPAR classification criteria. Psoriasis patients without arthritis were part of a prospective cohort of psoriasis patients and were evaluated by a rheumatologist to rule out inflammatory arthritis. All family members were evaluated for the presence of psoriasis and inflammatory arthritis by a rheumatologist. Extracted genomic DNA was amplified by PCR using locus specific primers for each of the HLA-B and -C loci. PCR amplicons were identified by Sequence Specific Oligonucleotide probes using a reverse line blot technique. In order to identify specific markers for PsA, PsA probands were compared to their siblings with psoriasis. Healthy siblings were excluded from the analysis. Since the disease status of the parents is not relevant for calculation of the Family Based Association Test (FBAT) statistics they were included in the analysis irrespective of their trait. FBAT version 2.0.3 software was used for the analysis. A family based test statistic (Z value) and p value were calculated. Z of more than 0 indicates over-transmission of the allele, while Z of less than 0 indicates under-transmission. An additive model was specified. Only alleles that were present in 10 or more families were included in the analysis.

Results: Altogether, 178 PsA and 30 psoriasis probands and 561 first degree family members belonging to 208 families were analyzed. Of those, 4 families were excluded due to Mendelian errors. 49.7% of the probands had a positive family history of psoriasis and 20.8% of the probands had a family history of PsA. The following HLA alleles were significantly associated and over-transmitted to PsA compared to psoriasis: HLA-C*12 (p=0.005), HLA-B*38 (p=0.04), HLA-B*39 (p=0.045), HLA-B*27 (p=0.002) (Table 1). HLA-C*06, the strongest risk allele for psoriasis, was not significantly associated with PsA. However, the test statistics (Z) indicates under-transmission of the allele to PsA compared to siblings with psoriasis.

Table 1. Family based association test Affected (PsA probands)—Unaffected (Psoriasis) sib-pairs and Trios ($N_{families}$ = 204, $N_{Pedigrees}$ = 234)

Allele	Allele frequency	No. Families	Z	P value
HLA-B*07	8.7%	29	−0.8	0.4
HLA-B*08	13.6%	36	−1.4	0.15
HLA-B*13	4.3%	14	−1.2	0.24
HLA-B*14	3.5%	11	−0.03	0.97
HLA-B*18	2.7%	10	0.6	0.52
HLA-B*27	8.5%	33	3.1	0.002
HLA-B*35	7.5%	31	−0.7	0.48
HLA-B*38	4.7%	15	2.0	0.04
HLA-B*39	3.5%	13	2.0	0.045
HLA-B*44	12.8%	41	−0.6	0.57
HLA-B*51	4.1%	15	−1.0	0.29
HLA-B*57	5.7%	23	0.6	0.57
HLA-B*60	5.3%	17	−0.4	0.65
HLA-C*01	4.7%	19	1.4	0.14
HLA-C*02	5.7%	22	1.1	0.27
HLA-C*03	8.9%	27	−1.2	0.22
HLA-C*04	10.9%	37	−1.7	0.09
HLA-C*05	8.2%	26	0.8	0.42
HLA-C*06	12.7%	35	−0.6	0.57
HLA-C*07	27.7%	69	−1.0	0.32
HLA-C*08	3.9%	13	0	1
HLA-C*12	8.7%	28	2.8	0.005
HLA-C*15	2.4%	13	−1.2	0.21
HLA-C*16	3.7%	11	−0.9	0.36

Conclusion: HLA-B*27, B*38, B*39 and C*12 alleles are potential specific genetic markers for PsA among patients with psoriasis.

1354

Enhanced Expression of KIR3DL2 in Natural Killer and CD3/CD4 Positive T Cells of Ankylosing Spondylitis Patients Compared to HLA-B*2705 or B*2709 Healthy Subjects. Alberto Cauli[1], Grazia Dessole[1], Giovanni Porru[1], Alessandra Vacca[1], Matteo Piga[1], Valentina Ibba[1], Pietro Garau[1], Simon Kollnberger[2] and Alessandro Mathieu[1]. [1]University of Cagliari, Cagliari, Italy, [2]Weatherall Institute of Molecular Medicine, Oxford, United Kingdom

Background/Purpose: The precise role of B27 in Ankylosing Spondylitis (AS) has still to be clarified. Among the possible explanation it has been proposed that the expression of beta2-microglobulin(β2m)-free homodimers ($B27_2$) on the cell surface may allow the interaction with KIR3DL2 (which does not bind the β2m-associated B27). Furthermore KIR3DL1 and KIR3DS1 recognise the Bw4 serological epitopes which is present in HLA-B27 and may thus also be relevant. The aim of this study was to evaluate the expression of KIRs possibly involved in the pathogenesis of AS in subjects bearing the HLA-B27 associated and non-associated alleles (B*2705 and B*2709).

Methods: Eighteen HLA-B*2705 AS patients, none on anti-TNF-α treatment, 12 HLA-B*2705 and 12 HLA-B*2709 positive healthy subjects (NC) were recruited from a bone marrow donors bank. No cases of spondyloarthopathy were reported in the family medical history of the NCs. Expression of KIR3DL2, KIR3DL1 and KIR3DS1 was evaluated on peripheral blood CD3−/CD56+ natural killer (NK) cells and CD3+/CD4+ T lymphocytes. KIR expression was evaluated as the percentage of positive cells and as the density of receptor expressed on the cell surface by cytofluorimetric analysis and quantified by comparison with standard beads (antibody binding capacity, ABC units, Dako Denmark). The differences between AS and NCs were analysed by one-way ANOVAs with Bonferroni post test and a two-tailed unpaired t-test with Welch's correction.

Results: KIR3DL2. We observed an increased number of NK cells expressing KIR3DL2 in AS 34.1%, IQR 23.4–47.2 compared with B*2705 NC 21.5%, IQR 13.9–25.9 (p=0.0004) and B*2709 NC 17.3%, IQR 9.0–25.5 (p=0.0007). Furthermore we also observed higher expression of the receptor on the cell surface in AS patients 1354 ABC units, IQR 1091–2048 compared with B27*2705 NC 1062, IQR 806–1244 (p<0.0035) and B*2709 NC 1004, IQR 816–1288 (p<0.0067). Lower percentages of cells staining positively for KIR3DL2 were found among CD4+ T lymphocytes in AS and healthy subjects, but the differences between patients and controls were still statistically significant; in details: AS 1.5%, IQR 1.1–2.2, compared with B*2705 NC 0.8%, IQR 0.5–1.1 (p=0.01) and B*2709 NC 0.9%, IQR 0.7–1.1 (p=0.01). Higher density of KIR3DL2 expression was also detected on the cell surface of CD4 T cells from AS patients 1134 ABC units, IQR 921.5–1134, compared with B*2705 NC 884, IQR 746.3–979.8 (p=0.01) and B*2709 NC 833, IQR 670.8–1042 (p=0.02). We also investigated levels of expression of KIR3DL1 in patients compared with

the NC group but the differences were not statistically significant, both as a percentage of positive cells and as the density of receptors on the cell surface of NK. KIR3DS1 was found to be expressed by 37% of NK cells in only one B*2709 healthy control from the the 42 B27 expressin subjects studied (this subject was negative for KIR3DL1).

Conclusion: This study demonstrates higher expression of KIR3DL2 receptors on NK and CD3/CD4 positive lymphocytes from B*2705 AS patients compared to B*2705 and B*2709 NCs, supporting the possible role of the KIR3DL2/B27$_2$ pair as relevant players in the pathogenesis of AS.

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Binding of Killer Immunoglobulin Receptors 3DL1 and 3DL2 Is Associated with Surface Expression of Major Histocompatibility Complex Class I Free Heavy Chains and Human Leukocyte Antigen B27 Presenting Abnormal Peptides. Nigil Haroon and Robert D. Inman. Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: Ankylosing spondylitis (AS) is strongly associated with the HLA B27 subtypes B2704 and 2705 but not with 2706 and 2709. The basis for this important observation has not been defined. We have shown that the B27 subtypes differ in their interaction with ERAP1. Killer immunoglobulin receptors (KIR) KIR3DL1 and KIR3DL2 are known to bind MHC class I free heavy chain (FHC) dimers and could play a role in the pathogenesis of AS. The antibody MARB4 has been shown to detect HLA B27 presenting abnormally long peptides as well as FHC dimers. We addressed whether KIR3DL1 and KIR3DL2 binding correlates with the FHC expression on the cell surface, and whether that differs amongst the B27 subtypes. We also examined the correlation of KIR binding to MARB4 binding in the cell lines.

Methods: C1R cells transfected with different HLA-B27 subtypes (B2704, B2705, B2706, and B2709) were cultured in media till confluent. Cells were stained with the following antibodies: HC10 (for FHC), ME1 (for intact HLA B27), W6/32 (for intact MHC I) and MARB4 (for abnormal peptides). KIR3DL1-Fc and KIR3DL2-Fc chimeras were used in binding assays and detected using goat anti-human Fc IgG. Cells were acquired using a FACScalibur to analyse mean fluorescence intensity (MFI) and analysis performed using Flowjo software. Spearman's correlation was used to analyze the correlation of KIR3DL1 and 3DL2 binding to the binding of HC10, ME1, MARB4 and W6/32.

Results: Surface FHC expression was lower in B2706 and B2705 expressing cells than in the B2709 and B2704 cells: MFI of HC10 was 228 for B2704, 204 for B2705, 183 for B2706, and 262 for B2709. MARB4 MFI was higher in B2704, B2705 and B2709 cells than B2706 cells: 372 (B2704), 304 (B2705), 233 (B2706) and 461 (B2709). The correlations of KIR3DL1 binding with FHC and MARB4 expression were excellent at $R = 0.97$ ($p=0.01$) and $R = 0.96$ ($p=0.01$) respectively. KIR3DL2 bound cells also had excellent correlation with FHC ($R=0.98$; $p=0.01$) and MARB4 expression ($R=0.97$; $p=0.01$). There was no significant correlation of KIR3DL1 or 3DL2 binding cells with ME1 or W6/32 MFI. There was no clear differentiation of AS associated and non-associated B27 subtypes with regards to KIR3DL1 or 3DL2 binding.

Conclusion: KIR3DL1 and KIR3DL2 binding is associated with surface expression of FHC and with MARB4 staining. MARB4 might be detecting a subgroup of HLA B27-peptide complexes identified by KIR or might be reacting with FHC dimers. Further studies on functional impact of KIR binding in the pathogenesis of AS is required.

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GDF15, a Distinct TGFb Family Member, Is Differentially Regulated in Spondyloarthritides Compared to Other Rheumatic Diseases. Stijn Lambrecht[1], Julie Coudenys[1], Filip De Keyser[2], Gust Verbruggen[3], Dieter Deforce[4] and Dirk Elewaut[5]. [1]Ghent University, Ghent, Belgium, [2]Universitair Ziekenhuis Gent, Gent, Belgium, [3]Universitair Ziekenhuis, B-9000 Gent, Belgium, [4]Laboratory for Pharmaceutical Biotechnology, Ghent University, Ghent, Belgium, [5]Gent University Hospital, Ghent, Belgium

Background/Purpose: The transforming growth factor-β (TGF-β) superfamily consists of a number of cytokines that regulate a variety of cellular processes. Growth differentiation factor 15 is a distant member of this TGF-β family with limited sequence homology to other members of this group. Its role in inflammatory arthritis is unclear. This study aims to evaluate the role of GDF15 across various inflammatory rheumatic diseases.

Methods: GDF15 levels were determined by ELISA in three different populations. An exploratory study included serum samples from a consecutive cohort of 555 patients where serum was collected initially during diagnostic investigation. A second population constituted of patients with an indication for an arthroscopic procedure for diagnostic purposes. A third consisted of a cohort of RA-patients in which the efficacy of infliximab was evaluated. Synovial tissue biopsies and peripheral blood mononuclear cells (PBMC) were collected, RNA isolated and qPCR for GDF15 conducted. The effect of IL-1 and LPS on GDF15 transcription in PBMC was measured.

Results: In all cohorts, inflammatory rheumatic diseases showed elevated GDF15 levels, except SpA. Interestingly, these patients showed near normal GDF15 serum levels. SpA, but not RA-patients, show a significant higher concentration of GDF15 in synovial fluid compared to serum, pointing to a local production of GDF15 in the synovial joint. In line herewith, GDF15 mRNA levels were markedly higher in synovial tissue versus PBMC, even when stimulated with IL-1 or LPS. In general, no significant correlations were observed between GDF15 serum levels and inflammation markers (CRP, ESR), indicating that GDF15 serum levels might be indicative for a distinct underlying disease process. Moreover, suppression of inflammation by anti-TNFa treatment does not affect GDF15 serum levels.

Conclusion: GDF15 shows an intriguing distribution profile in rheumatic diseases, which is markedly differentially regulated between SpA versus RA and other rheumatic disorders.

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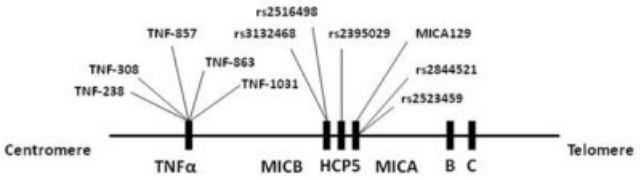
Extended Haplotypes Between Human Leukocyte Antigen-C and Tumour Necrosis Factor A Gene Loci Reveal Psoriatic Arthritis Susceptibility Hotspots. Remy Pollock[1], Fawnda Pellett[2], Renise Ayearst[2], Al Amin P. Rahman[3], Dafna D. Gladman[1] and Vinod Chandran[2]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Memorial University, St Johns, NE

Background/Purpose: Evidence suggests that while psoriasis is strongly associated with alleles of HLA-C, psoriatic arthritis (PsA) susceptibility may lie within the region centromeric to HLA-C that includes HLA-B, *MICA, HCP5, MICB*, and *TNFA* loci. Extensive linkage disequilibrium in the major histocompatibility complex makes identification of the exact PsA disease locus difficult. In carefully phenotyped cohorts of PsA, psoriasis, and control subjects, we examined the linkage of these loci and their putative role in disease susceptibility.

Methods: The following SNPs were genotyped in 451 Caucasian patients with psoriatic disease (PsD) (264 patients with PsA satisfying CASPAR criteria and 187 patients without arthritis (PsC)) and 183 Caucasian controls: rs2523459, rs2844521 (MICA); rs2395029 (HCP5); rs2516498, rs3132468 (MICB); and rs1799964 (TNF-1031), rs1800630 (TNF-863), rs1799724 (TNF-857), rs1800629 (TNF-308), rs361525 (TNF -238) (Figure 1). HLA-B and C typing was performed by PCR-SSO and MICA129Met/Val was assigned from allelic typing performed by PCR-SSP. The Cochran-Armitage trend test was used to identify alleles associated with (PsD) and PsA compared to controls, and differentiate PsA from PsC. Haplotypes were estimated using the EM algorithm and differences between subject groups were analyzed using GoldenHelix® software. Logistic regression was used to test for independent effects of linked alleles.

Figure 1. Map of the psoriatic disease susceptibility region on chromosome 6p21.3



Results: Psoriatic disease was associated with HLA-C*02, *06, *12, B*27, *38, *57, rs2526459, rs2844521, MICA129, rs2395029, and TNF-238. The following haplotypes were significantly associated with PsD: HLA-C*06/B*57/rs2523459C/rs2844521A/MICA129Met/rs2395029G/TNF-238A ($P = 0.01$, $OR = 2.2$), 12/38/C/A/Met/T/G ($P = 0.01$, $OR = 3.7$), and 2/27/C/A/Met/T/G ($P = 0.003$, $OR = 11.5$). Compared to controls, PsA was associated with HLA-C*02, *12, B*27, *38, rs2523459, rs2844521, MICA129, and rs2395029 and the haplotypes: C*12/B*38/rs2523459C/rs2844521A/MICA129Met/rs2395029T ($P < 0.01$, $OR = 4.4$) and 2/27/C/A/Met/T ($P < 0.01$, $OR = 19.4$). When comparing PsA to PsC, PsA was associated with HLA-C*02, *06, *07,

B*08, *27, *57, rs3132468, TNF-1031, TNF-863, TNF-308, and TNF-238 and the haplotypes C*07/B*08/ rs3132468T/TNF-1031T/TNF-863C/TNF-308A/ TNF-238G (P = 0.02, OR = 1.9), 2/27/T/T/C/G/G (P = 0.001, OR = 4.9), and 1/27/T/T/C/G/G (P = 0.03, OR = 3.7). Logistic regression showed that compared to controls, MICA129Met and HLA-C*06 were independently associated with PsD, while MICA129Met, HLA-B*27 and *38 were associated with PsA. Compared to PsC, rs3132468 (MICB) and TNF-863 were associated with PsA, independent of HLA-C*07, B*08, and B*27.

Conclusion: This study suggests that susceptibility haplotypes for PsD extend from HLA-C to *TNFA*, while hotspots for PsA susceptibility exist at HLA-B, *MICB*, and *TNFA*.

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Synovial Cytokine Expression in Psoriatic Arthritis and Associations with Lymphoid Neogenesis and Clinical Features. Raquel Celis[1], Raimon Sanmarti[1], Julio Ramirez[2], Antonio Palacin[2], Jose L. Pablos[3] and Juan D. Cañete[4]. [1]Clinic Hospital, Barcelona, Spain, [2]Hospital Clinic, Barcelona, Spain, [3]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [4]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain

Background/Purpose: Psoriatic arthritis (PsA) is an autoantibody-negative immune-mediated disease where synovial lymphoid neogenesis (LN) occurs. We determined whether LN is associated with specific patterns of inflammatory cytokine expression in paired synovial tissue (ST) and fluid (SF) samples and their potential correlation with the clinical characteristics of PsA.

Methods: ST and paired SF samples were obtained from the inflamed knee of 30 and 15 PsA patients, respectively. ST samples were immunostained with CD3 (T cell), CD20 (B cell), and MECA-79 (high endothelial vessels). Total ST mRNA was extracted and gene expression of CCR7, LT-b, IL-7, IL-10, IL-17A, IL-21, IL-22, IL-23, TNF-a, IL-1b, and IL-6 was measured by quantitative real-time PCR. IL-7, IL-10, IL-12, IL-17A, IL-22, IFN-g, IL-6, TNF-a and IL-23 levels in SF were quantified by ELISA. Clinical and biological data were collected at inclusion and after a median of 25 months follow-u

Results: 12 out of 30 patients (40%) had LN, which correlated with a significantly-higher expression of two molecular markers of LN, CCR7 and LT-b ($p<0.005$ and $p<0.038$, respectively). LN-positive patients had a non-significant trend towards higher IL-23 ($p=0.077$) and TNF-a ($p=0.075$) expression in ST and significantly-higher SF IL-6 levels ($p=0.048$). No other clinical or biological differences were identified in the LN group. In the whole study population, the expression of IL-1b, IL-6, IFN-g and IL-17 correlated with markers of disease activity.

Conclusion: PsA patients with LN show a trend towards higher expression of proinflammatory cytokines. The prognostic significance of this finding should be analyzed in prospective studies.

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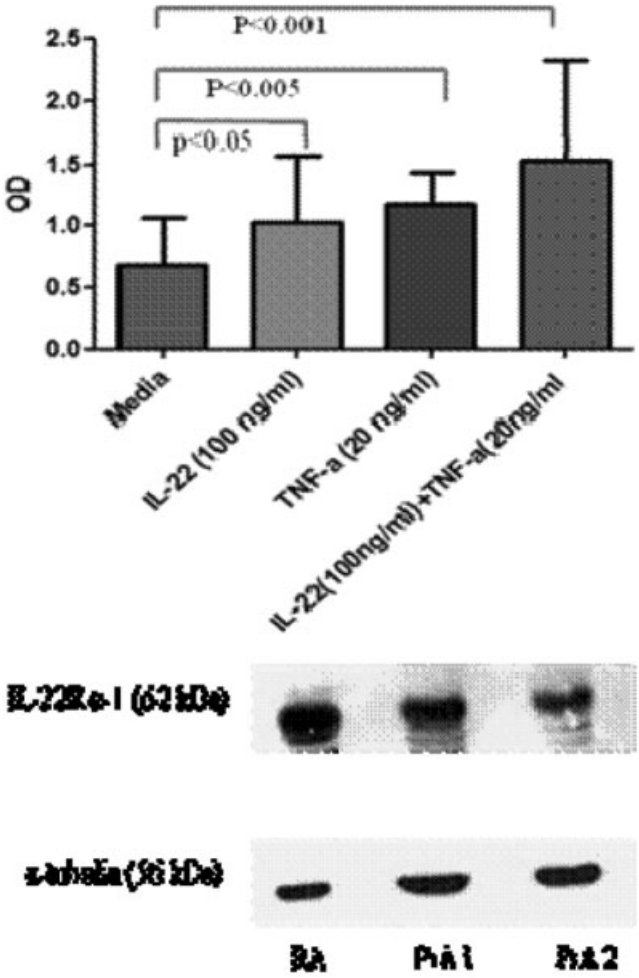
Immunopathogenic Role of IL-22 and Its Receptor In Psoriatic Arthritis: Synergistic Effect of IL-22 and TNF-α In FLS Proliferation. Siba P. Raychaudhuri[1], Anupam Mitra[2], Ananya Datta Mitra[3] and Smriti K. Raychaudhuri[3]. [1]Sacramento VA Medical Center/ UC Davis School of Medicine, Mather, CA, [2]UC Davis School of Medicine/VA Sacramento Medical Center, Mather, CA, [3]VA Sacramento Medical Center, Mather, CA

Background/Purpose: Th17 cytokine IL-22 plays a key role in the proliferation of keratinocytes and fibroblast like synovial (FLS) cells. Based on these functions of IL-22, there are studies reporting its role in the pathophysiology of pannus formation in rheumatoid arthritis (RA) and induction of acanthosis in psoriasis. Synovial hypertrophy and the proliferation of FLS are also the key factors in the pathogenesis of psoriatic arthrthritis (PsA). Here we studied IL-22, IL-22 receptor (IL-22Rα1) and its functional significance in PsA

Methods: We collected synovial fluids (SF) and blood from PsA (n= 10); RA (n=12); and osteoarthritis (OA, n=12) patients. IL-22 in SF and blood was measured by ELISA. FLS were derived from synovial tissues (PsA, n=5; RA, n=5; OA, n=5). MTT and flow cytometric (CFSE) assays were performed to determine IL-22 induced proliferation of FLS. Recombinant TNF-α was used as a positive control for FLS proliferation assays. IL-22Rα1 expression in FLS was identified by western blotting (WB). Samples from RA and OA patients were used as positive and negative control respectively.

Results: IL-22 levels in SF were significantly elevated in patients with PsA (14.02 pg/ml ± 3.61), RA (14.11 pg/ml ± 2.50) in comparison to OA (4.98 pg/ml ± 0.35), $p<0.001$. Serum level of IL-22 was also elevated in patients with PsA (7.87 pg/ml ± 0.84) than in OA (4.45 pg/ml ± 0.50), $p<0.05$. After 5 days of incubation, we observed significant proliferation with recombinant human IL-22 (100 ng/ml) and TNF-α (20ng/ml) in FLS from PsA (OD=1.02±0.12 and 1.17±0.06) compared to media (OD=0.68±0.08), $p<0.05$ (Figure 1). In RA patients too, there was significant proliferation with IL-22 and TNF-α compared to media, $p<0.05$. Moreover in this study, we had a novel observation that IL-22 (100 ng/ml) and TNF-α (20 ng/ml) had a synergistic effect in proliferation of FLS (Figure 1). In the western blot, we found expression of IL-22Rα1 in FLS of PsA, RA and OA (Figure 2).



Conclusion: To our knowledge this is the first report to demonstrate the functional significance of IL-22 in PsA. Here we had a novel observation that IL-22 and TNF-α have a synergistic effect in proliferation of FLS. Pathogenic role of IL-22 and its receptor IL-22Rα1 in psoriatic arthritis opens a new field to develop IL-22/IL-22R targeted therapies in PsA.

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Association Between Human Leukocyte Antigen and Killer-Cell Immunoglobulin-Like Receptor Gene Variants and Type II Psoriasis and Dactylitis in Psoriatic Arthritis. Vinod Chandran[1], Fawnda Pellett[1], Arane Thavaneswaran[1], Remy Pollock[1], Renise Ayearst[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: HLA and KIR genes are associated with PsA. However, since the vast majority of patients with psoriatic arthritis (PsA) have associated cutaneous psoriasis it is difficult to determine whether the primary association is with musculoskeletal disease or with skin disease. Markers associated with Type II psoriasis (onset after age 40 years) as well as dactylitis are likely markers for musculoskeletal disease in PsA. We therefore conducted association studies to identify HLA alleles and KIR genes

associated with type II psoriasis as well as with dactylitis in subjects with PsA.

Methods: 135 PsA cases with type II psoriasis and 688 healthy ethnically matched controls were selected to study association between PsA and type II psoriasis. For the study on dactylitis, a case-only study comparing 378 subjects with dactylitis to 299 without dactylitis was performed. KIR typing was performed by PCR-SSP, and HLA typing by PCR-SSO with appropriate quality control. The difference in the frequency of individual markers in cases and controls were tested for significance using χ^2 test and Fisher's exact test. Trends for increasing susceptibility to PsA from combined genotypes (HLA-KIR and HLA) were evaluated by the Cochran-Armitage trend test. Multivariate analyses were conducted using logistic regression.

Results: When comparing PsA with type II psoriasis to controls, HLA-C*01, C*12, B*27, B*38 increased risk, whereas HLA-B*51 decreased risk in univariate analyses. Multivariate analysis showed that only HLA B*27 (OR 3.3, $p<0.0001$, 95% CI 1.94, 5.61) and HLA B*38 (OR 8.95, $p<0.0001$, 95% CI 4.33, 18.49) independently increased risk. HLA-B Bw4 and *KIR2DS2* was also associated with PsA and type II psoriasis. When comparing PsA with dactylitis to PsA without dactylitis only HLA-C *02 and -B*27 was associated with dactylitis in univariate analyses. Multivariate analysis confirmed that both HLA- C*02 (OR 1.85, $p=0.05$, 95% CI 1.01, 3.38) and -B*27 (OR 1.74, $p=0.03$, 95% CI 1.06, 2.85) were independently associated with dactylitis. *KIR2DS2* was also associated with dactylitis in univariate and multivariate analysis.

Conclusion: HLA-C*02, -B*27, -B*38 and *KIR2DS2* may be specific markers for musculoskeletal disease in PsA. These results need to be confirmed in large scale studies comparing well-phenotyped patients with PsA to those with psoriasis without PsA.

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Investigating the Association Between Endoplasmic Reticulum Aminopeptidase 1 Gene Variants and Psoriatic Arthritis. Vinod Chandran[1], Fawnda Pellett[2], Remy Pollock[1], Al Amin P. Rahman[3] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Memorial University, St Johns, NE

Background/Purpose: Endoplasmic reticulum aminopeptidase 1 (ERAP1) gene variants are associated with ankylosing spondylitis (AS) and interact with HLA-B*27. ERAP1 gene variants are also associated with psoriasis and interacts with HLA-C*06. Since psoriatic arthritis (PsA) is closely related to AS and psoriasis, and associated with HLA-C and -B alleles, we sought to investigate the association between ERAP1 variants with PsA and its interaction with HLA-C and -B alleles.

Methods: The following ERAP1 SNPs were genotyped in 666 Caucasian patients with PsA satisfying CASPAR criteria and 692 Caucasian controls-rs10050860, rs30187, rs26653. HLA-C and B typing was performed by PCR-SSO. Association between ERAP1 SNPs were investigated using the Armitage trend test. Interaction between the ERAP1 SNPs and HLA alleles B*27, B*38, B*57, C*01, C*02, C*06, C*12 previously shown to be associated with PsA was investigated using logistic regression. To further dissect the genetic relationship between skin and joint disease in PsA, ERAP1 and its interaction with HLA alleles was investigated in 333 Caucasian subjects with chronic plaque psoriasis who did not have PsA (PsC).

Results: The 3 ERAP1 SNPs were genotyped with a success rate of >98% and were in Hardy-Weinberg equilibrium. No association between the 3 SNPs and PsA were demonstrated (trend $p = 0.93, 0.86, 0.77$, respectively). Logistic regression analyses demonstrated interaction between rs10050860 and HLA B*27 (interaction $p < 0.01$), rs26653 and HLA B*57 ($p < 0.01$), rs26653 and HLA C*06 ($p < 0.01$) and rs26653 and HLA C*12 ($p = 0.02$). The association between rs10050860 and PsA was present only in B*27+ cases ($p = 0.01$), whereas the association between rs26653 and PsA was present in B*57+ ($p< 0.01$), C*06+ ($p < 0.01$) and C*12+ ($p = 0.03$) PsA cases and not in PsA cases without these HLA alleles. In patients with PsC, no association with the 3 SNPs was demonstrated (trend $p = 0.71, 0.15, 0.78$, respectively). No interaction between rs10050860 and HLA B*27 and rs26653 and HLA C*12 could be demonstrated. However, interaction between rs26653 and HLA B*57 ($p = 0.02$) and between rs26653 and HLA C*06 ($p = 0.05$) was demonstrated. The association between rs26653 and PsC was present in B*57+ ($p= 0.04$) and C*06+ ($p = 0.06$) PsC cases and not in PsC cases without these HLA alleles.

Conclusion: Our study demonstrated that although ERAP1 variants were not associated with PsA, there is genetic interaction between ERAP1 variants and HLA alleles B*27, C*06/B*57 and C*12 known to be associated with PsA, the associations being present only in those cases having these alleles. Unravelling the genetics of PsA may require investigating PsA subsets defined on the presence/absence of major genetic risk factors such as HLA*B27 or HLA C*06/B*57.

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The Association Between Human Leukocyte Antigen and Killer-Cell Immunoglobulin-Like Receptor Gene Variants and the Development of Arthritis Mutilans in Patients with Psoriatic Arthritis. Vinod Chandran, Arane Thavaneswaran, Fawnda Pellett and Dafna D. Gladman. Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Genetic factors may influence the development of Arthritis Mutilans (AM) - the most severe form of psoriatic arthritis (PsA). We therefore conducted a case-only study to identify *HLA* and *KIR* polymorphisms associated with time to development of AM in patients with PsA.

Methods: Data on the presence of AM were obtained form a large cohort. In these cohort plain radiographs of the hands, feet and spine are obtained at baseline and 2-yearly intervals. The radiographs are scored using the validated modified Steinbrocker method by at least 2 rheumatologists by consensus. This methods scores each of 42 joints of the hands and feet on a 0–4 (0 = normal, 1 = soft-tissue swelling/osteopenia, 2 = erosion, 3 = erosion plus joint space narrowing, 4 = total joint destruction) scale. AM was defined as ≥5 joints with grade 4 radiographic damage. Data on the time when AM was first observed was obtained on 610 Caucasian subjects with PsA satisfying CASPAR criteria. HLA typing was performed by PCR-SSO, and KIR typing by PCR-SSP. Since AM is defined by the rapid onset of severe destruction, the principal outcome measure was the time to development of AM after diagnosis of PsA. Parametric survival analyses with interval censoring using a Weibull model adjusted for age at diagnosis of PsA and sex were conducted, HLA and KIR being predictor variables.

Results: The 610 subjects [352 (57.7%) males, mean age at diagnosis of 36 years, mean age at first visit is 43 years, mean duration of PsA 7 years, mean tender joint count 8.6, mean swollen joint count 4.9] had a median number of 3 radiographic assessments during a median follow up of 6.3 years. 97 (16%) subjects developed AM. The median time to development of AM was 1.3 years. Univariate analyses showed that HLA-B*27 and HLA-DQB1*02 alleles were associated with an increased hazard of developing AM whereas the allele HLA-A*11 and -C*04 were associated with a reduced hazard. A trend for association was noticed with HLA-C*02 and -A*29. Multivariate analysis with alleles significant at $p<0.1$ showed that HLA-B*27 (HR 2.14, 95% CI 1.35, 3.41, $p < 0.01$) and -DQB1*02 (HR 1.80, 95% CI 1.18, 2.75, $p < 0.01$) are independently associated with increased hazard whereas HLA- A*11 (HR 0.36, 95% CI 0.14, 0.91, $p = 0.03$) and -A*29 (HR 0.22, 95% CI 0.05, 0.910, $p = 0.04$) are independently associated with reduced hazard of developing AM. Among the KIR genes, only KIR3DS1 (HR 1.56, 95% CI 1.04, 2.36, $p = 0.03$) was associated with the hazard of developing AM. Since KIR3DS1 biologically interacts with HLA-B alleles that carry the amino acid isoleucine at position 80 (HLA- B Bw4 80ile) statistical interaction between KIR3DS1 and HLA-B Bw4 80ile was investigated in a multiplicative model. An interaction between the two genetic markers and the outcome was demonstrated (interaction $p = 0.05$). KIR3DS1 was associated with increased hazard (HR 2.13, 95% CI 1.26, 3.61, $p < 0.01$) of developing AM only in the absence of HLA –B Bw4 80ile.

Conclusion: PsA patients with HLA-B*27, -DQB1*02 and KIR3DS1 have an increased hazard of developing AM, whereas those with HLA-A*11 and A*29 have a reduced hazard. There is genetic interaction between KIR3DS1 and HLA-B Bw4 80ile, the risk associated with KIR3DS1 being present only in the absence of HLA-B Bw4 80ile.

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The Association Between Human Leukocyte Antigen and Killer-Cell Immunoglobulin-Like Receptor Gene Variants and the Development of Axial Arthritis Among Patients with Psoriatic Arthritis. Vinod Chandran, Arane Thavaneswaran, Fawnda Pellett and Dafna D. Gladman. Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Genetic factors may influence axial joint damage progression in psoriatic arthritis (PsA).Therefore we conducted a case-only study to identify *HLA* and *KIR* polymorphisms associated with

time to development of sacroiliitis and syndesmophytes in patients with PsA.

Methods: Data on the presence of radiographic sacroiliitis and syndesmophytes were obtained form a large cohort. Data on the time when at least unilateral ≥2 grade sacroiliitis and first syndesmophyte was observed on plain radiographs of the pelvis and spine was obtained on 633 Caucasian subjects with PsA satisfying CASPAR criteria. HLA typing was performed by PCR-SSO, and KIR typing by PCR-SSP with appropriate quality control. The principal outcome was the time to development of sacroiliitis/syndesmophytes after diagnosis of PsA. Univariate and multivariate parametric survival analyses with interval censoring using a Weibull model were conducted. The predictor variables were age at diagnosis of PsA, sex and genetic variables (HLA, KIR).

Results: The 633 subjects (362 (57.2%) males, mean age at diagnosis of 36 years, mean age at first visit 43 years, mean duration of PsA 7 years, tender joint count 8.7, swollen joint count 5.0, had a median number of 3 radiographic assessment during a median follow up of 6.0 years. 336 number of subjects developed sacroiliitis and 218 syndesmophytes. The mean time to development of sacroiliitis was 2.3 (4.9) years and that for syndesmophytes was 4.0 (6.7) years. Univariate analyses showed that HLA C*02, C*12, B*27 and DQB1*0609 alleles were associated with an increased hazard of developing sacroiliitis whereas the allele HLA A*29 was associated with a decreased hazard. Multivariate analysis showed that HLA C*02 [hazard ratio (HR) 1.83, 95% CI 1.34, 2.49, $p < 0.01$], C*12 (HR 1.33, 95% CI 1.01, 1.74, $p = 0.04$), and DQB1*0609 (HR 2.47, 95% CI 1.20, 5.11, $p = 0.01$) alleles were independently associated with an increased hazard of developing sacroiliitis whereas the allele HLA A*29 (HR 0.52, 95% CI 0.31, 0.88, p value = 0.02) was associated with decreased hazard. The activating KIR genes *KIR2DS1, KIR2DS5* and *KIR3DS1* were associated with increased risk of developing sacroiliitis in univariate analyses. Multivariate analysis however showed that only *KIR2DS1* (HR 1.32, 95% CI 1.05, 1.64, p = 0.02) was independently associated with time to development of sacroiliitis. A hierarchical risk depending on the presence/absence of *KIR2DS1* and its HLA-C C group 2 ligands was also demonstrated. With regard to time to development of syndesmophyte, in univariate analysis HLA C*01 and B*27 alleles were associated with an increased hazard; the alleles HLA A*29 and B*07 were associated with a reduced hazard. Multivariate analysis showed that only HLA B*27 (HR 1.66, 95% CI 1.21, 2.29, p value < 0.01) was independently associated with an increased hazard of developing syndesmophyte whereas HLA A*29 (HR 0.39, 95% CI 0.18, 0.85, p value 0.02) was associated with reduced hazard. Analyses of the KIR genes revealed only a marginal protective role for *KIR2DL3*.

Conclusion: Genetic factors are associated with development of sacroiliitis and syndesmophytes among patients with PsA.

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Family Based Association Study Confirms Human Leukocyte Antigen Allele Associations with Psoriatic Arthritis. Vinod Chandran[1], Fawnda Pellett[1], Proton Rahman[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]St. Claires Mercy Hospital, St. Johns, NF

Background/Purpose: We have shown in a population-based association study that the HLA alleles B*13, B*27, B*38, B*39, B*57 and DRB1*01 increases risk for PsA whereas the alleles A*03, C*03, B*49, B*51, DRB1*11 and DQB1*0602 are protective. Although less powerful than population-based designs, family-based designs have unique advantages over population-based designs, as they are robust to population stratification and allow both linkage and association to be tested. We therefore conducted a family-based association study to identify alleles in linkage and association with PsA.

Methods: A total of 283 families (202 from Ontario, 81 from Newfoundland, Canada) were recruited. Data from 263 nuclear families (1000 persons) were analyzed. Extracted genomic DNA was amplified by PCR using locus specific primers for each of the HLA-A, -C, -B, -DR and DQ loci. PCR amplicons were identified by Sequence Specific Oligonucleotide (SSO) probes using the reverse line blot technique. Alleles were examined for association with PsA using the family-based association test implemented in the FBAT program version 2.0.3. A family based test statistic (Z value) and p value were calculated. Z of more than 0 indicates over-transmission of the allele, while Z of less than 0 indicates under-transmission. An additive model was specified. Initially, association analyses were carried out using each individual allele. Alleles with < 10 informative families were excluded and significance level was set at $p<0.05$. Subsequently, haplotype based association tests using all 5 markers were also conducted.

Results: The significant results from the family-based association test using individual HLA alleles are given in the table. HLA alleles- A*02, B*27 and DRB1*07 increased risk for PsA, whereas the alleles A*03, A*28, B*51, DRB1*11 and DQB1*0301 were protective. A trend towards increased risk was found with HLA C*12, B*39, B*57, DRB1*16 & DQB1*0303 while a trend towards protection was found with the alleles C*15, B*07 and DQB1*0503. Haplotype analysis showed that A*02 C*06 B*57 DRB1*07 DQB1*0303 formed an extended haplotype that increased risk for PsA. HLA B*27 independently increased risk.

HLA allele	Allele frequency	Number of informative families	Z statistic	P value
A*02	0.309	120	2.783	0.0054
A*03	0.115	63	−2.281	0.0226
A*28	0.034	30	−3.376	0.0007
B*27	0.083	48	3.745	0.0002
B*51	0.035	26	−2.535	0.0112
DRB1*07	0.167	79	2.939	0.0033
DRB1*11	0.073	40	−3.822	0.0001
DQB1*0301	0.175	81	−2.659	0.0078

Conclusion: The results of this largest family-based association study in PsA show that the HLA alleles A*02, B*27 and DRB1*07 increases risk for PsA, whereas HLA A*03, A*28, B*51, DRB1*11 and DQB1*0301 decreases risk. These results partially confirm previously reported population-based study results.

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Proteomic Profiling of Synovial Fluid for the Identification of Psoriatic Arthritis Soluble Biomarkers. Daniel Cretu[1], Dafna D. Gladman[2], Fawnda Pellett[3], Eleftherios Diamandis[1] and Vinod Chandran[3]. [1]Mount Sinai Hospital, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON, [3]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: There is a high prevalence of undiagnosed psoriatic arthritis (PsA) in patients seen in dermatology clinics. Identifying soluble biomarkers for PsA will help in screening psoriasis patients for appropriate referral to a rheumatologist as well as provide further insight into disease pathogenesis. However, identification of novel protein biomarkers in peripheral blood is difficult and unreliable. Potential PsA biomarkers are likely to originate in sites of inflammation such as inflamed joints and subsequently enter systemic circulation. Therefore, we aimed to perform in-depth proteomic analysis of synovial fluid (SF) for the identification of putative biomarkers for PsA.

Methods: Using gel filtration and strong cation exchange chromatography, followed by LC-MS/MS on an LTQ-Orbitrap mass spectrometer, we extensively characterized the proteomes of SF from 3 individual PsA patients and 3 individual non-inflammatory (NI) (early OA) controls. All samples were analysed in triplicates. Two strategies were employed for identification of candidate biomarkers: (1) examination of differential protein expression between the PsA and NI controls, (2) tissue specificity analysis through mining of publicly available databases.

Results: Between 255 and 455 non-redundant proteins were identified with two or more peptides in each sample, with a false discovery rate <1.5%. A total of 591 high-confidence proteins were identified from all patient groups, 153 of which were PsA specific, 353 were common to PsA and NI, and 85 were unique to NI. Approximately 70% of proteins were extracellular, unannotated, or cell-membrane bound based on Genome Ontology classification. The three main functional categories of proteins represented in the PsA group based on STRING database are: extracellular matrix repair and destruction, collagen degradation, and complement activation. By applying specific filtering criteria, we obtained a preliminary list of ~40 potential PsA biomarkers, a number of which have been previously identified, such as Cartilage Oligomeric Matrix protein, Matrix Metalloproteinase 3, and S100A9 Protein.

Table 1.

Previously Investigated Biomarkers	Novel Identified Putative Biomarkers
CSF1R Macrophage colony-stimulating factor 1 receptor	NIF3L1 NGG1 Interacting Factor 3-like 1
MMP3 Matrix Metalloproteinase 3	PD3 Phospholipase D3
COMP Cartilage oligomeric matrix protein	ELA2 Elastase 2
COL1A1 Collagen alpha-1(I) chain	EFEMP1 EGF-containing fibulin-like extracellular matrix protein 1
CD14 Monocyte differentiation antigen CD14	ORM2 Alpha-1-acid glycoprotein 2
CRP C-reactive protein	MCAM Cell surface glycoprotein MUC18
CRTAC1 Cartilage acidic protein 1	MRC2 C-type mannose receptor 2

Conclusion: We have developed a high-throughput proteomics platform using LC-MS/MS allowing the delineation of the SF proteome from PsA patients and NI controls. Using this data and publicly available databases we have identified proteins that are differentially expressed, and may serve as putative PsA biomarkers. After validation, these markers will be investigated in the serum as soluble PsA biomarkers.

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Association of ERAP1, IL12B and IL23R Gene Polymorphisms with Subphenotypes of Psoriatic Arthritis. Deepak Jadon[1], William Tillett[1], Dinny Wallis[1], Charlotte Cavill[2], Anna Dixon[2], Nicola Waldron[1], Eleanor Korendowych[1], Anne Barton[3] and Neil J. McHugh[1]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]Bath Institute for Rheumatic Disease, Bath, United Kingdom, [3]University of Manchester, Manchester, United Kingdom

Background/Purpose: Genetic studies have demonstrated an association between interleukin-23 receptor (*IL23R*) and interleukin-12 beta (*IL12B*) gene variants and susceptibility to psoriatic arthritis (PsA)[1,2], ankylosing spondylitis (AS)[3] and psoriasis[4]. Endoplasmic reticulum aminopeptidase-1 (*ERAP1*) gene variants have shown association with AS[5] and psoriasis[6].

We now investigate whether single-nucleotide polymorphisms (SNPs) in the genes encoding *ERAP1*, *IL23R* and *IL12B* associate with specific clinical phenotypes within PsA, such as those with spinal involvement of PsA.

Methods: 262 PsA patients (131 males, median age at PsA onset 38 years) living in South-West England were compared with healthy controls derived from the Wellcome Trust Case Control Consortium; 3266 controls for *ERAP1* (rs30187), 5422 for *IL12B* (rs6887695) and 4941 for *IL23R* (rs11209026 and rs7530511) genes.

These SNPs were genotyped in PsA cases and controls using the Sequenom MassARRAY platform.

98.5% of cases fulfilled the CASPAR classification for PsA. The following clinical phenotypes were assessed; age at onset of psoriasis/PsA, number of arthritic joints, axial radiographic disease (defined as spondylitis/sacroiliitis or both), peripheral radiographic erosions, Psoriasis Area Severity Index, nail score and HAQ.

Statistical analysis was performed using the Pearson Chi-Square test or the Mann-Whitney-U test as appropriate.

Results: Genotype frequencies in cases and controls were in Hardy-Weinberg equilibrium.

There was a strong association between rs6887595 (*IL12B*) and PsA, with homozygosity for the major allele being more frequent in PsA than controls (odds ratio 1.7; 95% confidence interval 1.3–2.2; $p<0.001$).

A trend was demonstrated for the minor allele of rs11209026 to be less frequent in patients with erosive joint disease than in those without erosion or controls (6.9%, 13.3% and 12.8%, respectively).

None of the four SNPs associated with the presence of radiological axial disease or other clinical subphenotypes.

Conclusion: We have confirmed a strong association between rs6887595 (*IL12B* gene) and PsA. A trend has been demonstrated between an *IL23R* variant and peripheral erosive disease. Contrary to our hypothesis, no association was demonstrated between these known AS-associated SNPs and the presence of radiological axial disease, non-polyarticular or non-erosive disease that would suggest a PsA subphenotype towards the AS spectrum. *ERAP1* encodes a pair of trimming aminopeptidases located in the endoplasmic reticulum, that have complementary functions in human leucocyte antigen (*HLA*) class 1 peptide presentation. Therefore *ERAP1* in particular may exert an effect dependent on *HLA-B27* and *HLA-Cw6* status, as was demonstrated in a study of psoriasis[6]. We will now explore this with a larger sample size.

ACR/ARHP Poster Session B
Systemic Lupus Erythematosus - Clinical Aspects II
Monday, November 7, 2011, 9:00 AM–6:00 PM

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Clinical and Laboratory Correlates in Responders (by the Systemic Lupus Erythematosus Responder Index) in Phase 3 Belimumab Clinical Trials. R.A. Furie[1], Z.J. Zhong[2], W. Freimuth[2] and M. Petri[3]. [1]North Shore-LIJ Health System, Lake Success, NY, [2]Human Genome Sciences, Inc., Rockville, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: To evaluate the clinical and laboratory correlates of SLE Responder Index (SRI) response irrespective of treatment assignment.

Methods: Data from BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) were pooled, and parameters of importance in week-52 SRI responders were compared with those in SRI non-responders. SRI response was defined as: 1) ≥4-point reduction in SELENA-SLEDAI, and 2) no new British Isles Lupus Assessment Group [BILAG] A or 2 new B scores, and 3) no Physician's Global Assessment worsening [<0.3 points] vs baseline.

Results: Of the 1684 patients enrolled in both studies, 761 were responders to treatment with belimumab (1 or 10 mg/kg) or placebo plus standard therapy and 923 were non-responders using an intention-to-treat analysis. At wk 52, SRI responders had statistically significant improvements in disease activity measures and in the number of improved SELENA-SLEDAI and BILAG organ domains vs non-responders. Significantly fewer responders had SFI flares (all and severe). Significantly more responders reduced corticosteroid use, and fewer increased corticosteroid use at wk 52 vs non-responders. Responders also had greater improvements in complement and anti-dsDNA antibody levels at wk 52 compared with non-responders. Results are summarized in Table 1.

Table 1. Clinical and Serologic Correlates at Week 52 in BLISS-52 and BLISS-76 SRI Responders (SRI R) and SRI Non-responders (SRI NR)

	SRI Response Status		
	SRI R	SRI NR	P value
Patients, n[a]	761	923	
≥4-point SLEDAI reduction, n (%)[a]	761 (100.0%)	35 (3.8%)	<0.0001
≥7-point SLEDAI reduction, n (%)[a]	307 (40.3%)	12 (1.3%)	<0.0001
BILAG improvement (no A's: ≤1B), n (%)[a]	699 (91.9%)	331 (35.9%)	<0.0001
Number of organ domains improved[a]			
SLEDAI, mean ± SE	2.00 ± 0.03	0.39 ± 0.02	<0.0001
BILAG, mean ± SE	1.45 ± 0.03	0.40 ± 0.02	<0.0001
% Change in PGA from baseline (among patients with no 0.3-point worsening at wk 52) (n = 1216), mean ± SE[b]	−58.31 ± 1.17	−34.90 ± 1.75	<0.0001
Prednisone >7.5 mg/d at wk 52, with baseline prednisone ≤7.5 mg/d, n/N (%)[b]	12/290 (4.1%)	89/418 (21.3%)	<0.0001
Prednisone ≤7.5 mg/d at wk 52, with baseline prednisone >7.5 mg/d, n/N (%)[a]	120/471 (25.5%)	70/505 (13.9%)	<0.0001
Patients with SFI flares (all), n (%)	532 (69.9%)	763 (82.7%)	<0.0001
Patients with SFI flares (severe), n (%%)	47 (6.2%)	269 (29.1%)	<0.0001
% Change in anti-dsDNA antibodies (among patients positive at baseline) (n = 913), median (Q1,Q3)[c,d]	−34.21 (−57.04, −0.50)	−26.06 (−50.81, 6.76)	0.014
Normalization of anti-dsDNA antibodies (among patients positive at baseline), n/N (%)[c,d]	69/479 (14.4%)	47/434 (10.8%)	0.10
% Change in C3 (among patients with low C3 at baseline) (n = 585), median (Q1,Q3)[c,d]	14.47 (1.25, 35.46)	8.96 (−4.88, 26.51)	0.0014
Normalization of C3 (among patients with low C3 at baseline), n/N (%)[c,d]	89/292 (30.5%)	74/293 (25.3%)	0.16
% change in C4 (among patients with low C4 at baseline) (n = 740), median (Q1,Q3)[c,d]	40.00 (13.33, 81.82)	28.57 (0.00, 63.64)	0.0035
Normalization of C4 (among patients with low C4 at baseline), n/N (%)[c,d]	134/361 (37.1%)	112/379 (29.6%)	0.03
% Change in CD20+ B cells (n = 542), median (Q1, Q3)[d]	−39.93 (−64.07, 3.56)	−30.20 (−56.28, 12.86)	0.072

[a]Based on dropout = failure; [b]based on last-observation-carried-forward analysis; [c]SRI excluding serology; [d]includes patients with data available at wk-52/primary visit. BILAG, British Isles Lupus Assessment Group; C, complement; PGA, Physician's Global Assessment; SE, standard error; SFI, SELENA-SLEDAI Flare Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Conclusion: The SRI is a novel composite endpoint that was created during the development of belimumab and served as the primary endpoint for the pivotal studies that led to approval by regulatory agencies. This analysis, undertaken to explore the clinical significance of an SRI response, demonstrated that patients who are SRI responders have a global benefit that extends well beyond those parameters included in the composite index.

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Retrospective Validation of the 3 Laboratory Organ Systems of Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) Responder Index (SRI-50) Over 10 Years. Zahi Touma[1], Dafna D. Gladman[2], Dominique Ibanez[1] and Murray B. Urowitz[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: SRI-50, a valid and reliable index, measures partial ≥50% improvement in disease activity. A retrospective validation of SRI-50 required that the data is collected in a standardized way as is mandated by SRI-50 definitions and data retrieval form. The data was available on the 3 laboratory out of 9 organ systems of SLEDAI-2K. Our objective was to determine the frequency of ≥50% improvement in the 3 laboratory organ systems over 10 years as determined by SRI-50 definitions.

Methods: Patients who attended the Lupus Clinic from January 2000 to October 2010 and who had a minimum of 6 regular visits (every 4–6 months) were included. All items necessary to calculate the SLEDAI-2K are collected prospectively and tracked on an Oracle database.

Identification of patients with active descriptors at any point during the study period was based on SLEDAI-2K definitions. Identification of the patients who ever showed incomplete improvement, ≥ 50%, during the study, in descriptors at subsequent visits was based on SRI-50 definitions of improvement.

Table 1. SLEDAI-2K definitions and definitions of improvement by SRI-50

Descriptors	Definitions of SLEDAI	Weighted score	Definitions of SRI-50 Improvement	Weighted score
Urinary casts	Heme-granular or red blood cell casts.	‘4	Decrease by ≥50% in the total number of casts (heme-granular red blood cell casts).	‘2
Hematuria	>5 red blood cells/high power field. Exclude stone, infection, or other cause.	‘4	Decrease by ≥50% in the number of red blood cell/high power field	‘2
Proteinuria	New onset, recurrent, or persistent proteinuria of more than > 0.5 gram/24 hours.	‘4	Decrease by ≥50% in the range of proteinuria.	‘2
Pyuria	>5 white blood cells/high power field. Exclude infection.	‘4	Decrease by ≥50% in the number of white blood cells/ high power field.	‘2
Proteinuria	New onset, recurrent, or persistent proteinuria of more than > 0.5 gram/24 hours.	‘4	Decrease by ≥50% in the range of proteinuria.	‘2
Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.	‘2	≥50% increase in the level of any complement or normalization of one of them without a drop in either.	‘1
Increased anti-DNA antibodies levels	Increase in the level of anti-DNA antibodies above normal range for testing laboratory.	‘2	≥50% increase in the level of anti-DNA antibodies	‘1
Thrombocytopenia	<100,000 platelets/× 109/L. Exclude drug causes.	‘2	≥50% increase in the level of platelets but <100,000 platelets/mm3.	‘1
Leukopenia	<3,000 white blood cells/× 109/L. Exclude drug causes.	‘2	≥50% increase in the level of white blood cells but <3,000/ mm3/	‘1

We studied the renal (proteinuria, hematuria, pyuria and/or casts), immunological (complements and/or anti-DNA antibodies), and hematologic (thrombocytopenia and/or leucopenia) systems for which the needed data of SRI-50 was available through the database.

Results: 795 patients were identified. 88% were female, 64% Caucasian, 14% Black, 11% Asian. The length of the study period was 6.1 ± 3.1 years and Adjusted Mean SLEDAI-2K (AMS) was 4.66±3.42. Of the 795 patients, 748 patients (94%) had an active system at some point during the study period. 516 patients had renal, 667 immunological and 207 hematologic active system during the study period. 492 (66%) patients showed incomplete but ≥50% improvement in at least one descriptor as follows:

Of the 516 patients with active renal system, 174 (34%) met the definitions of SRI-50 and showed partial improvement. Of the 667 patients with active immunological system, 420 (63%) partially improved. Of the 207 patients with active hematological system, 52 (25%) partially improved.

Table 2. Frequency of incomplete but ≥50% improvement in active descriptors

Renal System Active Descriptors	Number of Active Patients	Patients who showed incomplete but ≥50% improvement
Overall	516	174 (34%)
Casts	324	32 (10%)
Hematuria	199	57 (29%)
Proteinuria	288	109 (38%)
Pyuria	308	60 (19%)
Immunological System Active Descriptors	Number of Active Patients	Patients who showed incomplete but ≥50% improvement
Overall	667	420 (63%)
Low complement	572	293 (51%)
Increased anti-DNA	542	288 (53%)
Hematological System Active Descriptors	Number of Active Patients	Patients who showed incomplete but ≥50% improvement
Overall	207	52 (25%)
Thrombocytopenia	69	10 (15%)
Leukopenia	166	42 (25%)

Conclusion: SLEDAI-2K scores descriptors as present or absent. None of these would be identified as responders using SLEDAI-2K. Although only the 3 laboratory organ systems were studied, 66% of the patients showed partial, ≥50%, improvement over the study period and thus would be considered responders. Thus, SRI-50 is good instrument to be used in clinical trials in SLE.

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Responders in the Phase 3 Belimumab Clinical Trials in Patients with Systemic Lupus Erythematosus Reported Improvements in Fatigue and Health-Related Quality of Life At Week 52. V. Strand[1], S. Cooper[2], Z.J. Zhong[2] and G. Dennis[2]. [1]Stanford University, Palo Alto, CA, [2]Human Genome Sciences, Inc., Rockville, MD

Background/Purpose: The effects of SLE on health-related quality of life (HRQOL) have been shown to be comparable to or worse than those of other chronic diseases such as AIDS, rheumatoid arthritis, diabetes, and congestive heart failure. In two phase 3 studies, patients with autoantibody-positive (antinuclear antibody ≥1:80 or anti-double-stranded DNA ≥30 IU/mL) systemic lupus erythematosus (SLE) and Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index (SELENA-SLEDAI) score ≥6 on stable standard therapy ≥30 days received belimumab 1 or 10 mg/kg, or placebo, plus standard therapy for 52 wk (BLISS-52 [N=865]; NCT00424476) or 76 wk (BLISS-76 [N=819]; NCT00410384). Primary endpoint: response rate at wk 52 by the SLE Responder Index (SRI): SELENA-SLEDAI improvement (≥4-point decrease), no new British Isles Lupus Assessment Group A or 2 new B scores, and no Physician’s Global Assessment worsening (<0.3-point increase). Wk-52 SRI response rates in patients with placebo, and belimumab 1 and 10 mg/kg, respectively, were 43.6%, 51.4% (p=0.013), and 57.6% (p=0.0006) in BLISS-52; 33.5%, 40.6% (p=0.089), and 43.2% (p=0.017) in BLISS-76; and 38.8%, 46.2% (p=0.006), and 50.6% (p<0.0001) in pooled analysis. Secondary endpoints included patient-reported outcomes (PRO) by Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and by SF-36® Health Survey.

Objectives: To assess if SRI responses were clinically meaningful, improvements in PRO were compared in responders vs non-responders.

Methods: Pooled analyses of FACIT-Fatigue and SF-36 outcomes at week 52 were compared in patients with vs without an SRI response across all treatment groups.

Results: Baseline SF-36 physical (PCS) and mental (MCS) component summary and domain scores were lower than those of an age- and gender-matched US population. By pooled analysis, reported mean improvements at wk 52 in SF-36 PCS, MCS, and all domain scores in SRI responders were significantly greater than in non-responders, and exceeded minimum clinically important differences of 2.5 (summaries) and 5.0 (domains) points (table). This was also true for improvements in FACIT-Fatigue; improvements in fatigue were consistent with those in the SF-36 vitality domain. As assessed by the SF-36 transition question–“Compared with 1 year ago, how are you today?”—more than twice the number of responders reported they were “somewhat/much better” (76%) or “much better” (34%) compared with non-responders.

Table. Patient-Reported Outcomes: Pooled Analysis (N = 1684)

	SF-36 FACIT-Fatigue	PCS	MCS	VITAL
Baseline, mean score	30.08	39.06	40.81	43.33
Wk 52, mean Δ				
Responders (n = 761)	5.2*	4.9*	4.4*	10.4*
Non-responders (n = 923)	3.0	2.6	1.7	6.5

	SF-36 Domains							
	PF	RP	BP	GH	VITAL	SF	RE	MH
Baseline, mean SF-36 domain score	58.88	52.07	48.53	41.15	43.33	59.48	61.20	59.63
Wk 52, mean Δ								
Responders (n = 761)	10.3*	12.3*	14.9*	9.8*	10.4*	10.8*	9.3*	8.5*
Non-responders (n = 923)	4.5	6.8	7.1	4.9	6.5	3.7	3.3	3.3

	SF-36 Transition Question	
	Somewhat/Much Better (% Patients)	Much Better (% Patients)
Responders (n = 761)	76.1*	33.8*
Non-responders (n = 923)	33.5	14.6

* $p < 0.001$ (all p values are nominal): statistically significant mean changes also exceeded minimum clinically important differences. BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; VITAL, vitality.

Conclusion: Regardless of treatment group, SRI responders reported statistically significant and clinically meaningful improvements in fatigue and HRQOL, and that their HRQOL was improved from 1 year ago compared with non-responders. The data indicate that SRI responders report improvements meaningful to them.

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Early Systemic Lupus Erythematosus Specific Antigens Predict Disease Characteristics. Jessica J. Hale[1], Jennifer A. Kelly[1], Chee Paul Lin[1], Stuart B. Glenn[1], Jourdan Anderson[1], Patrick M. Gaffney[2], Kathy L. Moser[2], John B. Harley[3], Judith A. James[4] and Courtney G. Montgomery[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [4]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, most prevalent in women of child-bearing age. It is characterized by autoantibody production leading to inflammation and ultimately, tissue damage. Some autoantibodies precede clinical disease by several years, are unique to SLE and have antigenic peptide sequences that closely mimic that of a suspected environmental trigger Epstein-Barr Virus (EBV). The objective of this study was to assess the relationship between early humoral autoimmune responses, select viral responses and the varied manifestations of SLE in both European and African American (EA and AA) patients to better characterize SLE etiology.

Methods: Data were collected for 519 AA and 1210 EA female SLE patients. Individual and familial correlation analyses were performed to determine the extent early epitope and viral production are associated with lupus clinical and lab criteria. Data included quantitaive measures of antibodies against: SmB' amino acids (aa) 191–198 (GMR), SmD1 aa 95–119 (GRx4) and 60kDRo aa 169–182 (Ro169), EBV viral capsid antigen (VCA), EBV nuclear antigen 1 (EBNA-1) EBNA-1 aa 398–404 (GRR), ENBA-1 aa 58–72 (EBNA58) and EBNA-1 aa 1–90 and 409–497 (EBNA1M). We also evaluated the 11 ACR criteria, CH50, anticardiolipin (APL) IgG and IgM as well as the following autoantibodies: nuclear (ANA), double stranded DNA (dsDNA), Ro, La, P, nRNP. Transformations were applied where necessary to achieve normality. We assessed self and familial correlations using FCOR (S.A.G.E. software suite) and used a threshold for significance of $5 = 10^{-4}$. Significant correlations were confirmed using linear regression in SAS.

Results: In the EA females, increased levels of EBV-VCA corresponded to the presence of six of the 11 ACR criteria, including hematologic, immune, skin and renal systems ($p<2 = 10^{-4}$). We also found both EBV-VCA and GRR to be significantly correlated with levels of APL-IgG ($p=1.7 = 10^{-4}$ and $4 = 10^{-6}$). Anti-GMR was positively correlated with anti-Sm, -RNP, -dsDNA, -ssDNA, -ANA, as well as IgG antibodies in EAs ($p<1 = 10^{-4)}$ and with anti–Sm, -RNP and –dsDNA in AAs ($p<1 = 10^{-4}$). Anti-GMR was negatively correlated with CH50 titers in both EAs and AAs ($p=1.5 = 10^{-4}$ and $4.9 = 10^{-4}$). Also in both EAs and AA, anti-GRx4 was strongly, negatively correlated with renal involvement ($p=4.6 = 10^{-3}$ and $3.2 = 10^{-3}$). Sibling correlations were significant for anti-GMR in EAs and anti-EBV-VCA in AAs (p=1.2 = 10-5 and 7.5 = 10-4).

Conclusion: High levels of EBV-VCA antibodies predict multisystem involvement in EAs and perhaps AAs as well. Similarly, high levels of anti-GMR in both EAs and AAs are indicative of an array of autoantibodies and of disease severity (as indicated by low CH50 levels). Conversely, high anti-GRx4 levels indicate that a patient is less likely to have renal involvement, regardless of ethnicity. Significant sibling correlations support a genetic component to the interplay of EBV infection and autoimmune response. Finally, the results of this study highlight the potential to predict disease outcome based on early indicators of SLE and a suspected viral trigger.

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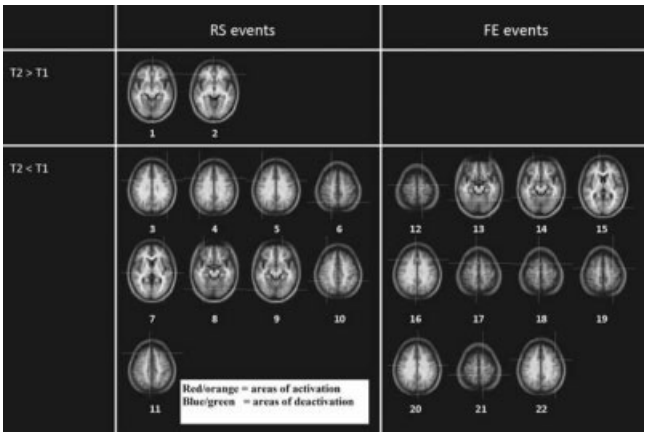
Inefficient Strategic Planning with Compensatory Recruitment of Neural Pathway for Conflict Processing and Error Detection Despite Sufficient Disease Control in Patients with New Onset Systemic Lupus Erythematosus: A Prospective Functional MRI Study. Anselm Mak[1], Tao Ren[2], Erin Hui yun Fu[1], Alicia AC Cheak[1] and Roger CM Ho[1]. [1]National University of Singapore, Singapore, Singapore, [2]National University of Singapore, Sinagpore, Singapore

Background/Purpose: Reliable tools which specifically probe the neuropsychopathology involved in cognitive functioning in patients with systemic lupus erythematosus (SLE) are lacking. Event-related functional magnetic resonance imaging (fMRI) allows excellent demonstration of real-time brain activation signal changes by utilizing the endogenous contrasting property of deoxyhaemoglobin which illuminates active brain areas as blood-oxygen-level-dependent (BOLD) fMRI signals under electromagnetic field. In this study, we used fMRI to address if differences in brain activation pattern existed between SLE patients and healthy controls (HC) and investigate whether unfavourable brain activation persisted even after sufficient control of lupus activity.

Methods: BOLD fMRI signals were recorded while 14 new-onset SLE patients (mean±SD age=39.38±13.9 years; 2 male, 12 female) without clinically-overt neuropsychiatric symptoms and 14 demographically and IQ-matched HC (mean±SD age=34.07±14.4 years; 2 male, 12 female) were performing the computer-based Wisconsin card sorting test (WCST) for assessing executive function which probes goal-directed task performance and strategic planning during response selection (RS) and feedback evaluation (FE) respectively. Composite beta maps were constructed by a general linear model to identify regions of cortical activation. BOLD fMRI signals were compared between (i) new-onset SLE patients and HC and (ii) SLE patients before and after sufficient control of their disease activity.

Results: Performance in WCST between SLE patients and HC, as well as within the SLE group before and after sufficient disease control was comparable. During RS, SLE patients demonstrated significantly higher activation than HC in both caudate bodies and Brodmann area (BA) 9 to enhance event anticipation, attention and working memory, in order to compensate for the reduced activation during FE in BA6, 13, 24 and 32 which serve complex motor planning and decision making, sensory integration, and error detection and conflict processing respectively. Despite significant reduction of SLE activity with conventional immunosuppressive therapies, BA32 was activated during RS to compensate for the reduced activation during FE in BA6, 9, 37 and 23/32, which serve motor planning, response inhibition and attention, color processing and word recognition, and error detection and conflict evaluation respectively (see Figure).



Conclusion: SLE patients recruited additional cortical areas to execute goal-directed tasks in order to compensate for their reduced strategic planning skill even their disease activity was significantly controlled. Targeted research and therapies towards these brain areas may therefore be attractive strategies to elucidate and manage cognitive dysfunction in SLE patients besides conventional therapies of SLE.

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The Effects of Smoking on Age of Onset, Autoantibodies and Interferon-α in Systemic Lupus Erythematosus. Kimberly Smith, Stephanie L. Green, Daniel F. Brandt, Beverly S. Franek, Timothy B. Niewold and Tammy O. Utset. University of Chicago, Chicago, IL

Background/Purpose: Environmental effects on SLE are poorly understood. Previous data suggests that smoking increased dsDNA antibody positivity in SLE. We wished to explore the impact of smoking on immunological aspects and age of onset in SLE.

Methods: 214 ambulatory patients fulfilling ACR criteria for SLE were enrolled in a clinical database at the University of Chicago. SLE history, smoking history, and demographics were obtained using standardized questionnaires. Serologic data was obtained by chart review; current titer was the titer performed nearest the time of study enrollment. In a subset of patients (N=72), interferon-α levels by WISH assay were also available. Associations between never-smokers/ever-smokers, current-smokers/other, high IFN-α, and autoantibodies were evaluated using Chi square, Fisher's exact test and multivariate regression. The association between smoking status, high IFN-α, and current/everpositive autoantibody titers were evaluated using Wilcoxon Rank-Sum analysis and logistic regression.

Results: Current anti-dsDNA titers were higher in never-smokers vs. ever-smokers (median 10 vs. 0, $p<0.01$). Never-smokers also had higher current titers of anti-Smith (mean 27 vs. 17, $p=0.01$), anti-SSA (mean 48 vs. 36, $p=0.01$), anti SSB (mean 14 vs. 7.7, $p=0.02$), and anti-RNP (mean 48 vs. 33, $p=0.01$) compared to ever-smokers. Additionally, the highest titers of anti-dsDNA were found in non smokers (median 160 vs. 22.5 in smokers, $p=0.02$). Similarly, the highest titers of anti-Smith (mean 35 vs. 26, $p=0.03$), anti-SSA (mean 54 vs. 40, $p=0.05$), and anti-RNP (mean 55 vs. 37, $p<0.01$) were found in never-smokers. IFN-α was lower in patients who had ever been smokers (high IFN-α in 44% of ever-smokers vs 69% of nonsmokers, $p=0.044$). However, total IgG did not differ between smoking groups. High IFN-α was not associated with current/ever-positive dsDNA, Sm or SSA, but both current and ever-positive RNP were associated with high IFN-α ($p=0.0008$ and $p=0.001$ respectively). On logistic regression of RNP positivity with pack-years, age and high IFN-α, smoking no longer correlated with RNP positivity (p=NS) while high IFN-α significantly correlated with RNP ($p=0.002$).

Furthermore, age of SLE onset appears to be later in smokers. In patients diagnosed after age 20 (N=164), the mean age of diagnosis in never-smokers was 34.6 vs. 39.2 in ever-smokers ($p=0.0013$). On multivariate regression of the age of onset by pack-years smoking, race/ethnicity, high IFN-α and education, the only significant relationship was between increased pack years and later age of SLE diagnosis ($\beta=0.22$, $p=.019$)

Conclusion: Smoking has been linked to numerous autoimmune diseases. In most diseases, smoking has a harmful effect. Our data suggests that smoking may suppress autoantibody production and delay age of onset in patients with SLE, similar to the protective effects seen in ulcerative colitis. As adjustment for high IFN-α obviates the association of smoking with RNP antibody, it is possible that the effects of smoking on autoantibodies is mediated by IFN-α.

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25-Hydroxyvitamin D Levels Are Inversely Correlated with Systemic Lupus Erythematosus Disease Activity Index, but Are Not Associated with Relapse-Free Survival During Six Months Follow-up of 171 Patients Included in a French Prospective Multicentric Cohor. Yoland Schoindre[1], Moez Jallouli[2], Benjamin Terrier[3], Marie-Laure Tanguy[2], Zahir Amoura[2], Jean-Charles Piette[2], Patrice Cacoub[2], Jean-Claude Souberbielle[4], Nathalie Costedoat-Chalumeau[2] and The group PLUS[5]. [1]Foch Hospital, Suresnes, France, [2]CHU Pitié-Salpêtrière, Paris, France, [3]Pitié-Salpêtrière Hospital, Paris, France, [4]CHU Necker, Paris, France, [5]Paris

Background/Purpose: Immunomodulatory actions of vitamin D, especially on self-tolerance and B-cell homeostasis, have been well documented, and growing evidence suggests the vitamin D plays a key role in the pathogenesis and progression of autoimmune diseases. Recent studies have found an association between lower serum 25-hydroxyvitamin D [25(OH)D] levels and higher systemic lupus erythematosus (SLE) disease activity. None of them studied the role of [25(OH)D] level in predicting SLE flares. The objectives of this study were to assess the relationship between serum 25(OH)D levels and disease activity and the disease flare during a follow-up of 6 months.

Methods: This study is ancillary to the PLUS study (ClinicalTrials.gov number n°NCT00413361), a randomized prospective, double-blind, placebo-controlled multicenter trial aimed at determining whether increasing the HCQ dosage to achieve an [HCQ] ≥1000 ng/mL reduces the risk of SLE flare. Serum 25(OH)D levels were measured in the M1 serum of the 171 randomised SLE patients who were followed-up 6 additional months.

Results: The mean SLEDAI score was 2.03 ± 2.43, and 12.3% patients had active disease defined by a SLEDAI ≥6. The mean 25(OH)D level was 20.6 ± 9.8 ng/mL. Thirty-one (18.2%) subjects had optimal vitamin D levels [25(OH)D ≥30 ng/mL], vitamin D deficiency [25(OH)D <10] was observed in 27 (15.9%) and vitamin D insufficiency [10 ≤25(OH)D <30] in 112 (65.9%) patients. In multivariate analysis, younger age (p = 0,016), higher body mass index (p = 0,007), photosensitivity (p = 0,034), absence of defined APS (p = 0,0004), and higher SLEDAI (p = 0,036) were associated with lower 25(OH)D levels. The mean SLEDAI scores were 2.6, 1.7 and 1.3 in subjects with deficiency, insufficiency, and optimal vitamin D levels, respectively. SLEDAI score was ≥6 in 3 (11.1%) patients with deficiency, 10 (8.9%) patients with insufficiency, and in 2 (6.5%) patients with optimal vitamin D status. The mean 25(OH)D level was not different in patients who developed flares during the 6 months of follow-up and in patients who did not (p = 0,8). Relapse-free survival was not statistically different in patients with 25(OH)D levels <10 ng/mL compared with those with 25(OH)D levels ≥10 ng/mL (p = 0,17), or in patients with 25(OH)D <30 ng/mL compared with those with 25(OH)D levels ≥30 ng/mL.

Conclusion: Similarly to others, we found a low vitamin D status in a vast majority of patients, and an inverse correlation between 25(OH)D levels and disease activity. These results raise the question of whether achieving and maintaining an optimal vitamin D status through adequate supplementation is associated with a reduction in the risk of SLE flare. Nevertheless, there was no association between 25(OH)D levels and relapse-free survival. Further studies should prospectively assess the effect of vitamin D supplementation on disease activity and outcomes in SLE.

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Association of Discoid Lupus with Clinical Manifestations and Damage Accrual in PROFILE: A Multiethnic Lupus Cohort. Yesenia C. Santiago-Casas[1], Luis M. Vila[1], G. McGwin Jr.[2], Michelle Petri[3], Rosalind Ramsey-Goldman[4], John D. Reveille[5], Robert P. Kimberly[2], Graciela S. Alarcon[2] and Elizabeth E. Brown[6]. [1]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]University of Texas Health Science Center at Houston, Houston, TX, [6]Department of Medicine and Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus and occurs in 15%–30% of patients with systemic lupus erythematosus (SLE). It is more common in African Americans and smokers. However, the association of DLE with other clinical features of lupus has not been clearly established. The aim of this study was to determine the association of DLE with clinical manifestations and disease damage in a large multiethnic SLE cohort.

Methods: SLE patients (per ACR criteria), age ≥ 16 years, disease duration ≤ 10 years at enrollment, and defined ethnicity (African American, Hispanic or Caucasian), from a longitudinal cohort were studied. Socioeconomic-demographic features, clinical manifestations and disease damage [as per the Systemic Lupus International Collaborating Clinics Damage Index (SDI)] were determined. The association of DLE with clinical manifestations and disease damage was examined using multivariable logistic regression adjusting for age, gender, race/ethnicity, disease duration, years of education, and smoking.

Results: A total of 2,228 SLE patients were studied. The mean (standard deviation, SD) age at diagnosis was 34.3 (12.8) years and the mean (SD) disease duration was 7.9 (6.0) years; 91.8% were females. Discoid lupus was observed in 393 (17.6%) of patients with SLE. In the multivariable analysis, patients with DLE were more likely to have malar rash (odds ratio [OR] 1.28, 95% confidence interval [95% CI] 1.02–1.62), photosensitivity (OR 1.66, 95% CI 1.30–2.13), oral ulcers (OR 1.35, 95% CI 1.07–1.70), leukopenia (OR 1.46, 95% CI 1.16–1.83) and vasculitis (OR 1.62, 95% CI 1.22–2.13), but less likely to have arthritis (OR 0.73, 95% CI 0.54–0.99), end-stage renal disease (ESRD) (OR 0.42, 95% CI 0.19–0.93), and antinuclear (OR 0.52, 95% CI 0.31–0.88), anti-dsDNA (OR 0.64, 95% CI 0.51–0.80) and anti-phospholipid antibodies (OR 0.71, 95% CI 0.52–0.98). No association was found with overall renal involvement. Patients with DLE had more damage accrual (OR 1.07, 95% CI 1.02–1.13), as well as some individual components of the SDI including chronic seizures (OR 1.84, 95% CI 1.08–3.13), alopecia (OR 5.71, 95% CI 3.91–8.35), scarring of the skin (OR 14.66, 95% CI 8.67–24.81), and skin ulcers (OR 2.43, 95% CI 1.06–5.60).

Conclusion: In this cohort of SLE patients, discoid lupus was associated with mucocutaneous manifestations, integument damage, leukopenia, vasculitis, and chronic seizures, but a lower frequency of arthritis, ESRD and immunologic abnormalities. Our findings highlight the importance of surveillance of SLE patients with DLE, particularly because of the association with serious manifestations such as vasculitis and seizures.

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Anti-C1q Antibody in Systemic Lupus Erythematosus. Ana-Maria Orbai[1], Gunnar K. Sturfelt[2], Ola Nived[3], Hong Fang[1], Graciela S. Alarcón[4], Caroline Gordon[5], Joan T. Merrill[6], Paul R. Fortin[7], Ian N. Bruce[8], David A. Isenberg[9], Daniel J. Wallace[10], Rosalind Ramsey-Goldman[11], Sang-Cheol Bae[12], John G. Hanly[13], Jorge Sanchez-Guerrero[14], Ann E. Clarke[15], Cynthia Aranow[16], Susan Manzi[17], Murray B. Urowitz[18], Dafna D. Gladman[19], Kenneth C. Kalunian[20], Melissa I. Costner[21], Laurence S. Magder[22], Systemic Lupus International Collaborating Clinics (SLICC)[23] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University Hospital Lund, Lund, Sweden, [3]University Hospital, Lund, Sweden, [4]University of Alabama at Birmingham, Birmingham, AL, [5]University of Birmingham, Birmingham, United Kingdom, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]Toronto Western Hospital, Toronto, ON, [8]A, Manchester, United Kingdom, [9]University College London, London WC1E 6JF, United Kingdom, [10]Cedars-Sinai/UCLA, Los Angeles, CA, [11]Northwestern University Feinberg School of Medicine, Chicago, IL, [12]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [13]Dalhousie University, Halifax, NS, [14]University Health Network/Mount Sinai Hospital, Toronto, ON, [15]Research Institute of the McGill Univ. Health, Montreal, QC, [16]Feinstein Institute for Medical Research, Manhasset, NY, [17]Allegheny Singer Research Institute, Pittsburgh, PA, [18]Toronto Western Hospital and University of Toronto, Toronto, ON, [19]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [20]UCSD School of Medicine, La Jolla, CA, [21]North Dallas Dermatology Assoc, Dallas, TX, [22]University of Maryland, Baltimore, MD, [23]Chicago

Background/Purpose: Anti-C1q antibody has been associated with SLE and SLE nephritis in single-center studies. We studied anti-C1q antibody specificity for SLE (vs. rheumatic disease controls) and its association with SLE manifestations in an international multi-center study.

Methods: Information and blood samples were obtained from 308 patients with SLE and 389 patients with other rheumatologic diseases from 25 clinical sites (84% female, 68% Caucasian, 17% African descent, 8% Asian, 7% other). Anti-C1q antibody was measured by an ELISA using IgG antibodies against the collagen-like region of C1q (anti-C1qCLR). P-values were calculated based on the chi-square test (SAS Institute, Cary, NC, USA).

Results: The prevalence of anti-C1q antibody was 28% (86/308) in SLE patients and 13% (49/389) in controls (P-value <.0001), odds ratio 2.7 (95% CI: 1.8, 4.0). By the submitting diagnosis, the frequency of anti-C1q antibody in controls was: 26% in scleroderma, 19% in rheumatoid arthritis, 15% in undifferentiated connective tissue disease, 15% in chronic cutaneous lupus, 14% in Sjögren syndrome, 8% in fibromyalgia, 7% in antiphospholipid antibody syndrome, 6% in dermatomyositis, and 5% in vasculitis.

Table 1. Association between Demographic Characteristics and Anti-C1q Antibody in SLE: Percentage of Patients with Anti-C1q Antibody, by Demographic Variables

		Percentage for Anti-C1q	P-value
Ethnicity	African Descent	21.7	0.15
	Caucasian	27.6	
	Asian	40.5	
	Other	30.0	
Gender	Female	26.9	0.25
	Male	36.4	
Age	≤30	35.5	0.017
	>30	23.0	

Table 2. Association between ACR Criteria and Anti-C1q Antibody in SLE: Percentage of Patients with Various Clinical Conditions, by Anti-C1q Status

	Positive Anti-C1q (%)	Negative Anti-C1q (%)	P-value	Odds Ratio (95% CI)	Adjusted P-value for Age
Malar Rash	47.7	46.9	0.90	0.9 (0.5, 1.5)	0.69
Discoid Rash	19.8	19.4	0.94	1.1 (0.6, 2.1)	0.71
Photosensitivity	53.5	53.2	0.96	1.0 (0.6, 1.7)	1.00
Oral Ulcers	38.4	46.4	0.20	0.7 (0.4, 1.1)	0.14
Arthritis	64.0	65.8	0.76	0.9 (0.5, 1.5)	0.70
Serositis	37.2	34.7	0.68	1.1 (0.6, 1.8)	0.84
Pleurisy	31.4	28.4	0.60	1.1 (0.6, 1.9)	0.74
Pericarditis	14.0	12.2	0.67	1.2 (0.6, 2.5)	0.66
Proteinuria	50.0	22.5	<.0001	3.0 (1.7, 5.1)	<.0001
Urinary casts	18.6	7.2	0.0033	2.6 (1.2, 5.4)	0.015
Seizure	5.8	4.1	0.51	1.2 (0.4, 3.8)	0.72
Psychosis	3.5	0.5	0.035	9.5 (0.9, 98.5)	0.059
Hematologic	64.0	58.1	0.35	1.2 (0.7, 2.0)	0.49
Leukopenia	40.7	35.1	0.36	1.2 (0.7, 2.0)	0.48
Lymphopenia	38.4	36.5	0.76	1.1 (0.7, 1.8)	0.73
Thrombocytopenia	15.1	12.2	0.49	1.1 (0.5, 2.2)	0.86
Anti-dsDNA	77.9	47.8	<.0001	3.4 (1.9, 6.1)	<.0001
Anti-Smith	33.7	14.4	0.0001	2.8 (1.5, 5.0)	0.0007
Antiphospholipid	57.0	54.5	0.70	1.1 (0.7, 1.8)	0.70

Table 3. Association with Renal Lupus: Percentage of Patients with SLE Serologies among those with and without Lupus Nephritis

Variable	Renal Lupus (%)	No Renal Lupus (%)	P-Value	Odds Ratio (95% CI)	Adjusted P-value for Age and Race
Anti-C1q	45.5	19.3	<.0001	3.2 (1.8, 5.6)	<.0001
Anti-dsDNA	80.2	44.4	<.0001	4.7 (2.5, 8.6)	<.0001
Anti-Smith	29.7	15.0	0.0023	1.9 (1.1, 3.6)	0.03
Low complement	78.2	50.2	<.0001	2.8 (1.5, 4.9)	0.0006

Conclusion: Anti-C1q antibody was found in 28% of SLE patients, although it was also found in other rheumatologic diseases. It was more common in Asians than in Caucasians or patients of African descent. In terms of SLE manifestations, it was associated with renal lupus, anti-dsDNA antibody, low complement and anti-Smith antibody. Anti-C1q antibody was more highly associated with renal lupus than anti-Smith antibody was. Although complexities of the assay have limited its introduction as a routine test, these data clearly point to its utility in SLE, especially in lupus nephritis.

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Comparison of Health-Related Quality of Life, Disease Damage, Disability, Age and Disease Duration in Pediatric Lupus Across Different Continents: An Expanded Sample. Lakshmi Nandini Moorthy and the International SMILEY Collaborative Group[1]. [1]UMDNJ/RWJ Medical School, New Brunswick, NJ

Background/Purpose: Simple Measure of Impact of Lupus Erythematosus in Youngsters© (SMILEY©) is a brief, 24-item health-related quality of life (HRQOL) assessment tool for pediatric systemic lupus erythematosus (SLE). Responses are in the form of a 5-faces scale for easy comprehension. SMILEY© is valid in US-English and we are conducting cross-cultural validation of SMILEY©. Our objective was to compare SMILEY© scores in different countries from North (N) and South (S) America, Europe and Asia.

Methods: Children ≤18 years with SLE and their parents completed the appropriate SMILEY© translation, as well as gold standard quality of life (QOL) and physical function scales. Demographic, medication and SLE–related data were obtained. We compared the means of age, child reports of SMILEY© total score and domain scores, PedsQL™ generic module total score, Child Health Assessment Questionnaire (CHAQ) disability index, and Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI). Depending on the data distribution of the above variables, we used one-way ANOVA or the Kruskal-Wallis (KW) test. Because of the limited sample size for some countries, we have combined data by continents.

Results: 436 children (356 girls) and 407 parents participated from: N. America (US=170, Mexico=10, Puerto Rico=7), S. America (Brazil= 89, Argentina=11), Europe (Italy=16, Spain=15, Denmark=14, Netherlands=10, France=8, UK=7), and Asia (China=29, Japan=17, Turkey=17, Saudi Arabia=5, India=10, Israel=1,). The mean disease duration was

37±36 months (median=26 months; range=1 – 188 months, n=397). Table 1 shows the comparison of the means/medians of child/parent reports of the SMILEY© (total/domain scores), PedsQL™ total score, parent CHAQ disability index, and SDI. There were significant differences found in damage and HRQOL score (PedsQL™ and SMILEY©). The children from Asia had the best child-reported generic and disease-specific HRQOL and the children from N. America had the worst HRQOL. Further, there were differences in the domains, Effect on self and Social, across the countries; but no differences in the domains of Limitation and Burden of SLE suggesting that these aspects may be similar across the world in children with SLE. The parent-report of HRQOL did not always follow the trend of the child-report HRQOL.

Table 1. HRQOL, SLE-damage, duration and age

	North America	South America	Europe	Asia	P Value
SDI	0.72 ± 1.4 (0–10, 181)	0.43 ± 1.0 (0–5, 87)	0.25 ± 0.7 (0–4, 69)	0.34 ± 0.8 (0–3, 44)	0.03 (KW)
Mean±SD (range, n)					
Duration (in months)	22 (1–184, 186)	34 (1–130, 91)	29 (1–150, 61)	32 (1–188, 59)	0.04 (KW)
Median (range, n)					
Age (in years)	14 ± 3 (3–18, 184)	14 ± 3 (4–18, 96)	14 ± 2 (7–18.64)	14 ± 3 (5–19,72)	0.06 (KW)
Mean±SD (range, n)					
CHAQ score	0.0625 (0–3, 170)	0 (0–2.3750, 79)	0 (0–2.1250, 49)	0.125 (0–1.75, 30)	0.9 (KW)
Median (range, n)					
Parent					
PedsQL™ total score	70 ± 17 (16–100, 180)	74 ± 16 (25–100, 83)	71 ± 19 (24–100, 53)	76 ± 14 (24–99, 78)	0.02 (ANOVA)
Mean±SD(range, n)	64 ± 21 (0–100, 163)	68 ± 20 (15–100, 80)	67 ± 20 (25–98, 49)	77 ± 18 (18–100, 63)	0.001 (ANOVA)
Child					
Parent					
SMILEY© score	65 ± 14 (33–98, 182)	67 ± 15 (33–100, 95)	68 ± 15 (26–93, 68)	71 ± 14 (35–98, 77)	0.02 (ANOVA)
Mean±SD(range, n)	62 ± 15 (27–96, 171)	65 ± 16 (29–100, 98)	66 ± 15 (35–94, 63)	67 ± 16 (33–100, 69)	0.1 (ANOVA)
Child					
Parent					
4 SMILEY© Domains					
Effect On Self	65 ± 17 (24–100, 181)	68 ± 20 (20–100, 95)	69 ± 20 (20–96, 68)	73 ± 17 (36–100, 78)	0.02 (ANOVA)
Mean±SD(range, n)	61 ± 18 (20–100, 170)	66 ± 20 (20–100, 98)	67 ± 20 (24–100, 61)	71 ± 20 (28–100, 68)	0.005 (ANOVA)
Child					
Parent					
Limitation	64 ± 17 (25–10, 182)	66 ± 19 (23–100, 95)	67 ± 19 (23–100, 68)	71 ± 17 (30–100, 77)	0.08 (ANOVA)
Mean±SD(range, n)	61 ± 18 (20–100, 171)	64 ± 20 (25–100, 98)	64 ± 20 (28–100, 63)	64 ± 21 (25–100, 68)	0.4 (ANOVA)
Child					
Parent					
Social	82 ± 16 (35–10, 182)	85 ± 14 (45–100, 95)	87 ± 14 (45–100, 67)	85 ± 14 (45–100, 77)	0.03 (ANOVA)
Mean±SD(range, n)	77 ± 17 (33–100, 171)	82 ± 16 (30–100, 98)	84 ± 14 (45–100,63)	80 ± 16 (40–100, 69)	0.01 (ANOVA)
Child					
Parent					
Burden of Disease	57 ± 17 (23–100,182)	57 ± 18 (20–100, 95)	60 ± 18 (20–94, 68)	61 ± 19 (26–100, 78)	0.3 (ANOVA)
Mean±SD(range, n)	56 ± 17 (20–100, 170)	56 ± 18 (23–100, 97)	58 ± 15 (20–91, 63)	60 ± 18 (5–100, 69)	0.4 (ANOVA)
Child					
Parent					

Conclusion: In the analysis, differences in HRQOL, disease duration and damage are found. Disease status, age, attitudes, and cultural differences can influence HRQOL. Although there are far more patients from the N. America, these results provide interesting patterns of HRQOL differences across the world. We are continuing to enroll from the above centers and from additional centers to expand our sample and exploring these differences further.

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Systemic Lupus Erythematosus (SLE) and Vitamin D (Vit D) Deficiency Are Associated with Shorter Telomere Length. Brett M. Hoffecker[1], Laura M. Tonks[2], Tamara K. Nowling[1] and Diane L. Kamen[1]. [1]Medical University of SC, Charleston, SC, [2]UNC Chapel Hill, NC

Background/Purpose: Premature shortening of telomere length, a marker of cellular senescence, has been observed in patients with SLE and in a population deficient in vit D. Vit D deficiency, alarmingly prevalent among African Americans with SLE, has important implications for health. Our study tested whether leukocyte telomere length (LTL) shortens more rapidly with SLE and if this would be compounded by vit D deficiency. Gullah African Americans enrolled in the SLE in Gullah Health (SLEIGH) case-control study are ideal to address this hypothesis because of genetic homogeneity with low non-African admixture.

Methods: Comparisons were made between female SLE patients (n=59, age 39.9 +/−11.6 years) and age- and gender-matched controls (n=59, age 39.9 +/− 11.6 years) from SLEIGH. Relative LTL was determined in triplicate by monochrome multiplex qPCR using stored DNA, with human Jurkat T cell line DNA used as standard on each plate. Serum 25-hydroxyvitamin D (25-D) was determined by RIA. Disease activity (SLEDAI), damage (SLICC) scores and SLE criteria (ACR) were compared among patients at baseline (n=59) and follow-up visits (n=29).

Results: SLE patients had shorter LTL (0.526 +/−0.166) compared to matched controls (0.581 +/−0.017), p=0.049. Age was inversely correlated with LTL (N=118, rho=−0.2, p=0.031) and higher baseline age predicts shorter (<=0.56) LTL, p=0.004. At baseline, subjects with deficient serum 25-D (<20 ng/mL, n=62) had shorter LTL (p=0.003). Among SLE patients, 25-D increased from 19.8 +/−12.9 to 29.3 +/−12.7, p<0.001, over a mean of 2.8 +/−1.9 yrs, without a significant change in LTL detected. Among patients with SLE no significant correlations between LTL and SLEDAI score, SLICC score, presence of end-stage renal disease (n=8), or number of ACR SLE criteria were found.

Conclusion: We found that Gullah African American SLE patients have shorter LTL compared to Gullah controls matched for gender and age. We found also that 25-D deficiency correlates with shorter LTL. These observations are consistent with autoimmunity and low vit D status contributing to cellular aging. Further studies are needed to determine if replacement of vit D can impact clinical expression of SLE and/or LTL shortening.

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Systemic Lupus Erythematosus Responder Index Assessment of Responders in EMBLEM, a Phase IIb Study in Patients with Moderate to Severe Systemic Lupus Erythematosus. Michelle Petri[1], Marilyn C. Pike[2], Lexy Kelley[3], Brian Kilgallen[4] and Caroline Gordon[5]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Med Pharm Consulting Inc, Cambridge, MA, [3]UCB, Smyrna, GA, [4]UCB, Brussels, Belgium, [5]Medical School, Birmingham, United Kingdom

Background/Purpose: Epratuzumab is an anti-CD22 monoclonal antibody under development for SLE. EMBLEM (SL0007 [NCT00624351]) was a randomized, multicenter, placebo-controlled, double-blind, phase IIb study. SLE is complex and challenging to evaluate. EMBLEM used a novel composite endpoint, the BILAG-based Composite Lupus Assessment (BICLA). Efficacy was seen at Week 12 after 4 doses of i.v. epratuzumab 600 mg weekly and 2 doses of 1200 mg every other week (treatment effect 24.8% and 19.4%). Another composite endpoint, the SLE Responder Index (SRI), was developed from the belimumab phase II program for use in phase III. The aim of this post-hoc analysis was to better understand drivers of response, by assessing subject response in EMBLEM using the SRI.

Methods: BICLA responders required: 1) BILAG-2004 improvement (BILAG A to B/C/D, BILAG B to C/D, and no BILAG worsening); 2) no deterioration in SLEDAI total score; 3) no worsening in physician's global assessment (PGA) by > 10%; and 4) must not have received non-protocol treatment. SRI responders required: 1) a reduction in total SLEDAI score of ≥ 4 points; 2) no new BILAG A or no more than 1 new BILAG B domain score; 3) no worsening in PGA by > 10%; and 4) must not have received non-protocol treatment. For both endpoints, patients not fulfilling all criteria or dropping out early were considered non-responders.

Results: Baseline mean total SLEDAI and BILAG scores in the whole study population were 14.8 and 15.2. Baseline characteristics were comparable between arms except for the number of SLEDAI 8-point items. SRI responder rate was higher than BICLA responder rate in all arms, with pronounced differences in the placebo, 1200 mg EOW and 1800 mg EOW arms (Table). Responder classification matched for most (166/227, 73%) subjects. Of subjects who differed (61/227, 27%), most (47/61, 77.0%) were BICLA non-responders but SRI responders. Of these, in 77% of cases response was due to improvement from baseline in a single item (SLEDAI 8 points, vasculitis [n = 7] or lupus headache [n = 15]; 4 points, arthritis [n = 14]), Overall SRI improvement requirement (≥ 4 point SLEDAI improvement) was more frequently achieved than BICLA improvement requirement (BILAG improvement): 121 [53.3%] pts vs 81 [35.6%] pts. Increasing SLEDAI cutoff to ≥ 6 and ≥ 8 points lowered placebo response to 39.5% and 31.6% but did not discriminate active therapy better.

Table. Comparison of responder rates and treatment effect in EMBLEM™ seen with BICLA and SRI endpoints

	Placebo (n = 38)	Epratuzumab 100 mg EOW (n = 39)	Epratuzumab 400 mg EOW (n = 38)	Epratuzumab 800 mg EOW (n = 37)	Epratuzumab 1200 mg EOW (n = 37)	Epratuzumab 1800 mg EOW (n = 38)
BICLA response rate	8 (21.1%)	12 (30.8%)	10 (26.3%)	17 (45.9%)	15 (40.5%)	9 (23.7%)
SRI response rate	19 (50.0%)	14 (35.9%)	12 (31.6%)	18 (48.6%)	23 (62.2%)	18 (47.4%)
Difference	+11 (+28.9%)	+2 (+5.1%)	+2 (+5.3%)	+1 (+2.7%)	+8 (+21.7%)	+9 (+23.7%)

EOW = every other week ×2 doses; QW = every week ×4 doses

Conclusion: BICLA and SRI are composite endpoints developed to improve SLE trial assessment. In this analysis of EMBLEM data, disagreement in BICLA and SRI response rates was driven by baseline distribution of items with high SLEDAI weights: greatest difference was seen in groups with more 8-point SLEDAI items at baseline. In SLE trials, assessment of individual SLEDAI and BILAG items should be monitored for consistency. Further work on the application of composite endpoints to SLE trials is warranted.

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Corticosteroid Use and Associated Risk of Adverse Events in Patients with Systemic Lupus Erythematosus: A Retrospective Claims Analysis.
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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by acute and chronic inflammation of various body tissues. Corticosteroids (CS) are often required to reduce inflammation and organ damage. However, CSs are associated with potential adverse events (AEs) when given in high doses or for prolonged periods. Little to no data are currently available on what the true risk of AEs might be among CS users within an SLE population.

Methods: A retrospective, cohort design using administrative claims data (study period: 1/1/2000–6/30/2010) was employed. Patients ≥18 years having at least 2 outpatient medical claims or 1 inpatient/emergency room claim with a primary/secondary SLE diagnosis (ICD-9-CM code 710.0x) from 07/01/2000–12/31/2007 were identified, with the index date deemed as date of first SLE diagnosis. Patients were required to have a prescription for CS within 6 months of their index date. Occurrence of CS-related chronic and acute AEs (Table 1) was assessed during the 24 months following CS initiation and compared to SLE patients with no exposure to CS during the same time period. CS users and non-users were required to be free of AEs during the 6-month period prior to index date. Risk differences in the development of each AE were determined using multivariate Cox proportional hazards models. To attenuate residual confounding, each model accounted for all measurable confounders including patient characteristics, SLE severity, other SLE treatments and risk factors (other than CS) associated with AEs.

Results: 989 SLE patients received CS and 1728 SLE received no CS in the sample. Patients receiving CS were younger (47.9 vs 49.7 years, $P=0.003$) and more likely to be female (88.8% vs 85.4%, $P=0.013$) than SLE patients with no CS use during the study period. After adjusting for baseline differences, the risk of each AE associated with CS use is highlighted in Table 1. SLE patients receiving CS were more likely to develop pneumonia, herpes zoster, fungal infections, cataracts, sleep disturbances, hypertension, type II diabetes, migraines and nausea/vomiting than SLE patients with no exposure to CS. There was no significant association between CS use and the remainder of AEs studied (Table 1). Under-coding of AE and short follow-up time may be contributors to the lack of association.

Table 1. Results of Adjusted Cox Proportional Hazards Models (Risk of AEs in CS Users Compared to Non-Users)

Adverse Event	CS Use Relative to No CS Use Hazard Ratio (95% Confidence Interval)
Chronic Adverse Events	
Depression	1.21 (0.959, 1.52)
Bipolar	1.48 (0.672, 3.24)
Osteoporosis	1.13 (0.849, 1.50)
Sleep disturbances*	2.01 (1.51, 2.66)
Metabolic syndrome	1.10 (0.516, 2.33)
Hypertension*	1.39 (1.14, 1.69)
Obesity	1.23 (0.831, 1.83)
Type II diabetes*	1.76 (1.27, 2.45)
Cataracts*	1.67 (1.26, 2.20)
Avascular necrosis	1.77 (0.652, 4.78)
Migraine*	1.59 (1.13, 2.25)
Dyslipidemia	1.16 (0.957, 1.41)
Acute Adverse Events	
Urinary tract infection	1.22 (0.99, 1.51)
Herpes zoster*	1.77 (1.06, 2.98)
Fungal infection*	1.97 (1.39, 2.79)
Gastrointestinal ulcers/bleeds	1.12 (0.832, 1.50)
Fracture	1.19 (0.86, 1.64)
Pneumonia*	2.50 (1.80, 3.46)
Nausea/vomiting*	1.89 (1.45, 2.49)
Sepsis	1.55 (0.787, 3.05)
Tuberculosis	1.59 (0.71, 3.55)

*$P<0.05$

Conclusion: While CS is frequently prescribed to control symptoms of SLE, the results highlight the potential risks associated with its use in this subset. Due to the retrospective, non-randomized nature of this study, a true causal link cannot be made between CS use and AEs. Although further work is necessary to quantify the relationship between amount of steroid use and risk of AEs, these results support the potential benefits of reducing CS use wherever possible.

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Prevalence and Associated Factors for Asymptomatic Pulmonary Arterial Hypertension in Patients with Systemic Lupus Erythematosus.
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Background/Purpose: Pulmonary arterial hypertension (PAH) is one of the rare but devastating complications in connective tissue diseases. PAH in systemic lupus erythematosus (SLE) is underrecognized in the clinical field. Early identification of PAH is important and can alter the natural course. The purpose of this study is to estimate point prevalence of asymptomatic PAH and determine the associated factors for PAH in a cohort of SLE patients.

Methods: A prospective cross-sectional study of 103 patients with SLE were recruited in a single tertiary centre. Transthoracic echocardiography was performed to estimate the pulmonary arterial pressures. PAH was defined as resting systolic pulmonary artery pressure (sPAP) ≥ 40 mmHg, in the absence of left heart disease. The patients were also evaluated with respect to their clinical and serologic features, and disease treatment.

Results: PAH was identified in eight patients (8.74%) who had no history of interstitial lung disease. Fourteen patients (13.59%) had sPAP of 30–40 mmHg. Higher SLEDAI score (11.7 ± 8.4 vs. 5.9 ± 5.1, $p = 0.004$ and lower positivity of anti-Ro/SSA antibody (22.2% vs. 65.9%, $p = 0.010$) was observed in patients with PAH than patients without PAH. Of note, serum uric acid (UA) was significantly higher in patients with PAH than in those without PAH (7.72 ± 0.70 vs. 5.45 ± 0.22 mg/dl, $p = 0.001$). However, no significant differences in disease duration, Raynaud's phenomenon, antiphospholipid antibodies were found between these groups. In multivariate analysis, higher serum UA level was independently associated with the presence of PAH. Interestingly, serum UA level correlated significantly with plasma B-type natriuretic peptide level ($r = 0.439$, $p < 0.001$). Serum monocyte chemoattractant protein-1 (MCP-1) levels were also elevated in patients with PAH (592.38 ± 165.51 vs 274.71 ± 26.48 pg/ml, $p = 0.001$). Crystal-free UA dose-dependently increased MCP-1 production in endothelial cells and enhanced monocytes chemotaxis by MCP-1.

Conclusion: Clinically asymptomatic PAH is not uncommon in SLE patients. Serum UA level may be useful as a surrogate marker for screening of PAH. Uric acid stimulates endothelial MCP-1 production and monocyte chemotaxis, potentially contributing to the pathogenesis of PAH.

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Feasibility of Implementing a Lifestyle Intervention and Its Effects on Metabolic Parameters and Adipokines in Overweight and Obese Patients with Systemic Lupus Erythematosus.
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Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at increased risk for cardiovascular disease, more likely to be sedentary, have chronic inflammation and altered metabolic parameters and adipokines. Few studies have evaluated the feasibility of a lifestyle intervention and its effects on metabolic parameters and adipokines in overweight/obese patients with SLE. Thus, it is important to examine interventions that can positively impact weight and physical activity in SLE patients. The purpose of this pilot study was to investigate the effect of a 16-week lifestyle intervention on weight loss and physical activity, in addition to its effects on metabolic parameters and adipokines in overweight/obese SLE patients.

Methods: A lifestyle program included a reduced calorie diet (1200/1500 kcal/d) and a progressively increased physical activity from 100 to 300 min/wk by week 16. Paired t-tests were used to determine significant differences between measurements at baseline and week 16.

Results: Fifteen SLE female subjects (mean age=39.7±10.4yrs, 53% Caucasian, mean body mass index/BMI=30.8±3.7 kg/m^2). Measurements were assessed at baseline and 16 weeks in 9 subjects (60% completion rate). The majority (88%) was insulin resistant by HOMA-IR at baseline (mean HOMA-IR: 2.82±1.03). Mean% weight change was −9.8±2.8%, mean weight lost was 8.2±2.0 kg, and self-reported physical activity was 190±59.4 min/wk (90% of subjects reached the 20 min/session goal in weeks 1 and 2 and 57% of subjects reached the goal of 60 min/session in weeks 15 and 16). All 9 subjects achieved significant reduction ($p<0.05$) in weight (−8.2±2.0 kg), BMI (−3.04±0.7 kg/m^2), waist circumference (−10.8±4.9 cm), leptin (−9.4±4.6 ng/mL) and adiponectin (−0.1±0.1 ug/mL) levels. Mean self-reported physical activity minutes/session significantly increased from weeks 1 and 2 to weeks 15 and 16 (+25.6 min/session). Significant correlations were observed between changes in weight and leptin (Spearman's correlation/r= −0.77, p=0.02), between changes in waist and adiponectin (r= 0.83, p= 0.01) and between changes in weight and fasting insulin (r=0.58, p=0.05).

Conclusion: These results demonstrate the feasibility of a pilot lifestyle program on weight loss and increased physical activity that can lead to significant improvements in metabolic profiles and adipokines in overweight/obese SLE patients. Additional research is needed to improve subject completion rate and compliance to physical activity goals in future programs. Moreover, research with a larger sample and compared to a control group should examine how a lifestyle program may impact SLE patients longer term and other health parameters (i.e. SLE-specific and psychosocial factors).

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Renal Mir-150 As Potential Biomarker of Chronicity in Lupus Nephritis. Hua Zhou[1], Sarfaraz A. Hasni[2], Mayank Tandon[1], Ilias Alevizos[1], Howard A. Austin[3], James E. Balow[3] and Gabor G. Illei[1]. [1]NIDCR, Bethesda, MD, [2]NIH/NIAMS, Bethesda, MD, [3]NIH/NIDDK, Bethesda, MD

Background/Purpose: Histological variations of kidney injury in lupus nephritis are associated with different renal outcomes. Novel quantitative biomarkers which can mirror the degree of renal damage may be useful to help clinical decision making and assist in the choice of optimal therapy. microRNAs (miRs) are involved in many biologic processes and have shown promise as biomarkers in other settings. In this study we assessed the association of miR expression profiles with histologic features of chronicity of kidney biopsies from proliferative lupus nephritis patients.

Methods: MicroRNA expression profiles were analyzed on total RNA obtained from 18 formalin fixed paraffin embedded (FFPE) kidney biopsies from 8 patients by Affymetrix miR microarray. The expression of miR-150 was assessed by Taqman qRT-PCR on 10ng of total RNA in 16 of these samples and an additional 7 samples from 6 patients. miR150 levels are expressed as their relative expression (deltaCt) compared to U48 used as an endogenous control. Repeat biopsies from the same patient were done based on clinical indication, primarily for nephritis flares. The association between miR-150 and histological chronicity index (CI) was analyzed using the Prism 5 statistical software package.

Results: miR-150 was the most differentially expressed miR on microarrays between the renal biopsies with high CI (CI >4, n=9) compared to low CI (n=9). miR-150 signal intensity was 4-fold increased in the high CI group by microarray analysis. deltaCt values of renal miR-150 obtained by qRT-PCR were significantly higher in the high CI (mean 2.83, SD 1.6) vs the low CI (mean 0.65, SD 1.2; p= 0.0017 Student's t test) groups. Moreover, the miR-150 deltaCt values showed strong positive correlation with CI scores (Pearson's r=0.73 $p<0.0001$).

Conclusion: microRNA can be isolated from archived FFPE specimens with good enough quality for miR microarray and qRT-PCR. Renal miR-150 level was differentially expressed in kidney biopsies from patients with proliferative lupus nephritis with either low or high degree of chronicity. The positive correlation of miR-150 with chronicity index suggests that it may be a useful quantitative biomarker for evaluating kidney injury in lupus nephritis.

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Prevalence of Direct Coombs Test in Systemic Lupus Erythematosus. Clinical and Immunologic Associations. Ana-Maria Orbai[1], Hong Fang[1], Graciela S. Alarcón[2], Caroline Gordon[3], Joan T. Merrill[4], Paul R. Fortin[5], Ian N. Bruce[6], David A. Isenberg[7], Daniel J. Wallace[8], Ola Nived[9], Gunnar K. Sturfelt[10], Rosalind Ramsey-Goldman[11], Sang-Cheol Bae[12], John G. Hanly[13], Jorge Sanchez-Guerrero[14], Ann E. Clarke[15], Cynthia Aranow[16], Susan Manzi[17], Murray B. Urowitz[18], Dafna D. Gladman[19], Kenneth C. Kalunian[20], Melissa I. Costner[21], Laurence S. Magder[22], Systemic Lupus International Collaborating Clinics (SLICC)[23] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Birmingham, Birmingham, United Kingdom, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Toronto Western Hospital, Toronto, ON, [6]A, Manchester, United Kingdom, [7]University College London, London WC1E 6JF, United Kingdom, [8]Cedars-Sinai/UCLA, Los Angeles, CA, [9]University Hospital, Lund, Sweden, [10]University Hospital Lund, Lund, Sweden, [11]Northwestern University Feinberg School of Medicine, Chicago, IL, [12]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [13]Dalhousie University, Halifax, NS, [14]University Health Network/Mount Sinai Hospital, Toronto, ON, [15]Research Institute of the McGill Univ. Health, Montreal, QC, [16]Feinstein Institute for Medical Research, Manhasset, NY, [17]Allegheny Singer Research Institute, Pittsburgh, PA, [18]Toronto Western Hospital and University of Toronto, Toronto, ON, [19]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [20]UCSD School of Medicine, La Jolla, CA, [21]North Dallas Dermatology Assoc, Dallas, TX, [22]University of Maryland, Baltimore, MD, [23]Chicago

Background/Purpose: To determine the prevalence of the direct Coombs in SLE and controls with other rheumatologic diseases, and to characterize its clinical associations.

Methods: The Systemic Lupus International Collaborating Clinics Revision of SLE Classification Criteria derivation and validation datasets were merged for the purpose of this study. The analyses were based on 868 patients with both direct Coombs measured and physician consensus diagnosis available (456 SLE and 412 controls). Of the 456 SLE patients, 412 (90.4%) were female, 279 (61.2%) Caucasian, and 89 (19.5%) African descent. Their mean age was 37.7±13.4. The results were based on the chi-square test (SAS Institute, Cary, NC, USA). A p-value ≤0.05 was considered statistically significant.

Results: The prevalence of the positive direct Coombs test was 21% (96/456) in SLE patients and 6% (25/412) in controls (P-value <.0001), sensitivity 21%, and specificity 94% for SLE. Of 96 SLE patients with positive direct Coombs, 79 (82.3%) had never had hemolytic anemia.

Table 1. Association between Demographic Characteristics and Direct Coombs in SLE

Variable		Positive Direct Coombs (%)	P-value
Ethnicity	African descent	16.8	0.39
	Caucasian	16.5	
	Asian	25.0	
	Other	12.5	
Gender	Female	17.7	0.46
	Male	13.6	
Age	≤30	21.1	0.15
	>30	15.6	

Table 2. Association between ACR Criteria and Direct Coombs Status in SLE, Excluding Patients with Hemolytic Anemia

Variable	Positive Direct Coombs (%)	Negative Direct Coombs (%)	Odds Ratio (95% CI)	P-value
Malar Rash	40.5	42.7	0.9 (0.6, 1.5)	0.72
Discoid Rash	12.7	18.3	0.6 (0.3, 1.3)	0.23
Photosensitivity	41.8	49.1	0.7 (0.5, 1.2)	0.24
Oral Ulcers	39.2	40.3	1.0 (0.6, 1.6)	0.86
Arthritis	69.6	61.3	1.4 (0.9, 2.4)	0.16
Serositis	36.7	31.8	1.2 (0.7, 2.1)	0.40
Pleurisy	32.9	25.2	1.5 (0.9, 2.5)	0.16
Pericarditis	15.2	12.2	1.3 (0.6, 2.6)	0.47
Renal criterion	36.7	34.2	1.1 (0.7, 1.8)	0.67
Neurologic	10.1	6.4	1.7 (0.7, 3.8)	0.23
Hematologic	60.8	47.5	1.7 (1.0, 2.8)	0.032
Leukopenia	36.7	26.8	1.6 (0.9, 2.6)	0.08
Lymphopenia	34.2	28.1	1.3 (0.8, 2.2)	0.28
Thrombocytopenia	21.5	13.8	1.7 (0.9, 3.2)	0.08
Immunologic	94.9	81.2	4.4 (1.5, 12.3)	0.0027
Anti-dsDNA	76	62.1	1.9 (1.1, 3.4)	0.02
Anti-Smith	34.2	23.6	1.5 (0.9, 2.8)	0.049
Antiphospholipid	64.6	52.8	1.6 (0.9, 2.7)	0.055
Anticardiolipin IgG	27.9	17	1.9 (1.1, 3.3)	0.025
Low complement	81	60.5	2.8 (1.5, 5.1)	0.0005

Conclusion: The great majority of patients with SLE and a positive direct Coombs had never had hemolytic anemia. A positive direct Coombs test was highly associated with SLE versus other rheumatologic diseases. It was associated with the ACR hematologic criterion, anti-dsDNA, anti-Smith, anticardiolipin IgG and low complement. These data justify the decision by SLICC to include direct Coombs in the new classification criteria for SLE.

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Predictors of Earlier Time to Renal Failure Among Those with Biopsy-Proven Lupus Nephritis. Alí Duarte-García[1], Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Prevention of renal failure is the ultimate goal of therapy of lupus nephritis (LN). Determination of risk factors and protective factors requires long-term follow up, not available in the clinical trial setting. We determined predictors of earlier time to renal failure in a longitudinal cohort of biopsy-confirmed LN.

Methods: Based on combined retrospective and prospectively collected data, we estimated the probability of renal failure within 10 and 20 years of biopsy based on 422 SLE patients with LN biopsy of either ISN Class I, II, III, IV, V, of VI. Based on prospectively collected cohort data, we used Cox regression methods to assess the relationship between time-varying clinical variables and progression to renal failure in the subset of these patients (393) who did not have renal failure before active follow-up in our cohort. The patients were 91% female, 50% African-American, 6% "other", with mean age at biopsy of 33 years of age.

Results: In our cohort, the risk of renal failure within 10 years of a positive LN biopsy was 16% (Table 1). Risk was substantially higher among those with Class IV LN than those with other classes of LN. During cohort follow-up, adjusting for Cockcroft-Gault eGFR at the start of follow-up, those who were younger or those who were more often positive for anti-dsDNA were at increased risk of renal failure (Table 2). After adjusting for age and ISN Class, the strength of association between anti-dsDNA and risk of failure was diminished (Rate Ratio comparing those with frequent anti-dsDNA to those with none, 2.6, p=0.13).

Table 1. Relationship between LN class and risk of renal failure, considering those with combined biopsy results as a separate class.

Subgroup	Estimated percent chance of developing Renal Failure within 10 years (95% CI)	Estimated risk of developing renal failure within 20 years (95% CI)
Any Class (n=422)	16.3 (12.4, 21.3)	25.7 (19.0, 34.4)
Class II (n=37)	13.3 (4.5, 35.7)	25.9 (18.8, 35.1)
Class III (n=63)	3.7 (1.0, 24.5)	32.9 (12.3, 70.3)
Class IV (n=129)	38.3 (20.0, 39.1)	38.9 (26.6, 55.1)
Class V (n=86)	3.7 (1.2, 11.2)	3.7 (1.2, 11.2)
Combination (n=105)	17.8 (11.1, 27.7)	22.4 (13.1, 36.7)

[1] This p-value assesses the degree of evidence against the hypothesis that failure probabilities in the two groups are equal at all time points.

Table 2. Association between predictors and kidney failure during cohort participation based on separate models for each variable, controlling for GFR at start of follow-up.

Variable		Rate Ratio (95% CI)	P-value
Gender	Male (vs. female)	1.1 (0.3, 3.6)	0.88
Age	30–39 (vs. < 30)	0.4 (0.2, 1.1)	0.076
	40+ (vs. < 30)	0.3 (0.1, 0.7)	0.0056
Race	African-American (vs. Caucasian)	1.4 (0.6, 2.9)	0.44
	Other (vs. Caucasian)	0.7 (0.1, 3.1)	0.62
Anti-dsDNA	Some but <50% of follow-up (vs. none)	0.9 (0.2, 3.7)	0.92
	50%+ (vs. none)	3.5 (1.2, 10.6)	0.024
Low Complement	Some but <50% of follow-up (vs. none)	1.8 (0.3, 9.3)	0.49
	50%+ (vs. none)	1.8 (0.7, 4.9)	0.25
Systolic Blood Pressure at start of follow-up	130+ mmHg (vs. <130)	0.9 (0.5, 1.9)	0.86
Plaquenil Use	Some, but <50% of time (vs. none)	1.2 (0.5, 3.3)	0.70
	>50% (vs none)	1.0 (0.4, 2.2)	0.94
ACE or ARB	Some, but <50% of time (vs. none)	1.3 (0.4, 3.7)	0.67
	>50% (vs none)	0.9 (0.4, 2.1)	0.90
Class II LN		0.9 (0.4, 2.1)	0.77
Class III LN		0.4 (0.2, 1.3)	0.12
Class IV LN		3.3 (1.5, 7.4)	0.0027
Class V LN		0.8 (0.4, 1.7)	0.56

Conclusion: These prospective cohort data indicate a 16.3% chance of renal failure at 10 years and 25.7% at 20 years, with Class IV having the worst prognosis. There was no evidence that Plaquenil or ACE-inhibitor use was protective. Those who were younger were at increased risk, and there was some evidence that those more often positive for anti-dsDNA were at increased risk. These data suggest that normalization of anti-dsDNA might be an important therapeutic target to reduce renal failure.

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Do Active Lupus Patients Continue to Improve At 12 Months by Systemic Lupus Erythematous Disease Activity Index 2000 Responder Index 50 (SRI-50)? Zahi Touma[1], Murray B. Urowitz[1], Dominique Ibanez[1], Shahrzad Taghavi-Zadeh[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: A previous study showed that SRI-50 detects partial but clinically important improvement, ≥50%, in disease activity between visits in response to standard of care treatment. Patients are deemed improved (responders) if their SLEDAI-2K decreases by ≥4. We aimed to determine if lupus patients continue to improve at 12 months as determined by SRI-50. To evaluate if SRI-50 identifies more responders at 6 and 12 months as compared to SLEDAI-2K.

Methods: This study was conducted on active lupus patients with SLEDAI-2K≥6 at baseline visit who attended the Lupus Clinic from September 2009 to April 2011. Patients were followed regularly every 3–4 months over 12 months. SLEDAI-2K scores were determined at baseline and at follow-up visits and SRI-50 scores were determined at follow-up visits. Patients received standard of care treatment. A patient was defined as responder when the total score on follow-up visit decreased by ≥4. We determined the percentage of responders at follow-up visits, using SLEDAI-2K definitions and scores and using SRI-50 definitions and scores.

Results: 66 patients with SLEDAI-2K≥6 at baseline visit were identified and followed over 12 months. Patient demographics are presented in table 1.

Table 1. Patients' characteristics

Sex	Female 60 (91%)/6 (9%)
Age at diagnosis (years)	28±12
Age at 1st visit in the study (years)	42±14
Disease Duration at 1st visit in the study (years)	14±11
Race	
Caucasian	36 (55%)
Black	36 (55%)
Asian	36 (55%)
Others	2 (3%)
SDI at 1st visit in the study	1.43±5.47
Prednisone at baseline visit: patients number (%)	51 (77%)
Anti-malarial number: patients number (%)	47 (71%)
Immunosuppressants: patients number (%)	44 (67%)

SLEDAI-2K at baseline was 10.36±4.77. SLEDAI-2K at 12 months was 6.34±4.69 and SRI-50 was 5.53±4.58 (Table 2).

Table 2. Results of disease activity assessment of 66 patients with active lupus at baseline visit (SLEDAI-2K ≥6)

Visits	SLEDAI-2K	SRI-50	SLEDAI-2K difference	SRI-50 difference	P values
Baseline	10.36±4.77	10.36±4.77	0±0	0±0	<0.001
3–6 months	6.75±4.12	5.90±3.82	3.64±5.25	4.50±5.17	<0.001
12 months	6.34±4.69	5.53±4.58	4.01±5.46	4.82±5.57	<0.001

More importantly the number of responders at 3–6 months as determined by SRI-50 was greater then SLEDAI-2K, 36(55%) and 39 (60%), respectively. Similarly, at 12 months SRI-50 identified more responders as compared to SLEDAI-2K, 39 (59%) and 42 (64%), respectively.

Conclusion: Lupus patients with moderate to severe disease activity continue to improve at 1 year as determined by SRI-50 and SLEDAI-2K. SRI-50 was able to indentify more responders at 6 and 12 months as compared to SLEDAI-2K. SRI-50 showed superiority over SLEDAI-2K in identifying responders throughout the study period.

1386

Lupus Disease Activity Does Not Improve Significantly in One System and Worsen in Another System. Zahi Touma[1], Dafna D. Gladman[2], Dominique Ibanez[1], Shahrzad Taghavi-Zadeh[1] and Murray B. Urowitz[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) is a global index that generates a score describing overall disease activity in 9 systems. The British Isles Lupus Assessment Group (BILAG) index generates scores for each organ system separately. It has been suggested that disease activity may improve in some systems while worsening in others making it difficult to interpret outcomes using a global activity index. We aimed to determine 1) if disease activity improves significantly in one system while worsening in another system. 2) if the global disease index SLEDAI-2K, is valid to identify patients who had a clinically important improvement with no worsening in other systems.

Methods: This is a cross-sectional study conducted on active lupus patients who attended the Lupus Clinic from September 2009 to May 2011. Patients were included if at baseline visit their SLEDAI-2K was ≥6. All patients had at least one follow-up. SLEDAI-2K and the BILAG index were determined initially and follow-up visit. Patients were treated with standard of care. We identified the first visit available in which patients had improved by decreasing their SLEDAI-2K ≥4. The assessment of the 8 systems was determined using the BILAG index grade (BLIPS V4.0.). In the group of patients who improved we identified any patients who had new A or new B score on BILAG on the follow-up visit as compared to the baseline visit. Descriptive statistics were used to describe the characteristics of the patients.

Results: The patient population included 103 lupus patients. The length of time interval between baseline and last visit was 5.3±3.5 months. Of the 103 patients studied 71 patients had improved their SLEDAI-2K score by ≥4 on follow-up visit. Patients' demographics are presented in table 1.

Table 1. Characteristics of 71 patients who improved

Sex	F 62 (87%)/M 9 (13%)
Age at diagnosis (years)	28.2±11.2
Age at 1st visit in the study (years)	40.8±13.8
Disease Duration at 1st visit in the study (years)	12.7±10.3
Race	
Caucasian	39 (55%)
Black	18 (25%)
Asian	4 (6%)
Others	10 (14%)
SDI at 1st visit in the study	1.4±1.8
Prednisone at baseline visit: patients number (%)	56 (79%)
Anti-malarial number: patients number (%)	51 (72%)
Immunosuppressants: patients number (%)	43 (61%)

Among the 71 patients who improved the mean SLEDAI-2K scores were at baseline visit 11.7±5.3 and 6.4±4.9 at follow-up visit. More importantly among the patients who improved none had a new A on follow-up visit as compared to baseline visit. 2 patients had each a new B on follow-up visits. In both patients new B resulted from a drop in hemoglobin to $<11\times10^9$/ liter (10.3×10^9/ liter and 10×10^9/ liter, respectively) despite the absence of active hemolysis and in the setting of a negative Coombs test. The change in the hemoglobin level was not clinically important to require a change in lupus medications and this change was not related to lupus disease activity.

Conclusion: In this study we showed that if disease activity improves significantly in one system it is unusual to have clinically important worsening in another system. SLEDAI-2K 30 days can be used as an independent single measure to determine improvement in disease activity in lupus patients.

1387

Low Placebo Responses and Clinical Components of the Biomarkers of Lupus Disease (BOLD) Study May Provide Useful Insights for Systemic Lupus Erythematosus Clinical Trial Design. Sudhakar T. Sridharan[1], T. Zhou[1], F. Immermann[1], M. Lehmann[1], J.L. Masferrer[1], M. Honczarenko[1], J.C. Rawdon[2], J.A. James[2] and J.T. Merrill[2]. [1]Pfizer Inc, Collegeville, PA, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Interpretation of lupus clinical trials may be confounded by background immune suppressants (IS) promoting high placebo response rates, and challenges defining efficacy in a heterogenous disease population. The BOLD study addresses whether withdrawal of background IS would be safe and lessen time to flare in a placebo group and also compares current trial measures as endpoints.

Methods: Discriminatory capacity of outcome measures and impact of IS are being assessed cross sectionally in 100 patients (pts) and longitudinally in 50 pts in whom IS are withdrawn, brief steroids given and subsequent flares evaluated. This interim report includes 80 active patients entered with >/=2 BILAG B or 1 BILAG A or SLEDAI >6.

Results: Of 80 subjects in this interim analysis, mean age was 40.9 (11.9) yrs, majority female (91%), Caucasian (60%) African American (21.25%), American Indian (17.5%), and Asian (1.25%). Ethnicity had no impact on baseline disease activity or outcomes. Disease activity was higher in pts on prednisone (n= 27 mean dose 11.4 mg/d) than not (n=53]: SLEDAI 10.0 vs 8.0 p=0.036, Classic BILAG 12.0 vs 8.0 p = 0.009) confirmed in a multivariate model including other IS (p=0.035 SLEDAI, p <0.001 BILAG). 31 pts have completed follow up after IS withdrawal and brief steroid burst (up to three 160mg IM Depomedrol injections within 2 weeks)..Median time to flare was 72 days (CI 43–91), and 100% flared by week 24. Significant differences between baseline, improving, and flare visits were detected by PGA (mean 1.889, 0.882, 1.857 p <0.001), SLEDAI (mean 8.2, 4.2, 7.7 p <0.001) BILAG (mean 9.4, 3.7, 9.2 p <0.001) and CLASI (skin) scores (median 4.0, 1.0, 2.0 p<0.001). Independent safety adjudication findings were 42 total AEs including 20 mild/moderate infections, one serious (bleeding ulcer) and one unexpected event (perianal abcess). 15 patients had flares exceeding baseline disease with 4 severe flares and no serious adverse events related to flare. All flares resolved within 6 weeks after treatment.

Relative Performance of Outcome Measures in Detecting Improvement

BASELINE versus:	SRI-4	SRI-5	SRI-BILAG	BOLD Criteria*
Week 4 n=31	**15** (p=0.068)	**8** (p<0.001)	**21**	23
Week 8 n=21	14	8	9	11
Imp Visit n=31	17 (p<0.001)	**11** (p<0.001)	**27**	31
Flare Visit n=31	4	2	0	0

* (>/= drop of one BILAG grade or SLEDAI 4 pt)
SRI-4/5 (from BLISS trials) SRI-BILAG (from EMBLEM trial)
Analysis by Fisher's exact test compared to BOLD criteria

Conclusion: Withdrawal of IS may be safe and well tolerated in SLE trials and produces rapid endpoints for placebo pts who can then receive early rescue therapy without confusing outcomes. The compound endpoint SRI-BILAG may be more sensitive to change than SRI when anchored to the simpler BOLD improvement criteria. These differences could be clinically meaningful given the known effectiveness of steroid treatment used in BOLD.

1388

Frequency and Characteristics of Prolonged Remission in Systemic Lupus Erythematosus. Amanda J. Steiman[1], Murray B. Urowitz[1], Dominique Ibanez[1], Anjali Papneja[2] and Dafna D. Gladman[3]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, incurable autoimmune disorder, classically characterized by a relapsing/remitting course. However, a small subset of SLE patients display a prolonged clinical remission. These patients represent a clinically important group that may provide further insights into SLE pathophysiology. In this study we characterize the clinical course of SLE patients, followed at a single centre, who have achieved prolonged remission.

Methods: Patients followed regularly in the Lupus Clinic between July 1970 and May 2011 were identified in our database. We defined a prolonged remission as SLEDAI-2K = 0 (serologically quiescent clinically quiescent (SQCQ)), or = 2 or 4 on the basis of active serology alone (serologically active clinically quiescent (SACQ)) for at least five consecutive years, with visits ≤ 18 months apart, during which time the patients could be taking antimalarials, but not steroids or immunosuppressives. Flare was defined as any clinical activity on SLEDAI-2K, or by the initiation of steroids or immunosupressives. Each patient's pre-remission clinical course was classified as monophasic (single flare followed by remission), relapsing/remitting (≥2 fluctuations in SLEDAI-2K of ≥4 on the basis of clinical activity), or chronic active (persistent clinical activity with SLEDAI fluctuating by ≤3 at

each visit). Adjusted mean SLEDAI (AMS) was calculated for each patient for the three years leading up to remission. Descriptive statistics were used.

Results: 38 of 1613 (2.4%) patients achieved prolonged remission. One patient experienced two discrete prolonged remission periods, thus 39 periods were studied. 32 (84.2%) patients were female. Mean duration of SLE clinic follow up was 21.8 ± 10.3 years, and the average time to remission from clinic entry was 9.1 ± 8.8 years. The mean prolonged remission duration was 11.6 ± 6.4 years. 17 remission periods were SQCQ, 11 were SACQ and 11 were mixed SQCQ/SACQ. When subdivided by type, mean remission duration was 9.7± 5.7, 9.7 ± 3.5 and 17.0 ± 6.9 years for SQCQ, SACQ and mixed remissions, respectively. All but one of the 28 patients who continue to be followed contemporarily were in remission at their last clinic visit. Antimalarials were being used by 16 (42.1%) of patients at remission onset, with a further 5 (13.1%) using them at some point during their remission. Twenty-three (60.5%) patients had relapsing/remitting disease, 7 (18.4%) had monophasic illness, and 3 (7.9%) had chronic active disease prior to remission; a further 5 (13.2%) were in remission on transfer to the clinic, with 4 maintaining their remission until their most recent clinic visit. Mean AMS over the three years prior to onset of remission was 2.9 ± 1.7.

Conclusion: Prolonged clinical remission is an infrequent outcome among SLE patients, lasts more than a decade, and is preceded by an atypically monophasic clinical course in a significant minority. These occurrences may be reflective of unique pathophysiologic mechanisms, and warrant further investigation.

1389

Comparison of the SF-36 Vs. Lupus Qol in Measuring Health-Related Quality of Life in Systemic Lupus Erythematosus Women with and without Activity. Claudia Mendoza-Pinto[1], Mario Garcia-Carrasco Sr.[1], Socorro Mendez-Martinez[1], Oscar Pazarán[1], Mario H. Cardiel[2] and Aurelio Lopez-Colombo[3]. [1]HGR 36 CMN Manuel Ávila Camacho, Instituto Mexicano del Seguro Social, Puebla, Mexico, [2]Hospital, Morelia, Mexico, [3]Delegación Estatal, Instituto Mexicano del Seguro Social, Puebla, Mexico

Background/Purpose: The Lupus QoL questionnaire was developed in the United Kingdom as a disease-specific health-related quality of life instrument for adults with systemic lupus erythematosus (SLE). The Short Form-36 (SF-36) is a valid, reliable tool that captures the physical, psychological, and social impact of SLE. The purpose was to compare health-related quality of life (HRQL) in women with and without SLE activity using the Lupus Qol vs. SF-36.

Methods: We conducted a comparative study of women aged ≥ 18 years, attended by our Lupus Clinic. HRQL was assessed by administration of the Lupus QoL and SF-36. In both surveys, each question is evaluated using a 5-point Likert response. Each of the 8 domain scores range from 0 to 100. Lupus activity was measured using the Mex-SLEDAI and chronic damage using the Systemic Lupus Collaborative Clinics Damage Index (SDI). Data were analyzed using descriptive statistics, the chi-square test and Spearman's correlation.

Results: A total of 106 were included with a mean age of 41.46 ± 13.32 years. The mean disease duration was 8.55 ± 5.7 years, the mean activity score was 2.6 ± 2.47, and the mean SDI score 0.75 ± 1.03.The mean SF-36 score was 60.43 ± 20.63 and the mean Lupus QoL 71.03 ± 20.75. The correlation between the SF-36 and Lupus QoL was rho = 0.748. The correlation between lupus activity and the SF-36 and the Lupus QoL was −0.376 and −0.336, respectively. The correlation between the SDI and the SF-36 and the Lupus QoL was 0.354 and 0.429, respectively. Correlations for comparable domains of the SF-36/LupusQoL were: physical health /physical function: 0.784, emotional health/mental: 0.651, pain/bodily pain: 0.648, fatigue/vitality: 0.554. Correlations for non-comparable domains were mental component score (MCS)/planning: 0.557, MCS/body image: 0.470, MPC/burden to others: 0.409, physical domain/intimate relationship: 0.421, and all $p < 0.001$. The correlation between activity and the SF-36 was 0.748, $p = 0.026$, while the correlation with the Lupus Qol was not statistically significant.

Conclusion: The SF-36 and Lupus QoL HRQL questionnaires showed a moderate correlation between comparable and non-comparable domains. However, the Lupus QoL was not superior to the SF-36 in assessing HRQL in lupus patients. The utility of the Lupus QoL should be evaluated in studies in patients with moderate-to-severe disease activity.

1390

Cognitive Dysfunction and Diffusion Tensor Imaging in Systemic Lupus Erythematosus. Elizabeth Kozora[1], Aziz Ulug[2], Doruk Erkan[3], Glendalee Ramon[3], An Vo[4], Robert Zimmerman[5], Emily Duggan[1], JoAnn Vega[3], Christopher Filley[6] and Michael D. Lockshin[3]. [1]National Jewish Health, Denver, CO, [2]The Feinstein Institute for Medical Research, Manhasset, NY, [3]Barbara Volcker Center for Women and Rheumatic Diseases: Hospital for Special Surgery, New York, NY, [4]The Feinstein Institute for Medical Reearch, Manhasset, NY, [5]Weill Cornell Medical College, New York, NY, [6]University of Colorado School of Medicine, Aurora, CO

Background/Purpose: Cognitive dysfunction is common in Systemic Lupus Erythematosus (SLE) patients and has been associated with microstructural cerebral white matter (WM) abnormalities (Kozora & Filley, 2011). Diffusion tensor imaging (DTI) provides an index of the structural integrity of WM by using quantitative directional diffusion properties of water molecules for each voxel. The technique is based on the principle of anisotropy, a term referring to the propensity for water in the normal state to diffuse along the direction of WM tracts. The purpose of this pilot project is to examine WM microstructure with DTI in relation to cognitive function in SLE.

Methods: SLE patients fulfilling the ACR Classification Criteria with no history of overt neuropsychiatric (NP) disorders such as stroke, seizures, or major depression were: a) interviewed regarding detailed neuromedical histories and perceived cognitive impairment; b) administered the ACR-SLE neuropsychological battery; c) and received MR images with a 3T MR scanner. The DTI protocol included 60 slices of 2.6mm thickness with field of view of 240mm and image matrix of 128χ128 zero filled to 256χ256.

Results: We enrolled 20 patients (40% Caucasian) with a mean age of 36.5 +/−11.7, mean education 15.6 +/− 2.4 years, mean disease duration 154.8 +/− 122.9 months, and mean SLEDAI score 3.7 +/− 4.6. Forty-seven percent of the patients were on prednisone (mean dosage 8.3 +/− 1.6 mg). During the formal neuromedical interview, 11/20 (55%) reported cognitive difficulties in aspects of attention and memory. Based on the neuropsychological assessments, 60% of the SLE patients had global cognitive impairment. On specific tests, SLE patients were impaired on immediate visual recall (65%), delayed visual recall (65%), visuomotor sequencing (50%), visuomotor speed (45%), visual attention (40%), verbal learning (35%) verbal fluency to letter cues (35%), verbal fluency to a semantic cue (35%) and complex auditory attention (32%). Using objective cut-off scores, SLE patients with cognitive impairment had lower fractional anisotropy (FA) in the left inferior longitudinal fasciculus (ILF) ($p<0.001$), an occipitotemporal association tract related to memory and language (Shinoura et al., 2007; Kantarci et al., 2011).

Conclusion: This is the first study to demonstrate abnormal DTI in SLE patients without overt NP activity but with significant cognitive dysfunction. Based on DTI analysis, the objectively impaired SLE patients had abnormalities in the ILF. Our study suggests that disruption of WM tracts may underlie aspects of cognitive dysfunction in SLE.

1391

Impaired Responses to Aspirin in Patients with Systemic Lupus Erythematosus: The Role of Inflammation and Oxidative Stress. Vivian K. Kawai[1], Ingrid B. Avalos[2], Annette M. Oeser[1], John A. Oates[1], Ginger L. Milne[1], Cecilia P. Chung[3] and C. Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]Harvard University, Boston, MA, [3]Vanderbilt Medical Center, Nashville, TN

Background/Purpose: Aspirin is a widely used effective therapy for decreasing the risk of thrombosis. However, in some patients aspirin does not adequately suppress platelet thromboxane formation, a phenomenon termed "aspirin resistance". Many patients with lupus (SLE) have increased risk of thrombosis and thus receive aspirin. We previously reported that 15% of patients with SLE have impaired response to aspirin, and that this was associated with features of the metabolic syndrome (obesity, diabetes, and hypertension). The mechanism is unknown, but oxidative stress, which is associated with obesity and inflammation, has been implicated as contributing to this impaired response. Therefore, we tested the hypothesis that impaired response to aspirin in SLE is associated with increased oxidative stress.

Methods: We prospectively studied 34 patients with SLE who had stable disease and no contraindication to aspirin therapy. Patients received immediate-release aspirin 81 mg/day for 7 days. NSAIDs were withdrawn for 7 days before and during the study. We collected blood and urine before and after aspirin treatment to measure concentrations of serum TxB_2 (in whole blood allowed to clot at 37°C) and urinary 8-iso prostanglandin $F_{2\alpha}$

(F_2-isoprostanes) excretion, a robust measure of oxidative stress. We defined an impaired response to aspirin as the inability to suppress serum TxB_2 concentrations to <10 ng/ml. We compared urinary F_2-isoprostane excretion in patients with and without impaired responses to aspirin. Continuous data are described as median with interquartile ranges [IQR].

Results: Impaired response to aspirin was present in 15% (5/34) of patients with lupus. Patients with impaired aspirin response (n=5) were 60% female, age 45 [34–46 years], and those who were aspirin sensitive (n=29) were 86% female, age 40 [29–48 years]) (p>0.05). SLE patients with impaired response to aspirin had higher BMI (36.2, [28.9–36.6 kg/m^2] vs. 24.5, [22.3–27.7 kg/m^2]), p=0.055) and serum CRP concentrations (17.2, [1.8–19.9 mg/L] vs. 0.9,[0.6–4.0 mg/L], p=0.018) (Fig 1), and were more likely to be obese (60% vs. 14%, p=0.018) and have diabetes (40% vs. 7%, p=0.034). However, urinary F_2-isoprostane excretion did not differ significantly in aspirin insensitive (1.48, [1.37–2.82 ng/mg of creatinine]) and sensitive patients (1.56, [1.24–2.71 ng/mg of creatinine]) (p=0.933) (Fig 2).

Fig 1: C reactive protein (mg/L) concentrations in aspirin resistant and sensitive SLE patients

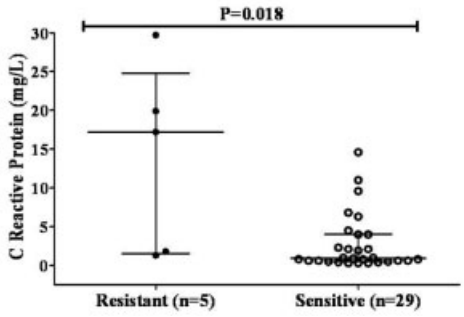
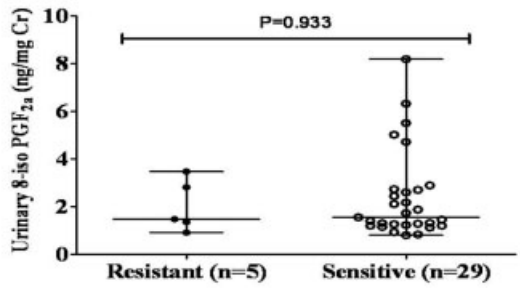


Fig 2: Urinary 8-iso PGF2α distribution in aspirin resistant and sensitive SLE patients



Conclusion: Oxidative stress, measured by urinary F_2-isoprostane excretion, was not associated with variability in sensitivity to aspirin in patients with SLE. However, decreased sensitivity to aspirin was associated with inflammation, as measured by CRP concentrations.

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Infection As a Predictor of Organ System Damage Accrual and/or Death in Systemic Lupus Erythematosus. Amanda Eudy[1], Deanna Hill[2], Qinggong Fu[2], Hong Fang[3] and Michelle Petri[3]. [1]UNC Chapel Hill, Chapel Hill, NC, [2]GlaxoSmithKline, Collegeville, PA, [3]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect many organ systems. Among individuals with SLE, infections are a leading cause of morbidity and mortality. Active SLE disease, deficiencies in the complement system, use of immunosuppressant therapy or prednisone and disease manifestations such as renal disease have been associated with an increased risk of infection. The majority of studies to date have focused on the risk factors for infection and subsequent death, but the association between incident infections as predictors of organ system damage has yet to be analyzed. Data from a prospective SLE cohort study were analyzed to determine the association between an infection during a 12-month period and risk of organ system damage accrual and death in SLE.

Methods: This study was comprised of 1,168 SLE patients from a prospective cohort. All patients had at least 24 months of follow-up during 1987–2010 and met the ACR criteria for SLE diagnosis. Patients were seen at least every three months at an academic tertiary medical center clinic. Disease activity was measured at each visit by SLE Disease Activity Index (SLEDAI), and organ system damage accrual was measured annually using the SLICC/ACR Damage Index (SDI). The analysis consisted of a 12-month observation period (OP) beginning 1 year after a patient's first clinic visit (index date) and a successive follow-up period (FP) of variable time lengths for each patient. The association between occurrence of any infection (viral, bacterial, thrush, or opportunistic) in the OP and death or subsequent organ system damage accrual in FP was measured by time-to-event analysis with Cox proportional hazard ratios (HR) and 95% confidence intervals (CI). Organ damage accrual was defined as a 1-unit increase in SDI score from start of FP. Multivariable analyses adjusted for age at cohort entry (years), gender, ethnicity, duration of disease at cohort entry (years), SDI at start of follow-up, adjusted mean SLEDAI (AMS) in OP, and oral prednisone use (>7.5 mg/day) during OP. Damage analyses were restricted to patients who did not have damage in the organ system of interest prior to the start of the FP.

Results: Thirty-two percent of SLE patients (n=374) experienced an infection during OP. Any infection during the OP increased the risk of subsequent overall organ damage accrual by 30% (HR= 1.30, [95% CI: 1.03, 1.64], Table 1). There was a lack of association between any infection during the OP and death in the FP (HR= 1.11, [95% CI: 0.71, 1.73]), as well as specific organ damage accrual.

Table 1. Any infection during the OP as a predictor of death or organ system damage accrual during follow-up

Outcome	Adjusted HR	95% CI	p-value
Death	1.11	(0.71,1.73)	0.665
Organ System Damage Accrual			
Overall	1.30	(1.03,1.64)	0.028
Renal	0.95	(0.44,2.08)	0.897
Neuropsychiatric	1.34	(0.90,1.99)	0.151
Pulmonary	1.19	(0.77,1.85)	0.439
Cardiovascular	1.54	(0.96,2.46)	0.074
Peripheral Vascular	1.16	(0.52,2.62)	0.714
Musculoskeletal	1.06	(0.76,1.47)	0.749
Stroke	1.27	(0.67,2.38)	0.465
Seizure	0.63	(0.17,2.28)	0.479

Conclusion: Our findings suggest that a prior infection is an important predictor of overall organ system damage accrual in SLE. However, a prior infection did not appear to predict death. (Study number: WEUKBRE4566) None.

1393

Low Prevalence of Use of ACEI/ARBS and Lipid Lowering Agents In African American (AA) Systemic Lupus Erythematosus Patients. Asha Thomas, Madhu-Kalyan Pendurthi and Vikas Majithia. University of Mississippi Medical Center, Jackson, MS

Background/Purpose: Cardiovascular (CV) and renal involvement in systemic lupus erythematosus (SLE) is common (up to 75%) and frequently associated with morbidity and mortality (31%). Blockage of ACE pathway and lipid lowering has been shown to have significant benefits in a number of systemic diseases. Previous evidence suggests that they may be associated with reduced risk of overall disease activity, renal and CV morbidity in SLE. Their role in SLE is not well defined, and their use by rheumatologists as a standard of care is not known. There are no specific studies addressing their usage and quantifying the benefits. We did this study to evaluate the prevalence and benefits of using ACEi/ARBs and lipid- lowering agents among AA lupus patients in the Rheumatology clinic at University of Mississippi Medical Center (UMMC).

Methods: Cross-sectional study using retrospective chart reviews of 204, AA SLE patients was done. Data collected includes demographics, BMI, past medical history, medications, antibody panel, complete blood counts, metabolic panel, lipid panel, complement levels, and spot urine Pr:Cr (protein, creatinine ratio). Data was de-identified and collected using Google forms and tabulated to Excel. All analyses were performed using SAS 9.2.

Results: Average age of the population was 38.51{13.255}. 91%(185) were females, 61.69% had hypertension, 9% had diabetes and 23.5% had LN. ANA was positive in 99% of patients and dsDNA was positive in 65%. Average BMI was 31.93{9}. 92% of the population was on hydroxychloroquine and 20% were taking aspirin. Results are summarized in the table below:

ACEi/ARB use	No	Yes
Overall use (n=204)	125 (61.58%)	78 (38.42%)
Hypertension (n=124, 61.69%)	51 (41.12%)	73 (58.87%)
		OR=2.29 (p=0.0003)
Proteinuria status		
Spot urine Pr:Cr>0.5 (n=44)	27 (61.37%)	17 (38.63%)
Spot urine Pr:Cr<0.5 (n=157)	118 (75.15%)	39 (24.85%)
		OR=1.009 (p=0.97)
Lupus nephritis (n=43, 21.07%)	15 (34.88%)	28 (65.22%)
		OR=2.99 (p=0.001)
Dyslipidemia		
Total screened = 196/204 (96%)		
Prevalence (LDL >129 or on treatment) = 51 (26%)		
Lipid-Lowering agents	**No**	**Yes**
Overall use (n=51, 26.02%)	22 (43.14%)	29 (56.86%)
LDL>100 & <129 (n=26)	22 (84.62%)	4 (15.38%)

In this analysis, 38.42% were on ACEI/ARBS as compared to 21% in the LUMINA study, showing that overall use is better but still low. They were more frequently used ($p<0.05$), if participants had hypertension (62%) or history of LN (21%). Presence of proteinuria did not lead to an increased use. Dyslipidemia was common in our participants, seen in about 26%. Use of lipid-lowering agents was low at about 55% of these patients and only 15% for LDL>100 &<129. In most cases, no clear reason for non-prescription was documented.

Conclusion: Despite potential benefits on the renal and CV complications in SLE, use of ACEi/ARBS and lipid-lowering drugs in SLE patients remains low. Possible explanations include lack of scientific studies addressing these medications' role, clear consensus or guidelines for their use in SLE. Lack of focus on treatment of concomitant conditions, cost, compliance and other administrative factors also probably contribute. Further studies and expert consensus guidelines to clearly establish the role of these drugs are needed. In the interim, awareness of their potential benefits may increase their use.

1394

Population Pharmacokinetics of Sifalimumab, An Investigational Anti-Interferon-α Monoclonal Antibody, in Systemic Lupus Erythematosus Patients. Rajesh Narwal, Lorin Roskos, Wendy White, Warren Greth and Gabriel Robbie. MedImmune, Gaithersburg, MD

Background/Purpose: Sifalimumab is a fully human immunoglobulin (Ig) G1κ monoclonal antibody (mAb) that binds to and neutralizes a majority of the subtypes of human IFN-α. Sifalimumab is being evaluated as a treatment for systemic lupus erythematosus (SLE). The primary objectives of this analysis were to (a) model the population pharmacokinetics (PK) of sifalimumab; (b) to identify and quantitate the impact of patient/disease characteristics on PK variability; and (c) to evaluate fixed versus body weight based dosing regimens.

Methods: Sifalimumab serum concentration-time data were collected from a phase 1b study (Study # MI-CP152) designed to evaluate the safety and tolerability of multiple IV doses of sifalimumab in adult patients with SLE. Sifalimumab was administered every 14 days as a 60-minute IV infusion with escalating doses of 0.3, 1.0, 3.0 and 10 mg/kg and trough serum concentrations were collected every 14 days. A total of 120 patients provided evaluable PK data with a total of 2370 serum concentrations (average of 20 samples per patient). Sifalimumab serum concentrations were determined using a validated colorimetric enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantitation (LLOQ) of 1.25 μg/mL. The population PK of sifalimumab was performed using a non-linear mixed effects modeling approach in NONMEM VII software. Impact of patient demographics, clinical indices and biomarkers on PK parameters were explored using a step wise forward selection and backward elimination approach. The appropriateness of the final model was tested using visual predictive check (VPC). The final population PK model was utilized for phase II dosing projections.

Results: Sifalimumab PK was best described using a 2-compartment linear model with first order elimination. Following IV dosing, the typical clearance (CL) and central volume of distribution (V_c) were estimated tobe 176 mL/day and 2.9 L, respectively. The estimates of between-subject variability for CL and V_c were 28% and 31%, respectively. Patient baseline body weight, IFN gene signature (21 genes), steroid use and sifalimumab dose were identified as significant covariates for CL, whereas only baseline body weight was significant covariate for V_c and V_p. Although the above mentioned covariates were statistically significant, they did not explain variability in sifalimumab PK parameters to any relevant extent. Thus no dosing adjustments are necessary. VPC results demonstrated good predictability of the final population PK model. Simulation results demonstrate that both fixed and body weight based dosing regimens yield similar median steady state concentrations (C_{ss}) and variability. Fixed sifalimumab doses of 200, 600 and 1200 mg monthly (with a loading dose at day 14) were selected for phase II clinical trial.

Conclusion: A population PK model of sifalimumab was developed and validated. The estimated typical PK parameters were similar to other monoclonal antibodies without a target sink. The population PK analysis also demonstrated the feasibility of evaluating fixed doses of sifalimumab in phase II clinical trials.

1395

Do Race/Ethnicity and Geography Affect Outcomes in An Inception Cohort of Patients with Systemic Lupus Erythematosus Followed for at Least 5 Years? D. D. Gladman[1], Murray B. Urowitz[1], Dominique Ibanez[1], Nicole Anderson[1] and Systemic Lupus International Collaborating Clinics (SLICC)[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto, ON

Background/Purpose: We have previously demonstrated that there are differences in the features of SLE at inception when studied by geographic and race/ethnicity origins. In this study we examined the influences of ethnicity and geography on outcomes in patients followed for at least 5 years.

Methods: An international research network comprising 27 centres from 11 countries has followed an inception cohort of SLE patients yearly according to a standardized protocol between 2000 and 2011. Of these, 537 patients followed for a minimum of 5 years constitute the study population. Disease activity was measured by SLEDAI-2K and Adjusted Mean SLEDAI-2K (AMS) at 5 years, damage using the SLICC/ACR Damage Index (SDI). Multivariate proportional hazards model were evaluated adjusting for age, sex, SLEDAI-2K, and use of medications at enrolment. AMS was analysed by linear regression.

Results: Of the 537 patients there were 469 (87.3%) females. At enrolment the mean age was 35.3 $\pm$ 14.1 years, SLEDAI-2K was 5.7 $\pm$ 5.6 and disease duration 0.5 $\pm$ 0.3 years. 70% were on glucocorticosteroids, 63% on antimalarials, and 38% on immunosuppressive medications. The average length of follow up was 7.2 $\pm$ 1.5 years. At 5 years, mean AMS was 3.8 $\pm$ 3.2, and SDI scores $\geq$ 1 were found in 240 patients, while the SDI was $\geq$ 3 in 87 patients.

Site	N	AMS-5 Mean	SDI $\geq$ 1 P	SDI $\geq$ 3 HR	95% CI	HR	95% CI
Asia	52	2.52	0.08	**0.37**	0.20, 0.69	0.54	0.18, 1.65
Canada	146	3.29		1.00		1.00	
Europe	150	3.03	0.40	0.81	0.57, 1.15	0.97	0.52, 1.82
Mexico	78	**4.14**	0.03	1.14	0.74, 1.77	1.88	0.93, 3.79
USA	111	2.95	0.31	1.14	0.79, 1.65	**1.87**	1.02, 3.45
Ethnicity							
Asian	78	3.30	0.69	**0.58**	0.36, 0.93	0.68	0.30, 1.52
African decent	81	3.64	0.15	1.33	0.93, 1.90	1.66	0.93, 2.97
Caucasian	277	3.16		1.00		1.00	
Hispanic	85	**4.31**	0.001	1.41	0.96, 2.07	1.60	0.85, 3.00

Conclusion: At 5 years of follow up the AMS is higher in Hispanics by ethnicity and in Mexicans by country. Presence of any damage is lowest among Asians and in Asia. High levelsof damage accrual is associated with country (USA) but not necessarily with race/ethnicity.

1396

Microstructural Abnormalities in White and Deep Gray Matter Visualized within the First Year of Diagnosis in Adolescents with SLE: A Pilot Magnetization Transfer Imaging Study. Eyal Muscal[1], Elfrides Traipe[1], Elisabeth Wilde[1], Douglas R. Bloom[1], Barry L. Myones[1], Zili D. Chu[1], Robin L. Brey[2] and Jill Hunter[1]. [1]Baylor College of Medicine, Houston, TX, [2]UTHSCSA, San Antonio, TX

Background/Purpose: White and gray matter (WM, GM) damage may be early sequelae of SLE-mediated neuroinflammation and vasculopathy. Novel MRI modalities such as magnetization transfer imaging (MTI) may detect tissue alterations prior to the appearance of discrete lesions on

conventional imaging. We postulated that WM and deep GM abnormalities would be detected by MTI early in the disease course of adolescents with SLE.

Methods: Right handed-adolescents with SLE and age-matched healthy controls completed 3T MRI scans with conventional anatomic and MTI sequences. The average signal intensity of 5 mm regions of interest (ROIs) without discrete lesions was calculated from images with (M_S) and without (M_0) an MT pulse in bilateral WM and GM regions. The magnetization transfer ratio (MTR) for an ROI was calculated as $MTR = 100\% \cdot (M_0 - M_S)/M_0$. MTI metrics were calculated by researchers blinded to clinical status. We compared the MTR values of a priori WM and deep GM ROI of SLE and control subjects. Descriptive statistics were expressed as medians. Continuous variable group differences were assessed via non-parametric testing. Assuming that larger sample size values would be normally distributed unadjusted effect sizes were calculated as Cohen's *d* using observed group means and SD values.

Results: MTR values were generated for 10 SLE subjects and 10 healthy controls. Median age at imaging was 14.7 for SLE cohort and 14.9 for controls (range 13–18). Both cohorts had a female predominance (SLE 80%, controls 90%) and multi-ethnic composition (SLE: 50% Caucasian, 30% Hispanic, 10% bi-racial, and 10% Asian; CONTROL: 40% Caucasian, 30% Hispanic, and 30% African-American). Median duration from SLE diagnosis was 4.7 months (range 2.7–22.0 months), and the SLEDAI median score was 2.0 (range 0–8). LAC positivity was 40%, aPL positivity 50% and history of biopsy-proven nephritis 20%. Median prednisone dose at imaging was 30 mg (range 5–40 mg). There were no previous NPSLE events documented.

Discrete WM hyperintensities were observed in frontal or prefrontal regions in 70% of the SLE subjects (1–2 mm lesions). Mild cerebral and cerebellar volume loss was seen in 60% of SLE subjects. MTR reductions suggestive of WM and deep GM tissue alterations were apparent when comparing SLE subjects to controls. Effect sizes for MTR reductions ranged between 0.35–1.37. Statistically significant lower MTR values were observed in bilateral **WM** (frontal, centrum semi-ovale, and posterior internal capsule) and bilateral deep **GM** regions (caudate and globus pallidus) of the SLE subjects. Significant effect sizes were all large (Cohen's $d > 0.78$, p values $<$ 0.01). SLE group MTR values did not correlate with SLEDAI scores, cumulative prednisone dose, or disease duration since diagnosis.

Conclusion: Microstructural brain tissue alterations were visualized by MTI in adolescents with mild disease (non-NPSLE). Microstructural alterations were visualized even in regions that appeared normal on conventional anatomic sequences. Significant MTR reductions were in regions supplied by small perforator arteries of the anterior and middle cerebral arteries and may represent a early and indolent vascular or inflammatory injury.

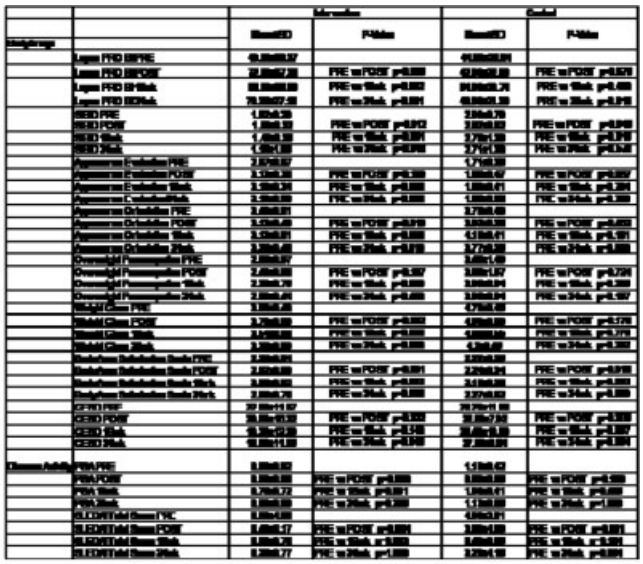
1397

Lupus and Body Image: An Intervention That Works. Meenakshi Jolly[1], Kristin Peters[2], Rachel A. Mikolaitis[1], Kali Evans-Raoul[3], Thomas F. Cash[4] and Joel A. Block[1]. [1]Rush University Medical Center, Chicago, IL, [2]University of Missouri Health Care, Columbia, MO, [3]The Image Studios, Chicago, [4]Old Dominion University, Norfolk, VT

Background/Purpose: Systemic Lupus Erythematosus (SLE) can be potentially disfiguring, involve multiple organs and adversely affect their physical and emotional health. Our previous work shows Body Image (BI) is poor among women with SLE and is predictive of poor health outcomes. This study aimed at determining the feasibility and effectiveness of a novel BI intervention in improving (1) BI and (2) Health outcomes, among women with cutaneous SLE.

Methods: Body Image Intervention comprising of education, cognitive behavioral therapy (tailored for SLE) and cosmetic training (tailored for SLE) was offered to 10 SLE patients (inactive to mildly active) once a week for 10 weeks, along with standard of care as a pilot study. Each session lasted 1hr-45 minutes. Five SLE patients (inactive to mildly active) were followed with standard of care but without any active intervention. Multi Dimensional Body Relations Satisfaction –Appearance Scale (MBRSQ-AS), Situational Inventory of Body Image Dysphoria (SIBID-SF) and Body Image in Lupus Screen (BILS) were used to measure BI. Center for Epidemiological Studies Depression (CES-D), Self Esteem (SE), Coping (Brief), Anxiety and Lupus-PRO were used for health outcomes. Data was obtained baseline, post intervention, followed by 18 and 24 weeks post intervention. Descriptive statistics and paired t tests analysis were performed. P value of ≤ 0.05 was considered significant on two-tailed test.

Results: Mean age (SD) was 42.4 (13.2) yrs. 25/29 had SLE. Ninety seven percent were women and 46% had a flare at the time of the study. Mean (SD) total scores were CLASI activity 8.8 (5.6), CLASI damage 9.6 (9.1), PGA 1.1 (0.8), SLEDAI 4.5 (4.1) and SDI 1.8 (2.2). Fifty-nine percent patients were on prednisone and 66% on hydroxy-chloroquine. Mean (SD) EQ5D VAS was 73 (15.1), and BIQLI 0.39 (1.5). CLASI activity score correlated with SLEDAI-rash item (r 0.46, p=0.01), LupusPRO Lupus Symptom item on skin flare (r 0.37, p=0.05), EQ5D VAS (r −0.49, p=0.04), but not with PGA (r 0.35, p=0.08) or total SLEDAI (r 0.19, p=0.33). CLASI damage score correlated with age (r 0.45, p=0.02), SDI items on cutaneous skin scarring/alopecia (r 0.51, p=0.001), skin extensive scarring/panniculum (r 0.51, p=0.01) and skin ulceration (r 0.37, p=0.05) and total SDI score (r 0.53, p=0.001). BIQLI was not associated with CLASI activity or damage score. However, CLASI face activity adversely affected patient's interactions with people of their own sex (r −0.53, p=0.001), interactions with people of opposite sex (r −0.49, p=0.01), experiences when they met new people (r −0.36, p=0.05), experiences at work/school (r −0.45, p=0.01), relationships with friends (r −0.40, p=0.03) and relationships with family members (r −0.39, p=0.04).



Conclusion: Body Image is modifiable in SLE. The proposed intervention was successful; improvements in BI persisted at 24 weeks after the intervention and lead to significant improvements in other health outcomes in this study.

1398

Clinical-Pathological Correlates of Proliferative Lesions in Lupus Nephritis. Claire Barber[1], Murray B. Urowitz[2], Dafna D. Gladman[3], Joan E. Wither[4], Carolina Landolt-Marticorena[2], Heather Reich[5], Wendy Lou[6], Jiandong Su[7], Jonathan Yip[8], Gan Qian[6], David Thomas[9], Samih Nasr[10], Rohan John[8], Ellie Aghdassi[8] and Paul R. Fortin[7]. [1]Mount Sinai Hospital, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]Toronto Western Hospital, University of Toronto, Toronto, ON, [4]Toronto Western Research Institute, University Health Network, Toronto, ON, [5]The Toronto Western Hospital, Toronto, ON, [6]Dalla Lana School of Public Health, Toronto, ON, [7]Toronto Western Hospital, Toronto, ON, [8]University Health Network, Toronto, ON, [9]Nephrocor, Long Island, NY, [10]Division of Anatomic Pathology, Mayo Clinic, Rochester

Background/Purpose: To examine the clinical-pathological correlates at time of renal biopsy in patients with lupus nephritis according to the 2003 International Society of Nephrology and Renal Pathology Society (ISN/RPS) classification.

Methods: We studied a large prospectively followed cohort of SLE patients from a single centre with renal biopsy slides available and matched clinical follow-up. Demographic and clinical data collected at time of renal biopsy included age, gender, disease activity (SLEDAI-2K) and damage (SLICC damage index). Renal biopsies were reviewed by two expert pathologists independently and by a third pathologist where disagreement occurred to determine a consensus score. The degree of agreement between pathologists on individual items of the ISN/RPS score was measured. We included only pathologic variables with at least moderate agreement (kappa ≥ 0.6). The variables included ISN/RPS class I-VI of nephritis. For class III, the subclasses of active (A), active and chronic (A/C) and chronic (C) had poor agreement and were considered as a single class. For class IV, the

agreement was poor for the segmental versus global subclasses but acceptable or the active A, A/C or C lesions. Correlates between these variables and clinical characteristics at time of biopsy were determined using chi-square or Fisher's exact test. Univariate and multivariate regression models were generated to examine the outcomes of complete remission (CR) defined as serum creatinine (sCr) $<$ 1.4 mg/dl and proteinuria of $<$ 0.33 g/d, partial remission (PR) defined as a $<$ 25% increase in baseline sCr and $>$ 50% reduction in baseline proteinuria to $<$ 1.5 g/d and no remission at 6, 12 and 24 months post-biopsy.

Results: 137 patients had biopsy slides available for review. The average age at time of biopsy was 37.2 $\pm$ 12.0 years, 81.5% were female and 64.2% were Caucasian. The majority of biopsies showed class III (24.8%) or class IV nephritis (IV-A: 12.4%, IV-A/C: 22.6%, IV-C: 4.4%) and 14.6% were pure class V. The estimated glomerular filtration rate (eGFR) was lower in patients with class IV- A/C (42.8 mL/min/1.73m^2) compared to all other groups (85.1 mL/min/1.73m^2, $p < 0.001$) and higher in class III (91.6 mL/min/1.73m^2, $p = 0.002$). The mean arterial pressure (MAP) was higher in patients with class IV-A/C compared to other classes (107.6 $\pm$ 18.4mmHg versus 98.1 $\pm$ 13.5mmHg, $p = 0.02$). The SLEDAI-2K and a non-renal SLEDAI-2K were no different between classes; however the anti-dsDNA levels by Farr assay at time of biopsy were highest in class III (40 U/mL versus 16 U/mL, $p = 0.02$) and lowest in class IV-C biopsies (5 U/mL versus 22.5 U/mL, $p = 0.01$) and C3 levels were lowest in class IV-A and IV-A/C (0.4 $\pm$ 0.2 vs 0.8 $\pm$ 0.30 $<$ 0.001; 0.6 $\pm$ 0.3 vs 0.8 $\pm$ 0.4, $p = 0.04$). On univariate analysis the presence of a higher C3 levels at time of biopsy was associated with CR at 24 months (OR 6.18, 95% CI: 1.33, 28.69). On multivariate analysis none of the pathologic variables was independently associated with CR or PR at any time point.

Conclusion: Distinct clinical features at the time of renal biopsy are associated with specific ISN/RPS subclasses of lupus nephritis however no pathologic features were independently associated with renal outcome.

1399

Chronicity Index, Especially Glomerular Sclerosis, Is An Independent Predictor of Renal Response Following Immunosuppressive Treatment in Patients with Lupus Nephritis. Dong-Jin Park[1], Sung-Ji Lee[1], Tae-Jong Kim[2], Yong-Wook Park[2] and Shin-Seok Lee[1]. [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Chonnam National University Medical School and Hospital, Gwangju, South Korea

Background/Purpose: Renal responses to immunosuppressive agents in patients with lupus nephritis (LN) differ widely depending on ethnicity, follow-up duration, disease severity, and treatment. Activity and chronicity indices seem to be better predictors of renal response than other factors. However, these results have not been uniformly confirmed by other studies. Thus, we evaluated the predictors of renal remission at the first year following immunosuppressive treatment in patients with LN.

Methods: We studied 79 patients who had kidney biopsy prior to the start of induction treatment, and who subsequently were treated with immunosuppressive drugs for at least 6 months and followed-up for more than a year. Sociodemographic, clinical, laboratory, and treatment-related data at the time of kidney biopsy and during follow-up were obtained by reviewing patients' charts. Renal response was defined as an inactive urinary sediment, a decrease in urinary protein to creatinine ratio $<$ 0.5, and normal or stable renal function. Multivariate analyses were performed using the logistic regression model to identify independent predictors of renal response in LN patients.

Results: After 1 year, renal response was achieved in 39 of 79 patients (49.4%) treated with immunosuppressive drugs. Intravenous cyclophosphamide was most commonly used as a treatment, followed in descending order of frequency by mycophenolate mofetil, azathioprine, and cyclosporine. Renal response was associated with disease duration at the onset of LN ($P<0.05$), chronicity index on renal histology ($P<0.05$), glomerular sclerosis ($P< 0.001$), tubular atrophy ($P<0.05$), interstitial fibrosis ($P<0.05$), and the use of hydroxychloroquine at the onset of LN ($P<0.05$). In multivariable regression analysis, glomerular sclerosis in the chronicity index ($P<0.01$) and disease duration at the onset of LN ($P<0.05$) were significant predictors of the renal response in LN patients.

Conclusion: Our findings suggest that glomerular sclerosis in the chronicity index is an independent predictor of renal response after the start of therapy in LN patients.

1400

Asian Ethnicity Is Associated with Increased Disease Severity in An Urban Australian SLE Cohort. Alberta Y. Hoi, Vera Golder and Eric F. Morand. Monash University, Melbourne, Australia

Background/Purpose: Limited information is available to describe disease differences between Asian and Caucasian SLE patients. We sought to investigate the hypothesis that Asian ethnicity is associated with increased disease severity, using prospectively collected clinical data from an Australian clinic in which patients of diverse ethnicities are managed.

Methods: Data was collected prospectively from all consenting patients seen at the Lupus clinic of an urban teaching hospital, between May 2007 and April 2011. ACR criteria, disease activity (SELENA SLEDAI), disease related damage (SLICC-SDI) were documented as published. Ethnicity was self-assigned, and was defined according to common heritage, often consisting of same country of birth, ancestry, linguistic and cultural traits. Analyses were done comparing Asians vs non-Asians. Persistently active disease was defined as $\geq$2 consecutive visits where SLEDAI was $\geq$6.

Results: 131 subjects, mean age 44 years (range 20–78), with mean disease duration 11 years (range 1–33) were prospectively followed for an average of 33 months (range 5–37). All fulfilled $\geq$4 ACR diagnostic criteria. Asian SLE patients (n=52, 40%) differed significantly to non-Asian patients (n=79, 60%) in multiple domains. Asians were significantly less likely to have photosensitivity (OR 0.44 95%CI 0.20–0.95 p=0.04), and significantly more likely to have renal disease (OR 2.89 95%CI 1.40–5.98 p=0.01). Asian SLE patients were significantly more likely to have anti-dsDNA (OR 4.15 OR 1.66–10.37 p<0.01), anti-RNP (OR 4.12 95%CI 1.68–10.12 p<0.01), anti-Sm (OR 4.44 95%CI 1.46–13.50 p=0.01), anti-Ro (OR 3.59 95%CI 1.72–7.51 p<0.01) and hypocomplementemia (OR 2.64 95%CI 1.04–6.71 p=0.04). In this cohort, 47% had persistently active disease, as defined; 24% had persistently active disease for over 6 months in duration. Asians SLE patients were significantly more likely to have persistently active disease (OR 2.14, 95%CI 1.05–4.38 p=0.04). Asians also had a higher maximum SLEDAI score (mean 10.82 vs 7.73, p<0.01), and time-adjusted mean SLEDAI (5.94 vs 4.26, p=0.01). There was no significant difference in disease activity according to household incomes or education levels. During the observed period, Asian patients were significantly more likely to be treated with prednisolone (OR 2.93, 95%CI 1.25–6.85 p=0.01), azathioprine (OR 2.16, 95%1.05–4.44 p=0.04), and mycophenolate (OR 2.48 95%CI 1.06–5.81 p=0.03), and trended towards greater likelihood of cyclophosphamide treatment (OR 3.94, 95%CI 0.97–16.02 p=0.04). Asians were significantly more likely to have had avascular necrosis (OR 22.23 95%CI 1.22–403.9 p<0.01), and trended towards greater likelihood of persistent nephrotic proteinuria (OR 8.30 95%CI 0.94–73.25, p=0.03) and cardiomyopathy (OR 11.24 95% CI 0.57–222.5 p=0.03).

Conclusion: In a single urban teaching-hospital lupus clinic in Australia, Asian ethnicity was significantly associated with serologically more active and clinically more severe SLE. Evidence of greater autoantibody positivity and a lack of correlation with socioeconomic factors suggest genetically-based regulation of autoimmune responses play an important role in disease severity.

1401

Incidence and Prevalence of Systemic Lupus Erythematosus in Buenos Aires, Argentina: A 11 Years Health Management Organization Based Study. Soledad M. Valeiras[1], Martin F. Marchese[1], Alejandro S. Talani[1], Nicolas L. Avellaneda[1], Alvaro Etchepare[1], Patricio Etchepare[1], Maria S. Plou[1] and Enrique R. Soriano[2]. [1]Instituto Universitario, Escuela de Medicina, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Background/Purpose: There are differences in the epidemiology of autoimmune diseases in different countries. Studies regarding the epidemiology of systemic lupus erythematosus (SLE) are lacking in Argentina. The purpose of this study was to estimate the incidence and prevalence of SLE in a University Hospital based Health Management Organization in Buenos Aires (HIMCP).

Methods: *Population*: For incidence calculation the population at risk was all adult members of the IHMCP (>18 years old), with continuous affiliation for at least one year from January 1998 to January 2009. Each person was followed until he/she voluntarily left the IHMCP, death or finalization of the study (final dates) contributing time at risk since January 1998 or enrollment date (whichever occurred later) to that final date. *Case ascertainment*: multiple methods for case finding were used to ensure complete ascertainment: a) patients with the problem SLE, undifferentiated autoimmune disease or mixed connective tissue disease in the IHMCP problem oriented Computer-based Patient Record System, b) patients with positive Antinuclear antibody test (ANA titule>1/160) and/or positive anti-sm antibodies and/ or anti dsDNA antibodies in the Hospital laboratory database, and c) patients who consumed hydroxichloroquine, chloroquine, azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine, and or rituximab, from the administrative IHMCP drugs database. Medical records of all patients found were reviewed, and only patients fulfilling ACR criteria for SLE were included. *Statistical analysis:* Global and by gender incidence rate (IR) was calculated with 95% confidence intervals (CI). Prevalence was estimated at 1/1/ 2009, and the denominator population was the number of active members > 18 years at that date (n= 127,959).

Results: In the study period 186,086 persons contributed a total of 1,082,817.6 person-years, of whom 68 developed SLE: IR: 6.28 (CI: 4.9 – 7.7) cases per 100,000 person-years. There were 57 females: IR: 8.95 (CI: 6.6 – 11.2) cases per 100,000 person-years; and 11 males: IR: 2.55 (CI: 1.2 – 3.9) cases per 100,000 person-years. On January 1/ 2009, 75 prevalent cases were identified: prevalence: 58.6 (CI: 46.1 – 73.5) cases per 100,000 inhabitants (females: 83.2 (CI: 63.9 – 106.4) and males: 23 (CI: 11.9 – 40.1) per 100,000 members).

Conclusion: This is the first report of incidence and prevalence of SLE in Argentina. Incidence and prevalence rates were similar to those from large series in Europe and lower than in other Latin American countries, perhaps reflecting the mainly European origin of this population in Buenos Aires. As expected incidence and prevalence of SLE was higher in females.

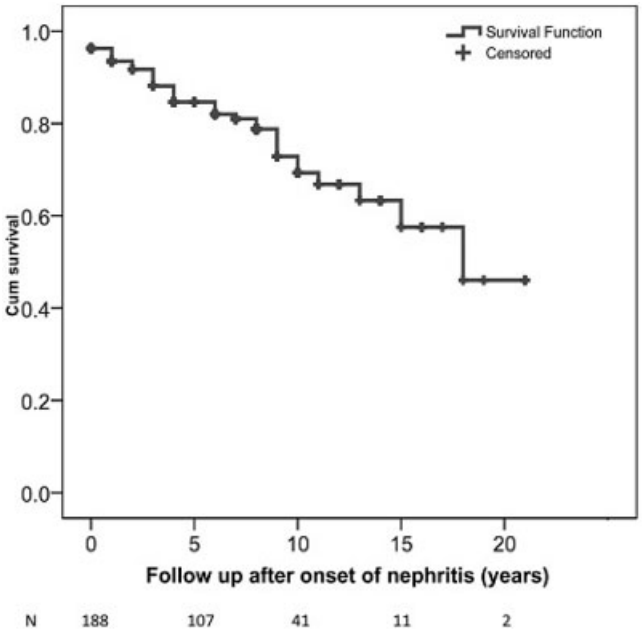
1402

Long-Term Outcome of Lupus Nephritis in Asian Indians Using Standard Therapy. Varun Dhir, Amita Aggarwal, Able Lawrence, Vikas Agarwal and Ramnath Misra. Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Lucknow, India

Background/Purpose: Lupus nephritis is an important complication in SLE. There have been impressive gains in outcome with current immunosuppressive regimens in developed countries. However, there is sparse data on the long-term outcome from developing countries including India. This study looked at outcome in Asian-Indians.

Methods: Retrospective study of SLE patients (fulfilling ACR 1997) with nephritis (unexplained proteinuria >=500mg with or without active sediments) seen at single Indian center over 20 years. They were treated as per standard regimens. Treatment response assessed by remission at 1 year (proteinuria<=2g/day with at least 50% reduction from baseline, no active sediments and serum creatinine<=1.5mg/dl). Primary outcome was development of chronic renal failure (CRF, serum creatinine>1.5mg/dl) or death. Secondary outcome was end-stage renal disease or death. Survival analysis was done using Kaplan-Meier and differences in survival by log rank test. Risk factors for poor outcome were assessed by cox-proportional hazards.

Results: The study included 188 patients of lupus nephritis, female: male ratio 11:1, mean age 23.6±10.5 years. Of these 136 patients had renal biopsy. Renal histology was: class II in 22, class III in 36, class IV in 61, class V in 16 and class VI in 1. Intravenous cyclophosphamide pulses (NIH) used as induction in most cases of proliferative nephritis: class III (85.3%), class IV (94.8%) and non-biopsied (71.1%). Most with non-proliferative nephritis received steroids with or without azathioprine: class II (73.7%) and class V (80%). The 1-year remission rate was 84.6%, with no statistical difference by class of nephritis. Median duration of follow up was 6 years (IQR 3–9). Survival with normal renal function was 84, 69 and 57% at 5, 10 and 15 years as shown in the figure (N= numbers at risk).



Survival curves were not different for various histological classes, however non-biopsied patients had lower survival compared to class II and class III or IV ($p<0.05$). Risk factors and hazard ratio (95% CI) for primary outcome on univariate analysis was number of infections 1.5 (1.1–2.0), initial serum creatinine 1.8 (1.4–2.2), hypertension 2.3 (1.0–5.1), hematuria 2.8 (1.3–6.1), low C3 3.0 (1.1–7.6) and absence of remission 13.8 (5.2–36.7). Only hematuria and absence of remission were significant on multivariate analysis. Renal survival at 5, 10 and 15 years was 91, 81 and 76%. Of 130 patients analyzed for complications, 45 (34.6%) had at least one serious infection, including tuberculosis in 17 (13.1%). There were 16 deaths, half due to infections (half of these were due to TB).

Conclusion: Outcome of lupus nephritis in Asian-Indians on standard treatment is comparable to developed nations. Lack of remission at 1 year and hematuria were risk factors for poor outcome. There was a high rate of infections especially tuberculosis; these were also a major cause of death.

1403

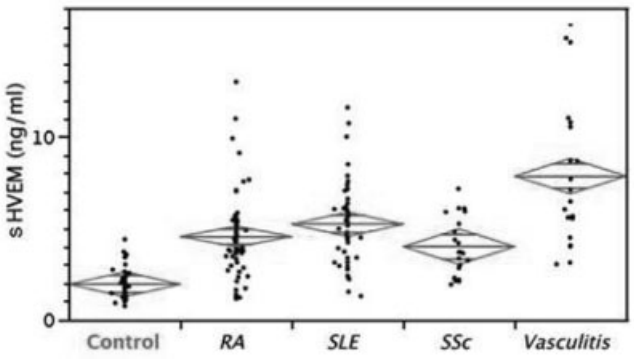
Soluble Form of Herpesvirus Entry Mediator (HVEM) Is Elevated in Sera of Active Collagen-Vascular Diseases and Might Be a New Biomarker of Disease Activity. Satoko Arai, Kazuhiro Kurasawa, Harutsugu Okada, Takayoshi Ohwada, Reika Maezawa and Takeshi Fukuda. Dokkyo Medical University, Mibu-machi, Tochigi-ken, Japan

Background/Purpose: Herpesvirus entry mediator (HVEM), a member of TNF receptor superfamily, regulates immune-responses. HVEM binds to LIGHT to activate both interacting cells. In addition, HUVEM interacts with BTLA and CD160 to deliver negative signals. Animal studies have shown that HVEM/ LIGHT/ BTLA/ CD160 interactions are involved in the development of autoimmune diseases. However, role of these molecules in human collagen-vascular diseases are not fully clarified.

The aim of this study are to determine whether there exists soluble form of HVEM (sHVEM) in sera from CVDs, and to clarify clinical importance of sHVEM in CVDs.

Methods: We developed a EIA system for detection of sHVEM and examined sera before treatment from SLE(n=44), RA(n=63), scleroderma(SSc)(n=21), vasculitis(n=21), and healthy controls(n=42). Clinical features of the patients were examined by reviewing medical records.

Results: Serum levels of sHVEM in controls were 1.93+0.85ng/ml. Soluble HVEM levels were significantly elevated in sera from CVDs (Fig.). The levels were 5.27+2.31 (average+ s.d.) in SLE, 4.50+2.23 in RA, 3.99+1.57 in SSc and 7.84+3.99 ng/ml. When cut-off level was determined as 3.63 ng/ml (average +2SD), elevation of s HVEM was found in 72.7% of SLE, 66.6% of RA, 52.3% of SSc and 95.2% of vasculitis.



In SLE, patients with low complement levels or high anti-DNA titers showed high sHVEM levels compared to those without the abnormalities. No significant relation was found between sHVEM levels and organ involvements. In RA, sHVEM levels from patients with moderate to high disease activity were higher than those with remission or low disease activity. In vasculitis, patients with more extended organ involvements had higher sHVEM levels. Moreover, immunosuppressive therapy reduced sHVEM levels significantly in SLE, RA and vasculitis.

Conclusion: Soluble form of HVEM exists in human sera. Serum levels of sHVEM were significantly elevated in varieties of CVDs compared to controls. The elevation of sHVEM reflects disease activity and treatment reduced titer of the molecules. Soluble form of HVEM could be a candidate of new biomarker of disease activity of CVDs.

1404

Utility of IFN-α As Biomarker in Central Neuropsychiatric Involvement in SLE. Hilda Fragoso-Loyo, Yemil Atisha-Fregoso, Carlos Nuñez-Alvarez, Luis LLorente-Peters and Jorge Sánchez-Guerrero. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico

Background/Purpose: An accurate indicator of central nervous system (CNS) involvement in SLE has not yet been identified. Aim: To assess the utility of interferon (IFN)-α in serum and cerebrospinal fluid (CSF) as biomarker of disease activity in central neuropsychiatric systemic lupus erythematosus (cNPSLE).

Methods: In 34 patients with cNPSLE, 44 non-NPSLE, 16 surgical-SLE, 4 primary-neuropsychiatric, and 25 non-autoimmune, serum and CSF samples were drawn at hospitalization, except non-NPSLE in whom only serum was studied. Six-months later, serum/CSF and serum samples were taken in 20 cNPSLE and 35 non-NPSLE patients. All patients were evaluated by the study rheumatologists and neurologists, at hospitalization and six months later using a standardized protocol. SLE activity (SLEDAI-2K) was assessed at hospitalization in all patients, and six-months later in cNPSLE and non-NPSLE. The central NP manifestations included: seizure disorders 13, severe refractory headache 7, acute confusional state 8, cerebrovascular disease 4, psychosis 1, and transverse myelitis 1. Interferon-a was detected by xMAP milliplex technology according to the protocol of milliplex MAP (Millipore) kits (LINCO, Millipore, Billerica, MA.).

Results: The mean $\pm$ SD age of cNPSLE patients was 31.4$\pm$12.2 years, which was similar across study groups (p=0.46). SLEDAI-2K scores among cNPSLE, non-NPSLE, and SLE-surgical patients were 15.3$\pm$8.2, 12.4$\pm$8.2, 3.8$\pm$1.5, respectively.

INF-α levels in serum were higher in cNPSLE than non-autoimmune patients (P=0.02), but were similar to non-NPSLE and SLE-surgical groups. In CSF, IFN-a levels were higher in cNPSLE than in non-autoimmune patients (P = 0.03), and non-significantly higher than SLE-surgical and primary-neuropsychiatric.

Six months later, serum levels of IFN-α did not vary from baseline values despite a significant decrease in SLEDAI-2K score in cNPSLE and non-NPSLE patients. CSF levels of IFN-α in cNPSLE also remained stable. IFNa levels in serum and CSF showed a fair correlation rs = 0.25 (P = 0.07), but the correlation of both of them with cNPSLE activity was poor.

Conclusion: Serum and CSF IFN-a levels in cNPSLE are not higher than in patients with non-NPSLE hence, IFN-a is not a useful biomarker of CNS involvement in SLE.

1405

Peripheral Arterial Disease in Systemic Lupus Erythematosus. Jose-Gabriel Erdozain[1], Irama Villar[2], Javier Nieto[2], María-Victoria Egurbide[2] and Guillermo Ruiz-Irastorza[2]. [1]Hospital de Mendaro, Mendaro, Spain, [2]Hospital de Cruces, UPV/EHU, Barakaldo, Spain

Background/Purpose: The prevalence of peripheral arterial disease (PAD) in lupus patients is unknown. An ankle-brachial index (ABI) < 0.9 has a good correlation with the presence of PAD. The aims of the study are: 1) To analyze the prevalence of PAD, cardiovascular disease (CVD) and cardiovascular risk factors in a cohort of systemic lupus erythematosus (SLE) patients. 2) To identify potential predictors of PAD in patients with SLE.

Methods: Two hundred seventeen SLE patients from the Lupus-Cruces prospective observational cohort were recruited. The ABI was determined in every patient. The relation of a low ABI with demographic and clinical variables, the presence of traditional risks factors and cardiovascular events, the cardiovascular risk calculated by SCORE and the treatments received by each patient was analysed.

Results: Ninety two percent of patients were women. The mean age (SD) was 49 years (15) at the time of the study and 36 years (16) at lupus diagnosis. Mean follow-up (SD) was 12 years (10). The prevalence of low ABI was 47 (21.7%). The mean cumulative dose of prednisone (SD) was 22 gr. (56). Twenty one patients (11%) had never received antimalarials. 22 patients (10.1%) had antiphospholipid syndrome and 74 (34%) had antiphospholipid antibodies. Lupus nephritis was present in 60 (27.6%) patients. Cardiovascular risk factors distribution was as follows: smoking 65 (30%), high blood pressure (HBP) 70 (32%), diabetes 7 (3.2%), dyslipidemia 74 (34%) and family history 25 (11.5%). Previous symptomatic arterial disease was present in 27 patients (12.4%).

Patients with low ABI were older (57 vs. 46 years, p<0.0001), and had more frequent HBP (34% vs. 15%, p=0.002), diabetes (57% vs. 20.5%, p=0,041), dyslipidemia (31% vs. 16%, p=0.015) and previous cardiovascular events (52% vs. 17.5%, p<0.0001). A high SCORE identified patients with low ABI (p=0.006). A history of lupus nephritis, antiphosphoiipid syndrome or positivity for antiphospholipid antibodies was not different between patients with low and normal ABI. Regarding lupus treatments, only a lower cumulative dose of cyclophosphamide was related to a low ABI (1.1 vs. 2.7, p=0.023). Patients with low ABI had higher levels of fibrinogen (425 mg/dl vs. 378 mg/dl, p=0.003).

Conclusion: The prevalence of PAD is higher in SLE patients than in the general population. Traditional risk factors are be associated with PAD in patients with SLE. The influence of lupus itself and lupus treatments is still unclear.

1406

Characteristics of Disease Activity and Organ System Involvement in a Cohort of patients with Systemic Lupus Erythematosus Followed for More Than One Year. Marta Mosca[1], Chiara Tani[2], Linda Carli[1], Grazia Maria Rizzelli[1], Rossella Neri[1], Antonio Tavoni[3], Anna d'Ascanio[4] and Stefano Bombardieri[4]. [1]University of Pisa, Pisa, Italy, [2]University of Pisa, Italy, [3]Via Roma 67, Pisa, Italy, [4]Rheumatology Unit, Pisa, Italy

Background/Purpose: The clinical picture of systemic lupus erythematosus (SLE) is very complex due to the wide variety of clinical manifestations, to the alternance of flares and remission and to damage accrual. It is common clinical experience the fact that in some patients many organ systems will be involved by active inflammation over disease history, while in some patients disease activity is mainly observed in few organ systems.

Aim of the present study was to evaluate the characteristics of disease activity and organ system involvement in a cohort of SLE patients regularly followed at a single Unit.

Methods: Patients regularly followed at our clinic with a disease duration of more than one year were selected for this analysis. Clinical charts were reviewed to obtain epidemiological and clinical data. A diagnosis of flare was based both on the judgement of the treating physician and on changes in the therapeutic approach. The predominant type of organ involvement at each flare was recorded. The disease was defined as "*monomorphic*" if during the disease course flares involved the same organ system, "*complex*" if different organ/systems have been involved in different flares.

Results: One hundred and sixty five patients were included in this

analysis, mean disease duration was 15.8 years ± 8.7 (min 2 max 41). During the disease course 121 patients (73%, mean disease duration 17.3 years) presented at least one disease flare; based on the previously reported definition 66 patients had a "*complex*" disease characterized by the sequential accrual of different organ involvement, while 99 patients had a "*monomorphic*" disease. More specifically we could identify three more common patterns of "*monomorphic*" disease which were those with predominant articular, cutaneous and renal manifestations. No differences were observed if patients were subdivided on the basis of disease duration (more or less than 15 years).

Conclusion: These observations support the general concept of SLE a single disease in which potentially any system might be involved by disease activity during the disease course, but highlight also the fact that subtypes of the disease also exist which are characterized by a less wide clinical picture. These differences might be related with differences in patient's genetic background and in environmental factors. Prospective studies to better clarify this aspect and characterize these subpopulations could allow the identification of biomarkers, specific therapeutic targets and help optimizing and possibly personalizing patients treatment.

1407

Medication Impact on Gene Expression Patterns May Depend on Biologic Subgroups in the Biomarkers of Lupus Disease (BOLD) Study. Margot O'Toole[1], Ying Zhang[1], Attila Seyhan[1], Frederick W. Immermann[2], Andrew A. Hill[3], Padmalatha S. Reddy[3], Sudhakar T. Sridharan[2], Monique Lehmann[2], Jaime L. Masferrer[4], Tianhui Zhou[2], William M. Mounts[3], Maryann Whitley[3], Terry Walker[1], Stan Kamp[5], Judith A. James[6], Marek Honczarenko[1] and Joan T. Merrill[7]. [1]Pfizer, Cambridge, MA, [2]Pfizer Inc, Collegeville, PA, [3]Pfizer, Cambridge, [4]Pfizer Inc, Cambridge, MA, [5]Oklahoma Medical Research Fund, Oklahoma City, [6]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [7]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Background immunosuppressives (IS) may augment or interfere with responses to targeted therapies in SLE patients, and be potent confounders in clinical trials and practice. The BOLD study examines the clinical-biological effects of medications commonly used in SLE.

Methods: An interim analysis of the first 55 patients and 15 healthy controls has tested expression levels of 270 known lupus or inflammation associated genes by TaqMan PCR.

Results: Significant ($p < 0.05$) expression differences vs controls were detected for 51% of assayed genes. Patients segment into an *IFN High* group (n=31) expressing IFN signature genes at levels higher than controls, and *IFN Low* (n = 24), who express many genes, including some IFN and IL21 pathway genes, at levels **lower** than control. Associations between medication use and gene expression were found in analyses of 34 patients on antimalarials, 15 on AZA, 11 on MTX, and 6 on MMF. The two IFN groups differ with respect to impact of medications on expression levels of genes associated with lupus. Examples include:

		Change with Medication in Lupus Patients	
Gene	**Medication**	***IFNHigh*Group**	***IFNLow*Group**
TBX21	Antimalarials	**Decreased (p = 0.02)**	NS (p = 0.47)
NOD2	Antimalarials	NS (p = 0.87)	**Increased (0.0006)**
IL1RL1	AZA	NS (p = 0.53)	**Increased (0.04)**
IFNGR2	MTX	NS (p =0.12)	**Decreased (0.02)**
USP18	MTX	**Increased (p = 0.02)**	NS (p = 0.42)
ITGAX	MMF	**Increased (p = 0.02)**	NS (p = 0.67)

To date 23 patients have completed the BOLD protocol: withdrawn from background IS, briefly treated with steroids, then followed until flare. Expression levels of 17 genes increased (eg. KLRG1, p = 0.0029), and 22 decreased (eg, CXCR2, p = 0.0017) with flare. Patients tend to remain within their IFN group irrespective of successful treatment or subsequent flare ($p<0.001$).

Conclusion: BOLD suggests there may be distinct lupus subsets characterized by IFN inducible gene expression, and that these groups may differ with respect to the impact of commonly used medications.

1408

Treatment Regimens of Patients Enrolled in the Lupus Clinical Trials Consortium (LCTC). Alana B. Levine[1], Doruk Erkan[2], Jill P. Buyon[3] and Michael D. Lockshin[2]. [1]Hospital for Special Surgery, New York, NY, [2]Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, New York, NY, [3]NYU School of Medicine, New York, NY

Background/Purpose: Systemic lupus erythematosus (SLE) has a wide spectrum of clinical manifestations requiring varied treatment regimens. The LCTC, an organization affiliated with 18 academic institutions across the United States and Canada, collects clinical information on SLE patients. Each center aims to follow 100 patients for five years. This study compares LCTC physicians' predictions to actual past and current treatment of LCTC patients and assesses variance of current treatment among centers.

Methods: *Phase 1:* We conducted a multiple choice survey of LCTC physicians regarding treatment expectations for the entire cohort. The expectation survey was performed without respondents' knowledge of full registry content. *Phase 2:* We assessed past and current treatment of patients enrolled in LCTC.

Results: *Phase 1:* 29 physicians from 18 institutions completed the survey (Table). *Phase 2:* We analyzed treatment regimens of 1242 patients, of whom 1136 (91.5%) are female, 599 (48.2%) Caucasian, 423 (34.1%) Black, 135 (10.9%) Asian, and 85 (6.8%) other; 146 (11.7%) are Hispanic. The mean age at the time of registry entry was 40.5 ±13.2 years (range 18–78) and mean disease duration 9.5 ±8.1 years (range 0–56). Since diagnosis, 93%, 76%, and 15% of patients had been treated with systemic corticosteroid, immunosuppressive, and biologic medications, respectively. At the time of enrollment in LCTC, 77%, 57%, 55%, and 5% of patients were currently receiving antimalarial, systemic corticosteroid, immunosuppressive, and biologic medications, respectively (Table). Frequency of use of these medications varied among participating centers. 79% of physicians accurately predicted rate of systemic corticosteroid use since diagnosis, 21% immunosuppressive use, and 74% biologics use. For treatment at the time of enrollment, 62%, 52%, 48%, and 79% of physicians correctly predicted antimalarial, systemic corticosteroid, immunosuppressive, and biologic medication use, respectively. Among centers, the ranges of frequency of actual current use of corticosteroids were 40–83%, immunsuppressants 30–80%, antimalarials 55–89%, and biologics 0–10%.

Physicians' (n: 29) Predictions of & Actual Medication Use (AMU) in LCTC Cohort (n: 1242)

	# of Physicians Based on *Prediction* Choices				% of LCTC Patients (*AMU*) (% range amongst centers)
Medication–Past Use	0–25%	25–50%	51–75%	>75%	
Antimalarial	0	1	3	25	—
Systemic corticosteroid	0	1	5	**23**	93% (75–100%)
Immunosuppressive	1	9	13	**6**	76% (49–100%)
Biologic	**20**	5	2	0	15% (3–27%)
Medication–Current Use	0–25%	25–50%	51–75%	>75%	
Antimalarial	0	1	10	**18**	77% (55–89%)
Systemic corticosteroid	1	3	**15**	10	57% (40–83%)
Immunosuppressive	3	11	**14**	1	55% (30–80%)
Biologic	**23**	5	1	0	5% (0–10%)

Conclusion: LCTC physicians accurately predicted the frequency of antimalarial, corticosteroid, and biologic use for the entire cohort. Centers varied in rate of actual use of these medications, a circumstance that may reflect differences in patient selection, disease severity, or prescribing practices across participating institutions and that will be further explored. LCTC offers a real-life look at treatment of SLE patients today; the variances among centers have important implications for comparisons of translational and outcome data as well as for treatment trials.

The authors would like to thank and acknowledge the Lupus Clinical Trials Consortium, Inc. (LCTC). The views expressed in this publication are those of the authors and LCTC is not responsible for its specific content.

1409

Hydroxychloroquine-Induced Hyperpigmentation in Patients with Systemic Lupus Erythematosus. A Series of 23 Cases. Moez Jallouli, C. Francès, Jean-Charles Piette, Du Le Thi Huong, M. Miyara, D. Saadoun, A. Mathian, J. Haroche, C. De Gennes, G. Leroux, C. Chapelon, Bertrand Wechsler, Patrice Cacoub, Zahir Amoura and Nathalie Costedoat-Chalumeau. CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: To describe the clinical features and outcome of hydroxychloroquine-induced pigmentation in patients with systemic lupus erythematosus (SLE).

Methods: This was a retrospective, monocentric (SLE clinic, Pitié-Salpêtrière, Paris) study of SLE patients with pigmented lesions considered to be related to hydroxychloroquine (HCQ). All patients fulfilled the 1997 ACR revised criteria for SLE. The medical files of patients were analysed and all patients were interviewed. Pictures of skin lesions were systematically reviewed by a dermatologist. In five patients, the concentration of iron was

measured on samples of skin biopsy performed both in healthy skin and pigmented lesions.

Results: We found 23 patients who developed HCQ-induced pigmentation. All were women. Mean age at pigmentation development was 33.8 ± 13.1 years. Skin pigmentation appeared after a median duration of HCQ therapy of 64 months (range: 3 months-22 years). At the time of cutaneous pigmentation development, the median cumulative dose of HCQ was 657 grams (range: 36–3,168). During follow-up, 21 patients had measurements of blood HCQ concentration [HCQ]. The median number of measurements in a patient was 3 (range: 1–11). The mean [HCQ] was 1,189 ± 436 ng/ml. This value was not significantly different from that in a group of 143 unselected SLE patients who had been receiving HCQ 400 mg daily for at least 6 months [1].

Hyperpigmentation was localized on the anterior side of the legs (n=23), on the arms (n=5), and on oral mucosa (n=1). Twenty one patients (91.3%) reported that appearance of pigmented lesions was preceded by the occurrence of ecchymotic areas, which gave way to a localized blue-gray or black pigmentation that persisted.

Twenty two patients (95.6%) had at least one condition predisposing them to easy bruising: at the onset of pigmented lesions, 1 patient had persistent thrombocytopenia, 14 patients were treated with platelet antiagregants and 8 with oral anticoagulants. Four patients recalled a previous severe trauma to their legs (accident in 3 cases and combat sport in 1 case).

Six patients also presented HCQ retinopathy, that occurred before (n=4) or after (n=2) skin pigmentation. One patient developed an atrioventricular block of first degree which was reversible after discontinuation of HCQ.

HCQ was discontinued definitively because of skin pigmentation in 2 patients who reported a gradual incomplete fading of hyperpigmentation. Among patients who continued HCQ (n=21), an improvement of pigmented lesions was reported in 6, despite the maintenance of a similar daily dose of HCQ. Pigmentation was found stable in the other 15 patients.

The median concentration of iron in the skin samples taken from five patients was higher in pigmented lesions (4115 nmol/g) compared to normal skin (413 nmol/g).

Conclusion: we report a large single-center series of SLE patients with HCQ-induced skin pigmentation. These lesions were often secondary to ecchymosis. They were not clearly related to duration, cumulative dose or blood concentration of HCQ.

[1] Costedoat-Chalumeau N. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. Arthritis Rheum. 2006.

1410

Response to Hydroxychloroquine in Japanese Patients with Cutaneous Lupus Erythematosus Using the Cutaneous Lupus Erythematosus Disease Area and Severity Index. Naoto Yokogawa[1], Takaharu Ikeda[2], Kyo Aizawa[3], Akiko Tanikawa[4], Masayuki Amagai[4], Yukihiko Kato[5], Yoko Momose[6], Satoru Arai[6], Hikaru Eto[6], Fukumi Furukawa[2] and Japanese Hydroxychloroquine Study Group[7]. [1]Tokyo Metropolitan Tama Medical Center, Section of Rheumatology, Tokyo, Japan, [2]Wakayama Medical University, Department of Dermatology, Wakayama, Japan, [3]Sanofi-Aventis K.K. Biostatistics & Programming, Tokyo, Japan, [4]Keio University School of Medicine, Department of Dermatology, Tokyo, Japan, [5]Tokyo Metropolitan Tama Medical Center, Section of Dermatology, Tokyo, Japan, [6]St. Luke's International Hospital, Department of Dermatology, Tokyo, Japan, [7]Japan

Background/Purpose: To evaluate the the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in Japanese cutaneous lupus erythematosus (CLE) patients to design a clinical trial of Hydroxychloroquine (HCQ) in Japan.

Methods: This is a prospective cohort study of CLE patients with or without systemic lupus erythematosus (SLE) who started HCQ at four major institutions of Japanese Hydroxychloroquine Study Group: Tokyo Metropolitan Tama Medical Center, Wakayama Medical University, Saint Luke's Hospital, Keio University. All institutions obtained the Institutional Review Board approval for the use of HCQ. Ophthalmologic exams were mandated before starting HCQ and every six months after starting HCQ. The dose of HCQ was 200–400mg/d, and less than 6.5mg/kg/d. The therapeutic responses are assessed at four months by the change of CLASI activity score. Patients were categorized into responders (improved) or non-responders (unchanged or worsened) using the criteria of 4-point or 20% decrease in the CLASI activity score.

Results: Thirty patients, 17 with SLE, were included. Median dose of prednisolone (PSL) before HCQ was 3.75 mg/d. Five patients experienced minor adverse reactions (3 pts with transient eye symptoms, 2 pts had mild gastrointestinal symptoms, 1 pt with possible eruption) but all patients tolerated HCQ. Twenty-six patients (87%) were categorized as responders. The median (range) CLASI activity score of all patients changed from 9.6 (2–24) to 4.1 (0–11). Treatment effect of HCQ was consistent across subgroups with regards to baseline characteristics [Table1]. We performed multivariable analysis including severity of CLE (CLASI activity score: 9 or more), presence of SLE, types of CLE (acute CLE, subacute CLE, annular erythema, discoid LE) duration of CLE (5 year or longer), dose of PSL (5mg or more), and smoking. Among them, only CLASI activity score before HCQ revealed statistically significant (F= 30.1 p<0.0001) [Table 2].

Table 1.

Pared t-test	n	CLASI Activity (Pre)	CLASI Activity (Post)	Difference	t	p value
total	30	9.6	4.1	−5.3	−6.17	<.0001
SLE	17	9.2	4.2	−5.0	−4.37	0.0005
not SLE	13	10.2	4.0	−6.2	−4.27	0.0011
ACLE	8	8.8	4.5	−4.3	−2.37	0.0493
not ACLE	22	10.0	4.0	−6.0	−5.76	<.0001
SCLE	5	10.8	2.8	−8.0	−3.95	0.0168
not SCLE	25	9.4	4.4	−5.0	−5.12	<.0001
DLE	11	12.7	6.0	−6.7	−3.91	0.0029
not DLE	19	7.8	3.0	−4.8	−4.80	0.0001
Annular erythema	8	6.3	1.6	−4.6	−5.95	0.0006
not annular erythema	22	10.9	5.0	−5.9	−4.92	<.0001
Duration < 5years	15	9.5	4.0	−5.5	−4.77	0.0003
Duration >= 5years	15	9.8	4.2	−5.6	−3.94	0.0015
PSL <5mg/d	15	9.4	3.5	−5.9	−4.1323	0.0010
PSL >=5mg/d*	15	9.9	4.4	−5.5	−4.598	0.0004
Smoking	17	12.9	5.6	−7.3	−3.31	0.0162
not smoking	13	8.7	3.7	−5.0	−5.199	<0.0001
CLASI Pre <9	17	4.9	2.8	−2.1	−2.9756	0.0089
CLASI Pre =>9	13	15.8	5.8	−10.0	−12.2747	<0.0001

* median of PSL was 3.75mg/d

Table 2.

Multivariable analysis	F	p value
Full model	3.64	0.0138
SLE	0.05	0.834
ACLE	0.63	0.4443
SCLE	0.33	0.5744
DLE	0.92	0.3557
Annular erythema	1.23	0.2887
Duration	1.08	0.3201
PSL	1.00	0.4899
Smoking	0.09	0.7749
Pre CLASI Activity	30.11	<.0001

Conclusion: The cutaneous aspects of SLE can be measured by the CLASI. The CLASI activity score may be a reasonable primary endpoint when performing a clinical trial of HCQ.

1411

Systemic Lupus Erythematosus and Sickle Cell Disease (SCD) As Comorbid Conditions. Asha Thomas, Madhu Kalyan Pendurthi, Robert W. McMurray and Vikas Majithia. University of Mississippi Medical Center, Jackson, MS

Background/Purpose: Systemic lupus erythematosus (SLE) and sickle cell disease (SCD) are chronic diseases with multisystem manifestations including arthritis, chest pain, proteinuria, and autoantiboides. The prevalence of SLE in an African-American (AA) population is about 1: 750 and that of SCD is 1:625. The exact prevalence of SCD in SLE is not known because most of the published studies are case reports. Surprisingly 20% of SCD patients have positive ANA. We aimed to measure the incidence of SCD among SLE patients at University of Mississippi Medical Center (UMMC) caring predominantly for African American population and characterize SCD complicated by SLE.

Methods: To characterize the incidence of comorbidity, we analyzed 115 clinic patients with SLE (> 4 ACR SLE criteria) with hemoglobin electrophoresis (HE) in consecutive patients seen between 2010 to2011. To further characterize the comorbid presentation of SLE/SCD we performed a retrospective chart review summary of SCD/SLE patients at our institution (7 patients identified) in addition to 39 cases reported in the literature. Data included demographic information, clinical features, medication history, hematologic and SLE parameters. Data was deidentified and tabulated.

Results: Based on HE, 2 SLE patients (1.5%) were HbSS and 11 SLE patients (13%) were heterozygotes, both of which are higher than the accepted population incidence of 0.25% HbSS and 8% SCD trait respectively. These are higher than accepted population prevalence of 0.25% HbSS and 8% SCD trait respectively. A summary result of the retrospective review of SCD with SLE is shown below:

Presenting Symptom/sign	n=46 cases
Age	24 + 2 years (mean + SD)
Sex	76% female
HbSS or Sickle positive	100%
ANA positivity	96%
Arthritis present	78%
Pleurisy present	39%
Proteinuria present	43%
Low C3/C4	22%
Anti-dsDNA positive	57%
APL positivity	24%

The majority of cases were successfully treated with corticosteroids and/or hydroxychloroquine, although some required azathioprine (17%) or cyclophosphamide (11%).

Conclusion: While the co morbid prevalence is rare, it is important to recognize the possibility of SCD complicated by or masquerading as SLE, especially in AA population. Surprisingly few cases of SCD/SLE were receiving hydroxyurea prophylaxis for SCD, although one report suggests a successful outcome for SLE/SCD co morbidity. Recognition of SCD in concurrence with SLE may be important to treatment strategies. A high index of suspicion is necessary as there did not appear to be markedly distinguishing characteristics of SLE/SCD disease manifestations. Further, the higher than expected incidence of SCD and SCD trait in our clinic population suggests that more rigorous epidemiologic and genetic investigation is necessary.

1412

Ultrasonographic Evaluation of Hand and Wrist in Systemic Lupus Erythematosus without Arthralgia. Hosung Yoon. The Catholic University, Incheon, South Korea

Background/Purpose: Articular involvement is one of the most common features of systemic lupus erythematosus (SLE) and includes joints and tendons, ranging from minor arthralgia to erosive or deforming arthropathy.[1, 2] Arthritis is typically non-erosive, non-deforming, and symmetric polyarthritis that usually involves the small joints of hands and wrists. Most SLE patients with arthritis have mild, transient course, a minority of SLE patients with chronic course may develop deformities, which could be erosive or non-erosive. Tendinopathies occur in SLE, leading to tendinitis, tenosynovitis, tendon rupture and tear.[3, 4] High resolution ultrasound (HRUS) is a sensitive imaging technique in evaluating joints and tendons. The addition of power Doppler ultrasound can detect active inflammation and are correlated with joint inflammatory activity.[5, 6] The purpose of this study is to evaluate ultrasonographic abnormalities in SLE without arthralgia in hand and wrist joints, and to correlate those with clinical parameters.

Methods: Eighty-two SLE without arthralgia (76 female, 6 male) were enrolled. Age and sex-matched 18 healthy volunteers (17 female, 1 male) and 13 SLE with arthralgia (12 female, 1 male) were included as controls. Physical examination of hand and wrist was recorded as tenderness and swelling. Disease activity was assessed using the SLEDAI (SLE Diseas Activity Index) score. MSUS using an 5– 13MHz linear array probe was used for imaging wrist, 2nd and 3rd MCP joints, and flexor tendons of 2nd, 3rd and 4th finger of nondominant side.

Results: Of Eighty-two SLE without arthralgia, wrist synovitis was found in 34 patients (41.5%) and MCP synovitis was noted in 45 patients (54.9%). Tendinitis and tenosynovitis were detected in 33 patients (40.2%) and 12 patients (14.6%), respectively. These abnormalities were observed more frequently in selected SLE with arthralgia (n=13). Synovitis thickness in joints and tendon thickness were greater in patients with arthralgia compared to those without ($p<0.002$ and $p<0.001$). Sum of synovitis grading score was positively correlated with SLEDAI ($r=0.49$, $p<0.001$) and anti-dsDNA antibody ($r=0.27$, $p=0.009$). Tendon thickness was positively correlated with sum of synovitis grading score ($r=0.22$, <0.031).

Conclusion: Synovitis or tendinopathies are common in SLE patients who do not suffered from arthralgia. Longitudinal study is needed to determine the meaning of sonographic abnormalities in SLE patients who do not suffered from arthralgia. SLE patients with high SLEDAI may need to take musculoskeletal sonography.

1413

Pregnancy Outcomes and Fetal Complications in Patients with Systemic Lupus Erythematosus: a Retrospective Analysis in Korea. Eun-Jung Park[1], Jiwon Hwang[1], Jaejoon Lee[2], Joong Kyong Ahn[3], Chan Hong Jeon[4], Hoon-Suk Cha[1] and Eun-Mi Koh[1]. [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul, South Korea, [3]Kangbuk Samsung hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Soonchunhyang University College of Medicine, Bucheon, South Korea

Background/Purpose: Systemic lupus erythematosus (SLE) predominantly affects women in reproductive year. The effect of pregnancy on the SLE disease activity and the influence of SLE activity on pregnancy outcomes are major concerns in the management of SLE. The aim of this study is to evaluate the pregnancy outcomes in SLE patients and to investigate the impact of pregnancy on disease activity and the effect of lupus activity on pregnancy with respect to fetal complications.

Methods: All pregnancies with SLE seen at Samsung Medical Center between November 1994 and December 2010 were included and retrospectively analyzed. Demographics, clinical manifestations, laboratory data and fetal outcomes were evaluated. SLE flare was determined by Lupus Activity Index-Pregnancy (LAI-P) score. Logistic regression analysis was used to determine the predictive factors for fetal complications.

Results: Sixty-two pregnancies were observed among 50 patients. Of these, 51 (82.3 %) live births and 11 (17.7%) fetal losses were seen. Of live births, 38 (74.5 %) full-term births and 13 (25.5 %) preterm births occurred. Thirteen cases of low birth weight and 9 intrauterine growth retardations were noted. Fetal losses included 3 spontaneous abortions, 2 stillbirths, and 6 therapeutic abortions. Proteinuria, 0.5g per day or more, during pregnancy was found to be a predictive factor for fetal complications adjusting for age, history of previous lupus nephritis, and history of steroid use (adjusted OR 5.59; $P = 0.024$). LAI-P score measurement was available in 36 pregnancies. Of these, SLE flare occurred in 12 pregnancies (33.3 %), mainly during the second trimester (37.5%). Renal involvement (69.2 %) was found to be the most common SLE flare during pregnancy, followed by thrombocytopenia (15.4 %), serositis (7.7 %) and vasculitis (7.7%). All flares were classified as severe flare according to LAI-P score. As expected, fetal losses, prematurity and low birth weights were observed more frequently in the flare group whereas live births and full-term births were observed more frequently in those without SLE flare.

Conclusion: Our data demonstrated a relatively higher rate of live births and lower rate of fetal losses in patients with SLE compared to previous reports. The rate of lupus flares during pregnancy was also lower and renal flare was the most common manifestation. Proteinuria, 0.5g per day or more, during pregnancy was found to be the sole predictive factor for fetal complications.

1414

Relationship Between Age of Onset and Clinical Profile In Systemic Lupus Erythematosus Patients. Julia Martínez-Barrio, Juan G. Ovalles, Francisco J. López-Longo, Inmaculada de la Torre, Lina Martínez-Estupiñán, Juan C. Nieto and Luis Carreño. Gregorio Marañón Hospital, Madrid, Spain

Background/Purpose: Several studies have shown that the clinical and immunological profiles of SLE are related to the age of onset[1]. However, other authors have not found any link between them[2]. To describe the clinical and immunological differences between Early, Adult and Late onset SLE.

Methods: 445 patients diagnosed with SLE between 1986 and 2006 were included in an inception cohort and followed up for a minimum time of one year (median 11, 1–20). Demographic, clinical and laboratory features were collected at recruitment time and every 12 months. Patients were divided into three groups: Early onset ≤ 18 years (n=92), Adult onset 19–50 years (n=276) and Late onset >50 years (n=77). Damage was scored at the end of the study using SLICC/ACR Damage Index. Sera samples were tested for autoantibodies, complement and immunoglobulins. Chi-square test and ANOVA with Bonferroni correction was applied for quantitative variables with a normal distribution, otherwise Kruskal-Wallis test was used.

Results: The sex ratio (F/M) was significantly higher in the Adult onset patients ($p=0.021$). At disease onset, the Early onset group presented more renal and skin manifestations ($p=0.023$; $p=<0.001$). During follow-up Early

onset group continued to have higher frequency of renal disease (p=<0.001), malar rash (p=<0.001), Raynaud's phenomenon (p=0.008), cutaneous vasculitis (p=0.006) and neurological manifestations (p=0.044) than the other two groups. Whereas arthritis was more frequent in the Adult onset group than in the others (p=0.031), the Late onset group had significantly more hypertension (p=0.048), neoplasias (p=0.017), disease duration (p=0.028), mortality (p<0.001) and accrual damage (p=0.037). As for laboratory data, lymphopenia was more frequent in Adults (p=0.005) and low serum complement (p=<0.001), anti-dsDNA, anti-U1RNP and anti-Sm were more common in Early onset patients.

Conclusion: Early onset SLE is clinically and immunologically different with more renal and neurological manifestations, cutaneous vasculitis, malar rash and Raynaud's phenomenon than Adult and Late onset SLE. The Early onset group presented higher frequency of low serum complement, anti-dsDNA, anti-U1RNP and anti-Sm antibodies. The accrual damage and mortality proportion observed in the Late onset patients may be related to the consequences of aging.

STATISTICALLY SIGNIFICANT FINDINGS

CHARACTERISTICS n=445	Early Onset ≤18 years (n=92)	Adult Onset 19–50 years (n=276)	Late Onset >50 years (n=77)
At Disease Onset			
DEMOGRAPHIC FEATURES			
Sex Ratio (Female/Male)	6.1(79/13)	8.9(248/28)	3.5(60/17)
Age, Mean±SD	12.9±3.7	31.9±8.5	61.2±8.0
CLINICAL MANIFESTATIONS (%)			
Renal	16(17.4)	23(8.3)	5(6.5)
Skin	36(39.1)	93(33.7)	8(10.4)
During Follow-Up			
Arthritis	78(84.8)	254(92)	64(83.1)
Malar rash	48(52.2)	130(47.1)	17(22.1)
Neurologic	37(40.2)	75(27.2)	20(26)
Renal	58(63)	124(44.9)	22(28.6)
Raynaud's Phenomenon	39(42.4)	82(29.7)	16(20.8)
Hypertension	35(38)	77(27.9)	31(40.3)
Cutaneous Vasculitis	30(32.6)	56(20.3)	10(13)
Neoplasia	2(2.2)	13(4.7)	9(11.7)
SLICC/ACR Index ≥1 (%)	63(68.5)	176(63.8)	61(79.2)
Disease Duration, Mean±SD	13.2±8.8	12.6±8.6	10±7.5
LABORATORY FEATURES (%)			
Lymphopenia	27(29.3)	134(48.6)	31(40.3)
Low complement	80(87)	220(81.2)	40(58)
ɣ-globulin increase	38(56.2)	155(56.2)	37(48.1)
Anti-U1RNP	41(46.1)	84(32.4)	19(29.7)
Anti-Sm	23(25.8)	42(16.2)	7(10.9)
Anti-dsDNA	75(82.4)	198(72.8)	37(54.4)
Exitus Letalis	7 (7.6)	17 (6.2)	13 (16.9)

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1415

Serum Cystatin C Is Affected by Inflammation and Renal Dysfunction in Patients with Systemic Lupus Erythematosus. Christine LY Chew[1], Awal Al-M Husain[1], Philip Pemberton[2], Sahena Haque[1], Allen Yates[2] and Ian N. Bruce[3]. [1]University of Manchester, Manchester, United Kingdom, [2]Manchester Royal Infirmary, Manchester, United Kingdom, [3]A, Manchester, United Kingdom

Background/Purpose: Systemic lupus erythematosus (SLE) patients have increased mortality due to complications, such as renal failure and cardiovascular disease. In clinical practice, glomerular filtration rate (GFR) is usually estimated using the modified Cockcroft-Gault (mCG) or the Modification of Diet in Renal Disease (MDRD) equations. Serum cystatin C (sCysC) has been suggested to be a more stable marker of renal dysfunction. We aimed to compare sCysC in SLE patients and healthy controls, to assess its agreement with standard tests of renal dysfunction and investigate factors contributing to higher sCysC in SLE patients.

Methods: Women with SLE patients (≥4 ACR criteria) were recruited from our Lupus Clinic and healthy women were recruited from the general population. Subjects underwent clinical assessment of their SLE as well as lifestyle factors, blood pressure and body mass index (BMI). We also ascertained their history of lupus nephritis and/or nephrotic syndrome, serum creatinine, and eGFR using the mCG an MDRD equations. Serum CysC was measured using R&D Systems' ELISA development method (working range up to 2ng/mL; intra-assay coefficient of variation (CV) = 6.49%, inter-assay CV = 12.70%). We assessed the agreement between different estimates of GFR using Deming plots. Univariate and multivariate linear regression analyses were applied to ascertain the predictors of sCysC in SLE patients.

Results: 178 patients and 68 controls were recruited with a median (IQR) age of 50 (39–60) and 53 (46–61) years old respectively. SLE patients had higher systolic blood pressure (P<0.05), and higher sCysC (Controls vs. SLE (median [IQR]) = 120 [110–130] vs. 127 [115–143], P=0.02; 0.950 [0.727–1.134] vs. 1.161 [0.980–1.359], P<0.0001; respectively). In both groups, sCysC correlated positively with serum creatinine, and inversely to both measures of eGFR (r= −0.530; p<0.0001 (mCG), and r= −0.620; p<0.0001 (MDRD)). Using Deming plots, there was closer agreement between the mCG and MDRD estimates of eGFR (P<XX) than these individual tests with sCysC (P= X and Y for sCysC and mCG and MDRD respectively). In a univariate analysis of SLE patients, sCysC also had significant correlations with age (β-coefficient, P value) (0.009; 0.05), hs-CRP (0.04; 0.001), SLEDAI (0.04; 0.007), SLICC damage index (0.18; <0.0001), serum creatinine (0.01, <0.0001), eGFR (0.01, <0.0001) and past history of nephritis (0.3, 0.004). BMI (0.003, 0.7) was included in the analysis due to its influence on plasma CysC. In multivariate analysis (β, P), age (0.0039, 0.06), hs-CRP (0.01, <0.0001) and serum creatinine (0.01, <0.0001) were all independently associated with sCysC in SLE.

Conclusion: SCysC is increased in SLE and in SLE patients with a history of nephritis. While 2 standard methods of estimating GFR agree well with each other they have lower levels of agreement with sCysC. This is supported by our observation that in SLE, sCysC is also influenced by BMI and low grade inflammation. SCysC should therefore not supplant current methods of assessing renal dysfunction in SLE patients.

1416

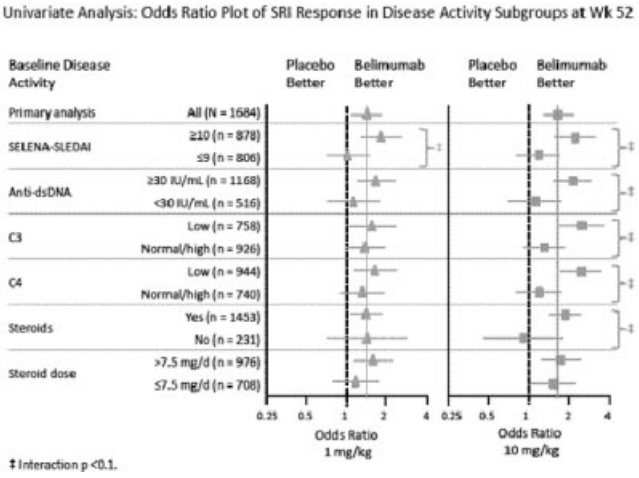
Factors Associated with Belimumab Treatment Benefit: Results From Phase 3 Studies in Patients with Systemic Lupus Erythematosus. R.F. van Vollenhoven[1], M. Petri[2], R. Cervera[3], C. Kleoudis[4], Z.J. Zhong[5], D. Roth[6], W. Freimuth[5] and BLISS-52 and BLISS-76 Study Groups[7]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Hospital Clinic, Barcelona, Spain, [4]GlaxoSmithKline, Durham, NC, [5]Human Genome Sciences, Inc., Rockville, MD, [6]GlaxoSmithKline, King of Prussia, PA, [7]Multicenter

Background/Purpose: To identify baseline systemic lupus erythematosus (SLE) disease characteristics that predicted belimumab treatment response in BLISS-52 (NCT00424476)/BLISS-76 (NCT00410384).

Methods: 1684 autoantibody-positive (antinuclear antibody ≥1:80 or anti-double-stranded DNA [anti-dsDNA] ≥30 IU/mL) SLE patients with SELENA-SLEDAI (SS) score ≥6 received belimumab 1 or 10 mg/kg, or placebo, plus standard therapy, for 52 wk (BLISS-52) or 76 wk (BLISS-76). Primary endpoint of both trials was response rate at wk 52 by the SLE Responder Index (SRI): SS improvement (≥4-point decrease), no new BILAG A or 2 new B scores, and no Physician's Global Assessment worsening (<0.3-point increase). Patients were classified as non-responders if they withdrew from study or received prohibited/restricted medication beyond protocol-specified limits. Subgroup analyses of SRI response at wk 52 were performed to evaluate the consistency of belimumab treatment effect. Multivariate logistic-regression analysis was performed on the pooled dataset to identify baseline characteristics associated with greater treatment benefit. The model was built using a stepwise forward selection process.

Results: Overall wk-52 SRI rates with placebo, and belimumab 1 and 10 mg/kg were 38.8%, 46.2% (odds ratio [OR]: 1.4; p = 0.006), and 50.6% (OR: 1.7; p <0.0001), respectively. Univariate analysis by baseline characteristics generally demonstrated positive treatment effects for belimumab in subgroups with odds ratios >1; patients with higher baseline disease activity (SS score ≥10, OR: 1.8 and 2.2 for belimumab 1 and 10 mg/kg, respectively; positive anti-dsDNA, OR: 1.7 and 2.1; and low complement [C3/C4], OR: 1.6 and 2.4) had greater response to belimumab vs placebo than those with lower disease activity (figure). Steroid use did not appear to be a predictor of a differential response to belimumab vs placebo when categorizing patients by a steroid dose of <7.5 and ≥7.5 mg/d. It did appear to be a predictor of a differential response when categorizing patients by no steroid use vs any steroid use, although the group using no steroids was small. In patients with baseline low C3/C4 and positive anti-dsDNA, wk-52 SRI response rates were 31.7% with placebo, and 41.5% (OR: 1.8; p = 0.002) and 51.5% (OR: 2.7; p <0.001) with belimumab 1 and 10 mg/kg, respectively. Results of the multivariate analyses were consistent with the univariate results with low C3/C4, steroid use, and SS ≥10 as predictors of better

outcome with belimumab. In patients with baseline SS ≥10, wk-52 SRI response rates were 44.1%, 58.0% ($p < 0.001$), and 63.2% ($p < 0.001$) with placebo, and belimumab 1 and 10 mg/kg, respectively.



Conclusion: Measures of high baseline disease activity in SLE patients, including high SS score, low C3/C4, positive anti-dsDNA, and steroid use, predicted better outcome with belimumab (10 mg/kg) treatment compared with standard of care alone.

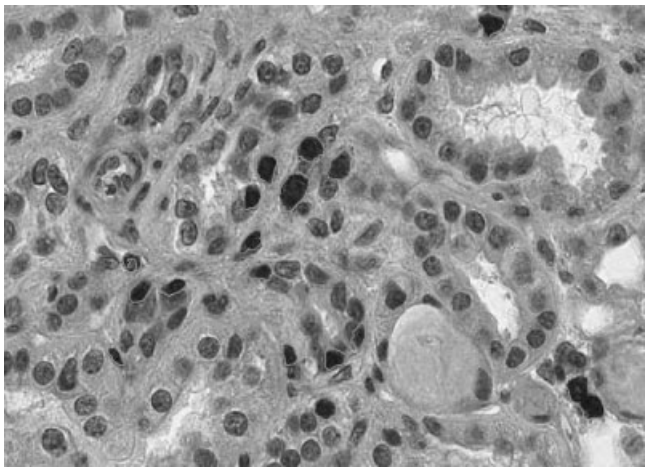
1417

Towards a Quantitative Assessment of Renal Biopsies for Lupus Nephritis. Siddharth S. Samsi[1], Brad H. Rovin[2], Sara Cole[3], Don Stredney[1] and Wael N. Jarjour[4]. [1]Ohio Supercomputer Center, Columbus, OH, [2]Ohio State University Medical Center, Columbus, OH, [3]The Ohio State University, Columbus, OH, [4]Ohio State University, Columbus, OH

Background/Purpose: Systemic lupus erythematosus of the kidneys is associated with high morbidity and mortality. Despite advances in treatment, significant variation in response to treatment exists. While some of this variation is undoubtedly related to genetic and environmental factors, inter-observer variation and sampling bias continue to confound the accurate interpretation of kidney biopsies, contributing to variations in treatment. Underestimating the severity of renal involvement or inaccurately assessing reversibility of lesions can result in significant morbidities related to under or over-treatment. Therefore, there is a need for additional, objective tools that pathology experts can use to assist in the evaluating kidney biopsy.

Methods: We present two approaches for quantification of tissue components in renal biopsies as the first step towards an automated image analysis system for quantifying histological findings associated with progression to renal failure, such as cellular crescents, extensive fibrinoid necrosis, glomerular sclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis. The first approach is used to analyze H&E stained tissue for glomeruli identification. The second approach analyzes fluorochrome-conjugated monoclonal stained human renal biopsies to identify positively stained infiltrating cells.

Results: First, our approach was applied to the analysis of H&E stained renal biopsies to develop the techniques required to identify glomeruli. This preliminary work was carried out using mouse kidneys due to the availability of entire kidney for the study. Tissue biopsies were scanned at 40x microscope resolution. Regions containing glomeruli were extracted from the images and used to develop and test the proposed algorithm. Using computer aided image analysis, it is possible to isolate glomeruli in renal biopsies. Analysis of glomeruli in a sample mouse renal tissue showed average thickness of Bowman's capsules around one glomeruli to be 3.32 microns with the major axis of the glomeruli being 140.28 microns. Second, techniques developed above were applied to the analysis of CD3 stained human kidney biopsy scanned at 40x microscope resolution. Ten random regions of 250 micron^2 were extracted from two whole slide images. A total of 543 CD3 positive cells were counted using automated image analysis as demonstrated in the figure.



Conclusion: Through the use of computer-aided image analysis, it is possible to isolate and measure physical dimensions of structures in renal biopsies. This approach will be further developed for quantification of fibrosis in the glomeruli. Furthermore, immunohistochemistry will allow for quantitation of various cellular infiltrates and their localizations. By correlating findings with clinical outcomes, this approach has the potential to advance the understanding of Lupus Nephritis and improve treatment outcome.

1418

The Relationship Between Pain Coping Skills and Pain, Fatigue, Mood, and Lupus Activity. Preethi Kurakula, Tamara J. Somers, Lisa G. Criscione-Schreiber, Francis J. Keefe and Megan E. B. Clowse. Duke University Medical Center, Durham, NC

Background/Purpose: Patients with systemic lupus erythematosus (SLE) experience distressing physical and psychological symptoms that are often not relieved by current pharmaceutical options. In this study, we sought to examine how two forms of pain appraisal (self-efficacy for pain and pain catastrophizing) are related to pain, stiffness, fatigue, mood, and self-reported memory problems in patients with SLE. Pain self-efficacy and pain catastrophizing are particularly salient because they have been shown to be modifiable through psychosocial interventions improving outcomes in patients with other rheumatological conditions.

Methods: We conducted a cross-sectional study of consecutive patients who met the 1997 ACR classification criteria for SLE. All participants completed a questionnaire that included symptom ratings (i.e., pain, stiffness, fatigue), mood, memory problems, and pain coping strategies (i.e., self-efficacy for pain control and pain catastrophizing). SLE disease activity was rated by the treating rheumatologist using the SELENA-SLEDAI. Correlational analyses were used to examine bivariate relationships between pain appraisals and SLE outcomes, followed by hierarchal regression (HLR) analyses to examine the independent contributions of self-efficacy for pain control and pain catastrophizing to the outcomes after controlling for demographic variables and disease severity. In each HLR, age and race were entered on Step 1, disease severity was entered on Step 2, and self-efficacy for pain control and pain catastrophizing were entered on Step 3.

Results: The 74 SLE patients in this study were 91% female with a mean age of 39 (SD=13) years; 59% Black and 38% White. Both self-efficacy for pain and pain catastrophizing correlated with pain, fatigue, stiffness, and mood (all $p < 0.05$). Results of our HLR showed that patients with lower levels of self-efficacy reported higher levels of symptoms of SLE including pain ($p<.001$), stiffness ($p=.001$), and fatigue ($p<.001$). Additionally, patients with higher levels of pain catastrophizing reported lower positive mood ($p=.003$) and showed a trend toward reporting more problems with memory ($p=.06$). Disease activity measured with the SELENA-SLEDAI was not associated with physical symptoms, mood, memory, or self-efficacy for pain control or pain catastrophizing.

Conclusion: Our results suggest that in patients with SLE, low self-confidence to control pain (self-efficacy) was related to a high level of physical symptoms and pain catastrophizing was related to mood and memory problems. Importantly, the effects of these pain appraisals do not appear to be explained by standard disease activity ratings. This finding suggests that pain coping skills training, which is designed to decrease

catastrophizing and enhance patients' ability to control pain and has been shown to be effective in other rheumatological conditions, may similarly help improve physical and psychological symptoms in SLE patients.

1419

Memory Complaints in Lupus Patients: Relationship to Lupus Activity, Symptoms, Quality of Life, Psychological Distress, and Coping. Megan E. B. Clowse[1], Lisa G. Criscione-Schreiber[1], Meenakshi Jolly[2], Francis J. Keefe[1] and Tamara J. Somers[1]. [1]Duke University Medical Center, Durham, NC, [2]Rush University Medical Center, Chicago, IL

Background/Purpose: Patients with systemic lupus erythematosus (SLE) often report distressing symptoms of cognitive impairment. Rheumatologists working with SLE patients are often unsure how such complaints are related to core outcomes such as SLE activity and emotional health. This study aimed to understand how reports of memory complaints are related to SLE disease activity and patient-reported physical symptoms, quality of life, and psychological distress.

Methods: We conducted a cross-sectional study of consecutive patients who met the 1997 ACR classification criteria for SLE. Participants completed the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to assess memory complaints. SLE disease activity was rated by the treating rheumatologist using the SELENA-SLEDAI and physician's global assessment (PGA). Patient reported symptoms of pain, fatigue, stiffness, and pain were recorded on a visual analog scale (VAS). The LupusPRO was used to assess lupus-related quality of life; a low score on a LupusPRO domain indicates increased distress. Additionally, psychological health was assessed using the Positive and Negative Affect Schedule (PANAS). Correlational analyses were used to examine bivariate relationships between memory complaints and outcome measures. A correlation with a p-value <0.05 was considered statistically significant.

Results: The 74 SLE patients in this study were 91% female with a mean age of 39 (SD=13) years; 59% Black and 38% White race. The average score on the MSNQ was 23.12 (SD=15.07), indicating that half of our sample is at high risk for neuropsychiatric impairment (score > 23) based on standardized scoring of this measure. Physician-reported SLEDAI and PGA did not correlate with memory complaints, nor did VAS based patient-reported measures of fatigue, stiffness, and rash. Memory complaints did correlate with the patient-reported pain VAS and the physical symptom LupusPRO domains (lupus symptoms (r=-0.27), pain (r=-0.39), physical health (r=-0.41)) and LupusPRO summary health-related quality of life (r=-0.62) and overall quality of life (r=-0.44) scores. In addition, memory complaints correlated with the LupusPRO emotional health (r=-0.48) domain and PANAS (low positive mood (r=-0.34) and high levels of negative mood (r=0.47)).

Conclusion: This study found that SLE patients varied in their reports of memory complaints with half of our sample reporting high levels of memory problems. Results showed that memory complaints were not related with physician measured disease activity, but were associated with outcomes important to SLE patients, including pain and psychological distress. Based on our cross-sectional study, it is not clear whether memory problems lead to lower quality life, pain, and more psychological distress, or vice versa. Future longitudinal studies could help identify the causal relationship between memory complaints and patient outcomes. An interesting direction for future research would be to explore how behavioral intervention designed to enhance how patients cope with memory problems could impact patient outcomes such as quality of life, physical symptoms, and psychological distress.

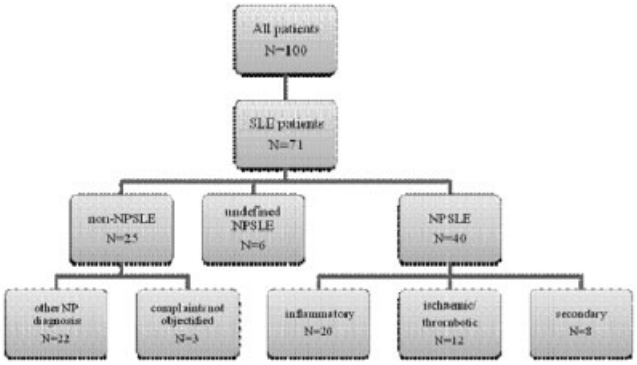
1420

The Leiden Neuropsychiatric Systemic Lupus Erythematosus Clinic; Establishing Clinical Phenotypes. E. Zirkzee, G. Steup-Beekman, H. Middelkoop, E. Bollen, N. Van der Wee, E. Baptist, R. Van der Mast, M. Huisman, J. Luyendijk, M. Van Buchem and T. Huizinga. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Understanding of pathogenesis of neuropsychiatric systemic lupus erythematosus (NPSLE) is emerging and recent animal studies show a link between auto-antibody activity and cognitive dysfunction[1]. To optimally correlate information derived from experimental research with findings in human NPSLE, well described clinical phenotypes are essential.

Methods: The Leiden NPSLE clinic is a tertiary referral clinic that evaluates patients suspected of NPSLE and leads to a prospectively collected database. Diagnosis and treatment are based on consensus of an experienced multidisciplinary team of medical specialists and a neuropsychologist. NPSLE phenotype is based on the clinically suspected putative pathogenetic mechanism and subsequently advised therapy. Cognitive dysfunction is objectified by neuropsychological tests. Sociodemographic and clinical characteristics of three phenotypes; inflammatory, ischemic/thrombotic and secondary NPSLE are described.

Results: From September 2007 until December 2009 we evaluated one hundred patients. The figure shows outcome of evaluation and attribution of NP manifestations. Twenty patients had inflammatory NPSLE of whom twelve (60%) patients had cognitive dysfunction. Mood disorder, seizure disorder and psychosis were present in three (15%) patients in this group. Mean age of patients was 42 years, mean disease duration 8.0 years and symptom duration 1.8 years. Clinical systemic activity was present in 80% of patients, antiphospholipid antibodies in 60% and MRI abnormalities in 75% of patients. Twelve patients had ischemic/thrombotic NPSLE of whom six (50%) patients had cognitive dysfunction. Eleven (92%) patients had cerebrovascular disease with various clinical manifestations. Mean age of patients was 47 years, mean disease duration 8.6 years and symptom duration 2.7 years. Clinical systemic activity was present in 25% of patients, antiphospholipid antibodies in 67% and MRI abnormalities in 100% of patients. Eight patients had secondary NPSLE of whom three (38%) had cognitive dysfunction. Mean age of patients was 34 years, mean disease duration 14 years and symptom duration 2.7 years. Clinical systemic activity was present in 25% of patients, antiphospholipid antibodies in 25% and MRI abnormalities in 50% of patients.



Conclusion: We identified three clinical phenotypes in NPSLE; inflammatory (50%), ischemic/thrombotic (30%) and secondary (20%) NPSLE and described their characteristics. Cognitive dysfunction was highly prevalent in all patients, especially in inflammatory NPSLE. High prevalence and emerging pathogenetic understanding make cognitive dysfunction an interesting target for further research. Furthermore, this study showed the feasibility of establishing a prospective database in NPSLE by means of a dedicated multidisciplinary clinic.

1. Lu XY PLoS One. 2010 Jun 15;5(6):e11124

1421

Limited Value of Soluble Urokinase Plasminogen Activator Receptor As a Disease Activity Marker in Patients with Systemic Lupus Erythematosus. Helena Enocsson, Jonas Wettero, Thomas Skogh and Christopher Sjowall. Linkoping University, Linkoping, Sweden

Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic rheumatic disease characterized by multiorgan involvement and varying degree of activity over time. Although measurements of anti-dsDNA antibodies, complement, blood cell counts and erythrocyte sedimentation rate (ESR) can be helpful, distinction of disease activity from organ damage remains a challenge. The urokinase plasminogen activator receptor (uPAR; CD87) is expressed *e.g.* on endothelial cells, monocytes, granulocytes and smooth muscle cells. During inflammation, cell surface uPAR expression and shedding increases, and the soluble form, suPAR, accumulates in the circulation. It has been shown that suPAR predicts disease outcome of infectious diseases and malignancies, and correlates to disease activity in inflammatory diseases, such as rheumatoid arthritis (RA). The aim of this study was to examine suPAR as a potential biomarker in SLE.

Methods: Cross-sectional sera from 100 healthy controls and 198 SLE

patients fulfilling the 1982 ACR classification criteria (80%) or the Fries (ANA positive + ≥2 typical organ manifestations) criteria (20%) were analyzed for suPAR by ELISA (suPARnostic®), kindly provided by Electra-Box Diagnostica AB, Tyresö, Sweden. In addition, 19 of the 198 patients (all with ≥4 ACR criteria) were selected on the basis of raised disease activity (SLEDAI score or physician's global assessment, PGA) for consecutive suPAR analysis (2–13 visits per patient). Routine analyses at all visits included blood cell counts, ESR, C-reactive protein (CRP), complement (C3, C4, C3d and classical function), creatine kinase, urinalysis and anti-dsDNA (*Crithidia luciliae* IF test, CLIFT). Disease activity was assessed by SLEDAI and PGA.

Results: In cross-sectional analysis, no significant difference was found between controls and patients regarding suPAR levels; and no correlations were found between suPAR and disease activity measures (SLEDAI, PGA or CLIFT). However, correlations between suPAR and CRP (r=0.33), ESR (r=0.25), C3d (r=0.27), leukocyte (r=0.36) and platelet count (r=0.19) were identified. In addition, thrombocytopenia and leukopenia were the only lupus manifestations where suPAR levels differed significantly between patients exhibiting *vs* not exhibiting the manifestation (p=0.048 and p=0.031, respectively). A linear regression analysis of the impact of platelet count and differential white blood cell count on suPAR levels revealed that neutrophils were the only cells with significant impact (38%, p<0.001). Comparing suPAR levels in controls with SLE patients at peak disease activity (consecutive samples), statistical significance was only reached when patients with cytopenia at flare had been excluded.

Conclusion: In contrast to RA, suPAR is not strongly associated with disease activity in SLE. The reason hereto may, at least partially, be explained by muted suPAR levels in patients with hematological activity, such as leukopenia.

1422

Caregiver Burden Is Associated with Worse Dyadic Relationship and Health Outcomes in Lupus. Amita Thakkar, Rachel A. Mikolaitis, Joel A. Block and Meenakshi Jolly. Rush University Medical Center, Chicago, IL

Background/Purpose: Systemic Lupus Erythematosus (SLE) inflicts young women and adversely impacts their quality of life (QOL). Informal caregivers of patients with chronic illness are generally their intimate partners. SLE, may impose care giver burden (CGB), and adversely impact the quality of dyadic relationship & caregiver's QOL. CGB and its recognition may be important in designing interventions to improve health outcomes in SLE.

Methods: Dyad is a unit consisting of the SLE patient & their caregiver. Ten SLE patients and his/her primary informal caregiver (n=10) were recruited from the Lupus Clinic. Data collected included demographics, CGB (caregiver burden scale, screen for caregiver burden), QOL (SF-36), & quality of dyadic relationship (Dyadic Adjustment Scale-DAS). Data were collected from dyads separately to avoid confounding. Correlation coefficients between CGB with DAS and Dyadic QOL were calculated.

Results: The mean (SD) age of caregivers was 37.3 (SD 9.64) yrs. Sixty percent of caregivers were employed and were providing care for 3.95 (SD 2.65) yrs. 9/10 were patient's intimate partner. Caregivers provided informal care for a mean of 10 hours/wk. All caregivers provided emotional support, while 70% assisted with activities of daily living, 30% dispensing medications, 70% transportation and 80% financially. Half of the caregivers reported other dependents, with a mean of 1.4 (SD 0.96) additional dependent members/household. Mean (SD) caregiver scores were: total CGB Scale score 9.1 (5.8), Subjective burden 8.3 (9.5), Objective burden 4.4 (4) & total DAS 94.4 (15.5). Mean (SD) age and disease duration of SLE patients was 35.2 (9) yrs and 7.9 (7.7) yrs. Mean (SD) Total DAS for SLE was 94.6 (17). Agreement between DAS scores was significant (R 0.96, p 0.001). Total CGB was inversely related to caregivers employment status, own QOL (Bodily pain (r −0.61, p 0.06)) and patients QOL (Physical Function (r −0.66, p 0.03), Role Physical (r −0.82, p 0.004), Social Functioning (r −0.65, p 0.06), Role Emotional (r −0.86, p 0.003)) & patients DAS (r −0.66, p 0.08).

Objective burden was associated with caregivers age (r 0.68, p 0.03), own QOL (Bodily pain (R −0.58, P 0.08), General Health (r −0.64, p 0.04), Vitality (r −0.56, p 0.09), Social Function (r −0.61, p 0.06), Mental Health (r −0.58, p 0.08)) & patient's QOL (Role Emotional (r −0.63, p 0.07)). Subjective burden was associated with caregiver age (r 0.79, p 0.007), own QOL (Physical Function (r −0.67, p 0.03), Bodily Pain (r −0.64, 0.05), General Health (−0.76, p 0.01), Vitality (r −0.62, p 0.06), Social Function (r-0.67, 0.04), Mental Health (r −0.75, 0.01)), & patients QOL (Role Emotional (r −0.73, p 0.03).

QOL of the patient and the caregiver were correlated. Caregiver DAS scores were associated with patients QOL, while patients DAS scores were associated with their own QOL (Data not shown).

Conclusion: This exploratory data shows that caregiver burden in SLE is associated with caregiver's own and their SLE partners QOL. Though dyadic QOL is interrelated, Dyadic DAS is linked primarily to patient's QOL. To optimize patient's health outcomes in SLE, focus should be on the dyadic unit rather than the patient in isolation.

ACR/ARHP Poster Session B

Systemic Lupus Erythematosus - Human Etiology and Pathogenesis II: Innate Immune System and Organ Damage

Monday, November 7, 2011, 9:00 AM–6:00 PM

1423

Genetic Ancestry, Serum Interferon-α Activity and Autoantibodies in Systemic Lupus Erythematosus. Kichul Ko, Beverly S. Franek and Timothy B. Niewold. University of Chicago, Chicago, IL

Background/Purpose: Systemic lupus erythematosus (SLE) is a heterogeneous disease that has different clinical and serological manifestations amongst various self-reported ancestral backgrounds. High levels of interferon-α (IFN-α), which plays an important pathogenic role in SLE, have been associated with positive serology and self-reported non-European ancestry. We aimed to explore and refine these relationships using quantitatively defined genetic ancestry in place of self-reported ancestry.

Methods: Data from 220 lupus patients were analyzed from a majority African-American multiancestal cohort. A panel of more than 300 ancestry informative markers (AIM) selected throughout the genome was genotyped, and principal component analysis was used to analyze the AIM data, providing quantitative variables representing continental ancestry. Univariate and multivariate logistic regression models were used to detect associations between serum IFN-α, autoantibodies, and genetic ancestry. Age and gender were included as co-variates.

Results: In univariate models, African American genetic ancestry (AA) was associated with positive anti-Ro, anti-Smith and anti-ribonucleoprotein (anti-RNP) antibodies and high levels of IFN-α (p-values 0.0194, 0.0112, 0.0002 and 6.1×10^{-6} respectively). Hispanic American ancestry was linked to presence of anti-La (p-value 0.0397). In multivariate models, AA ancestry was associated with positive anti-RNP antibody (p-value 0.0026). High levels of IFN-α were linked to presence of anti-RNP antibody (p-value 2.8×10^{-5}), but AA ancestry was not directly associated with IFN-α (p-value 0.1565), supporting a sequential relationship between these variables. Similar to previous work, younger age was independently associated with higher IFN-α (p-value 0.0014).

Conclusion: Our data support a model in which AA ancestry increases the likelihood of SLE-associated autoantibody formation, which subsequently results in higher levels of serum IFN-α. The relationship between higher IFN-α and younger age in SLE continues to be robust across multiple analyses and cohorts.

1424

Analysis of Longitudinal Gene and Protein Expression Data Classifies SLE Patients Based on Molecular Profiles Associated with Disease Activity, Serology and Specific Organ Manifestations. Mikhail Olferiev[1], Kyriakos A. Kirou[2], Dorthe Lundsgaard[3], Klaus S. Frederiksen[3], Jan Fleckner[3] and Mary K. Crow[1]. [1]Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, NY, [2]Mary Kirkland Center for Lupus Care, Hospital for Special Surgery, New York, NY, [3]NovoNordisk, Copenhagen, Denmark

Background/Purpose: Patients with systemic lupus erythematosus (SLE) are highly heterogeneous and are characterized by variable clinical manifestations and outcome. In order to define the immunopathogenic mechanisms that underlie this heterogeneity, with the goal of predicting clinical course and identifying therapeutic targets, we simultaneously identified mRNA profiles in longitudinal PBMC samples and determined the levels of pro-inflammatory cytokines and autoantibodies in plasma of patients with SLE.

Methods: One hundred sixty-nine PBMC and plasma samples were collected longitudinally (up to 3 years) from 23 SLE patients and 5 healthy donors (HD). All SLE patients fulfilled ACR criteria for the disease. PBMC mRNA transcriptional profiles for each visit were obtained using Affymetrix Human Genome U133 Plus 2.0 GeneChips. Plasma levels of 44 autoantibodies and 56 pro-inflammatory cytokines were evaluated using Multi-Analyte Profiling (MAP) technology (Rules-Based Medicine, Austin, TX). Data were analyzed using the significance analysis of microarrays algorithm and clustering analysis.

Results: Unsupervised hierarchical clustering demonstrated that gene expression in SLE patients was distinct from HD. The two most prominent gene signatures in peripheral blood of SLE patients, type I interferon-inducible genes (IFN-I) and neutrophil granule-related genes, classified SLE patients into three distinct groups. Clinical and serologic characteristics were significantly different among the groups. Group A patients, with neither the IFN-I nor neutrophil gene expression signatures, had only mild disease. Groups B and C had more frequent disease flares, but were distinguishable from each other based on gene expression, clinical manifestations, and cytokine profile: 8/11 SLE patients with both IFN-I and neutrophil signatures (group B) had increased anti-SSA/Ro autoantibodies ($p<0.02$) and significantly more frequent vascular involvement (by BILAG; $p<0.05$) compared to Group C. Group C expressed the IFN-I signature but not the neutrophil signature and was characterized by mucocutaneous manifestations ($p<0.02$) and 1.8 fold higher plasma TNFα compared with Group B.

Conclusion: Gene expression analysis of longitudinal PBMC samples classified SLE patients based on IFN-I and neutrophil gene signatures into three distinct groups that differ in clinical manifestations, autoantibodies and pro-inflammatory mediators. Interestingly, anti-SSA/Ro autoantibodies are associated with the neutrophil gene signature in PBMC, consistent with a recent demonstration of neutrophil activation by RNA-containing immune complexes. Comprehensive examination of molecular pathways associated with clinical features of lupus will help to unravel the heterogeneity of this complex autoimmune disease.

1425

Estrogen Stimulation of Endosomal Toll-Like Receptor Expression Lowers the Threshold of Activation in Peripheral Blood Mononuclear Cells and Contributes to the Gender Bias of Systemic Lupus Erythematosus. Nicholas A. Young, Alexandra Friedman, Benjamin Kaffenberger and Wael N. Jarjour. The Ohio State University Medical Center, Columbus, OH

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disorder with significant predilection for women. While disease pathogenesis remains an active area of investigation, correlation studies have shown that genetic, environmental, and hormonal factors all play a role in the development and progression of this immunological disorder. Gender bias can not be more clearly displayed than when simply looking at the SLE patient population. Childbearing age females are nine times more likely to be diagnosed with SLE than corresponding males of the same age range. Furthermore, this ratio drops dramatically when considering post-menopausal or pre-adolescent females. Recent work with large patient cohorts and high-throughput genetic analyses has led to the identification of several genetic susceptibility markers. Among these genes, toll-like receptors (TLRs) appear to have strong association with SLE in multiple studies. TLRs have been a great focus of recent scientific effort due to their close relationship to many diseases and potential as targets for immunomodulatory drugs.

Methods: In this work, we set out to examine the hormonal relationship between TLRs in influencing SLE pathology. Peripheral blood mononuclear cells (PBMCs) were isolated from both SLE and healthy patients. Healthy subject PBMCs were treated with a physiological dose of testosterone, 17b-estradiol (E2), and/or TLR agonist. Cells were incubated and harvested for collection and analysis of protein and mRNA expression.

Results: E2-induced expression was confirmed in healthy PBMCs *in vitro* with the endosomal TLRs; TLR3, TLR7, TLR8, and TLR9, while no effects were observed with testosterone treatment. Using TLR agonists to treat these cells, we identified an autocrine-mediated control over expression. This mechanism was observed in all endosomal, nucleic acid-binding TLRs. TLR4, which is located on the surface of the cell, was not subject to this pathway. Further, when SLE patients were analyzed, higher levels of TLR3, TLR4, TLR7, TLR8, and TLR9 were observed when compared to resting PBMCs of healthy subjects. A significant synergistic response between estrogen and TLR8 agonist-induced TLR8 expression was also displayed in healthy PBMCs. In order to examine gender differences further, PBMCs from healthy male and female volunteers were treated with estrogen and TLR8 ligand. Both male and female PBMCs increased the expression of TLR8 and enhanced cytokine (INF-g, IL-12 and MIP-1b) production in a synergistic response to these stimuli; however greater upregulation of TLR8 expression was observed in PBMCs from healthy females compared to males.

Conclusion: Taken together, these observations suggest a mechanism that explains, in part, the female bias in SLE through heightened sensitivity of TLR expression in response to E2. This novel mechanism may be relevant in other autoimmune disorders with female predominance, and could be targeted therapeutically to decrease autoinflammatory responses in women.

1426

Genome-Wide Analyses of IRF1 and H4 Acetylation in SLE Monocytes. Kathleen E. Sullivan[1], Lihua Shi[1], Li Song[1], Michelle Petri[2] and Zhe Zhang[3]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]Johns Hopkins Hospital, Baltimore, MD, [3]Bioinformatics, Children's Hospital of Philadelphia, Philadelphia, PA

Background/Purpose: SLE is characterized by chronic inflammation and multisystem end-organ dysfunction related to inflammation. Although treatments have improved morbidity and mortality, the disease continues to be associated with chronic cumulative organ damage. Disease chronicity could be impacted by changes to the epigenome, leading to durably dysregulated changes in gene expression. Patients with SLE have evidence of type I interferon effects but the expression of genes downstream of type I interferons is typically higher than the expression of the type I interferon genes themselves. We previously reported that H4 acetylation marks on genes from SLE monocytes were globally increased and the gene set characterized by increased H4 acetylation was enriched in potential IRF1 binding sites. IRF1 is of interest because it can be induced by exposure to type I interferons and can drive a set of pro-inflammatory genes.

We investigated epigenetic changes in SLE monocytes from patients with low disease activity to define epigenetic changes that could be attributed to ongoing exposure to type I interferons.

Methods: To directly examine the role of IRF1 in SLE, we performed ChIP-seq for IRF1 on monocytes from 8 SLE patients with low disease activity and 8 control subjects. The SOLiD platform was used and reads were mapped to the human genome using Bioscope.

Results: 89 IRF1 sites were identified unique to SLE patients and 445 IRF1 sites were found which were had increased peak height in the SLE group compared to the controls. IRF1 targets were validated using a standard ChIP assay. 70% of the IRF1 sites identified directly through ChIP-seq overlapped those identified bioinformatically based on increased H4 acetylation and a potential IRF1 binding site.

Conclusion: IRF1 binding is substantially altered in monocytes from SLE patients. The finding of increased IRF1 binding in SLE monocytes provides a potential link between the type I interferon signature and the pro-inflammatory milieu.

1427

Poly (ADP-Ribose) Polymerase 1 and Special AT-Rich Sequence Binding Protein 1 Bind to the TT>A System Lupus Erythematosus Associated Regulatory Downstream of TNFAIP3. Feng Wen[1], Michael Kinter[1], Joel Guthridge[1], Mary Beth Humphrey[2] and Patrick M. Gaffney[3]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by dysregulated interferon responses and loss of tolerance of self-antigens resulting in systemic inflammation and organ failure. The tumor necrosis factor alpha inducible protein 3 (TNFAIP3) gene encodes the ubiquitin-modifying enzyme A20, which negatively regulates NF-kB activity. We recently described a functional TT>A polymorphic dinucleotide, 42kb downstream of the TNFAIP3 promoter, as a prime candidate causal polymophism responsible for association with SLE in subjects of European and Korean ancestry that demonstrates reduced affinity for a nuclear protein complex that includes NF-kB.

Methods: In order to further characterize this nuclear protein complex we affinity purified proteins from LPS stimulated THP-1 cells using oligonucleotide probes specific for the wild type (TT) or polymorphic (A) sequence followed by mass spectrometry. Western blot was used for validation.

Results: Two primary proteins poly (ADP-ribose) polymerase 1 (PARP-1) and special AT-rich sequence binding protein 1 (SATB-1) were

isolated. The identities of these proteins were confirmed by Western blotting in independent experiments.

Conclusion: PARP-1 functions in DNA replication and chromatin remodeling, and also facilitates diverse inflammatory responses by promoting pro-inflammatory gene expression. SATB1 functions in tethering chromatin to the nuclear membranes at matrix attachment regions thus facilitating long-range regulation of gene transcription. These results suggest that the TT>A polymorphism may predispose to SLE through the recruitment of chromatin modifying proteins that modulate long-range transcriptional regulation of A20.

1428

IRF5 Activation in Monocytes of SLE Patients Is Triggered by Circulating Autoantigens Independent of Type I IFN. Rivka Stone[1], Di Feng[1], Jing Deng[1], Sukhwinder Singh[1], Lisong Yang[1], Patricia Fitzgerald-Bocarsly[1], Maija-Leena Eloranta[2], Lars Ronnblom[3] and Betsy Barnes[1]. [1]University of Medicine and Dentistry of New Jersey, Newark, NJ, [2]Section of Rheumatology, Uppsala University, Uppsala, Sweden, [3]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden

Background/Purpose: Genetic variants of interferon regulatory factor 5 (*IRF5*) are associated with susceptibility to systemic lupus erythematosus (SLE). IRF5 regulates the expression of proinflammatory cytokines and type I interferons (IFN) believed to be involved in SLE pathogenesis. The aim of this study was to determine the activation status of IRF5 by assessing its nuclear localization in immune cells of SLE patients and healthy donors, and to identify SLE triggers of IRF5 activation.

Methods: IRF5 nuclear localization in subpopulations of peripheral blood mononuclear cells (PBMC) from 14 genotyped SLE patients and 11 healthy controls was assessed using imaging flow cytometry. IRF5 activation and function were examined after *ex vivo* stimulation of healthy donor monocytes with SLE serum or components of SLE serum. Cellular localization was determined by ImageStream and cytokine expression by Q-PCR and ELISA.

Results: IRF5 was activated in a cell type-specific manner; monocytes of SLE patients had constitutively elevated levels of nuclear IRF5 compared to NK and T cells. SLE serum was identified as a trigger for IRF5 nuclear accumulation; however, neither IFNα nor SLE immune complexes could induce nuclear localization. Instead, autoantigens comprised of apoptotic/necrotic material triggered IRF5 nuclear accumulation in monocytes. Production of cytokines IFNα, TNFα and IL6 in monocytes stimulated with SLE serum or autoantigens was distinct yet correlated with the kinetics of IRF5 nuclear localization.

Conclusion: This study provides the first formal proof that IRF5 activation is altered in monocytes of SLE patients that is in part contributed by the SLE blood environment.

1429

Large Scale Analysis of Serum Tumor Necrosis Factor Alpha Levels in Systemic Lupus Erythematosus. Corinna E. Weckerle[1], Dorothy Imbuka[1], Beverly S. Franek[1], Jennifer A. Kelly[2], Marissa Kumabe[1], Kathy L. Moser[3], Judith A. James[4], John B. Harley[5] and Timothy B. Niewold[1]. [1]University of Chicago, Chicago, IL, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [5]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH

Background/Purpose: SLE disease manifestations are highly variable between patients, and the prevalence of individual clinical features differs significantly by ancestry. Serum tumor necrosis alpha (TNF-α) is elevated in some SLE patients, and may play a role in disease pathogenesis. We used logistic regression modeling to establish the network of associations between serum TNF-α, autoantibodies, serum interferon alpha (IFN-α), and clinical manifestations in large SLE cohorts from several different ancestral backgrounds.

Methods: We studied 653 SLE patients from the Lupus Family Registry and Repository at OMRF, including 214 African-American patients, 298 European-Americans and 141 Hispanic-American subjects. TNF-α was measured using an ELISA, and IFN-α was measured with a functional reporter cell assay. TNF-α and IFN-α levels were binned as a high versus low categorical variable using a cut-off value of 2 standard deviations above the mean of healthy controls. Logistic regression models were used to detect associations in each ancestral background separately, and meta-analyzed when appropriate.

Results: High levels of TNF-α were associated with high serum IFN-α activity across all ancestral backgrounds (OR=1.8, $p=1.2\times10^{-3}$). The proportion of high TNF-α/high IFN-α subjects was highest in African-Americans and lowest in European-Americans ($p=5.0\times10^{-3}$). Similarly, the proportion of low TNF/low IFN subjects was highest in European-Americans and lowest in African-Americans ($p=2.7\times10^{-4}$). TNF-α levels were not significantly associated with autoantibodies, clinical manifestations, or age at recruitment. Consistent with previous studies, IFN-α was closely correlated to autoantibodies, younger age, and non-European ancestry.

Conclusion: This represents the largest study of cross-sectional serum TNF-α levels in SLE patients, and we observed a positive correlation between TNF-α and IFN-α. While IFN-α was closely correlated with SLE-associated features such as characteristic autoantibodies and non-European ancestry, TNF-α was only associated with IFN-α in SLE patients, suggesting a secondary relationship between TNF-α and SLE disease characteristics.

1430

Low Programmed Death Ligand-1 Gene Expression in SLE Monocytes Coregulated by IL-10, TNF-α and TGF-β May Contribute to Chronic T Lymphocyte Activation. Jing-Ni Ou[1], Gretchen R. Henstorf[1], Matthew Crabtree[1], Alice Wiedeman[2] and Anne M. Stevens[1]. [1]Seattle Children's Research Institute, Seattle, WA, [2]University of Washington, Seattle, WA

Background/Purpose: Programmed death ligand 1 (PD-L1) expressed on monocytes and myeloid dendritic cells plays an important role in controlling T lymphocyte responses to self antigen released by apoptotic cells. We previously demonstrated poor PD-L1 expression in patients with SLE during an autologous MLR, in contrast to the reported high PD-L1 expression found in infection, malignancy, and rheumatoid arthritis. Normally induced by IL-10 and TNF-α while suppressed by TGF-β, PD-L1 gene expression may be a key step in the downregulation of T lymphocytes upon exposure to apoptotic cells. Lack of PD-L1 may contribute to the hyperstimulatory properties of SLE monocytes, leading to chronic T cell activation.

Methods: PD-L1 expression on $CD11c^{+}$ $CD14^{high}$ monocytes was assayed by flow cytometry in cultured peripheral blood cells from pediatric patients with SLE and age-matched controls. PD-L1 mRNA expression was assayed by RT-PCR. Early T cell activation was assayed by quantification of Calcium flux in CD4+ T cells by flow cytometry.

Results: Both PD-L1 surface protein and mRNA expression were induced by TNF-α, and TNF-α production correlated with PD-L1 expression in SLE patients in remission. IL-10, however, induced surface expression without an increase in mRNA, suggesting post-translational regulation. TGF-β suppressed both mRNA and surface expression, and correlated with PD-L1 expression during active SLE. Isolation of CD14+ myeloid DC and monocytes resulted in decreased PD-L1 expression, suggesting that lymphocytes may regulate PD-L1 on APC. Depletion of CD16+ NK and NKT cells resulted in a 50% drop in PD-L1 expression, whereas no significant differences were detected with depletion of CD19+, CD4+, or CD25+ lymphocytes. Early T cell activation was inhibited by CD14+ APC expressing PD-L1, but not by those with low or absent PD-L1.

Conclusion: Cytokine-mediated induction of PD-L1 expression on antigen presenting cells may be an important step in normally controlling the lymphocyte response to apoptotic cells. SLE monocytes fail to upregulate PD-L1 during active disease, because of a low ratio of stimulatory TNF-α to inhibitory TGF-β. Lack of PD-L1 on monocytes exposed to apoptotic cells may in part explain the hyperstimulatory phenotype in SLE.

1431

Impact of Aberrations In Xenobiotic Metabolism On the Susceptibility to Systemic Lupus Erythematosus. Yedluri Rupasree, Liza Rajasekhar, Addepalli Pavani, Shaik Mohammad Naushad and Vijay Kumar Kutala. Nizam's Institute of Medical Sciences, Hyderabad, India

Background/Purpose: The rationale of the study is to investigate whether aberrations in xenobiotic metabolism influence pathophysiology of Systemic Lupus Erythematosus (SLE) by inducing catechol estrogen mediated DNA-adduct formation that serves as better epitope for binding of anti-nuclear antibodies.

Methods: Six putatively functional polymorphisms in xenobiotic metabolism and three most common polymorphisms in one-carbon metabolism

were studied in 105 SLE cases and 106 healthy controls using PCR-RFLP and PCR-AFLP approaches.

Results: Among the Phase I enzymes, cytochrome P450 (CYP) 1A1 m1 and m4 variants that increase catechol estrogen production were associated with 2.11- (95% CI: 1.33–3.35) and 4.85- (0.96–32.89) folds risk for SLE. Among the Phase II enzymes, glutathione-S-transferase (GST) T1 null variant showed significant association with SLE (OR: 4.28, 95% CI: 1.96–9.50). Genetic variants of one-carbon metabolism i.e. edmethylene tetrahydrofolate reductase (MTHFR) C677T, thymidylate synthase (TYMS) 5′-UTR 28bp tandem repeat polymorphism, methionine synthase (MTR) A2756G showed no direct association with SLE. Correlating these variants with clinicopathological features of SLE showed positive association of CYP1A1 m1 variant with photosensitivity (r=0.20); and m4 variant with hemolytic anemia (r=0.24). Psychosis (r=-0.18) was inversely correlated with CYP1A1 m1 and positively correlated with GSTT1 null variant (r=0.18). Total glutathione levels in SLE cases were found to be low (362±113 μmole/L vs. 466±79 μmole/L), which will further augment the risk associated with GSTT1 null variant.

Conclusion: Aberrations in xenobiotic metabolism were found to inflate the risk for SLE through estrogen mediated oxidative stress and also to explain phenotypic heterogeneity in SLE.

1432

Metabolic Underpinnings of Systemic Lupus Erythematosus. Tianfu Wu[1], Chun Xie[1], Jie Han[1], Irene Blanco[2], Nancy J. Olsen[3], Chaim Putterman[2], Ramesh Saxena[4] and Chandra Mohan[4]. [1]University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, [2]Albert Einstein College of Medicine, Bronx, NY, [3]Penn State MS Hershey Medical Center, Hershey, PA, [4]University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: Although several genomic, transcriptomic and proteomic studies have been carried out in SLE, the metabolic disturbances that underlie SLE are largely unknown, prompting us to examine serum metabolites in SLE globally.

Methods: We executed a global metabolomic analysis of serum from 29 subjects (9 healthy controls, 10 SLE patients with SLEDAI 0–5, and 10 "active" SLE with SLEDAI>5) and active lupus nephritis, all drawn from UT Southwestern at Dallas, using a combined LC/MS and GC/MS based platform. Validation of key differences using orthogonal platforms was performed using an independent cohort of SLE patients (N=38; average age=38; average BMI=28.7; average SLEDAI=7), 14 matched healthy controls and RA disease controls, drawn from the Albert Einstein College of Medicine, New York.

Results: SLE sera revealed reduced levels of >100 metabolites, supportive of dampened glycolysis, Krebs cycle, fatty acid oxidation and amino acid metabolism. Whereas long-chain fatty acids, including the n3 and n6 essential fatty acids were significantly reduced, medium chain fatty acids and serum free fatty acids were elevated. The SLE metabolome exhibited a profound degree of lipid peroxidation, with 9-HODE and 13-HODE levels being significantly higher ($P < 0.01$), reflective of oxidative damage. Conversely, deficiencies were noted in the cellular anti-oxidant, glutathione (0.5±0.2μM, vs 2.9±0.7μM, P<0.0001), and all methyl group donors, including cysteine, methionine, and choline, as well as phosphocholines. SLE sera exhibited significantly elevated levels of multiple gamma-glutamyl peptides and the mediating enzyme GGT1 (1360±142 U/L vs 181±49 U/L, P<0.001; 459±235 U/L, P<0.01, respectively), compared to the healthy or RA disease controls, possibly alluding to a vigorous attempt to regenerate glutathione. Significant elevations were also seen in the levels of pro-inflammatory metabolites leukotriene B4 (966±142 ng/ml vs 132 ± 37 ng/ml, P<0.001) and 5-HETE (974350±116779 vs 2139±2016, P<0.0001). Random forest analysis and receiver operating curves revealed the best discriminators of SLE to be serum levels of lipid peroxidation products, MDA (AUC=0.92, P<0.0001), leukotriene B4 (AUC=0.99, P<0.0001), GGT1 (AUC=0.97, P<0.0001), and glutathione (AUC=0.84, P<0.0001). Importantly, these elevations were not observed in another chronic inflammatory autoimmune disease, rheumatoid arthritis (RA).

Conclusion: Comprehensive profiling of the SLE metabolome reveals heightened oxidative stress, inflammation, altered lipid profiles and a prothrombotic state. The observed reductions in multiple sources of cellular energy allude to reduced energy generation in SLE. Although further studies are warranted to dissect out the origins and consequences of the observed alterations, the completed studies have sprung forth several potential disease biomarkers that await longitudinal validation, and also novel opportunities for disease modulation, including targeted dietary support.

1433

Interferon Alpha Strikes Again: Modulation of Inflammasome Activity Results In IL-18 Mediated Vascular Dysfunction In Systemic Lupus Erythematosus. J. Michelle Kahlenberg[1], Seth G. Thacker[1], Celine C. Berthier[1], Jeffrey Hodgin[1], Clemens D. Cohen[2], Matthias Kretzler[1] and Mariana J. Kaplan[1]. [1]University of Michigan, Ann Arbor, MI, [2]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Individuals affected by systemic lupus erythematosus (SLE) develop heterogeneous manifestations including severe organ damage and complications from premature atherosclerosis and vascular dysfunction. Interferon-alpha (IFN-α) likely plays an important role in the development of lupus and lupus-related cardiovascular disease (CVD). IFN-α has a deleterious effect on the viability and function of endothelial progenitor cells (EPC)/circulating angiogenic cells (CAC), leading to impaired vascular repair. This disruption of EPC/CAC function by IFN-α is in part mediated by repression of IL-1β. Counter-intuitively, SLE patients also have increased levels of IL-18 and the IL-1β/IL-18 processing machinery, the inflammasome. This study attempted to understand this dichotomy and the potential role of inflammasome activation on SLE-related CVD.

Methods: Cultures of human and murine lupus and control EPC/CACs were used to assess the role of the inflammasome machinery in EPC/CAC differentiation. The role of specific caspase-1 inhibitors, recombinant IL-18 or IL-8 blockade in endothelial differentiation was analyzed. Serum levels of IL-18 and SLE-related autoantibodies were evaluated and correlated to EPC/CAC dysfunction. Microarray analysis of control and lupus kidney biopsies was completed to examine inflammasome regulation in SLE *in vivo.*

Results: In the presence of ac-YVAD-cmk, an inhibitor of caspase-1, a significant improvement in SLE EPC/CAC differentiation was evident. Additionally, inhibition of caspase-1 blocked IFN-α-mediated repression of EPC/CAC differentiation, implicating inflammasome activation as a downstream pathway of IFN-α signaling. Neutralization of IL-18 in SLE EPC/CAC cultures restored normal endothelial differentiation, while exogenous IL-18 inhibited differentiation of control EPC/CAC cultures in a dose-dependent manner. These observations suggest that IL-18 may have deleterious effects on vascular repair *in vivo* in SLE. Additionally, patients with anti-Ro antibodies, but not anti-ds DNA, anti-Sm or anti-RNP antibodies were significantly more likely to have elevated IL-18 levels and EPC/CAC dysfunction, indicating a putative link between autoantibody production and inflammasome activation. Inflammasome changes were operational *in vivo* in lupus nephritis, as evidenced by transcriptional upregulation of mRNA of inflammasome components in lupus kidney biopsies.

Conclusion: IFN-α impairs EPC/CAC function through modulation of the inflammasome to promote IL-18 over IL-1β production. This is detrimental to vascular repair and may be an important mechanism leading to increased CV risk in SLE. The role that inflammasome activation plays in atherosclerosis development and renal dysfunction in SLE warrants further examination. Additionally, the finding that anti-Ro antibodies correlate with serum IL-18 levels and EPC/CAC dysfunction indicates that cross talk between auto-reactive B cells and the inflammasome may result in premature vascular damage in SLE.

1434

Retroviral Vector System Identified FLRT2 As a Novel Cell Surface Autoantigen Against Anti-Endothelial Cell Antibodies in Systemic Lupus Erythematosus. Tsuyoshi Shirai[1], Hiroshi Fujii[1], Masao Ono[2], Kyohei Nakamura[1], Ryu Watanabe[3], Yumi Sasaki[1], Naruhiko Takasawa[1], Tomonori Ishii[1] and Hideo Harigae[1]. [1]Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan, [2]Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan, [3]Tohoku University Hospital, Sendai, Japan

Background/Purpose: Anti-endothelial cell antibodies (AECA) are detected in a number of patients with connective tissue diseases (CTD), and they have a potential to induce vascular lesions. Although targets of AECA have been intensively studied, most molecules reported so far are intracellular proteins and their pathogenic mechanisms for vascular injury remain unclear. The aims of this study are to identify autoantigens expressed on endothelial cell surface using retroviral vector system and to clarify their pathogenic roles.

Methods: Sera from systemic lupus erythematosus (SLE) patients were screened for AECA activity with human umbilical vein endothelial cells (HUVEC) by flow cytometry, and we selected one serum with high AECA activity for following cell sorting. cDNA library of HUVEC were generated and inserted into retroviral vector, pMx. Using retroviral vector system (Figure 1),

cDNA library was stably transfected to rat myeloma cell line. HUVEC cDNA expressing cells were FACS sorted with IgG that had high AECA activity and cloned by limiting dilution.

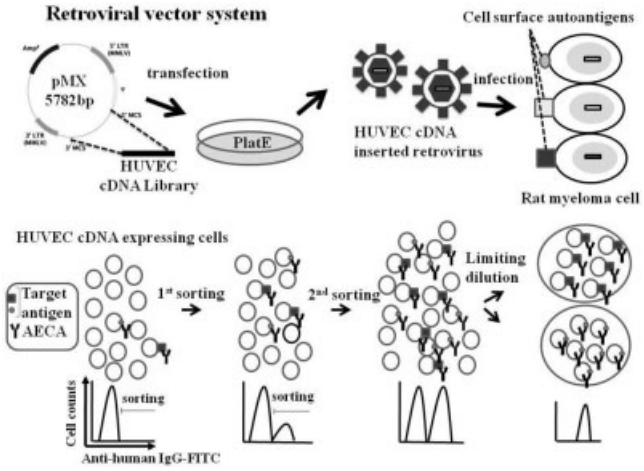


Figure 1. Retroviral vector system.

Results: Serum from one patient with active lupus nephritis had IgG that bound strongly to HUVEC. The patient's serum after treatment showed remarkably reduced binding activity, indicating this AECA activity correlates with disease activity. By expression cloning with FACS sorting, two distinct clones were isolated (Figure 2a). Polymerase chain reaction (PCR) (Figure 2b) and microarray analysis revealed both clones have an identical membrane protein, fibronectin leucine rich transmembrane 2 (FLRT2). We confirmed HUVEC express FLRT2 on cell surface. We also showed that 9 % of lupus patients had anti-FLRT2 activity, whereas normal control and other CTD did not have anti-FLRT2 activity except for one patient with Wegener's granulomatosis.

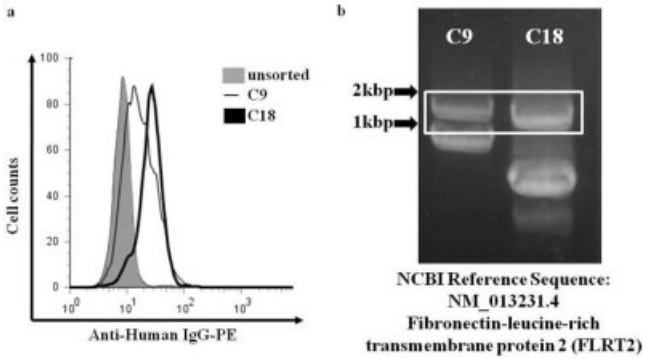


Figure 2. Isolated two distinct clones, C9 and C18. a: C9 and C18 were stained with IgG from the active lupus patient. b: PCR of genomic DNA to amplify inserted sequence. DNA sequencing of given bands in white box revealed both had FLRT2 mRNA coding sequences.

Conclusion: We identified cell membrane protein FLRT2 as a novel autoantigen against AECA in lupus patients. Autoantibody against FLRT2 might play roles in the pathogenecity of vascular injury and thus this retroviral vector system is a strong tool for identification of cell surface autoantigens.

1435

Binding of Serum IgG to Human Mesangial Cells and Its Correlation with Disease Activity in Patients with Lupus Nephritis. Desmond YH YAP[1], Susan Yung[2], Owen Chan[2], Florence Q. Zhang[2] and Tak Mao Chan[2]. [1]Queen Mary Hospital, Hong Kong, Hong Kong, [2]The University of Hong Kong, Hong Kong SAR, Hong Kong

Background/Purpose: Lupus nephritis is hallmarked by mesangial deposition of immunoglobulins, which result in subsequent glomerular injury and altered renal functions. Our group had previously demonstrated that human anti-dsDNA antibodies could bind to human mesangial cells (HMC) and this binding activity correlated with disease activity. In this study we assessed the binding activity to HMC by the serum IgG and its subclasses in lupus nephritis patients. Their associations with clinical and laboratory parameters in lupus nephritis patients were also evaluated.

Methods: Serial serum samples were retrieved from 23 patients with biopsy-proven diffuse proliferative lupus nephritis over a mean follow-up of 74 months. Binding activity (expressed as OD) of total serum IgG and its subclasses (IgG_1, IgG_2, IgG_3, IgG_4) to HMC was ascertained with a cellular ELISA and its correlation with clinical or laboratory parameters examined. Sera from 23 healthy individuals were used as controls. Sensitivity/specificity of total IgG or IgG_1 binding to HMC in the prediction of renal flare was calculated and ROC curves constructed.

Results: A total of 189 samples were analyzed - 48 samples during active and 141 during inactive disease, defined according to clinical assessment (SLEDAI >=10 as active and <=4 as inactive). Binding of serum total IgG to HMC was 0.12±0.09, 0.59±0.37 and 0.74±0.42 OD for healthy controls, inactive lupus, and active lupus respectively (P=0.023 active vs inactive, P<0.001 controls vs active or inactive disease). Binding of serum IgG_1 to HMC was 0.05±0.05, 0.41±0.38 and 0.55±0.40 OD for the three groups respectively (P=0.037 active vs inactive, P<0.001 controls vs active or inactive disease). Controls and lupus patients did not vary in the binding of serum IgG_2, IgG_3 or IgG_4 to HMC. Total IgG and IgG_1 HMC-binding activity correlated with anti-dsDNA levels (r=0.26 and 0.39 respectively, P<0.001 for both), and inversely with C3 levels (r=-0.17 and −0.45 respectively, P<0.05 for both). No correlation was observed between IgG binding to HMC and clinical parameters such as serum creatinine, albumin, or proteinuria. Sensitivity/specificity of total IgG or IgG_1 binding to HMC in the prediction of renal flare was 81.3%/39.7% (ROC AUC 0.61, P=0.03) and 83.8%/41.8% (AUC 0.63, P=0.009) respectively.

Conclusion: There is significant total IgG and IgG_1 mesangial cell-binding activity in the sera of patients with lupus nephritis, especially during active disease, and this binding correlated with the anti-dsDNA antibodies levels.

1436

Cardiovascular Disease and Cognitive Dysfunction in Systemic Lupus Erythematosus. Sara Murray, Jinoos Yazdany, Rachel Kaiser, Lindsey A. Criswell, Edward H. Yelin, Patricia P. Katz and Laura J. Julian. University of California, San Francisco, San Francisco, CA

Background/Purpose: Cognitive dysfunction and cardiovascular (CV) disease are common and debilitating manifestations of systemic lupus erythematosus (SLE). While there is substantial evidence linking CV disease and Framingham-type risk factors with cognitive dysfunction in the general population, these relationships have not been fully explored in SLE. In this study, we evaluated CV events, traditional CV risk factors, and SLE-specific risk factors (antiphospholipid antibodies (aPL), disease activity, disease duration) as predictors of cognitive dysfunction in a large cohort of patients with SLE.

Methods: Subjects included 694 participants from the Lupus Outcomes Study (LOS), an annual telephone survey querying demographic and clinical variables. The Hopkins Verbal Learning Test – Revised (HVLT-R) and the Controlled Oral Word Association Test (COWAT) were administered to assess cognitive function, and cognitive impairment was defined by a composite z-score average worse than −1.0 standard deviation below age-stratified normative values. CV risk factors and events were obtained from self-report, disease activity was assessed using the Systemic Lupus Activity Questionnaire (SLAQ), and patients were considered to be positive for aPL if they had at least one laboratory result indicating the presence of anticardiolipin antibodies (IgG or IgM), anti-beta2 glycoprotein-1 antibodies (IgG or IgM), or a lupus anticoagulant measured by an abnormal Russell viper venom test at least one point in time. Multiple logistic regression was used to investigate the cross-sectional relationship between self-reported CV events (myocardial infarction (MI), stroke), traditional CV risk factors (hypertension, hyperlipidemia, diabetes, obesity, smoking), and SLE-specific risk factors and cognitive impairment. Analyses also controlled for gender, education, poverty status, and depression.

Results: The prevalence of cognitive impairment was 15%. In multiple logistic regression analyses, aPL (OR=2.1, 95% CI 1.3–3.4), hypertension (OR=2.1, 95% CI 1.2–3.6), and a history of stroke (OR=2.3, 95% CI 1.2–4.4) were each significantly associated with cognitive dysfunction. In additional analyses evaluating the association between these predictors and severity of cognitive impairment, stroke was significantly more prevalent in subjects with severe impairment compared to those with mild or moderate impairment (p=0.036).

Conclusion: Our results suggest that aPL, hypertension, and stroke likely play a significant role in cognitive dysfunction in SLE and may serve as potential targets for therapeutic interventions to improve cognitive outcomes.

1437

Atherosclerosis and Cardiovascular Disease in Systemic Lupus Eryhematosus Are Related to An Inflammatory /Oxidative Status Linked to the Autoimmune Condition and the Clinical Activity of the Disease. Effect of Statins Treatment. Chary Lopez-Pedrera[1], Patricia Ruiz-Limon[1], Carlos Perez-Sanchez[1], M[a] Angeles Aguirre[1], Nuria Barbarroja[1], Antonio Rodriguez-Ariza[1], Eduardo Collantes-Estevez[1], Jose Manuel Villalba[2], Francisco Velasco[1], Munther A. Khamashta[3], Maria Laura Bertolaccini[3] and M[a] Jose Cuadrado[4]. [1]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [2]University of Cordoba, Cordoba, Spain, [3]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [4]The Rayne Institute, London, United Kingdom

Background/Purpose: Atherosclerosis (AT) and cardiovascular disease (CVD) are enhanced in autoimmune diseases, such as antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE).Characterization of the molecular and cellular basis of signalling abnormalities within the immune system that lead to auto reactivity and inflammation and their relationship to early AT and CVD development remain critical for understanding the pathogenesis of APS and SLE. Although there is evidence that statins have anti-inflammatory properties, their mechanism of action remains incompletely understood. Aims: i) To determine if the proinflammatory SLE profile is related to their oxidative status, and associated to the autoimmune condition and the clinical disease activity; ii) to test the anti-inflammatory effectiveness of fluvastatin.

Methods: The study was conducted in 64 SLE patients and 47 healthy donors. Flow cytometry, ELISA and enzymatic assays were used to evaluate markers of inflammation and oxidative stress in white blood cells and plasma. Carotid-intimate media thickness (CIMT) was used as surrogate parameter of AT. Microarray expression profiling was used in paired samples of SLE monocytes from 21 patients before and after one month of in vivo fluvastatin treatment. Real-Time RT-PCR of selected genes was used to validate microarray data.

Results: Increased TF and PAR2 levels were found in monocytes from SLE patients, which also displayed higher plasma levels of VEGF, IL8, MCP-1, TNFα and tPA. SLE monocytes displayed a decreased mitochondrial membrane potential (MMP) and increased levels of peroxides, GSH, and antioxidant enzymes (SOD2, catalase and GPx). aPL-IgG and anti-dsDNA levels significantly correlated with SLEDAI, markers of inflammation, thrombosis and oxidative stress. CIMT was associated to increased aPL-IgG, TF, VEGF and tPA, as well as to decreased MMP. The occurrence of cardiovascular events was associated with reduced MMP and SOD2, and increased catalase and GPx activity, as well as with increased levels of inflammatory markers. A total of 726 genes displayed significant changes in expression after 1 month of fluvastatin treatment, of which 30% were found associated to inflammation and CVD. Fluvastatin treatment led to downregulation of many genes related to inflammation, angiogenesis and the atherosclerosis pathways. Genes related to mitochondrial activity, NO, and oxidative stress signalling pathways were also found significantly altered. The expression changes in selected cytokines, associated intracellular pathways, and markers of oxidative stress were further confirmed at protein level.

Conclusion: i) SLE-related auto-antibodies significantly contribute to the development of AT and CVD. ii) A redox-sensitive pathway (in which mitochondrial membrane alterations seem to perform a main part) might play a key role in the elicitation of those pathologies in the setting of SLE. iii) Fluvastatin has significant anti-inflammatory effects on SLE monocytes, downregulating the expression of molecules mediating angiogenesis, AT and inflammatory signalling. Supported by JA0246/2009, P08CVI04234 and PS09/01809.

1438

Analysis of Endothelium from Systemic Lupus Erythematosus Patients Demonstrates a Marked Interferon Inducible Signature and an Associated Decrease in Transforming Growth Factor Beta Signaling Genes. Diana Goldenberg[1], Mikhail Olferiev[1], Duygu Onat[2], Ante Harxhi[2], Danieli Andrade[1], Mary K. Crow[1], Paolo Colombo[2] and Jane E. Salmon[1]. [1]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [2]Columbia University College of Physicians & Surgeons, New York, NY

Background/Purpose: Endothelial dysfunction may promote premature atherosclerosis in patients with systemic lupus erythematosus (SLE). Using a novel approach of endothelial sampling coupled with microarray analysis of amplified endothelial RNA, we have previously shown upregulation of interferon inducible genes in SLE patients compared with healthy controls. Herein, we used quantitative real time polymerase chain reaction (RT-PCR) and quantitative immunofluorescence microscopy i) to further validate our initial interferon findings and ii) to investigate the interaction between the interferon and transforming growth factor beta (TGFβ) signaling pathways.

Methods: Fourteen patients with SLE (age 30.9 $\pm$ 9.4 yrs, SLEDAI score 6.2; range 0–20) and 12 age-matched healthy subjects were studied. Endothelial cells were collected from arm veins using endovascular wires then separated using magnetic beads coated with endothelial specific antibodies. Analysis of the microarray profiles was performed on amplified RNA using GeneSpring GX 11 software. Student T test analysis was performed and differentially expressed genes with >1.5 fold expression and $p<0.05$ were selected. Microarray findings were further validated using RT-PCR and quantitative immunofluorescence microscopy (Scion Image Software 4.0).

Results: Microarray analysis showed that several interferon-inducible genes (i.e. IFIT3, IFI44L, IFI6, MX2, IFITM1, OAS1 and OAS2) were upregulated and that several genes in the TGFβ signaling pathway (i.e. TGFBR2, TGFBR3, SMAD2 and SMAD3) were downregulated in SLE patients compared with controls. RT-PCR confirmed upregulation of IFIT3 and downregulation of TGFBR2, TGFBR3 and SMAD2 in the SLE patients. Immunofluorescence analysis demonstrated increased protein levels of IFIT3 and ISG15 in SLE patients compared with controls.

Conclusion: We used a novel in-vivo approach of venous endothelial sampling coupled with gene expression and protein analysis to study the molecular events that promote endothelial dysfunction in SLE. Our results indicate an opposite expression pattern of interferon and TGFβ signaling pathways in the venous endothelium of SLE patients, the former being upregulated and the latter downregulated. These findings further characterize processes that appear relevant to the pathobiology of endothelial dysfunction in SLE.

1439

Anti NMDAR and Anti-P/NSPA Antibodies Contribute to Cognitive Dysfunction in Lupus Patients. Loreto Massardo[1], Patricia Flores[2], Jorge Calderón[2], Marcela Bravo-Zehnder[2], Angel Jurado[2], Carla Henríquez[2], Oslando Padilla[2], Marcela Babul[2], Andrea Slachevsky[3], Sergio Jacobelli[4], Betty Diamond[5] and Alfonso Gonzalez[6]. [1]Catholic University of Chile, Santiago 114-D, Chile, [2]Pontificia Universidad Catolica de Chile, Santiago, Chile, [3]Universidad de Chile, Santiago, Chile, [4]Universidad Catolica de Chile, Santiago, Chile, [5]Feinstein Institute Med Rsch, Manhasset, NY, [6]Marcoleta 367, Santiago, Chile

Background/Purpose: Cognitive dysfunction (CD) in SLE patients has been linked to psychosocial factors, including major depression (MD), autoantibodies and corticosteroids.

Purpose: To assess the contribution of autoantibodies (*anti N-methyl-D-aspartate receptor (NMDAR), anti-ribosomal P protein/neuronal surface P antigen (anti-P/NSPA)* antibodies in contrast with psychosocial factors and corticosteroids, to CD.

Methods: Eighty-four Chilean SLE consecutive patients and 24 controls, all female, median age 36 (range 17–64) had cognitive function assessment using *Cambridge Neuropsychological Test Automated Battery* system, CANTABeclipse™ (2006) assessing attention, visual memory, working memory, executive function, and decision making and response control domains. Lower than 2 SD test performances in ≥ 2 domains were considered CD (32% in patients and 0% in controls). Multivariate models analysis ANCOVA accounting for the effects on CANTAB tests were performed, considering psychosocial factors (*age, education, employment, MD, anxiety, suicidal risk)* and lupus factors such as autoantibodies (*anti-NMDAR, anti-P/NSPA, anti-NSPA, anti DNA Farr, anti phospholipids and anti La/Ro/Sm/Rnp),* SLEDAI-2k, prednisone, antimalarials and cytotoxics. $P<0.05$ was considered significant. Patients had median disease duration of 2 years (0.1–30), SLEDAI-2k score: 6 (0–28), 82% with >5 mg prednisone, and 21% with MD.

Results: Antibody frequencies: anti-*NMDAR* 17%, anti-P/NSPA 8%, anti-NSPA 5%, lupus anticoagulant 15%, anti-DNA 57%. Contributors to lower performances per domain: 1. Attention: anti-NMDAR, education, employment, age and prednisone; 2. Visual memory: anti-P/NSPA, age, SLEDAI-2K, education, and anti-DNA; 3. Executive function: anti-NMDAR, anti-P/NSPA, antiphospholipids, anti-RNP, antimalarials, anticoagulant, age, education, cytotoxics, prednisone and employment. Decision making and response control domain: anxiety, anti-NSPA, antiphospholipid, age and prednisone.

Conclusion: Both NMDAR and anti-P/NSPA antibodies, but not MD or any other psychiatric disorders, contribute to CD affecting specific task domains. Anti-NMDAR alone contributes to dysfunctions on attention domain and together with anti-P/NSPA affects executive function. Anti-P/NSPA antibodies alone contribute to visual memory and decision making and response control domain impairment. This is the first report of antiNMDAR and antiP/NSPA autoantibodies impact on neuropsychological performance in SLE patients.

Supported by FONDECYT grant 1110849 and CONICYT Basal grant PFB-12/2007.

1440

A Central Role of Plasmin in Cardiac Injury Initiated by Fetal Exposure to Maternal Anti-Ro Autoantibodies. Paraskeyi Briasouli[1], Joanne Reed[1], Jill P. Buyon[1], Robert M. Clancy[1], Mark Halushka[2] and Lucas Buyon[3]. [1]New York University School of Medicine, New York, NY, [2]John Hopkins Pathology, Baltmore, MD, [3]New York University School of Medicine, new York, NY

Background/Purpose: Cardiac neonatal lupus (cardiac NL) is thought to be initiated by surface binding of anti-Ro60 autoantibodies to apoptotic cardiocytes during physiological remodelling of the heart. Binding increases the expression of urokinase plasminogen activator receptor (uPAR) which acts as a 'don't eat me signal" resulting in accumulation of apoptotic cardiocytes and activation of uPA and plasmin protease activity. The latter may facilitate increased binding of anti-Ro60 by disrupting and cleaving the protective effect of factors such as circulating beta2-glycoprotein I (β2GPI). To further examine the significance of components of the uPA/uPAR system in cardiac NL, levels of soluble uPA, uPAR and plasminogen proteins were evaluated in umbilical cord blood as well as expression of these proteins in an autopsy specimen.

Methods: Enzyme linked immunosorbent assays (ELISA) were conducted to measure total uPA, uPAR, plasminogen, and plasmin inhibitory complex plasmin-anti-plasmin (PAP) in the umbilical cord blood from non-cardiac NL (n=26) and cardiac NL (n=35) anti-Ro exposed infants.

Results: uPA, uPAR and plasminogen levels were significantly higher in cardiac NL compared to non-cardiac NL children (3.3 ng/ml±0.1 vs 1.9±0.05 ng/ml; p<0.0001), (6.6±0.3 ng/ml vs 2.1 ±0.2 ng/ml; p<0.0001), (435±34 ng/ml vs 220±19 ng/ml; p<0.0001) respectively. In contrast, the plasmin-anti-plasmin (PAP) complex was significantly decreased in the cardiac compared to non-cardiac NL group (15±2 ng/ml vs 32±1 ng/ml; p<0.0001) suggesting that in the affected fetuses, circulating plasmin was accessible for activation. In 3 twin pairs discordant for cardiac NL, the twin with cardiac NL had higher levels of uPA (3.1±0.1 ng/ml vs 1.9±0.05 ng/ml; p=0.0086) and lower levels of PAP compared to the non-cardiac NL twin (15±2 ng/ml vs 27±2 ng/ml; p=0.034). Levels of uPAR and plasminogen were also higher in the cardiac NL twin but the differences were not significant (6.2±1.4 ng/ml vs 2.2±0.7 ng/ml; p=0.147) and (412±61 ng/ml vs 260±27ng/ml; p=0.152) respectively. There was no association between levels of uPA, uPAR, plasmin, PAP and gender, dexamethasone use, delivery, birth weight, or gestational age of the fetuses. uPAR levels were higher in cardiac NL children with higher titers of anti-Ro60, consistent with in vitro data demonstrating increased uPAR expression in Anti-Ro60 bound apoptotic cardiocytes. Immunohistologic evaluation of a heart from a fetus dying with cardiac NL, revealed an extensive inflammatory infiltrate in the AV node. Macrophages, giant cells and endothelial cells expressed uPA. Plasminogen was expressed in macrophages and giant cells. An age-matched fetal heart only stained endothelial cells for uPA and plasminogen.

Conclusion: The finding of increased soluble uPA, uPAR, and plasminogen in umbilical cord blood of fetuses with cardiac NL and expression of uPA and plasminogen in affected tissue supports the hypothesis that fetal cardiac injury is mediated, at least in part, by plasmin generation initiated by anti-Ro binding to the apoptotic cardiocyte.

1441

Vascular Events and HLA-DRB1 Genotypes in Systemic Lupus Erythematosus. Elisabet Svenungsson[1], Emelie Lundstrom[1], Johanna Gustafsson[1], Andreas Jonsen[2], Dag Leonard[3], Agneta Zickert[1], Kerstin Elvin[4], Gunnar K. Sturfelt[2], Gunnel Nordmark[3], Anders Bengtsson[5], Lars Ronnblom[3], Iva Gunnarsson[1] and Leonid Padyukov[1]. [1]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Department of Rheumatology, Lund University Hospital, Lund, Sweden, [3]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden, [4]Department of Clinical Immunology and Transfusion Medicine, Unit of Clinical Immunology, Karolinska University Hospital and Karolinska Institutet /Karolinska University Hospital, Stockholm, Sweden, [5]Department of Rheumatology, Lund University Hospital, Sweden

Background/Purpose: Vascular events are common in systemic lupus erythematosus (SLE) and SLE patients with antiphospholipid antibodies (aPL) are at particularly high risk. Genotypes in the HLA-DRB1 region on chromosome 6 are associated with SLE per se and genetic associations in this region have also been reported with the occurrence of pro-thrombotic aPL. We investigated if HLA-DRB1 genes are associated with vascular events in patients with SLE.

Methods: A total of 664 unrelated SLE patients of Caucasian origin from three different clinics (n = 364 + 160 +140) were included in this study. All fulfilled four or more of the 1982 American College of Rheumatology revised criteria for SLE. Two-digit HLA-DRB1 typing was performed by sequence-specific primer-polymerase chain reaction. Previous manifestations of objectively verified ischemic heart disease (IHD, myocardial infarction or angina), ischemic cerebrovascular disease (ICVD, stroke or transient ischemic attack) and venous thromboembolic events (VTE, deep venous thrombosis or pulmonary emboli)) were retrieved through patient interviews and medical files. aPL were measured with ELISA. Matched controls (n=1403) were genotyped. Odds ratios (OR) with 95% confidence intervals (CI) were calculated with the software JMP 9.0. Meta-analyses, presented below, of the combined results were calculated with RevMan 5.

Results: SLE per se was, as expected, strongly associated with HLA-DRB1*03 (OR: 2.75 95% CI: 2.32–3.26). After excluding HLA-DRB1*03 positive patients (due to common co-occurrence of DR*03 and DR*15) there was also an association with HLA-DRB1*15 (OR 2.02 95% CI 1.59–2.56), on the contrary HLA-DRB1*04 (OR: 0.81 95% CI: 0.64–1.02) was not associated with SLE. Yet, the HLA-DRB1*04 allele was associated with ICVD (OR: 1.68 95% CI: 1.00–2.82), but not with IHD or VTE. The HLA-DRB1*04 allele was furthermore consistently associated with the occurrence of aPL of all measured specificities: anticardiolipin IgG (OR: 1.96 95% CI: 1.32–2.90), and IgM (OR: 1.79 95% CI: 1.22–2.63), b2 Glycoprotein-1 IgG (OR: 2.73 95% CI: 1.81–4.10) and with a positive lupus anticoagulant test, performed in one cohort, (OR: 2.57 95% CI: 1.53–4.31, n=363).

Conclusion: The HLA-DRB1*04 genotype is not associated with SLE per se but it confers an increased risk for ischemic cerebrovascular disease among patients with SLE. Furthermore we confirm that the HLA-DRB1*04 genotype is consistently associated with the presence of pro-thrombotic aPL of different specificities. Our results demonstrate that genetic susceptibility merits further investigation as a possible cause of both aPL and the enhanced risk of cardiovascular disease, in particular stroke, among patients with SLE.

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Insulin-Like Growth Factor Binding Protein-4 As a Marker of Chronic Lupus Nephritis. Chun Xie, Tianfu Wu, Jie Han, Ramesh Saxena and Chandra Mohan. University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: Renal involvement is the leading cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Kidney biopsy remains the mainstay of Lupus Nephritis (LN) diagnosis and prognostication. In particular, the chronicity index (CI) on renal pathology is highly predictive of renal and patient mortality. Since renal biopsy is invasive, there is an urgent need for the identification of non-invasive, surrogate biomarkers that closely parallel renal pathology in SLE. Previously, we have been able to identify markers that predict renal pathology "activity" but not "chronicity". Hence, we sought to identify novel surrogates of this aspect of the disease.

Methods: The sera from adult patients with LN (N = 5, average SLEDAI = 8) were screened for ~280 molecules using an array-based proteomic platform. The molecules with increased serum levels were then validated by ELISA in 86 patients with LN. Normal healthy adults (N = 23) and patients with other glomerular diseases (N = 20) served as controls.

Results: Insulin-like growth factor binding protein-4 (IGFBP-4) was one of the several molecules that were elevated in the sera of patients with LN compared to normal healthy controls in the array-based screen (arbitrary unit, mean +/− SE, 878,825 +/− 305,430 vs 143,926 +/− 23,927, $P = 0.06$). Serum IGFBP-4 levels of 86 biopsy-proven LN patients were then validated by ELISA. Compared to healthy (442 +/− 62 ng/ml) or other glomerular disease controls (725 +/− 204 ng/ml), serum IGFBP-4 levels were significantly higher in the patients with LN (1422 +/− 109 ng/ml, $P < 0.01$ and < 0.0001, respectively). Serum IGFBP-4 did not correlate well with systemic lupus erythematosus disease activity index (SLEDAI), renal SLEDAI or proteinuria, but it did correlate with serum creatinine ($R = 0.6124$, $P < 0.0001$). Interestingly, in 19 patients with proliferative LN (ISN/RPS Class III or IV) whose blood samples were obtained at the time of renal biopsy, serum IGFBP-4 level correlated strongly with the chronicity index on renal pathology ($R = 0.742$, $P < 0.001$).

Conclusion: IGFBP-4 emerges a relatively specific biomarker of lupus nephritis, strongly reflective of renal chronicity changes in lupus nephritis. Taken together with previously identified activity biomarkers, IGFBP-4 may help predict prognosis and guide treatment in LN, hence supplanting renal biopsy. Mechanistic studies are in progress to understand the biology of IGFBP-4.

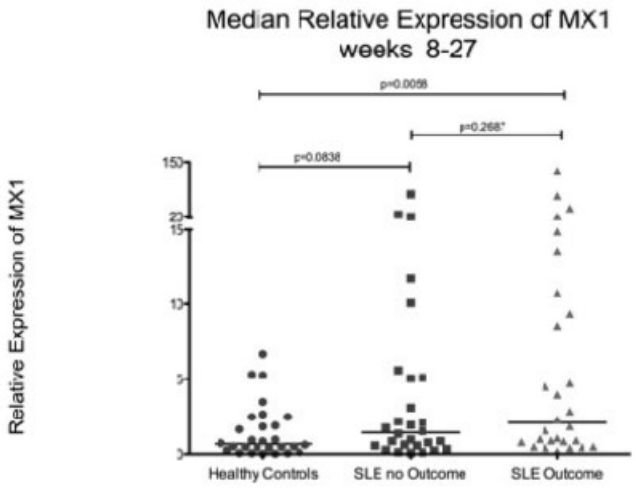
1443

Increased Relative Expression of the Interferon-Responsive Gene MX1 Is Present in Pregnant SLE Patients and May Distinguish Flare of SLE From Preeclampsia. Danieli Andrade[1], Gloria Koo[1], Patricia M. Redecha[1], Kyriakos A. Kirou[2], Mimi Kim[3], Mary K. Crow[1] and Jane E. Salmon[4]. [1]Hospital for Special Surgery, New York, NY, [2]Mary Kirkland Center for Lupus Care - Hospital for Special Surgery, New York, NY, [3]Albert Einstein College of Medicine, Bronx, NY, [4]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

Background/Purpose: Type I IFN (IFN-I) contributes to the pathogenesis of SLE. Elevated levels of IFN-I stimulated genes have been associated with increased disease activity. That IFN-α has anti-angiogenic effects raises the possibility that it may be deleterious for developing placenta in pregnant SLE patients. We hypothesized that MX1 (myxoma resistance protein 1), an IFN -I responsive gene, could be used as a single gene to determine the presence of IFN signature and predict outcomes in pregnant lupus patients.

Methods: We performed a nested case-control study of SLE patients in the PROMISSE Study- Predictors of Pregnancy Outcome: Biomarkers In Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus. Patients met ACR criteria for SLE. Exclusions were: prednisone >20mg, proteinuria >1gm/24 hr and creatinine >1.2 mg/dl. Each month, beginning at <12 wks gestation, SLEPDAI was measured and blood was collected. Poor pregnancy outcome was defined as: fetal death >12 wks; placental insufficiency or preeclampsia (PE), severe IUGR or severe hypertension. Each of 28 patients with SLE and poor pregnancy outcomes were matched 1:1:1 by age and ethnicity to an SLE patient with an uncomplicated pregnancy and a healthy pregnant control. Serum samples from 3 matched pregnancies were assayed simultaneously for IFN-α activity using a reporter cell assay. Real-time quantitative polymerase chain reaction was used to determine the RE of MX1 from samples obtained each month. To assess IFN-α activity in non-autoimmune patients destined for PE, we examined RE of MX1 through pregnancy in 11 healthy patients who developed PE and compared values to patients with SLE and PE as a pregnancy outcome. All analyses for Relative Expression (RE) of MX1 were done at 8–27 weeks of gestation and were expressed as medians.

Results: In early pregnancy, RE of MX1 is higher in SLE patients with outcome than controls (p=0.0058) and tended to be higher in SLE patients with no poor outcome (p=0.08). SLE patients with PE showed higher levels of RE MX1 than controls, (p=0.0052) and than SLE patients with no outcomes (p=0.0094). There was no correlation between SLEPDAIs and RE MX1 before the outcome. RE of MX1 was not different in patients who were positive for anti-Ro. Hydroxychloroquine use was not associated with decreased expression of RE MX1 (p=0.529). SLE patients with PE showed higher RE MX1 compared to non-autoimmune patients with PE (p=0.0002).



Conclusion: RE of MX1 may be used as a single gene to detect the IFN signature in pregnant SLE patients. RE of MX1 can distinguish pregnant SLE patients from those without SLE. Pregnancy does not abrogate induction of IFN-α genes. Our data show that PE, in and of itself, is not associated with increased IFN-α, and that high levels of RE of MX1 may differentiate lupus nephritis from PE in pregnant patients with hypertension and proteinuria.

1444

Immune Complexes (ICs) From Systemic Lupus Erythematosus (SLE) and Complement Activate ERK1/2 and PI3K/Akt Pathway in Primary Human Mesangial Cells. Anil K. Chauhan[1] and Terry L. Moore[2]. [1]Saint Louis University, St. Louis, MO, [2]Saint Louis University, Saint Louis, MO

Background/Purpose: In SLE patients, antibodies against nuclear antigens and other self-antigens ICs and activate the complement system. This results in type III hypersensitivity reaction. To better understand the physiology of the tissue damage from these immune reactants, we purified the ICs from SLE patients and studied the signaling events triggered by them in the presence of the fluid phase terminal complement complex (TCC) in the primary human mesangial cells.

Methods: The plasma from SLE patients with high disease index was collected with informed consent. ICs were purified from plasma of SLE patients using Proceptor™ affinity resin. These purified ICs were analyzed using 2D SDS-PAGE and their antigen composition was obtained using nano-LC/MS/MS. 1×10^6 primary mesangial cells were treated with purified ICs (2μg) and fluid phase TCC (2.5 μg) isolated from zymogen activated human serum. The cell lysate prepared from treated cells were probed for phosphorylation of ERK1/2 and PI3K/Akt in Western blot analysis.

Results: The nono-LC-MS/MS analysis of the ICs revealed the presence of proteins from several functional categories, such as signaling, protein-protein interaction, and protein transport. The ICs from SLE patients triggered phosphorylation of ERK1/2 at 2 h time interval, and this phosphorylation was over by 4 h. Activation of ERK1/2 is required for cellular proliferation, thus suggesting a role for ICs and TCC in inducing the proliferation of cells lining the mesangium. This proliferation will contribute to the tissue fibrosis such as observed in lupus nephritis. PI3K/Akt/mTOR is an important signaling pathway that is a therapeutic target and act by impacting apoptotic pathways. We observed over 396% increase in PI3K/Akt phosphorylation at the 4 h time interval in cells treated with ICs and TCC. These signaling events implicate the ICs and complement in cell survival. This suggests that ICs and TCC trigger both proliferative and cell survival responses. We also observed presence of a number of KIAA proteins within these ICs. In addition, we also identified C3, C4A, CD5L, hemopaxin, alpha-1B glycoproteins. The KIAA 1542 gene was identified as a risk factor in genome wide association studies. We will present the protein composition of ICs isolated from SLE patients obtained using nano-LC/MS/MS analysis.

Conclusion: Our results define two signaling events activated by ICs and complement in tissue where immune deposits are formed.

1445

Quantitative Analysis of Pathologic Cell Subsets Involved in Tubulointerstitial Inflammation in Human Lupus Nephritis. Vladimir M. Liarski, Daniel F. Brandt, Christine Hsieh, Natalya Kaverina, Christine Labno and Marcus R. Clark. University of Chicago, Chicago, IL

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease, the most frequent severe manifestation of which is nephritis. Pathologically, lupus nephritis (LN) is characterized by immune complex deposition and inflammation in both glomeruli and the tubulointerstitium. We have previously shown that tubulointerstitial inflammation is a usual feature of LN and the infiltrate is organized into either well-circumscribed T:B cell aggregates or germinal center (GC)-like structures.

Methods: To investigate the cellular make-up of the tubulointerstitial inflammation, we used multicolor confocal microscopy. These studies revealed that the infiltrate was composed of CD4+ICOS+ and CD4+PD-1+ cells, consistent with a T follicular helper [T_{FH}] subtype as well as CD20+ and Ki67+ cells, consistent with activated and proliferating B cells. We next sought to understand how these different subsets of cells could be cooperating to mediate inflammatory damage but were limited by the absence of quantitative tools for this purpose. Therefore, we

developed a novel proprietary algorithm based on ImageJ (W Rasbrand, NIH, http://rsb.info.nih.gov/ij/) to transform the obtained immunofluorescent images into binary form. From this, we were able to derive a data-rich analysis of inter-cell relationships across 40 human lupus nephritis biopsies.

Results: Our analysis demonstrated that CD20+ B cells were much more likely to be close to CD4+PD1+ (56% of cells within 0–3 microns, $p=1\times10^{-4}$) or CD4+ICOS+ (59% of cells within 0–3 microns, $p=2.46\times10^{-5}$) T cells than to other CD20+ B cells (<8% within 0–3 microns). This association remained unchanged after correction for cellular density. The relationship was also present but not as robust when compared with Ki67+ B cells (38% of cells within 0–3 microns, $p=1\times10^{-3}$), which may reflect the fractionation of the latter into centroblasts within GCs and plasmablasts or other intermediate cell types within less organized T:B aggregates. As expected, comparison with CD8+PD-1+ T cells failed to reveal an association ($p=0.1$).

Conclusion: Our data reveals that T_{FH} cells are more likely to form conjugates with naïve and activated B cells. This example indicates that our novel quantitative approach enables the identification of important cell-cell interactions within human tissues and serves as a powerful analytical tool that may be generalized to other cell types and human tissues.

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Gene Expression Profiles in Monocytes and Macrophages From Systemic Lupus Erythematosus Patients and Healthy Controls with and without An Atherosclerosis Phenotype. Benjamin Korman[1], Carly Skamra[1], Peggy Wu[1], Alexander Sandhu[1], Qi Quan Huang[1], Chiang-Ching Huang[1], William Pearce[1], Kim Sutton-Tyrrell[2], George Kondos[3], James Carr[1], Daniel Edmundowicz[2], Richard Pope[1] and Rosalind Ramsey-Goldman[1]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]University of Pittsburgh, [3]University of Illinois at Chicago, Chicago, IL

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have an increased risk of atherosclerosis. Given that monocytes and macrophages play an essential role in the pathogenesis of SLE and in the initiation and progression of atherosclerosis, we examined differential gene expression profiles of monocytes and macrophages in patients with SLE and controls with and without an atherosclerotic phenotype.

Methods: Monocytes and macrophages were isolated from 36 individuals: 20 with SLE and 16 healthy controls of whom 10 SLE patients and 8 healthy controls had an atherosclerosis phenotype with at least 3 of the following 4 abnormalities: plaque index [PI] >0, intima media thickness [IMT] > mean of the study group, coronary calcium score [CAC] >10, or aorta calcium score [ACS] > 100. RNA was extracted and whole genome expression profiling was performed on the Sentrix Human (Illumina) platform to measure expression of >47,000 transcripts in each sample. Cluster analysis was performed to identify gene expression patterns. The PANTHER database was used for gene ontology analysis.

Results: Cluster analysis demonstrated that, in monocytes, 9/20 SLE patients had an interferon-inducible signature compared to only 2/16 controls (OR 5.7, 95% CI = [1.02, 32.0]). 3 additional patients had a signature with upregulation of pro-inflammatory cytokines and chemokines, while 8 SLE patients could not be clearly differentiated from controls. In macrophages, there were no clear gene expression signatures. Expression profiling in monocytes and macrophages was unable to clearly distinguish individuals with and without atherosclerosis. However, in a stratified analysis of monocytes of SLE patients with atherosclerosis compared with patients without an atherosclerosis phenotype, we were able to reproduce our previous observation that individuals with subclinical atherosclerosis (defined by CAC > 100) had a substantial enrichment in the expression of 344 genes including those involved in TLR/IL-1R signaling (OR 9.3, 95% CI = [1.2, 72.9]). Furthermore, we identified genes with both a fold change >2 and $p<0.05$ that were differentially expressed during monocyte to macrophage differentiation between SLE patients and controls. There was significant ($p<0.001$) enrichment of genes involved in signal transduction, immune system processes, carbohydrate and lipid metabolic processes, and apoptosis. Further analysis of the signal transduction genes demonstrated differences between patients and controls in downregulated genes including *JAK2, STAT6, TLR8,* and *TLR2* and upregulated genes including *VEGFB, TGFB1, FN1, IL-1R2, SCARB1, MSR1,* and *CD163* all of which have previously been shown to be potentially involved in the pathogenesis of atherosclerosis.

Conclusion: Whole genome expression data analyzing monocytes supports the importance of the interferon-inducible signature in SLE. Furthermore, our results also suggest that the TLR/IL-1R-associated immune gene signature and other signal transduction molecules may be involved in the pathogenesis of SLE or associated with atherosclerosis development in patients with SLE.

ACR/ARHP Poster Session B

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics II

Monday, November 7, 2011, 9:00 AM–6:00 PM

1447

Treatment of Systemic Sclerosis: What to Use When First-Line Treatment Fails. A Consensus of Experts. Kyle M. Walker[1], Janet E. Pope[2], Scleroderma Clinical Trials Consortium (SCTC)[3] and Canadian Scleroderma Research Group (CSRG)[4]. [1]Trinity College Dublin, Dublin, Ireland, [2]St. Joseph's Health Care, University of Western Ontario, London, ON, [3]Boston, MA, [4]Montreal, QC

Background/Purpose: There is a need for standardization in systemic sclerosis (SSc) management, particularly after usual (1st-line) treatment.

Methods: SSc experts (n=118) were sent 4 surveys to gain consensus for SSc management. Cases were given for mild and severe organ involvement and experts chose treatments and the % of each drug chosen was recorded, and used to construct treatment algorithms which were voted on re: agreement from 0–9; (consensus was 7, 8 or 9).

Results: 55 (47%) responded to all surveys. After ACEi use for mild scleroderma renal crisis (SRC){97% agreement}, 2nd-line was to add either a CCB {37%} or ARB {35%}, then an alpha blocker (20%) in severe SRC. Treatment of mild and severe SRC was similar (75% agreement) {Fig 1}. ERAs were 1st-line in mild PAH (72%) and proceeded by adding PDE5i (77%) and then a prostanoid (73%). For severe PAH, treatment was any of: prostanoid (49%), combination of ERA and PDE5i (19%) or ERA and prostanoid (16%) {71% agreed} (Fig 2). For mild Raynaud's (RP), CCB (92%) were followed by adding a PDE5i (35%), then an ARB (32%) and finally a prostanoid (23%). For more severe RP, 54% agreed on adding a PDE5i or a prostanoid (32%) {Fig 3}. For prevention of digital ulcers (mild history) treatment was a CCB (73%), then to add a PDE5i (57%) then an ERA (47%), and a prostanoid (38%) {50% agreed}. A severe history was similar (Fig 3). For ILD, induction was usually IV cyclophosphamide (65%) or occasionally oral (64%) or mycophenylate mofetil (MMF) (48%) or azathioprine (45%). For maintenance, MMF was chosen by ¾ (56% agreed). For skin involvement after methotrexate, MMF was usually chosen (38% agreed). For GERD, half would exceed the maximum recommended PPI dose if required (72% agreed). For joint involvement after methotrexate (60%), corticosteroids (37%) or hydroxycholoroquine (31%), then biologics (20%) should be considered (62% agreed).

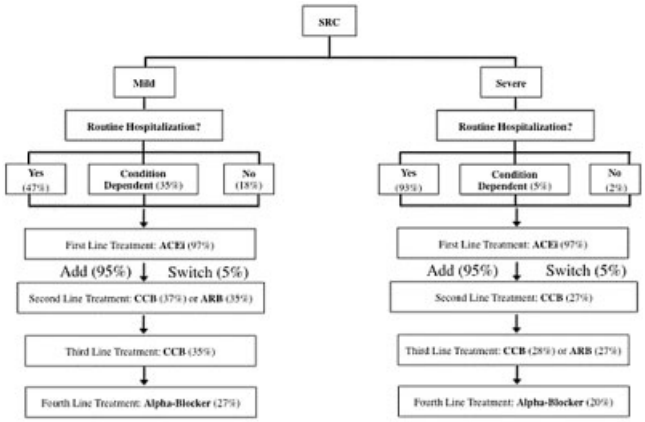

Figure 1. Algorithm for the treatment of mild and severe SRC

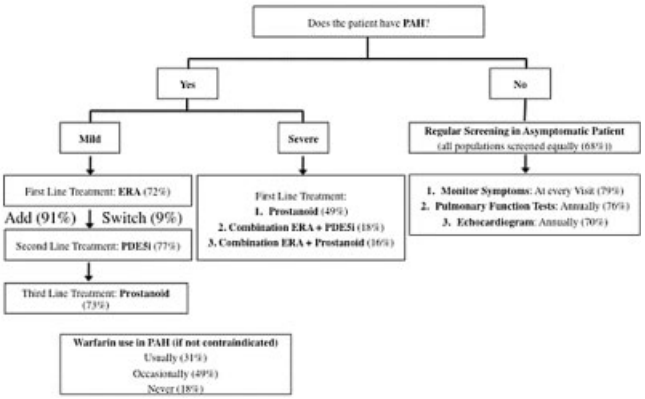

Figure 2. Algorithm for the management of PAH

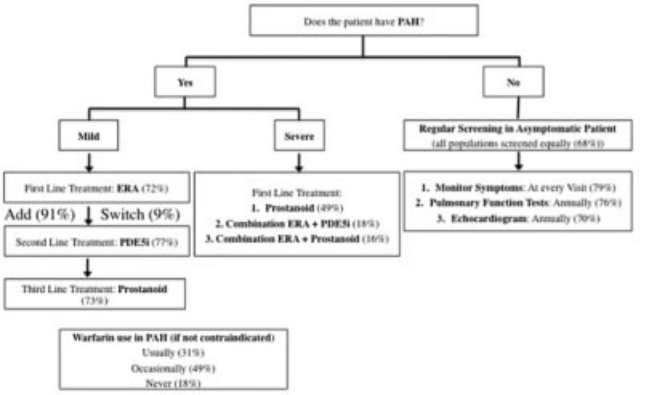

Figure 3. Algorithm for the treatment of RP and the treatment/prevention of DU

Conclusion: Discrepancies in drug choices occurred after 1st-line treatment in SSc. Not all algorithms had good agreement. This study provides some guidance for SSc management.

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Two Years Follow-up Results After Rituximab Treatment (baseline and month 6) in Patients with "Early" Systemic Sclerosis with Diffuse Skin Involvement. Vanessa Smith[1], Yves P. Piette[1], Saskia Decuman[1], Jens T. Van Praet[1], Ellen De Schepper[2] and Filip De Keyser[1]. [1]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [2]Biostatistics Unit, Ghent University, Ghent, Belgium

Background/Purpose: Systemic sclerosis (SSc) with diffuse skin involvement (DcSSc) has a bad prognosis. As yet, no treatment has been shown through randomized controlled trials to halt the natural progression of skin involvement in SSc. Nevertheless, it has been shown recently that in patients with early DcSSc who showed improvement of their skin score during two years of follow-up, survival was significantly better than in patients without such improvement. The purpose of this study is to examine safety and potential efficacy of rituximab in patients with "early" DcSSc.

Methods: Two years follow-up in an open-label study of eight patients with early DcSSc. Patients received an infusion of 1000 mg rituximab at baseline (w0 and w2) and at month 6 (w24 and w26), together with 100 mg methylprednisolone at each infusion. Clinical read outs, disease activity score and functional status were performed at month 0, 3, 6, 12, 15, 18 and 24, except for echocardiography which was performed at month 0, 3, 6, 12 en 24. Assessments included modified Rodnan skin score (mRSS), evaluation of internal organ functioning (lung function, echocardiography, creatinine clearance), the health assessment questionnaire disability index, the Medical Outcome Study Short Form 36 and CD 19+ peripheral blood count. Mixed models analyses (MMA) with random intercept for patients were used to evaluate changes in clinical parameters over time.

Results: There was a clinical significant change in skin score throughout the study with a mean mRSS of 24.8 at baseline (SD: 3.4) and 13.6 at month 24 (SD: 5.6) ($p<0.001$). There was also a significant decrease in Disease Activity Score (DAS), with a mean of 4.5 at baseline (SD: 1.9) and 2.1 at month 24 (SD: 2.4) ($p<0.001$). Indices of internal organ involvement remained stable throughout the study (Table 1). Rituximab induced effective B-cell depletion in all patients both at baseline and month 6 (<5 CD19+ cells/μl blood). Three serious adverse events (SAE) occurred (in addition to two SAE already previously described in the 6 months report of this study)[1], which were thought to be unrelated to the rituximab treatment.

Table 1. Changes in clinical and laboratory parameters in the study upon treatment with rituximab

Parameter	Statistic	0M		3M (n=8)		6M (n=7)		12M (=7)		15M (n=7)		18M (n=7)		24M (n=7)		P-value
Total Skin Score	Mean, SD	24.8	3.4	19.4*	5.4	14.3***	3.5	10.8***	4.6	10.0***	2.6	10.8***	2.6	13.6***	5.6	<0.001
	Median	24.5		18.0		15.0		10.5		9.0		11.0		11.0		
	Min, max	21.0	30.0	12.0	26.0	9.0	18.0	6.0	19.0	7.0	14.0	7.0	14.0	8.0	23.0	
DLCO (% of normal)	Mean, SD	73.3	22.7	68.5	22.1	73.0	18.1	74.7	18.3	75.3	19.1	75.2	23.8	72.6	15.8	NS
	Median	60.5		60.0		64.0		74.0		64.0		72.0		68.0		
	Min, max	54.0	111.0	46.0	106.0	55.0	98.0	56.0	96.0	58.0	105.0	50.0	104.0	54.0	98.0	
Lung Vital Capacity (% of normal)	Mean, SD	92.8	8.6	88.5	12.9	88.3	9.3	89.2	13.7	94.4	10.1	89.8	12.0	84.7†	13.3	0.047
	Median	92.5		92.5		91.0		92.5		96.0		92.0		88.0		
	Min, max	76.0	106.0	68.0	101.0	71.0	99.0	64.0	102.0	76.0	105.0	68.0	104.0	61.0	98.0	
Lung Total Capacity	Mean, SD	83.0	10.5	82.1	12.7	83.1	13.4	83.2	9.3	83.9	16.5	84.5	12.6	78.9	16.7	NS
	Median	81.0		82.5		90.0		85.0		91.0		86.0		74.0		
	Min, max	64.0	97.0	61.0	100.0	62.0	97.0	67.0	91.0	54.0	103.0	63.0	98.0	51.0	101.0	
Forced Expiratory Volume (% of normal)	Mean, SD	83.9	8.1	81.0	17.7	77.0	9.8	79.5	13.5	85.6	12.0	78.2	10.6	73.4†	13.7	0.028
	Median	87.0		82.5		78.0		84.0		84.0		78.5		75.0		
	Min, max	71.0	94.0	49.0	104.0	66.0	93.0	62.0	96.0	70.0	103.0	65.0	95.0	55.0	99.0	
Total SF36	Mean, SD	41.2	15.1	41.2	21.5	51.1	22.4	45.2	22.8	47.9	21.3	51.0	19.7	45.5	21.0	NS
	Median	40.9		31.0		39.7		45.4		39.8		50.6		43.6		
	Min, max	18.9	58.5	19.3	76.8	25.2	89.6	17.3	70.9	22.4	80.5	29.0	73.8	19.9	79.9	
HAQ-DI	Mean, SD	1.4	0.6	1.5	0.6	1.3	0.7	1.3	0.8	1.3	0.6	1.2	0.8	1.3	0.7	NS
	Median	1.3		1.4		1.1		1.5		1.0		1.1		1.6		
	Min, max	0.8	2.1	0.6	2.5	0.3	2.1	0.1	2.0	0.4	2.0	0.1	2.3	0.4	2.0	
Disease Activity Score	Mean, SD	4.5	1.9	2.3*	1.5	1.1***	0.8	0.8***	1.0	1.1***	1.1	1.1***	1.1	2.1*	2.4	<0.001
	Median	4.5		2.0		1.0		0.3		1.0		1.0		0.5		
	Min, max	1.5	7.5	0.0	5.0	0.0	2.0	0.0	2.5	0.0	2.5	0.0	2.5	0.0	5.5	
Creatinine Clearance (ml/min/ 1.73m²)	Mean, SD	83.0	32.5	80.2	30.0	74.2	20.2	71.1	19.8	68.6	17.3	68.5	22.9	71.0	19.5	NS
	Median	87.1		81.0		78.2		78.4		74.5		74.8		79.0		
	Min, max	30.8	143.6	35.3	140.0	36.7	91.8	34.0	86.9	35.4	87.2	31.9	96.0	32.0	86.7	
Systolic Pulmonary Artery Pressure (mmHg)	Mean, SD	31.0	4.0	28.0	5.3	30.0	3.7	28.3	4.7	NA	NA	NA	NA	30.6	4.3	NS
	Median	30.0		26.0		29.5		28.0		NA		NA		31.0		
	Min, max	26.0	36.0	23.0	37.0	26.0	35.0	23.0	36.0	NA	NA	NA	NA	23.0	35.0	
Left Ventricular Ejection Fraction (% of normal)	Mean, SD	69.6	2.3	67.4	2.2	67.0	4.2	64.6†	4.1	NA	NA	NA	NA	59.7**	6.8	0.001
	Median	70.0		68.0		66.5		67.0		NA		NA		59.0		
	Min, max	66.0	72.0	64.0	70.0	63.0	72.0	57.0	68.0	NA	NA	NA	NA	55.0	74.0	

† p<0.05; * p<0.01; ** p<0.001; *** p<0.0001
NA: not applicable, since echocardiography was only performed at month 0, 3, 6, 12 and 24
NS: not significant

Conclusion: Rituximab appears to be well tolerated and may have potential efficacy for skin disease in early DcSSc.

1. **Smith V**, Van Praet JT, Vandooren B, *et al.* Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. *Ann Rheum Dis* 2010;**69**:193–197

1449

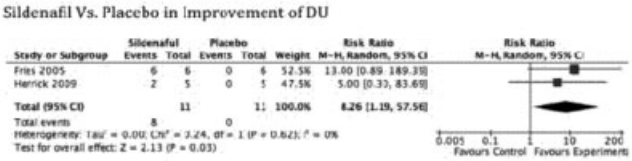
A Meta-Analysis of Randomized Trials in the Treatment and Prevention of Digital Ulcers (DU) in Systemic Sclerosis (SSc). Theresa Tingey[1], Joseph Smuczek[1] and Janet E. Pope[2]. [1]McMaster University, Hamilton, ON, [2]St. Joseph's Health Care, University of Western Ontario, London, ON

Background/Purpose: Digital ulcers (DU) in SSc occur in 50% and may be quite severe. Assessing data from DU trials in SSc may provide guidance for treatment.

Methods: The objective of this meta-analysis was to assess the efficacy of various pharmacologic therapies in treating and preventing DU in SSc including DU trials and Raynaud's Phenomenon (RP) SSc trials which recorded DU. MEDLINE, EMBASE (to November, 2010) and ACR and EULAR abstracts (2009–10) were searched for trials dealing with DU. Randomized trials comparing pharmacologic therapy with placebo or another agent were eligible. Inclusion criteria and trial quality were assessed by 2 reviewers. Quality was scored based on randomization, blinding, statistical methods, intention to treat analysis, and method of randomization. RevMan 5 software was used for analyses.

Results: 40 studies were found, and 19 excluded. Main reasons for exclusion were non-randomisation (7), no DU outcome (8) or insufficient data

(4). Quality score for trials was moderate (mean 2.9/5). Prostacyclins overall when combined were not effective, but intravenous (IV) iloprost was associated with significant prevention (reduction in new DU by standardized mean difference {SMD} of −0.77; 95% CI −1.46 to −0.08; P=0.03); oral prostaglandins were ineffective. Atorvastatin decreased the number of new DU (SMD −0.85; 95% CI −1.32 to −0.38; P=0.0004). Nifedipine was associated with an insignificant decrease in the number of patients developing new DU (RR 0.50; 95% CI 0.17 to 1.46) and no significant differences in overall number of DU and mean number of new DU. Sildenafil was not significant in complete DU healing but for improvement of DU in two trials (P=0.03) and tadalafil had healing and prevention of DU in one trial. In a head to head trial, iloprost was not superior to nifidipine for healing or prevention of DU. Two large bostentan trials were associated with a reduction in the number of new DU (SMD −0.36; 95% CI −0.59, −0.13, P=0.0002) but no difference in the proportion of people with DU healing (P=0.6). Antiplatelet treatment, heparin, dimethyl sulfoxide, ketanserin, prazosin, PGE1, beraprost, cicaprost, and cyclofenil were not statistically different from placebo.



Conclusion: Small sample size, secondary data from RP trials, variable definitions of improvement and prevention and few comparative trials limit the conclusions. The results suggest that there is evidence to support the use of IV iloprost in healing DU in SSc. Bosentan can decrease the number of new DU (prevention). PDE5 inhibitors may have benefit.

1450

Digital Ulcers in Patients with Systemic Sclerosis: Prevalence, Location, Nailfold Capillaroscopy and Functional Impact. Holly Ennis[1], A. Vail[2], Elizabeth Wragg[3], Adrienne Taylor[3], Tonia Moore[1], Andrea Murray[1], Lindsay Muir[4], Christopher E.M Griffiths[5] and Ariane L. Herrick[1]. [1]School of Translational Medicine, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [2]School of Community Based Medicine, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [3]Rheumatology Directorate, Salford Royal NHS Foundation Trust, Salford, United Kingdom, [4]Hand Surgery, Salford Royal NHS Foundation Trust, Salford, United Kingdom, [5]Dermatology Centre, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom

Background/Purpose: Although digital ulcers are a common manifestation of vascular abnormality in patients with systemic sclerosis (SSc) their prevalence, functional impact and pathophysiology have been relatively little studied. Our aim was to investigate point prevalence of active digital ulcers in a cohort of SSc patients and to assess ulcer location, associated findings on quantitative nailfold videocapillaroscopy, and impact on hand function.

Methods: Over a 12 month period, patients attending for routine annual review at a specialist SSc clinic were assessed by a tissue viability nurse who documented all active digital ulcers and performed the Hand Mobility in Scleroderma (HAMIS) test. Patients completed the Cochin Hand Function Scale (CHFS) and the Scleroderma Health Assessment Questionnaire (SHAQ) (both self-assessments), and underwent quantitative nailfold capillaroscopy.

Results: Clinical and demographic features of the 148 participants (74% of those approached) are shown in Table 1. A total of 25 ulcers (9 digital-tip and 16 extensor surface) were found in 15 patients, giving an overall point prevalence (95% CI) of 10% (6–16%) and a point prevalence of 6% (3–11%) for each ulcer type. There was a trend for intercapillary distance to be higher (and therefore density lower) in patients with active ulcers (log [distance], p=0.03). The presence of ulcers was associated with higher pain visual analogue scores (VAS), CHFS and HAQ scores but this was statistically significant only for pain VAS (mean difference 0.45 [0.04–0.88], p=0.04).

Variable	Total study population n=148	No digital ulcers n=133	Digital ulcers n=15
Female, n (%)	125 (84)	133 (85)	12 (80)
LcSSc, n (%)	109	100 (75)	9 (60)
Age, median (range), yrs	60 (21–88)	60 (21–83)	50 (36–88)
Disease duration, median (range), yrs	11 (1–54)	11 (1–43)	13 (1.54)
Capillary density (inter–capillary distance), median (range)	27821 (574–149840)	26914 (574–149840)	49924 (26540–74242)
Pain VAS, median (inter–quartile range)	0.8 (0.1–1.5)	0.8 (0–2.4)	1.2 (0.8–2.1)
CHFS, median (range)	17 (0–80)	13.5 (0–80)	24.5 (3–64)
HAQ, median (range)	1.4 (0–3)	1.3 (0–3)	1.75 (0–2.25)

All 15 patients with ulcers were right-handed. 5 had ulcers only on their left hand, 6 only on their right hand and 4 on both hands. The presence of ulcers on the left hand was associated with significantly reduced HAMIS left scores (mean difference 8.8 [3.2–14.5], p=0.002). This was similar regardless of location. There was a similar association with extensor surface, but not fingertip, ulcers on the right (dominant) hand.

Conclusion:

1. In this prospective study in which active digital ulcers were all identified in a standardised manner by a specialist nurse, the point prevalence was 10% overall and 6% for each of digital-tip and extensor surface ulcers.
2. Digital ulcers were associated with reduced capillary density (reflecting severity of microvascular disease).
3. The burden of pain and functional impairment associated with active digital ulcers was confirmed.
4. The finding that fingertip ulcers of the right (dominant) hand may have a less detrimental impact than others is unexplained but may reflect coping mechanisms in patients with chronic disabling disease.

1451

Elevation of Aldolase in Eosinophilic Fasciitis. Jennifer Nashel[1] and Virginia D. Steen[2]. [1]Washington, DC, [2]Georgetown Univ Medical Center, Washington, DC

Background/Purpose: Eosinophilic fasciitis (EF), is a rare, localized, fibrosing disorder of the fascia that was first described in 1974. The diagnosis of EF is often suspected based on skin findings and laboratory values such as peripheral eosinophilia, increased erythrocyte sedimentation rate (ESR) and hypergammaglobulinemia. These traditionally associated laboratory abnormalities may be transient in early disease and even absent in many confirmed cases. There are some reports that an increased aldolase with normal creatine phosphokinase (CPK) is seen in EF. We have reviewed a case series of patients to assess the presence of laboratory abnormalities in EF.

Methods: We performed a retrospective review of EF patients seen at Georgetown University Hospital in the Division of Rheumatology between 2009 and 2011.

Results: This review included 12 adult patients with EF with a mean age at diagnosis of 45 years (range 24 to 77 years). The majority of patients (10/12) had typical skin changes on all four extremities without evidence of systemic sclerosis. Only six patients had peripheral eosinophilia ranging between 8 and 38%. In these patients, the peripheral eosinophilia was an early and transient finding. The ESR was elevated in 4 out of 11 and C-reactive protein was elevated in 4 out of 8. At disease presentation only 1 of 11 patients had an elevated CPK, however the aldolase levels were elevated in 9 out of 10 patients. While the eosinophilia and inflammatory markers declined rapidly with initiation of steroid treatment, aldolase gradually normalized and more closely followed the clinical disease response.

Conclusion: In this case series of EF patients, aldolase was more likely to be abnormal than peripheral eosinophilia, hypergammaglobulinemia, and ESR. We suspect that aldolase elevation in the setting of a normal CPK is a reflection of perimysial fascial and focal muscle enhancement as illustrated on MRI and en bloc surgical biopsy. An elevated aldolase with a normal CPK may be a unique marker in EF. It may also play a useful role in following disease activity.

1452

HLA *DQB1*03:02* Is a Marker for Severity of Interstitial Lung Disease in Systemic Sclerosis. Shervin Assassi[1], Filemon K. Tan[1], Jun Ying[2], Olga Y. Gorlova[2], Brock E. Harper[3], Hilda T. Draeger[4], Emilio B. Gonzalez[5], Rosa M. Estrada-Y-Martin[1], Julio Charles[1], Xiaodong Zhou[1], Frank C. Arnett[1], John D. Reveille[1] and Maureen D. Mayes[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]UT M. D. Anderson Cancer Center, Houston, TX, [3]University of Texas Medical Branch, Galveston, TX, [4]University of Texas Health Science Center, San Antonio, TX

Background/Purpose: Interstitial lung disease (ILD) is associated with significant morbidity and mortality in systemic sclerosis (SSc). The major histocompatibility region (MHC) showed the strongest association with SSc in the first genome-wide association study, making it the prime genetic locus for studying the pathogenesis of SSc and biomarker development. The goal of the current study was to examine the association of MHC genetic markers with severity of ILD in SSc.

Methods: Patients with SSc were recruited from two US cohorts, GENISOS and the Scleroderma Family Registry. HLA Class II genotyping (*DRB1, DQA1, DQB1, DPB1*) was performed on extracted and purified genomic DNA. Furthermore, anti-centromere (ACA), anti-topoisomerase (ATA), and RNA Polymerase III were detected utilizing commercially available kits. The primary outcome was forced vital capacity (FVC)% predicted at enrollment. A two-step approach was used for the analysis in order to limit the number of performed comparisons. Initially, the top 10 most discriminating, independent clinical and genetic variables were identified in a random forest analysis. Subsequently, these variables were analyzed by linear regression following a forward variable selection strategy. A final multivariable model was constructed with independent variables, significantly associated with the outcome.

Results: A total of 793 patients with SSc were examined, from which 38 % had moderate (FVC=50%–80%) and 6% severe (FVC<50%) restrictive lung disease. Diffuse cutaneous involvement was present in 47% of patients. The mean disease duration was 6.2 years.

HLA *DQB1*03:02* (p=0.0001, b= 6.9, 95% C.I.: 3.4–10.4), disease duration, as well as presence of ACA and ATA were significantly associated with FVC in the multivariable model (adjusted for ethnicity). Addition of disease type (limited versus diffuse) did not significantly change the overall fit of the model. No other HLA Class II allele was associated with FVC.

In our multiethnic sample, 19.6% of patients had at least one HLA *DQB1*03:02* allele. In the multivariable model, patients with this HLA allele had on average 6.9% higher FVC levels, indicating that this HLA allele was a predictor of milder ILD, independent of autoantibody profile and disease duration (Table 1).

We also repeated the entire analysis with only Caucasian patients (n=553). HLA *DQB1*03:02* was again the only HLA Class II allele, significantly associated with FVC. HLA *DQB1*03:02* was present in 19% of Caucasian patients. The same clinical variables were the independent predictors of FVC among these patients in the final model (Table 1).

Table 1. Final Multivariable Model

	Caucasian Patients		All Patients*	
Variable	**b, 95% (C.I.)**	**p-value**	**b, 95% (C.I.)**	**p-value**
DQB1*03:02	6 (2.2,9.8)	0.002	**6.9 (3.4,10.4)**	**<0.001**
ATA	−4.1 (−7.7,−0.4)	0.031	−4.3 (−7.7,−0.9)	0.013
ACA	11.3 (7.6, 15)	<0.001	12.3 (8.6, 15.9)	<0.001
Disease Duration, yrs	−0.4 (−0.6,−0.2)	<0.001	−0.4 (−0.6,−0.2)	<0.001

* Adjusted for ethnicity

Conclusion: This is the first study linking an MHC locus/allele to severity of SSc-ILD. HLA *DQB1*03:02* is an independent predictor of milder ILD in SSc. Because of its high frequency, this allele can be used for risk stratification in patients with SSc beyond the known clinical predictors.

1453

Treatment of Idiopathic Retroperitoneal Fibrosis: A Single Center Experience. Pietro Tartaro and Renzo Marcolongo. Hematology and Clinical Immunology Unit, Padova, Italy

Background/Purpose: Idiopathic Retroperitoneal Fibrosis (IRF) is a rare collagen vascular disease of unclear origin, characterized by the development of fibro-inflammatory tissue in retroperitoneal space around the abdominal aorta, iliac arteries, vena cava and ureters. IRF has been associated with HLA-DRB1*03. The optimal treatment of IRF has not yet been established. Therapeutic options include periodic ureteral stenting, ureterolysis/omental wrapping and/or medical therapy with corticosteroids, alone and in combination with tamoxifen or an immunosuppressive agent. We evaluated our clinical experience on IRF, with particular attention to the response to therapy.

Methods: Retrospective review of clinical records of IRF patients observed over 25 years and followed for at least 6 months. Descriptive statistics were used.

Results: We found data about treatment of 67 patients; 56 received corticosteroids (84%), 5 prednisone alone (7,5%), 17 in combination with tamoxifen (26%), 21 with azathioprine (32%), 10 with cyclophosphamide (15%) and 33 with periodic ureteral stenting (49,2%); 6 underwent ureterolysis/omental wrapping (9%); 46 patients achieved complete remission (67%), with the removal of ureteral stents, and are currently off treatment; 16 patients are still under treatment (24%); 9 (13,4%) had important therapy-related side effects (1 azathioprine-related pancreatitis, 2 severe leucopenia, 3 intolerance to tamoxifen, 1 HBV reactivation, 2 sepsis). The disease recurred in 12 patients (32%) from 6 months to 5 years (average 26 months) after treatment discontinuation.

Additional clinical information was also available for 37 patients; 21 had the involvement of abdominal aorta (57%), 12 with periaortitis (33%) and 9 with aneurysm (24%); 16 (43%) had systemic symptoms (fatigue, weight loss, abdominal and/or back pain), 10 arterial hypertension (27%) and 1 thrombosis of vena cava (2.7 %). In single cases, we found IRF in association with autoimmune diseases such as morfea, retrobulbar fibrosis, Hashimoto's thyroiditis, Raynaud's phenomenon, primary sclerosing cholangitis and psoriasis. PET scan, performed in 15 patients, showed abnormal retroperitoneal uptake in 7 cases. Average follow-up was of 71 months.

Conclusion: In our experience, medical treatment with corticosteroids, alone and in combination with tamoxifen or azathioprine and, when the case, together with ureteral stenting, is usually safe and well tolerated. We conclude that, to make a correct therapeutic choice, it is first worth excluding every identifiable cause retroperitoneal fibrosis, in particular hidden malignancy. For this reason, as starting therapy, we usually prefer prednisone, ranging from 0.5 to 1 mg/Kg/day, alone or in combination with tamoxifen. In case of treatment failure or intolerance, after having carefully excluded every possible contraindications, we add to prednisone an immunosuppressive agent such as azathioprine. Nevertheless, since many IRF patients are aged people with a fragile metabolic condition or concomitant chronic diseases, for their potential side effects, immunosuppressive agents should be used carefully and only in cases non responsive to less aggressive treatments.

1454

Prevention of Digital Ulcers in Systemic Sclerosis Patients: A Proposal of Risk Chart. Andreina Manfredi[1], Marco Sebastiani[1], Roberto D'Amico[1], Valeria Carraro[2], Mario Bocci[3], Sheila Moscatelli[4], Michele Iudici[5], Michele Colaci[1], Dilia Giuggioli[1] and Clodoveo Ferri[6]. [1]University of Modena and Reggio Emilia, Modena, Italy, [2]Rheumatology Clinic, University of Padova, Padova, Italy, [3]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [4]University of Perugia, Perugia, Italy, [5]Second University of Naples, Naples, Italy, [6]Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy

Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease mainly characterized by fibrosis of skin and internal organs and by diffuse microangiopathy, responsible for digital ulcers (DU) in about 50% of patients. Management of DU is very challenging; it includes combined systemic and local treatments. Risk factors for the appearance of scleroderma DU are not defined and data from literature are discordant.

Recently, our group proposed a capillaroscopic index (CSURI: Capillaroscopic Skin Ulcer Risk Index), able to identify patients with high risk to develop DU within 3 months from capillaroscopic evaluation, with a positive and negative predictive value of 62.3% and 97.2%, respectively.

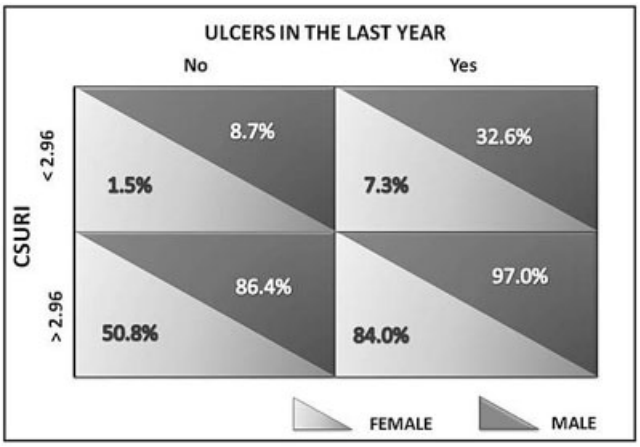
Aim of the study was to develop a predictive model, including CSURI, demographic, and clinico-serological parameters, in order to estimate the total risk of developing DU over next six months.

Methods: One hundred and seventy-two unselected SSc patients (male/female 19/153, limited/diffuse cutaneous SSc 121/51, mean age 53.4 years ± 13.8 SD, mean SSc duration 108.2 months ± 97.8 SD) from 5 Italian Rheumatology Centers were consecutively enrolled. Capillaro-

scopic parameters were defined and collected according to our previous study. All patients underwent videocapillaroscopy at baseline; 3 and 6 months later patients were investigated for the development of DU.

The main demographic, clinical, and serologic features were evaluated for the possible association with the occurrence of DU. Possible correlations among the variables and DU were investigated by multivariate logistic regression.

Results: The development of DU was significantly associated with CSURI (Odds Ratio [OR] - 66.8, confidence interval [CI] 17.9 to 248.7; $p < 0.001$), history of previous DU within the last year (OR 5.1, CI 1.7 to 14.9; $p = 0.003$), and male gender (OR 6.2, CI 1.1 to 34.5; $p = 0.039$). The proposed risk chart based on these three parameters is reported in the figure (the percentages are referred to the cumulative risk for DU).



Conclusion: Among different SSc parameters CSURI, recent history of DU, and male gender showed to be strictly associated with the appearance of DU within the next six months from baseline. Our composite predictive model, which must be opportunely validated, represents an attempt to classify patients with different risk levels to develop DU; a correct patient's classification may optimize the needed preemptive and therapeutical strategies.

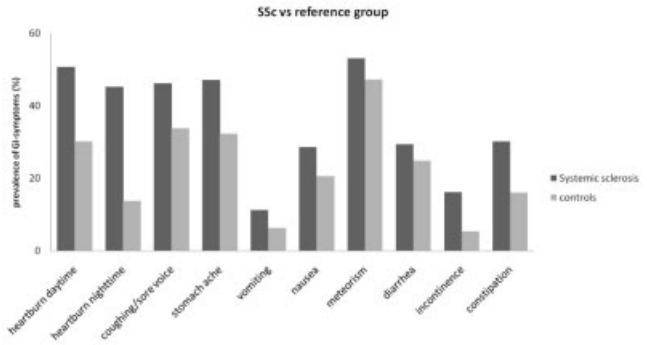
1455

Clinical Features of Gastrointestinal Involvement in Patients with Systemic Sclerosis. Christiane Strohbeck[1], Florian MP Meier[1], Gabriela Riemekasten[2], Christiane Pfeiffer[3], Andrea Himsel[4], Ilka Herrgott[5], Norbert Blank[6], Jorg HW Distler[7], Matthias Seidel[8], Nicolas Hunzelmann[9] and Ulf Müller-Ladner[10]. [1]Justus-Liebig Universität Gieβen, Kerckhoff-Klinik GmbH, Bad Nauheim, Germany, [2]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [3]University Hospital Ulm, Ulm, Germany, [4]University Hospital Frankfurt, Frankfurt am Main, Germany, [5]University Hospital Münster, Münster, Germany, [6]University of Heidelberg, Eppelheim, Germany, [7]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [8]University Hospital of Bonn, Bonn, Germany, [9]University of Cologne, Cologne, Germany, [10]Justus-Liebig-University of Gieβen, Bad Nauheim, Germany

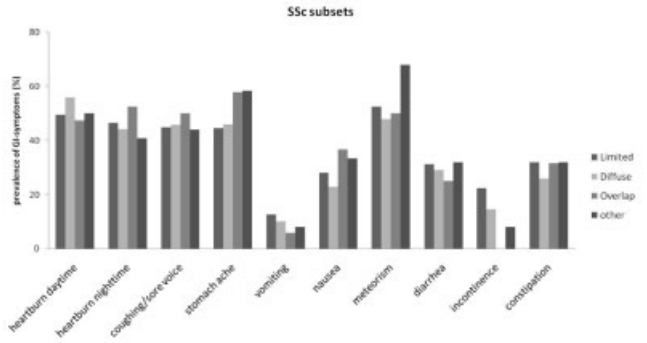
Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune connective tissue disease affecting various organ systems. A common feature of SSc is the involvement of the oesophagus, the stomach and the intestine. Our objective was to gather information about the extent and frequency of gastrointestinal (GI) symptoms in SSc patients. Therefore, the GI-expert center of the DNSS (German Network of Systemic Sclerosis) designed a questionnaire including patient characteristics, disease duration, symptoms and medications.

Methods: In detail, the questionnaire consisted of ten items about GI-symptoms and their occurrence, general aspects of the disease (e.g. time of occurrence), patient characteristics, questions about nicotine or alcohol abuse and about medications for either GI-symptoms or SSc in general. The questionnaire was approved by the local ethics committee. Throughout Germany, the questionnaire was distributed to SSc-patients in DNSS centers. Patients suffering from other rheumatic diseases served as control group. Altogether, 390 patients were included in this study, 222 in the SSc-group and 168 in the reference group.

Results: The results showed that only 5.4% of the SSc-Patients did not suffer from GI-symptoms at all, compared with 8.4% of the reference group. 87.4% were severely affected by clinically relevant GI sequelae, regardless of the SSc disease subset, compared to 73.8% in the reference group. The first diagram displays the distribution and frequencies of the symptoms.



All symptoms occurred more often in SSc-patients. The difference was most prominent for heartburn at nighttime and daytime, as well as for incontinence.



The second diagram demonstrates that the GI-symptoms were independent of the disease subsets. Besides, significant differences between the SSc-group and the reference group could be observed for weight ($p = 0.025$) and the body-mass index ($p < 0.001$). Of interest, only 55.9% of the SSc and 24.7% of the patients of the reference group received medication for their gastrointestinal involvement ($p < 0.001$).

Conclusion: The involvement of the upper and lower gastrointestinal tract in patients with SSc is clinically challenging. Our results demonstrate that almost every SSc-patient is affected by gastrointestinal disorders. Furthermore, these problems occur with higher frequency and severity in SSc patients than in other rheumatic diseases. Therefore, a detailed anamnesis with distinct attention to GI-symptoms is recommended as early as possible.

1456

Trends in Mortality in Patients with Systemic Sclerosis Over 40 Years: A Systematic Review and Meta-Analysis of Case-Control and Cohort Studies. Muriel Elhai[1], Christophe Meune[2], Jerome Avouac[1], Andre Kahan[1] and Yannick Allanore[1]. [1]Rheumatology A, Paris Descartes University, Cochin Hospital, APHP, Paris, France, Paris, France, [2]Paris Descartes University, Cardiology department, Cochin Hospital, Paris, France

Background/Purpose: Among the many different immune-mediated rheumatic diseases, Systemic Sclerosis (SSc) stands out as a severely incapacitating and life-threatening disease, the pathogenesis of which is largely unknown and for which therapeutic options are few and insufficient. Nevertheless, a recent cohort study has suggested a decrease in mortality with 10-year survival rates of 60% in the subgroup of patients included before 1985 as compared to 77% in the subgroup included later one. Thus we set out to determine whether mortality rate in SSc patients has decreased over the past 40 years through a meta-analysis of cohort studies.

Methods: We performed a systematic review and a meta-analysis of literature in MEDLINE and EMBASE databases from January 1960 to June 2010. All cohort studies or case-control studies reporting SSc mortality risk were included. Articles had to report enough data to compute a standardized mortality ratio (SMR). Eligibility of references retrieved by the search was assessed independently by two of the authors and disagreements resolved at each step. We then calculated pooled SMRs of SSc mortality and determined their evolution with time using meta-regression analysis. We also conducted adjusted meta-regression analyses, for the methodology of the studies and for relevant covariates (i.e. age, gender and cutaneous form), respectively.

Results: Among a total of 721 identified references, 637 were excluded on the basis of their title or abstract resulting in 84 articles examined for full text. There were finally 9 independent studies in which SMR was available. They were analyzed corresponding to a total of 2691 patients: mean age: 50.1 years, 2230 (83%) were women, 713/2691 (26%) had diffuse SSc. Mid-cohort year ranged from 1977 to 1995 (<1980: two studies; 1980–90: five studies; >1990: two studies). 732 deaths occurred during a mean follow-up of 7.3 years. The overall pooled SMR was 3.53 [95% CI: 3.03–4.11]. Among 732 deaths, 389/612 deaths (64%) were considered as related or possibly related to SSc whereas 223/612 deaths (36%) were defined as not related to SSc. Cardiac deaths were the most frequent causes of deaths (29%) followed by lung involvement (23%). All adjusted meta-regression analyses did not show any significant change in SMR over time ($p=0.523$). Exclusion of the studies before 1980 revealed a trend for a decrease in SMR but not significant ($p=0.112$).

Conclusion: Our results confirmed that SSc is a devastating condition associated with a high risk of mortality reflected by a pooled SMR of 3.5. Despite some data suggesting a decrease in the mortality risk in SSc, SMR has not significantly changed over the last40 years. Further studies are needed to assess the effect of recent available therapies on mortality in SSc.

1457

Comparison of Wide Field Nailfold Capillaroscopy and Videocapillaroscopy in the Assessment of the Microcirculation in Patients with Raynaud's Phenomenon. Juliana Sekiyama, Cintia Camargo, Luis Eduardo C. Andrade and Cristiane Kayser. Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Capillaroscopy is a well established method for the assessment of the microcirculation in patients with Raynaud's phenomenon (RP). Several equipments such as wide field nailfold capillaroscopy (NFC) and digital videocapillaroscopy are currently used. This study aimed to compare the different parameters evaluated by wide field NFC with those obtained by videocapillaroscopy, as well as to evaluate the reliability of both methods in the assessment of the microcirculation in patients with RP.

Methods: Fifty-six consecutive patients with primary RP (PRP; n = 14), and RP secondary to systemic sclerosis (SSc; n = 28) and undifferentiated connective tissue disease (n = 14) (three men and 53 women in total) were included. A control group of 14 healthy controls matched for sex and age was also included. Wide field NFC was performed using a stereomicroscope (Olympus - SZ40) under 10–25 x magnification. The following parameters were analyzed in eight digits of the hands (excluding the thumb): number of capillaries/mm, number of enlarged loops (about four times the normal capillary width) and giant capillary loops (10 or more times the normal capillary width), number of microhaemorrhages, and vascular deletion score (score 0–3). NFC parameters were calculated as the average obtained in all analyzed fingers. Videocapillaroscopy was performed under 200 x magnification contact lens connected to an imaging analysis software (Videocap 8.14, DS-Medica, Italy). The following parameters were measured over 32 fields (4 fields per finger in 8 fingers, excluding the thumb): number of capillaries/mm, presence of enlarged (capillary diameter >20 μm) and giant capillaries (diameter >50 μm), microhaemorrhages, and capillary loss. Except for the number of capillaries/mm, a score based on a semiquantitative rating scale (score 0–3) was used for each videocapillaroscopy parameter. Intra- and inter-observer reliability was evaluated by performing both exams in 20 individuals in two different days and with two different observers, respectively. Observers were blinded about patients' clinical diagnosis.

Results: There was a significant correlation ($p<0.000$) between wide field NFC and videocapillaroscopy in the comparison of all parameters: number of capillaries/mm ($r=0.817$), enlarged capillaries ($r=0.902$), giant capillaries ($r=0.689$), microhaemorrhages ($r=0.506$), and vascular deletion/capillaries loss ($r=0.784$). Inter- and intra-observer reliability (kappa-coefficient or intra-class correlation coefficient) was good for most parameters evaluated by wide field NFC and videocapillaroscopy.

Conclusion: In the present study both wide field NFC and videocapillaroscopy showed to be reproducible and reliable methods and could be equally useful for the evaluation of peripheral microangiopathy in patients with RP.

1458

Measuring Vascular Burden in Scleroderma and Raynaud Phenomenon. Laura K. Hummers[1], Stefan Zimmerman[1], Fredrick M. Wigley[1], John Carrino[2], Erik Schwetje[3], Warren Greth[4] and Ami A. Shah[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins Medical Institute, Baltimore, MD, [3]MedImmune, LLC, Gaithersburg, MD, [4]MedImmune LLC, Gaithersburg, MD

Background/Purpose: Patients with scleroderma (SSc) have various degrees of peripheral vascular disease including vasoreactivity and obliterative vasculopathy that may lead to significant morbidity in a subset of patients. Our goal in this study was to simultaneously determine blood flow, temperature, clinical features and vascular anatomy of the hand in patients with SSc and primary Raynaud phenomenon (RP).

Methods: Subjects were included in 3 groups: SSc with active digital ulcers (DU) and/or critical digital ischemia; SSc without DU or inactive DU; and primary RP. Subjects underwent MRI/MRA of the hand to determine vessel caliber, collateralization, and level of contrast filling of radial, ulnar, superficial palmar arch (SPA), deep palmar arch (DPA) and digital vessels. On the same day, subjects also had laser Doppler perfusion imaging (LDI) of the same hand and digital temperature measurements performed serially at 4 time points (0, 5, 15 and 45 minutes). Subjects also completed Raynaud Condition Score (RCS), Physician Global Assessment of Digital Ulcers Visual Analog Scale (VAS), Patient Global Assessment of Raynaud's VAS, and Patient Global Assessment of Digital Ulcers VAS. A telangiectasia score was also measured by the physician, and clinical data about their SSc and concomitant vascular disease were collected.

Results: Twenty-five subjects were enrolled (10 SSc without active DU, 11 SSc with active DU and/or critical ischemia, 4 primary RP). Two subjects could not tolerate the MRI study (both in the SSc with active DU group). Subjects were mostly female (21/25) and there was no significant difference in age between the groups although SSc patients without active DU were slightly older (Table 1). No subject had a history of other vascular disease. There were no significant differences in skin temperature or perfusion between the 3 groups when the 4 time points were averaged. There were no noted radial artery abnormalities in any subject, but more subjects with active DU had decreased opacification of the ulnar artery (44%, vs. 10% SSc without DU, 20% in primary RP, $p=0.213$). Also 3/9 patients with active DU had diminished SPA opacification compared to only 1 in each of the other groups ($p=0.8$). Perfusion was decreased in those with either ulnar artery or SPA abnormalities compared to those without, although this was not statistically significant. Subjects with SSc and active DU had a higher mean number of digital arteries with poor flow (either no fill or fill only to the proximal phalanx) than primary RP or no DU subjects, but did not reach statistical significance. However, there was a significant inverse correlation between perfusion and mean number of digits with poor flow ($p=0.003$).

	SSc without active DU	SSc with actitve DU and/or critcal ischemia	Primary RP
Age at visit 1, yrs	56.9 ± 3.7	47.5 ± 3.6	45.8 ± 14.7
Gender F:M	7:3	10:1	4:0
SSc duration, yrs	13.8 ± 9.6	17.3 ± 14.3	NA
Race, W:B	8:2	8:3	4:0
Diffuse subtype, %	70	45	NA
Current vasodilator use, %	20	55	0

Conclusion: All patients with RP have impaired perfusion on LDI, but SSc patients have more structural vascular disease, particularly if they have active DU, which correlates with diminished perfusion.

1459

Watermelon Stomach in Systemic Sclerosis: A EUSTAR Case-Control Study. Etienne Ghrenassia[1], Jérôme Avouac[1], Chris T. Derk[2], Paolo Airo[3], Dinesh Khanna[4], Alice Berezne[5], Kiet Tiev[6], Francesca Ingegnoli[7], Edoardo Rosato[8], Paola Caramaschi[9], Roger Hesselstrand[10], Valeria Riccieri[11], Sharon Bae[12], Virginia D. Steen[13] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [2]Jefferson Medical College, Philadelphia, PA, [3]Brescia, Italy, [4]University of Michigan, Ann Arbor, MI, [5]Paris Descartes University, Internal Medicine department, Cochin Hospital, Paris, France, [6]Internal Medicine Department, Saint Antoine Hospital, Paris, France, [7]University of Milan, Milan, Italy, [8]Department of Clinical Medicine, La Sapienza University, Rome, Italy, [9]Rheumatology Unit, Department of Medicine, Verona, Italy, [10]Lund University & Skåne University Hopsital, Lund, Sweden, [11]University of Rome, Medical Clinic and Therapy Department, [12]Division of Rheumatology, Department of Medicine, Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, [13]Georgetown Univ Medical Center, Washington, DC

Background/Purpose: Watermelon stomach (WS) or Gastric Antral Vascular Ectasia (GAVE) is a very rare gastric complication of Systemic Sclerosis (SSc). It has a unique endoscopic appearance that is characterized by multiple longitudinal stripes of red vessels which radiate in a spoke-like fashion from the pylorus to the antrum. In SSc, WS seems to be a component of the general microangiopathy that characterises the disease and it is thought as a severe complication. However, despite the large use of gastroscopy, prevalence of SSc-GAVE remains poorly known. Furthermore, the characteristics of SSc-GAVE remain poorly described and based on the few available data, SSc features of SSc-GAVE patients remain unclear. The aim of this study was to determine the subgroup at risk together with the outcomes of SSc patients with GAVE.

Methods: We performed a retrospective, multicenter, international, case/control study. We collected cases of SSc-GAVE cases through EUSTAR network. Every case was matched with 2 SSc controls recruited from the same center, matched for age, sex, cutaneous subtype and disease duration. Disease characteristics were recorded at the time of GAVE occurrence and the last observation was used to defined the outcomes.

Results: We included 23 cases of SSc patients with GAVE, who were compared to 42 SSc controls. These 23 SSc patients (20 women, 87%) had a mean ± standard deviation (SD) age of 58±13 years and a mean ± SD disease duration of 6±3 years; 13 had the diffuse cutaneous subset and 10 the limited. Among these patients, 22 (96%) had anaemia, 10 (43%) needed red blood cell transfusion, and 12 (52%) required endoscopic treatment. In addition, SSc patients with GAVE were more likely to have anti-RNA polymerase-III antibodies (14/23, 60% vs. 9/42, 21%, p=0.009), decreased frequency of anti-topoisomerase-I antibodies (1/23, 4% vs. 11/42, 26%, p=0.02) and DLCO/AV<75% predicted (16/23, 68% vs. 12/42, 28%, p=0.01) compared to SSc patients without GAVE. The likelihood of other SSc-related disease characteristics were not different between cases and controls. After a follow-up of 35±27 months, 7 (30%) SSc patients had a relapse of bleeding requiring new local endoscopic treatment. Among these 7 patients, 4 needed red blood cell transfusion.

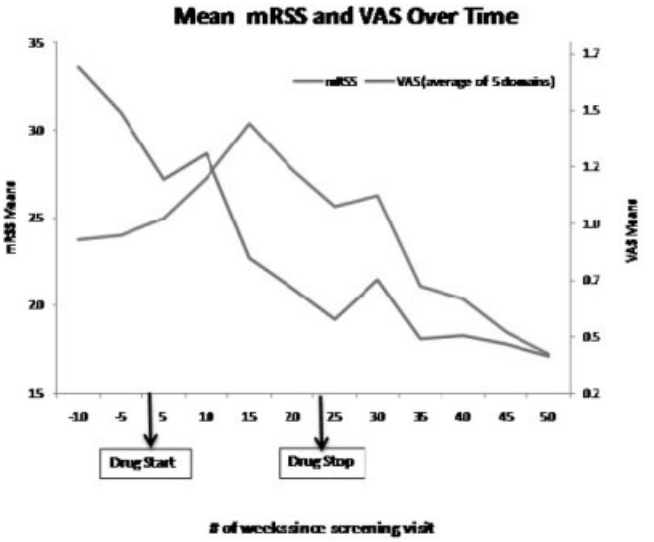
Conclusion: Absence of antitopoisomerase I antibodies and presence of antibodies to RNA-Polymerase-III antibodies may be useful to identify the subset of SSc patients with increased risk for GAVE. Despite it was described as a late complication, SSc patients with GAVE had early disease duration. GAVE appears as a cause of anaemia that clinicians should be aware of. This complication often requires local endoscopic therapy, which is usually efficient, despite frequent recurrent events. The inclusion of further cases in this ongoing project may help to better characterise the features of this rare complication.

1460

Patient Reported Measures of Skin Activity Associate with Disability in Diffuse Scleroderma. Julie J. Paik[1], Laura K. Hummers[1], Fredrick M. Wigley[1], Sharon R. Ghazarian[1], Natalie R. Daya[1], Ami A. Shah[1] and for the Imatinib Study Group[2]. [1]Johns Hopkins University, Baltimore, MD, [2]CH-4002 Basel, Switzerland

Background/Purpose: The modified Rodnan skin score (mRSS) is the current gold standard tool to assess skin disease severity in patients with diffuse cutaneous systemic sclerosis (SSc). While this physician-centered metric may reflect damage from the SSc disease process, it may not correlate with patient perceptions of disease activity and disability. Thus, the purpose of this study was to determine if a patient driven assessment of skin disease activity correlated with disability.

Methods: 27 subjects with early diffuse cutaneous SSc were enrolled in a multi-center, open-label study evaluating the efficacy of imatinib in the treatment of skin fibrosis. Subjects were older than 18 years, had disease duration of less than 18 months from the first non-Raynaud's symptom, and had a minimum mRSS of 20 without trunk involvement or 16 with trunk involvement. Imatinib was titrated to a goal dose of 600mg/day until Week 24 if safety and tolerability permitted. The Johns Hopkins Skin Scales Questionnaire (JHSSQ), scleroderma health assessment questionnaire (SHAQ), and the mRSS were assessed longitudinally in all subjects. The JHSSQ is a patient centered assessment consisting of 5 domains measured on a visual analogue scale (VAS): pain, itching, softening, flexibility, and global skin score. An overall patient score was obtained by averaging the 5 VAS domains for each subject at each time point. The mean mRSS and mean VAS scores were analyzed graphically, and the mean VAS score was correlated over time with our outcomes, disability (HAQ disability index) and generalized pain (HAQ Pain Score).



Results: The subjects had a mean age at enrollment of 45 years (SD 11.9), and 77.7% were female. The average mRSS at enrollment was 24.7 (SD 5.6), and the average JHSSQ score was 1.54 (SD 0.55). As shown in Figure 1, from baseline to week 15 the mean mRSS progressively worsened from a mean of 23.7 to 30.4 while the mean JHSSQ score decreased from 1.6 to.8, demonstrating subject perception of improvement. After week 30, the mean mRSS and JHSSQ continued to decline to a nadir of 16 and 0.4, respectively.

There were statistically significant correlations between the mean JHSSQ VAS score and mean HAQ disability index at visits 2, 6, 9, 10, 12, and 18 (Pearson correlation coefficients ranging from 0.40 to 0.63)and between the mean JHSSQ VAS score and mean HAQ pain score at visits 6, 8–12, and 18 (correlation coefficient range 0.59–0.89).

Conclusion: A patient driven assessment of skin disease activity (JHSSQ score) correlates moderately well with disability and pain in SSc patients with active, diffuse skin disease. The JHSSQ score may be used as an early indicator of disease activity. Initial improvement in the JHSSQ VAS was discordant with the mRSS early in the course of imatinib administration.

1461

Identification of Mesenchymal Cells Expressing Endothelial Markers in Small Pulmonary Arteries of Systemic Sclerosis Associated Pulmonary Fibrosis: Possible Role of Endothelial-Mesenchymal Transition. Fabian A. Mendoza[1], Sonsoles Piera-Velazquez[1], John L. Farber[2] and Sergio A. Jimenez[1]. [1]Scleroderma Center and Jefferson Institute of Molecular Medicine, Philadelphia, PA, [2]Department of Pathology and Cell Biology Thomas Jefferson University, Philadelphia, PA

Background/Purpose: Several pulmonary disorders including interstitial pulmonary fibrosis (IPF), systemic sclerosis (SSc)-associated interstitial lung disease (ILD) and some forms of pulmonary arterial hypertension (PAH) display a prominent fibroproliferative vasculopathy characterized by the accumulation of mesenchymal cells and abundant deposition of extracellular matrix in the subendothelial space of small and medium sized pulmonary arteries. The origin of the mesenchymal cells responsible for the subendothelial fibrosis and subsequent obliteration of the vessel lumen in these disorders is not known. The purpose of this study was to examine the possibility that endothelial to mesenchymal transition (Endo-MT) is involved in the accumulation of activated mesenchymal

cells in the subendothelial space of pulmonary arteries in systemic sclerosis (SSc) associated interstitial lung disease (ILD).

Methods: Lung tissues from 3 patients with SSc and pulmonary fibrosis were examined by histopathology, immunohistochemistry, and confocal laser microscopy for the simultaneous expression of markers of endothelial cells (CD-31) or hematopietic progenitor cells/ small vessel endothelial cells (CD-34) and myofibroblasts (alpha smooth muscle actin or type I collagen).

Results: Expression of the endothelial cell marker CD-31, or the hematopoietic progenitor cell/ small vessel endothelial cell marker, CD-34, was observed in mesenchymal cells embedded within the subendothelial neointima of small pulmonary arteries in the three SSc lung specimens. Co-expression of CD-31 with the mesenchymal markers, collagen type I or alpha smooth muscle actin was demonstrated employing confocal laser microscopy in numerous mesenchymal cells present in the subendothelial region of small pulmonary arteries.

Conclusion: The results indicate that mesenchymal cells bearing endothelial cell-specific markers are present in the subendothelial space of small pulmonary arteries from patients with SSc-associated ILD. These mesenchymal cells of endothelial origin are likely to be responsible for the production and accumulation of subendothelial fibrotic tissue in the affected vessels that in turn results in their luminal obliteration. Understanding of the mechanisms responsible for the transition of endothelial cells into mesenchymal cells (EndoMT) in SSc associated ILD may provide novel therapeutic approaches for this devastating and incurable disease.

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1462

Outcomes of Systemic Sclerosis Associated Polyarthritis Patients Treated by Biotherapies Tocilizumab or Abatacept: A EUSTAR Observational Study. Marine Meunier[1], Marco Matucci Cerinic[2], Britta Maurer[3], Gabriela Riemekasten[4], Raffaele Pellerito[5], Carlos Alberto von Mühlen[6], Alessandra Vacca[7], Paolo Airo[8], Francesca Bartoli[2], Ginevra Fiori[2], Oliver Distler[9] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [2]Department of Internal Medicine, Rheumatology Section, Transition Clinic, University of Florence, Firenze, Italy, [3]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [5]Ospedale Mauriziano, Torino, Italy, [6]Rheumatology Department, Saint Lucas Hospital, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil, Porto Alegre, Brazil, [7]Chair of Rheumatology II, Department of Medical Sciences, University of Cagliari, Italy, Cagliari, Italy, [8]Brescia, Italy, [9]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Joint involvement is frequent in systemic sclerosis (SSc) and up to 30% can develop clinical signs of synovitis or tenosynovitis (1). Treatment is not standardized and polyarthritis is not uncommonly refractory to DMARDS. Biologic agents are increasingly used in inflammatory rheumatic conditions. Among them, tocilizumab and abatacept have proven to be effective in rheumatoid arthritis but no trial has been performed SSc. The aim of this study was to evaluate the safety and effectiveness of tocilizumab and abatacept in SSc-polyarthritis, in a prospective multicenter observational study.

Methods: By querying the EUSTAR network, 13 SSc patients with active polyarthritis and insufficient response to DMARDS were included. Patients received tocilizumab or abatacept upon the decision of their physician in routine practice: 9 patients received tocilizumab at 8 mg/kg/month and 4 patients abatacept at 10 mg/kg/month. Clinical and biological assessments were carried out at treatment initiation and before the last infusion.

Results: The majority of patients were followed 6 months (9/13) but the last data were only obtained at 3 months for 4 patients. Mean age was 50±10 years, mean disease duration 10±5 years, 46% of patients had a diffuse cutaneous sub-type, 4 patients had positive anti-CCP antibodies. 3 out of 12 patients had severe lung fibrosis. Patients received biotherapy in association with DMARDs (n=9) or alone (n=4).

Tocilizumab induced a significant response for joint involvement with a mean DAS28 decrease of 2.2±1.2 (2.8±1 before the last infusion versus 5.0±0.9 at baseline, $p<0.0001$) a mean tender joints decrease of 6.5 (4.7±7 versus 11.2±7) and a mean swollen joints decrease of 4 (1.2±1.8 versus 5.2±5). 6/9 patients receiving tocilizumab achieved EULAR good response. Rodnan's skin score did not significantly change (8±8 versus 9±9, p=0.8) and neither quality of life (HAQ 1.4±0.5 versus 1.7±0.7, p=0.6). Treatment was stopped for three patients: two because of insufficient improvement and one for elevation of liver enzymes.

Abatacept induced a significant response for joint involvement with a mean DAS28 decrease of 1.8±0.9 (2.6±0.6 versus 4.4±1.1 at baseline, p=0.03), a mean tender joints decrease of 2.8 (1.2±0.9 versus 4.0±1.8) and a mean swollen joints decrease of 3.8 (0.2±0.5 versus 4.0±1.8). 3/4 patients receiving abatacept fulfilled EULAR good response criteria. Rodnan's skin score did not significantly change (10±7.6 versus 9±7.4, p=0.8) and neither quality of life (HAQ 0.7±0.2 versus 0.9±0.3, p=0.2).

Conclusion: In this very preliminary pilot study, both tocilizumab and abatacept appeared to be safe and to improve joint involvement after 3 to 6 months in refractory SSc arthritis patients. The follow-up is too short to estimate the impact on the fibrotic lesions. A larger number of cases is expected to be included with the support of EUSTAR network. Larger studies with longer follow-up are warranted to further determine the safety and efficacy of these drugs in SSc, and potentially raise the opportunity of developing randomised controlled trials.

1463

Features of Acute Denervation in Scleroderma Myopathy. Julie J. Paik, Fredrick M. Wigley, Laura K. Hummers and Andrew L. Mammen. Johns Hopkins University, Baltimore, MD

Background/Purpose: Coexisting myopathy is poorly understood in systemic sclerosis (SSc). We sought to determine the histological characteristics of myopathy in SSc.

Methods: SSc patients with proximal muscle weakness and a muscle biopsy read at our institution were identified in our longitudinal database. Clinical and laboratory data including Medsger muscle severity score, modified Rodnan skin score (mRSS), autoantibodies, creatine kinase (CK), aldolase, electromyography and nerve conduction studies (EMG/NCS), and Magnetic Resonance Imaging (MRI) of affected proximal muscles were obtained. Biopsies were contrasted to patients with dermatomyositis. Fisher's exact test was used to determine if there was any statistical association between different histological categories on muscle biopsy to clinical data ($p<0.05$ was considered statistically significant).

Results: 29 patients were included with a mean ±standard deviation age of 42 ±13 years. 82.7% were female, 55% Caucasian, 34% African-American, 34% limited and 65.5% diffuse SSc. The mean mRSS was 8.6 ±10.3. 41.3% of the patients had a Medsger muscle severity score of only 1 (4/5 proximal weakness); 10.3% had a severity score of 4 (requiring assistive device). Autoantibody profile was: anti-centromere (18.5%), Scl-70 (3.8%), RNP (25.9%), and RNA-polymerase III (15.3%). The mean ± standard deviation CK at biopsy was 2078 ±3544, and aldolase at biopsy was 23.2 ± 21.3. On EMG, 15/26 (57.6%) had irritable myopathy while 10/26 (38.4%) had non-irritable myopathy. MRI showed that 17/18 (94.4%) patients had edema.

Muscle biopsy histology Total N=29

Inflammation only	0
Necrosis only	8 (27.6%)
Inflammation and necrosis	14 (28.2%)
Esterase positivity	14 (48.2%)
Presence of Fibrosis with inflammation and/or necrosis	11 (37.9%)

Higher CK values showed a statistically significant association with the presence of necrosis on muscle biopsy (p=0.006) but did not associate with inflammation. The presence of fibrosis on muscle biopsy did not associate with diffuse skin disease and was seen in patients with shorter disease duration (mean 3 years; p=0.016).

Almost 50% of the biopsies had esterase positive angular atrophic fibers, a specific marker of acute denervation. In contrast to the SSc patients, only 1 out of 10 analyzed dermatomyositis muscle biopsies had features of acute denervation (p=0.057). Esterase positivity did not associate with neuropathy on NCS.

Conclusion: Acute denervation, not previously described, is a unique and common finding in SSc patients with myopathy. In addition, muscle fibrosis is rarely seen in isolation, is apparent in early disease, and not isolated to diffuse skin disease.

1464

Medium and Large Vessel Involvements Contribute to Digital Ulcers in Systemic Sclerosis. Christophe Meune[1], Marine Meunier[2], Jérôme Avouac[2], Andre Kahan[2] and Yannick Allanore[2]. [1]Paris Descartes University, Cardiology department, Cochin Hospital, Paris, France, [2]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France

Background/Purpose: Digital ulcers are a burden in systemic sclerosis (SSc). Microangiopathy is a cardinal feature of SSc that has a critical role in the development of DU. However, whether injury of the medium or large vessels also contributes to DU in SSc has been poorly investigated. The importance of large artery stiffening has been highlighted by

the observation that aortic pulse wave velocity (PWV), which is inversely related to distensibility, and central augmentation index (AIx), a composite measure that depends on the site and degree of wave reflection, are independent predictors of cardiovascular and total mortality in selected patient groups. In addition, previous reports suggested that Aix is a more sensitive marker of arterial stiffening and risk in younger individuals. Our aim was to measure PWV and Aix in SSc patients stratified according to the presence of digital ulcers.

Methods: Reflected waves assessed by radial applanation tonometry and PWV were measured and compared in a prospective cohort of consecutive SSc patients with and without active digital ulcers, recruited during a 6-month period.

Results: 63 consecutive SSc patients were included (male 14, age 57±12 years, diffuse cutaneous form 10, disease duration 9.7±7.1 years). Among these, 10 SSc patients (15.9%) had active digital ulcer. Systolic, diastolic aortic pressure, as well as aortic pulse pressure, were similar in patients with versus without active ulcers (p=0.104, 0.531 and 0.143 respectively). Regarding our primary criteria, when compared to patients without ulcer, SSc patients with active digital ulcer had increased AIx_75 (35% [28–38] versus 29% [21–34], p=0.048) without any significance difference in PWV (7.3 m/s [6.7–10.1] versus 7.6 m/s [6.7–8.6], p=0.913). By univariate analysis, age (p=0.002), the existence of active ulcer (p=0.048) and ESR (p=0.010) are the only associated factors with Aix_75. In bivariate analysis, after adjustment for age, the presence of active ulcer remained a strong determinant of AIx_75 (p=0.038). In addition, the AIx_75 of the reflected wave correlated with age (r=0.76, p=0.035) and NT-proBNP concentration (r=0.388, p=0.004), whereas PWV correlated only with age (r=0.520, p=0.001).

Conclusion: SSc patients with active ulcer have increased Aix_75 but similar PWV when compared to patients without active ulcer. These data suggest that patients with active ulcer have a different arteriolar site of reflection, possibly due to increased peripheral arteries vasoconstrictor tone. If confirmed this could suggest that this vascular component should be targeted by the drug regimen in SSc patients with active DU.

1465

Juvenile Systemic Sclerosis Outcomes After Treatment of Pulmonary Fibrosis with Cyclophosphamide or Methotrexate. Gretchen R. Henstorf[1] and Anne M. Stevens[2]. [1]Seattle Children's Research Institute, Seattle, WA, [2]University of Washington, Seattle, WA

Background/Purpose: Children with systemic sclerosis (SSc) usually develop alveolitis with progressive, potentially fatal interstitial fibrosis. Adult trials suggest stabilization of pulmonary function with cyclophosphamide (CY) therapy, though with significant risk for adverse events. There are no controlled trials for treatment of juvenile SSc. As part of a larger study to develop objective clinical and radiological measures for outcomes in juvenile SSc, we reviewed the courses of patients with SSc lung disease who were treated with extensive courses of CY or methotrexate.

Methods: Medical records were reviewed for all patients diagnosed with scleroderma at Seattle Children's Hospital between 1994 and 2010 to identify children who fulfilled ACR criteria for SSc. Twenty-four patients were identified: 20 girls and four boys. Medical records were reviewed for 13 patients who developed pulmonary fibrosis and/or alveolitis detected by high resolution CT scan. Patients were followed for a mean of 8 years (range 1.4–16.8, SD 4.1). The mean age at diagnosis was 10.4 years (range 2.4–14.7, SD 4.3).

Results: The DLCO adjusted for alveolar volume (DLCO) prior to therapy averaged 84.3%, ranging from 68–105% of normal. Nine patients (mean DLCO 83%, range 64–105%) were treated with CY at the first sign of alveolitis; three with less severe alveolitis were treated with methotrexate (DLCO 88% range 81–94%), and one received both CY and methotrexate. The treatment regimens were oral CY (1–3 mg/kg/day) and/or IV CY (750 mg/m2) for an average of 3 years (range 0.5 to 11.5 intermittently), with cumulative CY doses averaging 21.2 grams (range 7 to 29.5 grams, SD 9) or methotrexate 1 mg/kg, maximum 40 mg, subcutaneously once a week. All patients received corticosteroids.

We found that five of the nine CY patients had improved pulmonary function at the last test, with a mean increase DLCO of 2.2% (range −15 to +11%, mean increase 2% per year). Patients on methotrexate were stable with DLCO improving in two patients (88 to 91% and 81 to 102%) and decreasing in one (94% to 81%). Serial CT scans showed stable or improved disease (by estimated area of alveolitis and/or fibrosis) in all patients. There was two serious infections during the CY therapy, and one case of antibiotic-induced pneumonitis. One patient had mild gastritis that resolved with a reduction in oral CY dose. Of five cases of pulmonary hypertension three resolved; the two others died of restrictive lung disease and heart failure.

Conclusion: Juvenile patients with severe SSc lung disease can stabilize and even improve with cyclophosphamide or methotrexate and corticosteroid therapy. The low short-term rate of adverse events and high rate of morbidity and mortality of SSc reported without treatment argues for the benefit of cyclophosphamide or methotrexate in children with SSc lung disease. Long-term studies will be required to determine the true cost and benefit of aggressive cyclophosphamide therapy in juvenile SSc.

1466

The N-Terminal Fragment of Brain Natriuretic Peptide As An Outcome Predictor in Scleroderma Renal Crisis. Cecilia B. Chighizola[1], Henry Penn[2], Pier Luigi Meroni[1], Christopher D. Denton[3] and Voon Ong[4]. [1]University of Milan, Milan, Italy, [2]Northwick Park Hospital, Harrow, United Kingdom, [3]Royal Free Hospital, Medical School, London, England, [4]UCL Medical School, London, England

Background/Purpose: Scleroderma renal crisis (SRC) is a life-threatening complication of Systemic Sclerosis (SSc), clinically characterised by acute renal failure and hypertension. Although the outcome has improved with ACE inhibitors, there remains significant mortality and morbidity. Therefore, novel biomarkers to identify patients at high risk of poor renal outcome would be invaluable.

The N-terminal fragment of Brain Natriuretic Peptide (N-TproBNP), a neuroprohormone released from cardiomyocytes in response to pressure overload, is an important biomarker in heart failure and pulmonary arterial hypertension. Notably, N-TproBNP has shown clinical utility in renal impairment. Aim of this study was to assess the role of N-TproBNP in a retrospective cohort of SRC patients.

Methods: 19 SRC patients (16 dcSSc, 3 lcSSc) were enrolled in this study. Three patient subgroups were identified based on renal outcomes (no dialysis, temporary dialysis and permanent dialysis). Kruskal-Wallis test was used to compare N-TproBNP levels among the subgroups.

ROC curves were generated to identify N-TproBNP levels with optimal sensitivity and specificity to predict requirement for renal replacement therapy. Logistic regression analysis was performed to investigate the relationship between N-TproBNP levels and renal outcome, with adjustment for creatinine. N-TproBNP levels were compared at SRC presentation and at six-month follow up using Wilcoxon matched-pair test. Associations between N-TproBNP and clinical variables were determined by Spearman's coefficient.

Results: There was significant difference in N-TproBNP levels among three subgroups of patients based on renal outcome (median in the 3 subgroups: 'no dialysis' 119, 'temporary dialysis' 1729.5 and 'permanent dialysis' 3373 pg/ml; p= 0.003). Analysis of the ROC curves of N-TproBNP to predict requirement for dialysis provided a sensitivity of 87.5% at a cut-off N-TproBNP level of 1494 pg/ml with a specificity of 90.9% (95% CI 0.73–0.99, area under ROC curve 0.9545). At logistic regression analysis, N-TproBNP > 1494 pg/ml was strongly predictive of requirement for dialysis (OR 70, p <0.005, 95%CI 3–1317). In the logistic regression model adjusted for creatinine, N-TproBNP levels >360 pmol/L still significantly predicted renal outcome (p=0.019). Among the eleven patients (57.9%) who had N-TproBNP levels repeated at six-month follow up, there was a significant reduction in N-TproBNP values (p=0.0029). As expected, N-TproBNP levels strongly correlated with serum creatinine (r=0.6105, p=0.0055) and negatively with eGFR (r=-0.7446, p= 0.0009), Hb levels (r=-0.7123, p=0.0006) and disease duration (r=-0.7083, p=0.0007). Similar correlation was observed between N-TproBNP levels and left ventricular ejection fraction but this did not quite meet significance (r=-0.4594, p=0.0734).

Conclusion: These data strongly suggest N-TproBNP peptide may be a useful biomarker in risk stratification of renal outcome among SRC patients. Measurement of N-TproBNP may therefore complement assessment of renal function and selectively identify those patients likely to require renal replacement therapy.

1467

Systemic Sclerosis-Related Digital Ulcers: Influence of Location, Calcinosis and Perfusion on Time to Healing. Andrea Murray[1], Tonia Moore[1], Elizabeth Wragg[2], Holly Ennis[1], Andy Vail[3], Adrienne Taylor[2], Graham Dinsdale[1], Lindsay Muir[4], Charles Hutchinson[1], Christopher E.M Griffiths[5] and Ariane Herrick[1]. [1]School of Translational Medicine, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [2]Rheumatology Directorate, Salford Royal NHS Foundation Trust, Salford, United Kingdom, [3]School of Community Based Medicine, University of Manchester, Manchester Academic Health Science Centre, Salford, United Kingdom, [4]Hand Surgery, Salford Royal NHS Foundation Trust, Salford, United Kingdom, [5]University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom

Background/Purpose: Relatively little is known about pathophysiology of systemic sclerosis (SSc) related digital ulcers and of their healing. Our aim was to determine whether time to ulcer healing was related to location on the finger, the presence of underlying calcinosis, or perfusion.

Methods: Patients attending for annual review at a specialist SSc clinic were asked to report any ulcers occurring within the following 12 months and if so to attend regularly for specialist wound care and comprehensive assessment until ulcer healing. If more than one ulcer was present, then each ulcer was assessed and included in the study. The ulcer location was documented, photographed and an x-ray taken to identify the presence of any underlying calcinosis. To measure perfusion the ulcer site, an adjacent area of skin and an area of skin away from the ulcer (representing normal perfusion) were imaged using laser Doppler imaging (LDI). LDI data was measured as a ratio of perfusion at the ulcer site/normal (U) and adjacent/normal (A), where U or A <1 represents ischaemia and U or A >1 hyperaemia.

Results: 17 patients (median age 61, [range 41–88] years, duration of disease 16 [1–44] years, 82% female, 41% limited cutaneous SSc, 29% anticentromere antibody positive, 18% anti-Scl70 positive, 18% smokers) attended with ulcers over the 12 month period. A total of 61 ulcers was documented (number of ulcers per patient ranged from one [8 patients] to 13). Location data were available for 54 ulcers (61% were on the right hand, 15% occurred on a thumb, 35% were digital tip and 65% extensor surface). Site-specific calcinosis (clinical or radiographic) was reported in 33 ulcers (data available for 55 ulcers) and calcinosis was most common in digital tip (53%) and least common in extensor surface ulcers (23%).The median (95% confidence interval [CI]) time to ulcer healing was 62 (31–147) days for digital tip ulcers and 56 (36–78) days for extensor ulcers ($p=0.41$). Time to healing was longer for those ulcers with underlying calcinosis (83 [33–216 days]) compared to no calcinosis (49 [35–62 days], $p=0.06$). Median (range) LDI measurements (data available for 53 ulcers) for U and A at baseline were 0.79 (0.11–2.92), reflecting ischaemia, and 3.22 (1.22–24.01), reflecting hyperaemia, respectively. 32 ulcers (60%) were ischaemic ($U<1$, 19 fingertip, 13 extensor). Ischaemic ulcer healing time was 97 (CI 56–138) days compared to 43 (30–56) days for non-ischaemic ulcers.

Conclusion: The location of digital ulcers and the presence of underlying calcinosis or ischaemia affect digital ulcer healing time, with digital tip ulcers, ulcers overlying areas of calcinosis and ischaemic ulcers taking longest to heal.

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Spectrum of Muscle Disease in Scleroderma. Huma Sohail[1], Ann J. Impens[2], Elena Schiopu[2] and Kristine Phillips[3]. [1]University Of Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]University of Michigan Medical School, Ann Arbor, MI

Background/Purpose: Skeletal muscle disease commonly occurs in scleroderma, either alone or in combination with other autoimmune diseases. Neither the spectrum of muscle abnormalities associated with scleroderma, nor the prevalence of co-existing autoimmune diseases has been well defined. We conducted this study 1) to classify scleroderma patients based on their characteristic skeletal myopathy and 2) to determine the clinical, biochemical and histological characteristics of these patients.

Methods: We used electronic medical records to identify patients with a diagnosis of scleroderma evaluated at the University of Michigan Hospital from January 2000 to July 2010. Using structured medical record abstraction, we collected the following variables; autoimmune disease diagnosis, age, BMI, sex, EMG, muscle strength testing, histopathology and organ system involvement. Patients were identified based on abnormal muscle enzymes. Myopathy was defined as presence of muscle weakness, abnormal muscle enzymes and positive muscle biopsy. The time of onset of myopathy relative to development of scleroderma features was determined. The study protocol was approved by local IRB.

Results: Of the 1340 patients seen with a referral diagnosis of scleroderma, we identified 370 patients with abnormal muscle enzymes (CPK >180 or Aldolase >7). 206/370 satisfied criteria for a diagnosis of scleroderma. 5 had CPK elevation due to other causes (cardiomyopathy $n=2$, myocardial infarction $n=1$, rhabdomyolysis $n=1$, metastatic lung cancer $n=1$). 150/201 (75%) patients had no evidence of an additional autoimmune disease, while 51 (25%) had the following additional diagnoses; MCTD (30), SLE (5), Dermatomyositis/Polymyositis (10), possible Sjogren's (anti Ro positivity and sicca) (7), RA (1), and unclear diagnosis (2).

150 patients were classified as; morphea ($n=9$), limited or diffuse cutaneous systemic sclerosis ($n=139$) and sine scleroderma ($n=2$). Patients with morphea and incomplete documentation were excluded leaving us with 115. Mean CPK in this group was 407 (37–1706*)* and mean aldolase 9.85 (2–40). 29/115 (25.5%) had muscle weakness, 6/115 (5.2%) had myalgias only. 14/115 (12%) underwent muscle biopsy and were included in the final analysis. Myopathy was observed within the first year of diagnosis in 10/14 (71%). Mean age at onset of myopathy was 46years (30–88y), mean BMI 25.7, ANA positivity 13/14(92.9%). 14/14(100%) patients lacked muscle inflammation on histopathology. Predominant histopathological feature included muscle fiber atrophy 14/14(100%). Other systemic manifestations included ILD 12/14 (85.7%), GERD 14/14 (100%), esophageal dysmotility 7/9 (77%), lower GI involvement 5/14(35.7%), pulmonary HTN 4/14(28.6%) and renal crisis 1/14(7.1%).

Conclusion: Despite muscle enzyme abnormalities, not all patients with scleroderma undergo complete evaluation for myopathy. The risk of life threatening scleroderma related complications may shift a clinician's attention to the management of more severe manifestations. MCTD or clinical overlaps require a careful consideration. Muscle histopathology is critical in therapeutic considerations

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Circulating Endothelial Cells and Capillaroscopic Skin Ulcer Risk Index (CSURI) As Biomarkers of Scleroderma Microvascular Injury. Silvia L. Bosello, Mario Bocci, Giacomo De Luca, Annunziata Capacci, Barbara Tolusso and Gianfranco Ferraccioli. Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: Videocapillaroscopy is a non invasive technique useful to identify early microvascular abnormalities in patients with systemic sclerosis (SSc) and to predict the possible occurrence of ulcers (1). Increased levels of circulating endothelial cells (CEC) have been reported as a marker of vascular damage in various diseases, including SSc, and circulating endothelial precursors (CEP) are impaired in SSc patients. The purpose of this study was to assess the levels of CEC and CEP in a group of scleroderma patients, relating them to the capillaroscopic pattern and capillaroscopic skin ulcer risk index (CSURI).

Methods: 26 SSc consecutive patients underwent blood sample and videocapillaroscopy. Twelve patients presented digital ulcers. CSURI index was calculated, considering the number and size of megacapillaries and the number of total capillaries, as previously reported.

CEP were isolated in the peripheral blood by positive selection of CD34-expressing cells and quantified by flow cytometry as CD45-negative, CD133 and VEGFR2-positive cells. CEC were identified as CD45-negative, CD31-positive and CD146-positive cells.

Results: The mean percentage of CEC in SSc patients was of $6.7\pm7.5\%$, while the mean percentage of CEP was $4.9\pm3.1\%$. CSURI mean score in this cohort of SSc patients was 4.5 ± 5.2. A significant direct correlation emerged between the percentage of CEC and the CSURI score ($R = 0.53$, $p = 0.006$). When SSc patients were divided in patients with and without ulcers, the percentage of CEC was significantly higher in patients with ulcers ($8.6\pm8.8\%$) with respect to patients without ulcers (4.8 ± 4.7), ($p=0{,}008$). The percentage of CEP was comparable in both groups, while the ratio of CEC/CEPC was significantly increased in patients with ulcers (9.6 ± 15.8) than in patients without ulcers (3.3 ± 8.1), ($p<0.0001$). Furthermore CSURI score was lower in patients with SSc and ulcers(5.9 ± 7.2) than in SSc patients without ulcers (2.2 ± 1.6), ($p=$ns).

Conclusion: The results of this study suggest that the CSURI, proposed as a new prognostic tool for digital skin ulcer development in systemic sclerosis patients, may reflect persistent and widespread microvascular injury in SSc patients, characterized by increased circulating endothelial cells. On the other hand CEC values seems to be a possible biomarker of endothelial-vascular loss in SSc.

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Living with Connective Tissue Related Interstitial Lung Disease: Patient Experiences of the Disease Process Over Time. Shikha Mittoo[1], Lesley Ann Saketkoo[2], Jeffery J. Swigris[3], Daphne LeSage[4], Aryeh Fischer[3] and Sid Frankel[5]. [1]University of Toronto, Toronto, ON, [2]LSU Health Science Center, New Orleans, LA, [3]National Jewish Health, Denver, CO, [4]Center for CCH at State of Louisiana, New Orleans, LA, [5]University of Manitoba, Winnipeg

Background/Purpose: Very limited information is available about the patient experience of connective tissue disease-related interstitial lung disease (CTD-ILD), in terms of global effects on functioning in various psychological and social spheres or of the patients' approaches to coping with the disease and secondary problems related to it. Such information from the patients' perspective would be useful in informing clinical practice and in developing patient reported outcome measures.

Methods: Data were collected through a focus group interview, involving nine patients. After institutional review board approval a purposeful sample was recruited from a tertiary-referral hospital in Manitoba, Canada. Inclusion criteria involved English speaking adults with a diagnosis of ILD based on at least one of: histology, chest imaging, presence of shortness of breath or cough, restrictive pulmonary physiology and/or impaired DLCO, resting or exertion-related peripheral oxygen desaturation. Patients with pulmonary hypertension or hypersensitivity pneumonitis were excluded. The interview schedule included two questions ("How have you experienced your disease since the diagnosis of ILD?", "How has the disease changed?"), and the moderator used the WHO-100 domains to develop prompts to insure comprehensiveness. Data were analyzed through inductive development of analyst-constructed themes. The thematic structures of two independent analysts were triangulated.

Results: Of the 9 participants, 8 were female and 8 were Caucasian. Their mean age was 53.56 (SD =16.02); 4 out of 8 were smokers. The following CTD sub-types were represented: idiopathic inflammatory myositis, rheumatoid arthritis, scleroderma, and undifferentiated connective tissue disease; one had an overlap of scleroderma and lupus.

Three main themes emerged. One focused upon Living with Uncertainty in a Marginal Situation. Uncertainty flowed from areas of confusion between patients and physicians related to diagnosis, evaluation, prognosis, and therapeutic plan. Communication seemed to stagnate after diagnosis. Future disease course and the origin of current symptoms were not easily delineated. A second theme emerged on the Struggle Over the New Self, attempting to maintain an autonomous voice in resisting social and family pressures to relinquish normal roles and fully assume the sick role. Parenting and grand-parenting roles were especially important to many participants. The third theme involved the development of resilience through coping skills. These skills allowed the patients to actively manage their situation, and thus were empowering.

Conclusion: This is the first known effort to report patient reported qualify of life related outcomes (patient experience) in this population. These findings hold important implications for physicians related to enhancing and continuing communication, supporting competence and reinforcing empowered coping. Communication protocols might be developed, and advice might be given as to how patients might maintain as many normal roles as possible. Patient developed coping skills might be studied to identify their effectiveness.

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Functional Class Change in Patients with Connective Tissue Disease-Associated Pulmonary Arterial Hypertension: Associations with Survival and Exercise Capacity. Lorinda Chung[1], Lori S. Parsons[2], Paul M. Hassoun[3], Michael D. McGoon[4], David B. Badesch[5], Dave P. Miller[2], Mark R. Nicolls[6] and Roham T. Zamanian[6]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]ICON Late Phase & Outcomes Research, San Francisco, CA, [3]Johns Hopkins University, Baltimore, MD, [4]Mayo Clinic, Rochester, MN, [5]University of Colorado Denver, Aurora, CO, [6]Stanford University, Stanford, CA

Background/Purpose: Patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-APAH) have multi-organ system involvement with several factors contributing to their assessment of functional class (FC). A recent study including all PAH subtypes showed that improvement in FC within 1 year is associated with improved survival. We sought to investigate the effect of FC change on survival and exercise capacity in CTD-APAH patients.

Methods: The **R**egistry to **EV**aluate **E**arly **A**nd **L**ong Term PAH Management (REVEAL) is a prospective registry of >3,500 patients with PAH from 55 US centers. CTD-APAH patients diagnosed by right heart catheterization (mean pulmonary artery pressure > 25mmHg and pulmonary capillary wedge pressure ≤ 15mmHg) who did not have significant interstitial lung disease (ILD) (chest imaging with severe fibrosis, OR moderate fibrosis AND total lung capacity < 60% predicted) were included in our analyses. Only those who were assessed as FC III at enrollment and had at least one follow-up FC assessment within the first year after enrollment were included. We classified patients as: 1) improved if FC III improved to FC I/II; 2) stable if remained FC III; or 3) deteriorated if worsened to FC IV based on their first FC follow-up assessment after enrollment. Kaplan-Meier curves were estimated for survival from the time of the first follow-up FC assessment and differences between the groups were assessed by the log-rank test. The change in six minute walk distance (6MWD) between enrollment and the follow-up FC assessment was compared between the groups with ANOVA.

Results: Of the 275 CTD-APAH patients, 186 (68%) had systemic sclerosis, 44 (16%) had lupus, 8 (3%) had rheumatoid arthritis, 20 (7%) had mixed connective tissue disease, 4 (1.5%) had Sjögren's, and 4 (1.5%) had myositis. The follow-up FC assessment occurred 4.2±2.8 months after enrollment. 69% (n=189) of patients remained FC III at follow-up (stable), 24% (n=66) improved, and 7% (n=20) deteriorated. There were no differences among the groups with regards to presence of pericardial effusions, mild ILD, anemia, or brain natriuretic peptide levels at enrollment or at the follow-up assessment. Two-year survival from the follow-up FC assessment was 79±5%, 68±4%, and 22±11%, for the improved, stable, and worsened groups respectively (P=.022 for improved vs. stable; P<.001 for stable or improved vs. worsened) (Figure). The change in 6MWD was minimal in the stable group (−1.8±60.9 m), increased in the improved group (+25±63 m) and decreased in the worsened group (−29±51 m).

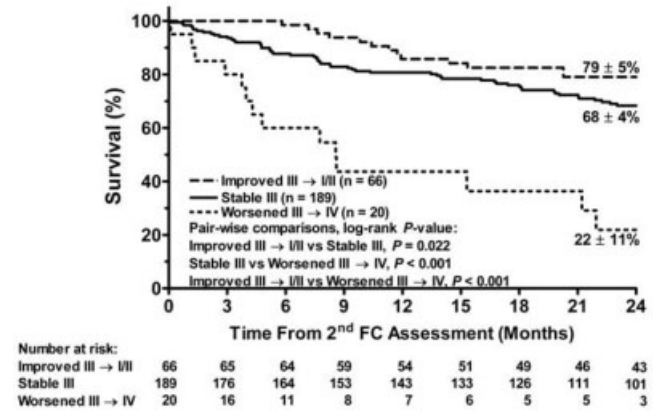

Figure 1. Two-year survival from second functional class assessment of CTD-APAH patients who are FC III at enrollment

Conclusion: Improvement in FC can provide prognostic information with regards to survival and change in exercise capacity in patients with CTD-APAH. Despite multiple factors contributing to the assessment of FC in CTD-APAH patients, FC should be monitored on a routine basis.

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Serum Interleukin-9 Levels Are Increased In Patients with Systemic Sclerosis: Association with Lower Frequency and Severity of Pulmonary Fibrosis. Koichi Yanaba and Shinichi Sato. The University of Tokyo, Tokyo, Japan

Background/Purpose: Systemic sclerosis (SSc) is a generalized connective tissue disorder characterized by sclerotic and vascular changes in the skin and various internal organs. It is generally regarded as an autoimmune disorder because of the presence of antinuclear antibodies. Although the pathogenesis of SSc remains unclear, many previous studies have suggested that cytokines or growth factors regulate its induction by stimulating the synthesis of extracellular matrix components, which may injure endothelial cells and modulate the function of leukocytes. These cytokines or growth factors are produced in part by inflammatory cells infiltrating the affected tissues, such as skin or lungs, of patients with SSc.

Interleukin (IL)-9 is a T cell-derived pleiotropic cytokine that was initially identified as a T helper (Th) 2 cytokine. A number of $CD4^+$ T cell subsets, named Th9, have recently been shown to share the capacity to secrete IL-9. IL-9 targets cells of the lymphoid, myeloid and mast cell lineages, as well as lung epithelial cells, and is likely to contribute to the development of allergic and autoimmune diseases such as asthma, silica-induced lung fibrosis, and experimental autoimmune encephalomyelitis. However, it is unclear whether IL-9 exerts mainly proinflammatory or anti-inflammatory activities.

We suggest that IL-9 plays a role in the pathogenesis of SSc and, in this study, examined serum IL-9 levels in SSc patients, and evaluated the results with respect to clinical features.

Methods: Serum IL-9 levels were examined by enzyme-linked immunosorbent assay in 71 patients with SSc, 15 patients with systemic lupus erythematosus, 15 patients with dermatomyositis, 39 patients with atopic dermatitis, and 28 healthy individuals. Furthermore, we also evaluated the results with respect to clinical features.

Results: Serum IL-9 levels were significantly elevated in SSc patients compared with healthy individuals, and patients with systemic lupus erythematosus or dermatomyositis or atopic dermatitis. Among SSc patients, there were no differences in serum IL-9 levels between those with limited cutaneous SSc and those with diffuse cutaneous SSc. Patients with SSc and raised IL-9 levels less often had pulmonary fibrosis and decreased percent vital capacity than those with normal IL-9 levels. IL-9 levels were positively correlated with percent vital capacity in patients with SSc. Thus, elevated IL-9 levels may be protective against the development of pulmonary fibrosis in SSc.

Conclusion: The current study suggests that elevated IL-9 levels may be protective against the development of pulmonary fibrosis in SSc. Further studies examining the contribution of IL-9 to the regulation of interstitial lung disease and other organ involvement in SSc are required. Nonetheless, the results of our study suggest that the administration of IL-9 might be a possible treatment in patients with SSc who have severe interstitial lung disease.

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High-Dose I.v. N-Acetylcysteine Increases Peripheral Tissue Perfusion and Improves Clinical Symptoms of Systemic Sclerosis Patients. A Pilot Study. Alberto Sulli, Barbara Ruaro, Giuseppe Zampogna, Carmela Ferrone, Francesca Ravera, Bruno Seriolo and Maurizio Cutolo. Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy

Background/Purpose: Systemic sclerosis (SSc) is characterised by progressive tissue hypoperfusion and morphological anomalies of the microcirculation, inducing functional and organic clinical manifestations. This is a pilot study to evaluate clinical efficacy of a single i.v. cycle of N-acetylcisteine (NAC) treatment at a high dosage in patients affected by severe Raynaud's phenomenon (RP) secondary to SSc with digital ulcers and non-responders to either calcium channel blockers or prostacyclin.

Methods: Ten SSc patients (mean age 67±11SD years, mean disease duration 9±4SD years) with the aforementioned characteristics were enrolled into the study after having obtained written informed consent. At baseline and at 5 days after continuous i.v. NAC infusion (20 g/24 hrs/day for 5 days) the following evaluations were carried out: laser Doppler flowmetry (LDF), nailfold videocapillaroscopy (NVC), biochemical assessments (routine haematochemicals, homocysteine, osteocalcin, pyridinoline, deoxypyridinoline, telopeptide, factor VIII), along with clinical parameter assessment. Peripheral digital perfusion (PDP) was assessed by LDF at basal temperature and after heating the probe at 36°C analysing the central area of the fingertips from 2nd to 5th finger bilaterally (1–2). NVC was performed at the level of the same fingers to establish the pattern of microangiopathy and quantify the morphological anomalies (3). Both frequency and severity of the RP attacks, pain intensity tied to digital ulcers, and the subjective elasticity of the skin were evaluated by visual analogical scales (VASs). Statistical analysis was carried out by non-parametric Wilcoxon signed rank test.

Results: Eight patients showed a "Late pattern" of microangiopathy at NVC, whilst two had an "Active pattern". A statistically significant increase of PDP was observed after NAC treatment in 8/10 patients, both at basal temperature (median from 72 to 95 PU) and at 36°C (median from 106 to 134 PU) ($p=0.05$). NAC administration did not interfere with capillary dilation capacity, as the magnitude of PDP rise was about 30% as at basal temperature assessment, as at 36°C. No change was observed in the score for the NVC parameters during the brief observation period. The blood concentrations of telopeptide and factor VIII showed statistically significant increase ($p<0.05$), whilst there was a statistically significant decrease in concentrations of homocysteine, osteocalcin, and phosphorus ($p<0.05$). When VASs were analysed, there was a notable reduction in both the frequency and severity of RP attacks when compared to pre-treatment values, as was the case for intensity of pain due to ulcers and the subjective cutaneous elasticity ($p=0.04$). The treatment was well tolerated and no side effects were observed.

Conclusion: Continuous i.v. infusion of high-dose NAC increases peripheral tissue perfusion, induces modifications in some biochemical parameters and improves clinical symptoms in SSc patients, possibly by interfering with the fibrotic skin process.

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Progression of Microvascular Damage Through Different Nailfold Capillaroscopic Patterns in Systemic Sclerosis Patients. Alberto Sulli[1], Francesca Ravera[1], Barbara Ruaro[1], Vanessa Smith[2], Carmen Pizzorni[1], Giuseppe Zampogna[1], Elisa Alessandri[1] and Maurizio Cutolo[1]. [1]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [2]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium

Background/Purpose: Systemic sclerosis (SSc) is characterised by early nailfold capillary anomalies and progressive internal organ involvement. This is a longitudinal study to investigate the transition of nailfold microangiopathy through different patterns of microvascular damage, looking for possible correlation with organ involvement, in patients with systemic sclerosis (SSc).

Methods: Forty patients (median disease duration 81 months) showing at baseline the "Early" scleroderma-pattern of microangiopathy were followed-up for a median time of 7.3 years. Transition from "Early" to "Active" to "Late" SSc patterns was evaluated by nailfold videocapillaroscopy (NVC) (to establish the pattern of microangiopathy and quantify the morphological anomalies) (1–2). In addition, organ involvement was yearly assessed as follows: oesophageal involvement by manometry, pulmonary function by lung volume tests, DLCO and CT; cardiac performance by Doppler echocardiography, renal function by laboratory tests and arterial Doppler echography; active or recent history of ulcers by both clinical interview and examination. Statistical analysis was performed by non-parametric tests.

Results: At the end of the follow-up, the NVC pattern was found still "Early" in 44%, "Active" in 36%, "Late" in 15%, and "Normal" in 5% of SSc patients. In the subgroup of patients whose microangiopathy progressed from "Early" up to "Late" NVC pattern, the mean time of progression from "Early" to "Active" pattern was only 8±1 months ($p=0.01$), significantly shorter when compared with the mean time of progression from "Early" to "Active" pattern of the other patients (28±20 months), identifying a subset of subjects with fast progression of the microangiopathy. Clinical signs/symptoms progressed in accordance with morphological nailfold changes in 60% of the SSc patients. Both digital ulcers and oesophageal, skin, and lung involvement were found more frequently in SSc patients with either "Active", or "Late" pattern at the end of follow-up, when compared with organ involvement al baseline ("Early" NVC pattern). Both oesophageal involvement and lung disease correlated with higher NVC scores for loss of capillaries and disorganization ($p<0.04$); pulmonary arterial hypertension with higher scores for loss of capillaries, ramifications and disorganization ($p=0.04$); digital ulcers with higher scores for loss of capillaries, ramifications and disorganization ($p=0.02$), as well as with lower scores for giant capillaries ($p=0.002$).

Conclusion: The results confirm a dynamic transition of the nailfold microvascular damage through different patterns of microangiopathy. Patients showing a rapid progression from "Early" to "Active" NVC pattern (lower than one year) should be strictly monitored since at risk of rapid progression to the advanced ("Late") NVC pattern of microangiopathy that is associated with greater organ involvement.

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1475

Serum Brain Natriuretic Peptide is a Reliable Marker for Survival of Pulmonary Arterial Hypertension Associated with Connective Tissue Diseases, Including Systemic Sclerosis, Mixed Connective Tissue Disease and Systemic Lupus Erythematosus. Sumiaki Tanaka[1], Kenta Hoshi[1], Junichi Tanaka[1], Tatsuhiko Wada[1], Jun Okada[2], Tatsuo Nagai[1] and Shunsei Hirohata[1]. [1]Kitasato University School of Medicine, Sagamihara, Japan, [2]Kitasato University, Sagamihara, Japan

Background/Purpose: Under the current circumstance where several potent effective drugs of therapy for pulmonary arterial hypertension (PAH), it is important to set attainment target of therapy for PAH improvement of survival. Because PAH is frequently complicated and is still a life-threating organ involvement in patients with connective tissue diseases (CTD), we studied to confirm the most reliable predictive factor for survival.

Methods: We performed a retrospective-cohort study among 75 PAH patients with CTD, including 37 patients with systemic sclerosis, 20 patients with systemic lupus erythematosus, and 18 patients with mixed connective tissue disease, who were followed between January 1980 and May 2011 in our hospital. We have used beraprost sodium for 56 patients, sildenafil for 20 patients, bosentan for 19 patients, epoprostenol for 8 patients, tadalafil for 7 patients, ambrisentan for 3 patients and treprostinil for 1 patient. Serum levels of brain natriuretic peptide (BNP) (pg/ml) were sequentially measured in these patients 2139 times, and systolic pulmonary artery pressures (sPAP) were estimated by Doppler echocardiogram 861 times. Based on the character of distribution, serum levels of BNP were converted logarithmic values with which the patients were grouped into R1, R2, R3 and R4 (Table 1 and 2). To assess which of serum levels of BNP or sPAP is more reliable predictive factor for survival, we paid attend to the maximum values of serum BNP (logBNPmax) and sPAP (sPAPmax) during observation periods. Mortality odds ratio of these factors adjusted with sex, age, variation of CTD, presence or absence of interstitial lung disease, and WHO-functional class at the start of PAH treatment were evaluated using stepwise logistic regression analysis.

Results: Table 1 showed the distributions of serum levels of BNP and systolic PAP. Twenty-two patients (29.3%) were died during observation. Shown in Figure 1, no patients whose logBNPmax was in R1 and R2 died. The results of stepwise logistic regression analysis disclosed that logBNPmax in R4 was independent risk factor for death, but sPAPmax. Adjusted mortality odds ratios were significant correlated with logBNPmax, but not with sPAPmax in univariate as well as multivariate analysis (Table 3).

Table 1. Distributions of serum levels of BNP and systolic PAP

point	logarithmic values of serum BNP levels	reversed BNP (pg/ml)	systolic PAP (mmHg)
minimum	0.415	2.60	21
1st quartile	1.471	29.58	43
median	1.861	72.61	53
3rd quartile	2.277	189.23	59
maximum	3.490	3020.30	143

Table 2. Definition of group for logarithmic values of serum BNP levels

group	range
R1	0.415–1.471
R2	1.471–1.871
R3	1.361–2.277
R4	2.277–3.490

Table 3. Logistic regression analysis for mortality of PAH in patients with CTDs

factor	mean	mortality odds ratio 95%CI	p
univariate analysis			
logBNPmax in R4	23.34	3.45–495.3	0.0004
sPAPmax (mmHg)	1.01	0.98–1.03	0.5021
multivariate analysis			
logBNPmax in R4	25.17	3.50–553.23	0.0005
sPAPmax (mmHg)	1.00	0.97–1.02	0.7519

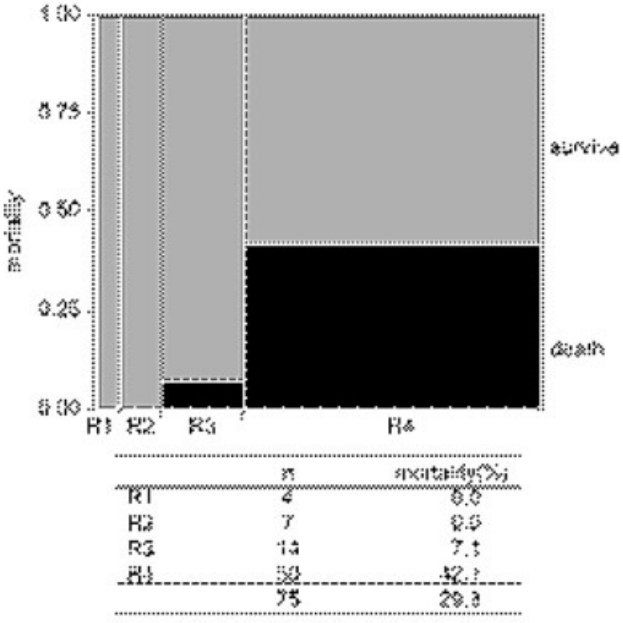

Figure. Mosaic graph showing mortality depend on logBNPmax in PAH patients associated with CTD (Cochran-Armitage trend test, p=0.0017).

Conclusion: These results confirm that serum level of BNP is a reliable marker for management of PAH in CTD. More importantly, maximal serum BNP level, but not sPAP, is critical parameters for prognosis of PAH.

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Long Term Safety and Effectiveness of Tumour Necrosis Factor Inhibitors In Systemic Sclerosis Patients with Arthritis. Mohammed Omair[1], Veerapong Phumethum[2] and Sindhu R. Johnson[3]. [1]Mount Sinai hospital, Toronto, ON, [2]Prapokklao Hospital, Chantaburi, Thailand, [3]Toronto Western Hospital, Toronto, ON

Background/Purpose: To assess the long term safety and effectiveness of Tumour Necrosis Factor (TNF) inhibitors in the treatment of systemic sclerosis (SSc) patients with inflammatory arthritis.

Methods: SSc patients who fulfilled the American College of Rheumatology criteria and had inflammatory arthritis followed in the Scleroderma Program at the Mount Sinai and Toronto Western Hospitals, Toronto, Canada who received a TNF inhibitors for 12 months or more were retrospectively reviewed. Safety outcomes included infection, allergic reaction, development of neurologic symptoms, malignancy, drug induced lupus, and death. Effectiveness outcomes included swollen joint count, tender joint count, and self-reported pain numeric analogue scale score (0 = no pain, 10 = worst pain) at 12 months, compared to baseline.

Results: Eleven SSc patients were identified: 7 (64%) were female and 4 (36%) had diffuse disease. The median age and disease duration at the time of starting TNF inhibitors were 49 years and 24 months respectively. At 12 months, the median swollen joint count and tender joint count significantly decreased from 9 to 0 ($p<0.01$) and 15 to 3.5 ($p = 0.02$), respectively. The median pain score decreased from 4.5 to 3 ($p = 0.10$). One patient developed uncomplicated herpes zoster. After 30 months, 4 out of eleven (36%) developed malignancy. No death, allergic reaction, serious infection, neurologic symptoms, or drug induced lupus was reported.

Conclusion: TNF inhibitors appear to be effective in the treatment of SSc-associated inflammatory arthritis. However, malignancy occurred in one third of our patients. Further studies are required to confirm these findings.

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Fascicular Block: A Predictor of Mortality In Early Systemic Sclerosis. Hilda T. Draeger[1], Shervin Assassi[2], Roozbeh Sharif[3], Emilio B. Gonzalez[4], Brock E. Harper[4], Richard A. Lange[1] and Maureen D. Mayes[3]. [1]Univ of TX Health Science Center-San Antonio, San Antonio, TX, [2]Univ of Texas Health Science, Houston, TX, [3]University of Texas Health Science Center at Houston, Houston, TX, [4]University of Texas Medical Branch, Galveston, TX

Background/Purpose: Previous data from the Genetics versus Environment in Scleroderma Outcome Study (GENISOS) indicated that abnormal electrocardiogram (EKG) findings at an early stage of disease are an independent predictor of mortality in patients with systemic sclerosis (SSc). The objective of this study was to examine the frequency of specific EKG abnormalities in these patients, their serological correlates, and their predictive significance for mortality.

Methods: SSc patients with disease duration of ≤ 5 years from their first non-Raynaud's phenomenon symptom were enrolled in the GENISOS cohort. At enrollment, a standard 12-lead EKG was obtained along with demographic, clinical and autoantibody information. All baseline EKGs were reviewed by a cardiologist (RAL). Although not routinely done, echocardiogram data were recorded when available. Social Security death search and the National Death Index database were used to determine vital status. Chi square (χ^2) was used to examine the correlation between EKG abnormalities and serologic findings. A Cox proportional hazards model was used to investigate the predictive significance of EKG abnormalities for survival after adjusting for age at enrollment. This was extended to include potential confounders for non-SSc related cardiac disease (i.e. gender, hypertension, smoking, diabetes mellitus, and known coronary artery disease).

Results: Of 265 SSc patients (222 women and 43 men with average age of 48.8 vs. 48.0 years, respectively) with average disease duration of 2.5 years, 50.6% had abnormal ECG findings. A detailed list of observed EKG abnormalities is provided in Table 1. The EKG findings were not associated with SSc disease type (i.e., limited or diffuse) or autoantibody profile. Survival analysis showed that over 9 years average follow-up, patients with fascicular block (i.e., LBBB, RBBB, LAFB or LPFB) were at increased risk of mortality (hazard ratio: 2.3; 95% CI:1.1, 4.6, $p=0.02$), after adjustment for age at enrollment (Table 1). In the multivariable model, the predictive significance of fascicular blocks for survival was independent of non-SSc related cardiac risk factors (hazard ratio: 2.1; 95% CI: 1.02, 4.28, $p=0.04$). Moreover, fascicular block was not associated with cardiac disease (i.e., decreased ventricular function or pulmonary arterial hypertension) found on echocardiogram.

Table 1. EKG findings in the GENISOS cohort: Frequency and survival analysis after adjustment for age at enrollment

ECG findings	Number of cases (Frequency)	Hazard Ratio (95% CI)	*p value**
Sinus bradycardia	19 (7.2)	0.75 (0.3, 1.89)	0.551
Sinus tachycardia	7 (2.6)	1.7 (0.54, 5.42)	0.530
First degree AV block	14 (5.3)	1.83 (0.8, 4.23)	0.217
Premature atrial contractions	7 (2.6)	0.38 (0.05, 2.74)	0.227
Premature ventricular contractions	8 (3.0)	1.61 (0.39, 6.59)	0.696
Left axis deviation	18 (6.8)	1.37 (0.59, 3.15)	0.683
Right axis deviation	13 (4.9)	0.77 (0.24, 2.46)	0.915
Delayed transition	8 (3.0)	1.15 (0.28, 4.69)	0.995
Fascicular block	**20 (7.6)**	**2.27 (1.12, 4.58)**	**0.022**
Widened QRS complex	25 (9.4)	1.23 (0.57, 2.69)	0.559
Left atrial enlargement	2 (0.8)	2.80 (0.39, 20.22)	0.254
Right atrial enlargement	3 (1.1)	N/A	1.000
Left ventricular hypertrophy	15 (5.7)	2.33 (1.16, 4.68)	0.103
Right ventricular hypertrophy	3 (1.1)	1.74 (0.24, 12.53)	0.480
Non-specific ST-T wave changes	32 (12.1)	1.52 (0.8, 2.89)	0.448
Prominent U wave	4 (1.5)	1.65 (0.41, 6.75)	0.568
ST elevation	18 (6.8)	1.28 (0.56, 2.96)	0.470
Prolonged QTc	6 (2.3)	0.41(0.06, 2.92)	0.341
Low voltage	20 (7.6)	1 (0.36, 2.76)	0.993
Previous myocardial infarction	11 (4.2)	1.54 (0.56, 4.24)	0.396
EKG findings consistent with PAH	30 (11.3)	1.48 (0.76, 2.89)	0.223

* *p-value adjusted for age; PAH:*pulmonary arterial hypertension

Conclusion: This is the first study reported to date, on correlation of EKG abnormalities with mortality in SSc. EKG abnormalities are common in patient with early SSc. We observed that fascicular block is an independent predictor of mortality. This EKG abnormality may be a surrogate for scleroderma heart disease.

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The Risk of Cancer in Japanese Patients with Systemic Sclerosis. Atsushi Hashimoto[1], Hirahito Endo[2], Toshihiro Matsui[3], Shigeto Tohma[3], Sumiaki Tanaka[4] and Shunsei Hirohata[4]. [1]Kitasato University School of Medicine, and Sagamihara National Hospital, National Hospital Organization, Sagamihara, Kanagawa, Japan, [2]Toho University School of Medicine, Tokyo, Japan, [3]Sagamihara National Hospital, National Hospital Organization, Sagamihara, Kanagawa, Japan, [4]Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan

Background/Purpose: Systemic sclerosis (SSc) is a chronic and multisystemic autoimmune disease of which pathogenesis is still unclear. In addition to severe organ involvement, including that of the lungs, heart and kidneys, cancer is a major cause of death in patients with SSc. To evaluate incidence and identify risk factors of cancer in SSc patients, we investigated Japanese cohort.

Methods: A cohort of 405 Japanese patients with SSc, who attended Kitasato University hospital during the period from 1973 to 2008, was retrospectively analyzed until the end of 2009. Clinical data containing autoantibody profile and overlap of other connective tissue diseases were obtained from medical records or autopsy reports. The standardized incidence ratio (SIR), the ratio between the observed incidence of the cohort in this study and the expected incidence in a comparable age- and sex-matched Japanese population, was calculated.

Results: In the cohort representing 6730 person-years of total disease duration of entire 405 SSc patients, 35 malignancies were found in 34 patients (16 diffuse cutaneous SSc and 18 limited cutaneous SSc) before or after onset of SSc, or at autopsy. Lung cancer, especially adenocarcinoma was the most frequent followed by gastric or breast cancer, which were the most common cancers in Japan. The Kaplan-Meier method with the log-rank test revealed a significant worse survival in patients with cancer than that without it ($p=0.0074$). Univariable analysis for risk factors of cancer detected lung involvement for lung cancer (odds ratio (OR) 5.7, $p=0.0252$). Similarly, multivariable analysis revealed heart involvement for breast cancer (OR 22.2, $p=0.0116$) in addition to lung involvement for lung cancer (OR 7.6, $p=0.0211$). SIR analysis demonstrated that only lung cancer in females had significantly elevated incidence in SSc patients (SIR 8.45; 95% confidence interval (CI) 3.67–13.23), whereas overall cancer (SIR 1.32; 95% CI 0.87–1.76) or another type of cancer did not when compared with the general population.

Conclusion: Except for lung cancer in females, the overall incidence of canser in SSc patients was almost equal to that in the general population. Because lung cancer was significantly correlated with lung involvement, in other words interstitial lung disease (ILD), ILD could play a causal role in developing lung cancer and carcinogenic effect of SSc itself might be little.

ACR/ARHP Poster Session B

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics I

Monday, November 7, 2011, 9:00 AM–6:00 PM

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Topical Vitamin D Analogue Calcipotriol Superinduces TSLP and IL-13 Expression in the Bleomycin Scleroderma Model but Does Not Modify Fibrosis. Alicia Usategui, Manuel J. Del Rey, Elena Izquierdo, Vanessa Miranda, Gabriel Criado and Jose L. Pablos. Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain

Background/Purpose: Patients with different autoimmune diseases, including systemic sclerosis (SSc), have low vitamin D (vitD) concentrations compared to healthy controls. Therapy with systemic vitD or topical vitD analogues has been reported as potentially beneficial in localized scleroderma. Topical vitD may induce atopic dermatitis-like skin irritation, a side effect that has been linked to strong induction of the potent Th2 polarizing cytokine thymic stromal lymphopoietin (TSLP) in the epidermis. We analyzed the potential effects of topical vitD non-calcemic

analogue calcipotriol on the expression of TSLP and Th2 cytokines, and skin fibrosis in the bleomycin model of scleroderma.

Methods: Skin fibrosis was induced in female CH3 mice aged 6 wk by subcutaneous injection of bleomycin (1mg/ml) into the shaved back skin every day for 4 weeks. Groups of 10 mice were given a daily topical application of 3 nM of the non-calcemic vitD analogue calcipotriol or control vehicle cream on the bleomycin injected skin area. Treated skin was harvested and histological examination and collagen content were determined by Masson's trichrome staining and total hydroxyproline content. TSLP, IL-4, IL-13, IL-17 and IFN-gamma mRNA expression were quantified by quantitative RT-PCR. Quantitative data were analysed by Mann-Whitney U-test.

Results: In bleomycin injected mouse skin, significantly increased expression of TSLP, IL-13 and IL-17, and a modest, non-significant increase in IL-4 and IFN-gamma mRNA expression were observed. Skin irritation with strong desquamation and intense inflammatory cell infiltration was observed in calcipotriol but not vehicle treated mice. In bleomycin injected mice treated with calcipotriol, a significantly higher increase in TSLP and IL-13 mRNA expression compared to vehicle treated mice was observed. Other Th cytokines were not modified by calcipotriol treatment. Skin fibrosis, measured as the increase in Masson′s trichrome stained collagen dermal area was similar in both bleomycin/vehicle and bleomycin/calcipotriol treated groups compared to control group. Collagen protein measured as hydroxyproline content was also similar in calcipotriol and vehicle treated groups.

Conclusion: Topical calcipotriol increases inflammatory infiltration and enhances the expression of TSLP and the Th2 cytokine IL-13 in the bleomycin induced model of skin fibrosis. Despite these effects, calcipotriol does not modify the development of fibrosis in this model. These observations suggest that vitD may induce complex effects, perhaps of different sign, that collectivelly do not result in changes on skin fibrosis in this model.

1480

Bosentan Reverses the Profibrotic Phenotype of Systemic Sclerosis Dermal Fibroblasts Through Increasing the DNA Binding Ability of Transcription Factor Fli1. Kaname Akamata[1], Yoshihide Asano[2] and Shinichi Sato[3]. [1]University of Tokyo, Bunkyo-Ku, Japan, [2]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [3]The University of Tokyo, Tokyo, Japan

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vascular injuries and fibrosis of skin and certain internal organs. Although the pathogenesis of SSc still remains unknown, mounting data have demonstrated the possible contribution of endohtelin-1 (ET-1) to the development of fibrosis and vasculopathy in SSc. ET-1 is indispensable for the profibrotic effect of transforming growth factr-b on fibroblasts and bosentan, a dual ET receptor antagonist, reverses the profibrotic phenotype of SSc fibroblasts. Clinically, bosentan prevents the development of new digital ulcers in SSc. Thus, ET-1 may be involved in the mechanism responsible for the constitutive activation of fibroblasts and endothelial cells in SSc.

Fli1 is a member of Ets transcription factor family, which functions as a potent repressor of type I collagen gene in dermal fibroblasts and as a pivotal regulator of angiogenic process in endothelial cells. In SSc skin, Fli1 levels are constitutively downregulated in these cells, especially through the epigenetic mechanism in dermal fibroblasts, suggesting that Fli1 is one of the genetic factors in SSc. Supporting this idea, gene silencing of Fli1 activates fibroblasts and endothelial cells *in vitro* and a series of Fli1 mutant mice reproduce the histopathological features of SSc skin, including collagen deposition and abnormal vascular structure.

Based on these backgrounds, the purpose of this study is to clarify the mechanism by which bosentan exerts its anti-fibrotic effect on SSc fibroblasts, especially focusing on Fli1, by using SSc dermal fibroblasts and SSc animal models.

Methods: Five strains of SSc dermal fibroblasts and closely matched healthy dermal fibroblasts were used in *in vitro* studies. Bleomycin-induced SSc mouse model was used to evaluate the anti-fibrotic effect of bosentan *in vivo*.

Results: mRNA levels of COL1A2 gene were increased by ET-1 around 15 minutes in normal fibroblasts. A responsive element of ET-1 was located between −353 and −264 bp of the COL1A2 promoter, where Fli1 binding site is included, suggesting that ET-1 increases the promoter activity of COL1A2 gene by decreasing the DNA binding ability of Fli1. Consistent with the previous finding that the DNA binding ability of Fli1 is diminished by phosphorylation at threonine 312, ET-1 stimulation increased the phosphorylation levels of Fli1 at threonine 312. In SSc fibroblasts, phosphorylation levels of Fli1 were constitutively elevated compared with normal fibroblasts. Furthermore, a responsive element of bosentan was located between −353 and −264 bp of the COL1A2 promoter in SSc fibroblasts. Moreover, bosentan decreased the phosphorylation levels of Fli1 and increased the DNA binding ability of Fli1 in SSc fibroblasts. Collectively, these results indicate that bosentan reverses profibrotic phenotype of SSc fibroblasts at least partially by increasing the DNA binding ability of Fli1. We also demonstrated that this mechanism is involved in the anti-fibrotic effect of bosentan *in vivo* using SSc animal models.

Conclusion: Bosentan reverses profibrotic phenotype of SSc fibroblasts at least partially by increasing the DNA binding ability of Fli1.

1481

Expression Profiling of Skin and Lung Tissue and Explanted Fibroblasts in a Transgenic Mouse Model of Scleroderma. Emma Derrett-Smith[1], Rachel Hoyles[1], Pia Moinzadeh[1], Cecilia B. Chighizola[1], Korsa Khan[1], Voon Ong[2], David J. Abraham[1] and Christopher P. Denton[1]. [1]UCL Medical School, London, United Kingdom, [2]UCL Medical School, London, England

Background/Purpose: Gene expression profiling of skin or lung tissue and fibroblasts in explant culture have been used to study intrinsic subsets and pathogenic mechanisms in systemic sclerosis (SSc) [1]. There are technical challenges integrating the results of whole tissue and fibroblasts, although the methods are often complementary. We have applied a similar strategy to analysis of a transgenic mouse model that is a phenocopy of many of the histological and biochemical features of SSc. This mouse strain has ligand-dependent upregulation of TGFb signalling due to altered TbRII receptor expression in fibroblasts.

Methods: In the present study we have analysed gene expression profiles of whole skin and lung from littermate TbRIIdk-fib mice and fibroblasts cultured from neonatal or adult skin and lung tissue ($n \geq 3$ in each group) using the illumina microarray platform. RNA was extracted, quantified and assessed for quality using standard methods. Technical validation of the data and additional quantitation of key gene expression was performed using quantitative RT-PCR assay using replicate samples.

Results: Cluster analysis identifies key gene profiles that are specific for skin or lung fibroblasts and also that are altered in whole tissues. In general the differential gene expression was much more marked in whole tissue and differences were more marked in neonatal compared with adult fibroblasts consistent with the higher levels of transgene expression previously described in younger mice. In particular, genes related to cytoskeletal and extracellular matrix structure and function (aSMA, troponin, tropomyosin 1, collagens type I, III, VI, VIII, XVII, matrix metalloproteinases 3, 9, 10, 13, 17, Timp3), endothelin (endothelin-1, Ednrb, Ednra), TGFb (Ltbp1, TGFb1, 2, 3, Ctgf), BMP (Bmp2, 4, Bmpr1) and VEGF (Vegfa, Vegfc) signalling axes and innate immunity (Il-6, Il-11, Il-13, Il-1r, Crp, Saa) were found to be differentially expressed both in transgenic whole skin, lung and explanted fibroblasts. In addition, genes coding for Pecam1 ($p=0.03$) and Elastin ($p=0.003$) were upregulated strongly in whole lung and skin. Some of these key genes that demonstrated significantly dysregulated expression in transgenic mouse skin and lung are summarised in more detail in Table 1.

Table 1. Representative genes that demonstrate dysregulated expression in transgenic skin and lung

Gene	Target tissue	Relative transgenic expression	P value
Mus musculus matrix metalloproteinase 3 (Mmp3), mRNA	Lung fibroblast	1.94	0.02
Mus musculus transforming growth factor beta 1 (Tgfb1), mRNA	Lung fibroblast	1.14	0.01
Mus musculus pleiotrophin (Ptn), mRNA	Skin fibroblast	−0.59	0.1
Mus musculus dual specificity phosphatase 1 (Dusp1), mRNA	Skin fibroblast	0.28	0.0004
Mus musculus homeo box B7 (Hoxb7), mRNA	Skin fibroblast	−0.49	0.01
Mus musculus annexin A1 (Anxa1), mRNA	Whole lung	−0.43	0.05
Mus musculus integrin alpha 6 (Itga6), mRNA	Whole lung	−1.89	0.02
Mus musculus collagen, type XII, alpha 1 (Col12a1), mRNA	Whole skin	0.82	0.01
Mus musculus similar to Fibrillarin, transcript variant 1 (LOC100044829)	Whole skin	0.40	0.02
Mus musculus vascular endothelial growth factor (Vegfa) transcript variant 2, mRNA	Whole skin	−1.86	0.05

Conclusion: These data are reminiscent of studies of human SSc tissue and illustrate another potential complementary strength for mouse models in better understanding the disease.

1. Gardner H, Shearstone JR, Bandaru R, Crowell T, Lynes M, Trojanowska M, Pannu J, Smith E, Jablonska S, Blaszczyk M, Tan FK, Mayes MD. Gene profiling of

scleroderma skin reveals robust signatures of disease that are imperfectly reflected in the transcript profiles of explanted fibroblasts. Arthritis Rheum. 2006 Jun;54(6):1961–73.

1482

The Effect of Trichostatin A, One of the Histone Deacetylase Inhibitor, on Skin Fibrosis Mouse Model. Fumihide Ogawa[1], Hajime Tomita[1], Yutaka Kuwatsuka[1], Kazuhiro Shimizu[1], Shinichi Sato[2] and Atsushi Utani[1]. [1]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]The University of Tokyo, Tokyo, Japan

Background/Purpose: Systemic sclerosis (SSc) is connective tissue disorder characterized by severe fibrosis of the skin and various internal organs. Tight skin (TSK/+) mouse is a putative murine model of SSc characterized by excessive collagen deposition in skin. Bleomycin-induced SSc model mouse, which is another model of SSc, is established using subcutaneous bleomycin treatment. Acetylation and deacetylation of histones play an important role in transcriptional regulation of eukaryotic cell. Histone deacetylases (HDACs) can act as transcription regressors and consequently promote chromatin condensation. Thus, HDACs play a key role in the regulation of gene transcription. Recently, trichostatin A (TSA), one of the HDAC inhibitor, was postulated as a therapeutic agent for fibrosis. Therefore, we investigated the role of TSA in the development of TSK/+ mice fibrosis and bleomycin-induced SSc model mouse.

Methods: TSA was injected subcutaneously into the back of the TSK/+, bleomycin-induced SSc model mice, and wild type mice daily for 4 weeks. Skin sections were assessed histologically. Skin thickness was assessed by hypodermal thickness in TSK/+ mice and by total skin thickness in bleomycin-induced SSc model. The mRNA levels of interleukin (IL)-4, IL-6, transforming growth factor (TGF)-β, type I collagen, fibroblast growth factor (FGF), and interferon (IFN)-γ were measured using real-time reverse transcription polymerase chain reaction (RT-PCR). Autoantibody and several cytokine levels in sera were assessed by enzyme-linked immunosorbent assay. In addition, cultured fibroblasts from mouse skin were stimulated with TSA. The mRNA expressions of collagen and fibrogenic cytokines were evaluated by real-time RT-PCR.

Results: TSA significantly decreased the development of TSK mouse skin fibrosis by reducing the hypodermal thickness. Furthermore, skin mRNA expressions of type I collagen and fibrogenic cytokines, including FGF, TGF-β, IFN-γ, IL-4, and IL-6, were markedly attenuated by TSA administration. However, serum levels of anti-topoisomerase I autoantibody, IL-4, IL-6, and IFN-γ were not affected by TSA percutaneous administration. In addition, TSA significantly down-regulated mRNA levels of collagen, FGF, and IL-6 in cultured fibroblast from mice skin. However, TSA could not decrease the skin sclerosis of bleomycin-induced SSc model.

Conclusion: These results suggest that TSA decreases skin fibrosis only in TSK mouse by regulating expression of collagen and fibrogenic cytokines and does not affect systemic immune level. The effect of TSA for skin sclerosis may depend on the pathogenesis of sclerosis.

1483

Notch Pathway Is Activated in Systemic Sclerosis (SSc). Kae Takagi[1], Yasushi Kawaguchi[1], Yuko Ota[1], Akiko Tochimoto[1], Chikako Fukasawa[1], Masanori Hanaoka[1], Hisae Ichida[1], Takahisa Gono[1] and Hisashi Yamanaka[2]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Systemic sclerosis is a chronic disease of unknown etiology characterized by autoimmunity, vascular damage, and progressive fibrosis of the skin and internal organs. However, it has not been elucidated how the fibrosis is achieved. Therefore, any effective treatments have not been established. Recently it has been reported that Notch signaling pathway was activated in lesional skin of SSc patient. Notch signaling pathway has been known to be associated with human development process and differentiation. Alterations in Notch signaling are implicated in the pathogenesis of several human diseases such as T-cell acute lymphoblastic leukaemia, melanoma. On the other hand, Notch pathway is context dependent, and the effects for fibrosis may depend on the cellular and physiologic environment in which fibroblast or connective tissue is placed. The aim of our study is to investigate whether Notch signaling pathway contributes to the uncontrolled activation of fibrosis in SSc.

Methods: The expression of Notch receptor and its ligand was determined by RT-PCR, Western blot analysis (WB) and flowcytometory (FCM) in cultured skin fibroblasts derived from SSc and healthy controls (HC). To investigate functional significance of Notch signaling pathway, Notch intracellular domain (NCID) was retroviraly transduced with SSc derived fibroblast. Then, concentrations of type I procollagen in the fibroblast supernatants were measured using EIA kit. After stimulating by TGFβ and PDGF, the expression of Notch was determined by real-time PCR and WB.

Results: Expression of Notch 1, 2, and 3 mRNA was lower in SSc derived fibroblast than HC. WB and FCM analysis revealed that SSc derived fibroblasts showed reduced expression of Notch1 than fetal derived control fibroblast. However, even in healthy control derived fibroblasts, Notch expression was variable. These indefinites results prompt us to investigate procollagen type 1C levels in supernatants of cultured mock or NICD transduced SSc derived fibroblasts. NICD transduction into SSc derived fibroblasts slightly augmented procollagen type 1C production. Expression of Notch was upregulated after TGFβ stimulation, but not by PDGF stimulation.

Conclusion: Importance of Notch signaling pathway for etiology of fibrosis in SSc was provided. Nevertheless, obvious relationship between Notch signaling pathway and fibrosis was not elucidated. Complexity and context dependency of Notch signaling pathway contributing to fibrosis was speculated.

1484

Mice Lacking the Receptor-Like Protein Tyrosine Phosphatase CD148 Are Protected From Bleomycin-Induced Pulmonary Fibrosis. Tamiko R. Katsumoto[1], Kevin K. Kim[2], Alexis N. Brumwell[1], John X. Nguyen[1], Connor E. Rosen[1], Elliott Callahan[1], Jing W. Zhu[1], Mark R. Looney[1], Harold A. Chapman[1] and Arthur Weiss[3]. [1]UCSF, San Francisco, CA, [2]University of Michigan, Ann Arbor, MI, [3]UC San Francisco, San Francisco, CA

Background/Purpose: Studies using the bleomycin (BLM) model of pulmonary fibrosis suggest that inhibitors of the later fibrotic phase rather than the early inflammatory phase of disease development may have a higher likelihood of clinical antifibrotic efficacy for diseases such as scleroderma. Protein tyrosine phosphatases and kinases regulate the equilibrium of tyrosine phosphorylation signaling pathways important in cell growth and differentiation. Tyrosine kinases have been implicated in fibrosis, and studies testing the anti-fibrotic activity of tyrosine kinase inhibitors in scleroderma patients are underway. The receptor-like protein tyrosine phosphatase (RPTP) CD148 is widely expressed on various hematopoietic and non-hematopoietic lineages, including lung epithelial cells, endothelial cells, and fibroblasts. Given the importance of tyrosine phosphorylation pathways in fibrosis, we explored the role of CD148 in the BLM model of pulmonary fibrosis.

Methods: Mice with a targeted deletion of the CD148 transmembrane domain (CD148KO) generated by our lab were used. Intratracheal bleomycin was instilled using standard methods. Acute lung injury was measured using extravasation of radioactive iodine-labeled albumin and wet-to-dry ratios. Fibrosis was evaluated by both Masson Trichrome staining of lung sections as well as by the Sircol Collagen Assay.

Results: CD148KO mice showed improved survival following intratracheal BLM administration, (WT 37% vs. CD148KO 92%, $p=0.0135$). Masson Trichrome staining of lungs demonstrated markedly attenuated lung fibrosis in CD148KO mice. Lung collagen content was increased 4.2-fold over saline controls in WT mice, compared with only 1.7-fold increase in CD148KO mice. Acute lung injury was induced 2-fold in both WT and CD148KO mice, suggesting no attenuation of the acute inflammatory response in CD148KO mice. Additionally, evaluation of cells obtained from bronchoalveolar lavage (BAL) at day 7 following bleomycin administration showed no attenuation in BAL cell counts in CD148KO mice. CD148, the predominant RPTP on platelets, positively regulates platelet aggregation via the GPVI collagen receptor. However mice lacking the GPVI receptor showed no attenuation of BLM-induced fibrosis, suggesting that CD148 on platelets was unlikely mediating this phenotype. Furthermore, mice in which CD148 was specifically deleted in lung epithelial cells showed no differences in survival, suggesting that CD148 on epithelial cells was not responsible for the phenotype observed.

Conclusion: Mice lacking CD148 show improved survival following intratracheal BLM administration. Attenuation of bleomycin-induced fibrosis does not appear to be the consequence of a diminished early acute lung injury response to bleomycin. CD148 on platelets or lung epithelial cells does not appear to explain the attenuation of fibrosis observed in CD148KO mice. Future studies will interrogate other specific cell types mediating this response, as well as elucidate the pathways regulated by CD148 underlying this phenotype. These data suggest that inhibition of the RPTP CD148 may present an attractive anti-fibrotic therapeutic strategy.

1485

Absence of Epithelial to Mesenchymal Transition Despite Activation of Keratinocytes in Scleroderma Skin. Joanna Nikitorowicz Buniak, Xu Shiwen, David J. Abraham, Christopher D. Denton, Carol M. Black DBE and Richard J. Stratton. UCL Medical School, London, United Kingdom

Background/Purpose: We have recently shown that scleroderma (SSc) epithelial cells exhibit an activated phenotype similar to wound healing. The interplay between keratinocyte-fibroblast is important in health and disease including epithelial to mesenchymal transition (EMT). EMT is regarded as an important mechanism potentially contributing to lung, liver, and kidney fibrosis. In the SSc epidermis we found active HGF signalling via c-Met and SMAD phosphorylation consistent with TGFβ signalling, both mechanisms implicated in driving EMT. Also we found increased vimentin levels in whole skin biopsy by proteomics. Therefore, we decided to look for evidence of EMT in the skin of scleroderma patients to determine if the skin fibrosis in scleroderma might involve EMT process.

Methods: Forearm skin biopsies taken from scleroderma patients diffuse subset (n=6) and age matched healthy controls (HC) (n=6) were analysed by immunohistochemical staining using antibodies against epithelial markers, K14 and E-cadherin as well as mesenchymal cell and cellular motility markers such as: vimentin, S100A4/FSP-1, α-SMA. Collagen IV was also identified in the sections to determine integrity of the basement membrane. The epidermal thickness and cell area was measured using Axiovision 4.8 software.

Results: Immunohistochemistry results showed activated skin phenotype. Epidermal thickness was increased from 51.27 μm in HC to 88.85 μm in SSc skin, (p=0.005). The mean area of basal cells was 73.37 μm^2 in HC and 111.71 μm^2 in SSc (p=0.0016). While spinous layer keratinocytes were 89.26 μm^2 in healthy control and 173.6 μm^2 in systemic sclerosis (p=0.0038). However, higher numbers of ki67 positive cells in SSc epidermis (8.48) were not significant (p=0.08) when compared with HC (5.62). We did not observe any loss of E-cadherin or gain of vimentin in basal keratinocytes. However, healthy control sub-epidermal cells in a 50μm area adjacent to epidermis had increased vimentin staining. The collagen IV layer in the basal membrane was not compromised. Although we observed increased levels of FSP-1 expression in scleroderma skin when compared with healthy control skin, the level of smad2/3 activation in the area showed no difference.

Conclusion: Our results indicate that despite keratinocytes activation and HGF signalling, EMT is not taking place in scleroderma skin. Although, FSP-1 was increased the marker is not specific to fibroblasts and also detects dendritic cells and macrophages. EMT process is an important step in tumour development and the findings are consistent with the clinical observation that skin cancers are not seen at increased frequency in scleroderma patients. However, more investigations should be done to fully explore the cell and molecular mechanisms underlying the activated epidermis seen in SSc.

1486

Abnormal Morphology and Excessive Synthesis of Collagen V Affects Skin Thickness and Disease Activity in Systemic Sclerosis. Patricia Martin[1], Walcy R. Teodoro[1], Ana Paula P. Velosa[2], Jymenez de Morais[1], Solange Carrasco[3], Francine F. R. Braga[1], Romy Christmann[4], Claudia Goldenstein-Schainberg[5], Edwin R. Parra[1], Vera L. Capelozzi[1] and Natalino H. Yoshinari[2]. [1]Universidade de São Paulo, São Paulo, Brazil, [2]Univerdidade de São Paulo, São Paulo, Brazil, [3]Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [4]Boston University, Boston, MA, [5]University of São Paulo, São Paulo, Brazil

Background/Purpose: Physiological and mechanical properties of skin, one of the primary organs affected in systemic sclerosis (SSc), depends on collagen types I, III and V assembly, forming heterotypic fibers. Collagen V (COLV) regulates fibril diameter and maintenance of its properties is important to keep normal tissue architecture and function. Based on experimental model of SSc discovered in our laboratory, in which over expression of abnormal COLV was a prominent feature, we assumed that this abnormality could be also present in SSc patients.

Methods: skin biopsies of 18 patients (5 at early and 13 at late disease stage) and 10 healthy controls were studied for histological, molecular and biochemical profiles of COLV. Assessment of skin thickness was performed using the Modified Rodnan Skin Score (MRSS) and disease activity was calculated by Valentini Disease Activity Index. Quantification of COLV was obtained by histomorphometry done in dermis and quantitative RT-PCR of dermal fibroblasts culture. Additionally, fibroblasts culture supernatant immunoblotting and tridimentional reconstruction of COLV were performed.

Results: The COLV content in the dermis was higher in early-SSc (44.60 + 10.63%) when compared to controls (24.61 + 5.61%, p<0.01) and late-SSc (33.30 + 4.38%, p<0.01) A positive correlation between COLV and MRSS (r=0.42, p=0.04) as well as disease activity (r=0.45, p=0.03) was observed. The gene expression of COLV alpha 1 and COLV alpha 2 was increased in SSc patients when compared to controls (2.2-fold, p=0.02 and 5.9-fold, p<0.01; respectively). Higher expression of both chains were observed in SSc dermal fibroblasts culture supernatant. Tridimensional reconstruction of collagen fibers confirmed expression of thickened and distorted COLV in SSc patients, different from thin fibrils observed in healthy controls.

Conclusion: Increased synthesis of structurally abnormal COLV is observed in dermis of SSc patients. Since this collagen participates of heterotypic fiber assembly, morphological changes of COLV could explain histoarchitectural disarrangement and skin thickening, mainly at early SSc stage. The positive correlation between dermal COLV expression and disease activity, suggests that besides structural role and loss of regulatory function, COLV may be involved in additional pathophysiological mechanisms.

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The Association Between the PTPN22 C1858T Polymorphism and Systemic Sclerosis: A Meta-Analysis. Young Ho Lee, Sung Jae Choi, Jong Dae Ji and Gwan Gyu Song. Korea University Medical Center, Seoul, South Korea

Background/Purpose: The 1858C→T SNP (single nucleotide polymorphism) of PTPN22 (rs2476601) changes the amino acid at position 620 of Lyp from arginine (R) to tryptophan (W) and disrupts binding between Lyp and Csk, which suppresses T cell activation. The aim of this study was to determine whether the functional protein tyrosine phosphatase nonreceptor 22 (PTPN22) C1858T polymorphism confers susceptibility to systemic sclerosis (SSc) in different ethnic populations.

Methods: A meta-analysis was conducted on the PTPN22 C1858T polymorphism across thirteen comparative studies. We examined the contrast of the allelic effect of T (the variant allele) versus C (the common allele). The random effects model was used in the presence of significant between-study heterogeneity. Otherwise, the fixed effects model was applied.

Results: A total of 13 separate comparisons were considered in this meta-analysis, which in total involved 4,488 SSc patients and 4,874 controls (9,362 study subjects). The analysis showed an association between the PTPN22 1858T allele and SSc in all study subjects (OR [odds ratio] 1.179, 95% confidence interval [CI] 1.016, 1.3662, $p = 0.030$). Analysis after stratification by ethnicity indicated that the PTPN22 1858T allele was significantly associated with SLE in Europeans (OR 1.210, 95% CI 1.042, 1.405, $p = 0.012$), and analysis showed an association between the T allele and SSc in anti-centromere antibody (ACA)-positive subjects (OR 1.210, 95% CI 1.042, 1.405, $p = 0.012$). However, no association was found between the allele and anti-topoisomerase antibody (ATA)-positive SSc European patients (OR 1.136, 95% CI 0.947, 1.364, $p = 0.169$). In addition, African Americans were found to have a much lower prevalence of the T allele (1.5%) than any other population studied, and Europeans had the highest prevalence (8.4%).

Conclusion: This meta-analysis confirms that the PTPN22 C1858T polymorphism is associated with SSc susceptibility and ACA status in Europeans, and that its prevalence is dependent on ethnicity.

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Augmented Expression of Inducible Costimulator (ICOS) and Its Ligand (ICOSL) in Patients with Systemic Sclerosis. Minoru Hasegawa, Manabu Fujimoto, Takashi Matsushita, Yasuhito Hamaguchi and Kazuhiko Takehara. Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

Background/Purpose: Although the pathogenesis of systemic sclerosis (SSc) remains unclear, tissue infiltrating leukocytes likely have critical roles via inducing fibrogenic growth factors and Th2 cytokines. Inducible co-stimulator (ICOS), expressed on activated T cells, and its ligand, ICOS ligand (ICOSL), expressed on antigen-presenting cells and other cells, have been considered a single receptor-ligand pair. The ICOS-ICOSL pathway promotes T cell activation, differentiation, and effector responses, and T cell-dependent B cell responses. ICOS-mediated costimulation of T cells leads predominantly to the production of effector cytokines such as interleukin (IL) −4 and IL-10 and, to a lesser extent, IL-2, interferon-gamma, and tumor necrosis factor-alpha, thereby playing a more important role in Th2 responses than Th1 responses. Recently, we have reported that ICOS-ICOSL signaling significantly affects the development of bleomycin-induced lung and skin fibrosis in mice. To investigate the role of ICOS-ICOSL signaling in the pathogenesis of SSc, we assessed its expression in patients with SSc.

Methods: Expression of ICOS on peripheral blood CD4 or CD8-positive T

cells and expression of ICOSL on CD19-positive B cells or CD14-positive macrophages were determined by flow-cytometry in 20 SSc patients. Expressions of ICOS and ICOSL were also assessed by immunohistological staining and real-time PCR in the legional skin of 20 patients with SSc. Serum levels of soluble ICOS were measured by enzyme-linked immunosorbent assay in 68 patients.

Results: ICOS expression levels were significantly increased on both CD4+ T cells and CD8+ T cells, especially on activated or memory T cells from early diffuse cutaneous SSc (dcSSc) patients compared with that from healthy controls. ICOSL expression was also significantly increased on both CD19+ B cells and CD14+ macrophages from early dcSSc patients than that in healthy controls. Expression levels of ICOS and ICOSL were significantly reduced after the immunosuppressive treatment. ICOS-expressed T cells and ICOSL-expressed B cells or macrophages were increased in the lesional skin tissues of patients with early dcSSc compared with normal skin. mRNA levels of ICOS and ICOSL were augmented in the lesional skin of early dcSSc patients. Soluble ICOS levels were significantly increased in sera from SSc patients than that from healthy controls. Increased soluble ICOS levels were associated with involvement of diffuse skin sclerosis and interstitial lung diseases (ILD).

Conclusion: Augmented ICOS-ICOSL signaling, via overexpressed ICOS and ICOSL, may be contributing to the development of SSc. Soluble ICOS levels may be used as a serum biomarker for skin sclerosis or ILD in patients with SSc.

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Impaired *In Vivo* Neovascularization Capacity of Endothelial Progenitor Cells In Patients with Systemic Sclerosis. Masataka Kuwana, Yuka Okazaki, Hidekata Yasuoka and Tsutomu Takeuchi. Keio University School of Medicine, Tokyo, Japan

Background/Purpose: It has been proposed that defective vasculogenesis with reduced and/or dysfunctional endothelial progenitor cells (EPC) plays a role in the pathogenesis of systemic sclerosis (SSc), but whether the number of $CD45^{-}CD34^{+}CD133^{+}VEGFR2^{+}$ 'real' EPC is reduced in SSc patients is a matter of debate. In this study, we established a system for evaluating *in vivo* EPC's capacity to promote neovascularization, and used it to assess functional properties of EPC in SSc patients.

Methods: Peripheral blood mononuclear cells were obtained from 16 patients with SSc (9 diffuse and 7 limited cutaneous SSc) and 12 healthy controls. For evaluating capacity of EPC to promote new blood formation *in vivo*, murine colon carcinoma line CT-26 cells were transplanted beneath the skin of severe combined immunodeficient mice in conjunction with or without immunomagnetically sorted human $CD133^{+}$ cells. The tumor volume and the density of tumor blood vessels were measured at 10 days. The efficiency of EPC incorporation into the vascular wall was evaluated by double-staining of tumor sections with anti-mouse CD31 and anti-human CD31 antibodies, followed by observation under a confocal microscopy.

Results: Co-transplantation of CT-26 cells with $CD133^{+}$ cells, but not with $CD133^{-}$ cells, markedly promoted tumor growth. In addition, histological examinations of the tumors showed that co-transplantation of $CD133^{+}$ cells increased the density of blood vessels compared with transplantation of CT-26 cells alone. These effects were lost when $VEGFR2^{+}$ cells were depleted from the $CD133^{+}$ cells before transplantation, indicating a primary role of $CD133^{+}$ $VEGFR2^{+}$ EPC in neovascularization in our system. Comparisons between SSc patients and controls showed that tumor growth was slower and blood vessel formation was inferior in SSc-derived $CD133^{+}$ cells ($P = 0.004$ and 0.009, respectively), while there was no difference in the proportion of $VEGFR2^{+}$ cells in the $CD133^{+}$ cell fraction between these two groups. The tumor size was correlated with the density of tumor vessels, and a correlation coefficient was 0.9 when SSc patients and healthy controls were combined together ($P < 0.001$). Finally, tumor vessels incorporating human endothelial cells expressing human CD31 but did not express mouse CD31 were significantly fewer in transplantation of SSc-derived $CD133^{+}$ cells than in transplantation of control-derived $CD133^{+}$ cells ($P = 0.01$). The majority of human endothelial cells expressed von Willebrand factor, a mature endothelial marker.

Conclusion: We have established a system to evaluate *in vivo* angiogenic and vasculogenic properties of human EPC. The EPC's ability to promote new vascular formation by being incorporated into vessel walls and differentiating into mature endothelial cells is impaired in patients with SSc.

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A Membrane-Associated Adaptor Protein DOK5 Is Upregulated in SSc and Associated with IGFBP-5-Induced Fibrosis. Hidekata Yasuoka, Yukie Yamaguchi and Carol A. Feghali-Bostwick. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Systemic sclerosis (SSc) is characterized by excessive fibrosis of the skin and internal organs due to fibroblast proliferation and excessive production of extracellular matrix (ECM). We have shown that insulin-like growth factor binding protein (IGFBP)-5 is upregulated in primary skin and lung fibroblasts of SSc patients, and IGFBP-5 induces fibrosis *in vitro* and *in vivo*. Using gene expression profiling of primary fibroblasts expressing IGFBP-5, we have identified a membrane-associated adaptor protein, DOK5, as an IGFBP-5 target gene. DOK5 is a tyrosine kinase substrate and signaling molecule. Our objective is to determine the role of DOK5 in fibrosis and specifically in IGFBP-5-induced fibrosis.

Methods: Primary human lung fibroblasts were infected with replication-deficient adenovirus expressing human DOK5, human IGFBP-5, or control adenovirus. Cells were also treated with recombinant IGFBP-5. DOK5 mRNA and protein levels were examined by RT-PCR and immunobloting, respectively. DOK5 levels were examined *in vivo* in mouse tissues expressing IGFBP-5 using immunohistochemistry. Intracellular DOK5 expression was measured using immunocytostaining and densitometric measurement of signal intensity. Intracellular localization of DOK5 was assessed using immunoblotting of cytoplasmic and nuclear cellular fractions. To determine the effect of DOK5 on fibrosis, DOK5 was expressed *ex vivo* in human skin in organ culture. Levels of DOK5 mRNA and protein were compared in primary fibroblasts and lung tissues of patients with SSc and healthy donors.

Results: DOK5 mRNA and protein levels were increased *in vitro* by endogenous and exogenous IGFBP-5. DOK5 protein levels were induced *in vivo* by IGFBP-5. DOK5 upregulation required activation of the MAP kinase signaling cascade. IGFBP-5 triggered nuclear translocation of DOK5. Furthermore, expression of DOK5 in human skin resulted in a significant increase in dermal thickness. Lastly, both DOK5 mRNA and protein levels were significantly increased in fibroblasts and skin tissues of patients with SSc compared with those of healthy controls, as well as in lung tissues of SSc patients.

Conclusion: IGFBP-5 induces DOK5 expression, and DOK5 exerts pro-fibrotic effects. DOK5 levels are increased *in vivo* in skin and lung tissues of patients with SSc. Our findings sugget that IGFBP-5 induces its pro-fibrotic effects, at least in part, via DOK5. Furthermore, IGFBP-5 and DOK5 are both upregulated in SSc fibroblats and tissues, and may thus be acting in concert to promote fibrosis.

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A Genome-Wide Association Study Follow-up Strategy Reveals the Association of *IL12RB2* Gene with Systemic Sclerosis in Caucasian Populations. Lara Bossini-Castillo[1], Jose Ezequiel Martin[1], Jasper Broen[2], Carmen Pilar Simeon[3], Lorenzo Beretta[4], Madelon C. Vonk[2], Patricia E. Carreira[5], Spanish Scleroderma Group, Gabriela Riemekasten[7], Nicolas Hunzelmann[8], Alexandre E. Voskuyl[9], Annemie Schuerwegh[10], Oyvind Palm[11], Roger Hesselstrand[12], Annika Nordin[13], Claudio Lunardi[14], Paul Shiels[15], Jacob M. Van Laar[16], Ariane L. Herrick[17], Filemon K. Tan[18], Shervin Assassi[19], Carmen Fonseca[20], Maureen D. Mayes[18], Timothy Radstake[2] and Javier Martin[1]. [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Nijmegen, Netherlands, [3]Hospital Valle de Hebron, Barcelona, Spain, [4]IRCCS Fondazione Policlinico-Mangiagalli-Regina Elena & University of Milan, Milan, Italy, [5]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [6]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [7]University of Cologne, Cologne, Germany, [8]VU University Medical Center, Amsterdam, Netherlands, [9]Leids Univ Medisch Centrum, Leiden, Netherlands, [10]Rikshospitalet, Oslo University Hospital, Oslo, Norway, [11]Lund University & Skåne University Hopsital, Lund, Sweden, [12]Karolinska Institute, Stockholm, Sweden, [13]Policlinico G B Rossi, Verona, Italy, [14]University of Glasgow, Glasgow, United Kingdom, [15]Musculoskeletal Research Group, Newcastle, United Kingdom, [16]Rheumatic Diseases Centre, Salford, United Kingdom, [17]University of Texas Health Science Center at Houston, Houston, TX, [18]Univ of Texas Health Science, Houston, TX, [19]Royal Free and University College Medical School, London, United Kingdom

Background/Purpose: Recently, our group published the first genome-wide association study (GWAS) conducted to date in Caucasian SSc patients. In the previously mentioned GWAS study, a single nucleotide polymorphism (SNP) at the *IL12RB2* locus showed a suggestive association signal.

IL12RB2 encodes IL-12Rβ2, which constitutes the transducing component of the IL-12 receptor heterodimer. Moreover, IL12Rβ2 knockout models develop autoimmune events and polymorphisms in the *IL12RB2* gene region have been related to several human autoimmune disorders.

Aiming to reveal the possible implication of *IL12RB2* gene in SSc, we conducted fine-mapping GWAS follow-up study in different Caucasian cohorts.

Methods: The whole analyzed set comprised 15,474 individuals of Caucasian Ancestry (5,991 SSc patients/9,483 controls). Ten GWAS genotyped single nucleotide polymorphisms (SNPs) in the *IL12RB2* region were analyzed. Then, we included three relevant SNPs in a first follow-up step comprising 7,192 European individuals (3,344 SSc / 3,848 controls). Only the most associated SNP was considered for a second follow-up phase comprising 1,736 US individuals (597 SSc/1,139 controls). Both follow-up cohorts were genotyped using TaqMan SNP genotyping assays in a real-time PCR System.

Significance was calculated using 2×2 contingency tables and Fisher's exact test or χ^2 when necessary, to obtain *p*-values, odds ratios (OR) and 95% confidence intervals (CI) using PLINK (v1.07) software. The logistic regression and conditioned logistic regression analyses, were performed using PLINK software. Linkage disequilibrium patterns across the region in the HapMap Project Phase I and II (CEU population) defined the haplotype tagging SNPs using Haploview (v.4.2) software.

Results: Ten SNPs in the *IL12RB2* region were included in the initial GWAS analysis set, six of them were found to be significantly associated with SSc. However, conditioned logistic regression revealed that the significance of the initially observed associations relied on the rs3790567 association. Both the most associated SNP (rs3790567) and its unique tag-SNP (rs3790566) were selected for replication. We also included rs924080 in the first follow-up phase due to its localization in a recombination hotspot in the intergenic region between *IL12RB2* and *IL23R*.

After the first follow-up phase, only the association of rs3790567 was consistent ($P_{MH} = 4.84\times10^{-3}$ OR = 1.12) (*Table 1*).

Interestingly, the second follow-up phase confirmed this finding ($P_{\chi2} = 2.82\times10^{-4}$ OR = 1.34) (*Table 1*). It is remarkable that rs3790567 pooled analysis in the whole set of individuals reached a highly statistically significant association ($P_{MH} = 2.82\times10^{-9}$ OR = 1.17) (*Table 1*).

Table 1. Genotype and allele distribution of *IL12RB2* rs3790567 genetic variant in SSc patients and controls in a three-step association study.

Population (CTRL/SSc)	CTRL				SSc							
	AA (N)	AG (N)	GG (N)	MAF	AA (N)	AG (N)	GG (N)	MAF	P_{MH}	OR	95% CI	P_{BD}
GWAS cohort (5,161/2,309)	0.06 (332)	0.37 (1,911)	0.57 (2,918)	0.25	0.08 (196)	0.40 (919)	0.52 (1,194)	0.28	1.92×10^{-5}	1.19	1.10–1.29	NS
European follow-up (3,183/3,085)	0.08 (241)	0.37 (1,169)	0.56 (1,773)	0.26	0.09 (282)	0.38 (1,187)	0.52 (1,616)	0.28	4.48×10^{-3}	1.12	1.04–1.22	NS
GWAS + European follow-up (8,344/5,394)	0.07 (573)	0.37 (3,080)	0.56 (4,691)	0.25	0.09 (478)	0.39 (2,106)	0.52 (2,810)	0.28	5.19×10^{-7}	1.61	1.09–1.22	NS
US follow-up (1,139/597)	0.05 (60)	0.37 (417)	0.58 (662)	0.24	0.10 (59)	0.39 (231)	0.51 (307)	0.29	2.82×10^{-4}*	1.34	1.14–1.57	NA
GWAS + European + US follow-up (9,483/5,991)	0.07 (633)	0.37 (3,497)	0.56 (5,353)	0.25	0.09 (537)	0.39 (2,337)	0.52 (3,117)	0.28	2.82×10^{-9}	1.17	1.11–1.24	NS

Controls are used as reference for all comparisons. CTRL: healthy controls; SSc: Systemic sclerosis; MAF: Minor allele (A) frequency; P_{MH}: allelic Mantel-Haenszel fixed effects model *p*-value; *: Allelic Chi-square uncorrected *p*-value; OR: odds ratio; 95% CI: 95% confidence interval; P_{BD}: Breslow-Day test *p*-value; NS: not statistically significant; NA: not applicable.

Conclusion: Our data clearly support *IL12RB2* rs3790567 association with SSc, and suggest a relevant role of IL-12 signaling pathway in SSc pathogenesis.

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The IRF7 Region Is Associated with Anti-Centromere Autoantibody Production in Systemic Sclerosis Patients. F. David Carmona[1], Ramana Gutala[2], Carmen P. Simeón[3], Patricia E. Carreira[4], Norberto Ortego-Centeno[5], Esther Vicente-Rabaneda[6], Francisco J. García-Hernández[7], Paloma García de la Peña[8], Mónica Fernández-Castro[9], Lina Martínez-Estupiñán[10], María-Victoria Egurbide[11], Spanish Scleroderma Group, Betty P. Tsao[13], Pravitt R. Gourh[14], Sandeep K. Agarwal[15], Shervin Assassi[16], Maureen D. Mayes[15], Frank C. Arnett[15], Filemon K. Tan[15] and Javier Martín[17]. [1]Consejo Superior de Investigaciones Científicas, Armilla (Granada), Spain, [2]The University of Texas Health Science Center, Houston, TX, [3]Hospital Valle de Hebron, Barcelona, Spain, [4]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [5]Hospital Clínico San Cecilio, Granada, Spain, [6]Hospital de la Princesa, Madrid, Spain, [7]Hospital Virgen del Rocío, Sevilla, Spain, [8]Hospital Universitario Madrid Norte Sanchinarro, Madrid, Spain, [9]Hospital Puerta de Hierro, Madrid, Spain, [10]Gregorio Marañón Hospital, Madrid, Spain, [11]Hospital de Cruces, UPV/EHU, Barakaldo, Spain, Barakaldo, Spain, [12]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [13]UTHSC-Houston Medical School, Houston, TX, [14]University of Texas Health Science Center at Houston, Houston, TX, [15]Univ of Texas Health Science, Houston, TX, [16]Consejo Superior de Investigaciones Científicas, Granada, Spain

Background/Purpose: The interferon (IFN) pathway plays a key role in the susceptibility to autoimmunity. For instance, type I IFNs were reported to have a central aetiopathogenic role in the development and progression of systemic lupus erythematosus (SLE), and a type I IFN signature has been also observed in patients with systemic sclerosis (SSc). Recent studies have reported an association between *IRF7* and autoantibody production in SLE. To further explore the potential role of this genomic region in SSc, we studied whether five single-nucleotide polymorphisms (SNPs) within this locus were implicated in the susceptibility to the disease and its main specific features.

Methods: Two case-control sets of Caucasian origin from the US and Spain were analysed, comprising a total of 2316 SSc cases and 2347 healthy controls. A meta-analysis was performed to test the overall effect of these genetic variants on SSc.

Results: The Mantel-Haenszel test under an allelic model revealed strong association signals in the ACA analysis for rs1131665 ($P_{FDR}=6.14\times10^{-4}$, OR=0.78, CI 95% 0.68–0.89), rs4963128 ($P_{FDR}=6.14\times10^{-4}$, OR=0.79, CI 95% 0.70–0.90), rs702966 ($P_{FDR}=3.83\times10^{-3}$, OR=0.82, CI 95% 0.72–0.93) and rs2246614 ($P_{FDR}=3.83\times10^{-3}$, OR=0.83, CI 95% 0.73–0.94). Significant *P*-values also were obtained when the global disease was tested; however, the statistical significance was lost when the ACA+ patients were excluded from the study, suggesting that these associations rely on ACA positivity. In addition, the combined analysis of the ACA+/ACA- comparison showed statistically significant differences between both SSc subgroups for rs1131665 ($P_{FDR}=0.015$, OR=0.80, CI 95% 0.69–0.93), rs4963128 ($P_{FDR}=0.035$, OR=0.85, CI 95% 0.74–0.98), and rs702966 ($P_{FDR}=0.029$, OR=0.83, CI 95% 0.72–0.96). Conditional logistic regression and allelic combination analyses suggested that the functional *IRF7* SNP rs1131665 is the most likely causal variant.

Conclusion: Our data show that variation in the *IRF7* genomic region is clearly associated with ACA susceptibility in SSc patients and, hence, it may represent a common risk factor for autoantibody production in autoimmune diseases.

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Atherosclerosis Biomarkers in Systemic Sclerosis—A Multiplex Analysis. Dinesh Khanna[1], Anagha A. Divekar[2], Ram Raj Singh[2], Mariana J. Kaplan[1], Maureen A. McMahon[3], Daniel E. Furst[2], Nagesh Ragavendra[3], Paul Maranian[2], Wenpu Zhao[1] and Karen M. Au[2]. [1]University of Michigan, Ann Arbor, MI, [2]UCLA Medical School, Los Angeles, CA, [3]UCLA David Geffen School of Medicine, Los Angeles, CA

Background/Purpose: Increasing evidence suggests that atherosclerosis is increased in systemic sclerosis (SSc) compared to healthy individuals. However, the pathogenesis of atherosclerosis in SSc remains unknown. This study aimed to identify markers of fibrosis, vasculopathy, and inflammation that may be involved in the pathogenesis of atherosclerosis in a female SSc cohort.

Methods: The multiplex antibody array, based upon enzyme-linked immunosorbent assay (ELISA) technology, can measure multiple proteins simultaneously within a single sample. We utilized a microplate-based multiplex platform (Aushon Biosystems SearchLight) to identify 100 proteins in plasma samples from females with SSc with no history of atherosclerosis (N=46). In addition, circulating type I Interferon (IFN) activity was quantified by exposing epithelial cells to SSc serum and quantifying IFN-inducible genes by real-time PCR. All subjects underwent bilateral carotid ultrasounds to quantify plaque and intima-medial thickness (IMT) and were read by a single reader (NR). Statistical analysis was performed using Wilcoxin rank-sum test and Spearman's correlation. Significance was determined at $P<0.05$; no statistical adjustment was performed for multiple-testing as this analysis was hypothesis generating.

Results: Mean age (+/− SD) of the subjects was 48.6 (+/− 13.3) years. Carotid plaque was detected in 21 (46%) of the SSc subjects. Multiplex analysis detected significant associations between biomarkers of inflammation, vasculopathy, and fibrosis with atherosclerosis in the SSc subjects. IL-2, IL-6, CRP, KGF, ICAM-1, endoglin, PAI-1, and IGFBP3 were associated with carotid plaque ($P<0.05$, Table 1). MPIF1, A-SAA, thrombomodulin, NTpBNP, and CC16 were correlated with carotid IMT ($P<0.5$, Table 2). Type I IFN signatures were not associated with plaque or CIMT in SSc.

Table 1. Proteins associated with carotid plaque in SSc

	BIOMARKER (pg/ml)	NO PLAQUE, mean(SD)	PLAQUE, mean(SD)	*P*-value
Inflammation	IL-2	3.0 (2.6)	5.0 (3.8)	0.03
	IL-6	11.0 (13.5)	25.2 (48.5)	0.05
	CRP	1627772 (2437838.6)	3856899.5 (4734651.2)	0.01
Vasculopathy	KGF	0.8 (2.1)	1.6 (2.1)	0.02
	ICAM-1	403423.3 (131159.9)	539301.8 (242768.3)	0.04
	Endoglin	22444.1 (9253)	28156.3 (8860.8)	0.04
Fibrosis	PAI-1	9607.8 (6527.1)	6680 (5898)	0.05
	IGFBP3	404848.8 (116838.8)	322117.3 (93709)	0.01

Table 2. Correlation of proteins with carotid IMT in SSc

	BIOMARKER	IMT (r)	*P*-value
Inflammation	MPIF-1	0.31	0.04
	A-SAA	0.31	0.04
Vasculopathy	Thrombomodulin	0.32	0.04
	NTpBNP	0.42	0.01
Fibrosis	CC16	0.37	0.01

Conclusion: Distinct biomarkers of inflammation, vasculopathy, and fibrosis are associated with carotid plaque and IMT in SSc. Factors associated with carotid IMT differ from those associated with plaque in SSc. Further studies are needed to confirm the validity of these associations in another SSc cohort and their putative role as biomarkers of vascular events in this disease.

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Immunochip Genotyping of 1,884 Systemic Sclerosis Cases and 4,325 Controls Reveals Novel Associations. Maureen D. Mayes[1], Olga Y. Gorlova[2], Lara Bossini-Castillo[3], Jose Ezequiel Martin[4], Jun Ying[2], Peter K. Gregersen[5], Annette T. Lee[6], Shervin Assassi[1], Sandeep K. Agarwal[1], Filemon K. Tan[1], John D. Reveille[1], Xiaodong Zhou[1], Frank C. Arnett[1], Fredrick M. Wigley[7], Laura K. Hummers[7], Marilyn Perry[1], Carmen Pilar Simeon[8], Patricia Carriera[9], Norberto Ortego-Centeno[10], Miguel Gonzalez-Gay[11], the Spanish Scleroderma Group[12] and Javier Martin[13]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]UT M. D. Anderson Cancer Center, Houston, TX, [3]Consejo Superior de Investigaciones Científicas (CSIC), Armilla (Granada), Spain, [4]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, [5]Feinstein Institute Medical Reschearch, Manhasset, NY, [6]Feinstein Institute Med Rsch, Manhasset, NY, [7]Johns Hopkins University, Baltimore, MD, [8]Hospital Valle de Hebron, Barcelona, Spain, [9]Madrid, Spain, [10]Hospital Clínico San Cecilio, Granada, Spain, [11]Hospital Marques De Valdecilla, Santander, Spain, [12]Granada, Spain, [13]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain

Background/Purpose: The goal of this study was to identify which single nucleotide polymorphisms (SNPs) were truly associated with systemic sclerosis (SSc) and to identify shared susceptibility loci between SSc and other diseases represented on the Immunochip.

Methods: Genotyping: Genotyping was performed using the Immunochip, which is a custom chip developed by the Immunochip Consortium and which contains 196,524 polymorphisms that provide deep coverage of loci previously reported from genome-wide association studies (GWAS) and candidate gene studies of major autoimmune and inflammatory diseases.

Cases and Controls: SSc was diagnosed on the basis of fulfillment of the 1980 criteria for the classfiication of systemic sclerosis or if 3 of 5 CREST features (Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, Telangiectasia) were present. Data on healthy controls were obtained from the Immunochip Consortium.

Data Analysis: After quality control measures were applied, a total of 1,884 SSc cases and 4,325 controls were included in the analysis. Case samples included white European-American subjects from the U.S. Scleroderma Registry (n=981, 88.6% female) and from the Spanish Scleroderma group (903 cases, 89.3% female). Control data on 3,993 race-matched U.S. subjects and 332 Spanish subjects were obtained from the Immunochip Consortium. P-values reported are adjusted for multiple comparisons by FDR-BH (False Discovery Rate using the step-up procedure of Benjamini and Hochberg).

Results: After quality control measures, the genotyping rate was 99.8% and 124,001 SNPs were included in the analysis.

As expected and previously reported in the SSc GWAS, the most highly associated loci (adjusted p-values ranging from 8.9×10^{-12} to 7.38×10^{-5}) included the major histocompatibility complex region (MHC) region on chromosome 6, *STAT4* on chromosome 2, *TNPO3/IRF5* on chromosome 7, and *BLK* on chromosome 8.

Aside from the regions noted above, 16 SNPs in 8 additional genes/intergenic gene regions were significantly associated with SSc with adjusted p-values ranging from 5.34×10^{-9} to 3.24×10^{-5}. These include *FAM69A* at 1p22 ($p=6.05\times10^{-7}$ for the most significant SNP), *IL12RB2* at 1p31 ($p=3.24\times10^{-5}$), *PARK7* at 1p36 ($p=6.73\times10^{-7}$), *DENND1B* at 1q31 ($p=1.75\times10^{-6}$), the intergenic region *LOC100121216/CXCR4* at 2q21 ($p=5.96\times10^{-7}$), *KIAA1109* at 4p27 ($p=5.34\times10^{-9}$), the intergenic region *LOC286016/LOC407835* at 7q32 ($p=2.32\times10^{-7}$) and *DDC* at 7p11 ($p=4.30\times10^{-6}$)

In addition, significant associations were seen with rare variants in 3 genes (*PER3, CD6*, and *IKZF4*) and 2 intergenic areas (*FCGR3A/FCGR2C* and *SMARCC2/RNF41*) but the numbers of subjects with these was quite small making estimates unreliable.

Conclusion: The Immunochip analysis has provided confirmation of previously reported genetic loci in SSc. In addition 8 genes/gene regions have been identified as potential susceptibility regions. The identification of rare variants, although affecting only a small number of subjects, deserves additional studies.

1495

Systemic Sclerosis As Prototypic Disease for Functional Antibodies Against Vascular Receptors: From Beside to Bench and Mouse Models. Angela Kill[1], Reinmar Undeutsch[2], Christoph Tabeling[3], Martin Witzenrath[4], Wolfgang M. Kuebler[5], Sebastian Bock[6], Rudi Samapati[5], Harald Heidecke[7], Ivo Lukitsch[3], Duska Dragun[4] and Gabriela Riemekasten[8]. [1]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, [2]Charité University hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, [3]Charité University Hospital, Berlin, [4]Charité University Hospital, Berlin, Germany, [5]Charité University Hosptial, Berlin, Germany, [6]Charité University Hospital and German Rheumatism Research Centre, a Leibiz, Berlin, Germany, [7]CellTrend GmbH, Luckenwalde, Germany, [8]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany

Background/Purpose: We have recently discovered functional cross-reacting autoantibodies against the angiotensin-II type-1 receptor (AT1R) and against the endothelin-1 receptor type A (ETAR) in the majority of patients with systemic sclerosis (SSc) linked with vascular and fibrotic complications and predicted disease-related mortality (Riemekasten et al. ARD 2011). The strong association between the presence of these antibodies with clinical SSc symptoms suggests a contribution of these antibodies in SSc pathogenesis. Due to the high homology of the receptors in different species we hypothesized comparable effects of the human antibodies in different species. Our aim was to test direct involvement of AT1R-Abs and ETAR-Abs on pathogenesis of SSc-lung involvement in vivo, ex vivo, and in vivo.

Methods: Biological effects of autoantibodies were studied *in vitro* in human microvascular endothelial cells and in human fibroblasts for induction of collagen synthesis, cytokines, and signaling pathways known to play a role in SSc. Blockers of AT1R and ETAR were used to determine the specificity of the effects. Small vessel myography of rat lung vessels was performed in the presence or absence of the natural ligands angiotensin II and endothelin-1. Direct effect of the antibodies on endothelial Ca influx was studied in vivo by using real-time fluorescence imaging (RFI). Finally, IgG from SSc patients with PAH and lung fibrosis highly positive for the presence of anti-AT1R and anti-ETAR antibodies as measured by a sandwich ELISA (CellTrend, Luckenwalde, Germany) were injected into C57BL/6 mice. BAL was performed 7 days after adoptive transfer.

Results: In microvascular endothelial cells, expression of different SSc-related cytokines and chemokines was induced that was partially ameliorated by AT1R or ETAR blockers. In fibroblasts, antibody-mediated induction of collagen-1 was completely ameliorated by both AT1R and ETAR blockers. The antibodies also amplified the vasoconstrictive responsiveness towards endothelin-1 and angiotensin II in pulmonary resistance vessels that could be blocked by corresponding receptor antagonists. There was no direct effect of the antibodies on vasoconstriction. Real-time fluorescence imaging revealed increased endothelial Ca influx in the presence of SSc-IgG not found in the presence of IgG from controls negative for anti-AT1R/ETAR antibodies. Finally, neutrophilic alveolitis was induced seven days after adoptive transfer.

Conclusion: Our data suggest a contribution of anti-AT1R and ETAR antibodies in SSc pathogenesis and revealed effects on different cells and species. Long-term in vivo experiments and long-term blockade will be performed to identify the full spectrum of the effects.

1496

Evidence for the Contribution of the X Chromosome to Systemic Sclerosis Susceptibility: Association with the Functional *IRAK1* 196Phe/532Ser Haplotype. Philippe Dieude[1], Matthieu Bouaziz[2], Gabriela Riemekasten[3], Paolo Airo[4], Martina Müller[5], Daniele Cusi[6], Gilles Chiocchia[7], Catherine Boileau[8], Yannick Allanore[9] and Genesys Consortium[10]. [1]Hopital Bichat, Paris, France, [2]Evry-genopole, France, [3]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [4]Brescia, Italy, [5]München, Germany, [6]Milano, Italy, [7]Institut Cochin, 75014 Paris, France, [8]Boulogne, France, [9]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [10]Paris

Background/Purpose: Several autoimmune disorders, including systemic sclerosis (SSc), are characterized by a strong sex bias. Until now, nothing is known about whether genes on the sex chromosomes can influence SSc susceptibility. Recently, an *IRAK1* haplotype that contains the 196Phe functional variant (rs1059702), located on Xq28, was found to confer susceptibility to systemic lupus erythematosus (SLE). OUr objective was to test for association with SSc the *IRAK1* SLE-risk haplotype.

Methods: We tested for association the *IRAK1* SLE-risk haplotype in a discovery set of 849 SSc and 625 controls. *IRAK1* rs1059702 was further genotyped in a replication set, which includes individuals from Italy (493 SSc, 509 controls) and Germany (466 SSc, 1083 controls), all individuals being of European Caucasian origin and of female gender.

Results: Association between the *IRAK1* haplotype and SSc was detected in the discovery set. In both discovery and replication sets the rs1059702 TT genotype was found to be associated with specific SSc subsets highlighting a potential contribution in disease severity. A meta-analysis provided evidence for an association between both T allele and TT genotype and the overall disease: OR 1.20 95%CI[1.06–1.35], P=0.003 and OR 1.49 95%CI[1.06–2.10], P=0.023, respectively. However, the most remarkable associations were observed with diffuse cutaneous, anti-topoisomerase I antibodies positive and SSc-related fibrosing alveolitis subsets: OR 2.35 95%CI[1.51–3.66], $P=1.56\times10^{-4}$, OR 2.84 95%CI[1.87–4.32], $P=1.07\times10^{-6}$ and OR 2.09 95%CI[1.35–3.24], $P=9.05\times10^{-4}$, respectively.

Conclusion: Our study provides the first evidence for an association between *IRAK1* and SSc, demonstrating that a sex chromosome gene directly influences SSc susceptibility and its phenotypic heterogeneity.

1497

Identification of Novel Genes Associated with Systemic Sclerosis Through Genome Wide Association Study Follow-up. Jose Ezequiel Martin[1], Jasper Broen[2], Olga Y. Gorlova[3], Madelon C. Vonk[4], Spanish Scleroderma Group[5], Alexandre Voskuyl[6], Annemie Schuerwegh[7], Marie Vanthuyne[8], Vanessa Smith[9], Rene Westhovens[10], Elfride de Baere[11], Alexander Kreuter[12], Gabriela Riemekasten[13], Roger Hesselstrand[14], Annika Nordin[15], Oyvind Palm[16], Paolo Airo[17], Nicolas Hunzelmann[18], Lorenzo Beretta[19], Filemon K. Tan[20], Frank C. Arnett[20], Maureen D. Mayes[20], Timothy Radstake[21], Javier Martin[22] and Bobby P.C. Koeleman[23]. [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, [2]Radboud University Nijmegen Medical Centre, Nijmegen, Nijmegen, Netherlands, [3]UT M. D. Anderson Cancer Center, Houston, TX, [4]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [5]Granada, [6]VU University Medical Center, Amsterdam, Netherlands, [7]Leids Univ Medisch Centrum, Leiden, Netherlands, [8]Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium, [9]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [10]University Hospital KU Leuven, Leuven, Belgium, [11]Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium, [12]Ruhr University Bochum, Bochum, Germany, [13]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [14]Lund University & Skåne University Hopsital, Lund, Sweden, [15]Karolinska Institute, Stockholm, Sweden, [16]Rikshospitalet, Oslo University Hospital, Oslo, Norway, [17]Brescia, Italy, [18]University of Cologne, Cologne, Germany, [19]IRCCS Fondazione Policlinico-Mangiagalli-Regina Elena & University of Milan, Milan, Italy, [20]University of Texas Health Science Center at Houston, Houston, TX, [21]Geert Groote Plein 8, Nymegen, Netherlands, [22]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [23]University Medical Center Utrecht, Utrecht, Netherlands

Background/Purpose: Systemic sclerosis (SSc) is complex autoimmune disease affecting the connective tissue; influenced by genetic and environmental components. Recently, we performed the first successful GWAS of SSc. Here, we perform a large replication study to better dissect the genetic component of SSc.

Methods: We selected 768 polymorphisms from the previous GWAS carried out in Caucasian individuals from Europe and US; and genotyped them in nine replication cohorts from Europe. Overall significance was calculated for replicated significant SNPs by meta-analysis of the replication cohorts and replication-GWAS cohorts (3,790 cases and 6,831 controls). Finally, we searched for differential association in the main SSc subgroups of limited (lcSSc) and diffuse (dcSSc) subtypes, and autoantibody positive for anti-centromere (ACA) and anti-topoisomerase I (ATA).

Results: We found evidence for replication and overall genome wide significance for one novel SSc genetic risk locus: *PSD3* (P value = 5.38×10^{-8}, OR = 1.451). Additionally, we found suggestive association in the loci *TMEM163* (P value = 4.50×10^{-7}, OR = 1.169) and *ADAMTS17* in the ATA+ subgroup (P value = 4.95×10^{-7}, OR = 1.392). As expected we strengthened the evidence for previously confirmed associations in the *CD247*, *STAT4*, *TNFAIP3*, *TNPO3*/*IRF5* and *IRF8* loci. Additionally, we shed new light on the association of *IRF5* with SSc, which suggests that this is a shared genetic risk factor with systemic lupus erythematosus.

Conclusion: This study significantly increases the number of known putative genetic risk factors for SSc, including the genes *PSD3*, *TMEM163* and *ADAMTS17*, and further confirms five previously described ones.

1498

Gut Fibrosis with Associated Diminished Colonic Contractility in a Transgenic Mouse Model of Scleroderma. Nora Thoua, Korsa Khan, Audrey Dooley, Emma Derrett-Smith and Christopher P. Denton. UCL Medical School, London, United Kingdom

Background/Purpose: Clinically significant gastrointestinal involvement occurs in up to 90% of patients with systemic sclerosis (SSc). Animal models of SSc mimic some of the pathophysiological disease processes of SSc and can help in the development of effective therapies. Animal models have helped to study different disease aspects such as systemic disease manifestations as well as organ damage such as lung fibrosis and pulmonary arterial hypertension. There is no mouse model to date that has specifically investigated the GI tract. The transgenic mouse strain TβRIIΔk-fib is characterized by ligand-dependent upregulation of TGF-β signalling and has been shown to develop skin fibrosis, lung fibrosis and diminished aortic ring contractility associated with adventitial fibrosis. We investigated if similar changes are observed in gut tissue in this mouse model.

Methods: Colonic tissue was examined using histology, immunohistochemistry and isolated organ bath studies. Gross tissue architecture was examined by haematoxylin and eosin stain (H&E), picrosirius red (staining for collagen) and immunohistochemical markers for alpha-smooth muscle actin (aSMA), phospho-Smad 2/3 (pSmad2/3) and Ki-67 (cell proliferation marker). To investigate the enteric nervous system, tissue was stained with PGP 9.5 (marker for general neural tissue) and S-100 (glial marker). Fibrosis was quantified using the NIS Elements BR 2.30 system (Nikon) allowing for quantification of the various colour wavelengths with pixels as the unit of measure. Colonic strip contractile responses to potassium chloride (KCl) and carbachol (a cholinergic agonist) were assessed in isolated organ baths and data was presented as % of maximal contraction.

Results: H&E staining showed no architectural differences between transgenic and wild-type mice gut tissue. However, a marked increase in collagen deposition in the transgenic mice compared to wild-type controls (% of tissue stained red: WT: 3.95±0.7 vs TG: 9.71±2, p=0.05). No significant difference was observed immunostaining for aSMA, Ki-67, pSmad2/3 between transgenic and wild-type control mice. There was no obvious difference in neural tissue staining. The organ bath studies showed colonic strip contractility was diminished in transgenic (TG) mice compared with wild-type (WT) controls to both KCl 80mM (WT: 53.5 ± 14.2 vs TG: 13.5 ± 12.8, p=0.022) and carbachol at the higher concentrations (10^{-5}: WT: 90.4 ± 8.7 vs TG: 50.6 ± 17.8; p=0.025 and 10^{-4}: WT: 64.6 ±7.2 vs TG: 31.97 ± 13.9; p=0.023).

Conclusion: We have shown that this transgenic mouse model previously shown to develop skin, lung and cardiac fibrosis also develops colonic fibrosis with associated effect in colonic tissue contractility. This may offer further insight in pathologic processes leading to the development of gut fibrosis as well as the effect in the gastrointestinal tract of therapies targeting fibrosis.

1499

Angiogenic Biomarkers Predict the Development of Digital Ulcers in Patients with Systemic Sclerosis. Jérôme Avouac[1], Christophe Meune[2], Andre Kahan[1], Gilles Chiocchia[3] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [2]Paris Descartes University, Cardiology department, Cochin Hospital, Paris, France, [3]Institut Cochin, 75014 Paris, France

Background/Purpose: To evaluate the possible merit of different endothelial markers for the prediction of ischaemic digital ulcers (DU). These biomarkers were also evaluated for the prediction of other microvasuclar complications that are pulmonary hypertension (PH), left ventricular (LV) dysfunction and scleroderma renal crisis (SRC).

Methods: Endothelial markers were assessed in a prospective cohort of 100 SSc patients without known cardiovascular involvement or severe comorbidities at presentation. Circulating endothelial progenitor cells (EPCs) and circulating endothelial cells (CECs) were quantified in peripheral blood by flow cytometry after cell sorting. Serum levels of placenta growth factor (PlGF), soluble vascular adhesion molecule (sVCAM) and vascular endothelial growth factor (VEGF) were measured by quantitative sandwich ELISA technique (Quantikine kits, R&D systems). The primary outcome was the occurrence during a planed 3-year follow-up of one or more new ischemic DU, defined by a painful area ≥2mm in diameter with visible depth and loss of dermis localized on fingertips. Secondary endpoint was the occurrence of at least one cardiac/vascular event, assessed by an exploratory composite index defined by the occurrence of at least one of the following event: a) one or more new ischemic DU, b) pre-capillary PH confirmed by RHC, c) left ventricular (LV) dysfunction, defined by a LV ejection fraction (EF)<50% d) SRC, defined by a sudden and marked increase in systemic blood pressure and acute renal failure.

Results: The mean ± standard deviation (SD) age of the 100 patients (89 women) was 56±13 year old and the mean ± SD disease duration was 9±8 years at baseline. Forty patients had the diffuse cutaneous subset, and 60 the limited. During the planned follow-up, seventeen patients developed new ischaemic DU (8 patients with a history of previous DU and 9 patients with no previous DU). Regarding other vascular complications, PH occurred in 5 patients, LV dysfunction in 4 and SRC in a single patient. By univariate analysis, low EPC counts (p=0.009), high PlGF (p=0.007) and sVCAM (p=0.04) serum levels were identified as predictive biomarkers of the occurrence of at least one new DU. Multivariate analysis including these three biomarkers and SSc-related disease characteristics identified high PlGF serum levels (HR: 5.04, 95% CI: 1.19–21.09) and a history of DU (HR: 9.51, 95% CI 1.54–58.77) as independent predictors of new DU. In an alternate model excluding patients with a history DU at baseline, low EPC counts (HR: 7.95, 95% CI 2.09–30.09) and high PlGF serum levels (HR: 13.46, 95% CI 1.58–114.73) were found as predictors of new DU. Regarding secondary outcome, Low baseline EPC counts (HR: 4.56, 95% CI 1.04–20.06, p=0.03) and elevated PlGF serum levels (HR 5.85 95% CI 1.42–24.15, *P*=0.02) were independent predictors in multivariate analysis of the occurrence of cardiac/vascular events, according to our exploratory index.

Conclusion: This study identified low circulating EPC counts and high PlGF serum levels as predictors of new DU in SSc. It highlights the critical role of angiogenesis in this vascular outcome. These markers may improve DU risk stratification and therefore allow earlier therapeutic intervention.

ACR/ARHP Poster Session B
Vasculitis I
Monday, November 7, 2011, 9:00 AM–6:00 PM

1500

Efficacy and Tolerance of Infliximab In Refractory Takayasu Arteritis: French Multicenter Study. Arsene Mekinian[1], Antoine Neel[2], Jean Sibilia[3], Pascal Cohen[4], Jerome Connault[5], Marc Lambert[6], Laure Federici[7], Sabine Berthier[8], jean Noel Feissinger[9], Bertrand Godeau[10], Isabelle Marie[11], Loic Guillevin[12], Mohamed Hamidou[5] and Olivier Fain[13]. [1]Jean Verdier Hospital, Bondy, France, [2]Nantes Hospital, Nantes, France, [3]Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, Strasbourg, France, [4]Service de médecine interne, Centre de Références des Vascularites, Université Paris Descartes, APHP, Hôpital Cochin, 75005 Paris, France, Paris, France, [5]Service de médecine interne, Hôpital Universitaire de Nantes, Nantes, France, Nantes, France, [6]Service de médecine interne, Hôpital Claude Huriez, Université Lille II, Lille, France, Lille, France, [7]Service de médecine interne, Hôpital Pasteur, F-68000 Colmar, France, Colmar, France, [8]Service de médecine interne, Hôpital Bocage, Dijon, France., Dijon, France, [9]Service de médecine vasculaire et d'hypertension artérielle, Université Paris 5, AP-HP, Hôpital HEGP, France, Paris, France, [10]Service de médecine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, Creteil, France, [11]Service de médecine interne, CHU de Rouen, Rouen, France., Rouen, France, [12]Cochin University Hospital, Paris, France, [13]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France

Background/Purpose: To analyze the efficacy and tolerance of infliximab in refractory Takayasu disease.

Methods: French multicenter retrospective study which included patients with Takayasu disease. Clinical disease activity was considered if the patient presented one of the following features: (1) new onset of carotodynia, pain over other large vessels or new ischemic vascular claudication, (2) transient ischemic episodes not attributed to other factors, (3) new bruit or asymmetry in pulses or blood pressure, (4) systemic features in the absence of infection or other factors. Biological activity was defined if the patient presented 2 of the following features: (1) VS>30 mm/h, (2) CRP>10 mg/l, (3) fibrinogen>3 g/l, (4) leukocyte count>10 10^3/mm^3 without any infection. Radiological activity was defined as the presence of at least 2 of the following features: (1) arterial wall thickening at angioscanner, (2) arterial wall thickening with mural enhancement in resonance magnetic imaging, (3) arterial hypermetabolism on PET-scan. Corticodependence was defined as prednisone≥20mg/day before infliximab.

Results: Fifteen patients with Takayasu disease (median age 41 years [17–61], 13 women) were included. At the time of infliximab beginning, 14 patients were treated with steroids (median dose 20 mg/day [5–35]), methotrexate (n=7) or azathioprine (n=4). Infliximab was used at 5 mg/kg [3–5] every 6 weeks [4–8]. Median follow-up after initiation of infliximab was 43 months [4–71]. A partial or good overall response was noted in 13/15 cases (87%), 10/13 (77%) and 8/11 cases (73%) at 3, 6, 12 months respectively. Clinical and biological activities were significantly decreased within 3 months (from 11 at baseline to 4 patients at 12 months; p<0.05), and similarly for corticosteroid dose (from 20 mg/day [5–35] at baseline to 6 mg/day [2.5–30] at 12 months; p<0.05). Only 1 patient was still steroid-dependent at 12 months (vs 8 cases before infliximab). C-reactive protein regressed from 30 mg/l [4–70] to 5 mg/l [0–57] and 6 g/l [0–50] at 3 and 6 months respectively (p<0.05). Side effects were 2 infusion-related reactions, 1 pulmonary tuberculosis, 1 severe bacterial infection and EBV reactivation. At the last visit, infliximab was continued in 7 patients (47%), and was discontinued in the 8 patients because of remission (n=3), inefficacy (n=2) or adverse reactions (n=3). In 3/8 patients infliximab was switched to adalimumab, which was effective in 1 case.

Conclusion: This study confirms the interest of infliximab in terms of clinical and biological response, as well as steroid-sparing agent.

1501

Takayasu Arteritis: Treatment and Outcome. An American Cohort of 126 Patients. Jean Schmidt[1], Tanaz A. Kermani[2], A. Kirstin Bacani[2], Cynthia S. Crowson[2], Eric L. Matteson[2] and Kenneth J. Warrington[2]. [1]Amiens University Hospital, Amiens, France, [2]Mayo Clinic, Rochester, MN

Background/Purpose: Takayasu arteritis (TA) is a rare inflammatory condition affecting the aorta and its branches. This chronic, relapsing disease is associated with significant morbidity, and treatment can be challenging. The aim of this study is to report the treatment and outcomes of a large cohort of patients with TA seen at a referral center in the USA.

Methods: We retrospectively studied a cohort of patients with newly diagnosed (within a year) TA evaluated at our institution between 01/01/1984 and 12/31/2009. ACR criteria for TA were used for inclusion (modified to include patients diagnosed between age 41 and 50 years). Disease activity was assessed according to the NIH (Kerr) criteria. Data are reported using descriptive statistics (median and [1^{st}-3^{rd} quartile of the distribution]); predictors of outcome were examined using Cox models.

Results: The cohort included 126 patients, predominantly white (82.5%) and female (91%). The median age at diagnosis was 31.5 years [22.9–39.6]. All patients had arteriographic abnormalities compatible with TA.

Eighty six percent of patients were treated with oral corticosteroids (CS). A CS sparing agent was prescribed in 56 % of patients, mainly methotrexate.

The longitudinal cohort was comprised of 79 patients followed for more than 1 year. The median length of follow up was 5.5 years [2.9–10.1]. After five years of follow up, 96 % of these patients had experienced remission of any duration, and 71 % sustained remission (remission of at least 6 months, while on <10 mg / day of prednisone). Among patients achieving remission (n = 77), 46 % experienced at least one relapse by 5 years after remission. The median time to achieve remission was 5 months [1.9–12.5]. The median time to achieve

sustained remission was 32 months [16.7–49.9]. The median time to first relapse was 8 months [3.4–23.3]. Factors associated with achieving a sustained remission were: an age at diagnosis above 40 (HR 9 (95 % confidence interval (CI) 1.4–55.3), p = 0.017), and a lower ESR at diagnosis (HR 0.88 per 10 mm/h (95 % CI 0.82–0.94), p < 0.001).

Vascular intervention was performed in 55% of the patients. The procedure success rate for open surgery (56 procedures) was 57%, and percutaneous angioplasty (20 procedures) was 35 %, p = 0.08.

Thirteen pregnancies were recorded in 10 women: 9 term deliveries, 2 preterm deliveries (newborns in good health), 1 miscarriage, and 1 medical abortion.

Among the 79 patients followed longitudinally, 10 developed infections, 9 cerebral ischemic disease, and 5 ischemic heart disease.

Survival at 10 years was 96.9 % ± 1.7, and survival at 15 years was 85.9 % ± 6.5. There were 6 deaths. The median age at death was 45.5 years [29–52], after a median follow up of 38 months [12–140].

Conclusion: Medical treatment achieves remission induction in most patients with TA, but almost half of the patients experience relapse. Open surgery may have better results than angioplasty. In this study, age at diagnosis above 40 years and a lower ESR at diagnosis were associated with increased likelihood of sustained remission.

1502

Tumor Necrosis Factor Inhibitors in Patients with Takayasu Arteritis: Experience From a Referral Center with Long-Term Follow-up. Jean Schmidt[1], Tanaz A. Kermani[2], A. Kirstin Bacani[2], Cynthia S. Crowson[2], Eric L. Matteson[2] and Kenneth J. Warrington[2]. [1]Amiens University Hospital, Amiens, France, [2]Mayo Clinic, Rochester, MN

Background/Purpose: Takayasu arteritis (TA) is a rare, primary vasculitis affecting the aorta and its branches, often characterized by a chronic course with disease relapses. There have been no randomized clinical trials to evaluate optimal therapy. A few case reports and small pilot studies suggest that tumor necrosis factor inhibitors (TNFi) may be effective for treating TA. We report our experience with use of TNFi in patients with TA seen at a major referral center in the USA.

Methods: We retrospectively studied a cohort of patients with newly-diagnosed TA evaluated at our institution between 01/01/2004 and 12/31/2009 and who received some TNFi in this period. The ACR criteria for TA were used for inclusion (modified to include patients diagnosed between age 41 and 50 years). Disease activity was assessed according to the NIH (Kerr) criteria: Sustained remission was defined as an inactive disease for at least six months while on a treatment regimen including prednisone <10 mg/day. Data are reported with descriptive statistics (mean (± SD), median [first-third quartile of the distribution]).

Results: We included 20 patients (19 women, 16 Caucasians), with a mean age of 33 years (± 10.2), and a median duration of disease of 15.9 months [2–32.7] at initiation of TNFi. The median total follow up for these patients was 54 months [34–82].

The indication for starting TNFi was active/relapsing disease in 19 patients (of whom 6 had new arterial lesions), and adverse effect of a previous treatment for 1 patient (alopecia due to mycophenolate mofetil).

Before use of TNFi, all 20 patients received prednisone at a median maximum daily dose of 60 mg [60–60]. Other prior immunosuppressive therapy included methotrexate in 18 patients, azathioprine in 5 patients, mycophenolate mofetil in 3 patients, and cyclophosphamide in 3 patients.

The TNFi used were infliximab in 17 patients, adalimumab in 2 patients, and etanercept in 1 patient. The median duration of treatment with TNFi was 15.24 months [8.45–31.96]. Eleven patients discontinued TNFi: 3 for treatment failure (1 relapse, 1 lack of steroid sparing effect, and 1 persistently active disease), 4 due to adverse effects (1 infection after hand surgery, 2 reactions to infusion, and 1 pancreatic cancer), 4 for other reasons.

Treatment with TNFi resulted in disease remission in 19/20 patients (time to achieve remission while on TNFi 3.6 months [1.4–6.2]), and sustained remission in 11 patients (time to achieve sustained remission 24.9 months (± 20)). Of 12 patients receiving 10 mg of prednisone or more at the time of starting a TNFi, 10 patients were able to taper prednisone below 10 mg, and 7 were able to stop prednisone. However 5/19 patients experienced relapse while on TNFi (time to relapse 2.9 months [2.9–4.1]). Despite good tolerance, two patients discontinued their treatment while in remission. Both experienced relapse with a new arterial stenosis, and both achieved remission again once the TNFi was resumed.

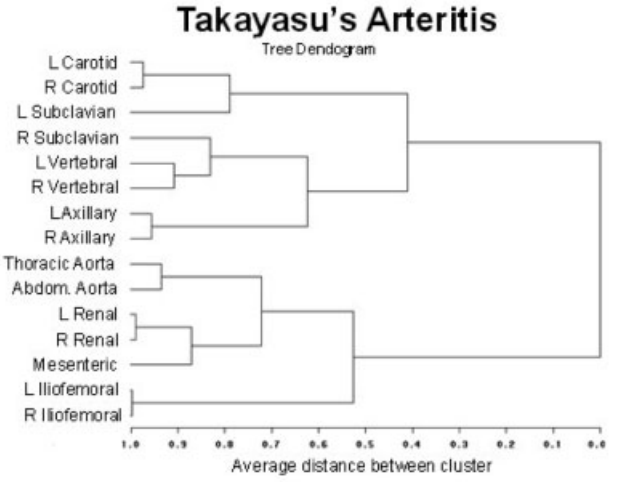
Conclusion: Treatment with TNFi can induce remission and even sustained remission in patients with refractory TA. However, drug continuation in our population was low and about 25% of our patients experienced disease relapse while on TNFi.

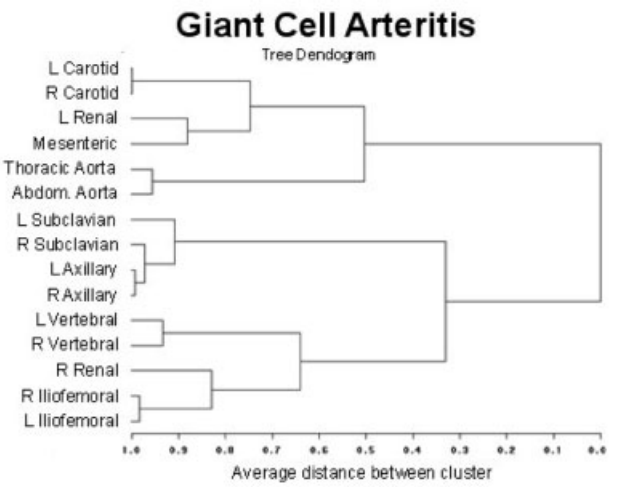
1503

Distribution of Large Artery Lesions in Takayasu's Arteritis Compared to Giant Cell Arteritis. Peter C. Grayson[1], Kathleen Maksimowicz-McKinnon[2], Tiffany M. Clark[3], Gunnar Tomasson[4], David Cuthbertson[5], Simon Carette[6], Nader A. Khalidi[7], Carol A. Langford[8], Paul A. Monach[9], Philip Seo[10], Kenneth J. Warrington[11], Steven R. Ytterberg[11], Gary S. Hoffman[12] and Peter A. Merkel[4]. [1]Boston University Medical Center, Boston, MA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Cleveland Clinic Foundation, Cleveland, [4]Boston University School of Medicine, Boston, MA, [5]University of South Florida, Tampa, FL, [6]Toronto Western Hospital, Toronto, ON, [7]McMaster University, Hamilton, ON, [8]Cleveland Clinic, Cleveland, OH, [9]Boston University, Boston, MA, [10]Johns Hopkins Vasculitis Center, Baltimore, MD, [11]Mayo Clinic, Rochester, MN, [12]Cleveland Clinic Found A50, Cleveland, OH

Background/Purpose: To compare the occurrence of aortic and primary branch arteriographic lesions in patients with large vessel vasculitis [Takayasu's arteritis (TAK) and giant cell arteritis (GCA)]; to determine if patterns of arteriographic disease differ between patients with TAK and GCA and between patients categorized by age at the time of disease onset; and to explore novel ways to classify large vessel vasculitis using computer-generated models of disease classification based upon patterns of arterial involvement.

Methods: Patients with arterial lesions (stenosis, occlusion, or aneurysm) on magnetic resonance angiography were selected from two North American cohorts of TAK and GCA. The frequency of lesions was calculated for 15 arteries: bilateral carotid, vertebral, subclavian, axillary, renal, and iliofemoral arteries; thoracic and abdominal aorta; and mesenteric arteries. Agglomerative, hierarchical cluster analysis was used to cluster arterial involvement. Tree diagrams were created to visualize clustering patterns in TAK and GCA and in subgroups defined by age at disease onset (<40 years; 40–55 years; and > 55 years). Latent class analysis was used to identify computer-derived subgroups of patients with large vessel vasculitis based upon patterns of arterial disease.





Results: Large arterial lesions were identified in 145 patients with TAK and 62 patients with GCA. There was significantly more left carotid ($p=0.03$) and mesenteric ($p=0.02$) artery disease in TAK and more left and right axillary ($p<0.01$) artery disease in GCA. There were no significant differences in involvement between disease subgroups in the 9 other large arteries studied. Similarities and differences in cluster patterns of arterial pathology were observed between the TAK and GCA subgroups (**Figure**). Arterial involvement was contiguous in the aorta and tended to be symmetric in paired branch vessels in both TAK and GCA. Subclavian involvement was different between TAK and GCA. Asymmetric subclavian disease with frequent left subclavian involvement was observed in TAK, and symmetric subclavian disease with concomitant axillary involvement was observed in GCA. Patterns of arterial disease for patients in the < 40 and the 40–55 year age groups at the time of disease onset resembled TAK and arterial patterns for patients in the > 60 year age group resembled GCA. Latent class analysis identified 3 subgroups of patients. Two subgroups, defining 26% and 18% of the dataset, were associated with the traditional diagnoses of TAK and GCA respectively. The majority of patients (56%), however, were classified into a subgroup that did not differentiate between TAK and GCA.

Conclusion: Strong similarities and subtle differences in the distribution of arterial disease were observed between TAK and GCA. These findings suggest that TAK and GCA may exist on a spectrum within the same disease.

1504

Outcome of Vascular Interventions in Takayasu Arteritis Using the Takayasu Arteritis Damage Score. Sivakumar M. Rajappa. Cerebrovascular and Vasculitis Research Foundation, Chennai, India

Background/Purpose: Takayasu's aorto-arteritis (TA) in India tends to present with vascular complications over time. We devised a clinical index to measure damage related to TA called the Takayasu Arteritis Damage Score (TADS). In North America, despite providing short term benefit, endovascular revascularization procedures are associated with a high failure rate in patients with TA. Using the TADS, we analyzed a large series of TA patients who underwent vascular interventions.

Objectives: To analyze the outcomes of vascular interventions in 232 patients with Takayasu's arteritis (TA) from India who were seen at the Cerebrovascular and Vasculitis Research Foundation (CVRF) at Chennai between 1988 and 2010.

Methods: TA database at CVRF were reviewed for the period 1988 to 2010. All patients received pre/post procedures immunosuppressive treatment with any combination of: corticosteroids, Azathioprine, Methoterate or Mycophenylate Mofetil and inteventions were performed when the arteritis was considered inactive with low Indian Takayasu's Arteritis Scores (ITAS). The primary outcome measure was patency of vessels as determined by repeated Digital Subtraction angiography or Computerized Tomography/ magnetic resonance angiography. The secondary outcome measures were: periprocedural complications, morbidity and mortality. Vascular Interventions performed were: Percutaneous transluminal angioplasty (PTA) with or without stenting for Carotids, Vertebrals, Subclavians, Renal arteries and Aorta; bypass grafts to Carotids, Inguinal and abdominal aorta/Inguinal arteries; Carotid endarterectomy, Coronary artery bypass surgery and Coronary angioplasty and stenting.

Results: 82 TA patients, underwent 122 vascular interventions. There were 31 men and 51 women. Mean age at onset of TA symptoms was 33.54 years with a mean disease duration of 8.9 years. The procedures performed were: Carotid angioplasty and stenting- 24, vertebral angioplasty and stenting-4, grafts from ascending aorta to Carotids-3, subclavian angioplasty and stenting- 16, renal angioplasty and stenting-26, angioplasty and stenting of Aorta- 14, coronary angioplasty and stenting- 24 and CABG Surgeries-11. The Mean follow up period was 136 months. Associated clinical features and drug therapy were recorded. Peri-operative complications included (infections- 5.3%, stroke- 8%, myocardial infarction-3.6%, renal failure-3.5%). There were no peri-procedural deaths. The patency of stents at 5 years was 92% and at 10 years was 83%. 18% of the total number of patients died and the TADS scores in fatal disease were higher than in non-fatal cases with good correlation between the duration of TA and total TADS scores.

Conclusion: Vessel occlusion is a major feature of TA. Recording a damage score (TADS) helps to delineate features associated with pulse loss and with long-term patency of stent procedures. Unlike the reports from North America, there is good long term patency of vascular interventions performed in TA patients treated with adequate immunosuppressive treatment pre/post interventions and when these interventions are done when the TA is inactive, as seen with low Indian Takayasu's Arteritis Scores.

1505

Tocilizumab: A Novel Therapy for Patients with Large-Vessel Vasculitis. Maria Grazia Catanoso[1], Luca Magnani[1], Nicolo Pipitone[1], Annibale Versari[1], Lucia Dardani[1], Lia Pulsatelli[2], Riccardo Meliconi[3], Luigi Boiardi[1] and Carlo Salvarani[1]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]Istituto Ortopedico Rizzoli, Bologna, Italy, [3]Istituto Ortopedico Rizzoli and University of Bologna, Bologna, Italy

Background/Purpose: Treatment of large vessel vasculitis (LVV) remains challenging. Patients usually respond to glucocorticoid (GC) therapy, but often relapse on tapering of the GC dose or after GC withdrawal. In addition, GC are fraught with numerous adverse events. The aim of this study was to assess the efficacy and safety of the anti-IL-6 receptor (IL-6R) antibody tocilizumab (TCZ) in patients with LVV.

Methods: Six patients with active LVV (one with giant-cell arteritis, four with Takayasu arteritis, and one with thoracic aortitis and retroperitoneal fibrosis) received monthly TCZ (8 mg/kg/ bodyweight) infusions for six consecutive months. Two patients were treatment-naïve patients (both with Takayasu arteritis), while the other four had relapsing disease which had failed to respond to immunodepressive drugs, including TNF-α blockers and abatacept. Disease activity and drug tolerability were assessed clinically and by laboratory tests at study entry and subsequently every month, while ^{18F}-Fluorodeoxyglucose positron emission (PET) was performed before and after TCZ treatment. In addition, a semiquantitative clinical evaluation was performed at baseline and at 3 and 6 months as well as every 3 months during follow-up using the ITAS (Indian Takayasu Activity Score) and the Kerr indices. After TCZ treatment, methotrexate was started as maintenance therapy in the two treatment-naïve patients, while the other patients continued with their previous treatments (three methotrexate and one mofetil mycophenolate).

Results: All patients treated with TCZ therapy had a satisfactory clinical and laboratory response (Table 1), while PET findings significantly improved in all cases. No serious adverse events were noted. Follow-up data are available for 5/6 patients. Three patients remain in clinical and laboratory remission, while two patients suffered a clinical relapse associated with an increase in inflammatory markers.

Table 1. Clinical data and laboratory findings before/after TCZ therapy

	ESR (mm/1h)	CRP (mg/dl)	ITAS	KERR
PT 1	45/3	4.02/0.06	4/0	4/0
PT 2	67/2	0.99/0.05	3/0	4/0
PT 3	84/2	4.80/0.01	8/0	4/1
PT 4	95/4	5.42/0.07	3/0	4/2
PT 5	33/6	4.27/0.12	3/0	3/1
PT 6	69/12	0.88/0.04	2/0	4/0

PT: patient; Normal values: Erythrocyte Sedimentation Rate (ESR) <40 mm/1st h; C-Reactive Protein (CRP) <0.5mg/dl; ITAS <1; Kerr ≤2

Conclusion: In this small group of patients with LLV, treatment with TCZ was effective and well tolerated. Further, larger studies are required to confirm our findings.

1506

Leflunomide in Takayasu Arteritis—Results from an Observational Study. Alexandre W. S. de Souza[1], Morgana D. da Silva[1], Luiz Samuel G. Machado[1], Ana Cecilia D. Oliveira[1], Frederico A. G. Pinheiro[1] and Emilia I. Sato[2]. [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil

Background/Purpose: Takayasu arteritis (TA) is a large vessel vasculitis that affects the aorta, its main branches, pulmonary and coronary arteries. Use of immunosuppressive agents such as methotrexate, azathioprine, mycophenolate mofetil and cyclophosphamide has been evaluated in TA either in open-label studies or in several cohort studies with positive results. Leflunomide was first reported in a patient resistant to corticosteroid and methotrexate with a successful result and it was used by 6% of patients with TA followed-up in a cohort study. The objective of this study is to evaluate the efficacy of leflunomide to control disease activity in patients with TA refractory or intolerant to conventional treatment.

Methods: Prospective open-label study, where TA patients with active disease based on clinical assessment, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and magnetic resonance angiography

(MRA) received leflunomide 20mg/day for at least 6 months. Adverse events attributable to leflunomide were also recorded.

Results: The study comprised 15 patients with TA with a mean age of 36.2 years followed for a mean of 9.1 months. At baseline, 14 TA patients had active disease despite therapy with corticosteroids and immunosuppressive agents, while intolerance to current treatment was observed in one patient. In the follow-up visit, we found a significant decrease in the frequency of patients with active TA (93% vs. 20%; $P = 0.002$), in the mean daily dose of prednisone (34.2 mg vs. 13.9 mg; $P < 0.001$) and in the median values of ESR (29.0 vs. 27.0 mm/hour; $P = 0.012$) and of CRP (10.3 vs. 5.3 mg/L; $P = 0.012$). Two patients (13.3%) developed new angiographic lesions in the follow-up MRA. Three patients (20%) experienced mild adverse events during the study and none discontinued therapy.

Conclusion: this the first open label study showing improvement of disease activity and acute phase reactants with 20 mg/day of leflunomide in TA patients who are refractory or intolerant to conventional therapy with corticosteroids and immunosuppressive agents. Leflunomide was safe and a steroid sparing effect was also observed. A double blind controlled study is desirable to confirm this finding.

1507

Tocilizumab for the Treatment of Large Vessel Vasculitis (Giant Cell Arteritis, Takayasu Arteritis) and Polymyalgia Rheumatica: A Case Series. Sebastian Unizony[1], Luis Arias-Urdaneta[1], Eli Miloslavsky[2], Sheila L. Arvikar[1], Arezou Khosroshahi[1] and John H. Stone[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hopsital, Boston, MA

Background/Purpose: Glucocorticoids (GC) are still the mainstay of therapy for giant cell arteritis (GCA), polymyalgia rheumatica (PMR), and Takayasu arteritis (TA). A sizeable percentage of these patients experience disease exacerbations upon GC tapering and require repeated GC courses, resulting in prolonged GC exposure and adverse effects. Interleukin (IL)-6 is an attractive target for therapy in these conditions because patients with GCA, TA, and PMR have increased levels of this cytokine in their peripheral circulation and inflamed tissues, and serum IL-6 concentrations correlate with disease activity. We retrospectively assessed the outcomes of 7 patients with large-vessel vasculitis (GCA and TA) and PMR treated with tocilizumab (TCZ), an anti IL-6 receptor humanized monoclonal antibody.

Methods: Patients with GCA, TA and PMR refractory to conventional therapy received monthly infusions of TCZ (8 mg/kg). Six subjects had failed at least one disease-modifying anti-rheumatic drug (methotrexate, azathioprine, or cyclophosphamide) or infliximab in addition to prednisone. Clinical improvement was assessed by evaluating symptoms of disease activity, inflammatory markers, ability to taper prednisone, and serial cross-sectional imaging when necessary before and during TCZ therapy. IL-6 level was measured at baseline and before each TCZ infusion.

Results: Seven patients with GCA (n = 4), TA (n = 2), or PMR (n = 1) received TCZ. The mean duration of disease at the time of anti-IL6R therapy initiation was 18 months (range 11–28), and the mean follow up on TCZ was 5.1 months (range 4–6). Clinical signs of active inflammation disappeared in all patients following the initiation of TCZ. Within eight weeks, all subjects were able to taper their prednisone dose to a mean of less than 5 mg. Before TCZ, the patients had experienced an average of 2 flares per year. Since the initiation of TCZ, all patients have entered and maintained remission. The mean erythrocyte sedimentation rate (ESR) declined from 36.8 mm/h (range 10.6–66) to 7.6 mm/h (range 3.2–14.6) after the start of TCZ (P = 0.001). The mean C-reactive protein (CRP) concentration declined from 22.4 mg/L (range 5.6–32.7) at baseline to 2.8 mg/L (range 0.28–13.4) after anti-IL-6R therapy (P = 0.001). The mean prednisone dose was tapered from 18.3 mg/day (range 7–34.3) to 4.9 mg daily (range 0–6.5) following the initiation of TCZ (P = 0.007). Baseline IL-6 levels were elevated in all except one TA patient [Mean 13.8 pg/ml (range 2.8–18.4)]. In 6 cases, the IL-6 concentration increased after the initiation of TCZ [mean 128.3 pg/ml (range 30.9–308)]. Serial positron emission tomography (PET) studies in one TA patient revealed complete resolution of fluorodeoxyglucose uptake in the great vessels after 4 TCZ infusions. No patient required treatment with other immunosuppressive medications while on TCZ. Adverse effects related to TCZ included mild neutropenia (n=2) and transaminitis (n=3).

Conclusion: IL-6 is important in the pathogenesis of GCA, TA and PMR. TCZ led to prompt clinical, serological and radiographic improvement in a group of patients with persistent disease who were unable to taper prednisone below acceptable doses despite concomitant second-line immunomodulatory agents.

1508

Results of a Randomized Controlled Study of Adalimumab for Steroid Sparing in Patients with Giant-Cell Arteritis. Xavier Mariette[1], Gabriel Baron[2], Eric Hachulla[3], Michel DeBandt[4], C. Larroche[5], Xavier Puéchal[6], Francois Maurier[7], B. de Wazieres[8], T. Quemeneur[9] and Philippe Ravaud[10]. [1]Université Paris-Sud, Le Kremlin Bicetre, France, [2]Epidemiology, Paris, France, [3]Internal Medicine, Lille CEDEX, France, [4]Abstract Medical Int'l, Boulogne, France, [5]Hospital University Bobigny, France, [6]Le Mans General Hospital, Le Mans, France, [7]Division of internal Medicine, CHR Metz, Metz, Metz, France, [8]CHU de Nimes, Nimes, France, [9]CHR de Valenciennes, Valenciennes, France, [10]Hopital Hotel Dieu, Paris Descartes University, Paris, France

Background/Purpose: Steroid is the basis of treatment of giant-cell arteritis (GCA) with very good efficacy but frequent drug dependence leading to side effects. Some case reports suggest that anti-TNF therapy could be useful in case of steroid dependence. Last, in rheumatoid arthritis, anti-TNF therapy given in very early disease associated with DMARDs can induce remission which may be sustained even after withdrawal of biologic therapy.

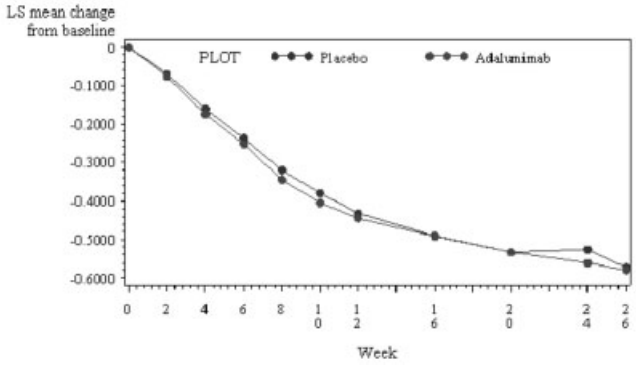
We evaluated the possibility that the association to steroids of a 10-week treatment of adalimumab (ADA) at the beginning of the treatment of GCA could allow a more rapid decrease of steroids without any increase risk of relapse.

Methods: Patients with GCA fulfilling 1990 Hunder criteria were randomized at diagnosis in 2 groups: prednisone (PDN) 0.7mg/kg + adalimumab 40mg or PDN 0.7mg/kg + placebo (PLA) SC at W0, W2, W4, W6, W8, W10. In responder patients, PDN was tapered progressively according to a fixed protocol and the primary end-point was the percentage of patients with less than 0.1 mg/kg of PDN at W26.

Results: 70 patients were included, 34 in the ADA arm, 36 in the PLA arm. 10 patients did not receive the 10-week procedure, 7 in the ADA arm (4 consent withdrawals, 1 serious adverse event (SAE) and 2 unknown reasons), 3 in the PLA arm (2 SAE and 1 death at W4). Analysis was done in intention to treat. At baseline, data were comparable between the ADA and the PLA groups: mean age 73.9 +/− 7.8 years and 73.9 +/− 9.2 years; mean CRP 66 +/− 66 mg/l and 61 +/− 68 mg/l; 1st hour ESR 69 +/− 34 mm and 69 +/− 34 mm; mean Hb level 11.6 +/− 1.6 g/dl and 11.5 +/− 1.4 g/dl.

Serious adverse events occurred in 20.8% and 48.6% of patients in ADA and PLA arms, respectively. 2 patients died in the PLA arm at W4 and W26 (from septic shock and from cancer) and 1 patient died in the ADA group from septic shock but without having received any injection of ADA. Serious infections occurred in 3 patients with ADA (septic shock, shingle and pneumonia) and in 5 patients with PLA. Cancer was observed in 1 patient in each group.

The primary end-point was not achieved: the percentage of patients in remission at 6 months with less than 0.1 mg/kg of PDN was 47.1% and 47.2% in the ADA and PLA arm, respectively. A sensitivity analysis on the 60 patients having effectively received the 10-week procedure gave identical non significant results: 60.0% and 47.2% in the ADA and PLA arm, respectively, p=0.20.The dose decrease of steroids with time was the same in the 2 groups:



Conclusion: In patients with GCA, a 10-week treatment of ADA, associated with a classical dose of steroids does not allow to decrease the percentage of patients in remission at 6 months with less than 0.1 mg/kg of steroids. The safety profile was the same between both groups with no unusual side effects observed with ADA in this group of aged patients with co-morbidities.

1509

Impairment of the Elastic Properties of Aorta and the Carotid Artery System in Patients with Takayasu's Arteritis. Selen Yurdakul[1], Fatma Alibaz Oner[2], Yelda Tayyareci[1], Haner Direskeneli[2] and Saide Aytekin[1]. [1]Florence Nightingale Hospital, Istanbul, Turkey, [2]Marmara University, School of Medicine, Istanbul, Turkey

Background/Purpose: Takayasu's arteritis (TA) is a chronic, inflammatory vasculitis of the aorta and its major branches. In this study, we aimed to evaluate aortic and carotid artery elastic properties and to assess carotid arterial mechanics by using a novel strain imaging method, "velocity vector imaging" (VVI).

Methods: We studied 20 patients with TA (F/M:18/2, mean age: 34.8±7.9 years) and 15 healthy controls (HC)(F/M: 14/1, mean age: 33.9±7.0 years). All patients and HC were assessed for aortic strain, stiffness, distensibility, carotid artery stiffness index and carotid artery intima-media thickness (CIMT) measurements. Additionally, VVI analysis was performed to determine longitudinal and radial tissue motion of the common carotid arteries (CCA), by off-line analysis of standard B-mode ultrasound images.

Results: Aortic strain was significantly impaired in patients with TA, compared to the control group (4.8±3.0% vs 14.4±5.5%, p=0.0001), whereas aortic stiffness (8.8±5.1 vs 2.3±1.4, p=0.0001) and carotid artery stiffness index (5.4±2.6 vs 1.7±0.6, p=0.0001) were markedly increased. Similarly, we observed a significant decrease in aortic distensibility in patients with TA (0.9±0.5 vs 1.3±0.5, respectively, p=0.03). Peak longitudinal strain and strain rate values were also significantly impaired in TA (Strain: 1.1±0.3% vs 5.9±0.7%, p=0.011; Strain rate: 0.3±0.1% vs 0.5±0.3, p=0.008). Total longitudinal displacement measurements were similar between the patient group and HC (p=0.13). However, peak radial velocity was decreased (0.1±0.02 cm/s vs 0.3±0.1 cm/s, p=0.02), while time to peak radial velocity was markedly increased in the patient group (208±49 ms vs 139±40 ms, p=0.0001). CIMT was also significantly increased in the patient group (0.1±0.02 cm vs 0.06±0.01 cm, p=0.0001).

Conclusion: TA is associated with reduced elasticity of the aorta and the carotid artery system. Longitudinal and radial wall motion of CCA is also impaired in patients with TA, possibly due to the vascular involvement. VVI is a feasible, novel "strain" imaging method in assessing the mechanical properties of the large arteries in systemic vasculitides.

1510

Giant Cell Arteritis with or without Suspicion of Aortitis At Diagnosis. A Retrospective Study of 22 Patients with a 12-Year Follow-up. Olivier Espitia[1], Antoine Néel[1], Christophe Leux[2], Jerome Connault[3], Thierry D. Ponge[4], Benoît Dupas[2], Mohamed Hamidou[3] and Christian Agard[1]. [1]Internal Medicine, Nantes University Hospital, Nantes, France, [2]Nantes University Hospital, Nantes, France, [3]Service de médecine interne, Hôpital Universitaire de Nantes, Nantes, France, Nantes, France, [4]Hotel-Dieu, Nantes CEDEX 1, France

Background/Purpose: During giant cell arteritis (GCA), aortitis is frequently suspected, up to 30–50% of cases, using different medical imaging techniques. Images of aortic involvement may be non symptomatic and their real outcome remain elusive. The objective of this study was to describe the long-term outcome of patients with or without suspicion of aortitis at the time of diagnosis of GCA.

Methods: In 1999, 22 patients with newly diagnosed biopsy-proven GCA were explored using aortic computed tomodensitometry (CT). Ten patients (group 1) had aortic inflammatory thickenings ≥ 3mm (n=7) and/or aneurism (n=3), whereas 12 patients had no suspicion of aortitis (group 2). A retrospective study of these 2 groups was conducted in 2011. We contacted and questioned the patients, their family and general practitioner, and analysed each medical file. The following items were investigated: demographic data, cardio-vascular risk factors, total and cardio-vascular mortality, cardio-vascular events, GCA relapses, corticosteroids regimen. Satistics were made using R development Core Team (2009) software.

Results: Seventeen women and 5 men (mean age at diagnosis=73.7±7.2y) were included. Inflammatory parameters and cardio-vascular risk factors were similar in group 1 and 2. The mean follow-up was 94.8 months. Twelve years after diagnosis of GCA, the total mortality was 50% without differences between group 1 (7/10) and group 2 (5/12). However, the 12y cardio-vascular mortality was statistically higher in patients with initial suspicion of aortitis (50%), than in patients without (0%, p=0.029, Log rank test). In group 1, the causes of deaths of cardiovascular origin were: rupture of abdominal aortic aneurism (n=1), thoracic aortic dissection (n=1), stroke (n=1), heart failure (n=1), peripheral arterial disease (n=1). Twelve cardio-vascular events occured in 7/10 patients of group 1 whereas only 5 occured in 4/12 patients of group 2. Stroke were statistically more frequent in group 1 (40% vs 0% in group 2, p=0.03). Recurrent GCA relapses were noted in 5/10 patients of group 1, 0/12 patients of group 2 and this difference was statistically significant (p=0.01). Moreover, definitive steroid treatment discontinuation was more frequent in group 2 (n=2) than in group 1 (n=8, p<0.05).

Conclusion: Despite the limitations due to its retrospective character and its small number of patients, our study suggests that GCA clinical course may differ according to initial CT signs of aortic involvement. CT suspicion of aortitis may lead to aortic fatal events and aortic thickenings deserve to be monitored. Initial aortic CT involvements seem to sign a particular form of GCA, with higher rate of cardio-vascular events and mortality, and with frequent relapses requiring longer steroids treatment.

1511

Increased Mortality in Giant Cell Arteritis with Large Vessel Disease: A Population-Based Cohort Study. Tanaz A. Kermani, Kenneth J. Warrington, Cynthia S. Crowson, Steven R. Ytterberg, Gene G. Hunder, Sherine E. Gabriel and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: To evaluate all-cause mortality in a population-based incident cohort of patients with giant cell arteritis (GCA) with large vessel disease.

Methods: A population-based cohort of patients diagnosed with GCA between January 1, 1950 and December 31, 2004 was studied. Cases of large vessel involvement were identified from medical records. We defined large vessel involvement as large artery stenosis, aortic aneurysm and/or aortic dissection that developed in the 1 year prior to GCA diagnosis or any time after. Diagnosis was based on imaging studies, pathology or autopsy. Patients were followed until death, last contact, or December 31, 2009. We evaluated mortality in GCA patients with large vessel disease compared to GCA patients without this manifestation, and then evaluated survival of GCA patients with large vessel disease to that expected in the general population. Cox proportional hazards models with time-dependent covariates were used to evaluate the influence of large vessel involvement on death after adjusting for age, sex and calendar year. Overall survival was estimated using Kaplan-Meier methods and compared to expected survival for the US population.

Results: Our study included 204 patients; 163 women (80%) and 41 men (20%). Mean age at diagnosis of GCA was 76.0 years (± 8.2 years) with a median length of follow-up 8.8 years (1996 total person-years). We observed 63 large vessel events including 27 large artery stenoses and 36 aortic aneurysms and/or dissections. Twelve patients had an aortic dissection.

Compared to GCA patients without this manifestation, patients with large vessel disease had an increased mortality (HR: 2.4; 95% CI: 1.6–3.6). This was significantly increased in the subset of patients who developed aortic aneurysm (HR: 3.4; 95% CI: 2.2, 5.4) and aortic dissection (HR: 155; 95% CI: 60–400). While there was a trend toward increased mortality in GCA patients with large artery stenosis (HR: 1.5; 95% CI: 0.9, 2.5), this did not achieve statistical significance.

Overall survival of the patients in the cohort was similar to that expected in the general US population (p=0.19). However, compared to the general population, GCA patients who developed any large vessel manifestation had a significantly decreased survival, p<0.001 (Figure). All-cause mortality was increased in the subset of GCA patients with an aortic aneurysm (p<0.001) and aortic dissection (p<0.001) but not in patients with large artery stenosis (p=0.11).

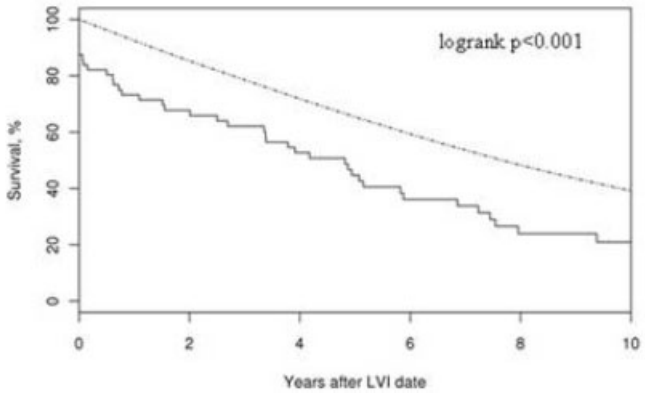


Figure. Survival in 56 patients with GCA who developed large vessel involvement (solid line) compared to expected survival in the US population (dashed line).

Conclusion: Development of aortic aneurysm and/or aortic dissection is associated with increased mortality in GCA. Screening efforts should focus on this serious complication but further studies are needed to determine the optimal screening modality and frequency.

1512

Statin Exposure and Risk of Giant Cell Arteritis: A Case Control Study. Jean Schmidt[1], Tanaz A. Kermani[2], Cynthia S. Crowson[2], Eric L. Matteson[2] and Kenneth J. Warrington[2]. [1]Amiens University Hospital, Amiens, France, [2]Mayo Clinic, Rochester, MN

Background/Purpose: In addition to their lipid-lowering properties, statins are known to have immunomodulatory and anti-inflammatory effects. A recent study reported that statin exposure is associated with a reduced risk of developing rheumatoid arthritis. Statins may influence other inflammatory conditions such as giant cell arteritis (GCA). The primary goal of this study was to examine a potential association between statin exposure and the risk of developing GCA. The secondary goals were to compare the clinical features and course of patients with GCA with/without statins.

Methods: Using a retrospective case-control study design, we reviewed the medical records of all patients with biopsy-proven GCA who fulfilled ACR criteria diagnosed between January 1, 1998 and December 31, 2008.The index date was the date of the temporal artery biopsy. Statin use at index date was recorded; statin use after diagnosis of GCA was not considered. Population-based controls (without GCA) were randomly selected. One control was matched with each case by sex, age, and calendar year. Data is presented as medians with first and third quartile of the distribution. The association between statin exposure and the risk of GCA was analyzed using a conditional logistic regression model, with adjustment for cardiovascular risk factors.

Results: We studied 297 patients with GCA (73 % female; mean age at diagnosis 75 years). At index date the rate of statin exposure was 18.1 % for the cases, versus 33.3 % for the controls ($p < 0.001$). Statin exposure was associated with a marked reduction in the risk of GCA: crude odds ratio (OR) 0.37 (95 % CI 0.27–0.58), $p < 0.001$. The OR was 0.31 (95 % CI 0.15–0.6), $p < 0.001$ after adjustment for comorbidities including hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, personal history of myocardial infarction, stroke, lower limb claudication, body mass index > 25 kg/m^2, and family history of ischemic heart disease.

In patients with GCA the presenting clinical features were similar between patients receiving statins compared to those who were not on statins at diagnosis (i.e. headache, abnormal temporal artery, jaw claudication, polymyalgia rheumatica symptoms, visual symptoms, constitutional signs). There was no significant difference in the acute phase reactants at diagnosis of GCA between patients on statins or not (ESR 64 [53–96] mm/h versus 69 [43–95] mm/h, $p = 0.92$; CRP 48.7 [35–94] mg/L versus 56.5 [27–100] mg/L, $p = 0.88$ respectively).

Follow-up data were available for 197 patients with GCA. In this sub-group the median follow-up was 56 [34–88] months. There was no statistically significant difference between the exposed (to statins) and non-exposed patients with GCA in relapse-rate, number of relapses, and relapse-free survival.

Conclusion: In this study, statin exposure was associated with a marked reduction in the risk of GCA, even after adjustment for cardiovascular risk factors. While it is unknown how statins reduce the risk of GCA, statin use at the time of diagnosis does not appear to modify the clinical presentation or the course of the disease.

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Relapses Among Patients with Giant Cell Arteritis. Tanaz A. Kermani[1], Kenneth J. Warrington[1], David Cuthbertson[2], Simon Carette[3], Gary S. Hoffman[4], Nader A. Khalidi[5], Curry L. Koening[6], Carol A. Langford[7], Kathleen McKinnon-Maksimowicz[8], Carol McAlear[9], Paul A. Monach[9], Philip Seo[10], Peter A. Merkel[9] and Steven R. Ytterberg[1]. [1]Mayo Clinic, Rochester, MN, [2]University of South Florida, Tampa, FL, [3]Toronto Western Hospital, Toronto, ON, [4]Cleveland Clinic Foundation, Cleveland, OH, [5]McMaster University, Hamilton, ON, [6]University of Utah, Salt Lake City, UT, [7]Cleveland Clinic, Cleveland, OH, [8]University of Pittsburgh, Pittsburgh, [9]Boston University School of Medicine, Boston, MA, [10]Johns Hopkins Vasculitis Center, Baltimore, MD

Background/Purpose: To evaluate the frequency, timing and clinical features of relapses in a prospective, multicenter, longitudinal cohort of patients with giant cell arteritis (GCA).

Methods: Patients with GCA enrolled in a prospective, multicenter, longitudinal study were included in the analysis. At each quarterly visit, standardized forms were used to collect clinical information. We defined relapse as either new disease activity after a period of remission or worsening disease activity. Kaplan-Meier method was used to evaluate time to first relapse in the subset of patients with newly diagnosed GCA.

Results: The study included 128 subjects – 102 women (80%) and 26 men (20%). Mean (±SD) age at diagnosis of GCA was 69.9 (±8.6) years. Mean follow-up for the cohort was 21.4 (±13.9) months. Median duration of disease at study enrollment was 4.6 (interquartile range (IQR): 1.2, 16.8) months.

At baseline evaluation, 49 patients with GCA (39%) reported at least 1 prior relapse. During follow-up 59 relapses were observed in 44 patients (34%); 10 patients (8%) experienced 2 or more relapses. Symptoms at relapse are summarized in the Table. At relapse 34 patients were receiving glucocorticoids. Other medications at the time of relapse were methotrexate (13 patients), anti-TNF therapy (2 patients), and mycophenolate mofetil (2 patients).

Disease activity at the time of relapse was rated as "low" in 30 flares and "moderate" in 15 flares. In 42 flares with active disease at the time of evaluation, mean ESR at relapse was 32 (±16) mm/hour with mean CRP of 13.5 (±12.9) mg/L. ESR was elevated during 25 flares (60%) while C-reactive protein was elevated in 22 flares (52%) ($p > 0.05$ for difference). Both test results were normal in 14 relapses (33%) despite active symptoms.

Sixty-nine patients (53%) were enrolled within 4 months of diagnosis. Time to first relapse in this subset is shown in the Figure with 24% of subjects experiencing a first relapse within 12 months after diagnosis.

Table. Clinical manifestations of giant cell arteritis during 59 relapses

Symptom	Number (%)
Cranial	32 (54%)
Headache	25
Scalp tenderness	19
New temporal artery pain	6
Carotidynia	2
Jaw/tongue claudication	8
Visual	3 (5%)
Partial vision loss	1
Diplopia	1
Ischemic retinopathy	1
Musculoskeletal	38 (64%)
Polymyalgia rheumatica	24
Arthralgias	19
Limb claudication	5 (9%)
Upper extremity claudication	5
Lower extremity claudication	1
Constitutional (weight loss, fatigue)	8 (14%)

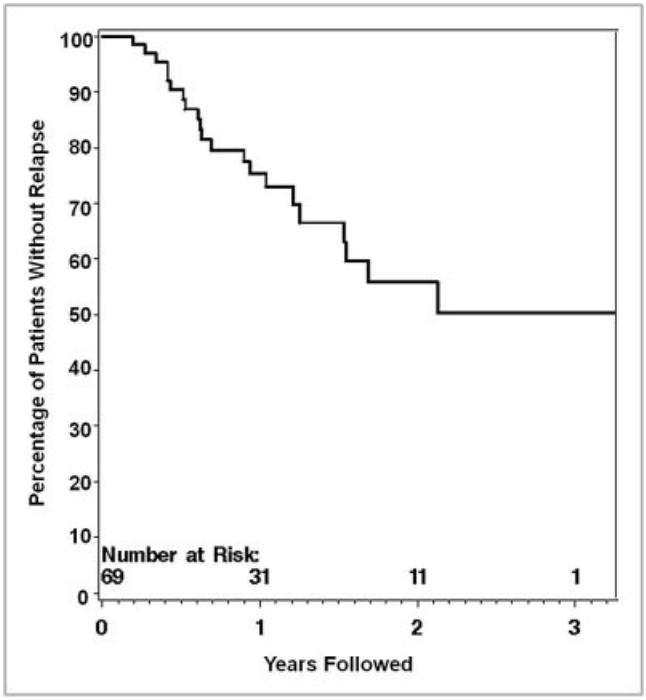

Figure. Time from diagnosis to first relapse in 69 patients with newly-diagnosed GCA

Conclusion: Relapses are common in GCA, occurring even 24 months after diagnosis. While headache and polymyalgia rheumatica were the most common manifestations at relapse, 2% of patients developed new visual symptoms and 4% had limb claudication. Both ESR and CRP were normal in one-third of the flares, highlighting the need for better biomarkers to assess disease activity. There remains an unmet need for more effective therapeutic alternatives to glucocorticoids.

1514

The Relationship Between the Polymyalgia Rheumatica Activity Score and Patient Reported Outcomes in Polymyalgia Rheumatica. EM McCarthy, Paul A. MacMullan, S. Al-Mudhaffer, A. Madigan, S. Donnelly, Cj McCarthy and G. M. McCarthy. Mater Misericordiae University Hospital, Dublin 7, Ireland

Background/Purpose: Patient reported outcomes(PROs) are increasingly being used for the assessment and monitoring of patients with rheumatic diseases. Standard PROs include the Health Assessment Questionnaire (HAQ),Visual Analogue Scale(VAS) for patient assessment of disease activity(VASDA) and VAS quality of life(VASQoL). PROs suitable for use in clinical care should be feasible with minimum respondent and administrative burden. In PMR, disease activity is measured using the PMR-AS as indicated by Leeb and Bird – PMR-AS = CRP(mg/dl) + VAS pain(0–10scale) + VASphysician (0–10scale)+Morning stiffness([min]x.1)+ Upper Limb Elevation (0–3 scale). Little data is available on how the PMR-AS reflects PROs.

Objectives: To prospectively evaluate the strength of correlation between PROs and PMR-AS in patients with known PMR and identify the best PRO measure for use in the clinical setting.

Methods: 60 patients with PMR were divided into Active disease (group 1, n=25) or Inactive disease(group 2,n=35), based on symptoms, physician assessment and ESR. Both groups underwent clinical and laboratory assessment at baseline and week 6. The following disease activity data were collected: PMR-AS, VasDA, VASQoL and HAQ. Between group disease activity data were assessed using Wilcoxon Signed Rank Test. Spearman's rank correlation coefficient(Spearman's rho) was used to directly compare the PMR-AS to the HAQ, VASDA and VASQoL. Measures of responsiveness including Standardised response means and effect size statistics were calculated for all outcome measures. Receiver operator curves (ROC) were calculated for the PROs.

Results: Demographic data was similar in all groups. Mean values for each disease measure are shown in Table 1. Disease activity scores improved significantly in the active group between week I and week 6 reflecting response to steroid treatment. There was no significant difference between the mean disease scores at week 6 in the Active group and the Inactive group.

Table 1. Mean disease measures at Weeks I and 6 in Active and Inactive Groups

	Active PMR-Week 1	Active PMR-Week 6	Wilcoxon p value	Inactive PMR –Week 1	Inactive PMR – Week6	Wilcoxon p value
PMR-AS	26.18	6.8	<.0001	5.16	4.8	n/s
HAQ	1.51	.51	<.0003	.53	.49	n/s
VASDA	7.38	2.78	<.0001	2.19	2.14	n/s
VASQoL	7.58	3.13	<.0001	2.08	2.19	n/s

Analysis of PMR-AS *vs* VASDA, VASQoL and HAQ showed correlation coefficients of 0.87(p<.001), 0.80(p<.001) and 0.68(p<.001), respectively.

VasDA and VasQoL are more responsive to change in disease activity than HAQ and PMR-AS (Table 2).

Table 2. Measures of responsiveness

	Standardised Response Means	Effect Size
VasDA	1.76	2.52
VasQoL	1.74	2.27
PMR-AS	1.54	1.84
HAQ	1.36	1.65

ROC analysis revealed VASDA to be more specific than either HAQ(.95 vs.85, p<.001) or VASQoL (.95 vs.93, p<.001) for the detection of response to treatment in active PMR.

Conclusion: VASDA, VASQoL and HAQ are strongly correlated with the PMR-AS. VASDA is more responsive to change in disease activity than the VASQoL, PMR-AS and HAQ. VASDA is inexpensive and easily administered in rheumatology clinics. We recommend its routine use in clinical practice.

1515

Plasma Fibrinogen Better Reflects patients' Functional Ability in Polymyalgia Rheumatica Than Either ESR or CRP. EM McCarthy, Paul A. MacMullan, S. Al-Mudhaffer, Anne M. Madigan, S. Donnelly, C. J. McCarthy and G M. McCarthy. Mater Misericordiae University Hospital, Dublin 7, Ireland

Background/Purpose: Measurement of disease activity in PMR is challenging due to the subjective nature of symptoms and absence of consistent physical signs in an elderly population.Previously we have demonstrated the enhanced specificity of fibrinogen over the standard biomarkers ESR and CRP for the detection of treatment response in patients with active PMR. The usefulness of patient reported outcomes(PROs) is increasingly being recognised in rheumatic disease. PROs reflect the impact of disease and its trearment from the patients perspective.Any biomarker that accurately reflects PROs in PMR would be of benefit in the clinical setting.

Objectives: To assess the correlation between patient reported outcomes(PROs) and the biomarkers fibrinogen, ESR and CRP in PMR.

Methods: 60 patients with PMR were divided into Active disease (group 1, n=25) or Inactive disease (group 2, n=35), based on symptoms, physician assessment and the standard biomarkers, ESR and CRP. Plasma fibrinogen was also measured. Groups underwent clinical and laboratory assessment at baseline and 6 weeks. PRO data collected included: Visual Analogue Scale(VAS) for patient assessment disease activity (VasDA), VAS for patient assessment of Quality of Life (VasQoL) and Health Assessment Questionnaire(HAQ). Demographic data were assessed using Fischers Exact Test and between group disease activity by Wilcoxon Signed Rank Test. Spearman's rank correlation coefficient was used to compare all biomarkers with the PROs. Standardised response means, a measure of a tests responsiveness to change, with a higher score indicating greater responsiveness were calculated for all 3 biomarkers.

Results: Demographic data was similar in all groups.There were significant differences in steroid dose between groups (15mg v 5mg) reflecting the institution of steroid therapy in the active group (p<.001). Mean scores for all PROs and biomarkers improved significantly in the

Active group between week 1 and week 6($p<0.001$).There was no significant difference between week 1 and 6 scores in the Inactive group (Table 1).

Table 1. Mean Scores for Patient Reported Outcomes and Biomarkers

	Active PMR-Week 1	Active PMR-Week 6	Wilcoxon p value	Inactive PMR – Week 1	Inactice PMR – Week 6	Wilcoxon p value
HAQ	1.51	.51	<.001	.53	.49	n/s
VASDA	7.38	2.78	<.001	2.19	2.14	n/s
VASQoL	7.58	3.13	<.001	2.08	2.19	n/s
Fibrinogen(g/L)	5.2	3.49	<.001	3.23	3.24	n/s
ESR(mm/hr)	59.6	24.3	<.001	17.6	18.3	n/s
CRP (mg/L)	45.9	12.6	<.001	5.2	5.3	n/s

All biomarkers showed significant correlation with the PROs ($p<.005$). Overall Fibrinogen showed superior correlation coefficients with the various PROs than either of the standard biomarkers ESR or CRP.

Table 2. Correlation coefficients of Patient Reported Outcomes and Biomarkers

	HAQ	VASDA	VASQoL
Fibrinogen	.51	.64	.61
ESR	.45	.57	.57
CRP	.39	.62	.64

Standardised Response Means for Fibrinogen, ESR and CRP were 1.63,1.2 and 1.05 respectively, indicating that plasma fibrinogen is the most responsive biomarker for assessment of change in disease activity.

Conclusion: Plasma fibrinogen better reflects PROs in PMR than the standard biomarkers ESR or CRP. It is also more responsive to changes in disease activity than either ESR or CRP. None.

1516

Sensitivity of the New EULAR/ACR Classification Criteria for Polymyalgia Rheumatica in Comparison with the Former Ones: A Single Centre Study. Pierluigi Macchioni, Maria Grazia Catanoso, Luigi Boiardi and Carlo Salvarani. Arcispedale S Maria Nuova, Reggio Emilia, Italy

Background/Purpose: To evaluate the diagnostic ability of the new ACR/EULAR classification criteria for PMR in a consecutive series of new onset PMR patients from a single centre.

Methods: All patients with suspected PMR seen at our centre are followed according to a standardized protocol which include clinical examination, determination of laboratory parameters, QOL questionnaire and US examination of shoulders and hips. Consecutive patients seen in our rheumatological centre with recent onset PMR and followed for at least 12 months were included prospectively during a 5 year period. Patients entered the study if diagnosis of PMR were confirmed at 12 month follow-up period according to rheumatologist opinion (PM). Diagnostic performance of new ACR/EULAR classification criteria were evaluated and compared to the sensitivity of the former diagnostic/classification criteria (Hunder's, Hazleman's, Bird's, Healey's criteria

Results: 112 patients entered the study (mean age 73.9+7.45y, female 72.3%, mean disease duration 13.8+2.8 w, mean ESR 62.6+20.9 mm/1sth, mean CRP 4.88+3.64 mg/dl, mean Leeb's index of disease activity 42.2+14.1). 103 (92%) pts had bilateral shoulders complains, 109 pts (97.3%) had increased levels of ESR/PCR, 74.1% had hip pain or LRM, 98.2% had normal RF and anti-CCP, 67% did not have peripheral joint involvement. At US examination 73.2% had bilateral shoulder involvement and 43.8% had US signs of at least one shoulder and one hip inflamed. 102 pts (91.1%) could be defined to have PMR according to the new ACR/EULAR classification criteria. Ninety-six pts (85.7%) satisfied the US criteria and no new patient could be diagnosed after US examination. Applying the former classification/diagnostic criteria 78.6% satisfied Hunder's criteria, 78.6% Healey's criteria, 59.8% Hazleman's criteria and 79.5% Bird's criteria.

Conclusion: In our series of recent onset PMR patients the new ACR/EULAR criteria seems to have higher sensitivity as compared to the previous criteria. US examination do not seem to have any impact to the sensitivity of these criteria.

1517

Annexin-A1: A Potential Novel Biomarker in Giant Cell Arteritis. Suchita Nadkarni[1], Jane Hollywood[2], Justin C. Mason[3], Bhaskar Dasgupta[4] and Mauro Perretti[1]. [1]Barts and the London School of Medicine, London, United Kingdom, [2]Southend Hospital, Southend, United Kingdom, [3]Imperial Coll/Hammersmith Hosp, London, United Kingdom, [4]Southend University Hospital, Essex, United Kingdom

Background/Purpose: Diagnosis of giant cell arteritis (GCA) relies on a multitude of parameters, including age of onset (>50yrs), temporal artery abnormalities (pulse) and abnormal temporal artery biopsies (ACR classification criteria 1990). Elevated ESR and CRP levels in serum are used as the gold standard laboratory diagnostic for GCA. However, these biomarkers are disease non-specific presenting the challenge to identify a GCA-specific biomarker. Annexin-A1 (AnxA1) is a 37-kDa glucocorticoid-regulated protein, abundant within the neutrophil, and rapidly mobilized to cell to the surface upon cell activation. Once mobilized, AnxA1 is able to exert anti-inflammatory actions including inhibition of leukocyte adhesion to the vessel wall during inflammation. Following activation, neutrophils (as well as other cells) are also capable of releasing microparticles (MP) into the plasma; these are small ($<1\mu m$), heterogeneous structures, which can induce cellular cross-talk and regulate inflammatory responses. Little is known about the role of neutrophils in GCA, classically identified as a T-cell-mediated disease. In the present study we report elevated AnxA1 on neutrophils and MP from patients with biopsy-positive GCA but not in disease controls, including polymyalgia rheumatica (PMR) and rheumatoid arthritis (RA). Thus, expression of AnxA1 on circulating neutrophils may be a potential biomarker for GCA.

Methods: Blood samples from GCA (n=8; F:M 6:2), were taken at week 1 post steroid commencement and every 4 weeks up to 24 weeks. Initial GCA steroid doses were 60mg/day, falling to 40mg, 20mg and 10mg at weeks 4, 12, and 24, respectively, with week 1 mean CRP levels at 106 mg/L, falling to 6mg/L at week 24. Using whole blood flow cytometry we have longitudinally measured AnxA1 protein expression on neutrophils and neutrophil-derived plasma microparticles, and used real-time PCR to detect AnxA1 gene expression in this cell type.

Results: Analyses revealed 50% of circulating neutrophils from GCA patients expressed AnxA1 on their surface 1-week post steroid treatment. Levels of expression steadily declined during the 24-week observation period, with only 20% of neutrophils expressing AnxA1 at 24-weeks post-steroid intervention. High AnxA1 expression was not observed on neutrophils from patients with PMR or RA: only 20% of circulating neutrophils expressing AnxA1 in either control patients. Furthermore, AnxA1 expression was largely confined to the neutrophils, as neither monocytes nor lymphocytes displayed high levels of AnxA1 on their surface.

AnxA1 levels were also detected in GCA patient plasma MP, with neutrophil-derived MP expressing high AnxA1 at week 1. The expression profile correlated with their circulating cell counterparts during the 24-week period. Finally, real-time PCR analysis revealed a 3-fold decrease in AnxA1 gene expression at week 24 when compared to week 1.

Conclusion: Taken together, we propose high AnxA1 expression on neutrophils could be a potential and novel disease-specific biomarker for GCA.

1518

Prospective Evaluation of Aortic Structural Damage (aneurysm/dilatation) Using a Predefined Screening Protocol in Biopsy-Proven Giant-Cell Arteritis Patients with Extended Follow-up. Ana García-Martínez, Pedro Arguis, Sergio Prieto-González, José Hernández-Rodríguez, Georgina Espígol, Marc Corbera, Marco Alba, Itziar Tavera-Bahillo, Ester Planas and María Cinta Cid. Vasculitis research unit. Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain

Background/Purpose: In a previous cross-sectional evaluation of 54 patients with biopsy-proven giant-cell arteritis (GCA) we found that 22.2% (12 patients) had significant aortic structural damage (ASD) (aneurysm/dilatation) after a median follow-up of 5.4 years. Development of ASD was not related to persistence of clinically apparent disease or elevation of acute-phase reactants or pro-inflammatory cytokines during follow-up (García-Martínez A et al. Arthritis Rheum 2008). The outcome of ASD after longer follow-up has never been prospectively evaluated.

Methods: Patients from the previously evaluated cohort who continued their follow-up visits in our department were subjected to the same screening protocol every four years approximately. The aim was to assess the development of new ASD and the outcome of previously detected abnormalities. The screening protocol consisted of a chest X-ray and a CT scan if aortic

aneurysm was suspected or changes respect to the baseline X-ray were observed. The abdominal aorta was evaluated by ultrasonography (US). ASD was defined when the ascending aorta measured > 4 cm in diameter, the aortic arch or the descending aorta ≥ 4cm, the abdominal aorta > 3 cm or, when the aorta exhibited a fusiform dilatation. Results were compared to those obtained from the previous screening.

Results: Eighteen of the 54 patients from the original cohort had died or were lost of follow-up before they could be evaluated a second time. The remaining 36 patients were subjected to a new screening (median follow-up at the time of second screening 8.5 years, range 8–12). In 7 of these patients ASD had been detected in the previous evalutation (1 involving the abdominal aorta and 6 the thoracic aorta). In the second screening the abdominal aneurysm remained stable whereas thoracic ASD increased in diameter. Three patients had newly discovered thoracic ASD not detected in the first screening. One of them died of an aortic dissection 9 years after the diagnosis of GCA. The remaining 26 patients did not show changes in the chest X-ray when compared to the baseline X-ray, or, if changes were suspected, the CT scan did not evidence significant aortic abnormalities. No new abdominal aneurysms were observed by US. To date, six patients have been subjected to a third screening, with no evidence of new ASD in any of them. Overall, 27.7 % of patients from the original cohort developed ASD after a median follow-up of 10 years (range 4.3–15).

Conclusion: Our study suggests that GCA-patients develop ASD mainly but not exclusively, within the first 5 years of follow-up. Once ASD occurs, dilatation increases over time, particularly in the thoracic aorta underlining the need for periodic evaluation. These results should be confirmed in a larger series of patients.

1519

Clinical Profile and Therapeutic Approaches in Polymyalgia Rheumatica: Is hydroxychloroquine a Useful Steroid-Sparing Agent in the Management of the Disease? Rosaria Talarico, Nicolò Giusti, Anna d'Ascanio, Pasquale Pepe, Maurizio Mazzantini and Stefano Bombardieri. Rheumatology Unit, Pisa, Italy

Background/Purpose: Polymyalgia rheumatica (PMR) is a relatively common syndrome of the elderly, characterized by severe pain and stiffness in the neck shoulder and pelvic girdles, along with increased acute phase reactants. The therapeutic approach to PMR remains mainly based on glucocorticoids (GC); however, growing studies suggest a steroid-sparing effect of some DMARDs in PMR.

The primary aim of this study was to retrospectively study the clinical findings in a cohort of patients with PMR. A secondary aim was to evaluate the therapeutic approaches used, comparing the efficacy of GC alone versus GC plus DMARDs.

Methods: We carried out an analysis by review of the medical documentation of all consecutive patients with a diagnosis of PMR seen in the last twenty years. Epidemiological and clinical data as well as drugs administered were evaluated. In order to evaluate the efficacy of the therapies received, we evaluated the number of disease relapse observed during the follow-up, defining relapse any further clinical manifestations compatible with the clinical spectrum of PMR and/or an increase of ESR ≥ 40 mm/hour, not otherwise justifiable, that required higher doses or new introduction of GC therapy.

Results: Five hundred patients (157 males and 343 females, mean age 77.6±8 years, mean age at disease onset 70±8 years; mean disease duration 34.5±30 months) were studied. The most frequent clinical features at disease onset were: pain of the shoulder and pelvic girdle 93%, stiffness of the neck 51%, peripheral arthritis 30%, fever 25%, fatigue 22%, anorexia and weight loss 7%; moreover, 89% of the patients had presented at the onset an erythrocyte sedimentation rate (ESR) higher than 40 mm/1st hr ± abnormal C reactive protein (CRP), while 7% presented isolated increased levels of CRP. A diagnosis of giant cell arteritis (GCA) was made in 25 patients, of which 65% at the onset of PMR and 35% during the follow-up. Any epidemiological difference was noted between isolated PMR and PMR/GCA patients. Fifty-nine percent of patients received GC alone, while the others were treated with GC plus DMARDs (methotrexate 48%, hydroxychloroquine 42%, others 10%). A significant difference was observed in the number of disease relapse, that was 305 in the group of GC alone and 196 in the group of GC plus DMARDs; specifically, the lower number of relapses was observed in those patients who received hydroxychloroquine.

Conclusion: The clinical spectrum of PMR seems quite typical, but on the other hand we certainly need large trials and longer observational studies to make more clear the therapeutic algorithm of the disease. According to the literature data, our results had shown that antimalarials brought the disease under control in the majority of patients, therefore it could be appropriate to study their early introduction in PMR management.

1520

Does Ultrasonography Guidance Increase the Yeld of Temporal Artery Biopsy in Patients with Giant Cell Arteritis? Preliminary Results From a Single-Blinded Randomized Study. Giuseppe Germanò, Nicolo Pipitone, Luigi Boiardi, Ilaria Chiarolanza, Luca Cimino, Maria Grazia Catanoso, Andrea Caruso and Carlo Salvarani. Arcispedale S Maria Nuova, Reggio Emilia, Italy

Background/Purpose: Temporal artery (TA) biopsy (TAB) is the gold standard to diagnose giant cell arteritis (GCA), but is negative in approximately 20% of patients. Aims: The study aimed to establish whether Color-doppler-ultrasonography (CDS)-guided TAB might provide a greater yield compared to standard TAB technique.

Methods: We enrolled 76 consecutive patients with suspected GCA from September 2009 through May 2011. Patients were randomized to undergoing CDS-guided TAB (group 1), or to undergoing TAB performed according to conventional technique (group 2). All patients were evaluated by physical examination of the temporal arteries (PETA), CDS and TAB. 2 patients were excluded because biopsy showed no evidence of arterial walls. 43/74 patients were taking prednisone at a mean dose of 17.3 mg/day and 7/43 had been taking steroids for <2 weeks. CDS was carried out by a physician blinded to the clinical data of the patients. CDS was performed using a ESAOTE MyLab 70 device fitted with a LA435 probe set on "standard" CDS vascular examination mode. The common trunk and the main branches of the TA were screened in a longitudinal and transverse plane along the entire vessel. In patients from group 1 the ultrasonographist marked with a dermographic pen the segment of the TA which showed the largest halo (if present). In the absence of a clear-cut halo, a site with doubtful halo, stenosis, occlusion, or wall thickening was marked. The surgeon performed the TAB in the segment marked by the ultrasonographist in patients from group 1, while TAB was carried out according to standard procedure in patients from group 2. PETA was performed before CDS. PETA was considered positive in the presence of tenderness or decreased/absent pulse of the TA. Fisher's exact test was used for statistical analysis. Informed consent from the patients and approval from the local Ethics Committee were obtained.

Results: TAB was positive in 13 patients in group 1 and 12 in group 2 (NS). In total, the halo was detected in 20 patients from group 1 and 12 in group 2 (NS). The full results are shown in Table I.

Conclusion: CDS-guided TAB was associated with a significally greater probability of being positive (OR 3..4, 95% CI=1.1–10.4). However, the percentage of TAB-positive patients was similar regardless of whether TAB was performed under CDS guidance or not.

Table 1.

	Group 1 (n=35)	Group2 (n=39)	p	OR (95% CI)
	CDS-guided TAB	Standard TAB		
Gender	M:12; F:23	M: 10; F:29	—	—
Mean age (years±SD)	75±3	71±4	—	—
TA abnormalities on physical examination.	17	20	NS	—
Mean ESR (mm/1st h)/CRP (mg/dl)	56/6	58/7	NS	—
Patients on GC therapy. n	20 Mean GS dose=18.6 mg/day	23 Mean GS dose=16.2 mg/day	NS	–
Patients on GC prior to undergoing TAB >2 Weeks n	17	19	NS	—
Patients with positive halo sign n (%)	20 (57%)	12 (54%)	NS	—
Patients with positive TAB n (%)	13 (37%)	12 (30%)	NS	—
Patients with positive halo and TAB n (%)	12/20*	**12/39** **	P= 0,049	3.4 (1.1–10.4)

*** TAB performed at site of Halo; ** TAB performed without CDS guidance**

1521

Incidence of Peripheral Vascular Disease and Myocardial Infarction Among Patients with Giant Cell Arteritis. Gunnar Tomasson[1], Christine Peloquin[1], Thorvardur Love[2], Aladdin Mohammad[3], Yuqing Zhang[1], Hyon K. Choi[1] and Peter A. Merkel[1]. [1]Boston University School of Medicine, Boston, MA, [2]Landspitali University Hospital, Reykjavík, Iceland, [3]Skåne University Helsingborg, Lund, Sweden

Background/Purpose: Involvement of the primary branches of the aorta is well documented among subjects with giant cell arteritis (GCA), but few studies have explored the association between GCA and peripheral vascular disease (PVD) or myocardial infarction (MI). The objective of this study was to determine the association of GCA with incident PVD and MI in a large population cohort.

Methods: Data from The Health Improvement Network (THIN), a medical record database of 7.3 million patients from general practices from across the United Kingdom, were used. Subjects with GCA were identified as those with diagnostic codes for GCA followed by prescription for glucocorticoids occurring at least one year after enrollment into the database. For each subject with GCA, five subjects free of GCA at the time of diagnosis of GCA for the index subject were selected to a reference group, matched on age, sex, and entry-time to the database. Outcome was defined as having a diagnostic code for PVD or MI respectively. Information on cardiovascular risk factors: smoking, hypertension (HTN), diabetes mellitus (DM), blood lipids, and body mass index (BMI) was obtained from health records for the period prior to the diagnosis of PVD or MI. Subjects with PVD or MI at baseline were excluded from the analysis. Subjects were followed until the occurrence of study outcomes or the time of censoring; censoring occurred when subject exited the database, developed GCA (for reference subjects only), or reached the study's common close out date of June 2010. Cox proportional hazards models were constructed to determine the association between GCA and study outcomes adjusted for cardiovascular risk factors. The analyses were stratified according to age and sex to account for matching in the data.

Results: There were 3,676 subjects that met criteria for incident GCA between January 1990 and January 2010. Median follow-up time was 4.2 years (IQR: 1.8–7.7), for both exposed and reference subjects. Current smoking, HTN, and DM were somewhat more common among exposed compared to reference subjects. During the follow-up time 80 (2.2%) of 3,676 subjects with GCA developed PVD and 204 (1.1%) of 18,430 reference subjects (1.2%) developed PVD. Subjects with GCA had a greater than two-fold increased risk of PVD, HR=2.12 (95% CI: 1.60–2.80), this effect estimate was almost identical among the 13,978 subjects (63.2%) with complete data with respect to smoking, BMI and blood lipids. After adjustment for cardiovascular risk factors there was no attenuation in the risk estimate for PVD, HR=2.44 (95% CI: 1.58–3.75). Out of 3,676 subjects with GCA, 194 (5.3%) had MI compared with 472 (2.6%) of 18,430 reference subjects, HR=2.26 (95% CI: 1.88–2.72), this effect estimate was slightly lower among those with complete data with respect to respect to smoking, BMI, and blood lipids, HR=1.91 (95% CI:1.50–2.43). After adjustment for cardiovascular risk factors there was no attenuation in the risk estimate for MI, HR=1.85 (95% CI: 1.45–2.36).

Conclusion: Patients with GCA have a two-fold elevated risk of PVD and MI compared to a reference group, even after adjustment for cardiovascular risk factors

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Incidence of Cerebrovascular Accidents Among Patients with Giant Cell Arteritis. Gunnar Tomasson[1], Christine Peloquin[1], Thorvardur Love[2], Aladdin Mohammad[3], Yuqing Zhang[1], Hyon K. Choi[1] and Peter A. Merkel[1]. [1]Boston University School of Medicine, Boston, MA, [2]Landspitali University Hospital, Reykjavík, Iceland, [3]Skåne University Helsingborg, Lund, Sweden

Background/Purpose: Giant cell arteritis (GCA) generally spares intracranial arteries but an increased incidence of cerebrovascular accidents (CVA) has been reported among patients with GCA. The objective of this study was to determine the association of GCA with incident CVA in a large patient cohort, after adjustment for cardiovascular risk factors.

Methods: Data from The Health Improvement Network (THIN), a medical record database of 7.3 million patients from general practices from across the United Kingdom, were used. Subjects with GCA were identified as those with diagnostic codes for GCA followed by prescription for glucocorticoids occurring after at least one year after enrollment into the database. For each subject with GCA, five subjects free of GCA at the time of diagnosis of GCA for the index subject were selected to a reference group, matched on age and sex and entry-time to the database. Outcome was defined as having a diagnostic code for vaso-occlusive-, hemorrhagic- or unspecified CVA. Information on cardiovascular risk factors, including smoking, hypertension, diabetes mellitus, blood lipids, and body mass index, were obtained from corresponding diagnostic and additional health records codes, and medications codes, occurring prior to the diagnosis of CVA. Subjects with no codes for hypertension or diabetes mellitus were considered free of those diseases. Subjects with CVA at time of diagnosis of GCA or, for the reference group, at the time of diagnosis of GCA for the index subject, were excluded from the analysis. Subjects were followed until the occurrence of CVA or the time of censoring; censoring occurred when subjects exited the database, developed GCA (for reference subjects only), or reached the study's common close out date of June 2010. Cox proportional hazards models were constructed to determine the association between GCA and CVA, adjusted for cardiovascular risk factors. The analyses were stratified according to age and sex to account for matching in the data.

Results: There were 3,811 subjects that met criteria for incident GCA between January 1990 and January 2010, included. Median follow-up time was 4.2 years (inter-quartile range: 1.8–7.7), for both exposed and reference subjects. Current smoking, hypertension, and diabetes mellitus, were slightly more common among exposed compared to reference subjects. During the follow-up time, 160 of 3,811 subjects with GCA (4.2%) had CVA and 626 of 18,763 subjects in the reference group (3.3%) had CVA. Subjects with GCA had a significantly increased risk of CVA, HR=1.40 (95% confidence interval (CI) 1.17–1.69), this effect estimate was somewhat higher among the 14,573 subjects (63.7%) with complete data with respect to cardiovascular risk factors, HR=1.70 (95% CI: 1.28–2.27). After adjustment for cardiovascular risk factors there was no attenuation in the risk estimate, HR=1.71 (95% CI: 1.27–2.29).

Conclusion: Patients with GCA have an elevated risk of CVA, after adjustment for cardiovascular risk factors.

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Age At Onset and Gender Are Associated with Differences in Giant Cell Arteritis (GCA) Initial Presentation and Outcome. Marco A. Alba, Ana García-Martínez, Itziar Tavera-Bahillo, Sergio Prieto-González, Georgina Espígol, Jose Hernandez-Rodriguez and Maria C. Cid. Vasculitis research unit. Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain

Background/Purpose: GCA is a chronic inflammatory disease involving large and medium-sized arteries. It is considered the most frequent primary vasculitis with higher incidence in women. Mean age of onset in different cohorts ranges between 72–74 years. Former studies have observed certain differences in GCA clinical spectrum depending on age at disease presentation and gender. Particularly polymyalgia rheumatica has been found to be more frequent in women and in patients younger than 70 years. The purpose of this study was yo evaluate differences in initial clinical manifestations, ischemic complications and clinical course according to age at onset and gender in a prospectively followed cohort of patients with biopsy-proven giant cell arteritis.

Methods: Between 1995 and 2005, 170 patients were diagnosed with biopsy proven GCA at our institution. Among them, patients with the following criteria were selected: prospective treatment by the authors according to uniform criteria, prospective recording of GCA-presentation, related complications, relapses, periodic screening for aneurysm, glucocorticosteroid doses, and follow-up duration of at least 4 years.

Based on the mean ± standard deviation (SD) of age at disease onset, patients were classified in 3 groups: age equal or below 67 years (mean -1SD) (early onset), age between 68 and 80 years, and age equal or older than 81 (mean+1SD) (late onset). Ninety-four patients fulfilled the selection criteria and were eligible for this study. Although retrospective in design, the study was performed on a prospectively followed cohort. Chi-square test, ANOVA test and Kaplan-Meyer survival analysis/log-rank test were used for statistical comparison.

Results: Mean age (±SD) at diagnosis was 74±7 years (58–89). Patients with early onset GCA (≤67 years) presented more frequently fever (p=0.002), and had higher erythrocyte sedimentation rate (0.039) than patients >68 years. Subsequent clinical course of this group did not differ from patients with disease onset between 68–80 years and >81 years. In contrast, late onset GCA (≥81 years) was characterized by higher prevalence of severe ischemic complications in the form of amaurosis fugax (6% for ≤67 years vs 9% for 68–80 vs 29% for ≥81 years, p=0.046) and blindness (6% for ≤67 years vs 7% for 68–80 vs 33% for ≥81 years, p=0.006). During follow-up, late onset GCA patients relapsed less frequently (p=0.027). Concerning to gender, we found no differences in the initial clinical presentation between men and women but men developed more frequently aortic aneurysm during follow-up (p=0.003).

Conclusion: Age at onset and gender are associated with differences in clinical presentation and outcome in patients with GCA

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Development of Ischemic Complications In Patients with Giant Cell Arteritis Presenting with Apparently Isolated Polymyalgia Rheumatica. Paula Estrada, Javier Narvaez, Laura Lopez-Vives, Irene Martín-Esteve, Carmen Gomez-Vaquero and Joan Miquel Nolla. Hospital Universitario de Bellvitge, Barcelona, Spain

Background/Purpose: Controversy exists over the risk of ischemic complications in patients with giant cell arteritis (GCA) presenting with apparently isolated polymyalgia rheumatica (PMR). Recent studies that have

analyzed this issue give conflicting results. Our objective was to investigate the frequency and type of GCA-related ischemic complications in a series of patients with GCA who, for a substantial period of time (at least 2 months), lacked vascular symptoms and presented with apparently isolated PMR.

Methods: Between 1986 and 2010, 159 patients were diagnosed with GCA by the Department of Rheumatology within the Hospital Universitario de Bellvitge (Barcelona, Spain), a referral, tertiary care hospital. Patients were diagnosed with GCA if they had a positive temporal artery biopsy (TAB) or, in cases with negative or no biopsy, if the fulfilled the remaining four ACR criteria for the classification of GCA and had a prompt and persistent response to corticosteroid treatment.

Patients that developed GCA on a background of a prior history of PMR were selected for the study. The diagnosis of PMR was based on the criteria proposed by Chuang et al *(Ann Intern Med 1982;97:672–80).* Patients were considered to have *severe ischemic manifestations* if they suffered visual ischemic manifestations, cerebrovascular accidents (stroke and/or transient ischemic attacks), jaw claudication, or large-artery stenosis of the extremities that caused signs of occlusive manifestations (limb claudication) of recent onset. For the purpose of this study, severe ischemic complications were attributed to GCA if they occurred within the time between the onset of GCA symptoms and 4 weeks after the onset of corticosteroid therapy

Results: Sixteen patients (10%) developed GCA on a background of a prior history of PMR. These 16 patients were diagnosed as having isolated PMR because they did not have clinical evidence of GCA at the time of diagnosis and showed a prompt response to low-dose steroid therapy (10 to 20 mg/d of prednisone), with normalization of the acute-phase reactants. Despite this observation, they later experienced an arteritic relapse during the course of steroid treatment. The median time to arteritic relapse from initiation of therapy was 214 ± 173 days and the total dose of prednisone received was 1707 ± 1268 mg (average daily dose, 7.2 ± 1.3 mg/d). Relapses usually occurred during the tapering of the prednisone dose or as a consequence of an unauthorized discontinuation of treatment (one case). Temporal artery biopsy was positive in 75% (12/16) of these cases.

Severe GCA-related ischemic complications were observed in 37.5% (6/16) of the patients (4 patients presented with 2 or more events): jaw claudication in 2 patients (12%); visual manifestations in 6 (35%), including 4 cases of amaurosis fugax and 2 cases of permanent visual loss; strokes in 2 (12%); and 1 case (6%) of upper limb claudication due to reversible stenosis of the axillary artery.

Conclusion: Patients with GCA presenting with apparently isolated PMR are not a benign subset and have a significant risk of developing severe ischemic complications (37.5% of the cases).

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Frequency of Pulmonary Arterial Hypertension Is Not Increased in Takayasu's Arteritis. Melike Kalfa[1], Oktay Musayev[2], Hakan Emmungil[1], Ozgul Soysal[3], Zevcet Yilmaz[1], Vedat Inal[1], Servet Akar[3], Nurullah Akkoc[3], Fatos Onen[3], Meral Kayikcioglu[2], Gokhan Keser[1] and Kenan Aksu[1]. [1]Dept. of Internal Medicine, Division of Rheumatology, Ege University, Izmir, Turkey, [2]Dept. of Cardiology,Ege University, Izmir, Turkey, [3]Dept. of Internal Medicine, Division of Rheumatology, Dokuz Eylül University, Izmir, Turkey

Background/Purpose: Takayasu's arteritis (TA) is an inflammatory disease that affects large and medium-sized arteries, especially the aorta and its branches. Although pulmonary artery involvement is common, the clinical manifestation is rare. In this study, we examined the presence of pulmonary arterial hypertension (PAH) in TA patients by using transthoracic Doppler echocardiography.

Methods: Seventy patients with TA (mean age 42.07±10.44 years; F/M: 63/7) diagnosed according to the 1990 American College of Rheumatology criteria were enrolled in this study. The control groups included 67 systemic sclerosis (SSc) patients (56.66±11.57 years; F/M:59/8) and 68 healthy controls (39.50±9.53 years; F/M: 61/7). Transthoracic Doppler echocardiography was performed by the same cardiologist to all the participants, and systolic pulmonary artery pressure (SPAP) was calculated for each individual. In accordance to ESC-ERS guideline, possible diagnosis of PAH was considered only in patients having SPAP>50 mmHg, with or without additional echocardiographic findings suggestive of PAH. SPSS 15.0 was used for statistical analysis. P value <0.05 was accepted as statistically significant.

Results: Mean SPAP values in TA, SSc and healthy control groups were 20.93±6.06, 31.57±12.75, and 18.88±5.385 mmHg, respectively. While SPAP values in SSc group were significantly higher than the other two groups ($p<0.001$), there were no differences between TA and healthy groups ($p=0.167$). Based upon the ESC-ERS guideline definition, possible PAH was present in 5 out of 67 SSc patients (7.4%). However, although pulmonary artery involvement was present in 4 out of 70 TA patients (5.6%), none of these had PAH.

Conclusion: Using transthoracic Doppler echocardiography and the ESC-ERS guideline, none of our TA patients, including those with pulmonary artery involvement fulfilled the criteria of possible PAH. Although the exact diagnosis of PAH requires classical angiography, our echocardiographic findings suggest that frequency of PAH is not increased in TA.

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Lower Respiratory Tract Involvement In Relapsing Polychondritis. Elisa Perry[1], Shirish Sangle[2], Rebecca Preston[1] and DP. D'Cruz[3]. [1]St Thomas' Hospital, London, United Kingdom, [2]Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom, [3]St. Thomas' Hospital, London, United Kingdom

Background/Purpose: Relapsing polychondritis (RP) is a rare autoimmune condition characterized by cartilaginous inflammation, degeneration and destruction. Airway involvement in RP is associated with high morbidity and mortality. Our purpose is to present the clinical and imaging features of airway involvement in patients with RP.

Methods: We retrospectively reviewed 28 patients with a diagnosis of RP who fulfilled Adam's criteria for RP. The studies were performed on 16 slice helical computer tomography (CT) scanners with collimation of 0.625 and 1.5mm, pitch of 0.98 and 1.074mm and reconstruction interval of 1mm respectively. All patients had inspiratory and expiratory images performed from thoracic inlet to diaphragm with or without intravenous contrast medium. All images were available in both soft tissue and lung window settings. All patients underwent Computed Tomography (CT) scan of the thorax in inspiratory and expiratory phase. Two radiologists reviewed all studies simultaneously with consensus agreement.

Results: Nineteen of 28 (68%) patients had abnormal imaging and 9/28 (32%) had normal imaging. The median age of patients with abnormal imaging was 50 years (26–68) at the time of imaging and disease duration was 7.1 (0.9–24.2) years. There were 24 Caucasians, 3 Afro-Caribbean and 1 Indian Asian in origin. Other clinical manifestation in this group were: auricular involvement (18/28), respiratory tract/thoracic symptoms (19/28), ocular involvement (17/28), nasal chondritis (15/28), arthritis (9/28) and constitutional symptoms (4/28). Of those with respiratory manifestations, symptoms included dyspnoea, tracheitis, stridor, sore throat, hoarse voice, costochondritis, chest pain, laryngeal cartilage tenderness and lower respiratory tract infective symptoms. One patient also had pulmonary emboli.

Characteristic changes seen in patients with abnormal imaging were: airway malacia (79%), increased wall attenuation (74%), airway wall thickening (68%), gas trapping (57%) and airway narrowing (53%). In one patient increased wall thickening and attenuation involved the posterior tracheal membrane, which has not been previously reported.

Conclusion: The most prevalent airway abnormalities seen in RP were of airway malacia (79%) and increased wall attenuation (74%). Respiratory tract involvement (68%) may be more extensive and prevalent than previously thought.

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Ischemic Colitis (IC) Associated with Rheumatic Diseases; A Colonoscopic Study of 23 IC Cases. Ikuko Masuda[1], Masako Hara[1], Hisae Ichida[2], Kae Takagi[2], Takahisa Gono[2], Yasuhiro Katsumata[2], Yasushi Kawaguchi[2] and Hisashi Yamanaka[2]. [1]International University of Health and Welfare, Sanno Hospital, Tokyo, Japan, [2]Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Ischemic colitis is caused by various predisposing factors such as arterosclerosis. Although patients with connective tissue disorders, such as systemic lupus erythematosus (SLE), are at risk for various ischemic events due to wide-spread vasculitis of small vessels, ischemic colitis is not common gastrointestinal complication. We herein reported 23 cases of ischemic colitis associated with various rheumatic diseases.

Methods: This retrospective colonoscopy study was performed on 600 consecutive patients with various rheumatic diseases from 2004 to 2008. Diagnosis of ischemic colitis was established from colonoscopic and pathologic findings. Written informed consent was obtained from each patient before colonoscopic examination. Clinical variables were obtained for all patients including age, gender, presenting symptoms, and associated risk factors.

Results: We have identified twenty-three cases of ischemic colitis, including 7 SLE, 5 rheumatoid arthritis/rheumatoid vasculitis, 4 scleroderma, 3 myositis, and 2 vasculitis syndrome, out of 600 patients. Twelve of twenty-three cases had gastrointestinal ischemic episodes such as abdominal pain or hematochezia. Ischemic colitis had been reported to be an uncommon gastrointestinal complication in patients with SLE. However, seven out of 74 SLE patients (9.4%) examined were diagnosed as ischemic colitis, which was significantly higher frequency than those with rheumatoid arthritis/rheumatoid vasculitis (5 out of 177 patients; 2.8%). Also, the age group of ischemic colitis with SLE was much younger than ischemic colitis with other rheumatic diseases (35 year old vs 76 year old). One of the SLE patients developed near-circumferential rectal ulcer and perforation in later year, where is very rare as a location of regular ischemic colitis.

Conclusion: Ischemic colitis with rheumatic diseases may not be uncommon as had been reported since half of our patients were asymptomatic. Colonoscopic screening may be useful to discern ischemic colitis associated with hidden intestinal vasculitis in patients with rheumatic diseases.

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Presentation and Outcome of Hepatitis C Virus-Related Mixed Cryoglobulinemia Cardiomyopathy. Benjamin Terrier[1], Alexandre Karras[2], Philippe Cluzel[3], Jean-Philippe Collet[4], Damien Sène[5], David Saadoun[6] and Patrice Cacoub[5]. [1]Pitié-Salpêtrière Hospital, Paris, France, [2]Nephrology, HEGP, Paris, France, [3]Radiology, Pitié-Salpétrière, Paris, France, [4]Cardiology, Pitié-Salpétrière, Paris, France, [5]CHU Pitié-Salpêtrière, Paris, France, [6]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France

Background/Purpose: Hepatitis C virus (HCV) infection may be responsible for mixed cryoglobulinemia vascultitis, ranging from mild clinical symptoms to fulminant life-threatening complications. In primary systemic vasculitides, cardiac manifestation is associated with a poor outcome and treated with immunosuppressive therapy. Cardiac involvement during HCV-related systemic vasculitis has never been evaluated. Objective: To describe clinical presentation and to evaluate clinical outcome of cardiac manifestation during HCV-related systemic vasculitis in the antiviral therapy era.

Methods: Data from 165 patients with HCV-related systemic vasculitis were retrospectively reviewed to describe the clinical presentation of HCV-related systemic vasculitis with cardiac manifestation and to compare clinical outcome of patients with (n=7) and without cardiac (n=158) involvement.

Results: The prevalence of cardiac manifestation was low (n=7.4%) and revealed by thoracic pain and congestive heart failure manifestations mostly (n=4 each, 57%). Cardiac imaging showed dilated cardiomyopathy in 5 patients and hypertrophic cardiomyopathy in 1. In multivariate analysis, patients with cardiac manifestations had more frequently B-cell non-Hodgkin lymphoma [odds-ratio (OR) 18.1; 95% CI, 2.8–116.7; P=0.0023)] and gastrointestinal involvement (OR 14.6; 95% CI, 2.0–104.9; P=0.0078). All cardiac manifestations were reversible early after the initiation of corticosteroids and agressive immunosuppressive therapy. However, after a median follow-up of 19 months, 3 patients (43%) died. Respective 6-month, 1-year and 2-year survival rates in patients with and without cardiac involvement were 86 and 99%, 71 and 96%, and 48 and 90%. Overall survival was significantly associated with cardiac involvement (HR 5.01, P=0.003). The analysis of causes of death, however, showed that they were more frequently related to extra-cardiac manifestations.

Conclusion: Cardiac damage is a rare manifestation of HCV-related vasculitis, associated with B-cell lymphoma and life-threatening manifestations. Despite a favorable early outcome, patients with cardiac damage had a poorer survival than those without.

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Lymphoma Prevalence in Patients with Serum Cryoglobulins with or without Cryoglobulinemic Vasculitis: Data Extrapolated From the Cryoglobulinemic Vasculitis Classification Criteria Database. Luca Quartuccio[1], Laura Corazza[2], Giuseppe Monti[3], Armando Gabrielli[4], Athanasios G. Tzioufas[5], Clodoveo Ferri[6], Gianfranco Ferraccioli[7], Manuel Ramos-Casals[8], Michael Voulgarelis[9], Marco Lenzi[10], Maria Teresa Mascia[11], Domenico Sansonno[12], Patrice Cacoub[13], Matija Tomsic[14], Antonio Tavoni[15], Maurizio Pietrogrande[16], Anna Linda Zignego[17], Salvatore Scarpato[18], Pietro Pioltelli[19], Serge D. Steinfeld[20], Peter Lamprecht[21], Stefano Bombardieri[22], Massimo Galli[23] and Salvatore De Vita[2]. [1]Rheumatology Clinic, DSMB, University of Udine, Italy, Udine, Italy, [2]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy, [3]Internal Medicine Unit, Saronno Hospital, Azienda Ospedaliera di Busto Arsizio, Saronno (VA), Italy, [4]Clinica Universitaria Ancona, Ancona, Italy, [5]Medical School-Univ of Athens, Athens, Greece, [6]Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy, [7]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [8]IDIBAPS, Hospital Clínic, Barcelona, Spain, [9]Department of Pathophysiology, Athens, Greece, [10]Department of Clinical Medicine, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy, [11]Dipartimento Apparato Locomotore, AOU Policlinico di Modena, Modena, Italy, [12]Section of Internal Medicine and Clinical Oncology, Department of Biomedical Sciences and Human Oncology, University of Bari, Medical School, Bari, Italy, [13]CHU Pitié-Salpêtrière, Paris, France, [14]University Medical Centre Ljubjana, Ljubljana, Slovenia, [15]Via Roma 67, Pisa, Italy, [16]Internal Medicine Unit, Policlinico San Marco, Bergamo, Italy, [17]viale Morgagni 85, Florence, Italy, [18]Rheumatology Unit, M. Scarlato Hospital, Scafati, Salerno, Italy, [19]Hematology, S.Gerardo Hospital, Monza, Italy, [20]Clinique Saint-Jean, Brussels, Belgium, [21]Oskar-Alexander-Street 26, Bad Bramstedt, Germany, [22]Rheumatology Unit, Pisa, Italy, [23]Istituto di Malattie Infettive e Tropicali, Università di Milano c/o Ospedale L. Sacco, Milano, Italy

Background/Purpose: Patients with cryoglobulinemic vasculitis (CV) or serum cryoglobulins without CV (CwV) a have an increased risk of lymphoma development. We compared the prevalence of lymphoma in HCV-positive or -negative patients with cryoglobulinemia.

Methods: Fifty hundred patients with positive serum cryoglobulins were studied. Mean age was 60.77±13.75 years, they were 356 females (71.2%) and 144 males (28.8%), and the first cryoglobulin positivity occurred thirty-four months before the last evaluation (range 3–290 months). 272 patients had CV (54.4%). The other 228 patients (45.6%) had other diseases associated with CwV. One hundred and seventeen HCV negative patients were collected and they were 42/272 (15.4%) among CV, while they were 75/228 (32.9%) among CwV.

Results: Globally, a lymphoma was diagnosed in thirty-two patients (32/500, 6.4%). Of them, fourteen patients were HCV negative (14/32, 43.7%). Furthermore, lymphoma was diagnosed in 18/383 HCV positive patients (4.7%), and 14/117 HCV negative patients (11.9%) (p=0.005, Pearson). Among the 18 HCV positive patients with lymphoma, a CV was present in 16/18 (88.9%), while among the 14 HCV negative patients with lymphoma, a CV was present in 10/14 (71.4%). In HCV positive, as well as in HCV negative patients, the diagnosis of a CV increases the risk of almost 5–6 times the risk of lymphoma (p=0.022, OR 5.7, 95% CI 1.3–25.1, and p=0.006, OR 5.5, 95% CI 1.6–19.0 for HCV positive and HCV negative patients, respectively). Among HCV negative patients, a Sjögren's syndrome (SS) was diagnosed in 55/117 (47%).

Conclusion: CV, much more than CwV, is associated with lymphoma prevalence. Lymphoma prevalence is higher in CV without HCV infection than in CV associated with HCV infection. Thus, lymphoma should be suspected with much higher attention in HCV negative CV patients, who often suffered from SS.

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Comparison of Clinical and Laboratory characteristics of Cryoglobulinemic Vasculitis Associated with Primary Sjögren's Syndrome and Hepatitis C Virus Infection. Svetlana G. Palshina[1] and Vladimir I. Vasiljev[2]. [1]Scientific research institute of rheumatology of RAMS, Moscow, Russia, [2]Scientific research institute of rheumatology of RAMS, Moscow, Russia, Moscow, Russia

Background/Purpose: To compare the clinical manifestations and laboratory data of cryoglobulinemic vasculitis (CV) in patients with primary Sjögren's syndrome (pSS) and hepatitis C virus (HCV) infection.

Methods: There were 54 patients with authentic CV included in the research, of whom 22 patients had HCV infection (group 1) and 32 - pSS

(group 2). The mean age in the cohort was 53,4 ±11,9 years, median duration of CV was 5 years (range, 0,75 −31), without statistical differences in the groups (p> 0,1). Females prevailed in both groups (92.6%). Kidney and liver involvement was confirmed morphologically. Electroneurophysiological methods evaluated the character of peripheral neuropathy. pSS/sSS fulfilled Russian criteria of SS. Real-time PCR, ELISA were performed for HCV. Lymphoma was confirmed morphologically/immunomorphologically after affected organ biopsy + bone marrow biopsy. Type of monoclonal secretion was assessed with high-resolution electrophoresis in agarose gel with subsequent immunofixation of sera and concentrated urine.

Results: There were no statistical differences (p> 0,05) in two groups in frequency of clinical symptoms such as purpura (81,8% vs. 93,8%), ulcers (18,2% vs. 25%), peripheral neuropathy (50% vs. 46,9%), glomerulonephritis (40,9% vs. 31,3%), lung involvement (18,2% vs. 18,8%), non-hodgkin lymphoma (NHL) (13,6% vs. 25%). We found no statistical differences (p>0,05) between groups in frequency of mixed monoclonal cryoglobulinemia (MMC) - (72,7% vs 74,2%), in median rheumatoid factor (RF) titer (337.8 IU/ml (9.5– 4890) vs. 147,4 IU/ml (9.5– 1714), and the percentage of seropositive patients (90,9% vs. 87,5%), mean levels of IgG (139,9±75,5 IU/ml vs. 161,6±107,7 IU/ml), median IgM (356,5 IU/ml(81–1900) vs. 333 (67–1607 IU/ml)), low levels of C4 (81% vs. 61,1%), median CRP (2,4 (0,2–44,9 mg/l) vs. 3,9 (0,2–101), ANA (81,8% vs. 84,4%), the median CD19+ (14,9% vs. 5,3%) and BAFF (0,64 vs 0,8 ng/ml). High levels of aRo (median 4,5 IU/ml (1,7–200) vs. 154 IU/ml (7,1–200)), aLa (median 6,6 IU/ml (0,8–33) vs. 36 IU/ml (1,2–200)), ANA>1/320 (27,8% vs 63%), increased IgA (9,1% vs 31,3%) were statistically more frequent in group 2 (p <0,05), while arthralgia/ arthritis (50% vs 28%) - in group 1 (p <0,05). 78.6% patients of group 1 had mild inflammatory grade of hepatitis, while 42.1% patients had severe liver fibrosis. 1b genotype of HCV prevailed (84.2%), the median viral load was 7,2 $\times 10^5$ cop / ml ($0–10^6$). 18.2% patients were chronic HCV-carriers with persistently normal liver enzymes. pSS/sSS was diagnosed in 27.3% patients of group 1. Of the 3 NHL associated with HCV, 2 patients had SS.

Conclusion: CV associated with pSS and HCV infection on the main clinical manifestations and laboratory parameters (MMC, RF, C4) doesn't differ significantly. Differences exist only in laboratory parameters such as aRo, aLa and ANA titer and arthralgia. The presence of pSS/sSS is one of the risk factors for NHL in patients with HCV-associated CV.

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Childhood Granulomatosis with Polyangiitis: Prevalence and Treatment of Airway Stenosis. Nicole M. Fowler[1], Jocelyn M. Beach[2], Paul Krakovitz[1] and Steven J. Spalding[1]. [1]Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Background/Purpose: Granulomatosis with polyangiitis, previously known as Wegener's granulomatosis (WG), is a necrotizing granulomatous vasculitis affecting the upper and lower respiratory tract, kidneys, and other small vessels throughout multiple organ systems. Recently, classification criteria for childhood WG (cWG) have been proposed and include the addition of airway stenosis. Airway inflammation occurs more frequently in children than adults and often proves difficult to diagnose and treat. Our objectives were to 1) determine the prevalence of airway involvement in a cohort of children with WG as defined by the European League Against Rheumatism/Pediatric Rheumatology European Society (EULAR) criteria, 2) document the frequency of specific airway findings and 3) review our treatment approach to children with WG-related airway disease.

Methods: Retrospective chart review performed on patients under 18 years old with a diagnosis of vasculitis evaluated at our institution between 2004 and 2010.

Results: 28 patients fulfilling EULAR classification criteria for the diagnosis of cWG were included in the analysis. Mean follow-up of 3.1 years. Larynotracheobronchial (LTB) disease occurred in 50% of patients. LTB disease was present at diagnosis in 36%, while in the remaining 14% it developed on immunosuppressive therapy. The development of airway disease or its progression occurred regardless of the immunosuppressant medication administered. In addition, medical management was inadequate for management of airway disease in 71% of patients. All patients underwent successful endoscopic intervention.

Conclusion: Airway manifestations frequently occur in cWG. Inflammatory changes can occur at any point in the disease course, necessitating diligent surveillance. Endoscopic interventions for LTB stenotic lesions represent a safe and effective therapeutic option.

1532

Comparison of CNS Vasculitis in Children and Adults: Is This the Same Disease Entity? Marinka Twilt[1], Tania Cellucci[2], Carlo Salvarani[3], Gene G. Hunder[4] and Susanne M. Benseler[1]. [1]The Hospital for Sick Children, Toronto, ON, [2]Hospital for Sick Children, Toronto, ON, [3]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [4]Mayo Clinic, Rochester, MN

Background/Purpose: Primary vasculitis of the central nervous system (CNS) is a devastating inflammatory disease restricted to the brain and spinal cord. Previously healthy children and adults can develop life-threatening neurological deficits including stroke and seizures. Recently distinct phenotypes have been proposed for childhood CNS vasculitis. However, clinical phenotypes have never been explored throughout the age spectrums. The aim of this study was to describe the presenting features of children and adults with CNS vasculitis, to compare distinct entities and their treatment regimens and to analyze disease progression and/or relapse.

Methods: Two cohorts of consecutive patients with primary CNS vasculitis based on Calabrese criteria were identified: 1) adult patients (Mayo Clinic, Rochester) and 2) pediatric patients (Sickkids, Toronto). Patient demographic characteristics, presenting clinical features, neuroimaging characteristics, brain pathology results, clinical course including progression and relapse and treatment regimens were recorded. Characteristics of cohorts were analyzed using descriptive statistics. Comparative analysis assessed distinct disease phenotypes and treatment regimens.

Results: A total of 227 patients were included in the study; 101 adult patients and 126 pediatric patients. In children the median age was 8 years (1–17 years) and in adults 47 years (17–84 years). Pediatric patients showed a male predominance (F: M = 1:1.5) in contrast with the adult cohort (F:M = 1.3: 1). In the children with angiography positive CNS vasculitis (n=97) there was a male predominance (F:M=1:2.2) and the main presenting clinical symptoms were hemiparis (74%) and speech problems (28%), while the adult patients with angiography positive CNS vasculitis (n=70) show a more female predominance (F:M= 1.6:1) and the main clinical features in adults were headache (69%) and visual symptoms (47%). Brain biopsy positive patients in the pediatric cohort (n=29) showed an almost exclusive female predominance (F: M = 4.2:1) and the presenting features in these children were mainly, seizures (83%), fever (38% and speech problems (21%), in the adults with biopsy positive CNS vasculitis (n=31) there was an equal gender distribution (F:M=1:1) and altered cognition (71%) and headache (52%) were most frequent. Histology showed exclusively lymphocytic inflammation in children (100%)and predominantly a granulomatous pattern in adults (58%). Treatment strategies: in children prednisone in 59 (47%) and cyclophosphamide in 34 (27%), in adults prednisone in 97 (96%) and cyclophosphamide in 46 patients (46%). Relapse or progression of the disease was seen in adults in 26% and in children in 15%.

Conclusion: Primary CNS vasculitis in adults and children encompassed distinct phenotypes across the age spectrum. Gender predominance varies significantly between subtypes. Presenting clinical features differed as well with more seizures, speech problems, hemiparesis and fever in the children and more altered cognition, visual symptoms and headaches in the adults. Although adults are treated significantly more frequently with steroids and cyclophosphamide, relapse rates are lower in children.

1533

Circulating Levels of Klotho In Kawasaki Disease: A Possible New Marker of Vascular Damage? Fernanda Falcini[1], Laura Masi[2], Francesco Franceschelli[2], Gigliola Leoncini[2], Serena Capannini[1], Francesco La Torre[3], Marco Matucci Cerinic[1] and Maria Luisa Brandi[2]. [1]Department of Internal Medicine, Rheumatology Section, Transition Clinic, University of Florence, Firenze, Italy, [2]Department of Internal Medicine, Endocrinology Unit, University of Florence, Firenze, Italy, [3]DIMIMP-University Rheumatologic Section, Policlinico of University, Bari, Italy

Background/Purpose: Vascular endothelial cell damage is critical in KD pathogenesis. FGF23/FGF23 receptor complex and its cofactor Klotho play an important role in the regulation of phosphate homeostasis, bone mineralization, control of vascular damage and atherosclerosis. Klotho is a circulating protein expressed in several tissues including vasculature. Pts with chronic renal failure have low serum levels of Klotho protein and develop vascular calcifications, and VEGF-mediated angiogenesis is impaired in Klotho-deficient mice. Several studies have shown that Klotho is a vasoprotective protein acting through multiple pathways. We previously demonstrated that KD pts have high serum levels of FGF23 indicating this factor as a potential predictor of atherosclerosis.

Aims: 1. To measure Klotho serum levels of in a cohort of KD pts. 2. To look for an association between Klotho levels and coronary damage.

Methods: Serum from 109 consecutive KD pts, median age 30.5 mnths, were collected for the measurement of Khloto protein using an ELISA method (Uscn Life Science Inc.). The intact assay is standardized to measure Klotho in nanograms per milliliter (ng/ml). 66 sex- and age-matched healthy children were studied as controls. In all pts data were recorded about familial predisposition to atherosclerosis.

Results: We found significant high amount of Klotho protein both in KD and healthy children. However, a trend characterized by lower levels of Klotho in KD *vs* healthy children was observed (KD: mean 246,97 +/− 174,6 vs. 302,3 +/−100 ng/ml). No significant differences in the serum Klotho levels between KD pts. with and without CA (235+/− 120 vs. 244+/−133 ng/ml) was detected.

Conclusion: The serum Klotho values in our subjects (both in KD and controls) was about 1000-fold higher than those reported in the literature. This may be due to the fact that our population was younger than that previously studied. The few data published in the literature indicate that serum alpha-Klotho correlated negatively with age. Indeed, alpha-Klotho is higher in prepubertal children in comparison with adults. In addition in umbilical cord blood klotho level is very high followed by a reduction after 4 days of life. It is plausible to hypothesize that the postnatal reduction of serum Klotho could be followed by an increment until the prepubertal age. This could in part explain the high values found in our population. Klotho is a pivotal vasoprotective protein and is considered an important factor attenuating atherosclerosis by several pathways. KD pts have a trend characterized by lower Khloto levels in comparison with health subjects. These preliminary results might open the way to a new marker of vascular damage in KD pts.

1534

Vessel Remodeling in Childhood Primary CNS Vasculitis: Impact of Corticosteroid Therapy. Gordon S. Soon, Ivanna Yau, Derek Armstrong, Pascal N. Tyrrell, Suzanne Laughlin, Gabrielle deVeber and Susanne M. Benseler. The Hospital for Sick Children, Toronto, ON

Background/Purpose: Childhood non-progressive primary CNS vasculitis (NPcPACNS) accounts for the single most common cause of vascular strokes in children. The aims of the study were 1) to describe the cerebral vessel imaging at presentation in children with NPcPACNS and 2) to determine whether corticosteroid therapy had any impact on follow-up imaging.

Methods: A single-centre cohort study of consecutive children diagnosed with cPACNS based on Calabrese criteria between January 1990 and December 2009 was performed. Children were included if they 1) had non-progressive cPACNS (unilateral proximal stenoses and no evidence of progression >3 months) and 2) had serial cerebral vessel imaging, including either Magnetic Resonance Angiography (MRA) or conventional angiography. The study excluded progressive cPACNS and angiography negative cPACNS. Data collection: Serial MRA and conventional angiography were blindly reviewed by two independent neuroradiologists following a previous developed protocol. Parenchymal lesions were characterized by number, size, and location (laterality, arterial territory, grey/white matter involvement). Cerebral vessel involvement was characterized by location and features of stenoses, including artery name, number affected, severity, laterality, and appearance (beading, dilatation, smooth, irregular). Analysis: frequencies were compared using descriptive statistics.

Results: A total of 44 children with NP-cPACNS were included. Initial cerebral vessel imaging included conventional angiography in 39 children (89%). Proximal middle cerebral artery (MCA) was involved in 35 children (80%), distal internal carotid artery (ICA) in 25 (57%), and proximal anterior cerebral artery (ACA) in 17 (39%). Left-sided vascular disease was detected in 28 children (64%). Sixteen children (36%) had a maximal stenosis of >75%, including 13 (30%) with complete occlusion. Children treated with corticosteroid therapy had a significantly higher degree of stenosis on initial imaging (p=0.02). At 3 month follow-up imaging, there was no statistical difference in the number of affected vessels, degree of stenosis, or maximum length of stenosis compared between children treated with and without corticosteroid therapy.

Conclusion: NPcPACNS likely represents an inflammatory attack on the arterial wall thus providing the rationale for considering immunosuppressive therapy on presentation. At our institution, corticosteroid therapy was not uniformly provided in children with NPcPACNS but was typically reserved for children with the most severe arteriographic abnormalities. Nonetheless, cerebral vessel imaging at 3 month follow-up was similar in children treated with and without corticosteroid therapy, thereby suggesting a possible role for immunosuppressive treatment of this disease.

1535

Systemic Vasculitis and Pregnancy: Maternal and Neonatal Outcome of 20 Prospectively Followed Pregnancies. Micaela Fredi[1], Marta Mosca[2], Tamara Ziglioli[1], Chiara Tani[2], Matteo Filippini[1], Francesca Strigini[2], Laura Andreoli[1], Cinzia Casu[1], Mario Motta[3], Andrea Lojacono[4] and Angela Tincani[1]. [1]Rheumatology Unit, University of Brescia, Brescia, Italy, [2]University of Pisa, Pisa, Italy, [3]Neonathology and NICU, Spedali Civili, Brescia, Italy, [4]Obstetric and Gynecology of Brescia, Brescia, Italy

Background/Purpose: The increasing knowledge in diagnosis and management of primary systemic vasculitis (SV) has led to an earlier detection and treatment of such diseases with the consequent improvement of survival rate and quality of life. SV are rare diseases and, unlike other autoimmune conditions, they do not preferentially affect women. Therefore our understanding of the relationship between pregnancy and SV is limited. The aim of this study was to describe pregnancy outcome in patients with diagnosis of SV followed in our Institution; to evaluate the influence of pregnancy on maternal disease.

Methods: Analysis of 20 pregnancies (prospectively followed by a multispecialistic team) in 15 patients with diagnosis of SV, according to Chapel Hill Consensus Conference and/or ACR Criteria for SV. Two patients were affected by Takayasu arteritis (TA), 3 by Churg-Strauss syndrome (CS), 2 by Polyarteritis nodosa (PA), 8 by Behcet's disease (BD). Data regarding the duration of disease, serological and clinical features, pregnancy outcome, neonatal and maternal complications and therapy during pregnancy were collected from clinical charts.

Results: All the patients conceived during clinical and serological remission of the disease. The median age of the patients at the conception was 33 (range 27–40); 13 patients were Caucasian, 1 from North Africa and 1 from South America. The mean duration of SV before pregnancy was 8 years (range 1–17). Reproductive history of each patient is detailed in the table. There were 2 miscarriages and 2 fetal death in 2 patients (20% of all pregnancies); 4 pregnancies (20%) had complications: 1 preeclampsia, 3 premature deliveries (before 34 week), 1 post-partum haemorrhage and a post-partum disseminated intravascular coagulation (DIC). Flares of the disease appeared in 5 patients (33,3%): 1 PA, 2 TA and 2 BD. We had 18 live births: 5 premature (28%), in particular 1 newborn small for gestational age (SGA), 1 suffered from necrotizing enterocolitis (NEC) and 1 from respiratory insufficiency.

Conclusion: Our data show that conceiving during the remission of the disease and strictly monitoring of the pregnancy seem to be not sufficient to prevent flare of the disease, maternal and neonatal complications. In particular we want to emphasize the elevated frequency of preterm delivery before the 34th week among the live births (28% vs 5% of the general obstetric population of our hospital).

Table.

Pt	Disease	N° pregnancy	Outcome	Week of delivery or loss	Maternal complications	Neonatal complications	Treatment
1	TA	3	a) miscarriage b) miscarriage c) live birth (twins)	a) 7 b) 8 c)32	Flare of the disease 2nd trimester, abruptio placentae	—	LDA, PDN
2	TA	1	a)live birth	a) 38	Flare of the disease 3rd trimester, PROM	—	LDA AZA LMWH
3	PA limited	2	a) live birth b) live birth	a)38 b)40	—	—	LDA
4	PA systemic	1	a)live birth	a)30	Flare of the disease 2nd trimester, preclampsia	SGA	LDA, PDN, antihypertensive therapy
5	CS	1	a) live birth (twins)	a)31	Abruptio placentae; post-partum haemorrhage	1 with NEC, 1 with RI	PDN, asthma therapy
6	CS	1	a)live birth	a)39	—	—	PDN, asthma therapy,
7	CS	1	a)live birth	a) 40	—	—	—
8	BD	1	a)live birth	a)38	Flare of the disease 1st trimester; post partum DIC	—	LDA cyclosporine, PDN
9	BD	1	a)live birth	a)39	—	—	LDA
10	BD	1	a)live birth	a)38	—	—	LDA, LMWH
11	BD	3	a) fetal death b) fetal death c) live birth	a) 12 b) 15 c)38	—	—	LDA, LMWH
12	BD	1	a)live birth	a)40	Flare of the disease 2nd trimester	—	LDA, M-PD
13	BD	1	a)live birth	a)40	—	—	—
14	BD	1	a)live birth	a)37	—	—	PDN, LDA
15	BD	1	a)VIP	—	—	—	MMF, LMWH, antihepileptic drug

LDA= low dose aspirin, LMWH= low-molecular-weight heparin, PDN= prednisone, M-PD=methyl prednisolone, MMF= mycophenolate mofetil, NEC= necrotizing enteritis, IR= respiratory insufficency, VIP= voluntary interruption of pregnancy, DIC= disseminated intravascular coagulation, SGA= small for gestational age

1536

Infertility Among Patients with Vasculitis. Megan E. B. Clowse[1], Rachel Richesson[2], Carl Pieper[1], Peter A. Merkel[3] and Vasculitis Clinical Research Consortium[4]. [1]Duke University Medical Center, Durham, NC, [2]University of South Florida, Tampa, FL, [3]Boston University School of Medicine, Boston, MA, [4]Boston

Background/Purpose: Fertility may be impaired in men and women with vasculitis due to morbidity from the disease and the high prevalence of cyclophosphamide (CYC) use. This study assessed the rate of infertility in patients who had and had not completed childbearing before the diagnosis of vasculitis, the frequency of discussions about the risks to fertility, and interventions to prevent infertility from CYC.

Methods: All participants in the Vasculitis Clinical Research Consortium Patient Contact Registry were invited to participate in an internet-based anonymous questionnaire about reproductive health. Participants were divided into two groups based on interest in having children at the time of diagnosis: i) childbearing completed; and ii) childbearing not completed. Other data collected included CYC exposure, infertility, whether the patient recalled discussing fertility prior to CYC dosing, and if they took steps to prevent infertility.

Results: 450 participants completed the questionnaire and reported a diagnosis of vasculitis by a specialist and/or received immunosuppressive medications other than prednisone. 304 of 450 (68%) had completed childbearing at the time of their diagnosis of vasculitis; this group had a mean age almost 20 years older at diagnosis than the 146 participants who had not completed childbearing at the time of diagnosis (Table).

	WOMEN		MEN	
	Completed childbearing prior to vasculitis	Not completed childbearing prior to vasculitis	Completed childbearing prior to vasculitis	Not completed childbearing prior to vasculitis
Number	221	122	83	24
Current Age (years)	54.1*	35.9	59.1*	41.4
Age at diagnosis (years)	47.9*	27.0	53.7*	30.1
Infertility	11.6%	17%	9.6%*	33.3%

* p-value <0.0001 comparing completed and not completed childbearing.

Infertility was not significantly different between women who had and had not completed childbearing. However, among women diagnosed before age 40, those who received CYC had an almost 3-fold higher rate of infertility compared to women without CYC (24.3% vs 8.8%, $p<0.01$). A discussion of the impact of CYC on fertility was recalled by 67.8% of women who hadn't completed childbearing, of whom 17 (43%) took steps to preserve ovarian function during treatment including using GnRH-agonists (7), oral contraceptives (8), both methods (1), and depot medroxyprogesterone (1).

Infertility was significantly higher among men who had not completed childbearing at vasculitis diagnosis, but receiving CYC did not impact this rate. Future fertility was discussed with 83.3% of men interested in having children prior to CYC, half of whom stored sperm for future use.

Conclusion: The rate of infertility was increased in young women with vasculitis exposed to CYC. A significant minority of women did not recall being informed of the risk of infertility at the time of treatment; of those informed, less than half took steps to prevent infertility. Interestingly, infertility did not appear to be associated with CYC in men, but a higher percentage of them had been informed of this risk and half took measures to protect against infertility. This data confirm that infertility is an important concern for patients with vasculitis and that physicians need to be more vigilant about discussing the risk of infertility with their patients with vasculitis.

1537

Pregnancy in Men and Women with Vasculitis. Megan E. B. Clowse[1], Rachel Richesson[2], Carl Pieper[1], Peter A. Merkel[3] and Vasculitis Clinical Research Consortium[4]. [1]Duke University Medical Center, Durham, NC, [2]University of South Florida, Tampa, FL, [3]Boston University School of Medicine, Boston, MA, [4]Boston

Background/Purpose: The outcome of pregnancies in men and women with vasculitis is unknown because of the relative rarity of the condition, but is an area of great concern to patients and physicians. In a survey of a large population of patients with vasculitis, this study assessed the pregnancy outcomes before and after a diagnosis of vasculitis.

Methods: All participants in the Vasculitis Clinical Research Consortium (VCRC) Patient Contact Registry were invited to participate in a one-time, internet-based anonymous questionnaire about reproductive health. Participants were asked to report the total number of pregnancies they had carried (women) or fathered (men), as well as the outcomes (live birth, pregnancy loss, preterm birth) of those pregnancies, the timing of pregnancy relative to the diagnosis of vasculitis, and medications taken during pregnancy or at the time of conception. Elective abortions and current pregnancies (4) were excluded from the analysis. Outcomes from pregnancies before and after vasculitis were compared, taking into account the effect of the individual propensity for a given outcome in the analysis.

Results: A total of 65 pregnancies after a diagnosis of vasculitis were reported by women and 17 by men. The rate of pregnancy loss was statistically higher in pregnancies in women after the diagnosis of vasculitis compared to prior to vasculitis (34% vs 23%, $p=0.03$). Among women with vasculitis, there was a non-significant increase in the rate of preterm births in pregnancies after vasculitis than before (23% vs 13%, $p=0.1$). For pregnancies that followed the diagnosis of vasculitis, 59% reported that vasculitis activity was not impacted by pregnancy, 23% reported improvement in vasculitis during pregnancy, and 18% reported worsening of disease during pregnancy. For men, the pregnancy loss rate was 59% in 17 pregnancies conceived after vasculitis, compared to 75% of 130 pregnancies prior to vasculitis ($p=0.7$). Pregnancy outcomes and vasculitis activity in pregnancy did not differ significantly between diagnoses for men or women, although the power to detect such differences was low.

24 pregnancies were exposed to prednisone (39% of the pregnancies after the diagnosis of vasculitis). The pregnancy loss rate and preterm birth rates were not statistically different between pregnancies with and without prednisone exposure. 7 pregnancies were exposed to azathioprine resulting in 1 elective abortion, 2 miscarriages, 2 live term births, with 2 pregnancies ongoing. 2 pregnancies were exposed to methotrexate, one was electively aborted and one ended in a miscarriage. One pregnancy resulted in a live term birth after exposure to cyclophosphamide. The pregnancy loss rate was not elevated in the 15 pregnancies conceived by women with prior exposure to cyclophosphamide.

Conclusion: Pregnancies conceived by women following the diagnosis of vasculitis had a higher rate of pregnancy loss compared to those conceived prior to diagnosis. Vasculitis was not worsened during the majority of pregnancies conceived after diagnosis. A larger study will be required to determine the impact of medications in pregnancy success among women with vasculitis.

ACR/ARHP Poster Session B
ARHP Epidemiology and Public Health
Monday, November 7, 2011, 9:00 AM–6:00 PM

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The Impact of Pain on Successful Ageing. Ross Wilkie[1], Abdelouahid Tajar[2] and John McBeth[1]. [1]Keele University, Newcastle-under-Lyme, United Kingdom, [2]University of Manchester, Manchester, United Kingdom

Background/Purpose: With population ageing there is growing drive to promote a healthier old age and ways to age successfully. Successful ageing is a multi-faceted state, which involves preservation of biomedical, physical, psychosocial and lay components to enable cognitive, physical and mental well-being, social participation and quality of life. Musculoskeletal pain is common in older adults and is considered as a stressor which impacts on a number of body functions. This is the first longitudinal study to investigate the relationship between musculoskeletal pain and successful ageing in the general population.

Methods: A population-based prospective cohort study of adults aged 50 years and over, the North Staffordshire Osteoarthritis Project (NorStOP) was conducted. Subjects were those who had completed questionnaires at base-

line, 3 and 6-year follow-ups. Based on their reports of pain, subjects (n = 2949) were classified into those reporting no pain, regional pain and widespread pain (American College of Rheumatology criteria). Using published methodology a 33-item successful ageing index (SA) was constructed by summing the number of deficits (health deficits across biological, psychological and functional domains). The SA score was calculated for each subject at baseline, 3 and 6 years by dividing the number of deficits by the total number of potential deficits and was expressed as a score from 0 to 100. Linear regression models were used to test the association between SA at each time point and pain status at baseline, first unadjusted and then adjusting for age, gender, education and social network. Mixed modelling was used to explore the longitudinal trends in SA across six years; pain was included as a time varying variable to examine the impact of change in pain on SA.

Results: The median age of the subjects was 61(inter-quartile range: 55 to 67) and 54% were female. At baseline 834 (28.7%) had no pain, 1296 (44.5%) had regional pain and 780 (26.8%) had widespread pain. Compared to those with no pain, subjects with regional pain had a higher SA score at all three time points ($p<0.01$). Those with widespread pain had the highest scores. Baseline regional and widespread pain were associated with SA scores after adjusting for covariates. Increasing pain was associated with increasing SA scores over time (Table1); an increase from none to regional and regional to widespread pain resulted in a 19% and 17% increase in SA scores respectively. An increase from none to widespread pain lead to a 40% increase in SA score.

Table 1. Longitudinal relationship between pain and Successful ageing index*

	M (I): Empty model	M (II): Adding time to M (I)	M: (III) Adding pain to M (II)	Model (IV): Adding age, gender education and social network to M (III)
βeta coefficients (95% CI)				
Intercept	3.07 (3.05, 3.09)**	2.94 (2.91, 2.96)**	2.76 (2.73, 2.79)**	2.68 (2.59, 2.76)**
TIME	—	0.07 (0.06, 0.08)**	0.06 (0.06, 0.07)**	0.06 (0.05, 0.07)**
Regional pain	—	—	0.18 (0.16, 0.21)**	0.19 (0.16, 0.21)**
Widespread pain	—	—	0.34 (0.31, 0.36)**	0.33 (0.30, 0.36)**

* Index scores have been log transformed. ** $p<0.001$. CI Confidence interval

Conclusion: The results from this study indicate that pain has a significant adverse affect on successful ageing. The cross-sectional results indicate that at baseline, individuals with regional and widespread pain have accumulated significantly more signs of less successful ageing than those with no pain. The longitudinal results indicate that increasing pain significantly accelerates the rate of less successful ageing.

1539

Not So Golden Years: Older (≥65 years) Women with Arthritis Are Employed Least and Disabled Most. Kristina A. Theis[1] and Sylvia Furner[2]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]University of Illinois at Chicago, Chicago, IL

Background/Purpose: Employment of older workers (≥65 years) increased >100% between 1977 and 2007; the U.S. Bureau of Labor Statistics projects further increases as Baby Boomers age. Employment is lower among working-age (18–64 years) adults with arthritis compared with non-arthritis peers. The purpose of this study is to estimate the prevalence and change over time of employment and work disability among older adults (≥65 years) with and without arthritis by sex.

Methods: Data were obtained from the 2002–2009 National Health Interview Surveys (mean n = 27,729; mean response rate = 70%), an annual, multistage probability survey by in-person interview designed to represent the U.S. civilian, non-institutionalized population. Arthritis diagnosis was identified by "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" We analyzed respondents ≥65 years who self-identified as employed or work disabled (unable to work due to disability). Weighted proportions and prevalence ratios with 95% confidence intervals (CI) were calculated accounting for complex sample design (SAS 9.2).

Results: The proportion of employed women with arthritis was significantly lower than that of men with or without arthritis in all years and significantly lower than for women without arthritis in all years except 2002 and 2007. The proportion of work disability among women and men without arthritis was lower than for men and women with arthritis. All groups had a higher probability of being employed compared with WA+ in all years (Table).

Table. Prevalence ratios (PR) and 95% confidence intervals (CI) for employment and work disability among older adults (≥65 years) with and without arthritis, by sex, NHIS, 2002–2009

	MALE Arthritis				FEMALE Arthritis			
	No		Yes		No		Yes (referent)	
	Employed							
Year	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI
2002	2.3	(1.8–2.9)	1.9	(1.4–2.4)	1.3	(1.0–1.6)	1.0	(1.0–1.0)
2003	2.3	(1.9–2.9)	2.2	(1.7–2.9)	1.7	(1.3–2.1)	1.0	(1.0–1.0)
2004	2.4	(2.0–3.0)	1.6	(1.3–2.1)	1.5	(1.2–1.9)	1.0	(1.0–1.0)
2005	2.6	(2.1–3.2)	1.8	(1.5–2.3)	1.8	(1.4–2.2)	1.0	(1.0–1.0)
2006	2.2	(1.7–2.9)	2.0	(1.5–2.6)	1.6	(1.2–2.0)	1.0	(1.0–1.0)
2007	1.8	(1.4–2.2)	1.6	(1.2–2.1)	1.3	(1.0–1.7)	1.0	(1.0–1.0)
2008	2.4	(1.9–3.2)	1.8	(1.3–2.4)	1.6	(1.2–2.0)	1.0	(1.0–1.0)
2009	1.9	(1.5–2.3)	1.7	(1.4–2.2)	1.4	(1.1–1.8)	1.0	(1.0–1.0)
	Work Disabled							
2002	0.6	(0.4−0.8)	0.7	(0.5–1.1)	0.5	(0.3−0.7)	1.0	(1.0–1.0)
2003	0.4	(0.3−0.6)	0.9	(0.6–1.2)	0.5	(0.4−0.7)	1.0	(1.0–1.0)
2004	0.5	(0.3−0.7)	1.0	(0.8–1.4)	0.7	(0.5−0.9)	1.0	(1.0–1.0)
2005	0.5	(0.4−0.7)	0.6	(0.4−0.9)	0.3	(0.2−0.5)	1.0	(1.0–1.0)
2006	0.5	(0.3−0.7)	0.8	(0.5–1.2)	0.4	(0.3−0.7)	1.0	(1.0–1.0)
2007	0.7	(0.5−0.9)	0.9	(0.6–1.3)	0.5	(0.4−0.8)	1.0	(1.0–1.0)
2008	0.4	(0.2−0.5)	0.6	(0.4−0.9)	0.4	(0.3−0.6)	1.0	(1.0–1.0)
2009	0.4	(0.3−0.7)	1.0	(0.6–1.4)	0.5	(0.3−0.8)	1.0	(1.0–1.0)

Conclusion: Older women with arthritis are at an employment disadvantage compared with other groups. High work disability in women with arthritis ≥ 65 years suggests these women want or need to be working and may benefit from evidence-based public health programs shown to reduce and delay disability. Vocational rehabilitation and job accommodations may also help. The aging of the population and projected employment trends suggest these adverse employment and work disability disparities will continue to grow unless addressed.

1540

A Population-Based Study Comparing the Impact of Arthritis and Chronic Joint Symptoms: Are There Implications for Arthritis Education and Health Care? Mayilee Canizares[1] and E. M. Badley[2]. [1]Toronto Western Research Institute, Toronto, ON, [2]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background/Purpose: Arthritis is one of the most common conditions, affecting 15%-20% of the population. Surveys suggest that a further 10%-15% of the population report chronic joint symptoms (CJS). CJS have been considered as an indication of possible arthritis with studies showing conflicting results. Most of these studies have compared predictors of CJS and arthritis but only a minority have considered health-related outcomes. This study compares predictors and health outcomes for individuals with self-reported arthritis and those without arthritis reporting chronic or sporadic joint symptoms.

Methods: Data from the 2008 Canadian Community Health Survey (15+; n=66,013) were used for analyses. Respondents were asked about arthritis as a long-term chronic health condition diagnosed by a health professional. Participants not-reporting arthritis were further asked about joint symptoms excluding the back and neck over the past 12 months. Analyses were conducted for the following mutually exclusive groups: arthritis, chronic joint symptoms (symptoms present on most days in the past month), sporadic joint symptoms (other joint symptoms in the past 12 months (SJS)), and no arthritis and no joint symptoms (NJS). Log-Poisson regression was used to examine risk factors for each of these groups. Similar regressions, adjusting for socio-demographic, lifestyle factors, and comorbidities were used to

estimate the risks of reporting physical inactivity, three health outcomes (poor/fair overall health, poor/fair mental health, activity limitation), and five measures of healthcare use.

Results: 16.0% of the population reported arthritis, 10.1% reported CJS and 11.6% reported SJS. Individuals with arthritis were older than those with CJS or SJS. Women reported arthritis and CJS more often while men reported SJS. Other than age, the profile of risk factors for arthritis and CJS was similar, notably obesity and overweight. After adjusting for age, sex, SES, lifestyle factors and comorbidities, prevalence ratios showed similar risks for physical inactivity, and all health outcomes and health care use measures for the arthritis and CJS groups, and these were higher than those for SJS group.

Conclusion: CJS was reported by one-in-ten of the adult population. The similarities in risk factors, other than younger age, for CJS and arthritis suggest that the CJS group might represent people in early stages of arthritis who have not yet been diagnosed. The similar impact of CJS and arthritis on health outcomes and increased healthcare use, suggests that arthritis education and management interventions are likely to be beneficial for the CJS group with possible unrecognized arthritis.

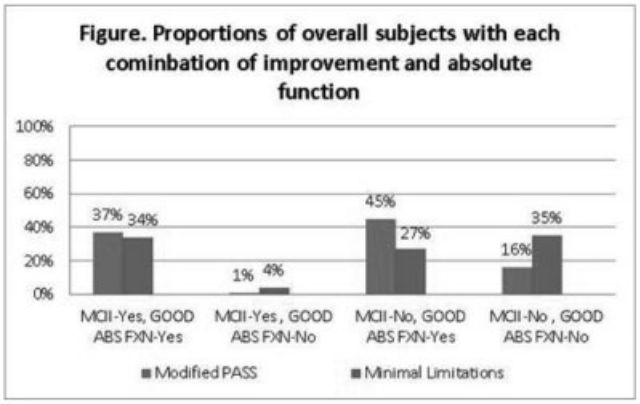
1541

Does Important Improvement in Function After Knee Replacement Guarantee Good Absolute Function. Jessica L. Maxwell[1], David T. Felson[2], Jingbo Niu[2], Barton Wise[3], Michael C. Nevitt[4], Jasvinder Singh[5], Laura Frey-Law[6] and Tuhina Neogi[2]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Ctr for Healthy Aging-UC Davis, Sacramento, CA, [4]University of California-San Francisco, San Francisco, CA, [5]University of Alabama at Birmingham and Birmingham VA Medical Center, Birmingham, AL, [6]University of Iowa, Iowa City, IA

Background/Purpose: Improvement in function is a goal of knee replacement (KR) surgery and the focus of prior studies. However, how relative improvement relates to absolute levels of functioning post-KR is important from a patient perspective as persons with knee OA care more about their absolute functional state than improvement (Tubach, 2006). It is possible that despite improvement, some may be limited in function post-KR. We investigated whether the attainment of a minimal clinically important improvement (MCII) in function indicates good absolute function post-KR.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort study of persons with or at high risk of knee osteoarthritis. A person-specific WOMAC physical function (PF) questionnaire was administered at each study visit (baseline, 30, and 60 months). We focused on those who had a KR during follow-up with pre- and post-KR data. Pre-KR function data was obtained from the clinic visit immediately prior to KR, and post-KR data was at the next immediate clinic visit, typically between 6 and 24 months post-KR. We examined the frequency of MCII post-KR (WOMAC-PF improvement of $\geq$14.2/68 (Escobar, 2007)) and good absolute function using 2 separate definitions: i) modified Patient Acceptable Symptom State (PASS) for knee OA using WOMAC-PF $<$25.9/68 (Tubach, 2006) ["modified PASS"]; ii) WOMAC-PF score $<$17/68 representing an average score of "mild" impairment on each of the 17 items ["mild limitations"]. The proportion of subjects who had pre-KR function sufficiently high so that they were unable to attain an MCII were analyzed separately.

Results: There were 245 subjects with pre- and post-KR data (mean age 65 years, 29% male). Overall, 44% achieved a MCII post-KR, and good absolute function post-KR was attained by 80% and 57% based on modified PASS and mild limitations, respectively. The majority of those with a MCII attained a good absolute function post-KR ($\sim$ 1/3 of total sample) (see Figure). A substantial proportion who did not attain a MCII had good absolute function by the modified PASS and to a lesser extent by the mild limitations definition. Good pre-KR function in 33 subjects precluded their ability to attain a MCII. Of these, 94% (modified PASS) and 79% (mild limitations) had good absolute function post-KR, indicating that some may have had a decline in function post-KR.



Conclusion: Improvement in function and absolute functional status post-KR are not necessarily related. While attainment of MCII is related to good absolute function, substantial proportions may have good absolute function without attaining an MCII. More research is needed to determine what measure of absolute function indicates good status post-KR as the PASS may represent functional status with greater-than-mild limitations and thereby overestimate the proportion with a good absolute level of function post-KR.

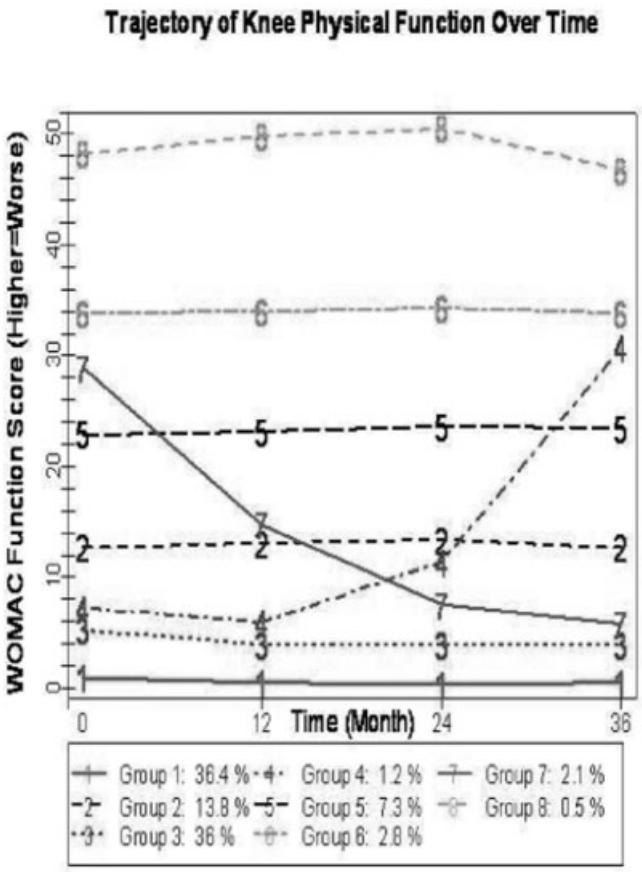
1542

Patterns of WOMAC Function in People with or At High Risk of Knee Osteoarthritis: The Osteoarthritis Initiative. Uyen Sa D. Nguyen[1], Bin Zhang[2], Jingbo Niu[1], Daniel K. White[1] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA

Background/Purpose: Despite people with knee osteoarthritis (OA) being at high risk of poor physical function, little is known of changes in physical function over time. Understanding these patterns of change and identifying risk factors of decline could help in preventing the development of poor physical function. We described the trajectories of change in physical function over time and evaluated factors associated with these trajectories of change.

Methods: Knee-specific WOMAC physical function scores were assessed in the participants at baseline and at three subsequent annual visits in the Osteoarthritis Initiative. We restricted this analysis to knees with 3 or 4 WOMAC function scores. We used SAS PROC TRAJ, a group-based finite mixture modeling, to identify distinctive sub-groups of knees that follow similar trajectories of physical function over time. The PROC TRAJ procedure, using likelihood estimation, assigned each knee into a discrete group according to its function trajectory within the population. Model fit was assessed using Bayesian Information Criteria. We compared characteristics across the sub-groups using χ^2 or ANOVA.

Results: Among 4,379 participants (58% women, 17% African Americans, mean age: 61, mean BMI: 29, mean WOMAC function at baseline: 8), we identified 8 distinctive trajectories of knee-specific WOMAC function over 3 years. As shown (Figure), 96.7% of the knees (Groups 1, 2, 3, 5, 6, 8) had stable physical function over time--average score changed $\leq$ 2 points or $\leq$ 10% from year to year; 1.2% of the knees had worsened function (Group 4), and 2.1% of the knees had improved function (Group 7). Two pairs of trajectories had similar baseline function scores but diverged over follow-up (Table, Group 3 vs. 4, and Group 6 vs. 7). Group 4 worsened over time compared with Group 3, and had a higher proportion of African Americans (32% vs. 14%) and people who were morbidly obese (25% vs. 8%), knees with severe ROA (47% vs. 32%) and replacement therapy (5% vs. 2%). Conversely, Group 7 improved over time compared with Group 6, and had fewer females (65% vs. 73%) and African Americans (35% vs. 57%), people with morbid obesity (19% vs. 36%) and major depressive symptoms (6% vs. 18%), but higher proportion of knee replacement therapy (9% vs. 5%). We repeated the analyses using worst function in the two knees and found similar results.



Conclusions: The majority of knees had stable function over three years; however, a small proportion had substantial change in function. Several factors such as socio-demographic, anthropometric, structural lesions and medical interventions may explain differences in the trajectories of function over time.

1543

Disease Impact of Osteoarthritis in Hands, Hip, Knee or Generalized Osteoarthritis—a Cross Sectional Study. Rikke Helene Moe[1], Margreth Grotle[1], Ingvild Kjeken[2], Kåre Birger Hagen[1], Tore K. Kvien[3] and Till Uhlig[3]. [1]National Resource Centre for Rehabilitation in Rheumatology, Diakonhjemmet Hospital, N-0319 Oslo, Norway, [2]Diakonjemmets Hospital, Oslo, Norway, [3]Diakonhjemmet Hospital, Oslo, Norway

Background/Purpose: Osteoarthritis (OA) is a leading cause of pain and disability. Knowledge is limited concerning disease impact and the localization of OA and. Therefore, we aimed to describe demographic characteristics, health status and disease impact in patients with hand OA compared to hip, knee or generalized OA.

Methods: We included 409 patients who were referred to a specialized rheumatology outpatient clinic with a clinical diagnosis of OA. Patients were examined clinically by a rheumatologist and classified into hand, hip, knee and/or generalized OA (defined as OA in at least two extremity localizations) based on the primary localization of complaints. Demographic variables included age, gender and body mass index (BMI). The patients completed questionnaires including pain, fatigue, and stiffness and patient global disease activity on numeric rating scales (NRS, range 0–10, 0 is best health), Hopkins Symptom Checklist-25 (HSCL-25, 1–4, 1 is best), Arthritis Self-Efficacy Scales (ASES, 0–100, 100 is best), Western Ontario and McMaster index (WOMAC) (0–30, 0 is best) and Australian/Canadian hand index (AUSCAN, 0–10, 0 is best) and SF-36 physical and mental component summary scores (PCS and MCS, 0–100, 100 is best).

Results: The 408 patients (86% women) had a mean (SD) age of 63.1 (8.0) years. Hand OA was the most frequent diagnosis (n=270, 66%), while hip (n=33, 8%), knee (n=75, 18%) and generalized OA (n=30, 7%) were less frequent. Patients with hand or generalized OA were significantly older and had lower BMI compared to patients with isolated knee OA (table). Frequent co-morbidities for all groups were allergies, hypertension, ischialgia and chronic inflammatory diseases.

All groups reported moderate to severe pain with mean values >5 on NRS. Hip and knee OA patients had highest scores for WOMAC and hand OA and generalized OA patients for on AUSCAN. Patients with hand OA and generalized OA scored overall better on physical functioning (SF-36 PCS) than patients with knee and hip OA. All groups reported high HSCL scores (mean value >1.5), indicating high levels of psychosocial symptoms (table).

Scale, Mean (SD) (range)	Hand OA n=270	Hip OA n=33	Knee OA n=75	Generalized OA n=30
Age (years)	63.18 (0.5)	61.0 (1.4)	60.8 (1.1)	63.2 (1.5)
BMI	25.9 (0.3)	26.3 (0.6)	27.7 (0.66)	24.1 (0.9)
Pain (1–10, NRS)	5.2 (0.1)	6.1 (0.4)	5.2 (0.26)	5.1 (0.4)
Fatigue (1–10, NRS)	3.9 (0.19)	4.9 (0.6)	4.8 (0.3)	4.5 (0.6)
Stiffness (NRS)	5.1 (0.17)	5.9 (0.5)	5.0 (0.3)	6.0 (0.4)
Disease act (NRS)	4.6 (0.14)	5.7 (0.4)	5.2 (0.3)	5.0 (0.5)
AUSCAN sum	5.11 (0.2)	3.7 (0.4)	3.8 (0.3)	5.1 (0.4)
Pain	5.04 (0.2)	4.0 (0.4)	3.9 (0.3)	4.9 (0.4)
stiffness	5.1 (0.2)	3.8 (0.6)	3.8 (0.4)	5.4 (0.4)
physical	5.2 (0.17)	3.3 (0.5)	3.7 (0.3)	4.8 (0.5)
WOMAC sum	10.4 (0.6)	11.9 (1.2)	13.5 (0.8)	11.6 (1.3)
Pain	3.3 (0.2)	3.9 (0.4)	4.8 (0.3)	3.7 (0.4)
stiffness	4.1 (0.2)	4.5 (0.4)	4.6 (0.3)	4.6 (0.5)
physical	3.0 (0.2)	3.5 (0.5)	4.1 (0.3)	3.3 (0.5)
HSCL-25	1.63 (0.0)	1.5 (0.1)	1.7 (0.0)	1.6 (0.1)
ASES pain	58.4 (1.7)	60.4 (3.09)	53.3 (2.6)	56.8 (6.0)
ASES symptoms	67.7 (1.53)	73.4 (1.9)	62.8 (2.1)	70.9 (5.0)
SF-36				
Physical functioning	68.78 (1.3)	50.2 (3.6)	50.0 (2.5)	65.46 (4.0)
Role physical	61.50 (1.9)	50.6 (5.6)	51.38 (3.4)	57.62 (5.4)
Pain	47.60 (1.5)	37.60 (3.2)	41.56 (2.1)	42.63 (1.7)
General health perception	46.39 (1.2)	37.59 (3.2)	42.11 (2.0)	41.79 (3.3)
Vitality	55.63 (0.7)	51.82 (1.5)	55.25 (1.1)	56.03 (2.1)
Social functioning	49.01 (0.7)	45.70 (1.2)	50.00 (1.1)	47.85 (2.2)
Role emotional	82.61 (1.6)	85.68 (4.6)	77.05 (3.2)	82.47 (4.6)
Mental health	68.83 (0.5)	69.22 (1.4)	67.82 (1.3)	69.27 (2.0)
PCS	38.5 (0.7)	37.5 (1.8)	35.9 (1.2)	36.6 (1.9)
MCS	46.5 (0.5)	47.5 (1.3)	46.7 (1.1)	46.2 (1.9)

Conclusion: OA patients who were referred to specialist care had high age and demonstrated considerable disease impact. Patients with hand OA reported especially pain and disability in hands but also disease impact for the lower extremities. Similarly, patients with lower extremity OA reported poor functioning of the lower extremities, but also of the hands. These findings indicate considerable disease impact with reduced health-related quality of life regardless of the OA localization.

1544

Association of Depressive Symptoms and Helplessness with Socioeconomic Status in People with Hip Osteoarthritis. My-Linh Luong, Leigh F. Callahan, Rebecca J. Cleveland, Britta L. Schoster, Jordan Renner and Joanne M. Jordan. University of North Carolina, Chapel Hill, NC

Background/Purpose: Individual and community socioeconomic status (SES) variables have demonstrated associations with psychosocial outcomes in self-report and other types of arthritis, but these associations have not yet been examined in hip osteoarthritis (OA). The purpose of this study is to evaluate the role of both individual and community-level SES as determinants of psychosocial outcomes of African Americans (AA) and Caucasians with hip OA.

Methods: A cross-sectional analysis was performed on 735 participants with hip radiographic OA (rOA) (defined as Kellgren-Lawrence (KL) grade ≥2) from the first follow-up evaluation and new enrollees (1999–2003) of the Johnston County Osteoarthritis Project. Psychosocial outcomes included depressive symptoms using the Center for Epidemiologic Studies Depression (CES-D) scale (range 0–60), and perceived helplessness using the Rheumatology Attitudes Index (RAI) (range1–5). SES measures included educational attainment (<high school diploma (<HS), or ≥HS), occupational status (managerial or non-managerial), and community poverty (defined from the U.S. Census household poverty rate for the block group in which the participant resided). Poverty rate was trichotomized as <12% (referent), 12–25%, and >25%. Separate analyses were performed for those with symptomatic hip OA (sOA) (defined rOA with pain or stiffness in the same hip). Regression analyses were used to examine the association between CES-D and RAI outcomes with all SES variables while adjusting for age, gender, race, and body mass index (BMI).

Results: Participants' average age was 67 years (45–94), 46% had a BMI≥30, 65% were female and 28% were AA. 35% of the population had <HS, 55% were in non-managerial occupations, and 72.4% of individuals resided in communities where more than 12% of the population live below the poverty rate. Average CES-D score was 6.09 and the average RAI was 2.45. Of those with hip rOA, 252 also met the definition of hip sOA. In covariate adjusted analyses of individual SES measures among those with hip rOA, those with <HS and non-managerial occupation had significantly higher CES-D (β=2.89, C.I. = [1.83, 3.95]); β=1.74, C.I. = [0.72, 2.76], respectively) and RAI scores (β=0.29, C.I. = [0.18, 0.41]; (β=0.25, C.I. = [0.14, 0.37] respectively). In multivariate regression analyses mutually adjusting for all SES variables and covariates, most associations remained, however occupation was no longer associated with CES-D. Results for hip sOA were similar to those for rOA, although we did not observe associations for education with CES-D or occupation with RAI. Community poverty showed little association with either depression or feelings of helplessness.

Conclusion: Low educational attainment is associated with higher levels of depression and feelings of helplessness in people with hip OA. Non-managerial occupation may also play an independent role, particularly for helplessness. These data highlight the importance of individual-level SES measures as risk factors for depression and feelings of helplessness in persons with OA.

1545

Current Social Position Associated with Rheumatoid Arthritis Severity and Self-Reported Health Outcomes in African Americans. Leigh F. Callahan[1], Rebecca J. Cleveland[1], Xia Li[1], Todd A. Schwartz[1], Beth L. Jonas[1], Ted R. Mikuls[2], Britta L. Schoster[1], Graciela S. Alarcon[3], Richard Brasington[4], Doyt L. Conn[5], Edwin A. Smith[6], George Howard[3], Larry W. Moreland[7] and S. Louis Bridges Jr.[8]. [1]University of North Carolina, Chapel Hill, NC, [2]Omaha VA and University of Nebraska, Omaha, NE, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Washington Univ School of Med, St. Louis, MO, [5]Emory Univ School of Medicine, Atlanta, GA, [6]Med Univ of South Carolina, Charleston, SC, [7]University of Pittsburgh, Pittsburgh, PA, [8]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Socioeconomic status (SES), has been shown to be associated with rheumatoid arthritis (RA) prevalence as well as physical and psychosocial outcomes. Ethnicity is sometimes used as a surrogate for SES, but recent findings suggest this may not be appropriate. The purpose of this study is to evaluate whether SES is associated with RA disease severity and patient reported outcomes (PROs), independent of ethnicity, in a population of African Americans (AA) with RA.

Methods: A cross-sectional analysis was conducted on 855 AA patients with RA who were enrolled from medical centers in the southeastern US. SES measures were educational attainment (≤ high school [HS] diploma, or >HS); occupation (OCC) (professional or non); home ownership (yes or no); and annual household income (INC) (≤$30,000 (30K) or >$30K). Outcomes were joint severity (tenderness, swelling and malalignment); radiographs (erosion, JSN score); laboratory measures (C-reactive protein [CRP] levels, rheumatoid factor [RF], and anti-cyclic citrullinated protein antibodies [anti-CCP]); and PROs (HAQ, pain and fatigue visual analog scales [VAS], helplessness Rheumatology Attitudes Index [RAI], and counts of poor physical, poor mental, and limited activity days). Covariates included gender, age, RA disease duration, current Methotrexate/Leflunomide and biologic agent use, clinical comorbidity index, and pack-years of cigarette smoking (0, <10, 10-<20, ≥20). Bivariate analyses were performed to examine mean values of RA severity markers according to SES. Regression models were used to determine associations of each RA severity outcome and PROs with SES measures, adjusting for covariates. All analyses were also performed in a subset of those with RA ≤2 years (N=413).

Results: The mean age was 54 years, 84% were female, and average RA disease duration was 84 months. Approximately 57% had ≤HS, 51% non-professional OCC, 52% non-homeowners, 71% INC≤$30K and 52% had ever smoked. In bivariate analyses, all measures of low SES were associated with poorer outcomes, with the strongest associations seen for ≤$30K and non-homeowners with PROs (P<0.01). In a covariate-adjusted multivariable regression model examining all SES measures, significant independent associations with joint severity measures and most PROs were limited to INC ≤$30K and homeowners. Similar results were seen in analyses limited to those with RA ≤2 years.

Conclusion: In AA with RA, disease severity and low PROs are associated with low levels of SES, particularly for those with low household income and not owning a home. These data support the importance of SES with clinical and self-reported RA disease severity measures. Our finding that SES is a significant predictor of RA severity in a population limited to AA highlights the importance of SES outside of racial context.

1546

Early Consultation with a Rheumatologist for Rheumatoid Arthritis: Does It Reduce Subsequent Use of Orthopaedic Surgery? Debbie Ehrmann Feldman[1], Sasha Bernatsky[2], Michelle Houde[3], Marie-Eve Beauchamp[2] and Michal Abrahamowicz[2]. [1]Université de Montréal, Montréal, QC, [2]McGill UHC/RVH, Montreal, QC, [3]Public Health Department of Montreal, Montreal, QC

Background/Purpose: Optimal care in rheumatoid arthritis (RA) includes early use of disease-modifying anti-rheumatic drugs to prevent joint damage and hopefully decrease surgical interventions. Our objective was to determine if persons with RA who saw a rheumatologist early in the disease course had a reduced rate of orthopaedic surgery.

Methods: All persons with a diagnosis of RA confirmed by a rheumatologist and based on billing code data in the province of Quebec, in 1995 were followed until 2007. Patients were classified as "early consulters" if they were seen by a rheumatologist within 3 months of being diagnosed with RA by their referring physician, "late consulters" if they were seen by more than 3 months after the initial RA diagnosis, and "undetermined" if they were first diagnosed with RA by a rheumatologist. Time to orthopaedic surgery, defined using ICD9 and ICD10 procedure codes, was compared with Cox's proportional hazards regression.

Results: There were 3,890 patients with a confirmed RA diagnosis: mean age at diagnosis was 56.3 years and 69.4% were female. Most (73%) were "undetermined consulters"; 13.7% were "early" consulters and 13.3% "late" consulters. Among all patients, 15.3% (610) had an orthopaedic surgery during the observation interval. Patients in the early consultation group were less likely to undergo orthopaedic surgery over the 12 year follow-up period than those in the late consultation group (adjusted hazard ratio: 0.63; 95% confidence interval: 0.46, 0.85).

Conclusion: Persons diagnosed with RA who consult a rheumatologist later in the disease course have a worse outcome in terms of eventual orthopaedic surgery. In addition to improving patient outcomes, appropriate medical treatment under the supervision of a rheumatologist may also decrease costly interventions such as orthopaedic surgery. Our results add more credence to support early treatment guided by a rheumatologist in patients with rheumatoid arthritis.

1547

Tumor Necrosis Factor Blocker Treatment Patterns After Discontinuation within the First Year of Therapy Initiation in Rheumatoid Arthritis Patients in a Real-World Managed Care Setting. Machaon Bonafede[1], Crystal Watson[2], Kathy M. Fox[3], Nicole Princic[1] and Shravanthi R. Gandra[2]. [1]Thomson Reuters Healthcare, Cambridge, MA, [2]Amgen Inc, Thousand Oaks, CA, [3]Strategic Healthcare Solutions, LLC, Monkton, MD

Background/Purpose: Clinical guidelines and published literature do not offer specific recommendations for treatment options after discontinuing a tumor necrosis factor (TNF) blocker for rheumatoid arthritis (RA). Some clinical trials have tested the efficacy of switching among TNF blockers, but patterns of TNF-blocker use after discontinuation in a real-world setting are not well characterized. The purpose of this study is to estimate the percentage of patients and time to restart the initial TNF blocker or switch to another biologic within the first year of therapy initiation among RA patients discontinuing etanercept (ETN), adalimumab (ADA), or infliximab (INF) in a real-world managed care setting.

Methods: MarketScan Commercial Database was used to identify biologic-naïve adult (18–64 years) RA patients with ≥1 claim for ETN, ADA, or INF between January 1, 2005 and June 30, 2009. Patients were followed for 1 year after the initial TNF blocker claim (index date) and had to be continuous enrolled 6-months prior to index (pre-index period) and 1-year after index. Patients diagnosed with psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease, or ulcerative colitis in the pre-index period were excluded. Discontinuation from index therapy was defined as either a >45 day gap in therapy or switch to another biologic. Time to restart or switch was measured in days from index date of initial TNF-blocker therapy.

Results: Overall, 2,933 ETN, 2,094 ADA, and 1,099 INF RA patients were included. Patient characteristics were similar between the treatment groups with a mean age (SD) of 50 (10) years and 76% female. The percentage of patients who discontinued within 1-year for ETN, ADA and INF were 59%, 57%, and 48%, respectively. The percentage of patients who discontinued and restarted initial TNF-blocker therapy were 23% for ETN, 18% for ADA, and 11% for INF. Mean (SD) time to restart from index date was 219 (79) days for ETN, 223 (82) days for ADA, and 241 (77) days for INF. Switch to any non-index biologic occurred in 15% of ETN, 14% of ADA, and 13% of INF patients. Of the patients who switched, the majority (84%) switched to one of the other TNF-blockers (ETN, ADA, or INF) with a mean time to switch between 170–207 days.

Conclusion: Among RA patients initiating a TNF-blocker therapy in a managed care setting, 11–23% of patients discontinued and restarted the initial TNF-blocker therapy and approximately 13–15% switched to another biologic in the first year. In the first year, the mean time to restart after discontinuing index therapy was between 219–241 days, whereas switching to another TNF blocker therapy occurred around 170–207 days from initiation of index therapy.

1548

Analysis of Radiographic Changes in Patients with Early Psoriatic Arthritis. Majed M. Khraishi[1], Rana Aslanov[2], Emmanouil Rampakakis[3], Anh Duong[4] and John S. Sampalis[3]. [1]Memorial University of Newfoundland, St Johns, NF, [2]Memorial University of Newfoundland, St.John's, NF, [3]McGill University & JSS Medical Research, Montreal, QC, [4]JSS Medical Research, Westmount, QC

Background/Purpose: Psoriatic arthritis (PsA) is a seronegative arthropathy characterized by axial involvement, peripheral arthritis, and enthesitis. Disease duration and severity of joint inflammation significantly affect the radiographic outcome which can be used as a prognostic factor for PsA progression. Radiography at early PsA (EPsA) stages can play a vital role in the patient evaluation, differential diagnosis from other arthritis types and management. The aim of this study was to describe the radiographic changes in EPsA, defined as <2 years since symptom onset

Methods: EPsA patients (pts) were assessed at a rheumatology clinic specializing in PsA. Standard clinical and laboratory assessments including conventional radiography of peripheral (hands, wrists and feet) and sacroiliac joints were conducted at baseline. All detected radiographic changes were classified as normal, abnormal-not clinically relevant-, and abnormal-clinically relevant-, and their association with patient demographics and baseline characteristics was analyzed

Results: A total of 84 pts with EPsA (mean (SD) disease duration = 1.0 (0.8) yrs) were included in this analysis. Table 1 shows the cohort baseline characteristics. The most common joint involvement was polyarticular (59.5% of pts) presentation (symmetric or asymmetric) and Distal Interphalangeal Predominant (DIP) involvement (57.1% of pts).

Among the 79 pts with available baseline radiological assessment until now, radiological damage was identified in 25 (31.6%) pts, of whom 10 (40%) had changes in 2 joints and 3 (12%) in ≥3 joints. The vast majority of these pts (n=19, 76%) experienced joint damage within the 1st year of PsA onset. The observed radiographic changes included new bone formation (often interpreted by radiologists as degenerative), slight to moderate narrowing of the joint space, and marginal and central bone erosions, with the majority of abnormalities appearing in the hands, feet and sacroiliac (SI) joints. Among the 66 pts evaluated, 15 (23%) had abnormal hand images, of whom 9 (60%) in both hands. Furthermore, 10% of the evaluated pts (5/50) had radiographic abnormalities in feet (3 (60%) in both legs) and 10.4% (7/67) in SI joints (2 (30%) in both sides).

Mean (SD) CRP was higher in pts with radiological damage compared to the rest of the cohort (8.8 (7.7) vs 5.8 (5.5);P=0.053). Mean (SD) SJC was also higher in former pts (4.4 (6.2) vs 3.0 (3.7)), although without reaching statistical significance. All other parameters were comparable between the groups

Conclusion: Radiological damage was detected in 32% of patients with EPsA, which was associated with increased CRP. Among these, 76% acquired the damage within the 1st year of symptom onset. Asymmetric oligoarthritis was not a dominant pattern in our cohort as was previously reported. The increased incidence of axial and DIP joint involvement are in agreement with previous studies showing that they represent the most common sites in PsA.

Table 1. Baseline Characteristics and Patient Disposition

Parameter	N=84
Mean (SD) Age (years)	48.04 (10.55)
Female Gender: n (%)	44 (52.4%)
Mean (SD) Age at PSO Diagnosis (years)	38.73 (14.17)
Mean (SD) Age at PsA Diagnosis (years)	47.85 (10.66)
Mean (SD) PASQ score	11.33 (4.83)
Mean (SD) PASI score	3.51 (5.94)
Mean (SD) CRP	6.71 (6.36)
Mean (SD) ESR	15.99 (18.43)
Mean (SD) TJC	8.32 (8.48)
Mean (SD) SJC	3.42 (4.60)
PsA Treatment n (%)	
NSAIDs	68 (81.0)
MTX	26 (31.0)
Sulfasalazine	9 (10.7)
Anti-TNFá	8 (9.5)

1549

Patients with Polymyositis, Dermatomyositis and Inclusion Body Myositis Have Activity Limitations Despite Low Disease Activity: A Registry Study. Li Alemo Munters[1], Malin Regardt[2], Therese Jansson[3], Susanna Johansson[3], Christina Ottosson[4], Maryam Dastmalchi[5], Ingrid E. Lundberg[3] and Helene Alexanderson[3]. [1]Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet, Stockholm, Sweden, [4]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [5]Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM) are rare diseases characterized by slowly progressive muscle weakness. Although patients with PM and DM respond to treatment with clinical improvement several develop a sustained disability that increase during the disease course, limiting activities in daily life. The knowledge of activity limitations in PM, DM and IBM is limited. All patients with PM, DM and IBM at Karolinska University Hospital are registered annually in the Swedish Myositis Network Registry (SWEMYONET). The aims of this registry study were to investigate activity limitation in a cohort of patients with PM, DM and IBM and to evaluate correlations between two activity limitation measures and disease activity.

Methods: All patients registered in SWEMYONET from Karolinska University Hospital during 2009 were included. Activity limitation was measured by Health Assessment Questionnaire (HAQ) (score range, 0–3.00) and Myositis Activities Profile (MAP) (score range, 1–7). The cohort consisted of 84 patients of whom 33 had PM (73% women), 40 had DM (55% women) and 11 had IBM (55% women). Median disease duration for PM was 9 years (range, 1–28), for DM 10 years (1–41) and IBM 6 years (2–11). Median of Physician's global assessment of disease activity (0–100mm) was 5 mm (range, 0–50). Mann Whitney U-test was applied to test the sub-groups differences, level of significance was set to <0.05. Spearman rang correlation (r_s) was used to test correlations between measures.

Results: Median HAQ values indicated mild activity limitation for both PM, Md=1.00 (range, 0–2.50) and DM 0.25 (0–1.88) and moderate for IBM 1.5 (0.5–2.75). Activity limitation measured by MAP in PM indicate moderate limitation Md=3.75 (range, 1–7), in DM mild limitation 2 (1–7) and for IBM moderate limitation 4 (1–7).The most limited activity domains measured by MAP in PM were *work/school work* and *leisure,* in DM *moving around, work/school work and leisure* and in IBM *moving around, work/school work* and *leisure*. Patients with DM had significantly less activity limitation compared to PM and IBM whereas IBM had significantly higher activity limitation than PM and DM. High correlations (r_s= 0.70 – 0.79) were revealed between HAQ and four domains of MAP (*Movement, Self Care, Moving around, Domestic*). There were low correlations between HAQ/MAP and Physician's global assessment of disease activity (r_s=0.39 / 0.21–0.41).

Conclusion: Although low disease activity was revealed in the cohort, patients still perceived mild to moderate activity limitation. Patients with DM had less activity limitation than patients with PM and IBM while

patients with IBM had greater activity limitation than PM and DM. The most limited activity domain in the cohort was *leisure*. The correlations between HAQ and MAP are equivalent to findings in a previous study (1).

Reference

(1) Alexanderson H, Lundberg IE, Stenström CH. Development of the myositis activities profile – validity and reliability of a self-administered questionnaire to assess activity limitations in patients with polymyositis/dermatomyositis. Journal of Rheumatology. 2002; 29 (11): 2386–2392.

1550

Influenza Vaccine Intervention in a Rheumatology Clinic Population. Sherece Black[1], Sarabjit Brar[1], Lee Chang, Sylvia Chico[1], Donald Makowski[1], Virginia Haiduc[1], Steven K. Magid[3], Julie A. Pollino-Tanner[1], Julita C. Reyes-Canu[1], Ann M. Rakowicz[1] and Monica C. Richey[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hosp for Special Surgery, New York, NY

Background/Purpose: The Center for Disease Control (CDC) recommends annual influenza vaccination for all immunosuppressed individuals. Persons with rheumatologic conditions are immunocompromised not only due to disease, but also because of the medication they take. As a consequence they have an increased risk of developing infections than the healthy individuals. In spite of the recommendation by the Advisory Committee on Immunization (ACIP) and the American College of Rheumatology (ACR), rheumatology patients overall have lower influenza and pneumococcal vaccination rate compared to the general population. During the 2009–2010 Influenza vaccine season, out of 1514 clinic patient visits to our Division of Rheumatology, only 100 (6%) clinic patients were vaccinated.

Objectives: The objective was to increase the number of patients who receive the influenza vaccine during the 2010–2011 Influenza season in our Rheumatology clinic.

Methods: In order to increase the vaccination rates for our patients, a nurse specific intervention was designed. Posters and flyers promoting the health benefits of the influenza vaccine were posted in the patient reception areas, and exam rooms. Using a paper survey in both English and Spanish, a registered nurse queried all patient: a) if they have been vaccinated b) if they wanted to be vaccinated c) the reason for refusal of the vaccine. Asking patients the "why not" question was thought to be helpful in organizing future strategies for patient education with the goal to increase the vaccination rate. To prevent duplication of surveys, stickers were attached to all charts, indicating patient acceptance or refusal of the vaccine. Patients that refused the vaccine were educated on the importance of receiving the influenza vaccine by the registered nurse.

Results: Of 1195 patients who visited our clinic during the 2010–2011 Influenza vaccine season, 440(36.8%) completed the survey. The survey results indicated that a) 256(21.4%) patients received the vaccine in our clinic, b) 133(11%) patients were previously vaccinated by their primary care physician (PCP), and c) 51(4.25%) patients refused.

Conclusion: The nurse specific intervention designed to increase the number of patients who received the Influenza vaccine in our Rheumatology Division was proven effective. The percentage of patients vaccinated during the 2010–2011 Influenza season increased from 6% (2009–2010 Influenza season) to 21.4%. Based on these results, we learned that a nurse specific intervention is an important step in promoting influenza immunization in our clinic. Our next year efforts will focus on improving our strategy and further patient education about the importance of receiving this particular vaccine

1551

What Is the Health Literacy and Numeracy in a Rheumatology Veterans Population? Janine A. Galasso. Philadelphia VA Medical Center, Philadelphia, PA

Background/Purpose: As defined in Healthy People 2010 (US HHS 2000), health literacy is: "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. Low health literacy has been shown to negatively impact patient well being and medication adherence. Health numeracy is the use of quantitative skills in the context of healthcare, and can negatively impact medication adherence as well. Patients with rheumatic disease who have limited health literacy are at higher risk for adverse outcomes due to the number of medications and complex treatment regimens often prescribed. The purpose of this project was to evaluate the health literacy and numeracy of Rheumatology patients in a Veterans rheumatology clinic

Methods: This prospective, cross-sectional, single center study was approved by the institutional review board at the Philadelphia VA Medical Center. Subjects were enrolled that met the inclusion criteria of; at least 18 years of age, English as the primary language and a diagnosis of one or more of the following: RA, OA, SLE, Gout or other rheumatic disease. Patients completed a validated Literacy Questionnaire (STOHLA), and a Rheumatology Numeracy Questionnaire previously published by one of the authors (JMVF;Rheum Disease 67 (supII):673, July 2008).

Results: Thirty-three subjects were enrolled in the study. 85% were male with a mean age of 54 (27–77 years) 51% self-identified as African American, 42% as Caucasian and 12% as Hispanic. The rheumatologic diagnosis distribution was:: gout 12%, RA 42%, OA 24%, SLE 6%, other 6%. The average number of medications per electronic health record was 7.9 (5.07174 SD). Completed level of educations were: $<6^{th}$ grade 0%, $7–11^{th}$ grade 3%, high school 21%, technical/vocational school 9.3%, some college 37.5%, B.S. degree 18.75% and Masters or above 6.25%. The majority of patients (88%) had adequate health literacy, The average score on the numeracy test was 56% (24.45927 SD), on a scale of 0–100%, suggesting that most subjects struggled with quantitative skills.

Conclusion: The majority of Veteran patients had adequate literacy, but inadequate health numeracy, In patients with low health numeracy and an average number of medications of 7.9, patient safety can be compromised and medication errors can occur If validated in a larger population, intervention strategies can be developed to improve patient education about medications, and circumvent health numeracy deficits.

1552

Factors Associated with Hallux Valgus: The Johnston County Osteoarthritis Project. Yvonne M. Golightly[1], Marian T. Hannan[2], Alyssa B. Dufour[3], Jordan Renner[4] and Joanne M. Jordan[1]. [1]UNC Thurston Arthritis Research Center, Chapel Hill, NC, [2]Hebrew SeniorLife & Harvard Med Sch, Boston, MA, [3]Hebrew SeniorLife & Boston Univ, Boston, MA, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: Prevalence of hallux valgus (HV) differs by gender and by race, but underlying factors that explain these differences are not well understood. This cross-sectional analysis examined 1) whether HV is associated with foot pain, and 2) potential factors associated with HV in a large, bi-racial cohort of men and women 50 years of age or older.

Methods: Of the 1,670 Johnston County Osteoarthritis Project participants clinically evaluated in 2006–2010, 1,416 had complete foot exam, foot symptoms, and clinical and demographic data available for analysis (mean age 68 years, mean body mass index [BMI] 31.7 kg/m^2, 66.2% women, 31.1% African American [AA]). Trained examiners used the validated Foot Assessment Clinical Tool to assess HV (present/absent based on angle of hallux toward lesser toes $>15°$), pes planus (present/absent), and presence of foot symptoms ("on most days, do you have pain, aching or stiffness in your [right/left] foot?"). Multivariate logistic regression models for the total sample and by each gender and race group (AA men, AA women, Caucasian men, Caucasian women) were performed to examine the effect of age (in 10 year increments), BMI (categorized as <25, 25–30, 30–35, and >35 kg/m^2), foot symptoms, pes planus, and presence of knee or hip radiographic osteoarthritis (OA) on HV.

Results: HV was present in 64.3% of the total sample (AA men=70.4%, AA women=69.0%, Caucasian men=55.4%, Caucasian women=65.5%). Table shows risk factors for HV for the total sample and by gender-and-race groups. In the total sample, female gender, AA race, older age, pes planus, and the presence of knee/hip OA elevated the odds of HV, and greater BMI lowered the odds of HV, adjusting for all other factors. When pes planus was present, the odds of HV in AA men were 2.6 times higher (adjusted odd ratio [aOR] =2.60, 95% confidence interval [95% CI] =1.09, 6.19). AA women, Caucasian men, and Caucasian women had non-significantly elevated ORs for HV and pes planus. A BMI of 25–30 kg/m^2 was inversely associated with HV among Caucasian men (aOR = 0.39, 95% CI = 0.16, 0.94). This association between BMI and HV was observed across other BMI categories, although it was not statistically significant. When radiographic knee/hip OA were present, the odds of HV were higher across groups, particularly in Caucasian men (aOR = 2.05, 95% CI = 1.28, 3.29).

Factors Associated with Hallux Valgus (adjusted for all other covariates)

	Total Sample (N=1416)	AA Men (N=135)	AA Women (N=306)	Caucasian Men (N=343)	Caucasian Women (N=632)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender (referent= male)	1.28 (1.01, 1.61)	—	—	—	—
Race (referent= Caucasian)	1.33 (1.03, 1.71)	—	—	—	—
Age (10 year increment)	1.19 (1.05, 1.35)	1.24 (0.80,1.93)	1.26 (0.94, 1.68)	1.15 (0.89, 1.50)	1.19 (0.98, 1.43)
BMI <25 (referent)	1.00	1.00	1.00	1.00	1.00
BMI 25–30	0.66 (0.46, 0.95)	0.33 (0.10, 1.09)	0.82 (0.26, 2.62)	0.39 (0.16, 0.94)	0.89 (0.55, 1.43)
BMI 30–35	0.75 (0.51, 1.10)	0.76 (0.21, 2.71)	0.48 (0.16, 1.46)	0.48 (0.19, 1.19)	1.09 (0.64, 1.85)
BMI >35	0.57 (0.39, 0.84)	0.36 (0.10, 1.25)	0.44 (0.15, 1.32)	0.46 (0.18, 1.18)	0.76 (0.45, 1.29)
Foot symptoms	1.27 (0.98, 1.67)	0.99 (0.38, 2.59)	1.64 (0.84, 3.20)	1.19 (0.67, 2.12)	1.25 (0.86, 1.81)
Pes Planus	1.69 (1.27, 2.24)	2.60 (1.09, 6.19)	1.64 (0.97, 2.77)	1.69 (0.89, 3.21)	1.52 (0.95, 2.41)
Knee or Hip osteoarthritis	1.41 (1.11, 1.79)	1.25 (0.55, 2.81)	1.54 (0.85, 2.79)	2.05 (1.28, 3.29)	1.20 (0.84, 1.70)

Conclusion: HV and pes planus were associated, most notably among AA men, and HV and knee/hip OA were associated, especially among Caucasian men. Higher BMI was generally inversely associated with HV. We believe this is the first report of the association between HV and knee/hip OA. Future studies should examine possible effects of genetics, shoe wear (especially toe box structure), multi-joint OA (joints in addition to knee and hip), and occupational factors to explain these differences and inform early intervention approaches.

1553

Foot Type Is Linked to Falls in Older Adults: The Framingham Foot Study. Jody L. Riskowski[1], Thomas J. Hagedorn[2], Alyssa B. Dufour[3], Virginia A. Casey[2] and Marian T. Hannan[4]. [1]Hebrew SeniorLife, Boston, MA, [2]Hebrew Senior Life, Boston, MA, [3]Hebrew SeniorLife & Boston Univ, Boston, MA, [4]Hebrew SeniorLife & Harvard Med Sch, Boston, MA

Background/Purpose: In the US, 30% of community-residing older adults fall each year. Although the causes of falls are multifactorial, few studies have investigated foot type (i.e., high, low and rectus arch) and fall risk, despite it being the main or only base of support. Therefore, the purpose of this study was to evaluate foot type and fall risk in a population-based study of older adults.

Methods: This study included participants in the Framingham Foot Study who were members of the Framingham Study Original and Offspring cohorts who had a valid standing and walking plantar pressure scan of each foot and information on falls between 2002 and 2008. Foot pressure scans were collected using Tekscan Matscan (Boston, MA). Participants walked barefoot at a self-selected pace across a 3.5m walkway, using the two-step method to collect a pressure scan for each foot. Foot type was assessed using the Modified Arch Index (MAI) from the dominant limb (as determined from the foot scan as leg with greater propulsive force, not self-report). Cut-points for foot type were based on sex-specific quartiles of MAI. The highest and lowest 25% of the MAI values categorized foot type (i.e., low arch was highest MAI quartile and high arch was lowest MAI quartile). The middle 50% was the referent (rectus foot type). Falls were recorded as yes/no based on participant self-report of falling in the past year. Sex-specific logistic regression models were used to examine foot type and fall risk relative to the referent. A second model further adjusted for age and body mass index (BMI).

Results: Of the 2131 participants, there were 954 men (age: 66.0 ± 9.9 years; BMI: 27.7 ± 6.0 kg/m^2) and 1177 women (age: 65.6 ± 10.6 years; BMI: 28.7 ± 4.6 kg/m^2). 236 men (14.8%) and 456 (22.7%) women reported falling in the past year.

The unadjusted and adjusted odds ratios showed that men who had high arches had a ~55% decreased fall risk (Table). Men who had low arches had an increased fall risk, although not statistically significant. No association was noted in the unadjusted model for women; however, the adjusted model showed a 12% decrease in fall risk for women with low arches.

	Unadjusted OR		Adjusted OR	
	Men	Women	Men	Women
MAI Rectus (referent)	1.00	1.00	1.00	1.00
MAI High Arch	**0.43 (0.25, 0.74)**	0.95 (0.69, 1.34)	**0.46 (0.29, 0.75)**	0.90 (0.81, 1.21)
MAI Low Arch	1.33 (0.88, 2.00)	1.08 (0.78, 1.37)	1.27 (0.92, 1.77)	**0.78 (0.68, 0.96)**

Conclusion: Both the unadjusted (clinically relevant) and adjusted (biologic mechanism relevant) models showed an association between foot type and falls, especially in men. Future studies should examine foot type and its role in balance and gait to understand how foot type influences fall risk in risk in older adult populations.

1554

The Effect of Foot Pain on Mobility Disability in Older Adults: The Framingham Foot Study. Virginia A. Casey[1], Alyssa B. Dufour[2], Jody L. Riskowski[3], Thomas J. Hagedorn[1], Robert R. McLean[4] and Marian T. Hannan[5]. [1]Hebrew Senior Life, Boston, MA, [2]Hebrew SeniorLife & Boston Univ, Boston, MA, [3]Hebrew SeniorLife, Boston, MA, [4]Hebrew Senior Life/Harvard Medical School, Boston, MA, [5]Hebrew SeniorLife & Harvard Med Sch, Boston, MA

Background/Purpose: Studies have shown that BMI is a strong and persistent predictor for mobility disability in older adults. Additionally, foot pain is also known to be more prevalent in obese individuals. The purpose of this study is to evaluate the independent relations between foot pain and mobility disability in a population of community-dwelling older adults.

Methods: A subset of participants from the Framingham Foot Study (2002–2008) who had performance measures of physical limitations and disability assessed were included in this cross-sectional analysis (n=1332). Mobility disability was assessed using the Short Physical Performance Battery (SPPB). The SPPB is a composite of 3 timed performance tests with each test scored on a scale of 0 to 4; the highest possible score of 12 indicates better physical function. Studies in healthy older adult populations have shown the SPPB to be predictive of physical limitations, disability and mortality. For this analysis, the SPPB score was dichotomized using 1–10 as an indicator of mobility disability and 11–12 as a good score. Foot pain (y/n) was queried by a trained examiner "On most days, do you have pain, aching or stiffness in either foot?" Age, sex, body mass index (BMI, grouped <25, 25–30, >30 kg/m^2), physical activity (PASE score from validated Physical Activity Scale for the Elderly), current smoker (y/n) and depression score (CES-D scale) were also obtained or assessed. Sex-specific multivariate logistic regression models were performed to examine the effect of the above factors upon mobility disability.

Results: Our study sample of 1332 older adults had a mean age of 70yrs (±SD 12.0) and mean BMI of 28 kg/m^2 (±5.3) with an age range of 41–98y in men and 36–100y in women. The 550 men had mean age of 70 yrs (± 11.3) and BMI of 29 kg/m^2(± 4.6) while women had mean age of 70 yrs (± 12.4) and mean BMI of 27 kg/m^2 (± 5.7). As age increased, both men and women had a greater probability of being in the poor mobility disability group (OR=1.2; p<0.0001). 26% of the men and 35% of the women had foot pain. Males with foot pain had greater than a two-fold odds of being in the poor mobility disability group (OR=2.5; p<0.007) even after controlling for the effects of age and BMI. The relation between disability and foot pain was less pronounced in females (OR=1.4) with only a trend toward significance. Surprisingly, physical activity, smoking status and depression score did not contribute to the models in either sex.

Conclusion: Presence of foot pain increased the odds of having mobility disability in our study of older adult men from the Framingham Foot Study with a similar, but not statistically significant relation, seen in women. As foot conditions and related foot pain are mostly easily treatable, clinicians should consider assessment of foot pain in general examinations of older adults who are at risk for mobility disability.

1555

Lesser Toe Deformities Are Highly Heritable in Older Men and Women: The Framingham Foot Study. Marian T. Hannan[1], Yi-Hsiang Hsu[1], Virginia A. Casey[2], Gouri Vadali[2] and Joanne M. Jordan[3]. [1]Hebrew SeniorLife & Harvard Med Sch, Boston, MA, [2]Hebrew Senior Life, Boston, MA, [3]UNC Thurston Arthritis Center, Chapel Hill, NC

Background/Purpose: Foot disorders affect 20–60% of adults and are often linked to physical limitations. Although genetics are commonly suspected in foot disorders, only two studies have been done: a family aggregation study showing that family history of hallux valgus may have an autosomal dominant transmission, and our work in 2010 that reported high heritability of hallux valgus and pes cavus. To our knowledge, no other studies have examined foot disorders and genetics in humans. Our purpose was to examine further heritability of several common foot conditions, linking data on specific foot disorders to a wealth of genetic data in the community-based Framingham Study, using their pedigree structure.

Methods: The Framingham Foot Study (n=2179 participants examined in 2002–2005) was designed to examine common foot disorders and functional limitations. A trained examiner used a validated foot exam to assess specific foot disorders in participants. Genotyping has been obtained in 959 men and 1220 women. We estimated overall, sex-specific and age (< 60, 60+y) heritability of lesser toe deformities (hammer toes, claw toes, overlapping toes), heel fat-pad atrophy (present/absent), forefoot fat-pad atrophy (present/absent), and pes planus in the Framingham participants. Pes planus was defined using a digital recording of foot pressure while walking (MatScan device, Tekscan, Inc. Boston MA), that

allowed calculation of the ratio of arch width (medial to lateral, to nearest 0.01 cm) to heel width. Pes planus (present/absent) was defined as either foot as having a weight-bearing arch width ≥ 75% of the heel width (previous work showed that this cut-point encompassed those with clinician impression of flat feet). We estimated heritability of the foot conditions by a standard quantitative genetic variance-components model implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package.

Results: Mean age was 66y (range 39–99y); 57% were female. The prevalence of lesser toe deformities was 35% (753 toe deformity cases with available pedigree structure). The overall heritability of lesser toe deformities was 0.79 for women and 0.61 for men (both p-value < 0.01) and 0.56 for both sexes combined ($p = 4 \times 10^{-7}$) For persons aged < 60y, the heritability was 0.63. The prevalence of heel fat-pad atrophy was 13%, of forefoot fat-pad atrophy was 30%, and of pes planus was 8%. Of these foot conditions, none showed significant heritability overall or by group. Thus, only lesser toe deformities were highly heritable for both men and women.

Conclusion: This study reveals new findings in an area that has received little attention, yet is critically important to general populations. We documented for the first time, the high heritability (strongly suspected by many) of a structural foot disorder phenotype: lesser toe deformities. As foot disorders are common, it is important to identify those at high risk, as effective interventions exist. Also, especially for lesser toe deformities, identification of individuals close to onset may lessen the impact of foot disorders or prevent development of physical limitations. Genome-wide association analyses are planned to identify potential genetic determinants for this common foot disorder.

1556

Factors Affecting Dynamic Foot Function in Older Adults: The Framingham Foot Study. Thomas J. Hagedorn[1], Alyssa B. Dufour[2], Yvonne M. Golightly[3], Jody L. Riskowski[4], Howard J. Hillstrom[5], Virginia A. Casey[1] and Marian T. Hannan[6]. [1]Hebrew Senior Life, Boston, MA, [2]Hebrew SeniorLife & Boston Univ, Boston, MA, [3]University of North Carolina, Chapel Hill, NC, [4]Hebrew SeniorLife, Boston, MA, [5]Hospital Special Surgery (HSS), New York, NY, [6]Hebrew SeniorLife & Harvard Med Sch, Boston, MA

Background/Purpose: Excessive pronation and supination of the foot are thought to be linked to worse physical function. The center of pressure excursion index (CPEI), a measure that characterizes pronation and supination, may be a useful indicator of dynamic foot structure and function. A larger CPEI value indicates supination, while a smaller CPEI indicates pronation. The purpose of this study was to identify important risk factors for CPEI or subsets with different CPEI among a large cohort of community-dwelling, ambulatory men and women with a wide age spectrum, as the initial step in understanding foot function and outcomes.

Methods: 2094 participants were included from the population-based Framingham Foot Study, examined between 2002 and 2008. Participants walked at a self-selected pace over a Tekscan Matscan system (Boston, MA) using the two step method, and plantar pressure scans were recorded for each foot. Bilateral CPEIs were averaged due to similarities between feet. Factors included sex, age (< 65 or ≥ 65 years), BMI (≥ 30 or < 30 kg/m^2), physical activity (PASE score from questionnaire dichotomized at the mean as ≥ 127, < 127), and type of shoewear. ("bad"= sandals, slippers, or high heels; "good"= athletic shoes, sneakers, leather shoes, rubber soled shoes, or work boots, based on previous work). We used Students t-Test to identify those factors associated with CPEI separately by sex. The effect of continuous age and BMI and sex were also evaluated using a linear regression model.

Results: Participants (55% female) had a mean age of 66.8 ± 10.16 yrs, and a mean BMI of 28.43 ± 28.4 kg/m^2. Results of t-Tests are shown in Table 1. The mean CPEI was smaller among women than men ($p < .0035$). Older men had smaller mean CPEI ($p = .0001$), and a similar, borderline significant, difference was seen in older women ($p = 0.0569$). Mean CPEI did not differ by BMI, PASE score, or shoewear. The regression model showed significant contributions by age and sex ($p < .0001$), but not BMI ($p = 0.17$).

Table 1. T-Tests for risk factors and CPEI in men and women: Framingham Foot Study

Males	N	Mean CPEI	Standard Deviation	p	Females	N	Mean CPEI	Standard Deviation	p
Sex	952	16.057	6.35		Sex	1142	12.87	6.45	<.0001
Age < 65	415	16.74	6.32	0.003	Age < 65	543	13.25	6.34	0.06
Age ≥ 65	537	15.53	6.33		Age ≥ 65	599	12.53	6.53	
BMI < 30	603	16.08	6.48	0.90	BMI < 30	794	12.72	6.52	0.23
BMI ≥ 30	341	16.03	6.13		BMI ≥ 30	348	13.22	6.27	
PASE <127	269	14.63	7.50	0.86	PASE <127	392	12.09	7.71	0.70
PASE ≥ 127	293	14.74	7.28		PASE ≥ 127	308	11.85	8.03	
Bad Shoes	932	15.76	7.95	0.78	Bad Shoes	1000	11.45	8.15	0.28
Good Shoes	17	15.21	7.68		Good Shoes	142	12.24	7.95	

Conclusion: We found significant differences in CPEI by age and sex, while noting that CPEI did not differ by BMI, physical activity, or shoewear. Sex differences may likely be due to anatomical differences in the lower extremity that give women a more pronated gait. The differences in older men might be the result of changes to the foot with age, such as an increased prevalence of flat feet but more research is needed to examine this possibility. Physical activity, BMI, and shoewear did not significantly influence CPEI in our analyses, suggesting that foot function is may be driven more by local anatomical than systemic considerations. This study is the first to show age and sex differences in foot function in a large population-based cohort. Future work will evaluate the relationship between CPEI and outcomes such as falls, sarcopenia, and lower extremity function.

ACR/ARHP Poster Session B
ARHP Rehabilitation Science
Monday, November 7, 2011, 9:00 AM–6:00 PM

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Non-Pharmacological Interventions for Fatigue in Rheumatoid Arthritis: A Cochrane Review. Fiona Cramp[1], Sarah Hewlett[1], Celia Almeida[1], John R. Kirwan[2], Ernest Choy[3], Trudie Chalder[4], Jon Pollock[1] and Robin Christensen[5]. [1]University of the West of England, Bristol, United Kingdom, [2]University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom, [3]Cardiff University, Cardiff, ENGLAND, United Kingdom, [4]Department of Psychological Medicine, London, United Kingdom, [5]Copenhagen, Denmark

Background/Purpose: Fatigue is a common and potentially distressing symptom for patients with rheumatoid arthritis with no accepted evidence based management guidelines. Non-pharmacological interventions, such as physical activity and psychosocial interventions have been shown to help people with a range of other long term conditions manage subjective fatigue. The purpose of the review was to evaluate the effectiveness and safety of non-pharmacological interventions for the management of fatigue in people with rheumatoid arthritis.

Methods: Randomised controlled trials were included that evaluated a non-pharmacological intervention in people with rheumatoid arthritis, with self-reported fatigue as an outcome measure. To identify relevant studies the following electronic databases were searched: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Current Controlled Trials Register; The National Research Register Archive; The UKCRN Portfolio Database; MEDLINE; EMBASE; AMED; CINAHL; PsycINFO; Social Science Citation Index; Web of Science; Dissertation Abstracts International. In addition reference lists of articles identified for inclusion were checked for additional studies and key authors were contacted. Two reviewers selected relevant trials, assessed methodological quality and extracted data. Where appropriate, data were pooled using meta-analysis with a random-effects model.

Results: Nineteen studies met the inclusion criteria with a total of 2240 participants with rheumatoid arthritis. Included studies investigated physical activity interventions (k=5), psychosocial interventions (k=10), herbal medicine (k=1), omega-3 fatty acid supplementation (k=1), Mediterranean diet (k=1) and the provision of Health Tracker information (k=1). The quality of the studies varied from low to moderate. Meta-analyses of available data demonstrated that physical activity was statistically more effective than the control with a small effect (SMD −0.29, 95% CIs −0.53 to −0.05) and psychosocial interventions were statistically more effective than the controls with a marginal effect (SMD −0.14, 95% CIs −0.28 to 0.00).

Conclusion: This review provides some evidence that physical activity and psychosocial interventions may provide benefit in relation to self-reported fatigue in adults with rheumatoid arthritis. There is currently insufficient evidence of the effectiveness of other non-pharmacological interventions. Further high quality research is still required to confirm the optimal non-pharmacological interventions and inform future clinical guidelines. Better understanding of the mechanisms of fatigue would also help to further develop effective interventions.

1558

Relationship Between Beliefs, Motivation and Worries about Physical Activity and Physical Activity Participation in Persons with Rheumatoid Arthritis. Linda S. Ehrlich-Jones[1], Jungwha Lee[2], Pamela A. Semanik[3], Cheryl Cox[4], Dorothy D. Dunlop[5] and Rowland W. Chang[2]. [1]Rehabilitation Institute Chicago, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Rehabilitation Institute Chicago, Oak Park, IL, [4]St. Jude Children's Research Hospital, Memphis, TN, [5]Northwestern Univ Med School, Chicago, IL

Background/Purpose: Among persons with arthritis, engaging in physical activity can help maintain or increase mobility, improve function, decrease pain, and decrease disability. In 2000, Behavioral Risk Factor Surveillance System surveys conducted by state health departments reported about 31% of people with arthritis were inactive. A sedentary lifestyle is associated with cardiovascular disease, osteoporosis, decline in physical function (strength, endurance, flexibility), and an increased risk of all-cause mortality. The interrelationships between beliefs, motivation and worries about physical activity are complex. Each factor contributes to behavior change; they are measurable and can be modified. The development of interventions that target potential predictors, moderators and/or mediators of physical activity have the potential to increase physical activity participation. Currently, there is a knowledge gap in persons with rheumatoid arthritis (RA) regarding the relationship between beliefs, motivation, and worries about physical activity in relation to physical activity participation. The objective of this study is to determine if stronger beliefs that physical activity can be beneficial (cognitive appraisal), increased motivation for physical activity (perceived competence) and increased levels of worry that not doing physical activity can be detrimental (affective response) are associated with higher levels of physical activity participation in a sample of patients with RA.

Methods: A cross-sectional study used baseline data from 185 adults with RA enrolled in a randomized clinical trial assessing the effectiveness of an intervention to promote physical activity. Data included patients' self-reported beliefs that physical activity can be beneficial for their disease, motivation for physical activity participation, worries about physical activity participation, and average daily accelerometer counts of activity over a week's time. The relationships between physical activity and beliefs, motivation and worries about physical activity were examined by multiple regression models adjusting for body mass index, gender, age, race and disease activity.

Results: Physical activity participation was greater for adults with higher scores on scales measuring beliefs that physical activity is beneficial for their disease (p for trend= 0.032) and motivation for physical activity participation (p for trend= 0.007) when adjusted for age, gender, body mass index, race and disease activity. There was a positive but non-significant trend in physical activity participation in relation to worries.

Conclusion: Stronger beliefs that physical activity can be helpful to manage disease and increased motivation to engage in physical activity are related to higher levels of physical activity participation. These data provide empiric rationale to promote development of interventions that target these factors with the goal of improving physical activity participation in adults with RA.

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A Qualitative Study of Exercise Habits of Individuals with Rheumatoid Arthritis Taking Anti-TNFαMedication Sixteen Weeks Following Participation in a Randomised Controlled Trial. Angela Reid[1], Audrey Brady[1], Catherine Blake[2], Anne-Barbara Mongey[3], Douglas J. Veale[3], Oliver M. FitzGerald[3] and Tara Cusack[2]. [1]Our Lady's Hospice and Care Services, Dublin, Ireland, [2]University College Dublin, Dublin, Ireland, [3]St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: A recent randomized controlled trial (RCT) investigated the effect of dynamic exercise programs (land-based or water-based) on function in people with rheumatoid arthritis (RA) taking anti-TNFα medication. The results of the RCT demonstrated that beneficial effects of the exercise interventions did not persist 16 weeks beyond completion of the exercise programs. Consistent engagement in exercise is essential in order for individuals with RA to maintain improvements in fitness and physical well-being. The qualitative component of this study sought to examine the exercise habits and adherence to exercise of participants 16 weeks following completion of the RCT.

Methods: A convenience sample of RCT participants (n=17) was recruited for the qualitative study. Semi-structured telephone interviews were undertaken 16 weeks following completion of the eight-week exercise programs. The interview schedule consisted of a series of questions designed to explore the exercise habits of participants since completion of the RCT. The factors that influenced their adherence to the exercise programs were also examined. Interviews were digitally recorded and transcribed verbatim. The data were coded and analyzed using the methods developed in grounded theory. A coding system was developed in order to facilitate the identification of recurrent patterns and themes.

Results: Of the 17 interviews conducted, nine were with land-based program participants (three male and six female) and eight were with water-based program participants (two male and six female). Their ages ranged between 27 and 70 years and the duration of their disease ranged between 1 and 39 years. Fourteen interviewees had not continued to carry out the exercise program while the three who continued to exercise had all completed the land-based intervention. Themes that were identified in terms of failing to continue to exercise included lack of access to suitable facilities or equipment (in particular hydrotherapy or suitable swimming pools), lack of motivation and time constraints. Six of the 14 interviewees who had not continued the exercise programs had changed their exercise habits by taking up more exercise while eight individuals had not altered their exercise habits. The main themes identified that might have aided participants in continuing to exercise included; access to facilities, and support in terms of exercising in a supervised group setting or at an organized time.

Conclusion: The results of these interviews demonstrate that few of this sample of RCT participants continued to engage in dynamic exercise programs on completion of the study. While some individuals reported changing their exercise habits the majority did not. Improved access to appropriate facilities and support in terms of organized, supervised exercise classes within the community may enable this population to continue to participate in dynamic exercise on a more regular basis thereby improving and maintaining functional abilities in the long term.

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Muscle Area and Muscle Quality Relate to Physical Activity in Subjects with Rheumatoid Arthritis. Samannaaz S. Khoja, Gustavo JM Almeida, Bret H. Goodpaster and Sara R. Piva. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: People with Rheumatoid Arthritis (RA) experience a reduction in lean muscle mass and an increase in fat mass due to metabolic abnormalities caused by the disease. Low lean muscle mass associates with decreased muscle strength and physical function, and may play a role in the low levels of physical activity (PA) reported in this population. To our knowledge, direct associations between lean muscle mass and PA have not been established in RA. Investigating this relationship may help optimize strategies to improve PA participation. In addition to muscle mass, muscle quality may also affect PA. Muscle quality may be characterized by its muscle attenuation (MA) coefficient and provides information about amount of fatty tissue present within the muscle. Studies in other populations suggest that increased intramuscular fat affects overall muscle function. The aim of this study was to investigate the association of thigh muscle area and muscle quality and PA in subjects with RA

Methods: Cross-sectional study on 17 subjects with RA (age 61.5$\pm$ 10.6 yrs; RA duration 17.2 $\pm$ 3 yrs; BMI 30.6 $\pm$ 7.6 kg/m^2; 13 female). PA was measured at several low intensity levels by the Sense Wear armband, a multi-sensor portable activity monitor that provides data on energy expenditure (EE) of PA performed above 1 metabolic equivalent level (PAEE$\geq$1MET), EE of PA performed above 2METs (PAEE$\geq$2METs), and EE of PA performed above 3METs (PAEE$\geq$3METs). Mid-thigh cross-sectional area (CSA) of each leg was measured by computed tomography (CT), and averaged for both sides. The mean MA of the mid-thigh CSA was calculated for each leg using the Slice-O-matic software, and averaged for both sides. MA coefficient ranges from 0 to 100 Hounsfield units (HU), higher numbers indicate lower intramuscular fat and better muscle quality. We calculated the correlations between mid-thigh CSA and MA with PAEE above 1, 2 and 3 METs. We accounted for body size in the analysis by controlling for BMI.

Results: Total mid-thigh CSA and mean MA both showed positive associations of moderate strength with PAEE$\geq$1MET, PAEE$\geq$2METs and PAEE$\geq$3METs after controlling for BMI. Results suggest that subjects with higher area of thigh muscle and lower amount of intramuscular fat have higher levels of PA. Variable descriptives and semi-partial correlation coefficients are depicted in the Table.

Table. Associations between Muscle Cross-sectional Area (CSA) and Mean Muscle Attenuation (MA) Coefficients with Physical Activity Energy Expenditure (PAEE)

Variables	Medians (IQ:25–75)	Semi-Partial Correlation Coefficients After controlling BMI		
		PAEE≥1MET	PAEE≥2METs	PAEE≥3METs
Mid-Thigh CSA (sq cm)	94.2 (84.2–111.3)	0.64*	0.59*	0.65*
Mid-Thigh mean MA (HU)	41.7 (38.9–44.5)	0.44	0.45*	0.52*
PAEE≥1MET (kcal/min)	913.0 (449.0–1212.5)			
PAEE≥2METs (kcal/min)	488 (165.5–773.5)			
PAEE≥3METs (kcal/min)	128.0 (29.0–332.0)			

* significant at α–level of 0.05.

Conclusion: The findings suggest that perhaps improving muscle mass and muscle quality may lead to an increase in PA participation in patients with RA. An increased participation in physical activities reduces cardiovascular risk, which is an important predictor of morbidity and mortality in RA. In order to optimize interventions to promote PA participation, future longitudinal trials should consider the effects of muscle mass and quality while investigating changes in PA.

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Associations Between Changes in Physical Function and Physical Activity in Response to An Exercise Program in Patients with Rheumatoid Arthritis. Gustavo JM Almeida and Sara R. Piva. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Measures of physical function (PF) characterize patient's ability to perform functional activities whereas measures of physical activity (PA) informs about the amount of activities patients perform. Cross-sectional studies in patients with Rheumatoid Arthritis (RA) have reported conflicting evidence about the associations between these two domains of PF and PA. Longitudinal studies investigating how well changes in PF associate with changes in PA are lacking. If changes in these two domains are associated targeting exercise to improve PF can result in increases in PA participation in patients with RA. The aim of this study was to explore the associations between changes in PF and changes in PA in patients with RA.

Methods: This is an interim analysis from a randomized controlled trial on the effect of a 12-week strengthening exercise for the lower extremities on muscle function in patients with RA. At this point, data from 12 subjects (9 females, age 65.1±9.5, BMI 30.4±8, disease duration 20.4±11.1 years, and Health Assessment Questionnaire-HAQ.82±.75) were analyzed. PF was measured by the Lower Extremity Functional Scale (LEFS), quadriceps strength measured in an isokinetic dynamometer, timed 5-chair rise, and time to go up and down a flight of stairs. PA was measured by the Physical Activity Scale for Individuals with Physical Disabilities questionnaire (PASIPD) and by the SenseWear armband, a multi-sensor portable activity monitor that provided data on energy expenditure (EE) of PA performed above 1 metabolic equivalent level (PAEE≥1MET), EE of PA performed above 2 METs (PAEE≥2METs), EE of PA performed above 3 METs (PAEE≥3METs). Spearman or Pearson correlation coefficients were calculated between changes in PF and changes in PA according to data distribution.

Results: The associations between changes in PF and changes in PA are shown in the Table. Results indicated that the associations between changes in PF and changes in PA were higher for the more demanding functional tasks such as chair rise and climbing stairs, and lower for changes in quadriceps strength and PA. Changes in self-reported PF and real-time PA did not associate, whereas the association between changes in self-reported PF and self-reported PA was moderate, which may have occurred due to both measures being self-reported.

Table. Associations between changes (Δ) in physical function (PF) and physical activity (PA) variables. Associations represent Pearson Correlations, unless otherwise indicated.

Variables explored	Correlation coefficients between PF and PA variables			
	Δ Quad Strength	Δ Chair time†	Δ Stair time†	Δ LEFS
Δ PAEE≥1MET	0.37	−0.70*	−0.51*	0.09
Δ PAEE≥2MET	0.27	−0.68*	−0.55*	0.10
Δ PAEE≥3MET	0.21	−0.43	−0.41	0.01
Δ PASIPD score	0.64*	−0.32	−0.88**	0.41

Quad Strength = quadriceps strength; Chair time = timed 5-chair rise; Stair time = time to go up and down a flight of stairs; † Spearman Rho Correlation Coefficients; *p≤.05; **p≤.01.

Conclusion: The clinical relevance of this study is that improvements in PF to perform demanding functional tasks seem to play a role in increasing PA in patients with RA. Perhaps targeting exercises to improve patient's ability to perform more demanding functional tasks may increase the participation in PA. Increasing participation in regular PA is important for patients with RA because it can prevent several co-morbidities associated with the disease, and maintain mobility that is also reduced in these patients.

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Sensorimotor Training Versus Resistance Training in Patients with Knee Osteoarthritis. Aline B. Gomiero[1], Virginia M. Trevisani[2], Andrea H. Kayo[2], Maria Stella Peccin[3] and Marcelo Abraão[4]. [1]Federal University of Sao Paulo, São Paulo, Brazil, [2]Federal University of São Paulo, São Paulo Brazil, Brazil, [3]Federal University of São Paulo, São Paulo, Brazil, [4]Federal University of São Paulo, Brazil

Background/Purpose: People with knee osteoarthritis (OA) have functional instability and defective neuromuscular function, it was recently suggested that sensorimotor exercises are important and may be needed to improve the effectiveness of training programs for these patients. This study objective was to compare the effectiveness of a supervised resistance muscular training (RT) versus sensorimotor training (SMT) for patients with Knee OA, on decrease of pain and functional improvement.

Methods: Randomized single blind clinical trial with 96 patients, 50–75 years old, with knee OA according to ACR criteria, were randomized into one of 3 groups. SMT group (n=32), RT group (n=32), and control group (CG n=32) for a 16-weeks intervention. The intervention for the RT group consisted in orientation plus quadriceps and hamstring strength training followed by stretching of this muscles. The SMT group consisted in orientation plus stability and agility training followed by stretching, and the CG received the same orientations, warm-up and stretching exercises made by the interventional groups without the intervention. Evaluations were made before (T0) and after intervention (T16). Outcomes measured included: Visual Analogue Scale of pain (VAS); electromyographic analysis of quadriceps muscle (EMG); isometric quadriceps strength with dynamometer (miotec medical supplies) and Timed-Up-Go test (TUG). Patients also completed 2 self-report measures of physical function and disability; the Medical Outcomes Study – Short Form (SF-36) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Data were analyzed using repeated measures ANOVA with Bonferroni corrections.

Results: There were no significant differences in age, gender distribution, height, or weight among groups ($p > .05$). There were significant differences between the two time points in RT group for the variable WOMAC $p=0.004$ and SF-36 subscales physical functioning $p<0.001$, vitality $p=0.001$ and role emotional $p<0.001$. We also observed significant improvement on quadriceps strength on RT group $p=0.006$ and on SMT group $p<0.001$. There were no differences among the groups or between the two time points for the variables VAS, EMG, TUG, and for SF-36 sub-scales role-physical and mental health.

Conclusion: Although our results showed no improvements on function and pain after resistance training or sensorimotor training in patients with knee osteoarthritis, experts recognize the importance of mechanical loading for maintaining healthy cartilage. Furthermore, more studies are necessary to demonstrate changes in performance-based physical function after a functional intervention.

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Reductions in Knee Joint Loading After Focused Hip Muscle Training. Laura E. Thorp, Markus A. Wimmer, D. Rick Sumner and Joel A. Block. Rush University Medical Center, Chicago, IL

Background/Purpose: The purpose of this investigation was to analyze the effects of a focused hip muscle training program on knee joint loading in subjects with medial compartment knee OA. We hypothesized that focused hip musculature training in individuals with mild to moderate knee OA would produce favorable changes in dynamic loading of the medial knee during walking, as evidenced by decreased external knee adduction moments.

Methods: 17 subjects with mild to moderate medial compartment knee OA ranging in age from 35–69 years of age completed the study protocol. Subjects underwent gait analysis walking barefoot at self-selected normal walking speeds. Both the peak external knee adduction moment and the knee adduction angular impulse were calculated for the index knee (more painful knee) before and after participation in a 4-week supervised, physical therapy intervention targeted at the hip abductor musculature. Additionally, subjects wore an accelerometer-based activity monitor for 7 days after the baseline visit.

Results: While there were no significant differences in the peak external knee adduction moment or the knee adduction angular impulse for the group as a whole, over half the subjects (10 of the 17) had a decrease in both the peak external knee adduction moment and the knee adduction angular impulse. For these subjects, the peak external knee adduction moment decreased from 2.7 to 2.5%BW*Ht ($p=0.03$) and the knee adduction angular impulse decreased from 0.9889 to 0.8850%BW*Ht*sec ($p=0.004$). Load reductions as high as 28% were observed in those who responded to therapy. As a group, the responders tended to be more active than the non-responders (8339 step/day vs. 6128 steps/day), though this difference was not significant ($p=0.125$).

Conclusion: Existing literature is controversial regarding the effect of lower extremity exercise on joint loading in individuals with knee osteoarthritis. Indeed in the present study, no significant effect was noted for the group as a whole. Targeted exercise interventions may not be ideal for all individuals, due to compliance, motivation, and baseline level of fitness. What cannot be overlooked is that for some individuals, targeted hip muscle training reduced knee joint loading. As with other conservative, biomechanically-based therapies, the challenge is how to identify appropriate candidates for treatment.

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A Survey of Physical Therapists' Use of Outcome Measures In Total Hip and Knee Arthroplasty. Catherine A. McAuley[1], Marie D. Westby[1], Alison Hoens[2], Ronda Field[3], UBC 2011 MPT Students[4] and W. Darlene Reid[2]. [1]Mary Pack Arthritis Centre, Vancouver, BC, [2]University of British Columbia, Vancouver, BC, [3]Richmond Hospital, Richmond, BC, [4]Vancouver, BC

Background/Purpose: Over 77,500 total hip and knee joint arthroplasty (TJA) surgeries are performed in Canada each year – almost 12,000 in British Columbia (BC). Physical therapists (PTs) play a key role along the continuum of care of these patients (pre-op through post-op rehabilitation) and have identified a need for standardized outcome measures (OMs) to assess treatment effectiveness, inform clinical decision-making, and facilitate communication across health care settings and providers. The aim of this study was to identify PTs' use of OMs with TJA patients in BC. It is part of a larger project to recommend and promote the use of standardized OMs along the TJA continuum.

Methods: We surveyed a stratified (according to practice area), random sample of PTs registered to practice in BC on their use of 18 OMs that were free, valid, reliable, and responsive in osteoarthritis and TJA care. Respondents indicated familiarity and experience with each measure on a 4-point ordinal scale. Open-ended questions invited comments and suggestions for other measures. Questionnaires were pilot tested with a representative sample and then mailed to 694 PTs with self-addressed stamped envelopes. Postcard and e-mail reminders were used to increase response rates. The survey was carried out over a 4-month period. We used descriptive statistics to examine use of measures and respondent demographics. Measures were grouped by type (patient reported outcome measures (PROM), performance-based or prognostic indicators) and by ICF domains (body structure/function and activity/participation) for further analysis. Chi-square tests were used to compare PTs who treat TJA patients and completed the full questionnaire to PTs who do not treat TJA and returned only demographic information. The McNemar test was used to compare use of OMs for clinical decision-making versus program evaluation.

Results: A total of 298 (43%) questionnaires were returned. Of these, 172 (58%) respondents worked with TJA patients. Respondents who work with TJA patients were more likely to work in an urban setting ($p=.04$) and to have graduated less than 10 years previously ($p=.008$). Of the 18 measures in the survey, eight were used by a majority (>50%) of respondents for clinical decisions compared to three for program evaluation purposes. This difference in purpose of outcome measurement was statistically significant ($p<.001$ to $p=.04$) for all but four measures. Performance-based measures were used more often (53%) than prognostic indicators (38%) or PROMs (36%). Of the nine listed PROMs, respondents were most experienced with the numeric pain rating scale (97.7%) in ICF 'body function' domain and the Lower Extremity Functional Scale (59.1%) in ICF 'activity and participation'. The most commonly used performance-based measure was the Timed Up and Go (75%). Less than half of the respondents used the prognostic measures - body mass index and waist circumference.

Conclusion: There is varied use of OMs for clinical-decision making and program evaluation by PTs treating TJA patients in BC. This finding provides a foundation to develop a standardized approach for OMs that is clinically meaningful for TJA patients along their continuum of care.

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Describing the Interventions in Home Care Physical Therapy for Patients Following Total Knee Replacement. Kimberly Nanovic[1], Amy Phillips[1], Elizabeth Childs[1], Patricia D. Franklin[2] and Carol A. Oatis[1]. [1]Arcadia University, Glenside, PA, [2]Univ of MA Med Schl, Worcester, MA

Background/Purpose: Total knee replacement (TKR) is one of the most common procedures performed; however, current literature on interventions used in home care PT following this surgery is understudied. This study describes the PT interventions used in the home care setting following TKR.

Methods: We requested 40 and received 27 home care physical therapy (PT) records for patients participating in a clinical trial. Eligible records were from patients who had received a primary TKR, completed their PT rehabilitation, used no outpatient PT services post-operatively and had completed the 6-month study assessment. All 27 records contained complete information for use of modalities, functional training, ROM, and quadriceps exercises; only 17 records contained complete information for strengthening exercises. PT records were used to determine the number of patients receiving modalities, functional training, ROM or strengthening exercises. Exercise progression was defined as increased difficulty of an exercise or the addition of a more difficult exercise. Documented interventions were compared to post-TKR interventions recommended in the literature. Descriptive statistics were used to describe home care PT interventions.

Results: Out of the 27 records, all received passive and/or active knee ROM exercises as well as quadriceps exercises. Of these records, 14 used cold packs and 11 used a CPM. 6 patients received one or more of the following modalities: joint mobilizations, patellar mobilizations, scar massages or soft tissue massages. 26 received gait training on even surfaces, 23 received stair training, and 12 performed gait training outdoors or on uneven surfaces. One-third or fewer performed bed mobility, sit to stand transfers and car transfers. All of these are recommended in the literature. In the 17 complete records, strengthening exercises were reported for: knee flexion (13), hip extension (13), hip flexion (14), hip abduction (15), and plantarflexion and dorsiflexion (10). These exercises target the same muscle groups recommended in the literature. Straight leg raises were reported in 15 of 17 records and 10 records reported squats. 6 or fewer records documented use of marches, lunges, step ups/downs, or wall slides, all of which are recommended in the literature. 15/17 records showed progression of multiple exercises, 1 progressed one exercise and 1 had no documented progression. 5 records had no documented quadriceps strengthening progression.

Conclusion: Much variability exists in the interventions performed in home care PT for patients post TKR. There is variable use and limited progression of recommended interventions. The variability in use of recommended interventions may contribute to variability in patients' functional outcomes. Further research is needed to examine these interventions and their contributions to functional outcomes. Limitations in the data resulting from unclear documentation demonstrate the necessity of a uniform documentation system in home care PT.

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Dysautonomia and Chronotropic Incompetence in Fibromyalgia. Roberta P. C. Ribeiro[1], Thalita Dassouki[2], Luiz A. Perandini[2], Guilherme G. Artioli[1], Ana L. G. Calich[3], Ana Lucia S. Pinto[4], Hamilton Roschel[5], Fernanda R. Lima[6], Eloisa Bonfa[7] and Bruno Gualano[8]. [1]University of Sao Paulo,, Sao Paulo, Brazil, [2]University of Sao Paulo, Rheumatology Division, LACRE, Sao Paulo, Brazil, [3]University of Sao Paulo, Sao Paulo, Brazil, [4]University of Sao Paulo, School of Medicine, Rheumatology Division, LACRE, Sao Paulo, Brazil, [5]University of Sao Paulo, School of Physical Education and Sport, Sao Paulo, Brazil, [6]University of Sao Paulo, School of Medicine, Rheumatology Division, Sao Paulo, Brazil, [7]Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil, [8]University of Sao Paulo,School of Physical Education and Sport, Sao Paulo, Brazil

Background/Purpose: The understanding regarding fibromylgia (FM) physiopathology has substantially advanced, with a growing body of evidence suggesting that autonomic nervous system dysfunction (also called dysautonomia) plays a role in this disease. We aimed to gather knowledge on the autonomic modulation in patients with fibromyalgia (FM) in response to

exercise and to investigate whether this population suffers from chronotropic incompetence.

Methods: Fourteen women with FM (age: 46 ± 10 years; BMI: 26.6 ± 5.2 kg/m^2) and 14 gender-, BMI- (25.4 ± 4.9 kg/m^2), and age-matched (age: 41 ± 14 years) healthy individuals (CTRL) took part in this cross-sectional study. A treadmill cardiorespiratory test was performed and heart-hate (HR) response during exercise was evaluated by the chronotropic reserve (CR). HR recovery (ΔHRR) was defined as the difference between HR at peak exercise and at both first (ΔHRR1) and second (ΔHRR2) minutes after the exercise test.

Results: FM patients presented lower peak VO_2 when compared with healthy subjects (22 ± 3 *vs.* CTRL: 32 ± 9 mL/kg/min, respectively; $p<0.001$). Additionally, FM patients demonstrated lower CR (72.5 ± 19.4 *vs.* CTRL: 106.1 ± 21.7, $p < 0.001$), ΔHRR1 (24.5 ± 12.2 *vs.* CTRL: 32.6 ± 9.1, $p = 0.059$) and ΔHRR2 (34.3 ± 14.2 *vs.* CTRL: 50.8 ± 10.8, $p = 0.002$) than their healthy peers. The prevalence of chronotropic incompetence was 57.1% among patients with FM.

Conclusion: The majority of the patients with FM undertaken a graded exercise test presented chronotropic incompetence and delayed HR recovery, both being indicative of dysautonomia and higher risk of events.

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Participation in Household and Community Activities by Persons with Systemic Sclerosis. Janet L. Poole[1], Betty Skipper[2], Kristal Hildebrand[1] and Annandhi Chandrasekaran[1]. [1]University of New Mexico, Albuquerque, NM, [2]University of New Mexico, NM

Background/Purpose: Pain, finger ulcers, Raynaud's phenomenon, and internal organ involvement, particularly decreased pulmonary function, make it difficult for people with systemic sclerosis (SSc) to participate in daily activities. Most outcomes measures used in scleroderma research measure perceived difficulty or importance of various activities. However, frequency of participation might be a more accurate indication of what people can do and actually do. Therefore, the purpose of this study was to examine frequency of participation in household and community activities by persons with SSc.

Methods: A convenience sample of 69 persons with SSc was recruited from the Scleroderma Foundation website and national conference. Participants completed a demographic questionnaire, questions regarding presence and severity of symptoms, the Health Assessment Questionnaire (HAQ), the Center for Epidemiologic Studies Depression Scale (CES-D), and the Adelaide Activities Profile (AAP). The AAP consists of 21 items divided into 4 subscales representing distinct domains of participation in household or community activities: domestic chores, household maintenance, service to others and social activities. Participants rate the frequency of participating in an activity during the previous three-month period, on a 4 point scale from 0 (never) to 3 (once a week or more). Items are summed to yield subscale scores and a total score (0–63). Higher scores indicate higher levels of participation.

Results: Participants were primarily female (94 %), married (65 %), and white (88 %). Mean age was 53.7 years, mean disease duration was 9.9 years and mean education level was 15.5 years. Fifty percent had diffuse SSc and 43% had limited SSc. The primary symptoms reported were Raynaud's phenomenon (98 %), finger ulcers (46 %), and lung involvement (52%). Participants had moderate pain (VAS = 4.2) and fatigue (VAS = 5.5). Mean HAQ and CES-D scores were 1.1 and 16.2 respectively. On the AAP, the mean total score was 37.4. Subscale scores were 16.2 for domestic chores, 9.5 for household management, 7.2 for service to others and 4.6 for social activities. There were no significant differences in AAP subscale or total scores between the types of SSc (limited and diffuse). However, having more fatigue ($p <.05$), and higher HAQ ($p <.001$) and CES-D ($p =.006$) scores resulted in higher total AAP scores. A three factor ANOVA on the AAP total score using the HAQ, CES-D and fatigue as independent variables showed that only the HAQ was statistically significant ($p <.005$) after adjusting for the other variables.

Conclusion: Persons with SSc reported participating in domestic chores, such as meal preparation and housework, more frequently than household maintenance, service to others and social activities. Reduced time spent in home maintenance and community activities has been shown to be related to lower life satisfaction in persons with other rheumatic diseases. Thus, strategies to help people manage domestic chores may free up time to engage in other activities.

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Effect of Physical Exercise in Systemic Sclerosis—a Pilot Study. Jenny Bergegård[1] and Helene Alexanderson[2]. [1]Karolinska University Hospital, Solna, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden

Background/Purpose: A few studies have reported improved aerobic capacity following aerobic exercise in systemic sclerosis patients without lung involvement. No previous studies have examined the effect of intensive physical exercise for patients with systemic sclerosis and pulmonary impairment. The aim of the study was to examine the effect of an 8-week exercise program for patients with systemic sclerosis and 50–100 % in vital capacity.

Methods: A single subject experimental design with repeated systematic measures during a six week A-phase (baseline-period) and an eight week B-phase (intervention-period) was used. Three women and one man with median age 66 years and median disease duration of four years completed aerobic exercise on a stationary bike corresponding to 15 on Borg RPE (strenuous) and muscular endurance training of shoulder flexors and hip flexors / knee extensors three times a week for eight weeks. Physical capacity (six minute walk test), aerobic capacity (sub maximal treadmill test) and muscle endurance in shoulder- and hip flexion (Functional Index 2) were assessed every other week. Level of activity limitation (Health Assessment Questionnaire), perceived health (Short Form 36), Raynaud, Fatigue and Global Health during the recent week (Visual Analouge Scale) were assessed at weeks 0, 6, 14. A mean value and 2 standard deviations (2SD) of measure time points in the A-phase were calculated. A statistically significant difference was defined as two consecutive measure points in the B-phase above or below the 2SD. Measures producing ordinal data were analyzed visually for trends and slopes.

Results: Three participants improved statistically significantly in muscular endurance and two participants improved significantly in aerobic capacity. There was a visual trend with three patients rating less fatigue after 8 weeks of exercise compared to measures in the A-phase. One patient rated between 83–91 mm on the VAS during the A-phase and dropped down to 47 mm after eight weeks of exercise, one rated 50 mm in the A-phase and dropped down to 22 mm, and one rated 41 mm and then dropping to 23 mm while one patient remained unchanged. All other variables remained unchanged.

Conclusion: This eight week exercise program was well tolerated with positive effects on aerobic capacity and muscular endurance. These preliminary results of an ongoing study need to be confirmed in a larger population ($n>10$).

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Mobility and disease Activity but Not Aerobic Capacity Relate to Functional Disability in Ankylosing Spondylitis. Fabio Jennings, Hilda A. Oliveira, Marcelo C. Sousa, Vaneska G. Cruz and Jamil Natour. Universidade Federal de Sao Paulo, Sao Paulo, Brazil

Background/Purpose: Ankylosing spondylitis (AS) is an inflammatory disease characterized by progressive stiffness and eventual fusion of the skeleton, restrictive ventilatory defect and functional limitations. The purpose of this study was to investigate the relationship between clinical variables, mobility, disease activity, aerobic capacity and functional disability in patients with AS.

Methods: A cross-sectional study enrolled thirty patients (23 male, 7 female) with definite AS (New York modified criteria) with no other cardiopulmonary disease. All the necessary information regarding clinical features was recorded. Mobility was measured using the BASMI (Bath Ankylosing Spondylitis Metrology Index) and disease activity was evaluated using the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). Levels of C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. BASFI (Bath Ankylosing Spondylitis Functional Index) was used to evaluate functional disability. Aerobic capacity was evaluated using an incremental cardiopulmonary exercise testing protocol by treadmill. Additionally, the 6-minute walking test was apllied.

Results: the AS patients had the mean age of 42.1 ±10.1 years and disease duration of 17.5±8,4 years. The mean BASMI score was 5.46 ±2.00, mean BASDAI score was 3.65 ±1.95 and the mean BASFI was 4.95 ±2.41. Levels of CPR and ESR were elevated (9.27 ±11.23 and 16.23 ±15.32, respectively). The mean peak VO2 was 30.8 ±6.37 ml.kg^{-1}.min^{-1}. The

BASFI score was correlated with BASMI (r=0.766; p< 0.01) and BASDAI (r=0.574; p=0.01). There was weak negative correlation between BASFI and peak VO2 (r=-0.366; p=0.47). Multivariate linear regression analysis showed that BASMI and BASDAI accounted for 58.7% (r^2) and 33% (r^2) of the total BASFI variance. BASMI and BASDAI together accounted for 67.4% (r^2 p< 0.001) of the total BASFI variance. The addition of peak VO2 to the model did not improved the explained variability in BASFI score.

Conclusion: this study shows that mobility and disease activity are the most important determinants of functional disability in patients with AS. The findings suggest that adequate control of inflammation and interventions to avoid joint stiffness are necessary to prevent disability in AS.

1570

A Multidisciplinary and Multidimensional Program for Hand Osteoarthritis Is Not Effective: Results of a Randomized Controlled Study. Mirelle J. Stukstette[1], Joost Dekker[2], Alfons A. den Broeder[1], Willemijn Noort van der Laan[3], Johannes W.J. Bijlsma[4] and Cornelia H.M. van den Ende[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]VU University Medical Centre, EMGO Institute, Amsterdam, Netherlands, [3]Maartenskliniek Woerden, Woerden, Netherlands, [4]UMC Utrecht, Utrecht, Netherlands

Background/Purpose: Although research on the efficacy of non-pharmacological interventions is very limited and mainly based on low quality studies, international guidelines for management of hand osteoarthritis (OA) strongly recommend to treat all patients with hand OA with a combination of pharmacological and non-pharmacological interventions. The aim of this study was to examine the efficacy of a multidisciplinary, multidimensional non-pharmacological intervention in patients with hand OA.

Methods: a single blinded randomized multicenter trial was conducted. Patients were recruited at three Rheumatology outpatient clinics in the Netherlands. Included were patients with Hand OA according to the ACR classification Criteria for clinical hand OA with limitations in activities (AUSCAN function > 25). Patients were randomly assigned to immediate start of multidisciplinary intervention (four weekly sessions, including individual goal setting, exercises, education, and splints if considered necessary) or 30 minutes of education followed by waiting time of 3 months. Data at baseline and 3 months were collected by a research assistant who was blinded for treatment allocation. Primary outcome measures after three months were pain and limitations in activities as measured with the AUSCAN and the OARSI-20 responder criteria. Secondary outcome measures included grip strength, self-efficacy, pain coping and quality of life. (Dutch Trial Register trial number NTR1191).

Results: 151 patients (83% female, mean (SD) age 59.2 (7.7)) were included. At baseline and after 3 months no significant and no relevant differences were observed between the treatment group (n=75) and the control group (n=76) in any of the primary and secondary outcome measures. About one third of patients were classified as responder (OARSI 20 responder criteria) (32% and 37% in the treatment group and control group, respectively).

Outcome measure	Groups				
	Experimental		Control		Difference*(95% CI) at 3 months
	Baseline (mean(sd))	3 months (mean(sd))	Baseline (mean(sd))	3 months (mean(sd))	exp-contr
Pain^	52.1 (16.8)	47.2 (14.0)	51.9 (16.0)	45.1 (18.4)	1.98 (−2.49;6.45)
Function^	58.4 (19.5)	51.6 (20.4)	60.8 (17.7)	52.2 (17.8)	1.35 (−2.81;5.52)

^normalised AUSCAN score (0–100); *adjusted for baseline

Conclusion: Patients with hand OA do not benefit on the short term from a multidimensional and multidisciplinary non pharmacological treatment program.

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Association of Pinch Strength with Hand Dysfunction, Finger Deformities and Contact Points In Patients with Rheumatoid Arthritis. Kenrin Shi[1], Akihide Nampei[2], Kosuke Ebina[1], Tsuyoshi Murase[1], Hideki Yoshikawa[1], Makoto Hirao[3] and Jun Hashimoto[3]. [1]Osaka University Graduate School of Medicine, Osaka, Japan, [2]Osaka Rosai Hospital, Sakai, Japan, [3]Osaka Minami Medical Center, Osaka, Japan

Background/Purpose: Among disabilities in rheumatoid hands, weakness of pinch strength severely deteriorates hand function. This study aimed to investigate the association of pinch strength with hand dysfunction in patients with rheumatoid arthritis (RA), as well as with several factors concerning thumb and index finger, such as deformities and contact points during pinch.

Methods: Eighty-one hands of 42 outpatients with RA were examined. Hand dysfunction was evaluated by Japanese version of Stanford Health Assessment Questionnaire in part, focusing on hand and finger function, as Hand Disability Index (HDI). Pinch strength was measured by pinch gauge, and was analyzed in relation to HDI as well as deformities and contact points during tip pinch in thumb and index finger.

Results: Average pinch strength was 1.05 kg in tip pinch, 1.55 kg in key pinch, and 1.48 kg in three-digit pinch, all of which demonstrated significant negative correlations with HDI. Tip pinch strength was significantly weaker in hands with volar dislocation of metacarpophalangeal joint of index finger than in those without, while that in hands with mutilated deformity of thumb demonstrated significant weakness. Tip pinch strength was the maximum with thumb contact at the pulp and with index finger at the apex, whereas abnormal contact points demonstrated significant weakness.

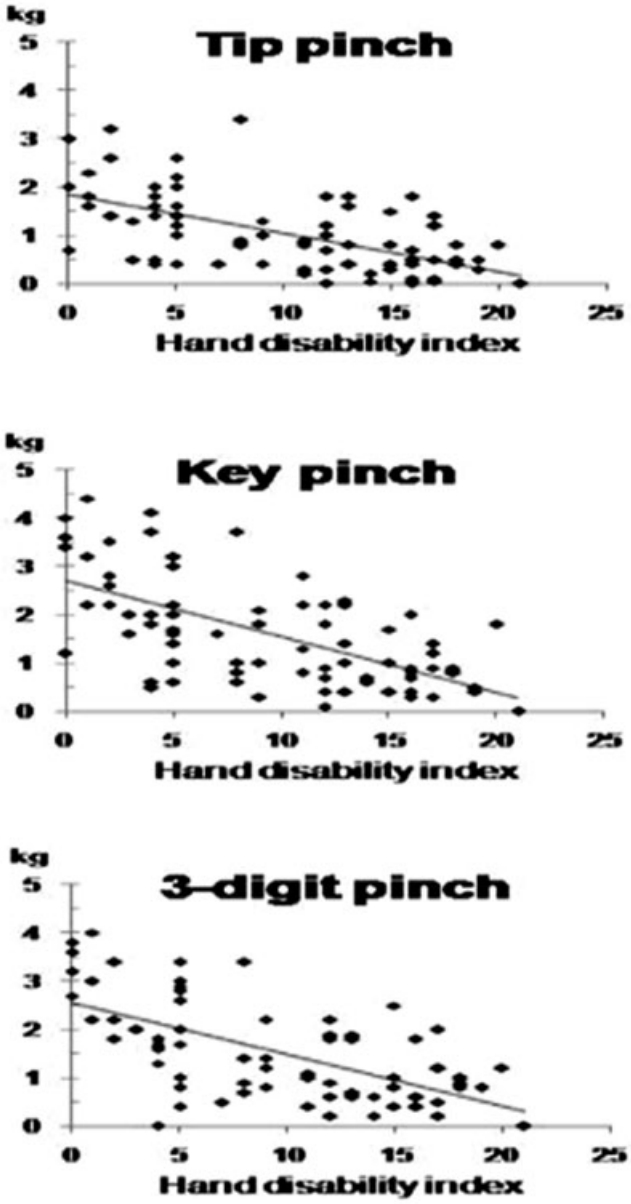

Figure. Correlation of hand disability index and pinch strength.

Conclusion: Since pinch strength significantly correlated to hand function, it is important to arrange good alignment with favorable contact points in thumb and index finger, not only in conservative management but also in planning of reconstructive surgeries of rheumatoid hands.

1572

Effects of Maximal Acute Physical Exercise on Prothrombin Time in Patients with Primary Antiphospholipid Syndrome (PAPS) Under Oral Anticoagulation with Warfarin and Exercise Capacity. Carolina B. Garcia[1], Luciana N. J. Matos[2], Carlos E. Negrao[2], Hamilton Roschel[3], Ana Lucia S. Pinto[4], Jozelio F. Carvalho[5], Eloisa Bonfa[6] and Fernanda R. Lima[1]. [1]Rheumatology Department, Sao Paulo, Brazil, [2]University of Sao Paulo, InCor, Sao Paulo, Brazil, [3]University of Sao Paulo, School of Physical Education and Sport, Sao Paulo, Brazil, [4]University of Sao Paulo, School of Medicine, Rheumatology Division, LACRE, Sao Paulo, Brazil, [5]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [6]Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil

Background/Purpose: The aim of this study was to evaluate the effect of acute physical exercise on prothrombin time (PT) in patients with primary antiphospholipid syndrome (PAPS) under oral anticoagulation therapy with warfarin.

Methods: Nineteen premenopausal sedentary women with PAPS (Sapporo and Sidney criteria with exclusive deep venous thrombosis(mean age: 32.4 ± 8.90 years; mean BMI 24.4 ± 3.77 Kg/m^2) were enrolled in the study. All of the PAPS patients were undergoing chronic anticoagulation therapy. PT was stable (INR between 2–3) for at least the past 2 weeks prior to the test. Also, other drugs administration and dietary intake were stable for 2 months prior to testing. Exclusion criteria were: chronic obstructive pulmonary disease, smoking, cardiovascular disease, diabetes, systemic hypertension, secondary antiphospholipid syndrome, body mass index (BMI) >30, and stroke. Capillary blood samples were drawn during a maximum cardiopulmonary stress test (RAMP protocol) at: baseline (B), anaerobic threshold (AT), immediately after the test (Im) and 1 hour after the test (1h). PT was assessed by a Coaguchek XS,(Roche Diagnostics, Indianapolis, USA). Data were analyzed by a one-way repeated measures ANOVA procedure. Significance level was set at $p<0.05$.

Results: PT did not significantly change between any of the time points (B: 2.29 ± 0.32; AT:. 2.33 ± 0.36;,Im: 2.29 ± 0.35; 1h: 2.37 ± 0.37), demonstrating that the PT was stable during and after (1h) exercise. Additionally, none of the patients presented any adverse symptoms or any thrombosis or bleeding events during the exercise or in a one month follow-up period.

Conclusion: This is the first study to demonstrate that an acute exercise bout of maximal intensity is safe and did not affect PT in patients with PAPS under oral coagulation therapy with warfarin.

1573

Applying the New Classification Criteria for Rheumatoid Arthritis to Patients (pts) with Early Rheumatoid Arthritis Treated with Abatacept Plus MTX—Insights From AGREE (Abatacept study to Gauge Remission and joint damage progression in MTX naïve patients with Early Erosive Rheumatoid Arthritis). Tanaka Ngcozana[1], Cecilia B. Chighizola[2], Louise Parker[1], Carol M. Black DBE[1], Voon Ong[3] and Christopher D. Denton[4]. [1]UCL Medical School and Royal Free Hosp, London, United Kingdom, [2]UCL Medical School, London, United Kingdom, [3]UCL Medical School, London, England, [4]Royal Free Hospital, Medical School, London, England

Background/Purpose: Sexual dysfunction is a great concern for many patients with scleroderma. Previous studies suggest that the prevalence of erectile dysfunction (ED) in male scleroderma (SSc) patients ranges from 12 to 81%. The objectives of this study were to (a) determine the prevalence of sexual dysfunction (b) evaluate its psychological impact on relationships (c) explore the interaction of these patients with key health professionals in sexual health.

Methods: 100 men with limited (lcSSc) or diffuse cutaneous scleroderma (dcSSc) were invited to complete a validated International Index of Erectile Function Questionnaire (IIEF). The questionnaire was expanded to evaluate the psychological effects of sexual difficulties in SSc patients' relationships and interaction with health professionals. IIEF assesses five domains of sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Potential confounding factors including smoking were analysed with logistic and linear regression.

Results: 62 patients responded to the questionnaire of which the mean age (mean ±SD, year) was 54 ±11.1. The mean disease duration (mean ±SD, years) was 8.4 ± 8.0 and 11.4 ± 7.3 for patients with dcSSc and lcSSc respectively. 71% of the respondents reported sexual difficulties in at least one of the domains. 39% of this cohort were considered as severe in all 5 domains of which half had diffuse disease. Interestingly, 34% developed sexual difficulties before they were diagnosed with SSc. For those who developed ED after the onset of SSc, the mean duration (mean±SD, years) from disease onset to emergence of ED was 4.0 ±3.1. As shown in the table below, intercourse satisfaction fared the worst of all the five domains with a score of 45% in the severe dysfunction category. Past or present smoking did not predict ED or severity of ED.

Domain	Severe Dysfunction n (%)	Moderate n (%)	Mild-Moderate Dysfunction n (%)	Mild Dysfunction n (%)	No Dysfunction n (%)
Erectile Function	23 (37)	4 (6)	3 (5)	11 (18)	16 (26)
Orgasmic Function	22 (35)	8 (13)	5 (8)	1 (2)	21 (34)
Sexual Desire	6 (10)	11 (18)	10 (16)	16 (26)	6 (10)
Intercourse Satisfaction	28 (45)	5 (8)	11(18)	3 (5)	10 (16)
Overall Satisfaction	24 (39)	3 (5)	5 (8)	16 (26)	9 (15)

55% of the respondents reported that their sexual difficulties had caused a significant strain on their relationships with their partner and 48% of these individuals did not discuss the difficulties with their partners. 45% of the patients reported that they had never been asked about their sexual health by a health professional. However 65% of the men would have discussed these issues had they been given the opportunity to do so.

Conclusion: ED is a common yet unexplored complication in scleroderma. It is a difficult subject to discuss, yet our results suggest that sexual functioning is an integral parameter in the assessment of quality of life for the affected men. Our results suggest that ED may occur even before diagnosis of SSc, implying that it could be an early feature especially in diffuse subset. Therefore multidisciplinary teams treating scleroderma patients should be aware of and actively enquire about sexual dysfunction.

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"Lo Que Me Diga El Doctor": Patient Reported Interpersonal Processes of Care in An Urban Rheumatology Clinic. Alice Fike[1], Katherine Kline[2], Jorel Martinez[3] and Mark F. Gourley[4]. [1]National Institutes of Health, Bethesda, MD, [2]NIH/NIAMS, Bethesda, MD, [3]Chicago, [4]Bldg 10, Room 6N216F, Bethesda, MD

Background/Purpose: To employ a patient-reported interpersonal processes of care (IPC) survey instrument to describe and assess the care of patients to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Community Health Center (CHC), an urban rheumatology clinic serving a majority foreign born, Hispanic population. We wondered whether foreign birth and/or the need for an interpreter would influence patient reports of their care.

Methods: Between March 2009 and December 2010, a total of 204 IPC surveys, validated in Spanish and English, were administered to established CHC patients. All patients were cared for by rheumatology fellows. The IPC instrument was designed to compare three key aspects of the patient-physician relationship: Communication, Decision-Making, and Interpersonal Style, across racial and ethnic groups. For each question, patients were asked to report their experiences over the past six months on a five-point scale ranging from "never" (1) to "always" (5). Domain scores were calculated and reported as positive or negative by dichotomizing the scales based upon the direction of the question. Patients were grouped by U.S. or foreign birth and foreign born patients were further grouped based on need for interpreter. Significance of associations was calculated using Chi-square analysis.

Results: Of the 196 individuals who reported ethnicity, 125 self-identified as Hispanic. Patients reported the highest scores for interpersonal style, followed by communication, and then decision making. Refer to Table 1 for scores by domain.

	Positive ratings (%)	Negative ratings (%)
DOMAIN		
Subdomain		
COMMUNICATION		
Lack of clarity	85	15
Elicited concerns	95	5
Explained results	90	10
DECISION MAKING		
Decided together	76	24
INTERPERSONAL STYLE		
Compassionate, respect	93	7
Discrimination/ethnicity	93	7

While 21% of foreign-born patients using an interpreter and 14% of foreign-born patients without an interpreter reported a high frequency of physicians speaking unclearly, only 10% of U.S.-born patient reported this ($p=0.252$). In their evaluation of decision making, 27% of U.S.-born patients reported negative scores for physicians, while 23% of foreign patients without an interpreter and 19% of foreign patients with an interpreter reported negative scores in this domain($p=0.553$).

Conclusion: Physician-patient communication is an important marker of healthcare quality. Assessing patient reports of interpersonal processes of care identifies areas of improvement for targeted intervention to assist in training fellows. This is especially important in our understudied, majority Hispanic cohort. The results of the IPC survey suggest physicians need to be more cognizant of sharing the results of physical exams and tests with their patients, attempt to involve patients in their own treatment plan, and speak more clearly to their patients. The differences in expectations related to participatory decision making are perhaps mediated by acculturation. Because communication between patients and physicians influences health outcomes, it is important to measure and evaluate patients' impressions of their care.

1575

Pilates in Juvenile Idiopathic Arthritis. Tania Mendonça IV. Osvaldo Marques da Silva e Valda Maria da Silva, Sao Paulo, Brazil

Background/Purpose: The incorporation of measures that evaluate the health-related quality of life (HRQL) of pediatric patients after the use of interventions will assure a better evaluation of the therapeutic program set to this population.To assess the HRQL of the JIA patients after an exercise program of the Pilates method.

Methods: Clinical trial of a consecutive sample of 26 JIA (ILAR) patients of the Oligoarticular (57.7%), Polyarticular (15.4%) and Systemic (26.9)% subtypes, with an average 10.6 ± 4.7 years of age. The patients participated in Pilates sessions twice a week for 6 months. The degree of satisfaction of the patients in relation to the intervention has been assessed by means of a Likert-type question with options for patients that are totally, very or little satisfied and those slightly or totally unsatisfied with the intervention using Turkey's variance analysis with *post hoc* in order to identify the differences. The HRQL has been assessed by means of the comparison between the PedsQL 4.0 in the baseline and end-of-6-months period after the intervention.

Results: 73.1 % of the patients were totally satisfied with the attributed exercise program ($p<0.05$). In the comparison between the PedsQL 4.0 scores averages in the baseline and end-of-6-months period a significant difference has been noted ($p<0.05$) in the *physical* (50.7 ± 18.1 vs. 90.3 ± 15.5), *emotional* (44.8 ± 18.2 vs. 88.7 ± 13.9), *social* (54.6 ± 15.3 vs. 66.0 ± 15.9), *school-related* (44.4 ± 17.7 vs. 80.0 ± 12.6), psychosocial summary (47.8 ± 14.7 vs. 85.4 ± 15.4) and total score (48.8 ± 12.7 vs. 83.6 ± 12.9).

Conclusion: The Pilates exercise program has promoted a positive impact in the HRQL of JIA patients in the domains, summaries and total scores of the PedsQL 4.0. These results call for the reflection of health professionals on the elaboration of projects intended for the release of funds for the modernization of the rehabilitation methodology of the pediatric population in general.

1576

Ambivalent Attitudes, Accessing Information and Decision-Making: An Interview Study of Medication Use in Early Rheumatoid Arthritis (RA). Anne F. Townsend[1], Paul M. Adam[2], Catherine L. Backman[3], Linda C. Li[3] and ERAHSE Team[4]. [1]Arthritis Research Centre of Canada, Vancouver, BC, [2]Mary Pack Arthritis Centre, Vancouver, BC, [3]University of British Columbia, Vancouver, BC, [4]Vancouver & Toronto

Background/Purpose: Timely treatment is important to control RA, prevent irreversible joint damage and limit impact on daily life. Prompt intervention with DMARDS is associated with improved outcome but delays exist between disease onset and effective medication use. Evidence shows that multiple factors delay early treatment including diffuse symptom onset, access to health care services, and difficulties in gaining a diagnosis. However, little is known of the patient perspective about early decisions and medication use. The current study investigates patient: 1) attitudes to and experiences of medication use; 2) information-seeking; 3) the decision-making process.

Methods: Participants were recruited from rheumatologist and family physician offices, and from newsletters of patient advocacy groups. We conducted in-depth interviews with 38 people (37 women, 1 man), with an RA diagnosis $\leq$12 months. The interviews were organized around 3 distinct but overlapping areas: 1) Pre-diagnosis symptoms, impact and management; 2) Experiences with health professionals leading up to the diagnosis; 3) Post-diagnosis experiences of symptoms, management and the health care system. Follow-up phone calls were made to check and elaborate on the interview generated data. Analysis was informed by grounded theory and a narrative approach.

Results: Medications were core to people's disease management. There was a both a reluctance to take medications and a need for them. Participants expressed ambivalence to medication use in a range of ways: 1) They identified an aversion to medications but required them; 2) They accessed information from multiple sources e.g. the Internet, health professionals and social networks, which was wide-ranging and contradictory; 3) There was little perceived opportunity to discuss options and patient knowledge in the rheumatologist consultation 4) There was post diagnosis delay in and resistance to, taking prescribed medications, and a desire to be 'weaned off' or reduce medications, but an ongoing search for relief and disease control.

Conclusion: A number of interrelated factors continued to hamper prescribed medication regimens, once diagnosis was confirmed. The obstacles to effective and timely medication treatment illustrated the importance of patient-physician communications. More opportunities for shared decision-making, based on dialogue and exchange of knowledge and information in the rheumatologist consultation may reduce some of the tensions around medication use and facilitate ongoing and effective treatment plans

1577

Conception, Family Size and Miscarriages in Fibromyalgia Patients. Robert S. Katz[1], Sharon M. Ferbert[2], Patricia Kuenzi[1], Jessica L. Polyak[3] and Susan Shott[1]. [1]Rush University Medical Center, Chicago, IL, [2]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL, [3]Rheumatology Associates, Chicago, IL

Background/Purpose: Fibromyalgia (FMS) imposes significant handicaps on patients. We asked female fibromyalgia patients about their experiences with childrearing because we anticipated that the patients' pain, fatigue, cognitive problems might create unique difficulties in raising a family and could affect their ability and/or desire to have more children.

Methods: As a part of an Internet survey administered by the volunteer community fibromyalgia organization, AFFTER, 763 female self-identified FMS patients and 115 female controls without FMS responded to questions about their desire and ability to have children. Only women's responses were analyzed to eliminate confounding by gender..

To validate the Internet Survey an identical rheumatology office questionnaire was administered to 115 FMS patients and 63 control patients with other rheumatic diseases. The chi-square test of association and Fisher's exact test were used to compare percentages and the Mann-Whitney test was done to compare FMS and control respondents with respect to the number of biological children. A 0.05 significance level was used and all tests were two-sided.

Results: In the Internet survey the mean respondent age was 49.8 ± 11.4 years. There was no statistically significant difference between FMS and control respondents with respect to the number of biological children (FMS 1.7 ± 1.3 vs. control 1.7 ± 1.6, $p = 0.88$). There were no apparent problems with conception among the FMS patients. Of the respondents who had tried to conceive, 59.6% of FMS patients and 68.8% of controls reported no difficulty conceiving ($p = 0.088$). In the rheumatology office questionnaire The mean age was 48.1 ± 12.3 years for FMS patients and 50.7 ± 13.6 for control patients ($p = 0.092$). 81.7% of the FMS patients and 61.9% of the control patients were women ($p = 0.004$). There was no statistically significant difference between FMS and control respondents

with respect to the number of biological children (FMS 1.5 ±1.4 vs. control 1.4 ±1.3, p = 0.78). Only 19.0% of FMS patients reported that they were raising or had raised their desired number of children with no particular difficulty, compared to 62.9% of control patients (p < 0.001). Of the respondents who had tried to conceive, 28.8% of FMS patients and 15.6% of control patients reported difficulty conceiving (p = 0.10). 15.1% of FMS patients and 4.4% of the control patients reported that they had miscarriages but were eventually successful in having a baby (p = 0.13)

Conclusion: Fibromyalgia does not appear to limit family size because of limitations imposed by the illness or problems with conception.. However, child rearing was frequently challenging in fibromyalgia patients.There was a trend toward more miscarriages reported in the fibromyalgia patients.

1578

Participation in Hospital Influenza Collaborative Is "inFLUential" in Improving Vaccination Rates in Patients with Juvenile Idiopathic Arthritis and Systemic Lupus Erythematosus. Janalee Taylor[1], Elaine F. Haddix[2], Kim Badinghaus[3], Mary Beth Burns[1], Terry M. Moore[4], Julie V. Ranz[1], Amy Anneken[1], Pam Fiorini[1], EVA Spiegel[1], Esi Morgan-Dewitt[1], Michael Henrickson[1], Hermine Brunner[1] and Jennifer L. Huggins[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Cincinnati Children's Hospital MC, Cincinnati, OH, [3]Cincinnati Children's Hospital Center, Cincinnati, OH, [4]Cincinnati Chiildren's Hospital Medical Center, Cincinnati, OH

Background/Purpose: Influenza (flu) is a contagious respiratory illness caused by influenza viruses. It can result in mild to severe illness, with noted reports of pediatric influenza related deaths. Influenza related morbidity and mortality can be decreased by improving flu vaccination rates. Children with rheumatic disease and those who are on immunosuppressive medications are at increased risk of complications related to influenza. The purpose of this study is to increase flu vaccination rates in patients with Juvenile Idiopathic Arthritis (JIA) and Systemic Lupus Erythematosus (SLE) through participation in hospital-wide influenza collaborative.

Methods: 2010–2011 CDC Influenza Vaccine Recommendations were reviewed. Target populations for pediatric rheumatology clinic were identified. Inclusion criteria for JIA consisted of: Rheumatology patients seen in the last year with a Primary DX code of 714.3, 714.32, 714.33 taking immunosuppressive medications of: methotrexate, sulfasalzine, leflunomide, cyclosporin, mycophenolate mofetil, azathioprine, etanercept, adalimumab, anakinra, infliximab, rituximab, abatacept, canakinumab, tocilizumab, rilonocept, or corticosteroids. SLE patients included rheumatology patients seen in the last year with a Primary DX code for Lupus is 710. Cohorts for JIA and SLE were pulled using Epic Clarity reports and lists were examined for appropriateness of eligibility criteria. Interventions included: reminder cards mailed to target patient population, Epic Influenza Best Practice Alert for target populations, standardized order sets, RN order placement for influenza, and process education for staff.

Results: Two hospital-wide goals for 2010 season were set: 1) 87% of divisions would achieve an 80% immunization goal (vaccinated or actively declined) by January 15, 2011; 2) 75% of target populations would achieve at least 75% actual vaccination (through clinic or PMD). 18 divisions participated in the collaborative with identification of 35 high risk populations. Collaborative-wide results revealed 72% of divisions achieving immunization goal. 80% of identified target populations received actual vaccine. The pediatric rheumatology 2010 patient cohort consisted of 313 and 124 JIA and SLE patients respectively. 94% of JIA and 89% of SLE patients achieved immunization goal of vaccination or decline. Percent of JIA and SLE receiving actual vaccination was 94% and 80% respectively. Comparison of vaccination rates from 2009 to 2010 revealed implementation of Best Practice Alert resulted in 20–25% improvement. Insurance status had no effect on immunization rates in rheumatology patients.

Conclusion: Participation in hospital-wide flu collaborative is valuable program to increase influenza vaccination rates for high risk pediatric rheumatology populations. Key interventions included involvement of front-line nurses with process and Epic implementation, development of Epic Best Practice Flu Alert system and standardized order sets. Consistent data feedback to teams/divisions and automated Best Practice Alerts are useful tools for driving performance.

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Incorporating the Patient Perspective: Developing a Patient-Focused Evaluation for An Early Rheumatoid Arthritis Support and Education Program. Meredith K. Wolrich, Adena Batterman, Roberta Horton, Linda Leff, Theodore R. Fields and Vanima Lalsa. Hospital for Special Surgery, New York, NY

Background/Purpose: OMERACT's work has inspired a paradigm shift in rheumatology research, emphasizing the need for the patient perspective in identifying and measuring RA treatment outcomes. Hewlett's (2003) research reveals that patients and clinicians often have different views concerning outcome prioritization. Without patient input, providers may fail to consider issues of paramount importance in making treatment decisions.

We previously reported on a free monthly support and education program designed to meet the disease-related psychosocial and educational needs of newly diagnosed (<1 yr.) RA patients. The Program is part of a hospital-based early arthritis initiative and was developed from a multi-level needs assessment. Consistent with OMERACT philosophy, format and content are driven by patient input obtained through biannual focus groups. However, our monthly written evaluations, consisting of Likert scale and open-ended questions, were developed *without* patient input. Thus, they may not measure outcomes most important to participants or in language that they find relevant. Our goal is to describe our process for ensuring the inclusion of this essential feedback and its outcome.

Method: Data was collected in 3 stages:

1) We reviewed psychosocial assessments of all past participants (n=40), completed prior to their entering the Program, to identify patient-centered outcomes. Based on the most frequent responses to questions regarding expectations of the Program and RA-related concerns, we created a list of themes and organized them into 3 key domains.

2) Volunteers from our group (n=8) were given a Likert scale survey to rate importance of the listed themes to confirm their relevance.

3) Two MSWs ran a two-hour focus group (n=8) that was recorded and transcribed. Participants were asked 3 questions, modeled on a study by Carr et al (2003), to identify the most important Program outcomes within the 3 domains and obtain patient language to describe them: 1) Which Program outcomes are most important to you? 2) What makes you satisfied? 3) How do you decide it is working for you?

Result: Demographics: *Gender* – Female 88%; Male 12%. *Ethnicity* – Caucasian 50%; Asian-American 25%; African-American 12.5%; Latino 12.5%. *Mean Age* – 53. *Education* –17+ yrs. 75%; 13–16 yrs. 25%.

Within the 3 domains – 1) managing/living with RA; 2) connecting with others with RA, and 3) coping with the emotional impact of RA – the most salient patient-identified outcomes include: obtaining information about RA; enhancing communication with MD; sharing experiences with others; feeling less anxious; feeling more hopeful and confident about managing RA; and not feeling alone with RA. Patient language was also obtained, giving us further insight into the meaning of these outcomes.

Conclusion: This data will drive the creation of new evaluation questions to reflect outcomes and patient language identified in the focus group. Next, we will conduct individual cognitive interviews – a technique used to gather information on how respondents think about and answer survey questions – to ensure these questions reflect patient intention. We will review responses to revise and finalize the evaluation, and assess its efficacy in meeting patient needs.

1580

Preferences for Arthritis Interventions: Comparison Between Blacks and Whites with Arthritis. Chivon A. Mingo[1], Jessica M. McIlvane[2] and William E. Haley[2]. [1]University of North Carolina, Chapel Hill, NC, [2]University of South Florida, Tampa, FL

Background/Purpose: Arthritis disproportionately affects Blacks in comparison to Whites. Blacks consistently report more pain, and more activity limitations. It is imperative to have effective interventions and treatment options for Blacks. The purpose of this study is to begin to identify factors needed to design arthritis interventions that will reduce barriers and increase appeal to Blacks.

Methods: Using a needs assessment survey, intervention preferences, barriers to healthcare, knowledge about interventions and care, utilization, and health beliefs among Black and White adults with self-reported physician-diagnosed OA were examined. Frequencies were examined to determine perceived needs related to arthritis healthcare of Blacks and Whites recruited from the community. Independent samples t-tests and Pearson's Chi-square analyses were computed to determine group differences between Blacks and Whites.

Results: Blacks were more likely to report cost, lack of trust, fear of being the only person of their race, lack of recommendation from their doctor, and lack of recommendation from a family member or friends as barriers to participating in arthritis interventions. There were also many commonalities across race. In addition, Blacks were more likely to prefer the intervention content, intervention structure and delivery methods, and arthritis resources presented in the needs assessment in comparison to Whites.

Conclusion: Findings suggest that similar interventions are needed across racial groups, but some minor practical adaptations could be made to existing arthritis interventions to minimize barriers, increase cultural sensitivity, and offer programs that would be appealing to Blacks and Whites with arthritis.

1581

Increased Awareness of Arthritis May Result in Earlier Diagnosis of Rheumatoid Arthritis. Sara Zafar[1], Humeira M. Badsha[2], Ayman Mofti[2], Arlene Delosantos[2], Janice Altares[2], Gerald Matudio[2] and Kok Ooi Kong[3]. [1]University of Edinburgh, Edinburgh, United Kingdom, [2]Al Biraa Arthritis Center, Dubai, United Arab Emirates, [3]Tan Tong Seck Hospital, Singapre, Singapore

Background/Purpose: Patients with Rheumatoid Arthritis (RA) in the United Arab Emirates (UAE) have been found to have a long delay in diagnosis, in addition to a low utilization of DMARD therapy (1, 2). Over the past 5 years, in addition to the establishment of support groups such as the Emirates Arthritis Foundation, a number of awareness programs and PR campaigns have also been instituted in the UAE. The aim of our study is to assess whether initiatives to increase awareness of arthritis among the general public have resulted in a shorter lag time to diagnosis.

Methods: We collected demographic, disease and treatment data on the first 100 patients who met ACR criteria for RA, and who were presenting to our practice for the first time. This data was compared with similarly collected data, on the first 100 patients presenting to our musculoskeletal clinic, 5 years previously.

Results: A total of 100 patients were seen with an average age of 40.2 ± 11.0 years (42.2 ± 12.3 years in previous data set, not statistically significant by Student's t-test); female 87% (as before); Arabs 28% and Indians 48% (Arabs 38% and Indians 36% previously). 62% were rheumatoid-factor positive, whereas 73% were titre positive in the previous study (not statistically significant, chi-square test). There was a mean reduction in lag time between symptom onset to diagnosis by 45.8%, from 14.4 ± 15.6 months to 7.8 ± 12.1 months (Student's t-test p=0.001). Furthermore, the lag to the first DMARD was also reduced by a mean of 34.9%, from 19.2 ± 24 months to 12.5 ± 21.7 months (Student's t-test p=0.04). There was no statistically significant difference between the mean DAS 28, ESR and patient global assessment of disease activity (VAS) score amongst the two groups (current data: ESR 36 ±28 mm/h, DAS 28 5.0 ± 1.4, VAS 58.0 ± 26.7 mm; 5 years prior: ESR 33 ±25 mm/h, DAS 28 5.2 ± 1.6, VAS 57.4 ± 25.0 mm).

Conclusion: These data suggest that there has been a reduction in both the lag to diagnosis and the initiation of DMARD therapy among patients in the UAE, as compared with 5 years prior. This may be attributed to the inception of patient support groups and a general drive towards increasing public awareness about RA. Studies of larger cohorts may be needed to substantiate our findings. In addition subsequent studies must address if the shorter lag time to diagnosis and first DMARD can result in higher levels of disease remission and improved quality of life for our patients with RA.

Table 1.

	2006 Data	2010 Data	p-values
	100 patients seen (average ± SD)		
Age:	42.2 ± 12.3	40.2 ± 11.0	
Gender: Female	87%	87%	
Arab	38%	28%	
Indian	36%	48%	
Caucasian and other	26%	24%	
RF positive	73%	62%	
Years since diagnosis	3.9 ± 5.7	3.5 ± 5.6	
Lag time between symptom onset and diagnosis (months)	14.4 ± 15.6	7.8 ± 12.9	p = 0.001
Lag to first DMARD (months)	19.2 ± 24	12.5 ± 21.7	p = 0.04
Mean Tender joint count	8.9 ± 7.9	7.0 ± 4.8	
Mean Swollen joint count	9.0 ± 7.6	6.7 ± 5.0	
Mean patients Global Assessment of Disease activity (mm)	57.4 ± 25.0	58.0 ± 26.7	
Mean ESR (mm/h)	33 ± 25	36 ± 28	
Mean DAS	5.2 ± 1.6	5.0 ± 1.4	
Physician global assessment	55.0 ± 23.8	—	

References:

1. Rheumatoid arthritis in Dubai – delayed diagnosis and low DMARD utilization. Badsha H, Kong KO, Tak PP. **Ann Rheum Dis** 2007 Jun;66(6):835

2. Rheumatoid Arthritis in the UAE. Badsha H, Kong KO, Tak PP. Clinical Rheumatology Nov 2007

1582

Effects of a Telephone Based Osteoarthritis Self-Management Program on Communication with Health Care Providers. Kelli D. Allen[1], Hayden B. Bosworth[1], Cynthia Coffman[1], Jennifer H. Lindquist[1], Nina R. Sperber[1], Morris Weinberger[2] and Eugene Z. Oddone[1]. [1]Duke and Durham VA Medical Center, Durham, NC, [2]University of North Carolina at Chapel Hill & Durham VA Medical Center, Durham, NC

Background/Purpose: Osteoarthritis (OA) self-management programs aim to improve patients' communication with health care providers about their OA and its treatment, but little is known about how effectively these programs meet this goal. These analyses examined whether a telephone-based OA self-management program improved patients' self-reported communication with providers and perceptions of participation in OA treatment decisions. We also examined whether there were differential program effects according to patient race and education level, since these characteristics have been associated with differences in communication with providers.

Methods: Participants (n=515, mean age = 60 years, 93% male, 46% non-white-primarily African American) were involved in a randomized controlled trial of a telephone-based OA self-management program, compared to health education (HE; attention control) and usual care control (UC) groups. The self-management program included education materials and 12 monthly calls from a health educator to facilitate personal goals for OA management. Outcomes for these analyses, collected at baseline and 12-month follow-up, included the Communication with Physicians Scale (CPS; range 0–5, higher scores indicate more active communication behaviors such as discussing OA-related problems) and the Medical Outcomes Survey Participatory Decision-Making Scale (PDMS; range 0–100, higher scores indicate greater participation). Linear mixed modeling was used to assess differential improvement in CPS and PDMS scores between the OA arm and control arms (HE and UC), between white vs. non-white participants and participants with some college vs. no college.

Results: At baseline mean CPS and PDMS scores were higher for those with some college than those with no college (2.6 vs. 2.2; p<0.01 and 77.4 vs. 72.5;p=0.05) There were no overall intervention effects on change in CPS scores over 12-months and no differences in change by race. However, compared with the UC group, OA intervention effects on CPS differed according to education (p=0.03). In the OA group, CPS scores improved by 0.4 points for those with no college education compared to 0.1 points for those with some college education. There were no overall intervention effects on change in PDMS scores and no differences in effects according to education. However, there were differences in OA intervention effects on PDMS according to race, compared with both HE (p=0.04) and UC (p=0.06) groups. In the OA self-management group, whites improved by 7.5 points, whereas non-whites declined by 4.3 points. In both the HE and UC arms there were small improvements in PDMS scores for both whites and non-whites.

Conclusion: Patients in this OA self-management program who had lower education levels improved in their self-reported communication with physicians about their OA (about a 20% increase in score), and this is a key demographic group for targeting these programs. Non-whites' decline in participatory decision-making scores may be due to a change in perception of how actively they participate in OA treatment decisions; a more robust intervention may be needed to increase participatory behaviors.

1583

How Do Self-Directed Participants Follow the Arthritis Foundation's *Walk with Ease* Program? Kirsten A. Nyrop, Britta L. Schoster, Mary Altpeter, Betsy Hackney and Leigh F. Callahan. University of North Carolina, Chapel Hill, NC

Background/Purpose: Our research team established the efficacy of the *Walk With Ease (WWE)* program for both a self-directed and an instructor-led group format. Self-directed participants were encouraged to walk at least 3 days/week for 30 accumulated minutes/day, and to follow the program at their own pace using the *WWE* workbook. The workbook includes basic facts about arthritis and exercise, motivational tools (e.g. self-check lists, walking diary), and warm-up and cool-down exercises. This study examines how self-directed participants followed the *WWE* components, throughout the 6-week intervention and 1 year later.

Methods: At the end of the 6-week trial, self-directed participants completed a self-assessment survey and at 1 year a follow-up survey of their continued use of the *WWE* program. Survey responses were analyzed using descriptive statistics to examine how participants followed the program.

Results: 270 *WWE* study participants opted for the self-directed format, of which 225 (83%) completed the 6-week and 204 (91%) the 1-year survey.

At the end of the *WWE* program, 52% reported walking an average of 3.7 (±1.8) days/week and 31.7 (±15.3) minutes/walk. 38% described themselves as more physically active, 76% would continue walking, and 97% would recommend *WWE* to a friend. At 1 year, 69% reported continued walking for exercise, 61% walked about the same amount of time/minutes, 54% about the same number of times/week, and 96% would recommend *WWE* to a friend.

Table 1 is an overview of how participants reported following components of the *WWE* program. Despite wide variation in self-reported use of the workbook and related tools, 81% found the workbook somewhat/very helpful with reaching their walking goals. 58% found the walking diary helpful, and 47% read 4 or more of the 6 workbook chapters. Although participants did not do the exercises regularly, 49% found the stretching and 53% the strengthening exercises somewhat/very helpful. At 1 year, 69% continued walking for exercise, 61% walked about the same number of minutes, and 54% the same number of walks/week.

Table 1. Use of the *Walk With Ease* Program by Self-Directed Participants at 6 Weeks

USE OF PROGRAM MATERIALS	Percent
WWE workbook	
Read 4 or more of the 6 chapters	47
Considered the workbook somewhat or very helpful with reaching walking goals	81
Self-Assessment Tools	
Used the Starting Point Self-Test	39
Used the Ending Point Self-Test	12
Used the Knowledge and Confidence Self-Check	27
Walking diary	
Used to keep track of times/distances walked	39
Tracked amount of time spent walking	57
Tracked distance walked	25
Used the walking diary to strengthen motivation to walk	22
Considered the walking diary somewhat or very helpful	58
Exercises	
Did the warm-up and cool-down stretches a couple of times a week	28
Thought the stretches were somewhat/very helpful	49
Did the strengthening exercises regularly	19
Thought the strengthening exercises were somewhat or very helpful	53
OVERALL ASSESSMENT OF THE PROGRAM	
Physical activity level	
Moderately or a lot more active now compared to before starting *WWE*	38
Key items learned from WWE	
The relationship between arthritis, exercise and pain	94
How to overcome physical and mental barriers to walking	81
How to exercise safely and comfortably	90
How to make a walking plan with realistic goals	88
Strategies to keep my motivation	80

Conclusion: Self-directed participants reported high satisfaction with and benefits from the *WWE* program, both at 6 weeks and 1 year. However, there was considerable variability in how they used specific program components. These findings indicate that the self-directed *WWE* format is acceptable and provides a flexible option for adults with arthritis symptoms who prefer to exercise on their own.

1584

Improving Doctor-Patient Communication Through Let's Talk Rheumatoid Arthritis. Arlene Vinci, Emily L. Creek and Cindy McDaniel. Arthritis Foundation, Atlanta, GA

Background/Purpose: In 2004, a telephone survey of 500 self-identified individuals with rheumatoid arthritis (RA) was conducted for the Arthritis Foundation (AF) by Harris Interactive. The study revealed:

- 70% of people in the survey with RA still experience pain, stiffness and fatigue on a daily basis
- The majority of RA participants taking either BRMs or DMARDs are very or extremely interested in having their physician:
- Spend more time explaining the RA medications
- Provide materials such as brochures about RA
- Talk about new RA therapies
- Talk about new RA clinical trials for which they may qualify

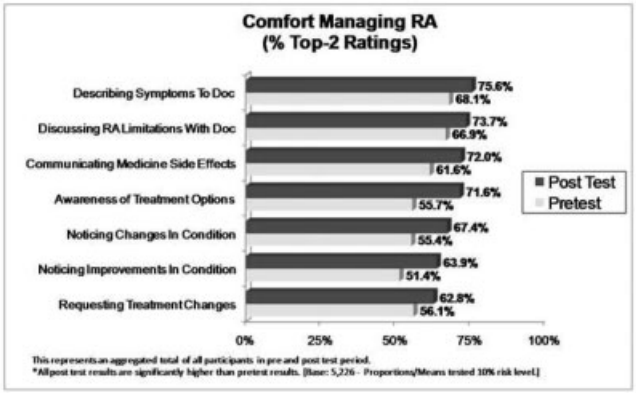
To address these unmet needs, the AF developed a communication guide designed to help RA patients improve the dialogue with their physicians. Three focus groups with both rheumatologists and patients were conducted to determine reaction, efficacy, and level of buy-in.

Methods: Using the communication guide as the centerpiece, a fulfillment kit containing RA educational materials, a health assessment questionnaire and a participant survey was developed and launched in 2006. A national year-round media campaign serves to promote the free Let's Talk RA Communication Kit to RA patients and their caregivers. In addition, 77 Let's Talk RA Town Hall meetings and Roundtable discussions featuring local rheumatologists have been conducted for some 3,600 RA patients nationwide.

The impact of Let's Talk RA is continuously assessed through the use of a pre-test survey found in the Kit and a post-test survey mailed six months later to all pre-test participants. A total of 5,226 surveys have been collected as of December 31, 2010 which includes 3,960 pretest and 1,266 post-test surveys. The participation rate is around 7% for the pretest period and 41% for the post test period. Resulting data was tabulated and tested for differences between the pre and post-test periods.

Results: Results of the surveys indicate that post-test participants are more likely than those in the pre-test period to report higher comfort levels in managing rheumatoid arthritis six months after they begin participation in Let's Talk RA:

- higher ratings for describing specific symptoms, discussing RA limitations, requesting treatment changes and communicating about medication side effects with doctors, and
- higher comfort levels in noticing improvements and changes in their condition.



In addition to increased comfort in managing RA, post-test participants are more likely to say that they are satisfied with their treatment changes and that the Let's Talk RA kit provides help in communicating with doctors than are those in the pre-test period.

Conclusion: Based on the research results, it is evident that Let's Talk RA is having a positive impact on program participants and their treatment experience.

1585

A Needs Assessment of Hospital for Special Surgery's Charla De Lupus/Lupus Chat® Teen and Parent Support Group: Gaining a Community Perspective on Nutritional Health to Inform Implementation of a Nutrition Education Intervention. Jillian A. Rose[1], Christie Carlstorm[2], Roberta Horton[1], Sandra Goldsmith[1], Robyn Wiesel[1] and Lisa F. Imundo[3]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital For Special Surgery, New York, NY, [3]Childrens Hospital of New York, New York, NY

Background/Purpose: Our national lupus support and education program is offered to people with lupus and their families in underserved Latino and African American communities. As part of our community service plan, we have collaborated with an affiliated urban medical center's pediatric rheumatology department, and our internal department of public and patient education's nutrition education program, designed to provide culturally sensitive education to children and their families. Health disparities (our targeted community is 71% Hispanic, with higher rates of obesity and lower SES than overall city rates) combined with increased risks (CVD, osteoporosis) related to SLE and its treatment indicate the need for sound nutritional practice. The goal of our needs assessment was to get a better understanding of teens and their parents' nutritional choices, knowledge and values, along with potential barriers, to assess the efficacy of a further intervention.

Methods: Written surveys were administered through telephone interviews (English/Spanish), with 48 questions (teens) and 55 questions (parents) of our lupus support program. The survey design incorporated assessment tools from the Dept. of Agriculture for a better understanding of the nutritional value, knowledge and practices of teens. The survey had 7 sections: demographics, home environment, food intake, knowledge of food pyramid /healthy diet/food labels, exercise, and interest in an educational intervention. Also, teen and parent focus groups were conducted for a more detailed understanding of survey results.

Results: We contacted 90 teens and parents; 35 (11 parents: mean age 46 and 24 teens: mean age 17) completed the phone interview. 46% were Latino; 83% female. 60% reported household income < $30,000/yr. and 34% reported Spanish as the primary language spoken at home. Although 63%of parents and 42% of teens say "the things I eat and drink now are healthy so there is no reason for me to make changes" 82% of parents and 33% of teens eat at fast food places 1–3 times per week. Importantly, 55%of parents strongly disagree that what one eats or drinks can affect lupus, yet 100% of parents know of health conditions related to eating too much fat (i.e Obesity, CVD). Almost 40% of teens did not know of any health conditions related to insufficient calcium; one quarter of teens did not know of any health conditions related to eating too much salt. Although 88% of teens felt reading food labels is important, many teens in our focus group felt that price and taste were more important, and food labels were hard to understand. They also felt that their neighborhoods didn't have a lot of "healthy" foods. Our phone survey and focus group results indicated a desire for a nutritional intervention that parents and teens they would attend together.

Conclusion: These findings, revealing incongruities between conveying socially acceptable responses and actual behaviors, as well as gaps in knowledge and access, are the first step in informing the development of an educational intervention that meets our community's needs.

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Citizen Engagement in Arthritis Research for Patient Centered Research: A Model of Success. Louise Bergeron, Dawn Richards, Linda Wilhelm, John Coderre, Delia Cooper, Janet Gunderson, Louise Crane, Christopher DeBow, Simone Hughes, Marie-Eve Veilleux, Iris Maurstad, Neil White, Elaine Wychreschuk and Katy Miller. Canadian Arthritis Network, Toronto, ON

Background/Purpose: The Canadian Arthritis Network's (CAN) Consumer Advisory Council (CAC) is a model of Citizen Engagement in Arthritis Research. The Council is comprised of Canadians living with various forms of arthritis. CAN consumers represent a wide range of professional experiences, ages, cultures, and languages. CAN consumers are Chronic Disease and Arthritis Self-management Program Facilitators, members of Health Canada's Expert Advisory Committees, Patient Partners in medical schools, community reviewers for the Canadian Institutes of Health Research, involved in consultative input into the Canadian Agency of Drugs and Technologies in Health reviews, Cochrane Musculoskeletal group and members of regional, national and international community groups and organizations.

Methods: In 1998, the Canadian Arthritis Network, funded by the Federal Government's Networks Centres of Excellence Program, a national, federally- funded, not-for-profit organization that supports integrated, multidisciplinary and multi-institutional research and training, struck a committee of people living with arthritis to provide advice on the priorities of arthritis research from the perspective of those living with the disease. Since arthritis receives only a small percentage of research funding in Canada, the goal was to spend dollars focused on areas that would have the most impact on improving health outcomes.

Results: The Canadian Arthritis Network's most basic methods of engaging citizens consist in giving consumers voting privileges as part of the governance structure of the organization, together with a budget supporting the activities of the Consumer Advisory Council. The Council in turn engages the larger citizen community by presenting CAN CARES, The Canadian Arthritis Network Research Exchange Seminar, where a slate of researchers presents their findings, followed by a discussion with the audience. The Canadian Arthritis Network involves consumers in all of its committees, funded research, and training programs. This citizen engagement model has been successful because of the following criteria:

Membership of the council on all committees & integration in the governance structure of the Canadian Arthritis Network.

Equal collaboration on research projects.

Participants and leaders in training activities

Participation in knowledge translation & exchange activities, both-internal and external.

Ongoing yearly financial budget dedicated to the operations of the council.

Validation, by the Canadian Arthritis Network, of the importance of the council in the pursuit of arthritis research.

Conclusion: Patient engagement is an integral part of the Canadian Arthritis Network; a unique model. Patients play an integral role in the Knowledge Translation process helping to choose research direction, ensuring research is translated into better health outcomes. Involving patients in health research creates champions who advocate the value of health research and demystify science to other Canadians so they will understand the importance of health research. Consumer participation increases the legitimacy of health research which is primarily pursued for the benefit of the public.

ACR Plenary Session II
Discovery 2011
Monday, November 7, 2011, 11:00 AM–12:30 PM

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Evidence for a Direct Role of Anti-Signal Recognition Particle Antibodies in the Pathogenesis of Necrotizing Myopathies. Coralie bloch-Queyrat[1], Laurent Drouot[2], Jean- Luc Charuel[3], Erika Yada[4], Dominique Langui[5], Saik Urien[6], Serge Herson[1], Lucie Musset[3], Gillian Butler Browne[4], Olivier Boyer[2] and Olivier Benveniste[1]. [1]Centre de Référence des Maladies Neuro Musculaire, Pitié Salpêtrière, Paris, France, [2]INSERM U905, University of Rouen, Rouen, France, [3]Laboratoire d'immunochimie, Pitié- Salpêtrière, Paris, France, [4]UMRS 974 INSERM UPMC, Paris, France, [5]Plateforme d'Imagerie Cellulaire, INSERM UMRS 975/CNRS UMR 7225/ UPMC ICM Centre de Recherche Pitié-Salpêtriere, [6]URC Cochin Necker CIC901-INSERM, France

Background/Purpose: Signal Recognition Particle (SRP) is a ubiquitous protein complex which mediates the transport of newly synthesized proteins to the endoplasmic reticulum in eukaryote cells. Anti-SRP auto-antibodies (Abs) are associated with a severe necrotizing myopathy. We have previously shown (Arthritis Rheum. 2011 Mar 11. doi: 10.1002/art.30344) that serum titers of anti-SRP Abs closely correlate with CK level and muscle weakness in patients. The aim of this study is to investigate a possible direct role of anti-SRP Abs in the development of this form of myopathy.

Methods: Muscle deposits of anti-SRP Abs were assessed by immunohistochemistery on normal mouse or human muscle tissues, by both light- and electron-microscopy, using different sources of anti-SRP Abs (sera from 5 patients, purified anti-SRP from a patient's plasma exchange on affinity column charged with SRP54 recombinant protein, goat anti-mouse SRP (SRP54, SANTA CRUZ BIOTECHNOLOGY), chicken anti-human SRP (SRP54, USBIOLOGICAL)). Cytopathic effect of anti-

SRP Abs was assessed on cultured primary human muscle cells (myotubes). Myotubes were cultured with purified anti-SRP Abs (200 μg/ml) or control polyclonal IgG (200 μg/ml). After 4 days of culture, cells were processed for scanning microscopy. Total area covered by myotubes was calculated using NIH Image J image analysis software.To appreciate the *in vivo* effect of anti-SRP Abs on muscle strength, serum (400 ml) from anti-SRP+ patient or healthy donor was injected intraperitonealy daily for 14 days to C57BL/6 mice and muscle strength was assessed by rotarod.

Results: Similar histological aspects were found by light microscopy after incubation with the different sources of anti-SRP Abs. Immunostainings appeared as a punctuated intracellular signal within the endomysium with reinforcement at the membranes of myocytes. Preincubation of purified anti-SRP54, or commercial anti-SRP54 Abs, with excess recombinant SRP54 led to signal disappearance. Immunogold staining followed by electron-microscopy revealed immunoreactivity located in the endoplasmic reticulum. When cultured with purified anti-SRP Abs, myotubes showed a dramatic decrease of their diameter as compared to those cultured with control polyclonal IgG or no Abs, leading to a 60% decrease in the surface they covered (surfaces (in arbitrary unit) respectively of 1.4 10^6(anti SRP); 3.6 10^6(polyclonal IgG) and 3.0 10^6(no Abs); p=0.003, Kruskal-Wallis test with Monte-Carlo resampling). In vivo injection of anti-SRP Abs (compared to normal serum) resulted in weight loss (−4 g in average) and significant decrease in muscle strength as attested by rotarod results (25 sec. vs. 130 sec. ($p<0.01$)).

Conclusion: In muscle, anti-SRP Abs deposited on the endoplasmic reticulum. This was associated with a direct cytopathic effect as observed *in vitro* on cultured primary human muscle cells and *in vivo* by a rapid decrease in muscle strength. These results provide the first experimental evidence that anti-SRP Abs may play a direct role in the pathogenesis of necrotizing myopathies.

1588

β-Catenin Is a Central Mediator In Systemic Sclerosis. Christian Beyer[1], Amelie Schramm[1], Alfiya Akhmetshina[1], Trayana Kireva[1], Clara Dees[1], Sonia C. Schindler[1], Makoto M. Taketo[2], Oliver Distler[3], Georg Schett[4] and Jorg HW Distler[4]. [1]Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany, [2]Kyoto University Yoshida-Konoé-cho, Kyoto, Japan, [3]University Hospital Zurich, Zurich, Switzerland, [4]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: β-catenin is the central integrator of canonical Wnt signaling. Binding of Wnts to their receptors causes stabilization of β-catenin, which translocates into the nucleus and regulates the transcription of target genes. Since recent evidence suggests a central role of Wnt signaling in fibrosis, we examined the Wnt pathway in SSc and focused on the role of β-catenin in fibroblast activation.

Methods: We performed qPCR for several Wnt ligands and axin-2 to examine Wnt expression in SSc skin. We further studied protein levels of Wnt-1, −4, −10b and β-catenin by IHC. To establish the effects of Wnt signaling on collagen release, we used fibroblasts with either stabilization of β-catenin (ΔEx3 β-catenin$^{wt/ex}$) or fibroblasts carrying a deletion of both β-catenin alleles (Ctnnb1$^{ex/ex}$). Finally, we created mice with fibroblast-specific stabilization of β-catenin (ΔEx3 β-catenin$^{wt/fl}$ × Col1a2;Cre-ER) as well as mice carrying fibroblast-specific deletion of β-catenin (Ctnnb1$^{fl/fl}$ x Col1a2;Cre-ER). We studied spontaneous fibrogenesis in ΔEx3 β-catenin$^{wt/fl}$ × Col1a2;Cre-ER mice 8 weeks after Cre-activation and challenged activated Ctnnb1$^{fl/fl}$ × Col1a2; Cre-ER mice with bleomycin for 4 weeks.

Results: We could demonstrate mRNA overexpression of Wnt-1, −10b, and −16 as well as increased Wnt-1 and Wnt-10b protein levels in SSc skin. The overexpression of several Wnt ligands resulted in a prominent nuclear accumulation of β-catenin in fibroblasts. Finally, increased mRNA levels of the target gene axin-2 confirmed the activation of canonical Wnt signaling.

In ΔEx3 β-catenin$^{wt/ex}$ fibroblasts, we addressed the consequences of enhanced Wnt signaling and increased accumulation of β-catenin for SSc fibrogenesis: In vitro stabilization of β-catenin resulted in an increase of collagen release by 112 ± 7 % ($p < 0.05$). By contrast, deletion of β-catenin in Ctnnb1$^{ex/ex}$ fibroblasts reduced collagen production by 55 ± 17 % ($p < 0.05$). Collagen mRNA levels were altered accordingly.

To confirm the crucial role of β-catenin in dermal fibrosis in vivo, we selectively targeted β-catenin in fibroblasts. Cre-activated ΔEx3 β-catenin$^{wt/fl}$ × Col1a2;Cre-ER mice showed massive and spontaneous dermal thickening with increases of 3.98 ± 0.1–fold ($p < 0.05$). Hydroxyproline content and myofibroblast counts were also increased prominently. In contrast to the pro-fibrotic effects of β-catenin stabilization, deletion of β-catenin in Ctnnb1$^{fl/fl}$ x Col1a2;Cre-ER mice protected from bleomycin-induced dermal fibrosis (reduction of skin thickness by 54 ± 4 %; $p < 0.05$).

Conclusion: We demonstrated a prominent activation of canonical Wnt signaling in SSc with nuclear accumulation of β-catenin in fibroblasts and activation of the target gene axin-2. Our results showed that fibroblast-specific stabilization of β-catenin resulted in enhanced collagen release in vitro and in vivo, whereas deletion of β-catenin potently reduced collagen production. Together, our findings highlight a key-role of β-catenin in fibroblast activation and fibrosis. Thus, β-catenin may be promising molecular targets for anti-fibrotic therapies.

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A Combined Fc-OPG/hPTH(1–34) Therapy to Restore Impaired Skeletal Growth and Bone Loss in a Mouse Model of IL-6 Dependent Juvenile Inflammatory Diseases. Andrea Del Fatore[1], Marta Capannolo[2], Barbara Peruzzi[2], Alfredo Cappariello[1], Nadia Rucci[2], Fabrizio De Benedetti[1] and Anna Teti[2]. [1]Children Hospital Bambino Gesù, Rome, Italy, [2]University of L'Aquila, L'Aquila, Italy

Background/Purpose: Premature osteoporosis and stunted growth are common complications of childhood chronic inflammatory diseases and have a significant impact on patients' quality of life. Presently no treatment regimens are available for these defects in juvenile diseases. To test a new therapeutic approach, growing mice overexpressing the pro-inflammatory cytokine IL-6 (TG) showing a generalized bone loss and stunted growth were used. Since TG mice present increased bone resorption and impaired bone formation, we hypothesized that a combined therapy with the antiresorptive modified osteoprotegerin, Fc-OPG, and the anabolic PTH could counteract their skeletal alterations and improve growth.

Methods: We therefore treated TG mice with Fc-OPG 0.25 mg/Kg once at the 4th day of life and with 80 μg/Kg hPTH(1–34) everyday from the 16th to the 30th day of age. No toxic effects were observed on vital organs.

Results: The treated mice presented a complete rescue of growth, as showed by a body weight of 93% and a tibia length of 92% of WT mice ($p<0.05$ *vs* TG vehicle), and of bone phenotype (BV/TV %; WT vehicle 6.38+2.46; TG vehicle 3.12+0.82; TG Fc-OPG/hPTH 5.24+0.66$^{\#}$; $^{\#}p<0.02$ *vs* TG vehicle), with a normalization of osteoclast and osteoblast parameters. Restoring of normal bone turnover was confirmed by RT-PCR on femurs of Fc-OPG/hPTH-treated mice that showed normalization of TRAcP, ALP and RUNX2 expression compared to vehicle-treated TG mice, with levels similar to WT mice. *In vitro* cultures from Fc-OPG/hPTH-treated mice confirmed the full rescue of osteoclast number and bone resorption and an increase of osteoblast ALP staining to levels similar to cultures from WT mice, with normal osteoblast progenitors determined by CFU-F-ALP assay. The phenotypic rescue of TG mice was due to the combined treatment, because TG mice treated once at the 4th day of life with Fc-OPG 0.25 mg/Kg alone showed an increase of body weight (WT vehicle 14.61+1.72 g; TG vehicle 7.64+0.7 g*; TG Fc-OPG 10.4+1.12 g*; *$p<0.03$ *vs* WT vehicle), tibia length (WT vehicle 1.59+0.14 cm; TG vehicle 1.30+0.05 cm*; TG Fc-OPG 1.40+0.04 cm*; *$p<0.05$ *vs* WT vehicle) and bone volume to intermediate levels between those observed in WT and in TG vehicle-treated mice. Similar intermediate rescue was observed treating TG mice with hPTH alone since the 16th day of life. Moreover, intermittent injections of hPTH since the 4th day of age caused distress of the mice with no effects on the somatic growth.

Conclusion: In conclusion, our results identified the sequential Fc-OPG/hPTH as a treatment regimen to rescue the somatic growth and bone disorder in TG mice, thus providing the proof of principle for a new therapeutic approach to correct these defects in juvenile inflammatory diseases.

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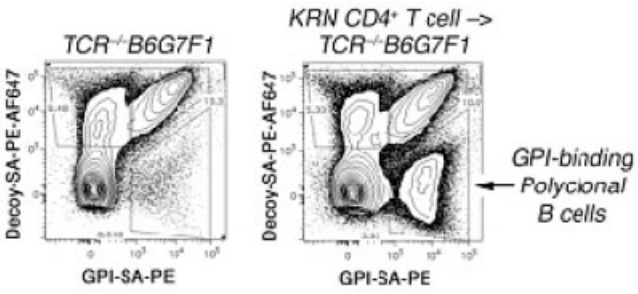
The Absence of CD4$^+$ T Cell Help Underlies the Maintenance of B Cell Tolerance to Glucose-6-Phosphate Isomerase and the Avoidance of Arthritis. Justin J. Taylor, Laura O. Barsness, Ryan J. Martinez, Stephanie R. Thomas and Daniel L. Mueller. University of Minnesota Medical School, Minneapolis, MN

Background/Purpose: Rheumatoid Arthritis (RA) in individuals expressing certain HLA DR4$^+$ (shared epitope) alleles is highly associated with the production of autoantibodies, including rheumatoid factors and anti-citrullinated protein antibodies. Mice carrying the H-2^{g7} MHC allele are also prone to the development of arthritis as a consequence of CD4$^+$ T cell autoimmunity directed against glucose-6-phosphate isomerase (GPI)/I-A^{g7} complexes and production of anti-GPI IgG1 autoantibodies. In both cases, those mechanisms responsible for the breakdown of natural B cell tolerance, such as a failure of peripheral clonal

deletion or restoration of functional responsiveness (e.g., reversal of clonal anergy), are not well understood because of our inability to easily identify and directly characterize low frequency polyclonal autoreactive B cells.

Methods: We now report the development of a B cell "antigen tetramer" system for use with multiparameter flow cytometry that can accurately detect and phenotype self antigen-specific B cells. Purified proteins of interest were biotinylated and multimerized using streptavidin (SA)-phycoerythrin (PE) conjugates. "Decoy tetramers" were also created using SA-PE-Alexa Fluor 647 (AF647) conjugates and biotinylated control proteins, to facilitate exclusion gating of B cells that bind biotin, SA, or PE.

Results: Using a combination of GPI and decoy tetramers, we observed in healthy mice a population of phenotypically naive B cells with the capacity to specifically bind GPI (*figure left*). Remarkably, an adoptive transfer of GPI/I-A^{g7}-specific KRN TCR-transgenic $CD4^+$ T cells into TCR-deficient B6G7F1 (H-$2^{b \times g7}$) mice caused these GPI–binding B cells to robustly proliferate and differentiate into both germinal center cells as well as anti-GPI IgG1–secreting plasmablasts, in association with the development of arthritis (*figure right*). Consistent with this breakdown in natural self tolerance to GPI, naive-appearing OVA–binding B cells in transgenic mice that ubiquitously express a soluble form of chicken ovalbumin (OVA) underwent a similar clonal expansion and differentiation when mice were immunized with antigen in the presence of normal OVA-specific $CD4^+$ T cells. In contrast, OVA–binding B cells that persisted in mice despite transgenic expression of a membrane-bound OVA protein did not respond to immunization with OVA, thus indicating that they were in an anergic state.



Conclusion: Membrane-bound self antigens lead to a clonal anergy in polyclonal self-reactive B cells that cannot easily be broken with $CD4^+$ T cell help, whereas B cell tolerance to cytosolic and soluble self proteins often relies solely on $CD4^+$ T cell tolerance.

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Identification of Robust and Disease-Specific Stromal Alterations in Spondyloarthritis Synovitis. Nataliya Yeremenko[1], Gemma M. M. Rigter[1], Iris Simon[2], Juan D. Cañete[3], Paul P. Tak[1] and Dominique L. Baeten[1]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Agendia BV, Amsterdam, Netherlands, [3]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain

Background/Purpose: The cellular and molecular pathways driving synovial inflammation and stromal remodeling in spondyloarthritis (SpA) remain largely unknown. As SpA and rheumatoid arthritis (RA) show clearly distinct patterns of structural remodeling and since stromal pathways of remodeling may be specific to the target tissues, systematic comparison of the inflamed synovial tissue in both conditions may help to identify disease-specific pathogenic mechanisms. We conducted this study in order to identify cellular and molecular pathways specific for SpA synovitis by an unbiased microarray screening approach.

Methods: Synovial tissue samples were obtained by arthroscopy from untreated individuals with SpA (n=55), RA (n=45) and gout (n=10). RNA was extracted and gene expression profiling was performed on a test cohort of 12 SpA versus 8 RA samples using microarrays (Agilent 44K). Top differentially expressed genes were validated on three independent cohorts of SpA versus control samples by qPCR and confirmed on the protein level by immunohistochemistry. qPCR was also performed on paired SpA synovial biopsies before and after TNF blockade.

Results: Using very stringent analysis and statistical criteria, the microarray experiments identified a signature set of 359 genes that discriminated with high certainty (a cut-off >1.5-fold change, $p<0.001$) between patients with SpA and RA. Technical validation by qPCR on the same samples yielded a strong correlation between the microarray and qPCR data (r=0.93, p= 1.95e-009) with 25 of the top genes being confirmed as differentially expressed ($p < 0.05$). Reanalysis of the top 25 genes in an independent cohort of early, untreated SpA and RA confirmed the differential expression of the genes with again a very good correlation with the original microarray results (r=0.97. p= 0.00004). The gene signature was not only reproducible but also consistent as pathway analysis revealed that almost all top-ranking upregulated transcripts in SpA were related to myocyte/myofibroblast biology. Several of these genes, including the alpha smooth muscle form of actin, showed up to 100-fold upregulation in SpA versus RA synovitis. Additional analysis of gout versus SpA samples confirmed that these genes were specifically upregulated in SpA synovitis rather than downregulated in RA. Immunohistochemistry for α-smooth muscle actin and smooth muscle myosin heavy chain identified expression of these proteins not only around the vessel walls but also in fibroblast-like cells in the intimal lining layer and synovial sublining. Expression in the latter two regions, but not in the vessels, was significantly increased in SpA versus RA. Double immunofluorescence and FACS analyses revealed a colocalization of α-smooth muscle actin and fibroblasts marker CD90. Finally, paired analysis of SpA samples obtained before and after 12 weeks of TNF blockade showed that the expression of these genes was not altered by this treatment.

Conclusion: This study identified a robust and disease-specific increase in myofibroblasts in SpA synovitis. The reason for this increase and the potential role of these cells in inflammation and, more importantly, structural remodeling in SpA are currently under investigation.

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Identification of Specific Amino Acids in the Uric Acid Transporter URAT1 Required for Uricosuric-Mediated Inhibition. Philip K. Tan, David Hyndman and Jeffrey N. Miner. Ardea Biosciences, San Diego, CA

Background/Purpose: Uricosuric agents are used for the treatment of gout and lower serum uric acid levels by blocking uric acid reabsorption in the kidney proximal tubule through inhibition of the uric acid transporter URAT1. We have identified a compound RDEA3170 that specifically binds to and inhibits URAT1 with nanomolar potency and examined its interaction with wild type and URAT1 mutants. We also compared the interaction of RDEA3170 with that of other known primary uricosuric agents.

Methods: Wild type and URAT1 site-directed point mutants were prepared and expressed in transfected cultured cells for cell-based uric acid transport and binding assays. Transport assays were performed by incubating the cells with ^{14}C-labeled uric acid in the absence or presence of URAT1 inhibitors, and the cell associated label was measured. Binding assays were performed by measuring binding of tritiated RDEA3170 to membranes prepared from URAT1-transfected cells in the absence or presence of unlabeled URAT1 inhibitors. For oocyte transport assays, wild type and URAT1 mutants were expressed by injection of URAT1 cRNA. Transport of ^{14}C-labeled uric acid was measured and URAT1 inhibitors were tested for extracellular or intracellular activity.

Results: RDEA3170 inhibits URAT1 activity with a half maximal inhibition constant of 24 nM, which is equipotent to the uricosuric benzbromarone and 200-, and 500-fold more potent than the uricosurics sulfinpyrazone and probenecid, respectively. Binding of radiolabeled RDEA3170 to URAT1 in membranes was specific, saturable, competitive with other uricosurics, and has a dissociation constant of 30 nM. To investigate the compound interactions in more detail, we analyzed URAT1 point mutants in the uric acid transport assay. URAT1 residues were mutated to the corresponding residues in the rat URAT1 ortholog (rRST) that has 75% sequence identity to URAT1 but is less sensitive to inhibitors. Mutation of human URAT1 F365 to Y decreases the potency of RDEA3170 by 100-fold, while mutation of rRST Y365 to F results in a gain of function, increasing the potency of RDEA3170 by 10-fold compared to wild type rRST. URAT1 mutants with conservative amino acid substitutions in the presumed substrate binding pocket were prepared and compared to wild type URAT1. URAT1 R477 to K decreases the potency to RDEA3170 and benzbromarone but responds similarly to sulfinpyrazone; URAT-F241Y decreases the potency to RDEA3170 and sulfinpyrazone but responds similarly to benzbromarone; and URAT-F448Y decreases the potency to benzbromarone and sulfinpyrazone but responds similarly to RDEA3170. From Xenopus oocyte experiments, RDEA3170 inhibits URAT1 activity extracellularly and intracellularly with similar potency.

Conclusion: RDEA3170 showed high potency, direct binding, and functional inhibition of URAT1. All inhibitors likely interact in the same general binding site within URAT1. However, each inhibitor likely utilizes a distinct but overlapping set of residues for URAT1 inhibition.

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A Controlled Pilot Study On the Use of Active Learning Techniques During a Rheumatology Elective for Medical Residents. Joshua Scheers-Masters[1], David R. Blumenthal[2], Jeanne Macrae[3], Matthew Avitable[3] and Deana M. Lazaro[4]. [1]SUNY Downstate, Brooklyn, NY, [2]VA NY Harbor Healthcare System, Brooklyn, NY, [3]SUNY Downstate Medical Center, NY, [4]Brooklyn VA, Brooklyn, NY

Background/Purpose: There is a need to train physicians to evaluate musculoskeletal (MSK) complaints. Previously, we found that providing passive learning materials to residents attending rheumatology clinic had no impact on measures of rheumatology knowledge and clinical exam proficiency. The purpose of this study was to examine the impact of active learning based upon Kolb's experiential theoretical framework on rheumatology knowledge, MSK physical exam skills, and subjects' attitudes towards rheumatology.

Methods: Forty SUNY Downstate medical and neurology interns were enrolled in the study and completed a 45 question multiple choice (MC) pre-test and questionnaire. All residents were randomly assigned to participate in either an ambulatory rheumatology elective or another subspecialty experience for four weeks although all Neurology residents were assigned to the control arm due to administrative constraints. 24 residents completed the study after 6 months. All residents received a copy of the Primer on the Rheumatic Diseases. Residents assigned to the rheumatology group were given 12 case-based learning modules and 12 quizzes; each quiz was reviewed and discussed with a rheumatology attending. The rheumatology group had additional instruction on the MSK exam using active learning techniques and arthrocentesis and injection techniques using simulators. They participated in 3 out-patient Rheumatology clinic sessions and journal club weekly. At the end of the elective month, both groups completed a 45 question MC post-test, a 4 station objective structured clinical examination (OSCE) on the evaluation and treatment of MSK diseases, and a post- questionnaire.

Results: No significant difference was seen on the pre-test between the two groups (0.508 vs 0.504, $p=0.913$), however, the rheumatology group had a significantly higher score on the post-test (0.716 vs 0.598, $p=0.011$). On the OSCE, the rheumatology group had a significantly better performance on all four stations, including arthrocentesis (0.776 vs 0.519, $p<0.0005$), lower extremity exam (0.684 vs 0.553, $p=0.019$), upper extremity exam (0.615 vs 0.479, $p=0.039$), and clinical cases (0.628 vs 0.424, $p=0.001$). On the questionnaires, the rheumatology group had a significantly greater change in confidence in their ability to treat arthritis compared with the controls (1.393 vs 0.167, $p=0.004$). Similarly, the rheumatology group had greater increase in confidence in their ability to treat as a specialist (1.014 vs 0.089, $p = 0.016$). No significant differences were found for questions relating to who should treat arthritis (primary care physicians or rheumatologists) or enthusiasm for the field of rheumatology.

Conclusion: In this small study, we found that integrating active learning techniques based upon Kolb's experiential theoretical framework into a rheumatology elective had a significant impact on interns' rheumatology knowledge as measured on a multiple choice examination, MSK clinical skills as measured on a 4 station OSCE, and confidence in treating arthritis based on a questionnaire.

Funding for this project was provided by the American College of Rheumatology Research and Education Clinician Scholar Educator Award.

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Rheumatology Decision 2011: Factors Influencing Career Decisions Among Rheumatology Fellows. Saira Sheikh[1], Michael Smith[1], Tony Ning[2], Erin Shiner[3], Dijana Christianson[4], Lisa G. Criscione-Schreiber[5], Marcy B. Bolster[6], Kenneth S. O'Rourke[7], Deb MacDonald[1], Leigh F. Callahan[8] and Beth L. Jonas[9]. [1]University of North Carolina Chapel Hill, Chapel Hill, NC, [2]Duke University, Durham, NC, [3]Wake Forest Univ. Baptist Med. Ctr., Winston-Salem, NC, [4]Medical University of South Carolina, Charleston, SC, [5]Duke University Medical Center, Durham, NC, [6]Medical Univ of South Carolina, Charleston, SC, [7]Wake Forest Univ School of Med, Winston-Salem, NC, [8]University of North Carolina, Chapel Hill, NC, [9]University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: There is a growing concern that fewer rheumatology fellowship graduates are entering academic medicine. Academic rheumatologists are critical to the development of an adequate workforce. The impending shortage of practicing rheumatologists in the United States makes it crucial to understand the factors involved in fellows' career choices. Here we present data on current and former rheumatology fellows regarding factors influencing their career decisions.

Methods: This project was a collaborative effort between the four programs of the Carolinas Fellows Collaborative (CFC). Fellows and faculty of the CFC developed a survey to assess career decision-making among rheumatology trainees. IRB approval was obtained. This survey was sent electronically, using Constant Contacts®, to current rheumatology fellows and recent graduates (previous 5 years) of the four programs. Data collected included demographic information, magnitude of student loan debt, views on fellowship training, and factors influencing career choice. Participants were asked to identify why they made their respective career choices and point out factors that might influence them to choose a career in academic medicine.

Results: The response rate was 46% ($N=67$). Of our respondents, 70% were female, 71 % were married, and 50% were fellows currently in training. Nearly three quarters of fellows (73%) had student loan debt of greater than $100,000. Responses indicated that at the initiation of fellowship 73% of current fellows aspired to pursue a career in academic medicine; however that number dropped to 40% during training. Those with plans to continue in academic medicine stated that personal choice (46%) was the most important factor leading to this decision. Among those choosing private practice, the majority stated that workplace flexibility (46%), debt burden (38%) and earning potential (38%) were most important in their decision. Respondents indicated that improved research mentoring (67%), protected research time during fellowship (60%), improved funding opportunities (47%), formal training in clinical education (60%), loan repayment plan (67%) and higher salaries(67%) were important factors that would have informed a decision to choose a career in academic medicine.

Conclusion: In this pilot study, we have identified trends and variables that may influence career choices by rheumatology fellows. We have also identified potentially modifiable aspects of fellowship training and other factors that may encourage fellows to pursue a career in academic medicine. Using this preliminary data, we are conducting a larger survey targeting fellows in training nationwide.

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Knowledge of Clinical Anatomy by Rheumatology Fellows and Rheumatologists in Latin America. José E. Navarro-Zarza[1], Cristina Hernández-Díaz[2], Miguel A. Saavedra-Salinas[3], Robert A. Kalish[4], Juan J. Canoso[5] and Pablo Villaseñor-Ovies[2]. [1]Mexican Taskforce for the Advancement of Clinical Anatomy, Mexico, Mexico, [2]Instituto Nacional de Rehabilitación, Mexico City, Mexico, [3]Centro Médico Nacional, México, Mexico, [4]Tufts Medical Center, Boston, MA, [5]ABC Medical Center and Tufts University, Mexico City, Mexico

Background/Purpose: It is generally agreed that knowledge of musculoskeletal anatomy is a prerequisite to performing an adequate rheumatologic physical examination. However, little information is available regarding the level of anatomical knowledge of rheumatology fellows (RF) and practicing rheumatologists (PR).

Methods: All participants in a series of musculoskeletal clinical anatomy seminars held in 5 Latin American countries under an ILAR grant in 2010 and 2011 had a one-to-one, standardized, pre-seminar evaluation in which they were asked to demonstrate or identify the structures or functions in the bodies of the participants and instructors of 20 anatomic structures (Table). The average duration of the evaluations was 7 minutes. This exercise was accepted by the national societies, participating rheumatology services and seminar attendees. Standard summary statistics are presented. Differences between groups were tested with T test or ANOVA.

Table. Anatomic Structures Tested. (D= demonstration, I= Identification of)

1	Anat. snuffbox, palmar limit I	11	Supraspinatus D
2	Anat. snuffbox, dorsal limit I	12	Infraspinatus D
3	Radial styloid I	13	Occipital-atlas motion D
4	Lister′s tubercle I	14	Atlas-axis motion D
5	Dorsal hand interossei D	15	Tensor fascia lata D
6	Palmar hand interossei D	16	Gluteus medius D
7	Thumb adduction D	17	Hoffa′s fat I
8	Thumb abduction D	18	Pes anserinus I
9	Biceps brachii I	19	Tibiotalar joint D
10	Brachialis I	20	Talocalcanean joint D

Results: There were 191 participants in the study. These included 113 (59.1%) RF from 15 training programs, 55 (28.7%) PR and 23 (12%) non-rheumatologist health care professionals (NRHP). PR had a median experience of 10 (range 3–46) yrs. Mean number of correct answers (out of 20 questions) was 9.04 (95CI: 8.49 to 9.53) for all participants. Of these, 37.7% answered correctly <5 questions, 56.7% 5–15 questions and 5.8% >15 questions. Correct answers in RF averaged 9.24 (95CI: 8.55 to 9.92), in PR 9.03 (95CI: 8.05 to 10.03) and in NRHP 7.91 (95CI: 6.47 to 9.36) (ANOVA p = 0.439). When 1st year fellows were compared with 2nd, or 2nd plus 3rd (one program) year fellows, a significant difference was found favoring the latter [8.38 (95CI: 7.37 to 9.40) vs 9.91 (95CI: 8.9 to 10.7), $p = 0.02$]. Anatomical knowledge in PR was unrelated to length of experience (Pearson's r= 0.21, p=0.11), [0–5yr 8.59 (95CI: 6.94 to 10.24), 6–10yrs 7.67 (95CI: 5.12 to 10.21) and >10yrs 9.70 (95CI: 8.2 to 11.21) (ANOVA p = 0.363].

Conclusion: Anatomical knowledge is far from satisfactory for most RF, PR and NRHP tested in Latin America. Although RF fared better in the 2nd plus 3rd year of training most fellows failed to correctly identify the majority of structures or functions and only 9.3% obtained >15 of the 20 correct answers. For PR length of practice had no bearing on anatomical knowledge. The lowest scores were found in NRHP. Efforts should be made to improve anatomical knowledge early during rheumatology training to improve physical examination skills and understanding of the anatomic basis of regional pain syndromes. Also, clinical anatomy should be emphasized in continuing medical education activities for PR and NRHP. Improved clinical skills in anatomic diagnosis and the resulting decreased dependence on technology may ultimately result in societal cost saving. Data from other parts of the world should be obtained as the knowledge gap we perceived may not be limited to Latin America.

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Development of a Novel Interactive Case Based Educational Website In Rheumatology. Christopher E. Collins. Washington Hospital Ctr, Washington, DC

Background/Purpose: With increasing utilization of the internet, online based e-learning has quickly risen to take a prominent role in medical education. Internet based education is easily available to a large audience, can provide a template for direct interaction with an individual, and can potentially eliminate the passive user experience. While a number of subspecialties have embraced the internet as a vessel for medical e-learning and medical education research, relatively few websites dedicated to rheumatology education exist. Furthermore, most of these have limited opportunities for interaction and even fewer have integrated methods for measuring outcomes for medical education effectiveness. Recently, through grant supported time under the ACR REF Clinician Scholar Educator Award, a new web-based educational website in rheumatology was developed.

Methods: An interactive rheumatology focused medical education website called the "Web-based Interactive Rheumatology Experience" or "WIRE" (www.rheumwire.com) has been developed and recently completed formative assessment. The content of the site draws from interesting cases presented by Rheumatology Fellows participating in the District of Columbia (DC) Intra-City Grand Rounds, a monthly conference attended by Rheumatology Fellows and staff from several DC area training programs. The site incorporates the concepts of basic web-design principles, an interactive user experience, built in elements for participant data gathering, and a variety of outcome measures. A pilot validation study (summative assessment) is currently underway utilizing internal medicine (IM) residents from several regional IM training programs. Measured outcomes include post test knowledge assessments as well as Likert based user satisfaction surveys.

Results: Currently, the WIRE has 59 unique pages incorporating a total of 295 unique files. Approximately 43,000 lines of code have been generated so far. The core structure of the website has been established including a login system to capture demographics of the participant as well as the ability to tailor user content. Imbedded interactions based in JavaScript and PHP provide a high level of participant interaction and two unique cases with accompanying didactics have been completed. Additional presentations and didactics are under development. Formative assessment of the WIRE was useful in identifying a few content and design specific problems as well as some cross-browser compatibility issues. Overall, the website was well reviewed and felt to have high value for a novel medical education experience.

Conclusion: The WIRE is an interactive online learning tool currently undergoing summative evaluation. Once validated as an effective educational tool, the WIRE website will serve not only as a valuable asset for medical education, but as a potential template for medical education research oriented design.

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Revision of Existing Osteoporosis Curriculum in Response to Fellows Feedback: 2011 Curriculum. Thomas P. Olenginski and Thomas M. Harrington. Geisinger Medical Center, Danville, PA

Background/Purpose: A formal Osteoporosis Curriculum was integrated within our institution's Rheumatology Fellowship in 2007 responsive to the ACGME's requirements for formal curriculum documentation. Responding to fellow feedback, staff evaluation and overall program needs as well as a unique system-based opportunity in osteoporosis care, we revised this curriculum and so report our 2011 curriculum changes.

Methods: Our previous curriculum was presented at ACR 2007 and is published in the abstract supplement (Arthritis Rheum Sept 2007, vol. 56: (9) s538). As fellows are evaluated, they offer feedback to program director and staff. Similarly, we appraise our fellowship program annually. We decided to make changes in curriculum structure to adapt to identified fellow needs as well as to enhance fellow education and osteoporosis exposure as we integrated our outpatient and inpatient High-Risk Osteoporosis Clinic (HiROC). HiROC potentially 'overexposed' our fellows to an already robust osteoporosis experience within reported curriculum.

Results: The overall curriculum is similar to that previously reported, with necessary additions of educational materials relative to Zoledronic Acid, Denosumab, FRAX, and atypical femur fractures, and 'drug holiday concept'. Additionally, fellows now see outpatient and inpatient consults related to system-wide HiROC program(begun 2008), enhancing the system-based care competency. Curriculum changes made responsive to fellow feedback include: our fellows requested more didactic sessions related to Biologic DMARD's, as well as to Xray study and interpretation and to expanded CARE Program study. We modified our teaching calendar to incorporate these needs. We deleted 4 hrs of 'blocked osteoporosis sessions' and inserted the 4 new sessions above (Table 1). Using the 'new' dedicated session times within teaching calendar, we have expanded our overall teaching curriculum (new Biologic sessions and dedicated Xray sessions as well as ongoing CARE Program sessions) without affecting overall osteoporosis education or clinical exposure.

Week	Monday	Tuesday	Wednesday	Thursday	Friday
1	Core Curriculum Conf		Fellow Conference	Best Practice	CARE
2	Core Curriculum Conf	Medical Student Lecture	Research Conf	**Rheum/Radiology Conf**	**CARE**
3	Core Curriculum Conf		Fellow Conference		CARE
4	Core Curriculum Conf		Journal Club	**Biologic Conf**	**CARE**

* Bold/underline indicate changes in curriculum calendar.

Since formal osteoporosis curriculum inception, every fellow has become ISCD-certified. Performances on ABIM Rheumatology Certification Exam since 2007 in Osteoporosis section is 75 percentile (6 fellows) and ACR in-training exam performance in Osteoporosis and Metabolic Bone Disease in 2011 was 82 percentile (4 fellows).

Conclusion: In summary, an osteoporosis curriculum has continually been implemented in our fellowship program. We have enhanced and expanded our teaching curriculum responsive to documented fellow needs. A defined curriculum structure, feedback, and fellowship annual review have allowed these refinements and modifications.

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Blog Versus traditional Seminar: A Comparative Trial in Rheumatology. Elaine L. M. Bezerra[1], Francisco A. Bezerra Neto[1], Maria J. Vilar[1] and Grupo de Estudos e Pesquisas em Educação Médica - UFRN[2]. [1]Federal University of Rio Grande do Norte, Natal, Brazil, [2]Natal, Brazil

Background/Purpose: New teaching methodologies have been adopted in medical education, nevertheless with little data on their effectiveness or on how they were compared with the traditional ones. The objective of this comparative study was to assess student learning in Rheumatology contents using either an innovative electronic (blog) or a traditional seminar format.

Methods: A randomized crossover study was carried out at the Federal

University of Rio Grande do Norte, in the city of Natal in north-eastern Brazil. All participants, fourth year medical students, signed terms of informed consent. During the Rheumatology discipline they were divided aleatorily in two groups (blog / group 1 or traditional seminar / group 2). At the first phase, the topic discussed was *Spondyloarthritis (Ankylosing Spondylitis, Psoriatic Arthritis, Reactive Arthritis and Enteropathic Arthritis).* At the second moment, the groups were crossovered to discuss some *Diffuse Disease of Connective Tissue (Systemic Sclerosis, Dermatopolimyositis, Sjögren's Syndrome and Mixed Connective Tissue Disease)*. Students of the blog group were required to post at least two writings to a faculty-moderated group blog and provide at least one comment on a peer's posts. Measurement of learning outcomes with a mixed cognitive assessment (multiple choice, short-answer and true-false questions) was done after both discussions resulting in a score ranging from 0 to 10. Anonymous surveys at the end of the study assessed student perceptions of teaching practices. The possibility that some of them could also observe the blog discussion of their friends (group 1) when they were in the group 2 ("contamination") was also questioned. Student's t-test was used to compare the means achieved by students.

Results: A total of forty four students (22 in the blog arm / group 1, 22 in the traditional seminar arm / group 2) completed this study. At the end of the first topic discussion, the means of assessment scores of groups 1 and 2 were, respectively, 8,44 and 8,29 (P= 0,6729). At the end of the second phase, the means of groups 1 and 2 were, respectively, 7,79 and 7,32 (P= 0,2949). About 81% of the students stated their experience with blogs as good or excellent. The majority of them also indicated that the blogs were either equally (38,64%) or more (31,82%) efficient than traditional seminars. The "contamination" of this educational intervention was 6,8% (3/44), which was not considered a great problem of approach transferability.

Conclusion: Our study suggests there is no statistically significant difference in themes learned when discussed by blog or traditional seminar. Given this, faculty staff should consider balancing the formats employed across their curricula to address different learning styles of students and avoid fatigue with any given method. Additional studies with a larger number of participants and combinations of the two methods are needed.

ACR Concurrent Abstract Session
Epidemiology and Health Services Research I: Gout
Monday, November 7, 2011, 2:30 PM–4:00 PM

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Allopurinol Initiation and the Risk of Death in the General Population. Yanyan Zhu[1], Yuqing Zhang[2], John D. Seeger[3], Young Hee Rho[4], Christine Peloquin[1] and Hyon K. Choi[1]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University Clinical Edpidemiology Reserach and Training Unit, Boston, MA, [3]Brigham and Women's Hospital/Harvard Medical School, Boston, MA, [4]Vanderbilt Medical Center, Nashville, TN

Background/Purpose: Allopurinol is an effective urate-lowering medication that might also have certain cardiovascular benefits; however, it is not free of adverse effects. Its rare but potentially fatal adverse effects have led to reluctance among some physicians to prescribe allopurinol, even when clinically indicated. If the impact of these severe side effects is substantial, it may shorten the survival of patients who were started on allopurinol. However, a recent VA study (98% males) suggested that allopurinol use may lower the risk of death (relative risk = 0.77). In this study, we evaluated the impact of allopurinol initiation on the risk of death among individuals with hyperuricemia in the general population.

Methods: We conducted an incident user cohort study with propensity score matching, using The Health Improvement Network (a UK general population database) data between January 2000 and May 2010. The source population included individuals aged ≥40 years who had a record of hyperuricemia (serum urate level >6 mg/dL for women and >7 mg/dL for men) at any time within the study period. Study cohort members are required to have ≥2 years of enrollment with the general practice before entering the study cohort. We constructed propensity score matched cohorts of allopurinol initiators and comparators (non-initiators) within 6-month cohort accrual blocks (to adjust for potential secular trends of allopurinol use). The index date was defined as the date of first allopurinol prescription for allopurinol initiators and a randomly assigned date within the cohort accrual block for comparators. The variables used in propensity score estimation were assessed over the 2 years prior to the index date, including demographics, comorbidities, medications, and laboratory data (**Table**). In order to approximate the 'intent-to-treat' design of a randomized trial, subjects were analyzed according to whether or not they initiated allopurinol at baseline, regardless of whether they stopped or started allopurinol during follow-up. We estimated the hazard ratios (HRs) using Cox proportional hazard model stratified by cohort accrual blocks.

Results: Of 5,927 allopurinol initiators and 5,927 matched comparators (70% males and mean age 67 years), 1,372 died during the follow-up. The mean follow-up time was 3.1 years. The majority of baseline characteristics were well balanced in two comparison groups (**Table**) through propensity score matching. Allopurinol initiation was associated with a lower risk of all-cause mortality (HR, 0.89 [95% CI, 0.80, 0.99]). Further multivariate adjustment did not change the estimate materially (adjusted HR, 0.86 [0.77, 0.95]).

Baseline Characteristic in the Propensity-Score Matched Cohort

	Allopurinol Initiators (N=5,927)	Non-Initiators (N=5,927)
Demographics		
Age, years	67.4	67.6
Male, %	69	72
BMI, kg/m^2	30.1	30.0
Measures of comorbidity		
Number of primary care visits	12.3	11.8
Charlson index	0.9	0.9
Hypertension, %	67.0	69.5
Stroke, %	10.5	11.9
MI, %	1.8	1.9
Diabetes, %	14.1	14.5
Gout, %	83.7	84.4
Medication		
Statin, %	57.0	54.6
Fibrate, %	2.6	2.3
ACE inhibitor, %	50.9	50.1
ARB, %	15.2	14.6
Beta-blocker, %	43.9	44.0
Calcium channel blocker, %	35.8	36.5
Aspirin, %	41.8	42.2
NSAID, %	73.0	75.4
Loop diuretic, %	34.0	31.1
HCTZ, %	36.7	37.3
Losartan, %	4.0	4.5
Insulin, %	4.0	3.8
Laboratory measurements		
Serum uric acid, mg/dL	8.8	8.7
Albumin, mg/dL	4.2	4.2
GFR, ml/min per 1.73 m^2	60	61
Cholesterol, mg/dL	191	191

Conclusion: In this general population study, allopurinol initiation was associated with a modestly reduced risk of death. The overall benefits of allopurinol may outweigh its impact of rare, potentially serious adverse effects at a population level.

1600

Increased Gout Risk Related to Diuretic Use Only Exists for Those with a Higher Genetic Risk: Detection of A Urate Gene-by-Diuretic Interaction in the Atherosclerosis Risk in Communities Cohorty. Mara McAdams DeMarco[1], Janet W. Maynard[2], Alan N. Baer[2], Anna Kottgen[3], Linda Kao[1] and Josef Coresh[1]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]University Hospital Freiburg, Freiburg, Germany

Background/Purpose: Diuretics and urate share renal tubular transport mechanisms. No cohort studies have quantified the association of diuretic use and gout risk among hypertensive adults with genetic susceptibility for higher serum urate levels.

Methods: Atherosclerosis Risk in Communities (ARIC) is a prospective population-based cohort recruited in 1987–1989 from 4 US communities, consisting of 4 visits. Gout was self-reported. Participants with hypertension (self-report of medication to treat hypertension, or a measured blood pressure ≥ 140/90 mm Hg) were included in this analysis if they had available SNP genotype data on urate handling genes.

Trained interviewers recorded diuretic use and type. A genetic urate score was created using common SNP for 8 genes shown in GWAS studies to be highly associated with serum urate levels [5 encode renal urate transporters or regulators thereof (*SLC2A9, ABCG2, PDZK1, SLC22A11, and SLC17A1*); three with unclear biological mechanisms related to serum urate levels (*GCKR, R3HDM2-INHBC*, and *RREB1*)]. Using logistic regression, we estimated the odds ratio (OR) of incident gout by diuretic use, stratified by the median of the genetic urate score.

Results: There were 3,529 hypertensive participants and 33% used a diuretic. The mean age at cohort entry was 55 years old and 47% of the participants were male. Over 9 years of follow-up, 109 (3.1%) developed gout. The 9-year cumulative incidence in those whose genetic urate score was below the median was 2.76% for those not taking a thiazide or loop diuretic and 1.03% for those taking either a thiazide or loop diuretic. For those above the median, the cumulative incidence was 3.08% for those not taking a thiazide or loop diuretic and 6.49% for those taking a thiazide or loop diuretic. Results are presented in the table. Compared with no thiazide or loop diuretic use, use of these diuretics was not associated with gout (OR=0.37, 95% CI: 0.13, 1.03) among those with a genetic urate score below the median but was associated with incident gout among those with a genetic urate score above the median (OR=2.18, 95% CI: 1.31, 3.64; p-value for interaction=0.003). Results were similar when adjusted for confounders.

Odds ratio (OR) for incident gout comparing those taking a diuretic to those not taking a diuretic by the median the genetic urate score (−0.29) in the ARIC cohort (n = 3,529)

	Genetic urate score		
Model	**Below median** (n = 1,764)	**Above median** (n = 1,758)	**p-value for interaction**
Any diuretic use	*OR (95% CI)*	*OR (95% CI)*	
Unadjusted	1.18 (0.63, 2.22)	2.07 (1.27, 3.38)*	0.168
Sex- and age-adjusted	1.43 (0.75, 2.73)	2.37 (1.44, 3.90)†	0.220
Adjusted for confounders	1.27 (0.66, 2.45)	2.11 (1.25, 3.54)*	0.247
Thiazide or loop diuretic use			
Unadjusted	0.37 (0.13, 1.03)	2.18 (1.31, 3.64)*	0.003
Sex-and age-adjusted	0.42 (0.15, 1.20)	2.42 (1.44, 4.08)†	0.004
Adjusted for confounders	0.42 (0.14, 1.15)	2.24 (1.31, 3.84)*	0.005

* p-value < 0.05.
† p-value <0.001
Adjusted for age, sex, body mass index, estimated glomerular filtration rate.
CI=Confidence Interval.

Conclusion: The increased risk of gout related to diuretic use in hypertensive subjects of the ARIC cohort was only observed among those with a higher genetic risk score for elevated serum urate levels, suggesting a urate gene-by-diuretic interaction. These findings delineate an important interaction of genetic traits influencing urate metabolism and handling with diuretic use in hypertensive subjects.

1601

Mortality Due to Coronary Heart Disease and Kidney Disease Among Middle-Aged and Elder Men and Women with Gout In the Singapore Chinese Health Study. Gim Gee Teng[1], Li-Wei Ang[2], Jian-Min Yuan[3] and Woon-Puay Koh[4]. [1]National University Health System, Singapore, Singapore, [2]Ministry of Health, Singapore, Singapore, [3]Masonic Cancer Center, University of Minnesota, Minneapolis, MN, [4]Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Background/Purpose: Impact of gout on mortality is underrated despite increasing evidence of gout being an independent mortality risk factor in Caucasian populations. Whether the link is causal or confounded by lifestyle factors or comorbidities remains unclear. Studies in the Asia are warranted due to rapid modernization, population growth and aging. We examined the association between gout and mortality in a prospective cohort of Chinese men and women in Singapore.

Methods: The Singapore Chinese Health Study comprised of 63,257 Chinese, ages 45–74 years, living in housing estates and enrolled in 1993–98 by in-person interview of lifestyle, dietary patterns and medical history. At follow up-I (1999–2004), 52,322 reported if they had a history of physician-diagnosed gout. Mortality in the cohort was identified via record linkage with death registry, through December 2009. Cox regression analyses examined the associations between gout and mortality risk, adjusted for age, body mass index (BMI), gender, dialect, education, alcohol drinking, physical activity, smoking, saturated fat and cholesterol intake, hypertension, coronary heart disease (CHD), stroke and diabetes.

Results: Among 52,322 subjects eligible for the present analysis, 2,117 (4.1%) had a history of physician-diagnosed gout. The mean age at diagnosis of gout was 54.7 (SD 10.0) years. Compared to subjects without a history of gout, subjects with gout were more likely to have diabetes, hypertension, stroke and CHD. People with gout were more educated, had higher BMI, and consumed more alcohol, saturated fat and cholesterol. After a mean follow-up period of 8.1 (SD 1.9) years, there were 6,660 total deaths, of which 33% were cardiovascular deaths. Relative to those without a history of gout, subjects with gout were at increased mortality from all causes [hazard ratio (HR) 1.17; 95% confidence interval (CI) 1.05–1.31], CHD (HR 1.34, 95%CI 1.07–1.68) and kidney disease (HR 6.08, 95%CI 3.76–9.84). Early age at initial diagnosis of gout was associated with higher mortality from all causes as well as CHD. Stroke mortality was also higher in subjects with gout but the increased risk did not reach statistical significance. The risk estimates associated with gout were higher among women compared to men for mortality from all causes, as well as from CHD, stroke and kidney disease.

Conclusion: Gout is moderately associated with total and CHD mortalities, and a strong risk factor for kidney disease mortality among Chinese in Singapore. Patients with gout should be screened and managed for CHD and kidney disease. Further research is needed to investigate if optimizing care for gout, especially for patients with younger age of onset, may improve survival.
None.

1602

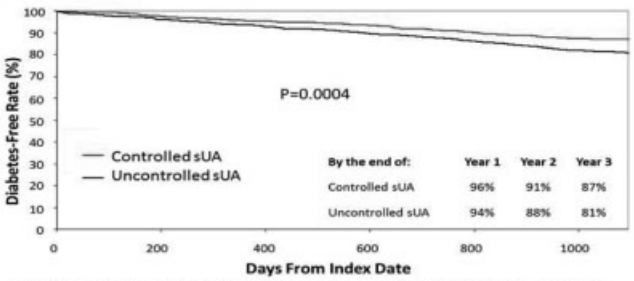
Uncontrolled Serum Uric Acid In Veteran Gout Patients Is Associated with a Higher Risk of Diabetes. Bhavik J. Pandya[1], Maryna Marynchenko[2], Hari Sharma[2], Andrew Yu[2], Eric Wu[2], Lizheng Shi[3], Jinan Liu[3] and Eswar Krishnan[4]. [1]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [2]Analysis Group, Inc., Boston, MA, [3]Tulane University, New Orleans, LA, [4]Stanford University, Stanford, CA

Background/Purpose: The association between high serum uric acid (sUA) levels and diabetes is not clear, with many studies claiming a positive connection, and other studies finding no such relationship. The goal of this study was to evaluate the association between uncontrolled sUA and the risk of developing diabetes among veteran gout patients (pts) in the United States.

Methods: Using the Veterans Integrated Services Network 16 (VISN 16) database, adult male pts (age ≥18 yrs) with at least 2 gout diagnoses (ICD-9 CM: 274.xx) and 2 sUA measurements between January 1, 2002 and January 1, 2011 were selected. Pts were required to be continuously eligible for at least 6 months prior to and 12 months after the index date (first sUA test date). Diabetes was identified using ICD-9-CM codes, or use of anti-diabetic medications, or HbA1c≥6.5. Pts with claims for inflammatory diseases at any point in their history (rheumatoid arthritis, lupus, scleroderma, vasculitis, psoriatic arthritis, autoimmune diseases, pseudogout, and other inflammatory arthritis) or those with diabetes prior to the index date were excluded. The study period for each pt (from index date until the end of eligibility) was broken into 6-month cycles to allow for a longitudinal design. sUA levels were assessed for each cycle; any cycle with sUA level >7 mg/dLwas considered to have an uncontrolled sUA level (sUA ≤7 was considered to be controlled). Time to first diabetes diagnosis was compared between pts with uncontrolled vs controlled sUAs. Average area under the curve (AUC) connecting sUA levels during the study period was used to classify pts into uncontrolled vs controlled sUA cohorts for Kaplan-Meier survival (K-M) analysis. Relative risk of diabetes associated with uncontrolled sUA levels was estimated using a Cox proportional hazard model with sUA levels as time-varying covariates, after controlling for: age at index date; year of index date; race; region; body mass index (BMI); and other risk factors at baseline (eg, hypertension, hyperlipidemia, and tobacco use).

Results: Among the 1,923 pts selected for the study, 52% were white; average age was 62.9 years; average BMI was 30.6; and average follow-up time was 80 months. Major comorbidities at baseline included hypertension (93%), hyperlipidemia (64%), cardiovascular diseases (30%), and smoking (8%). K-M analysis (Figure 1) found that pts with controlled sUA had significantly higher diabetes-free rates at year 1, 2, and 3 compared with pts with uncontrolled sUAs (96% vs 94%; 91% vs 88%; and 87% vs 81% respectively; p<0.001). In addition, uncontrolled sUA was associated with a significantly higher risk of developing diabetes, after adjusting for confounding factors (hazard ratio: 1.19, 95% confidence interval: [1.01–1.41]).

Figure 1. Kaplan-Meier Survival Curve for Time to First Diabetes Diagnosis: Controlled sUA vs Uncontrolled sUA



Interpretation: Pts with uncontrolled sUA have a significantly higher diabetes diagnosis rate than those with controlled sUA. sUA level was considered uncontrolled if average AUC was >7 during the study period.

Notes: Time to diabetes was measured from index date until: a) diabetes diagnosis; b) death; or c) the end of data, whichever comes earlier. Pts with diabetes prior to index date were excluded.

Sample size at the end of:	Baseline	Year 1	Year 2	Year 3
Controlled sUA	785	750	677	612
Uncontrolled sUA	1,138	1,065	939	789

Conclusion: Among VISN 16 pts with gout, uncontrolled sUA was associated with a higher risk of a new diagnosis of diabetes when compared with controlled sUA.

1603

Does Treatment of Asymptomatic Hyperuricemia Improve Cardio and Neurovascular Outcomes? A Decision-Analytic Evaluation. Roopa Akkineni[1], Alexandra Lee[2], Katherine L. Miller[3], Anna N A. Tosteson[4], Hyon K. Choi[5], Yanyan Zhu[5] and Daniel A. Albert[1]. [1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [2]Veterans Affairs National Center for Patient Safety, White River Junction, VT, [3]Northeastern Ohio Universities College of Medicine, Rootstown, OH, [4]Dartmouth Medical School, Lebanon, NH, [5]Boston University School of Medicine, Boston, MA

Background/Purpose: Recent studies suggest that elevated serum uric acid level is associated with increase in coronary and cerebrovascular disease. Treatment for asymptomatic hyperuricemia with urate lowering drugs like Allopurinol may reduce vascular events. However, some patients have experienced adverse drug reactions when treated with Allopurinol. A decision analysis was designed to identify the optimal treatment strategy for patients with asymptomatic hyperuricemia.

Methods: A Markov state-transition model was constructed to assess the occurrence of cardiovascular and neurovascular events and to estimate life expectancy in patients undergoing urate-lowering treatment with Allopurinol. The model simulated three hypothetical cohorts of male patients 50-years and older having asymptomatic hyperuricemia, each with different serum urate concentrations (4–5.9mg/dl, 6–6.9mg/dl and 7–7.9mg/dl). Age-specific incidences of gout, cardio- and neurovascular events were modeled across different serum urate concentrations.

Sensitivity analyses were conducted for probability of adverse drug reactions, incidence of gout, incidence and death from a vascular event. Probabilities and quality adjustment values were obtained from published literature. Number needed to treat (NNT), number needed to harm (NNH) and hypothetical trial sample size calculations were performed.

Results:

	Serum Urate (mg/dl)		
Decision	**4–5.9 mg/dl**	**6–6.9 mg/dl**	**7–7.9mg/dl**
Treat (QALYS)	31.837	**31.190**	**30.749**
Don't Treat (QALYS)	**32.152**	31.162	30.201

A serum urate level greater than 7mg/dl favored treatment and yielded the maximum gain in quality-adjusted-life-years [QALYs] compared to watchful waiting at 0.55 QALYs or 6.6 months.

Sensitivity analysis showed treatment with Allopurinol was favored even with drug reaction rates up to 27% (6–6.9mg/dl) and 84% (7–7.9mg/dl). Treatment strategy was most effective at higher serum urate levels in preventing incidence and death from vascular events.

The NNT to prevent one stroke and one fatality from myocardial infarction were 170 and 141 patients respectively. Treatment of 250 patients with Allopurinol would result in one case of Allopurinol hypersensitivity syndrome. A hypothetical trial of Allopurinol treatment versus placebo would involve 2,291 individuals with a serum urate level greater than or equal to 7.0mg/dl followed for one year in order to validate the prevention of cardio and neurovascular events.

Conclusion: Treatment with Allopurinol was an effective strategy for patients with asymptomatic hyperuricemia at serum urate concentrations above 6mg/dl based on QALY comparison with watchful waiting. Based on the results of our sample size calculation, a clinical trial evaluating the effectiveness of Allopurinol treatment to prevent cardio and neurovascular events in individuals with asymptomatic hyperuricemia would be both feasible and useful in validating these results.

1604

Comparative Effectiveness of Allopurinol and Febuxostat In Controlling Serum Uric Acid In a Large US Commercially Insured Population. Jasvinder A. Singh[1], Bhavik J. Pandya[2], Gabriel Gomez Rey[3] and Brett W. Pinsky[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [3]Innovus, Eden Prairie, MN, [4]Innovus, Lenexa, KS

Background/Purpose: The study goal was to assess the comparative effectiveness of allopurinol (ALLO) vs febuxostat (FEB) in lowering serum uric acid (sUA) level in a real-world managed-care setting in the US.

Methods: This retrospective study utilized 2009–2010 medical and pharmacy claims along with laboratory data from adults with gout enrolled in a large US commercial health plan. Study patients (pts) had at least 1 medical claim with a diagnosis of gout and 1 fill for ALLO or FEB. The date of first cohort medication fill was identified as the index date. Pts were also required to have at least 1 sUA measurement a minimum of 14 days post-index date. Pts had ≥6 months of continuous enrollment prior to their index date (baseline period) and were followed for ≥90 days after start of treatment. Effectiveness of lowering sUA was examined as both change in sUA from baseline to first available follow-up sUA, and percentage of pts achieving sUA goal (<6 mg/dL).

Results: The study sample included 451 pts taking FEB and 5,880 pts taking ALLO. More than 82% of FEB patients received an index dose of 40 mg and more than 95% of patients had an index dose ≤300mg (ALLO <300mg, 41% and ALLO = 300mg, 54%). At baseline, FEB pts had a higher Quan-Charlson comorbidity Index score (1.4 vs 1.0; $p<0.01$) and a higher mean sUA level (8.53 vs 7.80 mg/dL; $p<0.01$) compared with ALLO pts. FEB-treated pts had an average 2.2 mg/dL sUA decrease vs 1.3 mg/dL ($p<0.01$) for ALLO-treated pts. After controlling for baseline patient demographics, baseline sUA, and comorbidities, FEB was associated with a 0.50 mg/dL greater drop in sUA vs ALLO from baseline ($p<0.01$). Additionally, more FEB pts attained sUA goal at both <6 mg/dL (60.5% vs 48%) and <5 mg/dL (36.7% vs 22.7%) [Table 1]. After controlling for comorbidities (hypertension, peripheral artery disease, heart failure, rheumatoid arthritis, osteoarthritis, hyperlipidemia, kidney failure); presence of tophi; geographic region; gender; age; and insurance type, FEB-treated pts had 71% higher odds ratio of attaining sUA goal <6 mg/dL (OR 1.71 [1.39–2.11]; $p<0.01$) and 2x higher odds ratio of attaining sUA <5 mg/dL (OR 2.06 [1.65–2.57]; $p<0.01$). The mean dose at time of goal attainment was slightly higher in patient achieving an sUA goal of <5 mg/dL (FEB=55.6 mg; ALLO=308.3 mg) than <6 mg/dL (FEB=54.4; ALLO=288.5 mg). Median time to achieving sUA goal <6 mg/dL and <5 mg/dL was shorter for FEB-treated pts (157 and 194 days) than ALLO-treated pts (264 and 323 days; $p<0.01$ and $p<0.01$, respectively)

Table 1. Patients Attaining sUA Goal

	% of Patients Attaining Goal (<6.0 mg/dL)		% of Patients Attaining Goal (<5.0 mg/dL)	
	Unadjusted	*Adjusted*	*Unadjusted*	*Adjusted*
FEB-Treated Patients	56.1	60.5	32.6	36.7
ALLO-Treated Patients	48.4	48.0	23.0	22.7
p-value*	<0.01	<0.01	<0.01	<0.01

*Adjusted p-value represents the p-value associated with the logistic regression parameter estimate.

Conclusion: FEB lowered sUA in gout pts significantly more than ALLO as demonstrated by both the absolute value of the change in sUA, % of pts getting to sUA goal of <6 mg/dL and <5 mg/dL, and odds ratio of pts achieving sUA goal.

1605

Continued Opioid Use in Fibromyalgia Is Associated with Negative Health Related Outcomes. Peter A. Ste-Marie[1], Mary-Ann Fitzcharles[2], Marc-Olivier Martel[2], Ann Gamsa[2], Pantelis Panopalis[2] and Yoram Shir[2]. [1]University of Montreal, Montreal, QC, [2]McGill University, Montreal, QC

Background/Purpose: Opioids are not recommended for the treatment of fibromyalgia (FM), but are used by up to $^1/_3$ of patients, and were identified by patients as giving best symptom relief in an Internet survey. The effect of opioids on pain needs to be balanced with negative health and psychosocial effects, and similarity between adverse effects of opioids, such as sleep disturbance, poor energy and mood disturbance, and symptoms of FM need to be appreciated. Long-term risks are also unclear. We have examined the outcome in FM patients followed in a multidisciplinary setting stratified according to opioid use.

Methods: FM patients being followed prospectively in a multidisciplinary pain clinic were stratified according to opioid use at follow-up. Demographic information, work status and history of substance abuse were recorded. Outcome measures included: Patient Global Impression of Change (PGIC), employment and disability status, Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ), Pain Disability Index (PDI), patient global status and pain by Visual Analog Scale (VAS), and anxiety and depression by Arthritis Impact Measurement Scale (AIMS). Univariate comparisons of continuous variables were made using Student's t-tests, and for categorical variables using chi-squared tests. Logistic regression was used to model the association between selected variables.

Results: One hundred and thirty one of 159 patients (82%), mean age 50±10, 92% female, had at least one follow up visit at mean (SD) of 26±15months. Opioid use vs. non use was reported in 43 (33%; Group 1) vs. 88 (67%; Group 2). Twelve patients in Group 2 were given a trial of opioids, followed by discontinuation. Opioid use was significantly associated with poorer outcome for multiple measures of symptoms and function, including unemployment and disability benefit payments (Table 1). Change scores from baseline to follow-up only achieved significance for HAQ, with deterioration in group 1 (p=0.011). A logistic hierarchical regression analysis revealed that baseline level of pain was a significant predictor of opioid status at follow-up, even after controlling for demographic and substance abuse-related variables (p=0.007).

Table 1. FM patients stratified according to opioid use at follow-up.

	ALL at baseline n=131	Group 1 Opioid users Follow up n=43	Group 2 Non-users Follow up n=88
PGIC (Likert) ± SD		4.8 ± 1.6*	5.4 ± 1.6
Employed, n (%)	39 (30)	10 (23)*	36 (41)
Disability, n (%)	42 (32)	14 (33)*	13 (15)
Pain			
Pain VAS ± SD	6.4 ± 2.3	6.5 ±2.5*	5.4 ± 2.9
MPQ ± SD	42 ± 15	43 ± 17***	32 ± 18
Body Map ± SD	27 ± 10	27 ± 12*	22 ± 13
Function			
FIQ ± SD	66 ± 18	66 ± 20**	54 ± 23
PDI ± SD	37 ± 15	38 ± 16**	28 ± 18
HAQ ± SD	1.14 ± 0.66	1.27 ± 0.71**	0.87 ± 0.68
Patient global VAS ± SD	6.4 ± 2.4	6.7 ± 2.7**	5.5 ± 2.6
AIMS anx ± SD	6.1 ± 1.9	5.6 ± 2.1	5.4 ± 2.0
AIMS dep ± SD	5.0 ± 1.6	3.9 ± 2.1	3.3 ± 1.8

Group1 FU vs Group2 FU: *p≤0.05, ** p≤0.01, ***p≤0.001
SD: Standard deviation, PGIC: 1=much worse, 4= no change, 7=much better

Conclusion: In this first study reporting on health related outcomes and opioid use in FM, opioid users had poorer symptom, functional and occupational outcome compared to non users. Although opioids may have been initiated due to more severe symptoms, we have no evidence that these agents improved function, and rather may have contributed to this less favourable outcome. Only a formal study of opioid use in FM will clarify this issue, but until then physicians must be vigilant regarding the multiple adverse consequences of opioid therapy.

1606

5-HT2C Receptor Agonists Attenuate Muscle Pain in a Rat Model of Fibromyalgia. Shinichi Ogino, Mina Tsukamoto, Yukinori Nagakura, Tomonari Watabiki, Yasuaki Shimizu and Hiroyuki Ito. Astellas Pharma Inc., Tsukuba, Japan

Background/Purpose: Fibromyalgia (FM) is a chronic disorder believed to involve the dysfunction of biogenic amine-mediated pain control and is characterized by widespread pain, muscle tenderness, and decreased pain threshold to pressure and other stimuli. Interruption of 5-hydroxytryptamine (5-HT) transmission, a main neurotransmitter in the descending pain inhibitory system, results in hypersensitivity of the spinal nociceptive neurons. 5-HT2C receptors are present in the dorsal horn of the spinal cord and mediate 5-HT-induced analgesia in animal pain models. Here, we examined the effects of several 5-HT2C receptor agonists on muscle hyperalgesia using the reserpine-induced FM model rats.

Methods: Reserpine (1 mg/kg) was administered subcutaneously once daily for three consecutive days to male SD rats. Muscle pressure threshold of the gastrocnemius muscle was determined using the Randall-Selitto test, and extracellular 5-HT content in the spinal cord was measured using a microdialysis system. The effect of 5-HT2C (lorcaserin, vabicaserin, and YM348), 5-HT1A (buspirone), and 5-HT2A (TCB-2) agonists on muscle pressure threshold was evaluated 5 days after the final injection of reserpine. In addition, the effect of the 5-HT2C receptor selective antagonist SB242084 was examined by injecting the agent 15 min before the administration of lorcaserin.

Results: Reserpine treatment significantly reduced extracellular content of 5-HT in the spinal cord and the muscle pressure threshold in rats. Lorcaserin (1 and 3 mg/kg, p.o.), vabicaserin (1 and 3 mg/kg, s.c.), and YM348 (0.1 and 0.3 mg/kg, p.o.) dose-dependently and significantly attenuated the reserpine-induced decrease in muscle pressure threshold, while no effect was observed with either buspirone (10 mg/kg, i.p.) or TCB-2 (2 mg/kg, i.p.). The analgesic effect of lorcaserin was significantly reversed by pretreatment with SB242084.

Conclusion: Our findings indicate that 5-HT2C receptors play a critical role in pain transmission in the reserpine-induced muscle hyperalgesia and suggest the therapeutic potential of 5-HT2C receptor agonists in treating FM.

1607

Mechanisms of Improvement in Fibromyalgia Symptoms in a Clinical Trial of Exercise: Increased Fitness or Hawthorne Effect? Steven A. Mazzuca[1], Anthony Kaleth[2], Chandan Saha[3], James Slaven[3] and Dennis C. Ang[4]. [1]Indiana Univ Schl of Medicine, Indianapolis, IN, [2]Indiana University Purdue University Indianapolis, [3]Indiana University, [4]Indiana University, Indianapolis, IN

Background/Purpose: We have previously shown that initiation of supervised aerobic exercise for fibromyalgia (FM) patients, whether followed by a course of motivational interviewing (MI) to promote maintenance or standard instruction in FM self-care, was associated with an overall increase in self-reported physical activity levels and improvement in FM symptoms. To rule out the possibility that self-reported improvements reflected the generalized effects of attention, we explored whether the association between increased moderate-vigorous physical activity (MVPA) and improved clinical outcomes was mediated by an objective increase in physical fitness.

Methods: Subjects were 201 FM patients who completed the 36-week Research to Encourage Exercise for Fibromyalgia (REEF) trial. We measured changes in MVPA (CHAMPS), physical fitness [6-minute walk test (6MWT)], pain [Brief Pain Inventory (BPI)], and severity of FM symptoms [Physical Impairment (PI) subscale of the Fibromyalgia Impact Questionnaire (FIQ) and the FIQ global]. General linear models were used to perform a mediation analysis, following the approach described by Baron and Kenny (J Personal Soc Psych 1986;51:1173–82). All analyses were controlled for REEF treatment group (T).

Results: Subjects were divided into 3 subgroups, based on the achievement and/or maintenance of ≥90 min/wk increase in MVPA: Group A, achieved and maintained at week 36 (n=51); Group B, achieved but not maintained (N=80); Group C, not achieved (n=70). Groups A and B exhibited significantly greater improvements in fitness (6MWT) than Group C (P = 0.0069 and 0.0199, respectively). Changes in fitness correlated with changes in symptoms (P<0.05 for all outcomes). The table below character-

izes the association between MVPA and clinical outcomes, with and without adjustment for changes in 6MWT.

		Parameter Estimate (*P*-Value)			
Outcome	Adjusted for 6MWT	Group A vs. C	Group B vs. C	R^2 (MVPA|T)	ΔR^2 (%)
BPI	No	−1.03 (0.004)	−0.40 (0.199)	0.0434	
	Yes	−0.89 (0.017)	−0.44 (0.188)	0.0312	−28%
FIQ-PI	No	−1.74 (<0.001)	−0.85 (0.024)	0.0824	
	Yes	−1.39 (0.002)	−0.76 (0.054)	0.0522	−37%
FIQ Global	No	−13.64 (<0.001)	−4.94 (0.102)	0.0794	
	Yes	−10.20 (0.005)	−2.69 (0.404)	0.0470	−41%

Conclusion: The magnitude of the association (parameter estimate) between a maintained increase in self-reported MVPA and improved FM symptoms was diminished 14–25% by adjustment for a concurrent, objective measure of change in physical fitness (6MWT). Adjustment for fitness reduced the % of variance in outcomes associated with MVPA levels by 28–41%. These data suggest that while the Hawthorne Effect cannot be totally discounted, post-intervention changes in FM symptoms in the REEF trial were mediated, in part, by fitness-related changes in MVPA.

1608

Study of the Measurement Properties of the Arnold Fibromyalgia Diagnostic Screen: Results From a Cross-Sectional Study. Susan Martin[1], Cheryl Coon[2], Lori McLeod[2], Arthi Chandran[3] and Lesley M. Arnold[4]. [1]RTI-Health Solutions, Ann Arbor, MI, [2]RTI-Health Solutions, Research Triangle Park, [3]Pfizer, New York, [4]University of Cincinnati College of Medicine, Cincinnati, OH

Background/Purpose: The primary objectives of this study were to 1) conduct confirmatory analyses of the performance of a new patient- and physician-completed fibromyalgia (FM) screener, the Arnold Fibromyalgia Diagnostic Screen (AFDS), using the 1990 American College of Rheumatology (ACR) diagnostic criteria as the gold standard comparison and 2) select the AFDS scoring model that maximizes accuracy in predicting an ACR FM diagnosis. Secondary objectives included 1) evaluating the screening ability of the London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ) and the ACR Diagnostic Criteria (ACR-FDC) and 2) documenting time to completion and participant preference among the AFDS, LFESSQ, and the ACR-FDC.

Methods: 150 adult participants with chronic pain, half of whom had received a physician diagnosis of FM, were enrolled in this multicenter cross-sectional study. The study visit included a physician-conducted evaluation to capture the clinician-reported components of the AFDS, assessment of whether the patient met the ACR criteria for FM, and assessment of whether the patient had FM based on clinical judgment. Additionally, the study visit included patient completion of the three screening questionnaires and venipuncture. The sensitivity and specificity for an FM diagnosis based on the ACR criteria was tabulated for each of six AFDS scoring models. Kappa, Youden's index, overall accuracy, and a likelihood ratio were also calculated. Chi-square contingency tables with odds ratios were created predicting the dependent variable (0 = no ACR FM diagnosis, 1 = ACR FM diagnosis) for two of the AFDS models (the primary scoring model and the scoring model with the highest Youden's index) as well as for the LFESSQ and ACR-FDC. The three patient preference items were summarized using counts and percentages; means, medians, and standard deviations (SD) were calculated for the participant time to complete each questionnaire. All analyses were conducted using SAS. All statistical tests were 2-tailed. A conservative type 1 error rate of 1% ($\alpha = 0.01$) was applied to each individual hypothesis test.

Results: Item-level analyses provided support for the response categories and the predictive ability of most of the individual AFDS items. Additionally, the evaluation of the AFDS scoring models demonstrated that the greatest accuracy in predicting an FM diagnosis was provided by a combination of AFDS patient items and the AFDS clinician items that included an abbreviated (8 point) tenderpoint exam (sensitivity = 0.68, specificity = 0.82). Sensitivity of the ACR-FDC and the LFESSQ was 0.87 and 0.86, respectively, with specificity of 0.62 for the ACR-FDC and 0.49 for the LFESSQ. Most participants reported an overall preference for the AFDS (49%) over the ACR-FDC (22%) or LFESSQ (16%). Mean (SD) time to completion for each questionnaire was 5.2 minutes (3.9) for the AFDS patient items, 2.7 (2.8) for the ACR-FDC, and 1.8 (3.4) for the LFESSQ.

Conclusion: The study results indicate that the AFDS holds promise for identifying patients with FM and has measurement properties better than or similar to existing tools. The AFDS warrants further evaluation for use in the primary care setting.

1609

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Switch Study to Evaluate the Safety, Tolerability, and Efficacy of Milnacipran in Patients with An Inadequate Response to Duloxetine for the Treatment of Fibromyalgia. Lucinda Bateman[1], Allan Spera[2], Robert H. Palmer[2], Joel M. Trugman[2] and Jennifer Lin[2]. [1]The Fatigue Consultation Clinic, Salt Lake City, UT, [2]Forest Research Institute, Jersey City, NJ

Background/Purpose: As fibromyalgia (FM) treatments often do not have the same effectiveness in all FM patients; it is frequently necessary to switch therapies to achieve greater benefit or to avoid side effects. This study evaluates the safety, tolerability, and efficacy of milnacipran (MLN) following a direct switch from duloxetine (DLX) in FM patients with inadequate response to DLX. Although both compounds are serotonin/norepinephrine reuptake inhibitors, their pharmacologic properties differ, which may result in different responses and adverse-effect profiles in some FM patients.

Methods: Patients with FM were eligible for this study if they were currently receiving a stable dosage of DLX (60 mg/d) for ≥4 weeks at screening. After 2 weeks of open-label treatment with DLX 60 mg/d, patients with VAS pain scores ≥40 (range, 0–100 mm) and dissatisfied with DLX were randomized 4:1 to receive MLN 100 mg/d (n=86) or placebo (PBO, n=21) for 10 weeks. The purpose of the small PBO group was to minimize expectation bias rather than provide a comparator arm, since patients would be discontinuing a treatment that may have been partially efficacious. In keeping with anecdotal clinical practice, patients randomized to the MLN group were directly switched from DLX to MLN with no tapering or titration periods. MLN dosage could be adjusted if necessary (required to be ≥100 mg/d by Week 5). The primary efficacy parameter was the percentage of patients who rated themselves "much improved" or "very much improved" on the Patient Global Impression of Change (PGIC) scale. The secondary efficacy parameter was 1-week recall VAS pain score. Efficacy parameters were analyzed by using last observation carried forward.

Results: Among patients switched from DLX to MLN, 59.3% completed the double-blind treatment period, and 17.4% discontinued due to adverse events (AEs) (in patients switched to PBO, 52.4% completed the double-blind period and 9.5% discontinued due to AEs). At Week 10, 32.9% of patients switched from DLX to MLN were PGIC responders and the overall MLN group had a mean decrease from baseline in VAS pain of 12.3 mm (in the group switched to PBO, 23.8% of patients qualified as PGIC responders, but the mean decrease from baseline in VAS pain was only 1.3 mm). 34.2% of patients switched from DLX to MLN showed ≥30% improvement in VAS pain, whereas 29.1% of patients had ≥40% improvement, and 25.3% had ≥50% improvement. Treatment-emergent AEs in patients switched to MLN were similar to those reported in previous PBO-controlled trials. The most common TEAEs in those patients were nausea (21% of patients switched to MLN and 29% in patients switched to PBO) and dizziness (15% MLN, 5% PBO). For comparison, in previous studies conducted in patients not switching from another SNRI, at a dosage of MLN 100 mg/d, the incidence of nausea was 35% and dizziness was 11% (Savella package insert). There were 2 SAEs among patients switched from DLX to MLN: suicidal ideation and hypersensitivity.

Conclusion: These results suggest that FM patients with an inadequate response to DLX treatment may benefit from a switch to MLN for management of their symptoms. Additionally, a direct switch from DLX to MLN was safe and well tolerated in this study.

1610

An 11-Year Longitudinal Study of Pharmacologic Therapy in Fibromyalgia. Frederick Wolfe[1], Brian T. Walitt[2], Robert S. Katz[3], Yvonne C. Lee[4], Kaleb D. Michaud[5] and Winfried Häuser[6]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Washington Hospital Center, Washington, DC, [3]Rush University Medical Center, Chicago, IL, [4]Brigham and Women's Hospital, Boston, MA, [5]Univ of Nebraska Med Ctr & National Data Bank for Rheumatic Diseases, Omaha, NE, [6]Technische Universität München, Munich, Germany

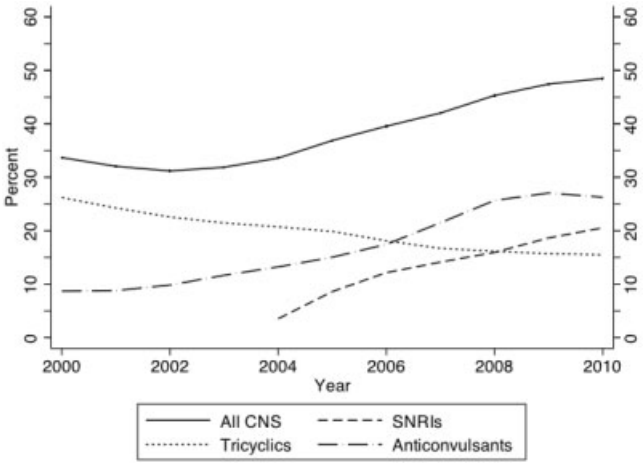
Background/Purpose: Fibromyalgia pharmacotherapy has undergone significant changes in the last decade with recommendations regarding opioids and the introduction of FDA-approved serotonin-norepinephrine reuptake inhibitors (SNRI) such as duloxetine and milnacipran and narcoleptic drugs such as pregabalin and gabapentin. SNRIs

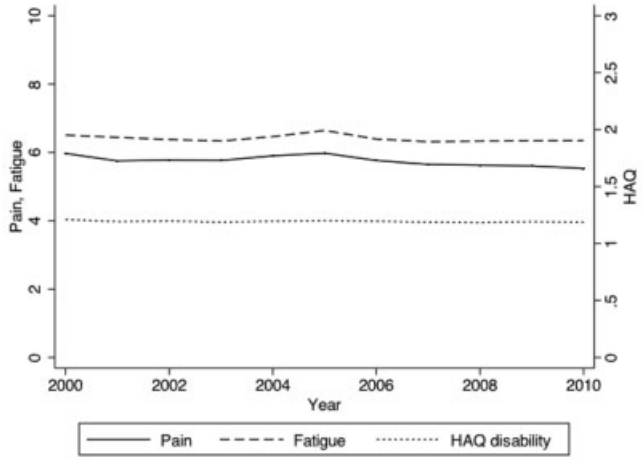
and anticonvulsants are heavily promoted to physicians and direct-to-patient advertising. However, there are few data on the prevalence of use of fibromyalgia treatments and their effect on the outcome of fibromyalgia. We report here the results of an 11 study of fibromyalgia pharmacotherapy.

Methods: We used a longitudinal fibromyalgia databank that assessed drug use and outcome variables at semi-annual intervals on 2,870 patients during 18,452 observations. We assessed outcomes by VAS pain and fatigue scales, and the HAQ functional disability index. Prevalence estimates were based on generalized estimating equations (GEE), and adjusted for demographic and severity variables.

Results: NSAID use fell from 73% in 2000 to 44% in 2010. At similar intervals strong opioids increased from 6% to 12% and weak opioids from 35% to 40%. Overall, non-NSAID analgesic use increased from 63% to 68%. During the same period the group of tricyclic antidepressants, SNRIs and anticonvulsants increased from 34% to 49% (Figure 1). These changes were brought about by a decrease in tricyclic use from 26% to 16% and increases in anticonvulsants from 9% to 26% and in SNRIs from 0% to 21%.

The mean pain, fatigue and HAQ disability scores were 5.6 (SD 2.6), 6.3 (2.8) and 1.2 (0.7), respectively, and these scores remained high and changed almost not at all over the 11-year period (Figure 2). In addition, the total drug cost ($2007) increased from $459 to $1,345.





Conclusion: Strong and weak opioid use remains high in fibromyalgia despite recommendations against opioids. Switching from inexpensive generic trycyclics to newer and expensive SNRIs and anticonvulsant agents was common. Drug costs increased substantially, but despite changes in therapy, no clinically significant changes in pain, fatigue or function were noted during 11 years of follow-up.

1611

Comparative Analysis of Bone Erosions and Cysts in Rheumatoid Arthritis, Psoriatic Arthritis and Erosive Hand Osteoarthritis. Stephanie Finzel[1], Christian Ernet[1], Juergen Rech Sr.[1], Christian M. Stach[1], Klaus Engelke[2], Matthias Englbrecht[1], Jochen Zwerina[1] and Georg Schett[1]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Rheumatoid arthritis (RA), psoriatic arthritis (PSA) and erosive hand osteoarthritis (EHOA) all lead to joint destruction via formation of erosive lesions but may differ substantially in their quality and distribution pattern. This study was performed in order to investigate the differences in the pattern of erosion formation in patients with RA, PSA and EHOA by a high-resolution micro-computed tomography scanner (μCT) designed to visualize bone architecture.

Methods: 25 patients with RA, 25 patients with PSA and 25 patients with EOHA (age- and sex-matched) received a micro- computed tomography scan of the dominantly affected hand to compare structural bone changes in the metacarpophalangeal joints. Number, size and distribution of bone erosions and prevalence of cystic lesions were recorded. In addition, joint space narrowing was measured.

Results: The number of bone erosions was similar in RA, PSA and EHOA, whereas their size was smaller in PSA and EHOA than in RA. Moreover, erosions in EHOA showed a specific distribution pattern affecting the ulnar and radial sites of the metacarpal heads (MCH). In EHOA patients, the MCH were far more frequently and more severely affected than the phalangeal bases. Cystic bone lesions, defined as the absence of trabecular structure in a circumscript area without cortical break were highly prevalent in EHOA (92%) and were localized in peripheral and central subchondral areas of periarticular bone, whereas they were significantly less frequent in RA (24%) and PSA (36%) ($p < 0.01$). Higher age, male sex and postmenopausal state were associated with bone cysts, subchondral erosions and joint spase narrowing (JSN) in EHOA Patients; MCP joints 2 and 3 were much more affected by JSN than MCP joint 4.

Conclusion: High-resolution μCT imaging shows profound differences in periarticular bone changes between RA, PSA and EOHA. The differential pattern of erosive lesions and bone cysts in the three different forms of arthritis and in particular the almost complete absence of bone cysts in RA and PSA suggest different mechanisms to be involved in bone remodeling in RA, PSA and EOHA. Our data indicate that it is possible to differentiate between inflammatory and degenerative bone erosion by advanced imaging technology.

1612

Baseline Levels of the Inflammatory Biomarker C-Reactive Protein Are Significantly Correlated with Magnetic Resonance Imaging Measures of Synovitis At Baseline and After 26 Weeks of Treatment in Patients with Early Rheumatoid Arthritis. Charles G. Peterfy[1], Boulos Haraoui[2], Arthur Kavanaugh[3], Josef S. Smolen[4], Sourav Santra[5], Hartmut Kupper[6], Tracy F. Nicholson[7] and Paul Emery[8]. [1]Spire Sciences LLC, Kentfield, CA, [2]Institut de Rhumatologie, Montreal, QC, [3]University of California San Diego, San Diego, CA, [4]Krankenhaus Lainz, Vienna, Austria, [5]Abbott GmBH & Co KG, Abbott Park, IL, [6]Abbott GmBH & Co KG, Ludwigshafen, Germany, [7]Abbott Laboratories, [8]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease, which results in joint inflammation and destruction. Early detection of inflammation and structural damage by magnetic resonance imaging (MRI) has been demonstrated to be a sensitive predictor of disease progression.[1,2] This sub-analysis assessed MRI scores after 26 wks of treatment with adalimumab plus methotrexate (ADA+MTX) or placebo (PBO)+MTX and the correlation of baseline disease characteristics with MRI scores at baseline, wk 26, and change over 26 wks.

Methods: OPTIMA was a phase 4 trial of MTX-naïve patients (pts) ≥18 years old with RA <1 year and active disease (DAS28 >3.2, ESR ≥28 mm/h or CRP ≥1.5 mg/dL, and either >1 erosions, RF+, or anti-CCP+) who were randomized to ADA+MTX (N=515) or PBO+MTX (N=517) for 26 wks. High-field 1.5-Tesla MRI was conducted on the metacarpophalangeal and wrist joints of the most clinically severe extremity per patient before and after i.v. gadolinium-based contrast. Synovitis, osteitis, and erosions were scored by 2 independent blinded radiologists using a modified OMERACT-RAMRIS scoring system. The changes in observed MRI measurements were compared between treatment groups using an ANCOVA model adjusted for baseline. The relationship between MRI scores and baseline disease traits was assessed for CRP, TJC68, SJC66, DAS28, and HAQ using Pearson correlation.

Results: The MRI substudy included 70 pts with at least 1 MRI; there were 59 pts (27 ADA+MTX, 32 PBO+MTX) with both baseline and wk 26 MRI. Mean MRI baseline values were similar between treatment groups: 6.22/6.77 (synovitis), 5.37/3.33 (osteitis), and 6.13/4.14 (erosion) for ADA+MTX and PBO+MTX pts, respectively. ADA+MTX pts showed significantly greater mean decreases in MRI scores from baseline to 26 wks for synovitis (−3.61/−2.03, *P*=.003), osteitis (−3.98/0.00, *P*=.006), and erosion (−0.78/1.41, *P*=.004) compared with PBO+MTX pts. MRI scores were all highly correlated with one another (*P*<0.001), both at baseline and wk 26, as were the changes in these scores. Baseline CRP levels were significantly correlated with all synovitis measures and the absolute erosion score at wk 26, while baseline osteitis demonstrated a significant correlation with baseline TJC68 (table).

Table. Correlation of Baseline Disease Variables with MRI Scores at Baseline and Week 26, and the Change in MRI Score (r values)

	Synovitis			Osteitis			Erosion		
	BL	Wk 26	ΔBL-wk 26	BL	Wk 26	ΔBL-wk 26	BL	Wk 26	ΔBL-wk 26
CRP	0.38**	0.30*	−0.34**	0.04	0.16	−0.02	0.12	0.27*	0.03
TJC68	−0.03	−0.05	−0.10	−0.24*	−0.09	0.10	−0.07	0.05	0.02
SJC66	0.09	0.02	−0.17	−0.18	−0.08	0.06	0.02	0.11	−0.08
DAS28	0.15	0.12	−0.24	−0.13	0.02	0.03	−0.05	0.14	0.08
HAQ	0.13	0.04	−0.25	−0.12	−0.12	0.01	0.02	−0.01	−0.05

* *P*<.05; ** *P*<.01; BL, baseline; ΔBL-wk 26, change in MRI score from baseline to week 26.

Conclusion: Treatment with ADA+MTX resulted in greater reductions in synovitis, osteitis, and bone erosion MRI scores compared with PBO+MTX at 26 wks in pts with early RA. Particularly striking was the lack of effect of MTX alone on osteitis. The strong correlation between change in osteitis and change in erosion corroborates the current view that osteitis is a precursor of erosion. That baseline CRP correlated with responsiveness of MRI synovitis to treatment supports the utility of CRP in pt selection.

References:
[1] Benton N, et al. *Ann Rheum Dis* 2004;63:555–61. [2] Hodgson RJ, et al. *Rheumatology* 2008;47:13–21.

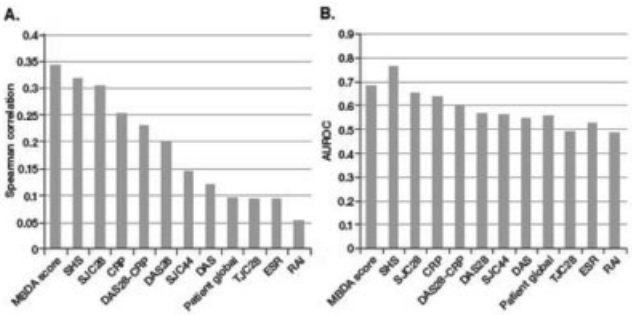
1613

A Multi-Biomarker Disease Activity (Vectra DA) Algorithm Score for Rheumatoid Arthritis Predicts Radiographic Progression in the BeSt Study. Cornelia F. Allaart[1], Linda Dirven[1], Shintaro Hirata[2], P.J.S.M. Kerstens[3], B.A.C Dijkmans[4], David Chernoff[5], Guy Cavet[5], Michael Centola[6], Lyndal K. Hesterberg[5], Yoshiya Tanaka[2], T.W.J. Huizinga[7] and Yijing Shen[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [3]Jan van Breemen Research Institute|Reade, Amsterdam, Netherlands, [4]VU Medical Center, Amsterdam, Netherlands, [5]Crescendo Bioscience, Inc., South San Francisco, CA, [6]Oklahoma Medical Research Fdn, Oklahoma City, OK, [7]Leiden University Medical Centre, Leiden, Netherlands

Background/Purpose: A novel multi-biomarker disease activity (MBDA) score for rheumatoid arthritis (RA) was significantly associated with DAS28CRP in multiple studies. Since disease activity is associated with structural damage, we set out to examine whether the MBDA algorithm score can also help predict progressive joint damage.

Methods: We analyzed 126 patients from the BeSt trial, which demonstrated the efficacy of early aggressive intervention in RA. The MBDA algorithm combines serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL40, Leptin, Resistin, CRP, SAA) into a single score. Serum samples from baseline (BL) and year 1 were examined. Total Van der Heijde Sharp Scores (SHS) and DAS28CRP were available at BL, year 1, and year 2. The performance of the MBDA algorithm score and continuous clinical variables at BL or year 1 was evaluated by Spearman correlation to change in SHS over the next 12 months (ΔSHS) and by Area under the receiver operating characteristic curve (AUROC) for identifying joint damage progressors (ΔSHS>0). For binary clinical variables, C-indices (comparable to AUROC) were used. The MBDA score and other variables at year 1 (presence of erosions, CCP status, CRP, DAS28CRP, and 28 joint counts) were assessed as independent predictors of ΔSHS by multivariate ordinary least squares regression.

Results: Among individual continuous measures from year 1 assessed for their ability to predict ΔSHS, the MBDA algorithm score had the highest correlation with ΔSHS (r=0.34), followed by starting SHS (r=0.32), SJC28 (r=0.31), CRP (r=0.25), DAS28CRP (r=0.23), and TJC28 (r=0.1, Figure panel A). Correlations of MBDA algorithm scores and other variables to 12-month ΔSHS were higher at year 1 than at BL. The MBDA algoirhtm score at year 1 had the second highest performance at identifying joint damage progressors (AUROC = 0.69) following SHS at 1 year (AUROC = 0.77, Figure panel B). In multivariate regression, only the MBDA algorithm score was a significant predictor of ΔSHS (p<0.05). Median MBDA algorithm scores dropped markedly from BL to year 1 (57 to 36, p<0.001).



Conclusion: A pre-defined, multi-biomarker algorithm for RA disease activity can also predict joint damage progression, suggesting that the combination of biomarkers accurately reflects underlying disease processes.

1614

Tocilizumab (TCZ) Inhibits Progression of Joint Damage in Rheumatoid Arthritis (RA) Irrespective of Its Antiinflammatory Effects: Disassociation of the Link Between Inflammation and Destruction. Josef Smolen[1], José Martinez-Avila[2] and Daniel Aletaha[3]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, Vienna, Austria, [2]Medical University of Vienna, Austria, [3]Medical University of Vienna, Vienna, Austria

Background/Purpose: Joint damage in RA correlates with disease activity (DA) by composite scores, swollen joint counts or acute phase reactants during its natural course or during therapy with synthetic drugs like methotrexate (MTX). In contrast, treatment with TNF blockers (TNFi) plus MTX inhibits joint damage progression even in patients (pts) with higher DA, disassociating this link. Such disassociation implies a profound direct interference with the events eliciting joint damage beyond effects on disease activity and has not been shown for other biologics. Here we evaluated if IL-6 inhibition with TCZ interferes with joint destruction beyond its effects on DA.

Methods: We used a random 90% sample of data from the LITHE trial on active RA despite MTX[1] with complete clinical and radiologic data at baseline (BL) and 1 year (yr) treated with placebo (PL; n=117), 4mg/kg TCZ (n=197) and 8mg/kg TCZ (n=217) every 4 weeks, pooling the TCZ groups because of similar radiographic effects[1]; all patients continued MTX. We calculated the SDAI, CDAI, DAS28 at BL and 1yr. We correlated BL and 1yr values of clinical and serologic variables with changes to 1yr of the Genant modified total Sharp score (TGSS) using Spearman test and also compared TGSS progression in low and high DA groups for PL and TCZ (Kruskal-Wallis).

Results: BL DA variables were similar among the groups. In line with published results[1], change of TGSS in this dataset was significantly lower in pts on TCZ than PL (TCZ:0.29±0.96; PL: 0.90±1.92; p=0.0007). In patients treated with PL, the correlation with TGSS change was low but significant for BL SDAI (r=0.18, p=0.047) and SJC28 (r=0.22, p=0.019) with similar trends for CRP (r=0.15, p=0.106) and CDAI (r=0.17, p=0.061), in line with previous notions mentioned above. Similar correlations were seen for SDAI, CDAI, DAS28 at 1yr with x-ray change during that year (r=0.26–0.28, p=0.002 – p=0.006). In contrast, none of the BL or 1yr variables showed significant correlation with x-ray

changes in pts on TCZ+MTX, suggesting a reduction or even abrogation of the link between DA and damage by TCZ.

Progression of TGSS was similar between treatment groups when remission or low DA was reached: PL: 0.4±1.1 (n=41); TCZ: 0.2±0.7 (n=217) (p=n.s). In contrast, when only moderate or high DA was reached after 1yr, PL treated patients had significantly higher TGSS change (1.2±2.2; n=76) than those treated with TCZ (0.4±1.2; p=0.0009).

Conclusion: IL-6 receptor inhibition with TCZ, in combination with MTX, appears to inhibit joint damage progression independent of its impact on disease activity. Similar effects have hitherto been reported only for TNF-i. These data indicate that the effects of IL-6 inhibition on progression of joint damage in RA are among the most profound currently attainable.

Acknowledgement: This study was supported by Roche and we thank Roche for providing us with the data for these analyses.

1. Kremer et al. Arthritis Rheum 2011; 63:609–621.

1615

Evidence for Limited Repair of Existing Bone Erosions in Rheumatoid Arthritis Patients Treated with the Interleukin-6 Receptor Blocker Tocilizumab. Stephanie Finzel[1], Juergen Rech Sr.[1], Sarah Schmidt[1], Klaus Engelke[2], Matthias Englbrecht[1], Christian M. Stach[1] and Georg Schett[1]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, Erlangen, Germany, [2]Institute of Medical Physics, University of Erlangen, Erlangen, Germany

Background/Purpose: The detection and quantification of bone erosion is an important outcome parameter in both clinical studies and clinical practice. This study was performed in order to investigate whether bone erosions in patients with rheumatoid arthritis (RA) treated with the interleukin-6 receptor blocker tocilizumab (TCZ) show evidence for repair.

Methods: A total number of 245 erosions were identified in the metacarpophalangeal (MCP) joints 2 to 4 of the right hand of 20 rheumatoid arthritis patients treated with TCZ in combination with methotrexate (MTX; mean dose 12.88 mg) and 21 sex-, age- and disease activity- matched patients treated with MTX monotherapy (mean dose 15.56 mg). All erosions were assessed for their exact maximal width and depth by high-resolution μCT imaging at baseline and after one year of treatment.

Results: All erosions detected at baseline could be found at follow-up after 1 year. At baseline, the mean width of bone erosions in the TCZ group was 1.57 mm, their mean depth was 1.67 mm, which was slightly less severe than in the MTX-treated group (width: 2.4mm; depth: 2.4 mm). In those patients reaching either clinical remission (DAS <2.6) or a DAS28 response of more than 1.5, the mean depth of erosions significantly ($p < 0.01$) decreased after 1 year of treatment with TCZ (−0.23 mm), whereas their mean width remained unchanged (−0.12 mm). In contrast, the mean depth (+2.16 mm) and width (+0.17 mm) of erosive lesions significantly increased in the MTX- treated group after 1 year. The reduction in depth of lesions was confined to joint areas containing spongiosal structure and associated with sclerosis at the base of the lesion.

Conclusion: Bone erosions in RA patients treated with TCZ show limited evidence for repair, which is in contrast to RA patients treated with MTX alone. Repair is associated with decreased depth of lesion and sclerosis at the bases of the erosion. These data indicate that TCZ can facilitate repair of existing bone erosions in RA, however repair is still incomplete after 1 year of treatment.

1616

Co-Localization of Non-Cartilaginous Articular Pathology and Cartilage Damage in Regard to Subsequent Cartilage Loss in Subjects with or at Risk for Knee Osteoarthritis - the MOST Study. Frank Roemer[1], David T. Felson[2], Ke Wang[1], Michel Crema[1], Monica D. Marra[1], Yuqing Zhang[3], Michael C. Nevitt[4], Cora E. Lewis[5], James Torner[6] and Ali Guermazi[7]. [1]Boston University, Boston, MA, [2]Department of Clinical Epidemiology, Boston University School of Public Health, Boston, MA, USA, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]University of California-San Francisco, San Francisco, CA, [5]University of Alabama, Birmingham City, Birmingham, AL, [6]University of Iowa, Iowa City, Iowa City, IA, [7]Boston Medical Center, Boston, MA

Background/Purpose: One of the strongest predictors of subsequent cartilage loss seems to be prevalent cartilage damage. Abnormally loaded areas of the knee joint are at increased risk of cartilage loss. Ipsi-compartmental meniscal damage and extrusion and prevalent bone marrow lesions (BMLs) may be considered markers for increased load to an adjacent cartilage subregion. The aim was to evaluate the impact of directly underlying BMLs and meniscal damage (called 'associated') pathology on the risk of subsequent cartilage loss at 30 months follow-up stratified by baseline cartilage damage severity.

Methods: The Multicenter Osteoarthritis (MOST) Study is an observational study of subjects with or at risk of developing osteoarthritis (OA). The MRI protocol (1.0 T) included axial and sagittal proton density-weighted fat-suppressed fast spin-echo and a coronal STIR sequence. MRIs were assessed according to the modified WORMS scoring system. Included were all knees with available baseline and 30 months MRI readings of the tibio-femoral joint (10 subregions). Ordinal logistic regression was used to estimate the risk of cartilage loss in each subregion, stratified by the severity of baseline cartilage damage. Cartilage loss was defined as at least within-grade progression in the same subregion. Subregions with associated articular pathology were stratified in subregions with one, two or three associated risk factors (i.e. meniscal damage, meniscal extrusion and BMLs). Subregions without adjacent pathology but with the same degree of prevalent cartilage damage (graded from 0 to 6) were the reference. Additional adjustment was performed for possible confounders.

Figure 1. Cartilage loss in the tibio-femoral joint by grade in regard to adjacent pathology

	Cartilage status in subregion (tibiofemoral joint – 10 subregions)						
Subregions and adjacent risk factor status	All Grades	Grade 0	Grade 2	Grade 2.5	Grade 3	Grade 4	Grades 5 and 6
Subregions included (%)	13524 (100.0)	9747 (72.1)	476 (3.5)	173 (1.3)	1983 (14.7)	49 (0.3)	1096 (8.1)
Subregions with cartilage loss (%)	1119 (8.3)	352 (3.6)	133 (27.9)	34 (19.7)	427 (21.5)	11 (22.4)	162 (14.8)
Subregions with cartilage loss and no adjacent feature (%)	375 (4.4)	180 (2.5)	66 (22.6)	11 (10.7)	106 (14.1)	1 (11.1)	11 (7.4)
aOR[1] (Reference)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Subregions with cartilage loss and one adjacent feature[2] (%)	268 (10.9)	99 (6.1)	35 (28.9)	12 (28.6)	93 (19.7)	3 (30.0)	26 (14.1)
aOR[1] (95% CI) p	2.53 (2.03-3.15) <.0001*	2.46 (1.74-3.46) <0.001*	1.45 (0.89-2.38) 0.13	3.60 (1.40-9.32) 0.008*	1.43 (1.00-2.04) 0.047*	3.54 (0.25-50.2) 0.34	1.95 (0.79-4.83) 0.15
Subregions with cartilage loss and two adjacent features[3] (%)	338 (18.2)	70 (8.8)	31 (53.4)	9 (40.9)	167 (27.7)	3 (13.6)	58 (16.0)
aOR[1] (95% CI) p	4.32 (3.42-5.47) <.0001*	3.70 (2.51-5.44) <0.001*	3.62 (1.98-6.63) <0.001*	4.86 (1.64-14.5) 0.004*	2.25 (1.58-3.21) <0.001*	1.47 (0.14-15.8) 0.74	2.47 (1.00-6.07) 0.048*
Subregions with cartilage loss and three adjacent features[4] (%)	138 (22.7)	3 (8.3)	1 (20.0)	2 (33.3)	61 (39.6)	4 (50.0)	67 (16.8)
aOR[1] (95% CI) p	5.30 (3.95-7.12) <.0001*	3.59 (1.10-11.7) 0.03*	1.03 (0.09-11.9) 0.98	4.73 (0.74-30.2) 0.09	3.75 (2.40-5.85) <0.001*	16.29 (0.89-296) 0.06	2.57 (0.97-6.83) 0.06
p for trend	<.0001*	<.0001*	0.0004*	0.0011*	0.0152*	0.1798*	0.0798

[1] aOR – adjusted odds ratio. Adjusted for potential confounders baseline effusion, synovitis, body mass index, age, gender, radiographic osteoarthritis severity and malalignment
[2] one adjacent feature: BML or meniscal damage or meniscal extrusion)
[3] two of three adjacent features: BML, meniscal damage, meniscal extrusion)
[4] three adjacent features: BML and meniscal damage and meniscal extrusion)
* significant at p < .05
95% CI - 95 % confidence interval

Results: 13524 subregions of 1365 knees were included. Subregional baseline cartilage scores were distributed as follows: grade 0: 9747 (72.1%); grade 2: 476 (3.5%); grade 2.5: 173 (1.3%); grade 3: 1983 (14.7%); grade 4: 49 (3.6%); grades 5 and 6 combined: 1096 (8.1%). 1119 (8.3%) subregions showed progressive cartilage loss at follow up. The risk of progressive cartilage loss was significantly increased for most grades in subregions where associated pathology was present when compared to subregions without adjacent pathology as the reference (Figure 1). For all grades of baseline cartilage damage combined, risk of cartilage loss increased significantly with number of associated features (test for trend $p<0.0001$).

Conclusion: For all prevalent grades of cartilage damage in the WORMS scale, the risk of cartilage loss is markedly increased for subregions with associated pathology indicative of abnormal loading conditions. Risk is further increased for subregions with more than one type of associated pathology. Integrity of meniscal structure/position and subchondral bone marrow is paramount for cartilage preservation.

ACR Concurrent Abstract Session

Metabolic and Crystal Arthropathies I: Concurrent Session on Pathogenesis of Gout, a Potential Novel Therapy, and Validity of Dual Energy Computed Tomography

Monday, November 7, 2011, 2:30 PM–4:00 PM

1617

Diagnosis of Gout Using Dual-Energy Computed Tomography: An Accuracy and Diagnostic Yield Study. Tim Bongartz[1], Katrina N. Glazebrook[1], Steven J. Kavros[2], Clement J. Michet[1], Stephen P. Merry[3], Naveen S. Murthy[1], Bharath Manu Akkara Veetil[1], John M. Davis III[1], Thomas G. Mason II[4], Kenneth J. Warrington[1], Nisha J. Manek[1], Tanaz A. Kermani[1], Deana D. Hoganson[1], A. Kirstin Bacani[1], Hailong Wang[1] and Cynthia H. McCollough[2]. [1]Mayo Clinic, Rochester, MN, [2]Rochester, MN, [3]Mayo Clinic, Rochester, [4]Mayo Clinic Rochester, Rochester, MN

Background/Purpose: Dual energy computed tomography scanning (DECT) is highly accurate in detecting and classifying renal uric acid stones. This technology has recently been modified to detect intra- or peri-articular monosodium urate (MSU) deposits. We aimed to formally assess the accuracy of this new imaging method to diagnose gout and explore whether it may have any substantial impact on clinical decision making beyond the established diagnostic approach using polarizing microscopy of synovial fluid.

Methods: To assess the sensitivity and specificity of DECT for diagnosis of gout, we included patients into two prospective cohorts: A control cohort of subjects without any history of gout who underwent arthrocentesis for other types of joint disease, and a second cohort of subjects with active gout diagnosed with a combined reference method of polarizing and electron microscopy. Accrual was stratified according to joint location and duration of symptoms (≤6 weeks>/6 weeks) in order to capture a wide spectrum of disease. All study participants underwent dual source, dual energy (80 and 140 kVP) CT scanning of the aspirated joint. Images were classified by a musculoskeletal radiologist as positive or negative for MSU deposition. To explore the diagnostic yield of DECT scanning, we assembled a third cohort of subjects who had clinical suspicion for gout but from whom an appropriate synovial fluid specimen for analysis could either not be obtained, or polarized microscopy was negative for the presence of MSU crystals. These subjects then had DECT imaging of the affected joint area. If the imaging findings suggested the presence of MSU deposits, we performed an ultrasound (US) guided aspiration of these areas with subsequent polarizing microscopy.

Results: The sensitivity and specificity of DECT for diagnosing gout was 0.93 (95%CI 0.79–0.98) and 0.95 (95%CI 0.82–0.99), respectively. These estimates were based on 40 patients with confirmed gout according to the reference method and 40 control patients with other types of joint disease. All 3 false negative subjects were observed in the stratum of 10 patients with acute podagra and no prior episodes of joint pain. The 2 false positive patients had advanced knee osteoarthritis with a DECT signal indicating intracartilaginous uric acid deposition. The diagnostic yield cohort consisted of 30 subjects with a clinical suspicion for gout but a negative synovial fluid aspiration. DECT imaging showed evidence for uric acid deposition in 14 of these 30 patients (46.7%). US guided aspiration of areas with positive DECT findings confirmed presence of MSU crystals.

Conclusion: DECT imaging provides high sensitivity and specificity for detection of MSU crystal deposits in subjects with gout. Sensitivity appears to be lower in patients with acute symptoms and no prior history of gout. DECT is a high-yield test with significant impact on clinical decision making when gout is suspected based on clinical presentation but polarizing microscopy of synovial fluid fails to demonstrate MSU crystals.

1618

Assessment of Tophus Size; A Comparison Between Physical Measurement Methods and Dual Energy Computed Tomography Scanning. Nicola Dalbeth, Opetaia Aati, Angela Gao, Meaghan House, Qiliang Liu, Anne Horne, Anthony Doyle and Fiona M. McQueen. University of Auckland, Auckland, New Zealand

Background/Purpose: A number of methods have been used to assess tophus size in clinical studies of chronic gout, from simple physical measurement techniques to complex advanced imaging methods. Dual energy computed tomography (DECT) has recently been described as a sensitive method to detect urate deposits in patients with gout. The aim of this study was to compare the reliability and validity of various physical methods with DECT assessment of tophus size.

Methods: Twenty-five patients with a history of gout according to ACR classification criteria and at least one subcutaneous tophus were recruited. For each patient, up to three index tophi were selected for analysis. Sites in the feet were preferentially selected. Tophus location was recorded in detail using a diagram and written description (n=64 tophi, 55 in the feet). Each tophus was assessed by two independent observers using Vernier calipers (longest diameter) and tape measure (area). The total number of subcutaneous tophi was also counted. All patients proceeded to DECT scanning of both feet. Index tophus DECT volume was assessed by two independent observers using automated volume assessment software (n=55 tophi). Five patients returned within one week for repeat physical assessment of tophus size. DECT scans from the returning patients were scored twice by both observers. Intra- and inter-observer reproducibility was assessed by intraclass correlation coefficient and limits of agreement analysis (Bland and Altman).

Results: Table 1 summarises the reproducibility analysis. Overall, DECT was more reproducible than the physical methods with an interobserver ICC of 0.95 [95% CI 0.92–0.97]. Vernier caliper and tape measurements correlated highly with each other (r_s=0.84, p<0.0001) but less well with DECT (for index tophi, r_s=0.46, p=0.004 for both). Variation was observed in the amount of urate deposits documented by DECT in tophi of similar physical size (Figure).

Table. Summary of reproducibility analysis for various methods of tophus size.

	Measurement, mean (SD)	Intraclass correlation coefficient, mean (95% CI)	Bias, mean (SD)
Interobserver reproducibility (Assessor 1 vs. Assessor 2)			
Vernier caliper longest diameter	25.7 (8.8) mm	0.78 (0.66–0.86)	2.1 (6.2) mm
Tape measure area	895 (713) mm^2	0.88 (0.82–0.93)	133 (320) mm^2
Tophus count	10 (8)	0.58 (0.25–0.79)	1.8 (8.5)
DECT volume	0.62 (1.15) cm^3	0.95 (0.92–0.97)	−0.07 (0.36) cm^3
Intraobserver reproducibility (Assessment 1 vs. Assessment 2)			
Vernier calipers longest diameter	28.1 (13.4) mm	0.75 (0.54–0.87)	−0.4 (10.1) mm
Tape measure area	1244 (1186) mm^2	0.91 (0.82–0.96)	64 (519) mm^2
Tophus count	14 (12)	0.94 (0.77–0.98)	−1.5 (4.3)
DECT volume	1.66 (2.1) cm^3	1.00 (1.00–1.00)	0.02 (0.13) cm^3

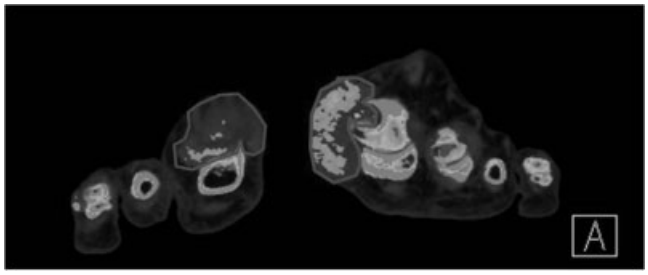


Figure. Example of two similar sized tophi from a single patient showing large variation in urate volume (green).

Conclusion: DECT scanning is a highly reproducible method for assessing tophus volume. This imaging modality reveals the composition of tophi which contain variable urate deposits embedded within soft tissue.

1619

A Novel Role for Monosodium Urate Monohydrate Crystals and Gouty Synovial Fluids in Monocyte Migration in Gout. M. Asif Amin[1], Qiang Shu[1], Jonathon W. Vargo[1], Jeffrey H. Ruth[1], Takeo Isozaki[1], Solhee Lee[1] and Alisa E. Koch[2]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]Department of Veteran's Affairs and University of Michigan, Ann Arbor, MI

Background/Purpose: Gout is characterized by intra-articular deposition of monosodium urate monohydrate (MSU) crystals. The role of neutrophil influx in acute gouty arthritis is well established, while the contribution of monocytes (MNs) and their secreted inflammatory mediators is not. Here we demonstrate the role of MSU in MN migration.

Methods: To examine the role of MSU crystals in normal human peripheral blood (PB) MN migration, we performed MN chemotaxis in a modified Boyden chamber *in vitro* using either MSU crystals or gouty synovial fluids (SFs) as stimuli. To examine mechanisms of MN migration, we performed MN chemotaxis with MSU in the presence or absence of chemical signaling inhibitors. We determined the *in vivo* role of MSU crystals or gouty SFs in homing of dye-tagged MNs using normal human

synovial tissue (ST)-severe combined immunodeficient (SCID) mouse chimeras. Gout often occurs after ingestion of rich foods, so to understand MN migration *in vivo*, we injected MSU crystals with fatty acid FFA C18:0 (FFA) into C57BL/6 mouse knees and examined them for MN ingress after 48 hours. To investigate the contribution of MSU to production of leukocyte chemoattractants macrophage migration inhibitory factor (MIF) and epithelial neutrophil activating factor-78 (ENA-78/CXCL5), and the signaling molecules involved in secretion of these cytokines, we stimulated MNs with MSU crystals, and performed ELISAs on conditioned medium. We also assayed for MIF in gouty SF by ELISA.

Results: We found that there was a significant 2 fold increase in *in vitro* MN migration in response to MSU crystals, while gouty SFs increased MN migration 5 fold compared to negative control ($n=3$, $p<0.05$). MSU crystal induced MN migration was significantly decreased by inhibitors of p38 MAPK, Src, and NFκB, suggesting that crystal induced MN migration occurs via these pathways. To determine if MSU crystals or gouty SFs induce MN migration *in vivo*, we engrafted SCID mice with normal human STs. After 4 weeks, we injected dye-tagged human PB MNs via tail vein. Simultaneously, we injected MSU crystals or gouty SFs into ST grafts. After 48 hours, we harvested the STs and found an increase in MN homing to the grafts injected with MSU crystals or SFs ($p<0.05$), indicating that either of these stimuli could recruit MNs *in vivo*. Likewise, we found a marked increase in mouse MN ingress in knees when these mice were injected with MSU crystals and FFA. Human MNs stimulated with MSU for 24 hours released significantly higher quantities of the potent leukocyte chemoattractants MIF and ENA-78/CXCL5 compared to nonstimulated MNs. MIF was a mean of 6 fold higher in gouty SFs compared to osteoarthritic fluids, suggesting the importance of MIF in gouty arthritis. Next, we examined the role of signaling molecules in the production of MIF and ENA-78/CXCL5 by stimulating MNs with MSU crystals in the presence of chemical signaling inhibitors. We found that MIF or ENA-78/CXCL5 secretion depended on the p38 MAPK pathway.

Conclusion: This data suggests an intriguing role for MSU crystals and gouty SFs in MN migration *in vitro* and *in vivo*. This data also provides evidence that MNs and their secreted products such as MIF and ENA-78/CXCL5 may be potential therapeutic targets for the treatment of diseases like gout.

1620

Bone Destruction by RANKL-Expressing T Cells in Chronic Gouty Arthritis. Sung-Ji Lee, Hye-Mi Jin, Young-Nan Cho, Seong-Chang Park, Dong-Jin Park, Tae-Jong Kim, Shin-Seok Lee, Seung-Jung Kee and Yong-Wook Park. Chonnam National University Medical School and Hospital, Gwangju, South Korea

Background/Purpose: To analyze the cellular expressions of pro-resorptive cytokines in gouty tophus tissues, to determine the capacity of monosodium urate monohydrate (MSU) crystals to induce these cytokines, and to understand the mechanisms of bone destruction in chronic gout.

Methods: Fourteen fixed, paraffin-embedded, uninfected tophus samples were analyzed immunohistochemically. Peripheral blood mononuclear cells (PBMCs) were cultured *in vitro* with MSU crystals, and gene expression was assessed by reverse transcription-polymerase chain reaction. *In vitro* osteoclastogenesis was performed using PBMCs and synovial fluid mononuclear cells (SFMCs).

Results: CD4+ T cells, CD8+ T cells, CD20+ B cells, and mast cells infiltrated tophus tissues. Tartrate-resistant acid phosphatase (TRAP)+ osteoclasts were present around tophi and in osteolytic lesions. Interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α were produced from infiltrated mononuclear cells, whereas receptor activator of nuclear factor κB ligand (RANKL) was strongly expressed in T cells. However, osteoprotegerin (OPG) was not or weakly expressed in tophus tissues. MSU crystals induced the expressions of IL-1, IL-6, TNF-α and RANKL in PBMCs, but inhibited OPG expression. In addition, the pro-resorptive cytokines were highly expressed in SFMCs of gouty arthritis patients. Furthermore, *in vitro* osteoclastogenesis was enhanced in SFMC cultures, but inhibited in T cell-depleted SFMC cultures.

Conclusion: Our study demonstrates that RANKL-expressing T cells and TRAP+ osteoclasts are present within gouty tophus tissues, and that infiltrating cells express pro-resorptive cytokines. Furthermore, our data show that MSU crystals have the potential to induce pro-resorptive cytokines, and T cells are involved in osteoclastogenesis in chronic gout.

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Pharmacological Inhibition of Interleukin-1 Receptor-Associated Kinase-4 Reduces Inflammation in a Murine Model of Gout and Is Consistent with IL-1 Signaling Blockade. Andrea Bree[1], Kathleen Phillips[1], Micah Benson[1], Ken Dower[1], Marina Shen[2], Katherine Lee[1], Vik Rao[1], Cheryl L. Nickerson-Nutter[2] and Melanie Ruzek[1]. [1]Pfizer, Inc., Cambridge, MA, [2]Pfizer, Cambridge, MA

Background/Purpose: Gout is an inflammatory disease associated with crystalline uric acid deposition within joints of affected patients. In a mouse model of this disease, where intraperitoneal injections of monosodium urate (MSU) crystals result in a neutrophilic peritonitis, IL-1 receptor signaling has been demonstrated to play a key role in this inflammatory response. As interleukin-1 receptor-associated kinase 4 (IRAK-4) is a critical signaling molecule downstream of the IL-1 receptor, we were interested in whether a highly specific IRAK-4 small molecule kinase inhibitor would be effective in this model system.

Methods: The IRAK-4 inhibitor was tested for activity in vitro on IL-1-induced cytokine responses in human whole blood and peripheral blood mononuclear cell (PBMC) cultures. In vivo we evaluated the cellular inflammation and cytokine responses to intraperitoneal injection of MSU crystals in IRAK-4-deficient/kinase inactive IRAK-4 transgenic mice, in wildtype mice treated with the IRAK-4 inhibitor and in IL-1R-deficient mice alone and upon coadministration of the IRAK-4 inhibitor. The IRAK-4 inhibitor was injected subcutaneously in a nanocrystal formulation to ensure adequate exposure over the course of the studies in mice.

Results: In vitro, the IRAK-4 inhibitor blocked interleukin (IL)-1-induced IL-6 production by human whole blood and peripheral blood mononuclear cells (PBMC) as well as the production of tumor necrosis factor-a by PBMCs. In vivo, MSU-treated IRAK-4-deficient/kinase inactive IRAK-4 transgenic mice showed a significant reduction in peritonitis compared to wildtype (WT) and heterozygous mice. A similar level of inhibition of MSU-induced peritonitis was observed upon treatment of WT mice with the IRAK-4 inhibitor. In addition, IL-6 levels in the peritoneal lavage fluid of MSU-treated mice were reduced by the IRAK-4 inhibitor treatment, suggesting that downstream cytokine responses are similarly affected by blockade of IRAK-4 signaling. To explore whether the IRAK-4 inhibitor mediates its effects through the IL-1 pathway in this model, we compared the IRAK-4 inhibitor treatment in WT mice to the response in IL-1 receptor (IL-1R)-deficient mice and found that the inhibition of peritonitis to MSU crystal injection was similar with IRAK-4 inhibitor treatment and in IL-1R-deficient mice. Furthermore, there was minimal additional inhibition observed when IL-1R-deficient mice were treated with the IRAK-4 inhibitor.

Conclusion: These results demonstrate that specific pharmacological inhibition of IRAK-4 can block human IL-1 responses in vitro as well as ameliorate the gout-like peritonitis in mice and indicates that IRAK-4 inhibitors have potential therapeutic application in IL-1-mediated diseases in humans.

1622

Association Between Sugar-Sweetened Beverage Consumption and Gout in the New Zealand Population. Tony R. Merriman[1], Nicola Dalbeth[2], Lisa K. Stamp[3], Marilyn E. Merriman[1], Ruth Topless[1], Peter J. Gow[4], Andrew Harrison[5], John Highton[6], Peter B. B. Jones[7] and Caitlin Glue[1]. [1]University of Otago, Dunedin, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]University of Otago, Christchurch, Christchurch, New Zealand, [4]Middlemore Hospital, Auckland, New Zealand, [5]Hutt Hospital, Lower Hutt, New Zealand, [6]Univ of Otago Med Sch, Dunedin, New Zealand, [7]Waikato Clinical School, Waikato Hospital, Hamilton, New Zealand

Background/Purpose: Association between the consumption of high fructose corn syrup (HFCS; 55% fructose)-sweetened beverages and fruit, and the risk of hyperuricaemia and gout, has been reported in North America. The objective was to examine the association of gout with sugar-sweetened beverages in a New Zealand (NZ) population. The population of NZ has a unique composition, and soft-drinks and fruit juices in NZ are predominantly sweetened with sucrose (50% fructose), rather than HFCS.

Methods: Survey data from 753 people with, and 633 people without, gout as determined by ACR criteria, were used to examine the association between gout and intake of sugar-sweetened beverages, including fruit juice, and fruit. One unit of drink was defined as a can or large glass. Three ethnic

groups were analysed; NZ Maori, Caucasian and Western Polynesian (Samoa, Tonga, Niue). STATA v8.0 statistical software was used.

Results: Significantly increased risk was apparent only in those drinking four or more sugar-sweetened beverages per day (Table). In all population groups, ingestion of 4 or more such drinks per day is associated with a 3–4-fold increased risk of gout. We observed a protective effect from daily fruit intake in the Caucasian participants (1 piece, adjusted OR=0.32, P=0.08; 2–3 pieces, OR=0.23, P=0.02; ≥4 pieces, adjusted OR=0.15, P=0.007). There were no significant associations with fruit intake in other ethnic groups.

Table. Analysis of frequency of sugar sweetened beverage intake and gout

	Frequency of sugar-sweetened beverage intake (servings/day)			
	0	1–1.99	2–3.99	4+
Caucasian				
Adjusted OR (95% CI)*	1.00	1.05 (0.51,2.15)	1.67 (0.66,4.24)	4.48 (1.22,16.50)
P Value	–	0.90	0.28	0.024
NZ Maori				
Adjusted OR (95% CI)*	1.00	0.70 (0.30,1.63)	1.61 (0.65,4.00)	3.46 (1.35,8.86)
P Value	–	0.41	0.30	0.010
Western Polynesian				
Adjusted OR (95% CI)*	1.00	1.72 (0.65,4.49)	1.66 (0.71,3.91)	4.34 (1.69,11.19)
P Value	–	0.27	0.24	0.002

* Adjusted by sex, body mass index, age, hypertension, kidney disease, alcohol intake, seafood intake and fruit intake.

Conclusion: These results demonstrate association between increased intake of sugar-sweetened beverages and gout in all NZ ethnic groups studied. A possible mechanism for this association is the direct effect of fructose on serum urate concentrations through production of AMP and subsequently urate, as well as the long-term effects of fructose on insulin resistance and the renal excretion of urate. The observed protective effect of fruit intake in Caucasian was consistent with one North American study (Williams PT. Am J Clin Nutr. 2008;87:1480) but not a second North American study (Choi H and Curhan G. Br Med J. 2008;336:309). The protective effect of fruit, despite its fructose content, may be due to fruit containing gout-protective chemicals, or to fruit intake being a marker of a gout-protective diet.

ACR Concurrent Abstract Session
Osteoarthritis - Clinical Aspects II
Monday, November 7, 2011, 2:30 PM–4:00 PM

1623

MRI-Detected Synovitis and Bone Marrow Lesions Are Associated with Joint Tenderness in Hand Osteoarthritis. Ida K. Haugen[1], Pernille Bøyesen[1], Barbara Slatkowsky-Christensen[1], Sølve Sesseng[1], Désirée van der Heijde[2] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Previous studies in knee osteoarthritis (OA) have shown that bone marrow lesions (BMLs) and synovitis are important for the experience of pain. No studies have explored the role of MRI features in relation to pain and physical function in patients with hand OA. The aim was therefore to explore the association between MRI features and joint tenderness, patient-reported pain, physical function and grip strength in hand OA.

Methods: 107 patients (98 women) with mean (SD) age of 68.9 (5.6) years underwent MRI and clinical joint examination of dominant hand. The interphalangeal joints were scored according to the preliminary Oslo hand OA score for MRI and assessed for tenderness upon palpation. Pain and physical function was assessed by self-reported questionnaires (AUSCAN pain/physical function, FIHOA and AIMS-2 hand/finger) and grip strength (Jamar dynamometer). We used Generalized Estimating Equations (GEE) to explore the association between the presence of MRI features and joint tenderness, and linear regression for the association between the amount of MRI features (i.e., MRI sum scores and number of affected joints) and patient-reported outcomes and grip strength of the same hand that was imaged by MRI. We adjusted for age and sex, and features with $p<0.25$ were introduced in a multivariate model (backward selection). In a second model we also adjusted for radiographic severity (Kellgren-Lawrence).

Results: Presence of most MRI features was significantly associated with tenderness upon palpation in the corrected univariate analyses (adjusted for age and sex) (table). The final multivariate model included osteophytes, erosions, bone attrition, moderate/severe synovitis and BMLs (table). Moderate/severe synovitis (OR 1.8;p=0.002) and BMLs (OR 1.8;p=0.007) remained significantly associated with joint tenderness after additional adjustment for radiographic severity (multivariate model).

The sum score of osteophytes was significantly associated with FIHOA (beta=0.22;p=0.002) and grip strength (beta=-0.33;p<0.001), malalignment was associated with AIMS-2 hand/finger (beta=1.19;p=0.03), while no significant associations were found for AUSCAN pain/physical function (corrected univariate analyses). Analyses with the number of affected joints as predictor variables provided similar results as the analyses with MRI sum scores (data not shown).

Table. The odds ratios (95% confidence interval) for tenderness upon palpation in joints with MRI pathology (adjusted for age and sex) compared to joints without the MRI feature.

	Separate models: OR (95% CI); p-value	Final multivariate model: OR (95% CI); p-value
Osteophytes	2.0 (1.4–2.7); p < 0.001	1.4 (1.0–2.0); p = 0.07
Joint space narrowing	1.6 (1.2–2.2); p = 0.002	—
Erosions	1.8 (1.4–2.4); p < 0.001	1.5 (1.1–1.9); p = 0.008
Bone attrition	2.6 (1.7–3.9); p < 0.001	2.5 (1.6–4.0); p < 0.001
Cysts	1.8 (1.0–3.3); p = 0.07	—
Malalignment	2.1 (1.3–3.3); p = 0.002	—
Synovitis #	2.1 (1.5–2.9); p < 0.001	1.9 (1.3–2.9); p = 0.001
Flexor tenosynovitis	1.3 (0.9–1.8); p = 0.20	—
Bone marrow lesions (BMLs)	2.4 (1.7–3.4); p < 0.001	1.6 (1.1–2.4); p = 0.02
Collateral ligament (CL) absence	1.9 (1.4–2.5); p < 0.001	—
BMLs at CL insertions	2.2 (1.4–3.4); p < 0.001	—

joints with synovitis grade 0–1 serve as reference.

Conclusion: Synovitis and BMLs were associated with joint tenderness independent of each other, other MRI features and also radiographic severity, and may represent potential targets for symptom-modifying treatment in hand OA.

1624

Breaking the Law of Valgus: The Surprising and Unexplained Prevalence of Medial Patellofemoral Cartilage Damage. K. Douglas Gross[1], Jingbo Niu[2], Joshua J. Stefanik[3], Ali Guermazi[4], Frank Roemer[3], Leena Sharma[5], Michael C. Nevitt[6], Neil Segal[7], Cora E. Lewis[8] and David T. Felson[2]. [1]MGH Institute of Health Professions, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Boston University, Boston, MA, [4]Boston Medical Center, Boston, MA, [5]Northwestern University, Chicago, IL, [6]University of California-San Francisco, San Francisco, CA, [7]University of Iowa, Iowa City, [8]University of Alabama, Birmingham City, Birmingham, AL

Background/Purpose: The Law of Valgus dictates that patellofemoral (PF) osteoarthritis (OA) involves excessive lateral loading and lateral PF cartilage damage. Many treatments for PF OA, including surgeries and braces, assume that disease affects the lateral compartment. Medial PF OA is expected to occur only rarely in the presence of varus knee malalignment. Yet, the assertion that medial PF OA is less prevalent than lateral PF OA has not been corroborated in large-scale studies or using MRI to detect cartilage damage. Thus, we compared the prevalence of medial and lateral PF cartilage damage in 3 large OA studies and determined the relationship of PF cartilage damage to varus, neutral, and valgus knee alignment.

Methods: In the Boston Osteoarthritis of the Knee Study (BOKS), the Framingham Osteoarthritis Study (FOA), and the Multicenter Osteoarthritis Study (MOST), MRIs were read for cartilage morphology at the medial and lateral patella and trochlea femoris by 2 experienced musculoskeletal radiologists using Whole-Organ MRI Scoring (WORMS). WORMS scores >2 (any cartilage thickness defect), >3 (areas of partial thickness loss), >4 (widespread partial thickness loss), and >5 (areas of full thickness loss) were all variously considered as thresholds to identify of cartilage damage that might indicate OA. Weighted kappa for inter-rater reliability in WORMS scoring was 0.80 in BOKS, 0.73 in FOA, and 0.78 in MOST. Using a standard protocol, standing long-limb radiographs were measured for mechanical axis alignment and varus (<-2 degrees), neutral (-2 to 2 degrees), and valgus (>2 degrees) aligned knees were identified.

Table. Prevalence of medial and lateral patellofemoral (PF) cartilage damage in BOKS, FOA, and MOST studies

		Definition of PF Cartilage Damage							
		Patellar Cartilage Morphology Score				Either Patellar or Trochlear Cartilage Morphology Score			
		≥ 2	≥ 3	≥ 4	≥ 5	≥ 2	≥ 3	≥ 4	≥ 5
BOKS (baseline)	Medial PF Damage % (n /N knees)	75.00 (168/ 224)	68.75 (154/ 224)	48.21 (108/ 224)	26.79 (60/ 224)	84.38 (189/ 224)	79.02 (177/ 224)	55.80 (125/ 224)	30.36 (68/ 224)
	Lateral PF Damage % (n /N knees)	61.61 (138/ 224)	58.04 (130/ 224)	45.54 (102/ 224)	24.11 (54/ 224)	73.66 (165/ 224)	68.75 (154/ 224)	54.46 (122/ 224)	28.57 (64/ 224)
FOA	Medial PF Damage % (n /N knees)	64.72 (277/ 428)	50.00 (214/ 428)	23.36 (100/ 428)	17.76 (76/ 428)	69.95 (298/ 426)	57.51 (245/ 426)	27.00 (115/ 426)	21.13 (90/ 426)
	Lateral PF Damage % (n /N knees)	50.93 (218/ 428)	43.22 (185/ 428)	16.59 (71/ 428)	10.98 (47/ 428)	55.40 (236/ 426)	47.65 (203/ 426)	21.60 (92/ 426)	16.43 (70/ 426)
MOST (baseline)	Medial PF Damage% (n /N knees)	62.74 (1017/ 1621)	51.63 (837/ 1621)	20.30 (329/ 1621)	18.63 (302/ 1621)	69.19 (1116/ 1613)	56.11 (905/ 1613)	21.64 (349/ 1613)	19.78 (319/ 1613)
	Lateral PF Damage % (n /N knees)	45.34 (735/ 1621)	38.43 (623/ 1621)	19.74 (320/ 1621)	16.59 (269/ 1621)	51.08 (824/ 1613)	43.15 (696/ 1613)	23.56 (380/ 1613)	20.52 (331/ 1613)

Results: The prevalence of medial PF cartilage damage exceeded that of lateral damage in all 3 OA studies and according to nearly every threshold definition (see table). This was true whether the patella alone was considered (left of table), or the trochlea femoris was also considered (right of table). Only when consideration was limited to severely involved knees (WORMS > 4 or >5) did the prevalence of lateral PF cartilage damage approximate that of medial PF damage. Moreover, the high prevalence of medial PF cartilage damage persisted within all strata of knee alignment. Even among knees with valgus malalignment, it was only when the threshold used to identify cartilage damage was specific to the most severely involved knees (WORMS > 4 or >5) that the prevalence of lateral PF cartilage damage surpassed that of medial PF damage.

Conclusion: Contrary to the Law of Valgus, these findings indicate that medial PF cartilage damage may be more prevalent among older adults than lateral PF cartilage damage. These findings are likely to have major implications for the treatment of PF OA since many surgical and rehabilitative interventions attempt to unload the lateral PF compartment by medially realigning the patella. Such interventions may be contraindicated in the presence of medial PF disease.

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Change in Knee Cartilage Volume and Incident Meniscal Extrusion As Predictors of Change in Joint Space Width of the Tibiofemoral Joint: 5 Year Longitudinal Study. Joanna Hall[1], Laura Laslett[1], Johanne M. Pelletier[2], Jean Pierre Pelletier[2], François Abram[3], Chang-Hai Ding[4], Flavia Cicuttini[5] and Graeme Jones[1]. [1]University of Tasmania, Hobart, Australia, [2]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [3]ArthroVision Inc., Montreal, QC, [4]University of Tasmania & Monash University, Hobart, Australia, [5]Monash University, Central and Eastern Clinical School, Melbourne, Australia

Background/Purpose: Joint space width (JSW) on X-ray is the current gold standard for assessing osteoarthritis disease modification. Recently, concerns have been raised about this measure. However, there are limited longitudinal data comparing the predictive validity of MRI cartilage volume change and incident meniscal extrusion (IME) for X-ray change. The aim of this study was to determine whether change in these MRI indices over 2.6 years predicted change in JSW over 5 years in randomly selected community dwelling older adults.

Methods: Participants (N=180) had X-rays and MRI's of the right knee at baseline and after 2.6 years for MRI and 5 years for X-ray. IME as well as articular cartilage volumes at baseline and 2.6 years were determined at the medial and lateral tibial and femoral compartments by MRI. Sagittal T1-weighted fat-suppressed MR images were obtained and processed on an independent computer work station. X-ray was performed using a standard fixed semi-flexed view and scored only on those with adequate alignment (N=150).

Results: Participants were aged 50–80 years (mean 62 years, range 51–78), 49% were male. Medial and lateral cartilage volume reduced over time (medial −612 μL/year, p=<0.001, lateral −392μL/year, p<0.001), as did JSW (medial −0.048 mm/year, p=0.0043, lateral −0.12 mm/year, p<0.001). IME occurred in 7% (primarily medial). In multivariate analysis, change in compartment specific cartilage volume was a weak but significant predictor of change in JSW in both the medial ($R^2$5%, p=0.008) and lateral compartments ($R^2$2%, p=0.05). In the medial compartment, IME was a stronger predictor of change in JSW than cartilage volume loss (R^2=14%, p<0.001).

In subgroup analysis by cartilage measurement site, change in tibial cartilage volume was not a significant predictor of change in JSW at the medial or lateral compartments ($R^2$0.4%, p=0.37; $R^2$2%, p=0.056). Change in femoral cartilage volume was weakly predictive of change in JSW in the medial ($R^2$2.5%, p=0.05) but not lateral compartments ($R^2$1.2%, p=0.17). In patients with prevalent radiographic osteoarthritis (n=84), change in cartilage volume had a better goodness of fit but was not significantly predictive of JSW change at the medial or lateral compartments, ($R^2$9.6%, p=0.132; $R^2$2.6%, p=0.16).

Conclusion: Despite both outcome measures decreasing significantly from baseline, change in JSW was only weakly predicted by change in cartilage volume. This provides some evidence of face validity for X-ray. However, incident meniscal extrusion was a stronger contributor to change in JSW than cartilage volume loss at the medial compartment while over 80% of the variation in JSW change remains unexplained. Given that MRI examines cartilage directly while radiographs examine it indirectly, these results cast doubt on the validity of radiographs as a proxy measure of cartilage loss, suggesting it is time for a re-evaluation of the choice of key outcome measure for disease modifying trials.

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Novel MRI Ultrashort TE Enhanced T Mapping Shows Subsurface Cartilage and Meniscus Changes Clinically in Human Subjects After Anterior Cruciate Ligament Tear (ACLT). Constance R. Chu. Ashley A. Williams and Yongxian Qian, University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Joint injury leads to accelerated development of OA. Human subjects with ACL and meniscus injuries provide a unique clinical opportunity to study early OA and potential intervention strategies for early-stage disease modification. Improved ability to diagnose and stage subsurface cartilage and meniscus injury and degeneration are critical to this effort. Ultra-short TE-enhanced T2* (UTE-T2*) mapping is a novel, non-invasive, and quantitative MRI technique we have shown potentially discerns subsurface cartilage degeneration confirmed by microscopy (1) with high clinical reproducibility (2). This study was performed to test the hypothesis that UTE-T2* changes can be quantified in surface-intact human menisci and articular cartilage after ACL tear (ACLT).

Methods: Thirty-five human subjects were imaged on a 3T Siemens MRI scanner using an 8-channel knee coil according to IRB-approved protocols. Ten asymptomatic subjects, with no known knee problems (mean age = 27 yrs), and 25 consecutive human subjects with ACLT who completed UTE scans (mean age = 30 yrs) were studied. Images were acquired at eleven echo times (TE range 0.6–40 ms) with the acquisition-weighted stack of spirals (AWSOS) sequence (3). UTE-T2* maps were generated with a mono-exponential T2 fit (1,2). All ACLT subjects underwent arthroscopy for clinical treatment where Outerbridge cartilage grading and confirmation of meniscal tear status were performed. Non-parametric statistics were used as appropriate.

Results: Of the 25 ACLT subjects, 80% (20/25) had intact articular surfaces to the central weight-bearing study area of the medial femoral condyle, and 60% (15/25) had intact menisci. The UTE-T2* values in the deep articular cartilage of ACLT subjects with both intact medial menisci and intact articular surfaces (n=13) were higher than that of the same regions of asymptomatic (n=10) subjects (14.5 *v* 10.4 ms, P=0.009). Meniscus UTE-T2* values in subjects with ACLT and surface intact medial menisci (n=15) were higher than that of asymptomatics (P=0.001). Meniscus UTE-T2* in subjects with ACLT and medial meniscus tear (n=10) were higher than both ACLT with intact medial menisci (18.3 *v* 13.1 ms, P=0.01) and asymptomatics (18.3 *v* 9.8 ms, P<0.0001).

Conclusion: This human clinical study shows quantitative and noninvasive MRI evidence for subsurface cartilage and meniscus matrix changes following ACL tear, a substantial joint injury associated with rapid OA development. Continued longitudinal study is needed to determine whether elevated meniscus and cartilage UTE-T2* are potential markers of subsurface injury that lead to OA. The ability to diagnose, stage and quantify meniscus and cartilage injury prior to visible surface breakdown are important for identifying early disease states that may be amenable to molecular, biological, and mechanical interventions to delay the onset of OA.

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Pressure Pain Threshold and Knee Pain in Osteoarthritis: The Multicenter Osteoarthritis Study. Tuhina Neogi[1], Jingbo Niu[1], Lars Arendt-Nielsen[2], Joachim Scholz[3], Laura Frey-Law[4], Clifford Woolf[5], Yuqing Zhang[1], Larry Bradley[6], Michael C. Nevitt[7] and David T. Felson[1]. [1]Boston University School of Medicine, Boston, MA, [2]Aalborg University, Aalborg, Denmark, [3]Columbia University, New York, NY, [4]University of Iowa, Iowa City, IA, [5]Children's Hospital, Boston, MA, [6]University of Alabama, Birmingham, AL, [7]University of California-San Francisco, San Francisco, CA

Background/Purpose: Mechanisms contributing to knee pain in osteoarthritis (OA) are not well understood. Sustained mechanical and inflammatory stimuli in the joint may lead both to changes in the peripheral threshold of nociceptors (peripheral sensitization) and a central amplification of signals in the CNS (central sensitization), resulting in heightened pain sensitivity. We hypothesized findings of sensitization, as assessed by pressure pain threshold, may be associated with symptomatic knee OA (SxOA) and knee pain severity.

Methods: The Multicenter Osteoarthritis (MOST) Study is cohort study of persons with or at high risk of knee OA. At the 60-month clinic visit, participants underwent knee radiography, answered pain questionnaires, and had pressure pain threshold (PPT) assessed, which is a marker of peripheral +/− central sensitization at sites of disease/inflammation, or of central sensitization when assessed at an otherwise normal area. PPT was assessed with an algometer (1cm^2 tip) at the patella (site of pathology: peripheral +/− central sensitization) and wrist (free of pathology: central sensitization) as the point at which the participants indicated that the pressure first changed to slight pain. The average of 3 trials was used to calculate the PPT, which was then categorized into tertiles. Knees were categorized according to presence of SxOA based on KL≥2 and presence of consistent frequent knee pain (answering yes to a question about frequent knee pain at a telephone screen and a subsequent clinic visit within 30 days). Pain severity was categorized as the maximum of none, mild, or at least moderate pain on any of the 5 knee-specific WOMAC pain questions. We evaluated the association of PPT with SxOA and presence of frequent knee pain using logistic regression with GEE, and with knee pain severity using proportional odds logistic regression with GEE, adjusting all analyses for age, sex, BMI, race, clinic site, KL grade, depressive symptoms, catastrophizing, and widespread pain.

Results: 2033 subjects (3823 knees) had all measures performed (mean age 68±8, mean BMI 30.6±5.9, 60% female). The range of PPT at the wrist was 0.38 to >9 kg/cm^2 and at the patella was 0.30 to >9 kg/cm^2. The lowest tertile of PPT assessed at the wrist (central sensitization) was significantly associated with presence of SxOA, presence of frequent knee pain, and greater knee pain severity, and at the patella (peripheral +/− central sensitization) was significantly associated with frequent knee pain and greater pain severity (Table).

Table: Association of PPT with Knee Pain in Knee OA

	Symptomatic Knee OA		Frequent Knee Pain		Knee Pain Severity	
PPT tertiles:	Crude OR	Adj* OR (95% CI)	Crude OR	Adj* OR (95% CI)	Crude OR	Adj* OR (95% CI)
Patella						
Lowest	1.87	1.26 (0.94-1.69)	2.11	1.53 (1.19-1.95)	2.72	1.93 (1.59-2.34)
Middle	1.23	1.00 (0.75-1.32)	1.20	1.03 (0.81-1.30)	1.60	1.45 (1.22-1.72)
Highest (referent)	1.0	1.0	1.0	1.0	1.0	1.0
P for trend		0.1		0.001		<0.0001
Wrist						
Lowest	1.65	1.44 (1.08-1.91)	1.56	1.31 (1.02-1.68)	2.07	1.84 (1.51-2.24)
Middle	1.25	1.40 (1.04-1.87)	1.34	1.37 (1.08-1.76)	1.44	1.53 (1.26-1.85)
Highest (referent)	1.0	1.0	1.0	1.0	1.0	1.0
P for trend		0.01		0.03		<0.0001

*adjusted for age, sex, BMI, race, clinic site, ROA severity, depression, catastrophizing, widespread pain

Tertile categories (kg/cm^2):
Patella: lowest: 0.30-3.79; middle: 3.80-5.64; highest: >=5.65
Wrist: lowest: 0.38-2.63; middle: 2.64-3.71; highest: >=3.72

Conclusion: Low pressure pain threshold was associated with pain in knee OA, as assessed by presence of symptomatic knee OA, frequent knee pain, and greater knee pain severity. These findings support the contribution of both peripheral and central sensitization in the pain experience of knee OA.

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Association of Knee Pain Patterns Determined From the Intermittent and Constant Osteoarthritis Pain Instrument with Knee Pain Severity: The Multicenter Osteoarthritis Study. Tuhina Neogi[1], Jingbo Niu[1], David T. Felson[1], Michael C. Nevitt[2], C.E. Lewis[3], James Torner[4], Melissa French[5] and Gillian A. Hawker[5]. [1]Boston University School of Medicine, Boston, MA, [2]University of California-San Francisco, San Francisco, CA, [3]University of Alabama, Birmingham City, AL, [4]University of Iowa, Iowa City, Iowa City, IA, [5]Women's College Hospital, Toronto, ON

Background/Purpose: Knee OA-related pain changes over time as disease progresses, related both to frequency and severity of pain. At the early stages, OA-related knee pain is thought to be activity-related (intermittent) only, while as disease progresses, the pain becomes more constant, and eventually is constant punctuated with intermittent episodes of greater pain. A new pain assessment tool for knee OA, the Intermittent and Constant OA Pain (ICOAP) instrument, can be used to describe these intermittent and constant knee pain patterns. We evaluated whether ICOAP-defined pain patterns were associated with knee pain severity.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded cohort study of persons with or at high risk of knee OA. Knee-specific WOMAC, VAS (0–10) and ICOAP scores were ascertained at the same study visit. The ICOAP assesses presence and severity of intermittent and constant pain, and for intermittent pain, its frequency (5-point Likert scale for each). Using the knee-specific ICOAP, pain patterns were defined as increasing in severity as: 1) no intermittent or constant pain; 2) intermittent pain only (of at least mild severity occurring at least sometimes); 3) constant pain only (of at least mild severity); and 4) a combination of constant + intermittent pain, as defined above. We evaluated the relationship between ICOAP pain patterns (exposure) and knee pain severity (WOMAC, VAS as outcomes) using proportional odds logistic regression with generalized estimating equations. We also assessed the relation of knee pain severity (exposure) to presence of constant or constant plus intermittent pain *vs.* intermittent pain alone.

Results: We studied 2322 participants (4632 knees) with ICOAP data (mean age 68±8, mean BMI 31±6, 60% female). On ICOAP, the majority of knees (62%) had no intermittent or constant pain, 30% had intermittent pain, 4% had constant pain, and 4% had both by ICOAP. By WOMAC and VAS, ~55% of knees had mild-moderate pain, and ~11% had severe/extreme pain. Higher ICOAP pain pattern categories were associated with greater pain severity by WOMAC and VAS (Table). Further, greater WOMAC and VAS pain severity were more likely to be associated with constant rather than intermittent only pain (Table).

Table: Association of ICOAP pain patterns with Knee Pain Severity

Crude Knee Pain severity by ICOAP Pain Pattern Category:	Mean (SD) WOMAC pain (0-20)	Mean (SD) VAS pain (0-100)
ICOAP pain pattern:		
1) No intermittent/constant pain (n=2874)	1.2 (2.0)	6.0 (11.0)
2) Intermittent pain (n=1409)	4.9 (3.1)	27.5 (19.3)
3) Constant pain (n=167)	8.2 (3.8)	43.5 (25.6)
4) Constant + intermittent pain (n=182)	9.0 (3.9)	53.2 (24.4)
Outcome: Knee Pain Severity by WOMAC and VAS (proportional odds logistic regression model)	Maximal WOMAC knee pain [adj OR* (95% CI)]	Maximal VAS knee pain [adj OR* (95% CI)]
ICOAP pain pattern:		
5) No intermittent/constant pain (n=2874)	1.0 (ref)	1.0 (ref)
6) Intermittent pain (n=1409)	16.0 (12.7-20.1)	16.0 (12.5-20.5)
7) Constant pain (n=167)	40.2 (26.4-61.3)	45.9 (28.9-72.7)
8) Constant + intermittent pain (n=182)	43.2 (28.5-65.5)	71.2 (45.7-110.9)
p for linear trend	p<0.0001	p<0.0001
Outcome: ICOAP constant *vs.* intermittent knee pain (logistic regression model)	ICOAP constant vs intermittent pain [adj OR* (95% CI)]	
Maximal WOMAC knee pain:		
1) None (n=1638)	1.0 (ref)	
2) Mild/moderate pain (n=2471)	1.4 (0.6-3.3)	
3) Severe/extreme pain (n=514)	3.8 (1.5-9.4)	
	p for linear trend <0.0001	
Maximal VAS knee pain:		
1) 0 (n=1560)	1.0 (ref)	
2) 1-4 (n=2529)	1.2 (0.5-3.3)	
3) >4 (n=534)	4.7 (1.7-12.6)	
	p for linear trend <0.0001	

*adjusted for age, sex, BMI, catastrophizing, depressive symptoms, widespread pain, clinic site, race, Kellgren and Lawrence grade

Conclusion: Knee pain patterns defined by the ICOAP instrument, thought to be related to disease duration, were associated with greater knee pain severity. These findings support the hypothesis that knee pain patterns (intermittent, constant, constant+intermittent) are meaningful patterns that are associated with overall pain severity and likely stage of disease.

ACR Concurrent Abstract Session
Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogenesis
Monday, November 7, 2011, 2:30 PM–4:00 PM

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Risk Factors Associated with Incident Hip Fractures in 9,720 Japanese Patients with Rheumatoid Arthritis: A Prospective Observational Cohort Study. Takefumi Furuya[1], Eisuke Inoue[1], Takayuki Hosoi[2], Atsuo Taniguchi[1], Shigeki Momohara[1] and Hisashi Yamanaka[1]. [1]Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan, [2]National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

Background/Purpose: Patients with rheumatoid arthritis (RA) have a high risk of hip fracture. Limited data exist in the literature concerning risk factors for incident hip fractures in patients with RA. Previously, utilizing data from our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort study, we reported clinical risk factors for both incident vertebral and non-vertebral fractures in Japanese patients with RA. However, we did not evaluate the risk factors for hip fractures alone, because in our previous studies, the number of hip fracture patients was small. In this study, we evaluated the association between potential risk factors and incident hip fractures in Japanese patients with RA.

Methods: IORRA is a prospective observational cohort study of Japanese RA patients at the Institute of Rheumatology, Tokyo Women's Medical University (Tokyo, Japan) that was begun in 2000. A total of 9,720 patients (82% female, mean age 56 years) with RA were enrolled in the IORRA cohort study from 2000 to 2010. Self-reported hip fractures were verified with patient medical records. Cox proportional hazards models with time-dependent covariates were used to analyze independent contributions of various risk factors to hip fracture incidence.

Results: During a mean (SD) follow-up of 5.2 (3.3) years, 152 patients (male 22, female 130) reported 152 hip fractures. Among these 152 patients, 107 hip fractures in 107 patients (male 16, female 91) were verified with medical records. Japanese version of the Health Assessment Questionnaire (J-HAQ) score (hazard ratio [HR], 2.35; 95% confidence interval [CI], 1.86–2.97; $P = 1.1 \times 10^{-12}$), age (per 10 years; HR, 1.60; 95% CI, 1.31–1.94; $P = 2.4 \times 10^{-6}$), history of total knee replacement (TKR) (HR, 3.25; 95% CI, 1.37–7.74; $P = 0.0076$), and body mass index (BMI) (HR, 0.93; 95% CI, 0.87–0.99; $P = 0.021$) were significantly associated with hip fractures (model (1) in Table). Among the scores on the 8 domains of the J-HAQ, HAQ (arising) (HR, 1.65; 95% CI, 1.29–2.11; $P = 7.0 \times 10^{-5}$) and HAQ (hygiene) (HR, 1.49; 95% CI, 1.11–2.00; $P = 0.0076$) were significantly correlated to incident hip fractures (model (2) in Table). While inconclusive, past fracture history appeared to be associated with hip fracture risk (model (1) and (2) in Table). We did not find significant associations of incident hip fractures with gender, smoking, RA duration, the Disease Activity Score in 28 joints, visual analog scale (VAS) for pain, VAS by physician, daily prednisone dose, weekly methotrexate dose, bisphosphonate use, active vitamin D_3 use, biologic use, folic acid use, or proton pump inhibitor use.

Hazard ratios (95% CI) for incident hip fractures: Cox regression models with stepwise selection.

Risk factor	Model (1)	Model (2)
J-HAQ score	2.35 (1.86–2.97)	N/A
J-HAQ score (arising)	N/A	1.65 (1.29–2.11)
J-HAQ score (hygiene)	N/A	1.49 (1.11–2.00)
Age, per 10 years	1.60 (1.31–1.94)	1.61 (1.33–1.96)
History of total knee replacement	3.25 (1.37–7.74)	2.86 (1.20–6.80)
Body mass index, kg/m^2	0.93 (0.87–0.99)	0.91 (0.86–0.97)
Past fracture history	1.51 (0.99–2.30)	1.49 (0.98–2.27)

CI, confidence interval; HAQ, health assessment questionnaire.

Conclusion: High HAQ disability score, old age, history of TKR, and low BMI appear to be associated with incident hip fractures in Japanese patients with RA. Among the 8 domains of the J-HAQ, disabilities of arising and hygiene appear to correlate to incident hip fractures in Japanese RA patients.

1630

The Impact of MKK6 and MKK3 on Physiological Bone Architecture and Postmenopausal Bone Loss. Jean-Paul David[1], Meghan Edgar[2], David L. Boyle[2], Georg Schett[3] and Gary S. Firestein[2]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]UCSD School of Medicine, La Jolla, CA, [3]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: The p38 MAP kinases are known regulator of bone homeostasis. In particular the alpha isoform of p38 (p38a) regulates bone formation by osteoblasts and bone resorption by osteoclasts. The two upstream activators of p38 MAP-kinases, namely MKK3 or MKK6, are interesting targets for bone disease. Recent studies showed that MKK6 deficiency protects from bone destruction in arthritis. We therefore analyzed the bone structure of mice deficient for MKK3 and MKK6 before and after ovariectomy.

Methods: Structural bone parameters, i.e. bone volume per tissue volume (BV/TV), trabecular number and thickness were MKK3 and MKK6 deficient mice were compared to wild type controls using micro-computed tomography analysis. Effect of estrogen withdrawal on the bone parameters of these mice were compared following ovariectomy (OVX) performed on 10 week old mice. All mice were sacrificed at 14 weeks of age. The efficiency of the surgery was confirmed by measuring the levels of circulating luteinising hormone (LH) in the sera of the mice.

Results: A significant increase in bone mass (BV/TV) (MKK3−/−: 61.3±9.8%; MKK6−/−: 87.6±7.3% increase compared to wild type) and trabecular number (MKK3−/−: 46.7±2.6%; MKK6−/−: 84.7±9.6% increase compared to wild type) were found in MKK3- and MKK6-deficient mice, the phenotype being more pronounced in the latter ($p<0.001$ for each). Ovariectomy was performed in order to determine the potential involvement of MKK3 and MKK6 in post-menopausal bone loss. A significant increase in the level of circulating LH was found in the sera of all ovariectomized mice confirming the success of the surgery. In all groups of mice, bone loss was found in the ovariectomized compared to the sham operated mice of the same genotype (MKK3−/−: 51.7±3.7%; MKK6−/−: 37.6±7.5%; wild type: 48.8±3.0% decreased bone mass). Due to the original increase in bone mass, the effect of ovariectomy was less pronounced in MKK6 deficient mice (MKK3−/−: 52.2±11.8%; MKK6−/−: 128.8±27.4% increased bone mass compared to ovariectomized wild type; $p<0.01$) showing a partial protection from bone loss.

Conclusion: MKK3 and MKK6 are negative regulators of bone homeostasis indicating that both kinases mediate the function of p38 MAP-kinases in bone. The pronounced increase in bone mass as well as the resulting partial protection against OVX-induced bone loss in MKK6-deficient mice suggest a more promising potential for pharmacological inhibitors of MKK6 in the treatment of bone loss.

1631

Denosumab Decreases Cortical Porosity in Postmenopausal Women with Low Bone Mineral Density. C. Libanati[1], S. K. Boyd[2], K. K. Nishiyama[2], R. M. Zebaze[3], D. A. Hanley[2], J. R. Zanchetta[4], Thierry Thomas[5], S. Boutroy[6], C. E. Bogado[4], M. Austin[1] and E. Seeman[7]. [1]Amgen Inc., Thousand Oaks, CA, [2]University of Calgary, Calgary, AB, [3]University of Melbourne, Melbourne, Australia, [4]Instituto de Investigaciones Metabólicas, Buenos Aires, Argentina, [5]INSERM U1059 and University Hospital, Saint-Etienne, France, [6]INSERM U831 and Université de Lyon, Lyon, France, [7]Austin and Repatriation Medical Centre, University of Melbourne, Melbourne, Australia

Background/Purpose: Intracortical remodeling, particularly in the cortex adjacent to the marrow cavity, is responsible for most of the bone lost during advancing age.[1,2] Indeed, patients who suffer a hip fracture have large coalescent pores that precipitously compromise bone strength as porosity increases.[3] Denosumab reduces bone remodeling and ovariectomy-induced intracortical porosity in subhuman primates. In postmenopausal women, denosumab rapidly reduces bone remodeling intensity and increases cortical density.[4–6] We propose that this increase in cortical density is the result of (i) partial reversal of intracortical porosity that is present prior to treatment, (ii) reduction in the appearance of new pores by suppression of remodeling, and (iii) more complete secondary mineralization of osteons (which would be

removed had remodeling continued at the same intensity). We now present evidence to support several of these mechanisms.

Methods: Postmenopausal women (N=247) aged 61 ± 5 years with low bone mineral density were randomized in a double-blind, double-dummy fashion to denosumab 60 mg every 6 months (N=83), alendronate 70 mg weekly (N=82), or placebo (N=82). Porosity was evaluated in the compact-appearing cortex of the distal radius at baseline and month 12 from HRpQCT scans using an enhanced method that accurately[7] and reproducibly[8] identifies the cortex with automatic threshold segmentation.[9] Pores above ~82 μm were quantifiable; porosity was expressed as a percent of the total cortical volume.

Results: Baseline cortical porosity at the distal radius was 2.6%. Over 12 months, cortical porosity (mean [95% CI]) increased with placebo (5.19% [1.41, 8.98]) and alendronate (2.86% [–2.32, 8.04]) but decreased with denosumab (–2.98% [–6.39, 0.43]) (Figure). Denosumab reduced cortical porosity by 8.18% ($P < 0.01$) compared with placebo and by 5.84% ($P = 0.06$) compared with alendronate.

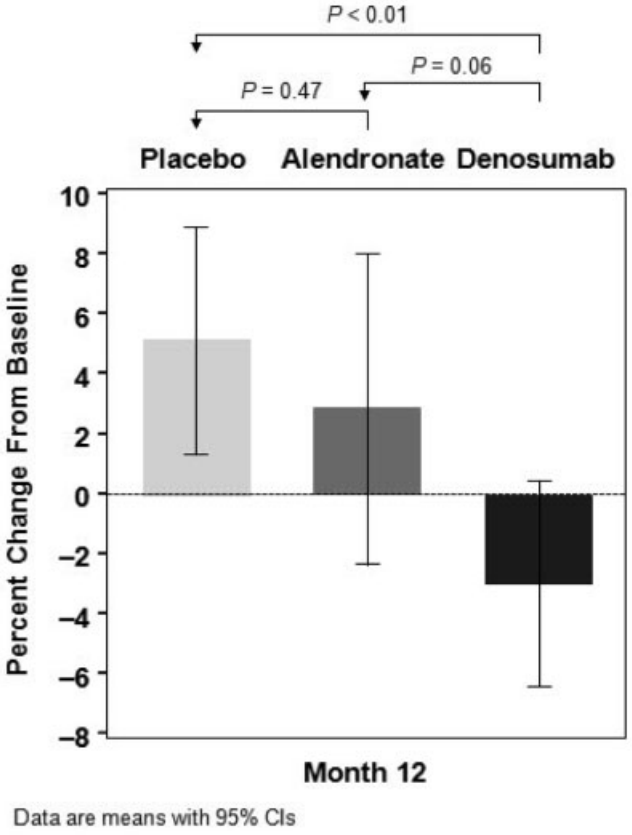

Figure. Denosumab Decreases Cortical Porosity at the Distal Radius in Postmenopausal Women With Low Bone Mineral Density

Conclusion: In summary, denosumab prevented the progression of porosity seen with placebo, an effect that differs from that of alendronate. The changes in porosity are likely to partly reverse bone fragility and prevent its progression and thus reduce fracture risk. Ongoing work exploring non-threshold methods and assessing porosity over the entire cortex, including the trabecularized cortex is underway and may improve quantification of bone morphology and differences between therapies.

References:
[1]Zebaze, *Lancet* 2010; [2]Holzer, *JBMR* 2009, [3]Bell, *Bone* 2000; [4]Seeman, *JBMR* 2010; [5]Genant, *Bone* 2010; [6]Baron, *Bone* 2011; [7]Nishiyama, *JBMR* 2010; [8]Burghardt, *Bone* 2010; [9]Buie, *Bone* 2007

1632

Fracture Risk Is Increased in Young Women with Rheumatoid Arthritis. Shreyasee Amin, Sherine E. Gabriel, Sara J. Achenbach, Elizabeth J. Atkinson and L. Joseph Melton III. Mayo Clinic, Rochester, MN

Background/Purpose: Rheumatoid arthritis [RA] is the only cause of secondary osteoporosis singled out in the WHO's fracture [fx] prediction algorithm, FRAX®. Nevertheless, the risk for fx among younger women and men with RA is not well established. We examined the risk for fx by sex and by age at diagnosis in a population-based RA cohort.

Methods: We studied a population-based inception cohort of women and men with RA (age ≥18 yrs) who fulfilled 1987 ACR criteria for RA between 1955–2007 and an equal number of age- and sex-matched controls from the same underlying population, who were followed until death, migration or the present. All incident fxs were identified through a complete review (inpatient and outpatient) of medical records. Excluding fxs resulting from severe trauma, the risk for first osteoporotic fx [OP fx] (hip, spine, wrist and proximal humerus), and for any first fx following their RA diagnosis was compared with their matched control, stratified by sex, using a Cox proportional hazards model, where follow-up time (until death or last follow-up) ended at the first date reached by either within a pair. We then stratified by age at RA diagnosis (<50 yrs, ≥50 yrs). For those <50 yrs with RA, we examined their risk for fx over all available follow-up as well as until age 50 yrs.

Results: In 1155 RA cases, (810 women and 345 men, mean age at RA diagnosis ± SD: 56 ± 16 yrs and 58 ± 14 yrs, respectively), followed for 12,585 person-yrs [p-y], 205 women, (25%, 23 per 1000 p-y), and 67 men, (19%, 19 per 1000 p-y), had an OP fx, while 276 women, (34%, 31 per 1000 p-y), and 87 men, (25%, 24 per 1000 p-y), had any fx. Women and men with RA were at increased risk for fx relative to controls, regardless of age stratification at diagnosis, although did not reach statistical significance in men when stratified by age (see table). When follow-up was limited to age 50 yrs in the 304 women <50 yrs with RA (mean age at RA diagnosis: 39 yrs), the hazard ratio [HR] for OP fx was 6.7 (95% CI:1.5, 29.5), with 13 women having at least one OP fx (7 per 1000 p-y) vs. 2 (1 per 1000 p-y) in matched controls; the HR for any fx was 1.9 (95% CI: 1.04, 3.4), with 31 women with RA having at least one fx (16 per 1000 p-y) vs. 17 (9 per 1000 p-y) in matched controls. In men <50 yrs with RA (N=109, mean age: 41 yrs), too few had a fx before age 50 yrs (N=2 with OP fx; N=5 for any fx) for robust conclusions on fx risk relative to controls.

	Hazard Ratio (95% CI) by Age at RA Diagnosis		
Women	**All**	**<50 yrs**	**≥50 yrs**
OP Fx*	1.7 (1.4, 2.2)	4.3 (2.4, 7.8)	1.4 (1.1, 1.8)
Any Fx*	1.6 (1.3, 1.9)	2.4 (1.6, 3.5)	1.4 (1.1, 1.7)
Men			
OP Fx*	1.6 (1.1, 2.4)	1.4 (0.7, 3.0)	1.8 (1.1, 2.8)
Any Fx*	1.4 (1.02, 1.9)	1.7 (0.9, 3.2)	1.4 (0.9, 2.0)

*excludes any severe trauma fx

Conclusion: Men <50 yrs with RA appear to be at increased risk for future fx, but few fxs occurred before age 50 yrs. Women <50 yrs with RA are not only at high risk for future fx, but their fx risk is increased even before they reach age 50 yrs. Fx prevention strategies for young women with RA are thus important to consider.

1633

Incident Vertebral Fractures (VF) 12 Months After Glucocorticoid (GC) Initiation in Children with Rheumatic Disorders (RD). Bianca A. Lang[1], Celia Rodd[2], David A. Cabral[3], Peter B. Dent[4], Janet E. Ellsworth[5], Adam M. Huber[1], Kristin M. Houghton[3], Roman Jurencak[6], Maggie Larché[4], Claire MA LeBlanc[5], Brian Lentle[3], MaryAnn Matzinger[6], Paivi M. Miettunen[7], Kiem Oen[8], Johannes Roth[6], Claire Saint-Cyr[9], Rosie Scuccimarri[2], Nazih Shenouda[6], Leanne M. Ward[6] and the Canadian STOPP Consortium[10]. [1]Dalhousie University, Halifax, NS, [2]McGill University, Montréal, QC, [3]University of British Columbia, Vancouver, BC, [4]McMaster University, Hamilton, ON, [5]University of Alberta, Edmonton, AB, [6]University of Ottawa, Ottawa, ON, [7]University of Calgary, Calgary, AB, [8]University of Manitoba, Winnipeg, MB, [9]Université de Montréal, Montreal, QC, [10]National Pediatric Bone Health Working Group

Background/Purpose: Compromised bone health is recognized as an important source of morbidity in children with RD. The aims of this study were to determine the frequency of incident vertebral fractures (VF) 12 months after starting GC treatment in a prospectively-followed cohort of children with RD, characterize these VF and examine risk factors for their development.

Methods: Children initiating GC for treatment of RD between January 2005 and December 2007 in ten participating Canadian tertiary pediatric

centers were enrolled in the Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) study. Enrolled patients had baseline (within 30 days of GC initiation) and six monthly BMD studies, as well as x-rays of the thoracolumbar spine at baseline and at 12 months which were evaluated using the Genant semi quantitative method. An incident VF was defined as a new VF or worsening of an existing VF. Patients also had baseline and 3 monthly assessment of medications, including cumulative GC dose, and clinical status including disease activity (10 cm visual analog scale), physical activity (HAES questionnaire), presence of back pain, and vitamin D/calcium intake. Clinical features, including cumulative GC dose, back pain, disease and physical activity, calcium and vitamin D intake, and spine aBMD Z-scores were analyzed for association with incident VF.

Results: Of 136 patients enrolled, data were available on 118 (64% female, median age 10.8 y) at 12 months. Diagnoses included juvenile dermatomyositis (JDM) (23%), juvenile idiopathic arthritis (JIA) (36 %), systemic lupus erythematosus (SLE) and related conditions (18%), systemic vasculitis (14%), and other (9%). At 12 months, 7 patients (6%, 95% CI 2–11%) had 12 incident VF (3 SLE, 2 JDM, 1 vasculitis, 1 mixed connective tissue disease). All incident VF were new fractures; 5 patients had a single VF, one had 2 VF and one had 5 VF. Nine (75%) of the incident VF were thoracic and 11 (92%) had wedge morphology. One child was excluded from the natural history of bone health analyses after 4 months because she received osteoporosis treatment for symptomatic VF. Patients with and without incident VF did not differ with respect to age, gender, pubertal status, disease activity, physical activity, vitamin D/calcium intake or presence of back pain. Children with incident VF received on average 50% more GC than those without ($p=0.030$), had a greater increase in BMI at 6 months ($p=0.010$), and had greater decrements in spine aBMD Z-scores in the first 6 months ($p=0.048$). Four of 6 children (67%) with incident VF and natural history data to 12 months had spine aBMD Z-scores less than −2.0 at 12 months compared to 16% of children without VF ($p=0.011$).

Conclusion: Children with rheumatic diseases exhibited an incident VF rate of 6% at 12 months following GC-initiation. Children with incident VF received more GC, had greater increases in BMI and greater declines in spine aBMD Z-scores in the first 6 months of GC treatment.

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1634

Does Identification of Prevalent Vertebral Fracture on Densitometric Vertebral Fracture Assessment (VFA) in Clinical Practice Influence Physician Prescribing Behavior? John T. Schousboe. Park Nicollet Health Services, Minneapolis, MN

Background/Purpose: Densitometric vertebral fracture assessment (VFA) improves estimation of subsequent vertebral fracture risk, and the presence of a vertebral fracture on a lateral spine image is widely considered to be an indication for pharmacologic fracture prevention therapy. Previous studies have shown that selected use of VFA in those having bone densitometry does identify significant numbers of individuals with previously unknown vertebral fracture who otherwise would not be considered candidates for pharmacologic fracture prevention therapy. No prior study has examined whether or not physician prescribing behavior is actually influenced by use of or results of VFA. We hypothesized that in those who do not have osteoporosis by BMD criteria, that performance amd results of VFA will be associated with new prescriptions for pharmacologic fracture medication.

Methods: All individuals who had a VFA with a bone density test between 7/1 2005 and 6/31/2010 were identified from billing records of a large multispeciality clinic. Among the subset of osteopenic individuals (worst T-score between −1.5 and −2.49), we did a nested case control analysis to estimate the association between results of the VFA and commencement of pharmacologic fracture prevention therapy within 90 days of the date of the test. All 108 treatment naïve individuals who were started on therapy to prevent fractures were selected as cases, and 142 who remained off of drug therapy were selecgted as controls. A manual medical record review of the VFA report was done by a person blinded to changes in the person's medications to assess whether or not a possible or definite vertebral fracture was diagnosed. Logistic regression models were done to estimate the association of prevalent vertebral fracture identified on VFA and subsequent commencement of drug therapy to prevent fractures.

Results: Among 9,250 patients with osteopenia, 3,223 treatment naive patients with T-score >-1.5 and ≤ −2.5 also had a VFA at the time of their DXA. Within the nested case control cohort, the associations of predictors with start of drug therapy to prevent fractures were as follows:

Predictor	Odds Ratio (95% C.I.)
Age Category: <65 (reference) 65-74 75+	 1.0 0.31 (0.15 – 0.64) 0.50 (0.24 – 1.07)
Sex (reference is female)	2.65 (1.12 – 6.26)
Prior Fracture	0.80 (0.42- 1.53)
Current Use of Glucocorticoid Rx	1.55 (0.57 – 4.24)
VFA negative (reference) Possible Vertebral Fracture Definite Vertebral Fracture	1.00 2.89 (1.18 – 7.05) 2.08 (0.98 – 4.41)

Of an estimated 158 patients in the entire cohort of 3223 who had a prevalent vertebral fracture, only 24 (14.3%) were started on drug therapy to prevent fractures.

Conclusion: Diagnosis of a possible or definite prevalent vertebral fracture at the time of a bone density test among those without osteoporosis is associated with subsequent prescription of drug therapy to prevent fractures, but the majority of those with a prevalent vertebral fracture but without osteoporosis by BMD criteria are not being treated.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Animal Models II
Monday, November 7, 2011, 2:30 PM–4:00 PM

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Impaired Lymphatic Vessel Maturation in Mice with TNF-Induced Inflammatory Arthritis. Qianqian Liang[1], Ronald Wood[2], Brendan Boyce[1], Edward M. Schwarz[1] and Lianping Xing[1]. [1]University of Rochester, Rochester, NY, [2]University of Rochester School of Medicine and Dentistry, Rochester, NY

Background/Purpose: Lymphangiogenesis occurs in response to joint inflammation, limiting the severity of synovitis. Arthritis overwhelms this process, but the mechanism is unknown. Lymphatic vasculature is composed of primary capillaries and mature vessels, which have different morphology, structural composition, and functions. Lymphatic capillaries are composed of LYVE-1+ endothelial cells, while mature lymphatic vessel endothelial cells are LYVE-1-, covered by smooth muscle actin+ cells, and contain valves for the uni-directional lymph flow. Thus, proper lymphatic vessel maturation is essential for efficient lymph drainage. The effects of joint information on lymphatic vessel maturation have not been studied. We hypothesize that lymphatic vessels in arthritic joints are abnormal, resulting in insufficient lymphatic drainage to local lymph nodes, which aggravates chronic synovitis. We tested this hypothesis using a combination of functional, morphologic, and biochemical approaches in TNF-Tg mice that develop chronic inflammatory arthritis.

Methods: TNF-Tg mice (1, 2.5 and 5-m-old, N=4–10 mice/genotype) and WT littermates were used. Lymphatic draining function from the footpad to popliteal lymph nodes (PLN) were assessed by near-infrared (NIR) indocyanine green (ICG) lymphatic imaging. Lymphatic capillaries (LYVE-1+), mature lymphatic vessels (SMA+/CD31+), and lymphatic valves (Intergrin-9+) in ankle tissues were identified using whole mount immunostaining. Expression of *angiopoietin 1 and 2*, and *forkhead box protein C2*, genes that are known to regulate lymphatic vessel maturation and valve formation were examined by real time qPCR.

Results: NIR-ICG imaging showed no difference in lymphatic draining function between pre-arthritic 1-month-old TNF-Tg and WT mice. However, a clear defect in lymphatic drainage was observed in 2.5-month-old TNF-Tg mice with severe ankle arthritis. The time to initial ICG detection in lymphatic vessels following footpad injection (T-initial) was significantly longer in TNF-Tg mice (13±5 vs 8±2 min in WT; $p<0.05$). The ICG clearance from the footpad was significantly decreased (%clearance: 64±12 vs 92±5

p<0.05) in TNF-Tg vs WT mice. ICG leakage from the lymphatic vessels was observed in 7 of 9 legs of TNF-Tg mice >5-month old, but not in WT mice. Whole mount immuno-staining revealed altered lymphatic vasculature in the foot of TNF-Tg mice: increased diameter of LYVE-1+ lymphatic capillaries (48±5 vs 37±4 μm p<0.05) and decreased smooth muscle actin+ cell coverage of mature lymphatic vessels (65±2 vs 86±1% p<0.05) vs WT. No differences in structure of lymphatic valves between TNF-Tg and WT mice were observed. Real-time qPCR demonstrated a 6-fold reduction in *angiopoietin 2* expression in foot skin of TNF-Tg vs WT mice, while changes in *angiopoietin 1* were reduced 2-fold.

Conclusion: Ankle inflammation in TNF-Tg mice inhibits lymphatic vessel maturation, resulting in decreased smooth muscle actin+ cell coverage and leakage, thereby reduced draining function. Identification of factors and mechanisms that regulate lymphatic vessel maturation in inflammation may lead to a new lymphatic-based therapy for chronic inflammatory arthritis.

1636

A Distinct Tolerogenic Subset, Splenic IDO+CD11b+Dcs From Orally Tolerized Mice Suppresses Collagen-Induced Arthritis. Min Jung Park[1], Kyung-Su Park[1], Mi-La Cho[1], Ji-Min Kim[2], Sang Heon Lee[3] and Ho Youn Kim[4]. [1]The Catholic University of Korea, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea, [3]Division of Rheumatology, Seoul, South Korea, [4]Rhematism Research Center, Seoul, South Korea

Background/Purpose: To define the systemic immunoregulatory effect of dendritic cells (DCs) expressing Indoleamine 2,3-dioxygenase (IDO), we examined the characteristics of splenic DCs after induction of oral tolerance in collagen-induced arthritis (CIA) mice.

Methods: Oral tolerance was induced by feeding bovine CII 6 times, beginning 2 weeks before the first immunization to induce CIA. Splenic cells, DCs and Tregs purified by magnetic-activated cell sorting (MACS) were analyzed by FACS. IDO activity was measured by enzyme assay, and its expression was assessed by 1-methyl tryptophan (1-MT) treatment. CD11b+DC and IDO expression on splenic tissues were examined by a confocal microscopy.

Results: CD11b+ subset of the splenic DCs was a major contributor to IDO expression in tolerized CIA group. The IDO+DCs which express low level of CD80 were strongly induced after stimulation with CII antigen. The IDO+CD11b+DCs effectively induced the differentiation of Tregs, along with increased expression of CTLA-4 and programmed death 1 (PD-1), in the presence of CII antigen. When adoptively transferred into untolerized CIA mice, tolerized CD11b+DCs suppressed the development of arthritis. The suppression was correlated with the increase in IDO expression and Treg/Th17 ratio, and with the decrease in serum levels of IL-1b, IL-6, IL-21 and TNF-a.

Conclusion: A distinct splenic subset, IDO+CD11b+DC was induced after induction of oral tolerance and exerted tolerogenic effect in the systemic immune regulation.

1637

Collagen Triple Helix Repeat Containing 1 Protein Is a New Synovial Lining Biomarker Overexpressed in Antibody-Mediated Arthritis. Mohammed Talha Shekhani[1], Toni S. Forde[1], Anne S. Cuttler[2], Volkhard Lindner[2] and Vyacheslav A. Adarichev[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Maine Medical Center Research Institute, Scarborough, ME

Background/Purpose: Hypertrophy of the synovial membrane accompanied by enhanced cell invasiveness and boosted production of cartilage and bone degrading enzymes are a hallmark of rheumatoid arthritis (RA). To find new synovial biomarkers whose expression is affected by sex, and to dissect mechanisms of higher female preponderance in RA, we generated congenic murine strain carrying sex-affected arthritis-protective locus Pgia8a.

Methods: To induce arthritis, mice were injected i.p. with cocktail of mAbs to collagen type II followed by LPS stimulation. Differential gene expression analysis of RNA isolated from arthritic paws was performed using Affymetrix GeneChip® Mouse Gene 1.0 ST Array. Collagen Triple Helix Repeat Containing 1 (Cthrc1) transgenic mice FVB-Tg[Cthrc1] were crossed to BALB/c strain to generate mice carrying the discovered sex-affected differentially-expressed Cthrc1 gene in inflammatory-susceptible genetic background. Immunohistochemical staining was performed to identify Cthrc1 in synovial joints and investigate whether the protein expression co-localizes with fibroblast-like and macrophage-like synoviocyte markers.

Results: Using transcriptome analysis, we found that arthritis severity in congenic males is under the control of Cthrc1, Adamts12 and C1qtnf3 locus-specific genes whose expression was tightly correlated with inflammation, r>0.87. Genetic association between Cthrc1 and arthritis was replicated in F1(BALB/c x FVB-Tg[Cthrc1]) mice that showed 30% stronger inflammation than Tg-negative F1 hybrids. Even naïve Tg[Cthrc1] mice exhibited pre-inflammatory phenotype of neutrophilia (30% up, p<0.014) accompanied with peripheral monocytopenia (50% down, p<0.025) and longer blood coagulation time. Immunohistochemical staining of sections of articular joints confirmed a highly inducible pattern of Cthrc1 protein expression, which we observed initially at RNA level using RT-PCR. Importantly, Cthrc1 was localized in synovial lining of arthritic mice, and protein expression was co-localized with pannus development. In synovium of naïve mice, Cthrc1 was almost undetectable. In transgenic mice, protein was expressed in synovial lining even in naïve mice, which might partially explain a stronger arthritis in F1-Tg[Cthrc1] mice when compared to Tg-negative F1 hybrids. Co-localization of Cthrc1 with fibroblast, macrophage and T cell markers is in progress.

Conclusion: Secreted promigratory protein Cthrc1 is a novel biomarker for inflammatory arthritis and hypertrophic synovial lining. When Cthrc1 protein is overexpressed in transgenic mice, it affects multiple systems including blood cell composition, and both normal and inflamed synovium.

1638

Intra-Articular Injection of the Selective IκB Kinase β Inhibitor NEMO-Binding Peptide Ameliorates Collagen Induced Arthritis by Inducing Regulatory T Cells and Alternatively Activated Macrophages. Soyoun Min[1], Mei Yan[1], Yong Du[1], Cristina Arriens[1], Tianfu Wu[1] and Chandra Mohan[2]. [1]University of Texas, Southwestern Medical Center at Dallas, Dallas, TX, [2]University of Texas Southwestern Medical Center, Dallas, TX

Background/Purpose: Nuclear factor (NF)-kB is a transcription factor that is critical in the pathogenesis of various autoimmune disorders including rheumatoid arthritis (RA). To examine whether local NF-κB inhibition had efficacy in reducing inflammation in collagen induced arthritis (CIA) without systemic immune suppression, we tested intra-articular delivery of an IKK inhibitor, NEMO-binding domain peptide (NBP).

Methods: NBD peptides were injected intra-articularly into the knee joint of DBA1 mice (N = 6) (150ug/joint) at the onset of disease, while the control mice were administered a scrambled peptide. The severity of arthritis was determined by visual examination of the paws, and the mice were sacrificed 6 weeks after the first immunization. Joint specimens were examined for pathology. Serum levels of anti-collagen antibodies and cytokine production were measured by ELISA. The induction of regulatory T cells and macrophage were assessed by flow cytometry analysis and immunofluorescence staining.

Results: Intra-articular NBD injection ameliorated the severity of arthritis scores (9.0 ± 1.1 vs 5.5 ± 0.7 U, P < 0.01) and reduced bone destruction on histological analysis, compared to vehicle injected mice. The serum concentrations of type-II collagen-specific IgG2a antibodies were significantly lower in NBD-treated mice compared to vehicle-treated mice (0.379 ± 0.05 vs 0.125 ± 0.01 OD units, P < 0.05), whereas the levels of type-II-collagen-specific IgG1 antibodies were mildly increased by NBD treatment. NBD treatment also diminished serum pro-inflammatory cytokines including IFN-g and IL-17 while the regulatory cytokine IL-10 was increased in sera. NBD-treated CIA mice had significantly higher percentages and numbers of $CD4^+CD25^+$ cells in dLN compared to the control (4.1 % ± 0.3 vs 0.41 % ± 0.1, P < 0.01). Furthermore, $CD4^+$ cells from dLN of NBD-treated CIA mice expressed higher levels of Foxp3than those isolated from dLN of control CIA mice. Immunohistochemical analysis of NBD treated mice revealed that Foxp-3 and Ym-1 (a marker of alternatively activated macrophages) were present and adjacent to each other within dLNs, compared to control CIA-subjected mice.

Conclusion: These results indicate that IKK-β-targeted NF-κB blockade using the NBD peptide appears efficacious as a local intra-articular therapy for arthritis, potentially reducing unwanted systemic effects. Together these data demonstrate that NF-kB inhibition promote induction of $CD4^+CD25^+$ T reg cells and alternatively activated macrophages, which together may confer therapeutic benefit in inflammatory arthritis.

1639

Inflammatory Arthritis in Mice Is Dependent on the Mast Cell-Restricted Signaling Protein Ras Guanine Nucleotide Exchange Protein 4 (RasGRP4). Richard Stevens[1], Roberto Adachi[2], Peter A. Nigrovic[3], Matthew J. Hamilton[3] and Steven Krilis[4]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]University of Texas M. D. Anderson Cancer Center, Houston, TX, [3]Brigham and Women's Hospital, Boston, MA, [4]St George Hospital, Kogarah NSW, Australia

Background/Purpose: Ras guanine nucleotide exchange protein-4 (RasGRP4) is a calcium-regulated, guanine nucleotide exchange factor and diacylglycerol/phorbol ester receptor that is expressed in human, rat, and mouse mast cells (MCs), and their circulating progenitors. Although the other three members of this family of intracellular signaling proteins participate in the development of T cells, B cells, and platelets, the importance of RasGRP4 in the development and function of MCs has not been elucidated. We created a transgenic RasGRP4-null C57BL/6 mouse to deduce the possible role(s) of this evolutionarily conserved signaling protein in MC-dependent inflammatory diseases.

Methods: A targeting construct was prepared in which the Cre gene was placed at the translation-initiation site of the 17-exon, 19-kb mRasGRP4 gene. To ensure that no functional RasGRP4 protein could be expressed in the resulting transgenic mice, the first 8 exons of the gene were deleted, including those nucleotides that encode the protein's guanine nucleotide exchange domain. Using homologous recombination methods and C57BL/6 mouse embryonic stem cells, a RasGRP4-null mouse was obtained which was then backcrossed 10 times with wild-type (WT) C57BL/6 mice to eliminate possible nonspecific mutations created during the homologous recombination step. The resulting transgenic mouse line was characterized and then subjected to inflammatory arthritis induced by K/BxN mouse serum.

Results: RasGRP4-null C57BL/6 mice were healthy and contained normal numbers of granulated MCs in their tissues that histochemically resembled those in WT C57BL/6 mice. Thus, RasGRP4 is not essential for the Kit-dependent development of tissue MCs. Immature MCs (mBMMCs) could be generated from RasGRP4-null mice by culturing their bone marrow cells for 4–6 weeks in IL-3 enriched conditioned media in the presence or absence of Kit ligand. Nevertheless, microarray analysis of IL-3-developed mBMMCs revealed altered expression of numerous transcripts compared with WT mBMMCs. Exposure of IL-3-developed RasGRP4-null mBMMCs to calcium ionophore resulted in the release of the cell's preformed mediator β-hexosaminidase and increased expression of tumor necrosis factor-α and other cytokines and chemokines, as occurs in calcium ionophore-treated WT mBMMCs. Although the latter data revealed that signaling pathways downstream of RasGRP4 are intact and functional in MCs, arthritis was reduced >90% in RasGRP4-null mice that had received K/BxN mouse serum relative to similarly-treated WT mice. In support of these inflammatory arthritis data, MC-dependent colitis also was reduced in RasGRP4-null mice.

Conclusion: The exciting finding that RasGRP4 is essential in inflammatory arthritis in mice suggests that the pharmaceutical inactivation of this signaling protein might be of efficacy in the treatment of patients with inflammatory arthritis and other MC-dependent disorders.

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The CYLD/IKKbeta Axis Functions in Synovial Fibroblasts to Regulate TNF-Driven Arthritis. Maria Armaka[1], Manolis Pasparakis[2], George Mosialos[3] and George Kollias[1]. [1]Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece, [2]Institute for Genetics, Centre for Molecular Medicine, University of Cologne, Cologne, Germany, [3]School of Biology, Aristotle University of Thessaloniki, Thessaloniki, Greece and Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece

Background/Purpose: Synovial fibroblasts (SFs) are major cellular players in rheumatoid arthritis. We have shown previously in the human TNF transgenic (TghuTNF, Tg197) model of inflammatory polyarthritis that SF targeting by TNF is sufficient for the orchestration of the complete pathogenic process. Here, we have sought to identify SF-specific TNF-driven signaling pathways with physiological roles in the arthritogenic process. The deubiquitinating enzyme (DUB) CYLD is a tumor suppressor protein known for its role in repression of NF-kB and MAPK activation. The aim of this study was to assess the role of SF-specific ablation of the DUB CYLD and/or the NF-kappaB-related kinase, IKKbeta, in the development of arthritis in the TghuTNF model.

Methods: ColVI-Cre mice providing floxed-allele recombination specificity for SFs were crossbred into the TghuTNF, CYLD and/or IKKbeta conditional knock-out backgrounds. Histological analysis of synovial inflammation, as well as cartilage and bone destruction was performed in week 4, 8 and 14. SF cultures were generated in order to study the TNF-mediated responses of gene-deficient SFs by RT-PCR, western blot and FACS analysis.

Results: TNF stimulation of CYLD-deficient SFs revealed that CYLD negatively regulates NF-kappaB whereas it does not affect MAPK responses of SFs. As a consequence, the expression profile of arthritis-related NF-kappaB-regulated genes was affected. Notably, the TghuTNF ColVI-Cre CYLD$^{f/f}$ mice show exacerbations of the arthritic phenotype over controls as early as 4weeks of age with profound synovial inflammation and cartilage degradation. Significant exacerbations over controls were also evident at the age of 8 weeks with intense TRAP activity in the joint area and complete loss of joint architecture. SFs from these mice showed a stronger activation phenotype exhibiting upregulation of VCAM-1, ICAM-1, high gelatinase activity and deregulated inflammatory gene expression compared to their non-Cre littermate controls. Furthermore, we show that TghuTNF ColVI-Cre IKKbeta$^{f/f}$ mice exhibit attenuated arthritic manifestations and that concomitant loss of both CYLD and IKKbeta expression in SFs from TghuTNF mice also results in the amelioration of the arthritic phenotype.

Conclusion: Our results demonstrate a physiologically significant role of the CYLD/IKKbeta pathway in modeled arthritis by showing that in TghuTNF mice the CYLD/IKKbeta axis regulates SF–specific arthritogenic responses downstream of TNF.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Existing Biologics

Monday, November 7, 2011, 2:30 PM–4:00 PM

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Low Serum IgG Level After Rituximab Is Associated with An Increased Risk of Serious Infections in Rheumatoid Arthritis: Data of the AIR Registry. Jacques-Eric Gottenberg[1], Philippe Ravaud[2], Thomas Bardin[3], Patrice Cacoub[4], Alain G. Cantagrel[5], Bernard G. Combe[6], Maxime Dougados[7], Rene-Marc Flipo[8], Bertrand Godeau[9], Loic Guillevin[10], Xavier X. Le Loet[11], Eric Hachulla[12], Thierry Schaeverbeke[13], Jean Sibilia[14], Isabelle Pane[15], Adelina Abbe[15], Gabriel Baron[16] and Xavier Mariette[17]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Hotel Dieu University hospital, France, [3]Service de Rhumatologie. Centre Viggo Petersen. Hôpital Lariboisiere, Paris, France, [4]CHU Pitié-Salpêtrière, Paris, France, [5]Hopital Purpan, Toulouse CEDEX 9, France, [6]Hopital Lapeyronie, Montpellier, France, [7]Paris-Descartes University, Cochin Hospital, Paris, France, [8]Hopital R Salengro CHRU, Lille CEDEX, France, [9]Service de médecine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, Creteil, France, [10]Cochin University Hospital, Paris, France, [11]CHU de ROUEN, Rouen CEDEX, France, [12]Internal Medicine, Lille CEDEX, France, [13]Pellegrin Hospital, Bordeaux, France, [14]Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, Strasbourg, France, [15]France, [16]Epidemiology, Paris, France, [17]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: Rituximab (RTX) might result in decreased serum immunoglobulin levels, in a proportion of patients with rheumatoid arthritis (RA) increasing with the number of RTX cycles. Very limited real life data are available regarding the risk of serious infections in patients who develop hypogammaglobulinemia after RTX. The present study aimed to investigate the association between low gammaglobulin levels after RTX and the occurrence of serious infections.

Methods: The 5-year prospective and multicenter AIR registry has been set up by the French Society of Rheumatology in 2006. Serious adverse events, including serious infections (which require either hospitalization or intravenous antibiotics) are validated by two investigators using chart copies.

Results: Among the 2000 patients with RA included in the AIR registry, gammaglobulin, IgM or IgG after RTX levels were collected in 1146 (57.3%), 1148 (57.4%) and 1150 (57.5%) patients, respectively. Low levels after RTX (gammaglobulins <6g/l, IgM<0.5g/l, or IgG<6g/l) were observed in 178 (15.5%), 306 (26.6%), and 139 (12.1%) patients. Serious infections occurred in 24 patients (13.5%) with a low gammaglobulin level after RTX and in 85 (8.8%) patients with a normal gammaglobulin level, resulting in 6.3 vs 4.6 serious infections/100 patient/years (4.9 serious infections/100 patient/years in the whole population who had a gammaglobulin assessment after RTX). Serious infections occurred in 36 (11.8%) patients with a low IgM level and in 68 (8.1%) patients with a normal IgM level, resulting in 5.5 vs 4.3 serious infections/100 patient/years (4.7 in all patients

with IgM assessment after RTX). Serious infections occurred in 21 patients (15.1%) with a low IgG level and in 83 (8.2%) patients with a normal IgG level, resulting in 10.0 vs 3.8 serious infections/100 patient/years (6.2 serious infections/100 patient/years in all patients with IgG assessment after RTX). In univariate analysis adjusted on follow-up duration, only low IgG after RTX was associated with an increased risk of serious infections(OR 1.99 95% CI [1.2–3.3], P= 0.008), but not low gammaglobulin (OR 1.5 95% CI [0.9–2.5], P= 0.09) or low IgM level (OR 1.5 95% CI [0.9–2.3], P= 0.08). Preliminary results showed that hypoIgG after RTX was associated with an older age, history of cancer or of serious or recurrent infections. In multivariate analysis taking into account these latter parameters, low IgG after RTX remained associated with the risk of serious infections.

Conclusion: Converse to low gammaglobulin or low IgM level, low IgG after RTX is associated with a significant increase in the risk of serious infections in common practice. This had not been reported in long term extension phases of controlled trials, maybe due to the limited comorbidities of patients included. These results confirm that serum IgG level should be checked after RTX and the benefice/risk balance of retreatment with RTX discussed for each patient with low IgG level after RTX.

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Risk Factors for Major Adverse Cardiovascular Events in Rheumatoid Arthritis Patients Treated with Tocilizumab. Vijay Rao[1], Andrey Pavlov[2], Micki Klearman[1], David Musselman[3], Jon T. Giles[4], Joan M. Bathon[4], Naveed Sattar[5] and Janet S. Lee[3]. [1]Genentech, San Francisco, CA, [2]Everest, Toronto, [3]Roche, Nutley, NJ, [4]Columbia University Medical Center, New York, NY, [5]University of Glasgow, Glasgow, United Kingdom

Background/Purpose: To examine the associations of lipids, inflammation, and rheumatoid arthritis (RA) disease activity measures with risk for cardiovascular events in moderate to severe RA patients treated with tocilizumab (TCZ).

Methods: Post-hoc analyses of the combined data from 5 pivotal TCZ phase-III trials and long-term extension periods were conducted in a stepwise fashion. First, demographic, laboratory, and disease characteristics were compared for patients with (n = 42) and without (n = 3944) major adverse cardiovascular events (MACE: non-fatal myocardial infarction, non-fatal stroke, or death due to cardiovascular cause) determined by independent, blinded adjudication. Univariate Cox proportional hazard modeling was performed to evaluate potential risk factors for MACE at baseline (BL) and post-BL (wk 24) with time to MACE as the time variable. Multivariate Cox proportional hazard models were also fit to obtain best prediction of time to MACE. Statistically significant predictors were considered as those with $P<0.05$.

Results: For all MACE events occurring during TCZ exposure including open-label extension treatment, univariate modeling revealed BL age, history of coronary artery disease (CAD), disease activity (DAS28), total cholesterol/HDL ratio, and albumin as predictive characteristics (P<.05), but only age and history of CAD consistently remained predictive in a series of multivariate sensitivity analyses. Neither reductions in measurements of inflammation (CRP and ESR), nor increases in lipid parameters at 24 wks were associated with MACE on TCZ therapy. Additional Cox models employing single predictors and adjusting for BL age revealed that the following wk 24 outcomes were statistically significant predictors of future MACE: DAS28 based scores (DAS28, AUC of DAS28, EULAR response), TJC, SJC, and Patient Global Assessment (Table). Additionally, greater reductions in DAS28 score from BL to wk 24 were inversely associated with MACE, after adjusting for age and BL DAS28 score (Table).

Univariate Associations Between RA Parameters and MACE, Adjusted for Age at Baseline

Disease Activity Assessments at Week 24	Age-adjusted Hazard Ratio (95% CI)	P Value
# Swollen Joints (28)*†	1.101 (1.055, 1.149)	<0.0001
DAS28 score†	1.482 (1.201, 1.828)	0.0002
# Tender Joints (28)†	1.069 (1.030, 1.110)	0.0005
EULAR (Good vs. No Response)	0.219 (0.084, 0.569)	0.0018
Reduction from baseline in DAS28†‡	0.704 (0.556, 0.891)	0.0036
AUC of DAS28 to week 24, score-years	2.154 (1.208, 3.840)	0.0093
Patient Global Assessment Score, mm†	1.015 (1.002, 1.028)	0.0256

* Interpretation of HR: After adjustment for age, one additional SJC at week 24 is associated with an increased 10.1% hazard for MACE.
† Observed values; LOCF for missing SJC or TJC at Week 24
‡ Also adjusted for baseline DAS28 score.

Conclusion: Traditional cardiovascular risk factors at BL (history of CAD, total cholesterol/HDL ratio, and albumin), as well as disease activity parameters are associated with MACE for patients on TCZ therapy. Only age and CAD history remained statistically significantly associated with MACE on multivariate analysis of BL characteristics. Further, in this on-treatment analysis, risk of MACE was broadly linked to elevated disease activity at BL and a less robust therapeutic response at week 24. There was no association between lipid change and risk for MACE. We hypothesize that mitigating cardiovascular risk in RA patients may require a multifaceted approach that includes effective control of RA disease activity.

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B Cell Repopulation and Rheumatoid Factor Predict Duration of Response to Rituximab in Rheumatoid Arthritis. Edward M. Vital[1], Sudipto Das[2], Shouvik Dass[1], Maya H. Buch[3], Frederique Ponchel[1], Andrew Rawstron[1] and Paul Emery[4]. [1]NIHR Leeds Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [2]NIHR Leeds Musculoskeletal Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]University of Leeds, Leeds, United Kingdom, [4]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom

Background/Purpose: Duration of response to rituximab in rheumatoid arthritis is variable. It is currently unclear whether fixed or on-demand retreatment produces better overall long term outcomes. Predictors of time to relapse may therefore be valuable. We investigated known predictors of response to rituximab to test whether they could predict sustained response to 12 months.

Methods: 104 rituximab-treated patients pooled from 3 clinical trials were analysed and results from 78 patients with EULAR response at 6 months used. All protocols restricted NSAID and corticosteroid use similarly. DAS28 and EULAR response criteria were measured at 0, 14, 26 and 40 weeks. Patients who had relapsed by worsening EULAR criteria were retreated. Naive and memory B and plasmablast subsets were measured by highly sensitive flow cytometry (as previously described) at 0, 2, 6, 14, 26 and 40 weeks.

Results: Of the 78 patients with response at 6 months, 57% had moderate response (MOD) and 43% had good response (GOOD). In patients with detectable B cells at 6 months DAS28 worsened by mean(SD)0.45(1.06), whereas in patients with undetectable B cells DAS28 improved by mean 0.44(0.45), p<0.001 between groups. At 12 months NR/RT, MOD, GOOD rates were 51, 28, 21%. We tested a binary logistic regression model including B cell detection, level and RF, IgG and DAS28 for prediction of continued EULAR response at 12 months, which produced a significant model (p=0.001) with overall accuracy 70.4% (see table).

Prediction of EULAR Moderate or Good Response at 12 months

Variable	Odds Ratio	CI	p
Rheumatoid Factor (per IU/mL)	0.996	0.992–0.999	0.02
IgG (per g/L)	0.990	0.828–1.183	0.91
DAS28	0.582	0.343–0.988	0.04
B cells detectable (Y/N)	0.211	0.033–1.363	0.10
Plasmablast count	1.271	0.844–1.914	0.25

Based on these results we also tested a simplified two-variable categorial model with RF and DAS28 using thresholds of 108 IU/mL and 3.7 (derived from ROC analysis) as predictive of relapse, which also produced a significant model with overall accuracy 69%(p=0.001). Response rates at 12 months by these two criteria were as follows: DAS28<3.7 and RF<108 (n=30): 73%; DAS28>3.7 and RF<108 (n=15):53%; DAS28<3.7 and RF>108:35%; DAS28>3.7 and RF>108:8%.

Conclusion: Following an initial response to rituximab at 6 months, many patients lose response over the next 6 months. This may be predicted at 6 months by B cell repopulation and rheumatoid factor, after correcting for disease activity. These findings need to be validated, but may allow for selection of retreatment regime based on B cell biomarkers.

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Is Screening for JC-Polyomavirus by PCR or Detection of Antibodies Useful in Patients with Rheumatic Diseases Who Are Treated with Rituximab? Jens Verheyen[1], Eugen Feist[2], Kseniya Maizus[1], Zebulon Tolman[1], Elena Knops[1], Tim Waterboer[3], Gerd R. Burmester[4], Michael Pawlita[3], Herbert Pfister[1] and Andrea Rubbert[1]. [1]University of Cologne, Cologne, Germany, [2]Charité Medical School, Berlin, Germany, [3]German Cancer Research Center, Heidelberg, Germany, [4]Charité University Medicine, Berlin, Germany

Background/Purpose: Monoclonal antibodies like Natalizumab and Efalizumab have been associated with an increased risk of progressive multifocal leukoenzephalopathy (PML), which is caused by reactivation of the human JC-polyomavirus (JCPyV). However, the impact of Rituximab (RTX) treatment on JCPyV replication and the development of PML is less clear. The present study was undertaken to analyse patterns of JCPyV infections in patients with rheumatic diseases treated with Rituximab.

Methods: Urine and blood samples were obtained from 64 patients with rheumatic diseases receiving RTX treatment. None of the patients developed neurological symptoms suggestive of PML at any timepoint during the observation period. In 49 cases multiple urine samples could be anaylsed, including baseline samples before the start of RTX treatment (n=20). Blood samples were tested for the presence of JCPyV-DNA and serum antibodies in most patients at a single time point. Antibodies to JCPyV VP1 were detected using a GST-capture ELISA in combination with fluorescent bead technology. JCPyV genotyping (n=23) was performed by amplifying and sequencing the control region and VP1.

Results: In patients, from whom samples were available at baseline (before the start of rituximab treatment) and during follow-up, JCPyV DNA detection stayed either negative (n=13) or positive (n=5) during the observation period (2.0+/−0.9 RTX cycles, 630+/−323 days) in most patients. Interestingly, in two patients, even though initially tested positive, JCPyV DNA detection was negative after the start of RTX treatment.

Urine samples from patients already pretreated with Rituximab (n=44, 3.1+/−1.9 RTX cycles) were tested positive in 17 cases. During the follow up period before and after additional RTX cycles (n=29, 1.1+/−0.3) JCPyV DNA detection remained stable either positive (n=11) or negative (n=15) in most patients. In two patients after one RTX cycle, one negative and multiple positive JCPyV DNA results were obtained. Only in one patient the JCPyV DNA detection switched to positive after two additional RTX cycles.

Patients constantly shedding JCPyV DNA in the urine (n=15) had significant higher JCPyV antibody titers in the blood than patients who always tested negative (n=24). Nevertheless in two cases antibody titers were low despite the detection of JCPyV in the urine and vice versa high in six patients without detectable JCPyV DNA.

JCPyV DNA was only once detected in the blood of one patient. JCPyV isolates obtained from urine and blood could be assigned to four different genotypes according to the VP1 sequences but did not harbour any mutational patterns in the control region associated with PML.

Conclusion: The patterns of JCPyV infections do not seem to be influenced by the Rituximab treatment in patients with rheumatic disorders. According to our results, routine screening of patients for the presence of replicating JCPyV or serum antibodies does not seem to be warranted.

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Efficacy of Different Doses of Rituximab for the Treatment of Rheumatoid Arthritis: Data From the CERERRA Collaboration. Katerina Chatzidionysiou[1], Elisabeth Lie[2], Evgeny L. Nasonov[3], Galina Lukina[3], Merete L. Hetland[4], Ulrik Tarp[5], Ioan Ancuta[6], Karel Pavelka[7], Dan C. Nordström[8], Cem Gabay[9], Helena Canhao[10], Matija Tomsic[11], Piet LC van Riel[12], Juan J. Gomez-Reino[13], Tore K. Kvien[2] and Ronald F. van Vollenhoven[1]. [1]Karolinska Institute, Stockholm, Sweden, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]ARBITER, Institute of Rheumatology, Moscow, Russia, [4]Copenhagen University Hospital at Glostrup, on behalf of DANBIO, Copenhagen, Denmark, [5]Aarhus University Hospital, Aarhus, Denmark, [6]Cantacuzino Hospital, Bucharest, Romania, [7]1Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [8]ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, [9]for the SCQM registry, University Hospitals of Geneva, Geneva, Switzerland, [10]Lisbon Medical Academic Medical Center on behalf of Rheumatic Diseases Portuguese Register, Lisbon, Portugal, [11]University Medical Centre Ljubjana, Ljubljana, Slovenia, [12]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [13]Hospital Clinico Universitario, Santiago, Spain

Background/Purpose: The approved dose of RTX in RA is 1000mg ×2, but some data have suggested similar clinical efficacy with 500mg ×2. The purpose of this analysis was to compare the efficacy of the two dosages given as first or second treatment course.

Methods: Ten European registries submitted anonymized datasets with demographic, efficacy and treatment data for patients who had started RTX. Efficacy of treatment and retreatment was assessed based on DAS28 reductions and EULAR responses after 6 months.

Results: Data on RTX dose were available for 2873 out of 3266 patients in CERERRA. 2625 (91.4%) and 248 (8.6%) patients received 1000mg ×2 and 500mg ×2, respectively. Patients who were treated with the lower dose (LD) were significantly older (mean±SD: 55.2±15.8 vs. 52.6±12.6, yrs, p=0.002), had longer disease duration (13.6±11.9 vs. 10.9±8.2, yrs, p<0.0001), higher number of prior DMARDs (2.6±1.3 vs. 2.4±1.4, p=0.04) but lower number of prior biologics (0.7±0.9 vs. 1.0±1.0, p<0.0001) and lower baseline DAS28 (5.7±1.3 vs. 5.9±1.3, p=0.02) than those treated with the higher dose (HD). Additionally they were less likely to receive concomitant DMARDs (72.6% vs. 83.1%, p<0.0001) but more likely to receive concomitant corticosteroids (65.7% vs. 59.3%, p=0.03).

Both dosages lead to significant clinical outcomes at 6 months. Patients with the HD achieved numerically slightly greater DAS28 reductions at 6 months compared to those treated with the LD (mean DeltaDAS28±SD = 1.9±1.4 vs. 1.7±1.4, p=0.5 corrected for baseline DAS28). Similar percentages of patients achieved EULAR good response (55.2% vs. 50%, p=NS) and remission (10.5% vs. 10.7%, p=NS) in the HD and LD groups, respectively.

At 6±1.5 months 579 patients received retreatment with HD RTX and 26 patients with LD. Patients who received a different dose at retreatment than at first treatment, as well as patients who were retreated at different time points during the first year, were disregarded from the analysis. Retreatment with HD led to even greater DAS28 reductions at 12 than at 6 months (DeltaDAS28 6m = 1.85±1.19, DeltaDAS28 12m = 2.52±1.47, p by paired t-test <0.0001), while retreatment with LD led to no significant further DAS28 reduction (6m = 1.61±1.41, 12m = 1.27±1.78, p=0.2). A significantly higher good responders rate was observed for the HD of RTX in retreated patients (60.7% vs. 32.1%, p=0.003).

Conclusion: In this large observational cohort initial treatment with RTX at 500 mg ×2 and 1000 mg ×2 led to comparable clinical outcomes. The HD was associated with further DAS28 reductions when given as a second treatment course.

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Seropositivity and Response to RTX: Data From the CERERRA Collaboration. Katerina Chatzidionysiou[1], Elisabeth Lie[2], Evgeny L. Nasonov[3], Galina Lukina[3], Merete L. Hetland[4], Ulrik Tarp[5], Ioan Ancuta[6], Karel Pavelka[7], Dan C. Nordström[8], Cem Gabay[9], Helena Canhao[10], Matija Tomsic[11], Piet LCM Van Riel[12], Juan J. Gomez-Reino[13], Tore K. Kvien[2] and Ronald F. van Vollenhoven[1]. [1]Karolinska Institute, Stockholm, Sweden, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]ARBITER, Institute of Rheumatology, Moscow, Russia, [4]DANBIO, Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [5]Aarhus University Hospital, Aarhus, Denmark, [6]Cantacuzino Hospital, Bucharest, Romania, [7]1Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [8]ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, [9]for the SCQM registry, University Hospitals of Geneva, Geneva, Switzerland, [10]Hosp Santa Maria, Lisbon, Portugal, [11]University Medical Centre Ljubjana, Ljubljana, Slovenia, [12]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [13]Hospital Clinico Universitario, Santiago, Spain

Background/Purpose: Predictors of response to biologic therapy in rheumatoid arthritis (RA) are needed to achieve a more individualized therapy. Seropositivity has been associated with better response to rituximab (RTX). The purpose of this study was to assess the 6-month response to the first RTX course in RA according to RF and ACPA status.

Methods: Ten European registries submitted anonymized datasets from RA patients who had started RTX, and datasets were pooled and analysed. Chi-square test for comparison of categorical variables and t-test for continuous data were used. Predictors of response were identified by logistic regression analysis.

Results: 3266 patients were included in the cohort. 79.9% of patients were RF (+) (2041 out of 2553) and 73.2% were ACPA (+) (877 out of 1198). 718 patients were double positive (DP) and 147 double negative (DN).

2200 patients were RF (+) and/or ACPA (+). Improvements of DAS28 (ΔDAS28) at 6 months were significantly better for RF (+) than RF (−) patients as well as for ACPA (+) than ACPA (−), DP vs. DN and RF and/or ACPA (+) vs. DN (table 1). A significantly higher percentage of ACPA (+) and DP patients achieved EULAR Good Response at 6 months compared to ACPA (−) and DN, respectively (table 1). The completeness of data was very similar for seropositive and seronegative patients, with the percentages of missing data at 6 months being approximately 50% in all groups. A significantly higher percentage of seronegative patients received retreatment by 6 months than seropositive patients. In univariate analyses adjusted for age and gender ACPA positivity (OR=2.03, p=0.016) and DP (OR=2.43, p=0.03) but not RF positivity (OR=1.53, p=0.07) predicted EULAR good response to therapy with RTX at 6 months after the first treatment.

Table 1. Clinical outcomes at 6 months for RTX treated patients according to RF and ACPA status.

	RF (+)	RF (−)	p-value	ACPA (+)	ACPA (−)	p-value
Baseline DAS28	5.85 ± 1.36	5.63 ± 1.34	0.02*	5.8 ± 1.35	5.68 ± 1.32	NS
DeltaDAS28 6m	1.94 ± 1.5	1.65 ± 1.34	0.005	1.93 ± 1.51	1.40 ± 1.47	<0.0001
EULAR Good/Moderate/ No 6m	21.5/62/16.5%	17.4/63.4/19.2%	0.06	23.9/58.7/17.4%	14.9/62.9/22.2%	0.009
Remission 6m	13.8%	11.3%	NS	13.5%	10.9%	NS
	DP	**DN**	**p-value**	**RF and/or ACPA (+)**	**DN**	**p-value**
Baseline DAS28	5.81 ± 1.36	5.65 ± 1.36	NS	5.84 ± 1.35	5.65 ± 1.36	NS
DeltaDAS28 6m	1.95 ± 1.54	1.41 ± 1.51	0.007	1.93 ± 1.49	1.41 ± 1.51	0.005
EULAR Good/Moderate/ No 6m	24.7/58.4/ 16.9%	13.8/65/21.2%	0.06	21.4/61.9/16.7%	13.8/65/21.2%	0.038
Remission 6m	13.9%	12.5%	NS	13.7%	12.5%	NS

* Corrected for baseline DAS28.

Conclusion: In this large observational cohort of RA patients treated with RTX, seropositive patients achieved significantly greater reductions in DAS28 at 6 months compared to seronegative patients. Baseline ACPA positivity may be a better predictor for good response to RTX than RF positivity.

ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment II
Monday, November 7, 2011, 2:30 PM–4:00 PM

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Sclerostin As Marker of Bone Formation in Ankylosing Spondylitis Under Anti-TNF Therapy: A 12-Month Longitudinal Analysis. Carla G.S. Saad[1], Ana C. M. Ribeiro[1], Julio C. B. Moraes[1], Liliam Takayama[1], Celio Goncalves[1], Ricardo M. Oliveira[2], Clovis A. A. Silva[1], Eloisa Bonfa[1] and Rosa M.R. Pereira[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]RDO Diagnosticos Medicos, São Paulo, Brazil

Background/Purpose: Sclerostin was reported to be low in AS patients and associated with bone formation. However, there is no data regarding anti-TNF therapy effect in this natural inhibitor of Wnt signaling and its possible association with bone mass. The present study longitudinally evaluated serum levels of sclerostin and lumbar spine bone mineral density (BMD) in Ankylosing Spondylitis (AS) patients under TNF blockage.

Methods: Thirty active AS patients according the modified New York classification criteria were assessed at baseline (BL), 6 (6M) and 12 months (12M) after anti-TNF therapy. Thirty aged- and sex-matched healthy individuals comprised the control group. Patients were evaluated for clinical parameters (BASDAI, BASFI, BASMI, AsQol), inflammatory markers (ESR, CRP, MMP3), baseline radiographic damage (mSASSS). BMD and laboratory analysis of sclerostin (ELISA-SCLEROSTIN; *Biomedica*, *Vienna*, Austria) and sclerostin binding to LRP6 (using recombinant human LRP6-Fc chimera; R&D Systems and human anti-sclerostin biotinylated antibody; *Biomedica*, *Vienna*, Austria) were performed in patients and controls.

Results: At entry, AS patients had lower sclerostin levels (60.5 ± 32.7 vs. 96.7 ± 52.9 pmol/l, $P=0.004$) with comparable sclerostin binding to LRP6 to controls ($P=0.387$). Baseline lumbar spine, femoral neck and total femur BMD were alike in both groups ($P>0.05$). A significant clinical improvement of BASDAI ($P<0.001$), BASFI ($P<0.001$), BASMI ($P=0.003$) and AsQoL ($P=0.001$) was observed evaluating BL vs. 6M vs. 12M. Concomitantly, a significant gradual increase in lumbar spine BMD was observed analyzing baseline vs. 6M vs. 12M of anti-TNF therapy ($P<0.001$) suggesting bone formation, since baseline mSASSS and lumbar spine BMD values were positively correlated (r=0.61, $P<0.001$). A significant reduction in ESR, CRP and MMP-3 levels was observed after TNF therapy comparing baseline vs. 6M vs. 12M ($P<0.001$). These inflammatory markers remained stable comparing 6M and 12M ($P>0.05$). Serum levels of sclerostin progressively increased from baseline to 6M and 12M after biological treatment ($P<0.001$), these increase was sustained between 6M and 12M of anti-TNF therapy ($P=0.024$). Of note, at 12M sclerostin levels remained significantly lower compared to controls (72.7 ± 32.3 vs. 96.70 ± 52.85 pmol/l, $P=0.038$). No change in sclerostin binding to LRP6 was observed from baseline to 12M of anti-TNF treatment ($P=0.472$).

Conclusion: The persistent low levels of sclerostin, in spite of its gradual increase after resolution of inflammation, may underlie the syndesmophyte bone formation in AS patients under anti-TNF therapy.

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Serum Leptin Levels Are Associated with the Presence of Syndemophytes in Male Patients with Ankylosing Spondylitis. Ki-Jo Kim[1], Ji-Young Kim[2], Su-Jung Park[2], Hosung Yoon[3], Chong-Hyun Yoon[1], Jin-Jung Choi[4], Wan-Uk Kim[5] and Chul-Soo Cho[1]. [1]College of Medicine, Catholic University of Korea, Seoul, South Korea, [2]Research Institute of Bone & Joint Diseases, Catholic University of Korea, Seoul, South Korea, [3]The Catholic University, Incheon, South Korea, [4]CHA University, Bundang CHA General Hospital, Seongnam, South Korea, [5]St. Vincent's Hospital, Suwon, South Korea

Background/Purpose: Osteoporosis is detected more frequently in patients with ankylosing spondylitis (AS) with syndemophytes and is associated with bone-marrow adiposity. Leptin is produced in adipose tissue and modulate bone metabolism and phenotypes in animal model. However, the association between leptin and syndemophytes has not yet been elucidated in AS. The purpose of this study is to determine the association between serum leptin concentration and the presence syndemophytes and bone metabolic markers in male patients with AS.

Methods: Seventy-two consecutive male patients with AS and nineteen sex- and age-matched healthy controls were included. Baseline assessment included age, disease duration, treatment, clinical, radiologic and laboratory data. Bone mineral density (BMD) at the spine and femur was measured by dual-energy x-ray absorptiometry (DEXA). Radiographs of the lumbar spine were used to detect syndesmophytes. Serum concentration of leptin and bone metabolic markers including bone specific alkaline phosphatase, osteocalcin and telopeptide of type I collagen were measured. Serum leptin levels are adjusted for body mass index (BMI). Multivariate logistic regression model was used to evaluate the independent effect of clinical and laboratory variables on the presence of syndemophyte.

Results: Serum leptin/BMI levels were not significantly higher in male patients with AS than in healthy individuals (169.94 ± 21.80 vs 131.21 ± 18.22 $pg*m^2/ml*kg$, $p = 0.339$). However, 30 male AS patients with syndemophytes have significantly higher serum leptin/BMI levels than 42 male AS patients without syndemophytes and 19 healthy controls, respectively (222.45 ± 38.59 vs 129.78 ± 22.89 and 131.21 ± 18.22 $pg*m^2/ml*kg$, $p = 0.010$ and 0.040). In multivariate analysis including age, disease duration, c-reactive protein, and serum TNF-α level, higher serum leptin/BMI levels were independently associated with the presence of syndemophytes ($p = 0.029$). Interestingly, serum leptin/BMI level correlated positively with serum bone-specific alkaline phosphatase (Pearson correlation = 0.279, $p = 0.039$). But, there was no significant association between serum leptin/BMI levels and BMD.

Conclusion: Serum leptin levels are elevated in a substantial fraction of male patients with ankylosing spondylitis and are associated with the presence of syndemophytes, suggesting a potential role of leptin on new bone formation in AS.

1649

Eotaxin: A Novel Biomarker in Ankylosing Spondylitis That Predicts Less Structural Damage. Walter P. Maksymowych[1], Nigil Haroon[2], Nathalie Morency[1], Richard J. Cook[3], Ker-Ai Lee[3], Stephanie Wichuk[1], Proton Rahman[4], Dafna D. Gladman[2] and Robert D. Inman[2]. [1]University of Alberta, Edmonton, AB, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [3]University of Waterloo, Waterloo, ON, [4]St. Claires Mercy Hospital, St. Johns, NF

Background/Purpose: About a third of patients with ankylosing spondylitis (AS) have been shown to exhibit radiographic progression over 2 years

but there is limited prospective data on the factors that predict progression. We have previously identified 22 high priority candidate biomarkers from a panel of 58 biomarkers reflecting inflammation and joint tissue turnover that were assessed in a multiplex assay of a subset of The Spondyloarthritis Research Consortium of Canada (SPARCC) prospective cohort[1]. In this subsequent study, we aimed to identify which of the 22 biomarkers was predictive of progression in the entire study cohort.

Methods: The SPARCC cohort comprises patients with AS followed prospectively with clinical and radiographic outcomes. Readers scored X-rays obtained at baseline and year 2 using the mSASSS method. Pre-specified dependent variables were: 1) change in mSASSS >0 and >2 units from baseline through 2 years, 2) development of new syndesmophytes at year 2, 3) spur and ankylosis score (SAS: score for ankylosis = 3 and spur = 2 per vertebral corner). Multivariate analyses were controlled for age, sex, disease duration, biologic treatment, baseline and 2-year change in CRP, and baseline radiographic score.

Results: Baseline and 2-year radiographs were available on 241 patients with AS according to the modified New York criteria. Mean (SD) age was 40.5 (13.3) years, males 81.1%, mean (SD) disease duration 20 (11.2) years), 48.9% received biologics, and 51.1% received standard therapies. At baseline, mean (SD) mSASSS was 15.1 (20.7) and mean (SD) SAS was 12.3 (20.7). Mean (SD) change in mSASSS and SAS over 2 years was 1.8 (3.8) and 1.9 (4.9), 20.6% had mSASSS progression > 2 units, and 28.6% developed ≥1 new syndesmophyte. Multivariate linear regression analysis with either the mSASSS or the SAS as dependent variable showed that only baseline eotaxin was significant in the model so that higher levels predicted lack of progression (Table). Metalloproteinase 3 was also a significant independent predictor in patients on biologics (Est = 0.03 (95% CI 0.003–0.064), p = 0.03).

		Univariate Model			Multivariate Full Model		
Dependent variable	**Treatment**	**Est**	**95%CI**	**P value**	**Est**	**95%CI**	**P value**
SAS	All	−1.09	−1.89, −0.28	0.0085	−1.09	−1.89, −0.28	0.0085
SAS	Standard	−1.60	−3.01, −0.19	0.026	−1.60	−3.01, −0.19	0.026
mSASSS	All	−1.12	−1.87, −0.36	0.0037	−1.12	−1.87, −0.36	0.0037
mSASSS	Biologic	−1.25	−2.59, 0.082	0.066	−1.45	−2.74, −0.15	0.029

Conclusion: Higher levels of eotaxin, a biomarker previously unconnected with SpA, predict less progression irrespective of treatment.

1650

Smokers in Early Axial Spondyloarthritis Have An Earlier Disease Onset, More Inflammation and Damage: Results From the *DEvenir Des Spondyloarthropathies Indifferenciées Récentes* Cohort. Pedro Machado[1], Ho Y. Chung[2], Désirée van der Heijde[3], Maria-Antonietta D'Agostino[4] and Maxime Dougados[5]. [1]Leiden University Medical Center, Leiden, Netherlands & Coimbra University Hospital, Coimbra, Portugal, [2]Leiden University Medical Center, Leiden, Netherlands & Queen Mary Hospital, Hong Kong, China, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Versailles-Saint Quentin en Yvelines University-APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, France, [5]Paris-Descartes University, Cochin Hospital, Paris, France

Background/Purpose: Few studies have investigated the influence of smoking in axial spondyloarthritis (SpA) and previous analyses have focused on ankylosing spondylitis (AS) rather than the early disease stage of axial SpA. In patients with AS, it has been shown that smokers have more limited physical function (1–3) and increased radiographic damage (4). Our aim was to investigate the associations of smoking with various clinical and imaging outcomes in early axial SpA patients.

Methods: Seven hundred and eight patients with IBP of less than 3 years duration defined by Calin or Berlin criteria were recruited in the DESIR (*DEvenir des Spondyloarthropathies Indifferenciées Récentes)* cohort, a multicenter study in France. Six hundred and fifty four fulfilled at least one of the SpA criteria sets (Modified New York (mNY), European Spondyloarthropathy Study Group (ESSG), Amor, and/or ASAS axial SpA) and were included in the analyses. Clinical, demographic and imaging parameters were compared between smokers and non-smokers and variables with significant differences in univariate analyses were used as dependent variables in multivariate linear and logistic regression models adjusted for age, gender, duration of inflammatory back pain, race, HLA-B27 status and other potential confounders.

Results: Our study population was characterized by young age (mean 33.6, median 33.0 years) and short duration of symptoms (mean 1.5, median 1.4 years). Thirty seven percent of the patients were smokers. In multivariate analysis, smoking was associated with earlier onset of inflammatory back pain (IBP) (regression coefficient (B)=-1.46; p=0.04), higher disease activity reflected both by the Ankylosing Spondylitis Disease Activity Index (ASDAS-CRP) (B=0.20; p=0.03) and BASDAI (B=0.50; p=0.003), worse functional status reflected by the BASFI (B=0.38; p=0.02), more MRI inflammation of the sacroiliac (SI) joints (odds ratio (OR)=1.57; p=0.02) and of the spine (OR=2.33; p<0.001), MRI structural lesions of the SI joints (OR=1.54; p=0.03) and of the spine (OR=2.02; p=0.01) and higher modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (B=0.54; P=0.03). Smoking was also associated with poorer health-related quality of life (HRQoL), assessed both by the AS Quality of Life (ASQoL) score (B=1.38; p<0.001) and by the Short Form 36 (SF-36) physical (B=-4.89; p<0.001) and mental (B=-5.90; p<0.001) component scores.

Conclusion: In patients with early axial SpA, smoking was independently associated with earlier onset of IBP, higher disease activity, poorer functional status, increased axial inflammation on MRI and axial structural damage on MRI and radiographs, and worse HRQoL. These observations may have important implications in the education of patients with axial SpA and highlight the need to consider smoking as one of the potential prognostic factors in axial SpA as well as one of the environmental factors potentially involved in the pathogenesis of the disease.

References:

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1651

The Incidence of Infection in Psoriatic Arthritis - Results From a Longitudinal Observational Cohort. Amir Haddad[1], Arane Thavaneswaran[2], Vinod Chandran[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Many patients with psoriatic arthritis are treated with biologic agents. The main adverse event is infection. However, the rate of infection among patients with psoriatic disease is unknown. The purpose of this study was to investigate the rate, type and characteristics of illness in patients with psoriatic arthritis (PsA) in contrast to a control group of patients with psoriasis without arthritis (PsC).

Methods: The PsA cohort was initiated in 1978. Patients are followed at 6–12 month intervals according to a standard protocol which includes history, physical examination laboratory evaluation and radiographic assessment. It collects documentation of the presence, site and type of infection at each visit. In 2006 a cohort of patients with PsC was initiated. Patients with psoriasis are all assessed by a rheumatologist to exclude the presence of inflammatory arthritis, and are followed at yearly intervals according to the same standard protocol. Data are tracked in a computerized database. Descriptive analyses were conducted using t tests and chi-square tests. Only infections observed after 2006 were included.

Results: 695 patients with PsA and 511 patients with PsC and were followed up in our respective clinics since 2006. A total of 607 infections were detected among 318 patients with PsA, and 176 observed infections among 144 patients with PsC. The incidence rate of infection was similar in both groups with 0.33 (95% CI 0.31, 0.36) per patient-year in the PsA cohort and 0.29 (95% CI 0.25, 0.30) per patient-year in the PsC cohort (p=0.15). The incidence rate of infection for patients on biologics was higher at 0.44 (95% CI 0.39–0.50) and 0.66 (95% CI 0.39–1.04) in the PsA and PsC cohorts respectively. Patients with PsA were more likely to have 4 or more infections during the course of follow-up compared to patients with PsC (p=0.0001). Among patients with PsA the most common infections were lung, sinus, skin (cellulitis) and upper respiratory whereas among PsC patients skin, genitourinary, lung and upper respiratory were most prevalent. Patients with PsA had less bacterial infections compared to PsC (62% vs. 77.1% p=0.005), and were less likely to have been treated with antibiotics than patients with PsC (73.6% vs. 87.1% p=0.0003). Patients with PsA and PsC with infection shared similar background comorbidities. In the PsA group patients were older (51.8 vs. 46.7 yrs, p=0.0002) and as expected required more treatment with NSAIDs, DMARDs and biologics (p<0.0001), while patients with PsC were more likely to be treated with phototherapy (p<0.0001). Patients with PsA had a lower prevalence of smoking and alcohol consumption than patients with PsC (p=0.0002 and 0.0015, respectively).

Conclusion: The incidence rate of infection was similar in PsC and PsA cohorts at 29–33 infections per 1000 patient-years. Patients with PsA suffered from recurrent infections more commonly than patients with PsC. Patients in the two cohorts were more likely to have a bacterial etiology for infection and required in the majority of cases antibiotic treatment. The most commonly reported infection was pneumonia in the PsA group and cellulitis in the PsC group.

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Efficacy and Safety of Apremilast, An Oral Phosphodiesterase Inhibitor, in Ankylosing Spondylitis. E. Pathan[1], S.M Abraham[1], L. Van-Rossen[2], Robin Withrington[3], AC Keat[4], Peter J. Charles[5], E. Paterson[5], Muslima Chowdhury[6], L. Hastings[1], A. Fox[1], C. McClinton[1] and Peter Taylor[7]. [1]Kennedy Institute of Rheumatology, London W6 8RF, United Kingdom, [2]Kent and Canterbury Hospital, Canterbury, Kent CT1 3NG, United Kingdom, [3]Kent & Canterbury Hosp, Canterbury, United Kingdom, [4]Northwick Park Hospital, Harrow, United Kingdom, [5]Kennedy Institute of Rheumatology, Imperial College, London, United Kingdom, London, England, [6]Imperial College London, London, United Kingdom, [7]Kennedy Institute of Rheumatology, London, United Kingdom

Background/Purpose: Apremilast (APR) is a novel, orally available small molecule that specifically inhibits phosphodiesterase-4, increasing intracellular cAMP and thus modulates multiple pro- and anti-inflammatory mediators. APR has been shown to significantly improve PASI-75 and ACR 20 in subjects with psoriasis and psoriatic arthritis, respectively.

Objectives: To evaluate the efficacy and safety of APR by monitoring changes in signs and symptoms in a pilot study of patients with ankylosing spondylitis (AS) and to investigate the effect of APR on blood levels of sclerostin, Receptor Activator of NFκB Ligand (RANKL) and Osteoprotegrin (OPG) as biomarkers of bone biology in this cohort.

Methods: This was a double-blind, Placebo (PBO)-controlled Phase II unpowered pilot study in AS patients, symptomatic for ≥2 years, uncontrolled on conventional non-steroidal anti-inflammatory drugs and with daily spinal pain and stiffness for ≥2 weeks before being randomised equally to oral APR 30 mg BID, titrated over 5 days, or PBO. Treatment was assessed using Bath indices over 12 weeks, followed by a 4-week observation phase. Results were compared at each time point using analysis of co-variance (ANCOVA).

Plasma levels of sclerostin and serum levels of RANKL and OPG were measured by ELISA at baseline and after 12 weeks of therapy. Differences in the 2 treatment groups were expressed as percentage change from baseline and compared using the Mann Whitney U test.

Results: 38 subjects were randomised (safety population) and 36 subjects had ≥1 post-baseline assessment (intent-to-treat population) and completed the study. At week 12, APR was associated with a trend to greater mean improvement from baseline for all clinical assessments compared with PBO (Table). There was a significant mean percentage change from baseline in levels of Sclerostin and RANKL, but not of OPG levels, in the APR group vs PBO.

Clinical Parameter	Mean change from baseline (SD)		p value (ANCOVA)
	Apremilast (n = 17)	Placebo (n = 19)	
BASDAI	−1.59 (1.48)	−0.77 (1.47)	0.139
BASFI	−1.74 (1.91)	−0.28 (1.61)	0.108 (non-parametric)
BASMI	−1.36 (2.35)	−0.17 (2.83)	0.166
BASG	−0.51 (1.02)	−0.21 (0.67)	0.617
Laboratory marker	**Mean percentage change from baseline (SD) [No change = 100%]**		**p value (Mann Whitney U test)**
RANKL	73.2 (30.9)	108.2 (32.01)	0.016
OPG	97.8 (18.3)	92.8 (18.8)	0.41
RANKL:OPG	78.3 (33.8)	108.5 (34.6)	0.08
Sclerostin	84.8 (23.03)	110.1 (32.68)	0.011

More APR-treated vs PBO subjects reported loose stools (26.3% vs 10.5%) and headache (42.1% vs 26.3%), but there was no relevant difference in the incidence of diarrhoea, nausea and upper respiratory tract infections: 10.5%, 15.8% and 31.6%, respectively. There were no serious AEs reported.

Conclusion: Although a small pilot study, these results show that APR may be effective and well tolerated in AS and modulates biomarkers of bone biology. Given the current lack of oral DMARDs for AS, these encouraging pilot data support further research of APR in axial inflammation.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects: Renal
Monday, November 7, 2011, 2:30 PM–4:00 PM

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Incident Lupus Nephritis: Predictive and Protective Factors. Ana-Maria Orbai[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: To assess predictive and protective factors (hydroxychloroquine and ACE inhibitors/ARBs) for incident lupus nephritis.

Methods: This analysis was based on 1300 patients in a longitudinal cohort from 1987 to the present who did not have renal involvement prior to or at the time of cohort entry. Incident lupus nephritis was defined as proteinuria of 3 or 4+ on dipstick urinalysis or urine protein > 500 mg (on spot urine or 24h collection), reproducible at 3 months. Using this definition, we estimated rates of incident nephritis, in subgroups defined by clinical and demographic characteristics. Pooled logistic regression was used to estimate the association between characteristics and rates, adjusting for confounding by other variables (SAS Institute, Cary, NC, USA). A p-value ≤0.05 was considered statistically significant.

Results: There were 55 incident cases of lupus nephritis (7.6/1000 person-year). The incidence was significantly higher in African-Americans (RR 4, p<0.0001), those with history of low C3 (RR 10.6, p<0.0001), low C4 (RR 2.6, p=0.0011), anti-dsDNA (RR 3.4, p=0.0015), anti-Smith (RR 4.5, p=0.0001), anti-Ro (RR 2.3, p=0.0017), anti-La (RR 2.3, p=0.011), anti-RNP (RR 3, p<0.0001), high titer anticardiolipin IgG (RR 2.4, p<0.0038) or leukopenia (RR 2.3, p=0.003). Use of hydroxychloroquine for more than 6 months was associated with a reduced incidence (RR 0.5, p=0.043). ACE inhibitor or ARB use was not significantly protective against incident lupus nephritis.

In the multivariable model (Table), predictors significantly associated with incident lupus nephritis were African-American ethnicity (RR 3, p=0.0009), history of low C3 (RR 6.5, p<0.0004), anti-Smith antibody (RR 2.2, p=0.0076), anti-Ro antibody (RR 1.8, p=0.036) and history of cutaneous lupus (RR 2.3, p=0.014). In the multivariable model, current use of Plaquenil for more than 6 months was protective (RR 0.3, p=0.0024).

Table. Association of various predictors and incident nephritis, controlling for each other in a multivariable model.

Variable		Rate Ratios (95% CI)	P-value
Ethnicity	Caucasian	1.0 (Ref. Gp)	0.0009
	African-American	3.0 (1.6, 5.7)	
History of low C3	No	1.0 (Ref. Gp)	0.0004
	Yes	6.5 (2.3, 18.5)	
Testing positive for anti-Smith	No	1.0 (Ref Gp)	0.0076
	Yes	2.2 (1.2, 3.9)	
Testing positive for anti-Ro	No	1.0 (Ref. Gp)	0.036
	Yes	1.8 (1.0, 3.1)	
History of Cutaneous Lupus	No	1.0 (Ref. Gp)	0.014
	Yes	2.3 (1.2, 4.4)	
History of Leukopenia	No	1.0 (Ref. Gp)	0.15
	Yes	1.5 (0.9, 2.9)	
Plaquenil Use	Never	1.0 (Ref. Gp)	0.17
	Past, not current	0.5 (0.2, 1.3)	0.89
	Current < 6 months	1.0 (0.5, 2.5)	0.024
	Current > 6 months	0.3 (0.2, 0.7)	
Proportion of cohort time on	<20%	1.0 (Ref Gp)	0.57
	20–79%	0.8 (0.3, 2.0)	0.10
	80%+	2.0 (0.9, 4.5)	

Conclusion: Predictors significantly associated with incident lupus nephritis were African-American ethnicity, history of low C3, anti-Smith antibody, anti-Ro antibody and history of cutaneous lupus. In the multivariable model, current use of Plaquenil for more than 6 months was protective (RR 0.3, p=0.0024). The results strongly support early and consistent use of Plaquenil, in that it must be used for 6 months or more to be protective. Our results do not support a previous cohort study that ACE inhibitor use was protective.

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Urinary and Serum Monocyte Chemotactic Protein-1 and Interferon Gamma-Induced Protein-10 Are Good Markers to Assess Lupus Activity. Bonnie Abujam, Satyanarayana Swamy and Amita Aggarwal. Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Lucknow, India

Background/Purpose: Interferon gamma-induced protein-10 (IP-10) and Monocyte chemoattractant protein-1 (MCP–1) are pro-inflammatory chemokines. IP-10 promotes the recruitment of monocytes, T and NK cells bearing CXCR3 receptor into inf lamed sites whereas MCP-1 plays a role in recruitment of monocytes and lymphocytes. These chemokines may be involved in the immunopathogenesis of lupus nephritis. Data on urinary MCP-1 and IP-10 are limited in human SLE.

Methods: SLE patients fulfilling ACR 1997 criteria and providing consent were included. SLEDAI was assessed and blood and urine samples collected. Active lupus was defined as SLEDAI>=4. Active patients were divided into active renal lupus if they had proteinuria >=500mg/day or active sediment (>=5 RBC or 5 WBC or any cellular casts per hpf) and

active non-renal lupus. 'Renal SLEDAI' was calculated using four urinary parameters of SLEDAI. Patients with active renal lupus were followed till the nephritis became inactive when a second sample of urine and blood were collected. Serum and urinary levels of MCP-1 and IP-10 (pg/ml) were measured by ELISA (BD Opt EIA). Urinary values were normalised for urinary spot creatinine (pg/mg creatinine).

Results: The study included 78 active and 58 inactive lupus patients. Of 78 active patients, 46 were active renal whereas 32 were active non-renal. Their median age was 25 (IQR 10–55) years and SLE duration was 23 (IQR 6–48) months. The levels of MCP-1 and IP-10 in different groups is given below:

Parameter	Active renal (N = 46)	Active non renal (N = 32)	Active total (N = 78)	Inactive (N = 58)
Urinary MCP-1	46.2 (19.9–125.3) ##	12.7 (5.8–43.9)	35.1 (12.7–71.8)**	9.5 (4.4–17)
Urinary IP-10	12.5 (5.6–22.7) #	5.2 (2.9–12.1)	9.5 (4.4–17.9)**	3.9 (1.9–9.3)
Serum IP-10	690 (465–1000)	477 (327.5–1307.5)	665 (387–1189.3)**	334 (220–512.3)
Serum MCP-1	703.5 (542.5–1000)	680 (455–987.5)	700 (500–1000)*	520 (354.5–789.5)

[Values are median (Inter Quartile Range); *p<0.05, ** p<0.001 as compared to inactive lupus, #p=0.01,##p<0.001 as compared to active non-renal lupus]

Most markers had good correlation with SLEDAI, urinary MCP-1 (r= 0.57, 95% CI 0.38–0.70), urinary IP-10 (r= 0.40; 95% CI 0.19–0.57), serum IP-10 (r=0.51; 95% CI 0.32–0.66) and serum MCP-1 (r= 0.21; 95% CI 0.01–0.38). On longitudinal follow (n=24) of active renal patients, there was a significant decrease in urinary levels of MCP-1 and IP-10 (p=0.005) as well as serum levels of IP-10 (p=0.003) however there was no difference in serum MCP-1 levels.

Conclusion: Urinary and serum IP-10 and urinary MCP-1 are good markers of lupus activity. Further, urinary MCP-1 and IP-10 can differentiate between renal and non-renal active disease. Urinary MCP-10 and IP-10 can also be used for follow up of lupus nephritis patients. Thus, urinary levels seem to be specific for renal inflammation whereas serum levels are reflective of generalised lupus activity.

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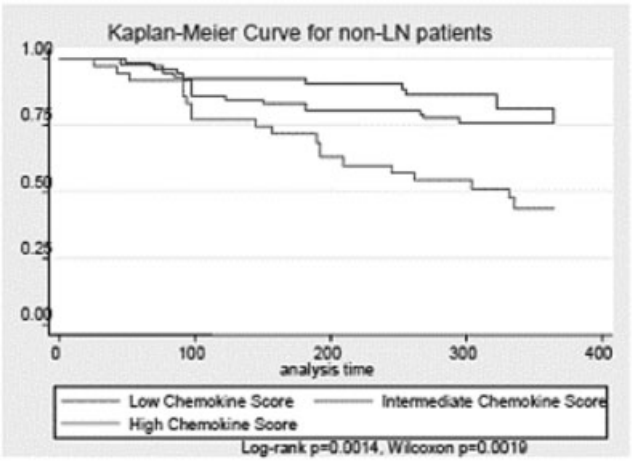
Association of Serum-Based IFN-Induced Chemokine Scores with Lupus Nephritis Disease Activity. Irene Blanco[1], Chaim Putterman[1], Michelle Petri[2] and Emily Baechler Gillespie[3]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]University of Minnesota, Minneapolis, MN

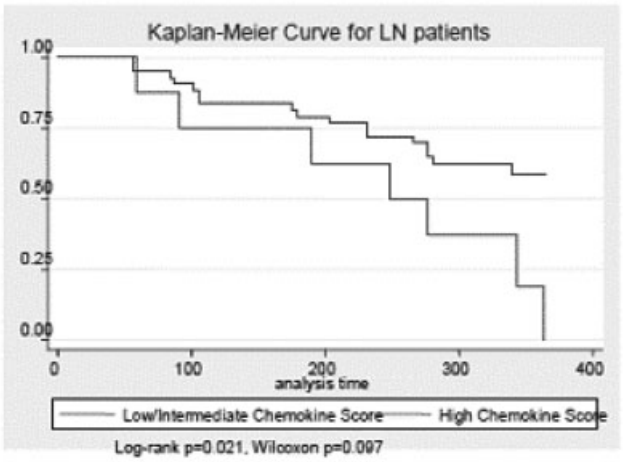
Background/Purpose: A serious complication of Systemic Lupus Erythematosus is lupus nephritis (LN). Despite treatment, many patients still develop renal failure. It has been previously shown that serum based IFN-induced chemokine scores are associated with overall lupus activity. However, it is unclear what the association of these scores are to disease activity in LN patients and how they compare to non-LN SLE patients.

Methods: 224 participants from the Autoimmune Biomarkers Collaborative Network (ABCoN), with IFN regulated serum chemokine (MCP-1, CXCL-10, and CCL-19) scores and longitudinal follow-up, were included in this study. MCP-1, CXCL-10 and CCL-19 were measured using chemiluminescence sandwich-based immunoassays. Individual chemokine scores were calculated and made into a composite score (CK Score). The composite CK score was evaluated in its ability to predict disease flare by survival analysis in LN and non-LN patients, by categorizing levels into: high (top quartile), intermediate (2nd and 3rd quartiles combines) and low (bottom quartile). We then performed a subset analysis of 62 patients at times of remission and flare to assess the score's relation to disease activity using the Wilcoxon matched-pairs signed-rank test. Flare was determined as a change in baseline SLEDAI≥3.

Results: Of the 224 participants included in this study, 54.7% were White, 37.5% Black and 7.4% were of other Races. 89.1% were female; the mean age was 43.2 ±11.9y. Median disease duration was 8y (IQR4–13); 52 participants have biopsy-proven LN.

Baseline CK scores were modestly correlated with disease activity as measured by SLEDAI (rho=0.198, p=0.0226). There was no difference at baseline in CK scores for non-LN and LN patients (31.3 v 31.5, p=0.87). Overall, higher CK scores were predictive of flare in non-LN patients (Log-rank p:0.0014, Wilcoxon p:0.0019). In those with LN however, only the highest quartile predicted a flare when compared to low and intermediate values. (Log-rank p=0.021)





Next, for patients in remission who then flared, non-LN patients had significantly higher serum CK scores at flare than at remission (40.21 v 31.66, p=0.01). In patients with LN and renal activity during the flare (renal SLEDAI≥4), flare CK scores were also significantly elevated compared to remission scores (43.47 v 33.66, p=0.047). However median levels for both LN and non-LN patients at flare fell into the range of the intermediate quartile (24.18–46.65) that was not predictive of flare in non-LN patients.

Conclusions: CK scores are correlated with SLEDAI scores, where the highest quartile of baseline score is predictive of increased disease activity in both non-LN and LN patients. Nevertheless at flare median levels are lower than the highest quartile. Therefore, further studies are needed to determine adequate cut-off points of the CK score to have the best sensitivity and specificity to predict flare.

1656

Predictors of Renal Failure in Systemic Lupus Erythematosus. Michelle Petri[1], Hong Fang[1] and Laurence S. Magder[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Renal failure remains a major issue in SLE, in spite of treatment with mycophenolate mofetil or cyclophosphamide. Although risk factors for lupus nephritis are well studied, fewer studies have investigated risk factors for renal failure because this requires a larger cohort. We investigated this in a large prospective cohort.

Methods: The cohort consists of patients with SLE who are followed quarterly. This analysis was based on the cohort experience of 1996 patients who did not have renal failure prior to cohort entry. The sample was 93% female, 57% Caucasian, 36% African American, with a mean age at entry of 37. We estimated the association between demographic and time-varying clinical variables and rates of renal failure, controlling for Cockcroft-Gault eGFR at cohort entry, using pooled logistic regression.

Results: 53 patients in our sample developed renal failure during cohort participation. Controlling for eGFR at cohort entry, the rate of renal failure was significantly elevated for those who were younger, African-American, had higher systolic blood pressure at entry, had anti-dsDNA or low C3 during follow-up (Table 1). Rates were significantly lower for those who were treated with hydroxychloroquine for more than 50% of their cohort follow-up (Rate Ratio=0.3, p=.0003). There was not a reduced rate among those treated with ACE inhibitors or ARB. The association between low C3 and failure rates diminished after controlling for other variables in a multivariable model, but the other associations persisted (Table 2).

Table 1. Association between predictors and kidney failure during cohort participation based on separate models for each variable, controlling for GFR at start of follow-up.

Variable		Rate Ratio (95% CI)	P-value
Gender	Male (vs. female)	1.9 (0.8, 4.5)	0.14
Age	30–39 (vs. < 30)	0.4 (0.2, 0.9)	0.018
	40+ (vs. < 30)	0.2 (0.1, 0.4)	<0.0001
Race	African-American (vs. Caucasian)	2.9 (1.6, 5.2)	0.0006
	Other (vs. Caucasian)	1.7 (0.5, 6.0)	0.38
Anti-dsDNA	Some but <50% of follow-up (vs. none)	1.6 (0.5, 4.4)	0.41
	>50% of follow-up (vs. none)	5.9 (2.5, 13.8)	<0.0001
Low Complement	Some but <50% of follow-up (vs. none)	1.7 (0.5, 6.3)	0.43
	>50%+ of follow-up (vs. none)	2.7 (1.3, 5.8)	0.011
Systolic Blood Pressure at start of follow-up	130+ mmHg (vs. <130)	2.0 (1.2, 3.5)	0.011
Hydroxychoroquine Use	Some, but <50% of time (vs. none)	0.4 (0.1, 1.3)	0.12
	>50% of follow-up (vs. none)	0.3 (0.1, 0.5)	0.0003
ACE or ARB[1]	Some, but <50% of time (vs. none)	2.0 (0.9, 4.7)	0.094
	>50% of follow-up (vs. none)	1.1 (0.5, 2.5)	0.87

[1] Controlling also for history of hypertension.

Table 2. Association between predictors and kidney failure during cohort participation based on a multivariable model.

Variable		Rate Ratio (95% CI)	P-value
Age	30–39 (vs. < 30)	0.4 (0.2, 0.9)	0.035
	40+ (vs. < 30)	0.2 (0.1, 0.5)	0.0005
Race	African-American (vs. Caucasian)	2.0 (1.0, 4.3)	0.066
	Other (vs. Caucasian)	0.6 (0.1, 3.1)	0.57
Anti-dsDNA	Some, but <50% of time (vs. none)	2.1 (0.6, 6.7)	0.22
	>50% of follow-up (vs. none)	6.4 (2.3, 17.8)	0.0004
Low Complement	Some, but <50% of time (vs. none)	1.2 (0.2, 5.5)	0.85
	>50% of follow-up (vs. none)	1.1 (0.5, 2.5)	0.87
Systolic Blood Pressure at start of follow-up	130+ mmHg (vs. <130)	2.4 (1.1, 4.9)	0.023
Hydroxychoroquine Use	Some, but <50% of time (vs. none)	0.4 (0.1, 1.4)	0.16
	>50% of follow-up (vs. none)	0.3, (0.2, 0.7)	0.0070

Conclusion: Anti-dsDNA was strongly associated with progression to renal failure in our SLE cohort. Thus, new biologic treatments which reduce anti-dsDNA early and effectively should be explored in trials of lupus nephritis. Our study also provides strong evidence that treatment with hydroxychoroquine reduces the risk of progression to renal failure. However, this protective effect requires that it be present for greater than 50% of followup time.

1657

$CD4^+CD25^-Foxp3^+$ T Cells Are Indicative for Kidney Involvement in Systemic Lupus Erythematosus (SLE) Patients and Respond to Cyclophosphamide Therapy. Michael Bonelli[1], Lisa Goeschl[1], Anastasiya Hladik[1], Josef Smolen[2] and Clemens Scheinecker[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: $CD4^+CD25^-Foxp3^+$ T cells resemble regulatory T cells and are increased in SLE patients. Their precise role in SLE pathogenesis, however, has not been determined so far. We therefore analyzed $CD4^+CD25^-Foxp3^+$ T cells in SLE patients with different organ manifestations as compared to healthy controls (HC).

Methods: Proportions of $CD4^+CD25^-Foxp3^+$ T cells were determined by 6 color flow cytometry (FACS) within peripheral blood mononuclear cells (PBMC) in HC (n=21) and SLE patients (n=61) with different organ manifestations. In selected SLE patients with active glomerulonephritis, proportions of $CD4^+CD25^-Foxp3^+$ T cells were also determined in urine samples. $CD4^+CD25^-Foxp3^+$ T cells were analyzed for the expression of novel Treg markers Helios and Icos and proportions were correlated with clinical data, the immunosuppressive therapy and different disease activity indices. Finally time course analyses of proportions of $CD4^+CD25^-Foxp3^+$ T cells were performed in patients with active glomerulonephritis before and after treatment with cyclophosphamide and in patients with active skin involvement before and after cortisone treatment.

Results: Proportions of $CD4^+CD25^-Foxp3^+$ T cells were significantly increased in SLE patients as compared to HC and expressed Helios and Icos. We observed a significant correlation of % $CD4^+CD25^-Foxp3^+$ T cells with the SLEDAI, ECLAM and SIS disease activity score and with the daily cortisone dose. The analysis of patients with different organ manifestations revealed increased proportions of $CD4^+CD25^-Foxp3^+$ T cells in SLE patients with renal involvement. Moreover, $CD4^+CD25^-Foxp3^+$ T cells were also detected in urine samples of patients with active glomerulonephritis and proportions of $CD4^+CD25^-Foxp3^+$ T cells significantly correlated with the extent of proteinuria. Time course analysis revealed no influence of cortisone treatment on the percentage of $CD4^+CD25^-Foxp3^+$ T cells in patients with active skin involvement, whereas cyclophosphamide treatment of patients with active glomerulonephritis led to a decrease in $CD4^+CD25^-Foxp3^+$ T cells. Ongoing experiments have been designed to further reveal the origin of $CD4^+CD25^-Foxp3^+$ T cells. For this purpose $CD4^+CD25^-Foxp3^+$ T cells are analyzed for their cytokine profile and the expression of T cell lineage specific transcription factors.

Conclusion: The increase in proportions of $CD4^+CD25^-Foxp3^+$ T cells in patients with SLE who suffer from glomerulonephritis suggests their involvement in kidney pathology. In addition the analysis of $CD4^+CD25^-Foxp3^+$ T cells might allow to recognize and monitor patients with renal involvement.

1658

Serum Cytokines in Lupus Nephritis, Levels of IL-17 and IL-23 in Association to Histopathology and Response to Treatment. Agneta Zickert[1], Petra Amoudruz[1], Johan Rönnelid[2], Vivianne Malmström[1] and Iva Gunnarsson[1]. [1]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Uppsala University, Uppsala, Sweden

Background/Purpose: The pathogenesis for lupus nephritis (LN) is complex and involves many components of the immune system. Recent studies indicate an important role for the T-cell subset Th-17, and the associated cytokines IL-17 and IL-23, in LN. Increased knowledge of cytokines in LN, originating from both the innate and adaptive immune system, may contribute to further understanding of the pathogenesis, identification of new biomarkers and to development of new treatment strategies.

The aim of the study was to investigate cytokines, previously indicated in LN, in association to clinical and histopathological findings and response to therapy.

Methods: Fifty-two patients with active lupus nephritis were included. Renal biopsies were performed at baseline and after 6 months of standard induction treatment. Clinical and laboratory data were collected at baseline and at repeated biopsies and serum levels of TNFα, IFNγ, IL-2, IL-4, IL-6, IL-10, IL-6R, IL-17, IL-21, IL-23 and TGF-β were analyzed at both occasions. Biopsies were evaluated regarding WHO-classification and renal disease activity was estimated using the BILAG index. An improvement of at least 2 grades in renal BILAG was regarded complete response (CR), whereas 1 grade as partial response (PR). Serum samples from 13 healthy volunteers were used as controls.

Results: Baseline biopsies showed WHO-class III-IV (n=44) and V (n=8) and all patients had high renal disease activity (BILAG A/B). Follow-up biopsies showed WHO I-II (n= 19), III-IV (n=19) or V (n= 14). 22 patients were regarded CR, 20 PR and 10 non responders. At baseline, serum levels of IL-6, IL-10, IFNγ, IL-17-1L-23 and IL-6R were significantly higher in patients vs. controls and TGFβ was significantly lower ($p<0.05$ for all). Overall, the high cytokine levels except IFN γ decreased significantly after treatment.

Serum levels of IL-17 at baseline were significantly higher in patients with a persisting active nephritis at follow up (WHO III, IV or V) vs. those with a good histopathological response (WHO I or II) ($p<0.01$). The highest levels of IL-17 were found in class V. Overall, BILAG non-responders had significantly higher levels of IL-23 at follow up vs. CR and PR ($P<0.05$), most pronounced among non-responder patients with WHO class V at follow up ($p<0.02$).

Conclusion: Levels of IL-17 at baseline were significantly higher in patients not responding histopathologically to treatment, suggesting that patients with high levels of IL-17 may represent a subgroup of patients with more severe disease. Levels of IL-23 at follow up were significantly higher in BILAG non-responders than in responders, especially in LN class V. This study indicates a role for Th-17 (IL-17/IL-23) in LN regarding treatment response, especially in class V LN, and suggests that these cytokines may be used as biomarkers.

1659

HMGB1 Is An Important Mediator in Cutaneous Inflammation in Systemic Lupus Erythematosus (SLE). Deena A. Abdulahad, Johanna Westra, Gerda Horst, Pieter C. Limburg, Cees GM Kallenberg and Marc Bijl. University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: Systemic Lupus Erythematosus (SLE) is systemic autoimmune disease affecting many organs. Sunlight sensitivity is one of the characteristics of SLE, present in about one third to half of the patients. When exposed to physiological amounts of UVB these patients develop inflammatory skin lesions in the vicinity of apoptotic cells. High mobility group box 1 (HMGB1) is a DNA binding protein that is released from apoptotic cells and is secreted by activated cells. HMGB1 exerts its inflammatory actions through binding to several receptors such as RAGE (receptor for advanced glycation end products) and Toll-like receptors (TLRs) 2, 4, 7, and 9.

Objectives: To investigate whether HMGB1 release contributes to the development of inflammatory skin lesions in SLE patients after UVB exposure.

Methods: Eleven SLE patients and 10 healthy controls (HC) were exposed to a standard dose UVB. Biopsies were taken before and 1, 3, and 10 days after irradiation. Paraffin embedded sections were stained for HMGB1, CD3 and CD68, and frozen skin biopsies were analysed for mRNA expression of IL-8, HMGB1, RAGE, and TLRs (2, 4, 7 and 9) using RT-PCR. Primary keratinocytes were cultured and irradiated with UVB light for different timepoints. HMGB1 and IL-8 release were measured in supernatants by Western Blotting and mRNA expression of above mentioned markers were determined.

Results: A significant higher release of HMGB1 from the nucleus was seen in the un-irradiated skin of SLE patients compared to HC. Also after UVB irradiation, HMGB1 release was significantly higher in SLE patients compared to HC at all time points and HMGB1 release was correlated with presence of CD3 and CD68 positive cells. Only HMGB1 mRNA levels were increased in unirradiated skin of SLE patients compared to HC. After UVB mRNA levels of HMGB1, RAGE, TLR 2, 4, 7, and 9 all decreased and were lowest at day 3, whereas mRNA levels of IL-8 increased 24 hours after UVB irradiation without difference between patients and HC. Primary keratinocytes released HMGB1 and IL-8 into the supernatant starting from 24 hours after UVB irradiation.

Conclusion: HMGB1 protein release and mRNA expression are higher in the skin of SLE patients compared to HC. Upon UVB exposure release of HMGB1 in SLE further increases suggesting that SLE skin is more prone to release of HMGB1. As this release correlated with presence of macrophages and lymphocytes and as mRNA of the HMGB1 receptors before and after UV exposure are present in SLE patients our data suggest that HMGB1 release in SLE might be an important mediator of skin inflammation in SLE.

1660

Overexpression of Lupus-Susceptibility Gene HRES-1/Rab4 Causes Enhanced Microautophagy and Defective Mitochondrial Macroautophagy (Mitophagy) in Lupus T Cells. Tiffany Telarico[1], Edward Doherty[2], Brandon Clair[1], Walter Malorni[3] and Andras Perl[4]. [1]SUNY Upstate Medical University, Syracuse, NY, [2]SUNY Upstate, Syracuse, NY, [3]Istituto Superiore di Sanita, Rome, Italy, [4]Upstate Medical University, Syracuse, NY

Background/Purpose: T lymphocytes from systemic lupus erythematosus (SLE) patients show activation of the mammalian target of rapamycin (mTOR), that regulates autophagy. mTOR blockade by rapamycin is therapeutic in human and murine lupus. mTOR promotes expression of HRES-1/Rab4, an early endosomal trafficking protein that targets its cargo, including CD4 and CD3ζ, for lysosomal degradation. Despite increased protein degradation mediated by HRES-1/Rab4, mitochondrial mass is increased in SLE T cells. Mitochondrial mass depends on mitochondrial biogenesis, fusion and fission, the latter regulated by dynamin-related protein 1 (Drp1). Here, we examined the effect of HRES-1/Rab4 and mTOR blockade on microautophagy of proteins and macroautophagy of mitochondria (mitophagy).

Methods: Glutathione-S-transferase (GST) pull down assays were used to identify binding partners of HRES-1/Rab4, GDP-locked HRES-1/Rab4^{S27N}, GTP-locked HRES-1/Rab4^{Q72L} and phosphorylation-defective HRES-1/Rab4^{S204Q} in peripheral blood lymphocytes (PBL). Adeno-associated viruses (AAV) expressing HRES-1/Rab4 isoforms in pAAV-IRES-GFP were used to infect PBL. Jurkat cells expressing HRES-1/Rab4 or HRES-1/Rab4^{S27N} were also utilized. Macroautophagy of mitochondria was studied by flow cytometry and expression of Drp1 by western blot. Microautophagy was evaluated by expression of CD4 and CD3ζ. To determine whether autophagy is altered in lupus, expression of autophagy regulators Beclin-1, LC3, and Drp1 were measured in resting and CD3/CD28-stimulated PBL of SLE patients treated *in vivo* with and without rapamycin as well as of healthy controls matched for age, sex, and ethnicity. ANOVA and t-test were used for data analysis.

Results: HRES-1/Rab4 directly interacted with Drp1 and reduced its expression and phosphorylation in Jurkat cells (66% decrease, $p=0.01$) and PBL (62% decrease, $p=0.005$) that is consistent with formation of megamitochondria in lupus T cells. Along this line, expression of dominant-negative HRES-1/Rab4^{S27N} reduced mitochondrial mass in Jurkat cells (27% decrease, $p=0.005$) and in AAV-infected PBL (8% decrease in $CD4^+$ T cells, $p=0.025$; 19% decrease in $CD8^+$ T cells, $p=0.03$). In contrast, HRES-1/Rab4 overexpression in PBL diminished CD4 (26% decrease, $p=0.003$) and CD3ζ protein levels via lysosomal degradation (33% decrease, $p=0.049$) which are consistent with increased microautophagy. Expression of autophagy initiator protein Beclin-1 was reduced in lupus PBL in comparison to healthy controls (66% decrease, $p=0.0008$) and was normalized in SLE patients' T cells by *in vivo* rapamycin treatment ($p=0.036$, compared to SLE patients treated without rapamycin). CD3/CD28-stimulated PBL from rapamycin-treated SLE patients exhibited increased LC3II/LC3I ratio, indicative of restored autophagy via mTOR blockade ($p=0.01$). Drp1 expression was reduced in SLE PBL (48% decrease, $p=4 \times 10^{-5}$), but was not corrected in rapamycin-treated patients (50% decrease, $p=0.003$).

Conclusion: These results provide evidence for increased microautophagy and decreased mitophagy in lupus T cells which are mediated through the activation of the HRES-1/Rab4/mTOR axis.

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Rapamycin Treatment Normalizes CD3 and CD4 Recycling in Lupus T Lymphocytes. Tiffany Telarico[1], Brandon Clair[1] and Andras Perl[2]. [1]SUNY Upstate Medical University, Syracuse, NY, [2]Upstate Medical University, Syracuse, NY

Background/Purpose: Activation of the early endocytic pathway in T cells from systemic lupus erythematosus (SLE) patients is evidenced by increased expression of Rab5A and HRES-1/Rab4 mediate the increased internalization, recycling, and lysosomal degradation of signaling receptors, such CD3ζ and CD4. Diminished CD3ζ and CD4 and increased HRES-1/Rab4 expression inversely correlate in SLE T cells, which are targeted for lysosomal degradation by HRES-1/Rab4. SLE T cells exhibit increased recycling of CD3 and CD4 receptors. HRES-1/Rab4 directly interacts with CD3ζ and CD4, whose expression directly impacts T cell activation. Activity of the mammalian target of rapamycin (mTOR) is upstream of the endocytic pathway, as treatment with mTOR inhibitor rapamycin reduces HRES-1/Rab4 expression in SLE T cells. Here, we examined the effect of rapamycin treatment and HRES-1/Rab4 expression on CD3 and CD4 receptor recycling in SLE T cells.

Methods: SLE patients treated *in vivo* with and without rapamycin as well as healthy controls matched for age, sex, and ethnicity were studied. Flow cytometry was used to measure recycling of CD3, CD4, and CD8 surface receptors in untouched T cells prepared by negative isolation. To measure recycling, cells were stained with CD3, CD4, and CD8 antibodies in the presence of cycloheximide on ice, washed, and incubated at 37°C to induce receptor turnover. Samples were taken every 30 minutes for 2.5 hours and re-stained at the conclusion of the assay. T cell, $CD4^+$ T cell, $CD8^+$ T cell, $CD4^-CD8^-$ T cell, and B cell populations were compared among subjects by flow cytometry of freshly isolated peripheral blood lymphocytes (PBL). To determine whether enhanced recycling in SLE T lymphocytes is HRES-1/Rab4 dependent, PBL from healthy controls and SLE patients were infected with adeno-associated viruses (AAV) expressing HRES-1/Rab4 or a vector control (pAAV-IRES-GFP), and recycling was measured 48 hours post-infection. Two-way pair-wise repeated-measures analysis of variance (ANOVA) was used for statistical analysis.

Results: Treatment of SLE patients with rapamycin *in vivo* reversed the accelerated recycling of CD4 ($p=0.005$) and CD3 on $CD4^+$ T cells ($p=0.007$). Rapamycin also reduced the recycling of CD3 on $CD8^+$ T cells ($p=0.008$) and $CD4^-CD8^-$ T cells in comparison to SLE patients not treated with rapamycin ($p=0.0009$). PBL from rapamycin-treated SLE patients had a reduction in total B cell number, in comparison to SLE disease controls (30% decrease, $p=0.001$). Overexpression of HRES-1/Rab4 in SLE PBL promoted the recycling of CD3 ($p=0.02$) and CD8 ($p=0.005$), but reduced recycling of CD3 ($p<0.001$) and CD8 ($p=0.01$) in healthy controls.

Conclusion: The results suggest that HRES-1/Rab4 overexpression may be responsible for increased CD3 recycling in SLE T cells and rapamycin may normalize CD3 and CD4 recycling in SLE T cells through diminishing HRES-1/Rab4 activity.

1662

Lipid-Antigen Presentation by $CD1d^+$ B Cells Is Essential for the Maintenance of *I*nkt Cells: Aberrant B Cells From Patients with Systemic Lupus Erythematosus Impair *I*nkt Cell Homeostasis. Anneleen Bosma[1], Azza Abdel-Gadir[1], David A. Isenberg[2], Claudia Mauri[1] and E.C. Jury[1]. [1]University College London, London, United Kingdom, [2]University College London, London WC1E 6JF, United Kingdom

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by a profound breakdown in immune-regulatory mechanisms. Disease pathogenesis is complex but recent research has centred on the role of B cells secreting pathogenic auto-antibodies. However, B cells have other essential functions including CD1d-mediated lipid-antigen presentation to invariant natural killer T (iNKT) cells, a specialised T cell subset with regulatory function in both innate and adaptive immunity. Very few studies have examined the role of B cells on the maintenance of iNKT cells in the context of lupus. Profound reductions in iNKT cell frequency have been reported in SLE patients. To consider the *in vivo* role that B cells play in iNKT cell homeostasis and whether B cell dysfunction drives iNKT cell abnormality in lupus patients, we exploited B cell depletion therapy (rituximab) as an *in vivo* human model.

Methods: Peripheral blood mononuclear cells (PBMC) were collected from 250 patients with SLE and 90 healthy controls. Patients had active disease (BILAG>6) before rituximab treatment. Patients were considered B cell depleted (BCD) when B cell levels were below 5 cells/μl and in most cases their disease became inactive (BILAG <6). Responding patients remained in remission with inactive disease after B cell repopulation; non-responding patients developed active disease when B cells repopulated. B cell and iNKT cell phenotyping was determined by flow cytometry. To assess iNKT cell function PBMC were stimulated with a-galactocylceramide (aGC) for 7 days and iNKT cell proliferation and aGC driven cytokine profiles determined.

Results: SLE iNKT cells displayed an activated phenotype with clustered invariant (i)TCRs compared with dispersed iTCR distribution in iNKT cells from healthy individuals. In addition, compared to healthy, lupus iNKT cells expressed increased levels of CD69 paralleled by enhanced expression of surface Annexin V. Furthermore, we show that while healthy iNKT cells proliferate in response to *in vitro* a- aGC stimulation, SLE iNKT cells lack this capacity. When lupus patients were treated with rituximab, iNKT cell numbers remained low in the absence of B cells and in patients who had repopulated their B cell populations but did not respond clinically to treatment. However, iNKT cell numbers increased in patients with repopulated B cells responding to treatment, iNKT cells from these patients also regained their capacity to proliferate in response to aGC. We found that B cells from patients with SLE display significantly reduced levels of surface CD1d, compared to the levels expressed by healthy B cells. The expression of CD1d on B cells was exclusively recovered on B cell-repopulated patients responding to rituximab therapy and directly correlated with iNKT frequency.

Conclusion: These findings support our hypothesis that auto-reactive B cells in SLE patients impair iNKT cell-mediated responses and that B cell depletion therapy may restore this interaction by "resetting" the balance of B cell-iNKT cell homeostasis.

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Altered Soluble Mediators of Inflammation At Baseline in Individuals Who Subsequently Transition to Systemic Lupus Erythematosus: Early Studies From the Lupus Autoimmunity in Relatives (LAUREL) Study. Melissa E. Munroe[1], Joel M. Guthridge[1], Diane L. Kamen[2], Jill M. Norris[3], Kathy L. Moser[1], Timothy B. Niewold[4], Gary S. Gilkeson[5], David R. Karp[6], Michael H. Weisman[7], Mariko L. Ishimori[8], Daniel J. Wallace[9], John B. Harley[10] and Judith A. James[11]. [1]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Medical University of SC, Charleston, SC, [3]University of Colorado Denver, Aurora, CO, [4]University of Chicago, Chicago, IL, [5]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [6]UT Southwestern Medical Center, Dallas, TX, [7]Cedars Sinai Med Ctr, Los Angeles, CA, [8]Cedars Sinai Medical Ctr, Los Angeles, CA, [9]Cedars-Sinai/UCLA, Los Angeles, CA, [10]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [11]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: SLE is a multifaceted autoimmune disease marked by autoantibody production and immune dysregulation. Identification of at-risk populations is essential to curtail chronic inflammation and prevent end-organ damage. Healthy blood relatives of lupus patients are known to have a significantly increased risk of SLE development. Using a unique resource of family members with samples available before and after transition to SLE, this study seeks to identify early biomarkers of at-risk populations, as well as to understand roles of select inflammatory mediators in SLE development.

Methods: This study has re-enrolled 448 first-degree relatives (FDRs) of known SLE patients with samples available from previous genetic studies for follow-up evaluation. We have 19 previously unaffected FDRs who have now transitioned to SLE ($\geq$ 4 ACR criteria). Each individual provided detailed clinical (symptoms, medical history, medication usage, etc.) and demographic (age, race, etc.) information, and completed the Connective Tissue Disease Screening Questionnaire (CSQ) at baseline and follow-up. Where appropriate, medical records were obtained and reviewed for ACR classification criteria. Baseline and follow-up serum samples were tested for autoantibody production, including ANA, anti-dsDNA, aCLs and precipitating levels of Ro, La, Sm, nRNP, and ribosomal P autoantibodies. In addition, we assessed 52 soluble inflammatory mediators, including cytokines, chemokines, and soluble receptors, using either xMAP multiplex technology or sandwich ELISA (BLyS and APRIL). Samples from participants who transitioned to SLE were compared with two separate matched (age, race, gender) control groups, either ANA(−) or ANA(+).

Results: FDRs who transitioned to SLE had significantly higher BL CSQ scores than either ANA(−) or ANA(+) matched, unaffected FDRs ($p < 0.0001$). FDRs who transitioned to SLE had significant ($p \leq 0.01$) alterations in 34 (of 52) soluble mediators compared to ANA(−) and (+) matched FDRs. Compared to ANA(−) matched FDRs, FDRs with SLE had significantly lower ($p \leq 0.01$) levels of 29 analytes, including innate and adaptive mediators of inflammation and the cytokine APRIL; significant enhancement ($p \leq 0.01$) of 5 analytes, including BLyS, were also shown. Of particular interest were unaffected, ANA(+) matched FDRs, who showed no difference from FDRs with SLE with respect to BLyS, innate cytokines, sFasL, and sCD40L but showed significant differences compared to ANA(−) controls ($p < 0.05$). With respect to Th1, Th2, Th17, and regulatory-type cytokines, matched ANA(+) FDRs showed intermediate levels of analytes, significantly higher than FDRs with SLE, but significantly lower than matched ANA(−) FDRs ($p < 0.01$).

Conclusion: FDRs of known SLE patients who transition to clinical disease demonstrate significantly altered levels of soluble inflammatory mediators compared to matched FDRs who remain unaffected. That these alterations are present prior to the transition to active SLE suggests that multiple perturbations in immune-mediated inflammatory processes occur long before clinical classification and suggest that high-risk, pre-clinical individuals can be identified.

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Urinary Angiostatin As a Novel Biomarker in Lupus Nephritis. Tianfu Wu, Chun Xie, Jie Han and Chandra Mohan. University of Texas, Southwestern Medical Center at Dallas, Dallas, TX

Background/Purpose: Searching for biomarkers of immune-mediated nephritis, we previously conducted a 2D-gel based proteomic analysis of

urine from mice with anti-GBM disease, and identified urinary angiostatin as a marker of nephritis. In a more recent array-based screen of ~280 molecules using urine from patients with lupus nephritis, angiostatin again surfaced as a potential marker of nephritis. Angiostatin is a bioactive fragment of plasminogen, and has been known to have modulatory function in angiogenesis and inflammation. The goal of this study is to further investigate the potential of urinary angiostatin as a marker of lupus nephritis.

Methods: Three sets of studies were carried out. First, we screened the urine of 5 patients with lupus nephritis (average age = 38.3, average SLEDAI = 19.4) and matched controls for the levels of ~280 molecules using an array-based proteomic platform. Next, to validate the array findings, we assayed the urine of 17 patients with active lupus nephritis (average SLEDAI = 14), 10 with inactive lupus nephritis (average SLEDAI= 2.4), and 10 healthy controls. Finally, we examined a cohort of 21 patients with ISN/RPS Class III/IV lupus nephritis where urine was collected at the time of renal biopsy, so that the urinary profiles can be related to concurrent pathology.

Results:

1. In the array-based screen, urinary angiostatin was significantly increased in SLE patients compared to healthy controls (10964 ± 7130 vs 944 ± 822 AU, $P < 0.05$).
2. In the ELISA-based validation assays, urinary angiostatin was significantly increased in active lupus nephritis patients compared to the inactive group (1672±372 vs 189±72 pg/mg urine creatinine, $P < 0.02$) and healthy controls (12±4 pg/mg urine creatinine, $P < 0.01$).
3. When concurrent urine-kidney paired samples from patients with lupus nephritis were examined, we found that urine angiostatin was strongly related to concurrent ISN/RPS Class IV GN ($r = 0.50$, $P < 0.011$), performing better than urine protein/creatinine ($r = 0.22$, $P = 0.17$). Urine angiostatin levels were correlated weakly with concurrent renal pathology activity index ($r = 0.27$, $P < 0.12$), but better with concurrent renal pathology chronicity index ($r = 0.44$, $P = 0.02$).

Conclusion: Thus, urinary angiostatin emerges as a novel biomarker of clinically active Class IV nephritis in SLE, and a marker of concurrent renal pathology activity and chronicity. Longitudinal studies are in progress to assess the predictive potential of this novel biomarker in comparison to currently used yardsticks. Mechanistic studies are also in progress to fathom how angiostatin functions within the kidneys.

ARHP Concurrent Abstract Session
ARHP Education and Community Programs
Monday, November 7, 2011, 2:30 PM–4:00 PM

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Everyday Life and Rheumatoid Arthritis—Implications for Patient Education. Tine Mechlenborg Kristiansen[1], Jette Primdahl[1], Rasmus Antoft[2] and Kim Hørslev-Petersen[1]. [1]University of Southern Denmark, Graasten, Denmark, [2]Aalborg University, Aalborg, Denmark

Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease affecting several aspects of everyday life. The purpose of patient education is to help people with RA to manage their chronic illness. There is no tradition in Denmark to engage people with RA in developing and implementing patient education. This study aims to explore how everyday life is affected by RA and to discuss the implications for patient education.

Methods: In total six focus groups were conducted including 19 women and 13 men with RA. The groups were selected according to purposeful sampling, aimng to span the greatest possible variation in age, educational background and illness duration. Three groups were made up of participants with newly diagnosed RA (max. 1,5 years of diagnosis) and three groups of participants with diagnosis more than 1,5 years. The interviews were transcribed verbatim and content analysis inspired by Coffey and Atkinson was used in managing and analyzing the data.

Results: The analysis resulted in four distinct categories that describe how everyday life was affected by RA. Self-identity and self-perception was affected, social relations within the family and friendships changed, work relations were challenged and new relations within health- and social systems were established that affected the individuals in both positive and negative ways. The most important for the participants was the wish to continue "normal life". The analysis showed that a few individuals were able to continue most daily activities as RA had only a minimal impact on normal life. This was due to receiving a fast diagnosis and effective medical treatment that kept symptoms under control.

Implications for future patient education—four interrelated areas of support:

(1) Support to manage the symptoms in everyday life including disease-specific knowledge about RA
(2) Support for areas of social interaction, as for instance work and support to understand how RA can affect one's social life
(3) Support to manage psychological and emotional reactions related to how RA affects conceptions of self and identity, especially in the early phases of RA
(4) Support to facilitate meeting others with RA

Conclusion: For the most people, living with RA affects almost every aspect of everyday life. This has important implications for patient education. To ensure that patient education is perceived as relevant and supportive, it should be inter-disciplinary and should incorporate not only disease-specific knowledge about RA and managing RA symptoms but also social and psychological dimensions related to everyday life, and it should facilitate meeting others with RA.

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One-Year Outcomes of Systemic Lupus Erythematosus (SLE) and/or Antiphospholipid Antibody (aPL) Positive Patients Enrolled in An Ongoing Cardiovascular Disease (CVD) Prevention Counseling Program (PCP). Aeshita Dwivedi[1], Virginia Haiduc[1], Monica C. Richey[1], Sotiria Everett[1], Lisa Konstantellis[1], Ann R. Garment[2], Hassan Ghomrawi[1] and Doruk Erkan[1]. [1]Hospital for Special Surgery, New York, NY, [2]Weill Cornell Medical Center, New York

Background/Purpose: SLE patients have high-risk CVD profiles as they have increased prevalence of traditional CVD- and lupus-related thrombosis risk factors. In addition, aPL-positive patients are at increased risk for thrombosis. We have developed a free-of-charge counseling program for SLE and/or aPL-positive patients that provides a basic assessment of and education about the CVD and thrombosis risk factors (Arthritis Rheum 2009;60;S743). We report one-year outcomes of patients enrolled in our ongoing CVD-PCP.

Methods: The *assessment* phase of CVD-PCP includes the evaluation of blood pressure (BP), blood glucose, cholesterol profile, waist circumference, body mass index (BMI), diet and exercise habits, smoking status, Framingham 10-year CVD risk calculation, aPL-profile, and medications. The *education* phase includes detailed discussion of the above risk factors as well as CVD and thrombosis prevention strategies. At the end of the counseling, patients: a) receive tailored lifestyle recommendations and a written report; and b) are referred to the Nutrition and Physical Therapy Departments as needed based on pre-set criteria. Patients are followed every 3–6 months based on their CVD risk-profiles, and their rheumatologists receive a report after each counseling. While analyzing one-year outcomes, in order to estimate change over time, we used repeated measures regression analysis with time as the predictor.

Results: Between March 2009 and December 2010, 100 patients were enrolled in the program (mean age: 41.7 ± 14.3y; female: 87%; SLE with/without aPL: 74%; and aPL-positive patients without SLE: 26%) with a total of 344 visits (mean: 3.4 ± 1.9; range: 1–7). *At baseline:* a) 83% and 65% of patients required further nutrition and exercise counseling, respectively; b) 62% of patients were overweight or obese with a mean BMI of 28.4 (16.5–49.9); and c) 47%, 5%, and 75% of patients required better BP, blood sugar, and cholesterol management, respectively in order to meet the guidelines (cholesterol profile was available in 70% at baseline). *Based on the analysis of 77 patients who completed at least one-year follow-up:* a) there was a significant improvement in diet and exercise habits (Table), however not in BMI; b) the percentage of patients requiring better BP, blood glucose, and cholesterol management did not differ significantly (cholesterol profile was available in 93% at one-year follow-up).

Variable	3 or 6m Visit OR (95%CI)	9 or 12m Visit OR (95%CI)
Increased Fruits & Vegetables in Diet	1.51 (0.76–2.99)	1.94 (0.94–3.97)
Increased Whole-Grain & High-fiber in Diet	1.67 (0.84–3.32)	2.04* (1.00–4.16)
Increased Fish in Diet	2.35* (1.16–4.74)	2.10* (1.01–4.34)
Increased Attention to Cholesterol Free Diet	2.14 (0.93–4.93)	1.11 (0.43–2.85)
The Need for Further Nutrition Counseling	0.36* (0.16–0.78)	0.51 (0.23–1.17)
Increased Exercise at Least 30 min/day	2.95* (1.38–6.33)	3.42* (1.57–7.47)
The Need for Further Exercise Counseling	0.27* (0.19–0.68)	0.14* (0.06–0.35)

* $p < 0.05$

Conclusion: The one-year preliminary analysis of our ongoing CVD Prevention Counseling Program demonstrates positive changes in diet and exercise habits of SLE and/or aPL-positive patients. However, the lifestyle changes have not yet translated into clinically meaningful outcomes at one-year follow-up. The three-year longitudinal analysis will determine the true effectiveness of the program whether it decreases the prevalence of CVD risk factors.

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Designing a Community-Based Intervention to Improve the Health of Medically-Underserved Women with Systemic Lupus Erythematosus. Candace H. Feldman[1], Patricia A. Fraser[2], Bonnie L. Bermas[1], Melanie Zibit[1], Derrick J. Todd[1], Paul R. Fortin[3], Elena M. Massarotti[1] and Karen H. Costenbader[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Genzyme Corporation, Cambridge, MA, [3]Toronto Western Hospital, Toronto, ON

Background/Purpose: Medically-underserved women with systemic lupus erythematosus (SLE) have disproportionately high morbidity and mortality. We conducted focus groups to discuss 4 potential interventions to improve the health status of medically- underserved women with SLE.

Methods: From our Lupus Registry of 1,650 patients with SLE, defined according to the ACR Criteria, we identified 282 women, age 18 and older, residing in 11 urban, federally-defined medically-underserved area (MUA) zip codes. IRB-approved flyers were mailed to these women inviting them to participate. Additional flyers were distributed by the leaders of 2 predominantly African-American SLE support groups. In 90 minute focus groups, 3 trained moderators followed a detailed guide to present 4 potential interventions: 1) SLE-specific health navigators; 2) a peer support program; 3) a booklet of personal medical and SLE information ("Lupus Passport"); and 4) initiation of rheumatology specialty care at community health centers. The focus groups were tape-recorded, transcribed and coded, based on themes. Discussions concerning the interventions were analyzed in terms of perceived benefits, limitations, ideal target populations, and implementation questions.

Results: 29 women with SLE were divided randomly into 3 focus groups (n=9, n=9, n=11). 80% were African American, 10% Hispanic and 10% White. 83% were from urban MUAs. Mean age was 51 years (SD 18) and mean age at SLE diagnosis was 35 years (SD 15). Dominant themes included the desire for increased SLE education for patients and their families, the need for a patient navigator and advocate, the feeling of isolation at the time of SLE diagnosis, and the potential benefit of an assigned peer supporter. The Lupus Passport's explanations in plain English and inclusion of past and present medications interested many women. Several women felt that an assigned healthcare worker would be necessary to update the passport. The majority of participants already received their care at major academic medical centers and did not feel they would benefit from a rheumatologist at a community health center. Most women believed that any intervention, particularly a peer support program, should target newly diagnosed women. The women suggested quality of life and self-efficacy for disease control as potential measures of outcome.

Conclusion: Women with established SLE living in urban MUAs who participated in these focus groups were eager to partner with researchers to design interventions to improve their health and well-being. These women were enthusiastic about the development of a peer support program, and the utilization of a Lupus Passport, in particular for women with newly diagnosed SLE. Further collaboration with the community is needed to develop and test such interventions.

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A Randomised Comparison of Interactive and Conventional Education to Increase Adherence with a Dutch Physical Therapy Practice Guideline for Hip and Knee Osteoarthritis. Wfh Peter[1], Ph van der Wees[2], J. Verhoef[3], Z. de Jong[1], L. Vos[1], Wkha Hilberdink[4], M. Fiocco[1] and Tpm VlietVlieland[1]. [1]Leids University Medical Center, Leiden, Netherlands, [2]The Royal Dutch Society of Physical Therapy (KNGF) Amsersfoort, CAPHRI Maastricht University, IQ Health Care, Nijmegen, Netherlands, [3]Hogeschool Leiden, Leiden, Netherlands, [4]Paramedical Center for Rheumatology and Rehabilitation, Groningen, Netherlands

Background/Purpose: There is insufficient use of physical therapy (PT) guidelines in the Netherlands. The literature (1) and daily practice indicate a need for interactive forms of education to enhance guideline usage, but the evidence on their effectiveness is lacking. The aim of this study was to compare the effectiveness of two educational courses (interactive (IT) and conventional (CT)) as a part of the implementation of the Dutch PT guideline for hip and knee osteoarthritis (HKOA) (www.kngfrichtlijnen.nl/654/KNGF Guidelines in English.htm).

Methods: In 3 regions in the Netherlands, all PTs who were a member of the KNGF and working in primary care were randomly offered one of two educational courses. IT comprised the presentation of 3 clinical cases with the cooperation of 3 patient partners and 3 expert PTs per region, executed according to the method of clinical reasoning. CT included a presentation by one expert PT about the guideline development process and the most important recommendations. Both courses were pilot-tested among 10 PTs and adapted according to the comments received. Assessments were done before the educational course, immediately afterwards and three months thereafter. Assessments consisted of a self-developed electronic questionnaire, 18 questions on the usage of the guideline (5-point Likert scale, total score range 18–90) and 19 questions on knowledge (mixed format of items; total score range 0–76) which was pilot-tested among 15 PTs. In addition, sociodemographic characteristics of the participants were recorded. Statistical analysis included comparisons of total mean scores between the IT and CT groups across 3 time points by using General Linear Model analyses.

Results: In total 2059 PTs were invited, of whom 203 (9.9%) were willing to take part in the study and randomized in IT (n=108) or CT (n=95). The baseline characteristics of the participants of the IT and CT groups were comparable concerning age, gender, work setting, years of experience, the number of patients treated in the past three months and advanced education in OAmanagement. The unadjusted statistic analyses showed a significant difference for the total mean change usage of the guideline over 3 time points between CT (73.87(6.97)–74.31(6.18)–75.31(6.79)) and IT (75.05(6.69)–76.91(5.83)–78.31(5.77)), p=0.008 in favour of IT. Concerning knowledge there was no significant difference between the total mean change over 3 time points of CT (54.95(12.07)–60.87(12.35)–57.96(12.27)) and IT (55.43(11.08)–62.54(10.12)–59.73(10.19)), p=0.19.

Conclusion: An interactive educational course was found to be more effective with respect to improvement of self-reported guideline usage than a conventional educational course, whereas knowledge increased in both groups but did not differ significantly. A further analysis of the effectiveness of both educational strategies will facilitate the optimization of comprehensive PT guideline implementation strategies.

Funding: This project was funded by the Royal Dutch Society of Physical Therapy and the Dutch Arthritis Association.

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Development and Usability Testing of ANSWER: A Web-Based Methotrexate Decision Aid for Patients with Rheumatoid Arthritis. Linda C. Li[1], Paul M. Adam[2], Anne F. Townsend[3], Diane Lacaille[3], Charlene Yousefi[3], Shawn Turnau[1], Dawn Stacey[4], Jessie McGowan[5], Peter Tugwell[6], Catherine L. Backman[1] and ANSWER Team[7]. [1]University of British Columbia, Vancouver, BC, [2]Mary Pack Arthritis Centre, Vancouver, BC, [3]Arthritis Research Centre of Canada, Vancouver, BC, [4]University of Ottawa, Ottawa, ON, [5]Universtiy of Ottawa, Ottawa, ON, [6]Institute of Population Hlth, Ottawa, ON, [7]Vancouver & Ottawa

Background/Purpose: Decision aids are evidence-based tools designed to inform people of the potential benefits and harm of treatment options, clarify their preferences, and provide a structure for discussion at a clinic visit. For patients with rheumatoid arthritis (RA) who are considering methotrexate, we have developed an interactive web-based decision aid called the ANSWER. The current study aims to: 1) assess the usability of the ANSWER prototype; and 2) identify important components of usability testing from the patient's perspective.

Methods: Development of the ANSWER was consistent with the International Patient Decision Aid Standards.[1] This decision aid consists of: 1) six animated patient stories and narrated information on the evidence of methotrexate for RA; and 2) interactive questionnaires to clarify patients' treatment preferences. Eligible participants for the usability test were patients with RA who had used methotrexate. We used the concurrent think-aloud method, whereby participants were asked to verbalise their thoughts while using the ANSWER. Sessions were audiotaped and field notes taken. Participants completed the System Usability Scale (SUS) [2;3] to assess the overall usability of the decision aid (range=0–100; higher=more user friendly). We conducted content analysis to identify major themes to understand the user experience.

Results: 15 patients participated in the usability testing; the majority were age 50 or over and university/college graduates (n=8, 53.4%). The median disease duration was 5 years (IRQ=0.83–10). Participants took an average of 56.1 minutes (SD=34.8) to complete the program. The mean SUS score was 81.2 (SD=13.5), indicating high usability. Content analysis of audiotapes and field notes revealed three themes that participants focused on while testing the ANSWER: 1) user engagement (i.e., the relevance of the decision aid design and content to the user); 2) information quality (i.e., clarity and credibility of information); and 3) user-tool interaction (i.e., consistency of the design; ease of use). Across these themes, participants commented extensively on the overall integration of the content and navigation (e.g., challenges of moving from one task to the next). We made revisions to the prototype based on the findings.

Conclusion: Although the SUS score indicated high usability, findings from the think-aloud sessions highlighted additional areas where further modifications were needed for the online ANSWER decision aid. Our results highlight the importance of direct observation methods in usability testing. With an increasing number of online and mobile programs being developed to improve arthritis knowledge and care, further research to advance the methodology of usability testing is warranted.

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The Impact of An Evidence-Based Community-Delivered Exercise Program on Arthritis Symptoms and Health-Related Quality of Life. Dina L. Jones, Jennifer L. Eicher, Matthew J. Gurka, Ruoxin Zhang, Melissa Himes, W. Lynn Harrington, Abhishek Vishnu and R. Turner Goins. West Virginia University, Morgantown, WV

Background/Purpose: Although the efficacy of exercise in people with arthritis has been established, there is less literature to support the effectiveness of these interventions when delivered in the community setting. The EnhanceFitness® program is an evidence-based, community-delivered intervention that is effective in older adults, however, its effectiveness in people with arthritis has not been studied. Thus, the purpose of this study was to determine if participation in 12 weeks of EnhanceFitness® resulted in arthritis-specific health benefits and improvement in health-related quality of life (HRQOL) for the participants.

Methods: One-hour exercise classes were offered three times per week for 12 weeks at 11 senior centers, three churches, one rehabilitation facility, and one recreational center in nine counties in West Virginia. Each class was limited to adults, aged 18 years and older, with self-reported physician-diagnosed arthritis who were sedentary or low active (reported ≤ 60 minutes per week of moderate-intensity activity). Participants were assigned to an immediate exercise group or a delayed-intervention group that began exercise 12 weeks later. The program consisted of low-impact aerobics, strength-training exercises, flexibility, and balance exercises. Data on demographics, arthritis symptoms, and HRQOL were collected at baseline (pre-exercise) and after the 12-week class (post-exercise). Arthritis pain, fatigue, and stiffness were assessed using 10-centimeter Visual Analogue Scales. The SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were used to measure HRQOL. Participants who attended at least 50% of classes and all data collection sessions were defined as study completers and included in the analysis. Within-group comparisons between baseline and 12 weeks were conducted using generalized linear mixed models and natural log transformations where appropriate.

Results: The 323 participants who enrolled in the study were primarily female (86%) and white (95%) with a mean age ± standard deviation of 68 ± 11 years old (range 27 to 95 years). The immediate exercise group contained 181 (56%) people and the delayed intervention group included 142 (44%) people. There were 175 (54%) study completers (Group 1, n = 108; Group 2, n = 67). Participants were more likely to withdraw if they were in the delayed-intervention group, younger, had lower physical and mental HRQOL, or more chronic health conditions. There was no significant difference in the SF-12 PCS ($p = 0.42$) or MCS ($p = 0.23$) scores from baseline to 12 weeks. There was, however, an improvement in pain, stiffness, and fatigue during the intervention ($p < 0.01$).

Conclusion: Participants who attended at least 50% of an evidence-based exercise program delivered in the community setting reported an improvement in arthritis pain, stiffness, and fatigue. Physical and mental HRQOL did not change perhaps due to the differential loss of participants with poorer health and lower HRQOL from the intervention. Overall, the EnhanceFitness® exercise program appeared to improve arthritis symptoms in inactive older adults with arthritis.

ACR Concurrent Abstract Session
Cytokines, Mediators, and Gene Regulation I
Monday, November 7, 2011, 4:30 PM–6:00 PM

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The TNFα Induced Microrna-17/92 Cluster Promotes Synovial Fibroblast Aggressiveness by Repressing Key Signaling Pathway Inhibitors. Michelle Trenkmann[1], Matthias Brock[1], Renate E. Gay[1], Christoph Kolling[2], Rudolf Speich[3], Beat A. Michel[1], Steffen Gay[1] and Lars C. Huber[3]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Clinic and Policlinic for Internal Medicine, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: The miR-17/92 cluster encompasses six distinct microRNAs (i.e. miR-17, −18a, 19a, −19b, −20a and −92a) and has been associated with various (patho)physiological processes such as the maturation of the immune system or the development of malignant tumors. To elucidate the role of this microRNA cluster in the pathogenesis of rheumatoid arthritis (RA) we studied expression and function of the primary transcript C13orf25 and mature miRs derived from miR-17/92 in RA synovial fibroblasts (SF).

Methods: RASF (n=5) were stimulated with 10ng/ml TNFα for 1h, 2h, 4h, 8h, 16h and 24h. The C13orf25 mRNA and the mature miR-18a, −19a, −20a and −92a were measured by SYBR Green quantitative real time PCR (qPCR). RASF (n=5) were transfected with C13orf25 promoter constructs and reporter gene assay was performed after 8h of TNFα stimulation. RASF (n=5) were transfected with pre-miRs and then stimulated with TNFα for 24h. IL6 and MMP1 were measured by qPCR and ELISA. 3′UTRs of potential target genes were cloned into luciferase vectors and reportergene assays were carried out in pre-miR-18a transfected Hek293 cells (n=4).

Results: TNFα significantly induced the expression of both the C13orf25 transcripts and of the mature miRs-18a, −19a, and −20a in a time dependent manner with peak induction observed at 16h of stimulation. The activity of the C13orf25 promoter was significantly enhanced by TNFα as assessed by reporter gene assay; conversely, deletion of the NF-κB binding site within the promoter region abolished this induction (wt 1.47±0.23-fold, ΔNF-κB 1.17±0.15-fold; $p<0.05$). Transfection of pre-miRs and subsequent stimulation of SF with TNFα increased the mRNA expression levels of IL6 and MMP1 in miR-18a transfected cells. Thus, the expression of IL6 and MMP1 was upregulated by 2.4±1–fold and 4.9±4.9–fold ($p=0.046$ and $p=0.068$). Additionally, miR-18a transfection strongly enhanced the TNFα-induced expression of IL6 (190±58-fold) and MMP1 (1044±864-fold) to 418±139–fold and 2207±1479-fold, respectively ($p<0.05$). These data were confirmed on protein level by ELISA showing an increase of MMP1 by 5.9±5.1-fold (basal; $p=0.1$) and 1.13±0.09-fold (TNFα; $p=0.03$), and of IL6 by 1.85±0.79-fold (basal; $p=0.07$) and 1.63±0.43-fold (TNFα; $p=0.03$) Following a TargetScan database search, the MAP kinase phosphatase PTP4A3 and PIAS3, an inhibitor of Stat3 and NF-κB signaling, were studied as potential target genes of miR-18a. Reporter gene assays utilizing the respective 3′UTRs (wt or mutated miR-18 seed match) demonstrated that PIAS3 and PTP4A3 are direct miR-18a targets ($p<0.05$).

Conclusion: We show here for the first time that the miR-17/92 cluster is induced by TNFα in SF via the NF-κB pathway. We demonstrate that miR-18a targets inhibitors of major signaling pathways involved in the activation of RASF which, in turn, may result in the upregulation of inflammatory cytokines and matrix degrading enzymes. Our data thus provide first evidence that miR-18a might have a pivotal role in the regulation and integration of signal transduction pathways in RASF.

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MiR-323, a Novel MicroRNA in Rheumatoid Arthritis, Promotes the Activated Phenotype of Synovial Fibroblasts. Mary Connolly[1], Michelle Trenkmann[1], Joanna Stanczyk[1], Emmanuel Karouzakis[1], Christoph Kolling[2], Beat A. Michel[1], Douglas J. Veale[3], Ursula Fearon[3], Renate E. Gay[1], Steffen Gay[1] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Dublin Academic Medical Centre, University College Dublin, Dublin, Ireland

Background/Purpose: MicroRNAs (miRNA) belong to a class of small, evolutionarily conserved noncoding RNAs that function as post-transcriptional repressors of gene expression. An accumulating body of evidence suggests that up to 50% of the human genome is regulated by miRNAs. The aim of this study was to examine expression of miRNA-323 in synovial fibroblasts from patients with rheumatoid and osteoarthritis (RA and OA) and to elucidate the role of miR-323 in the pathogenesis of arthritis.

Methods: Synovial fibroblasts (SF) were isolated from RA and OA patients undergoing joint replacement surgery. Total RNA was isolated using the mirVana™ miRNA isolation kit. MiR-323 levels were analyzed by real-time PCR and data was calculated by the dCt method using miR-let-7a as an endogenous control. The effect of pro-inflammatory stimuli and DNA methylation was examined by stimulation of SF with IL-1β (10ng/ml), TNFα (10ng/ml), poly(I:C) (10μg/ml) or 5-azaC (0.5μM). Overexpression/silencing of miR was analysed using a synthetic precursor of Pre or Anti-miR™-323 respectively. Cytokine and MMP levels were measured by PCR and ELISA. Cell migration, adhesion and proliferation were examined using scratch, fibronectin-based adhesion or MTT assays. Cytoskeletal rearrangement was examined by immunoflourescent staining of filamentous actin (F-actin). The 3′UTR of TIMP-3 was cloned into a luciferase vector and reporter gene assays were carried out in pre-miR-323 transfected Hek293 cells.

Results: Expression of miR-323 was significantly higher in RA (n=6) compared to OASF (n=4, $p<0.05$). Levels of miR-323 remained unchanged in RASF following treatment with IL-1β, TNF-α and TLR-3 ligand, poly(I:C). Incubation of OASFs with hypomethylating agent, 5-azaC, resulted in a 2.8 fold increase in miR-323 mRNA, suggesting that epigenetic mechanisms mediate regulation of miR-323 in synovial fibroblasts. Overexpression of miR by transfection with pre-miR-323 resulted in significant upregulation of IL-8, MMP-1 and MMP-3 in RASF (n=4, $p<0.05$), however no significant differences were observed in transcript levels of IL-6. Conversely, transfection of cells with anti-miR-323 resulted in marked downregulation of MMP-1,3 and IL-8. Similar results were observed with pre/anti miR when protein levels were examined (n=4). Overexpression of miR-323 accelerated RASF migration in a scratch assay and significantly increased cell adhesion and proliferation (n=3, $p<0.05$). Furthermore, pre-miR induced cytoskeletal disassembly in RASF, resulting in filopodia and microspike formation. Reporter gene assays confirmed TIMP-3 as a direct target of miR-323, since transfection of the 3′UTR of TIMP-3 sense construct with miR-323 resulted in lower relative luciferase activity as compared with mock transfected HEK cells.

Conclusion: Our data provides evidence that miR-323 is significantly increased in RA and thereby involved in the upregulation of proinflammatory cytokines and matrix metalloproteinases in RASF. miR-323 also potentiates cell migration, proliferation and adhesion, other key processes in the pathogenesis of RA. We conclude that miR-323 is involved in the development of the activated phenotype of RASF.

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The Role of Microrna-34 and Microrna-22 in Dendritic Cells and Monocyte Activation in Rheumatoid Arthritis. Stefano Alivernini[1], Derek S. Gilchrist[2], Lynn Crawford[2], Lucy Ballantine[2], John Hunter[3], Derek Baxter[2], Barbara Tolusso[4], Elisa Gremese[4], Gianfranco Ferraccioli[4], Iain B. McInnes[2] and Mariola Kurowska-Stolarska[2]. [1]University of Glasgow, Glasgow, United Kingdom, [2]University of Glasgow, Glasgow, United Kingdom, [3]Gartnavel General Hospital, Glasgow, United Kingdom, [4]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: MicroRNAs (miRs) are a novel class of post-transcriptional regulators that have been implicated in the pathogenesis of distinct human diseases, including Rheumatoid Arthritis (RA). We have previously shown that miR-34 family members and miR-22 are overexpressed in synovial fluid (SF) monocytes compared to matched peripheral blood (PB) monocytes in RA patients. The aim of this study was to investigate the functional role of miR-34 and miR-22 in the biology of monocytes and monocyte-derived DCs in the context of their abnormal activation in RA.

Methods: Expression of miR-34a and miR-22 in RA and osteoarthritis (OA) synovial tissues were evaluated by *in situ* hybridization. To characterize miR-34a positive cells, fluorescent *in situ* hybridization and immunostaining for CD68 were performed on RA tissues. Expression of miR-34a and miR-22 was evaluated by qPCR on DCs isolated by CD1c and CD304 specific microbeads from matched PB and SF of RA patients (n=3). Monocytes from PB of healthy donors (n=5) were isolated by CD14+ microbeads (AutoMACS) and transfected with miR-34a, miR-22 or control mimics. Cells were subsequently stimulated with LPS (10 ng/ml) or CL097 (1 mg/ml). DCs were generated from PB CD14+ cells stimulated with GM-CSF (100 ng/ml) and IL-4 (20 ng/ml) for 7 days. Once generated, CD14+ derived DCs (n=4) were transfected with miR mimics and stimulated as described above. After 18h of stimulation, supernatants were collected and evaluated for chemokine and cytokines levels (Luminex assay). To identify miR-34/22 targets HumanTargetScan cross-referenced with transcriptomic profile of SF CD14+ cells was employed. Identified targets were experimentally verified by miR luciferase assay and qPCR.

Results: miR-34a and miR-22 are overexpressed in SF DCs compared to matched PB DCs in RA patients. *In situ* hybridisation showed that miR-34a and miR-22 are widely expressed in RA synovium compared to OA. Double immunofluorescence staining revealed that miR-34a is present in RA synovial tissue myeloid cells. Enforced overexpression of miR-34a but not miR-22 in PB monocytes increased TLR7/8 triggered TNF-alpha production. Overexpression of miR-34a and miR-22 in monocytes-derived DCs increased spontaneous, TLR4 and TLR7/8 triggered TNF-alpha production. In addition, miR-22 but not miR-34a induced production of chemokines and interferon alpha by DCs. Computational target ranking system cross-referenced with transcriptomic profile of RA SF CD14+ cells identified Axl and Tyro3, receptor tyrosine kinases involved in negative feedback mechanism limiting TLRs-induced myeloid cells activation, as potential direct targets for miR-34a and miR-22. Experimental validation confirmed that miR-34a and miR-22 target 3′ UTR of Axl and Tyro3 mRNAs, respectively. Consistently, Axl and Tyro3 levels are downregulated in myeloid cells overexpressing miR-34a and miR-22, respectively.

Conclusion: This study indicates that overexpression of miR-34a and miR-22 in myeloid cells can lead to the disregulation of their self-regulatory mechanism. Thus, high levels of miR-34a and miR-22 in synovial myeloid cells of RA patients may be responsible for an excessive pro-inflammatory activation of these cells.

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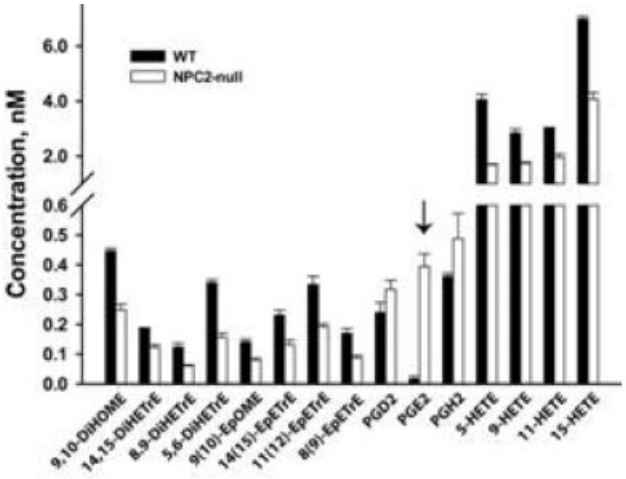
Niemann-Pick Type C2 Protein As a Negative Regulator of Innate Immunity: Inflammatory Cytokines and Eicosanoids. Andrey Frolov[1], Min Jiang[2], Hua Dong[3], Lihua Yang[1], Rahul Matnani[1], Bruce Hammock[3] and Leslie J. Crofford[1]. [1]University of Kentucky, Lexington, KY, [2]University of Cincinnati, Cincinnati, OH, [3]University of California Davis, Davis, CA

Background/Purpose: Synovial fibroblast (SF) activation has been proposed to be a central event in RA initiation. SF activation is characterized by upregulated production and secretion of inflammatory cytokines and eicosanoids. We have recently identified Niemann-Pick type C2 (NPC2) protein as a negative regulator of fibroblast activation and demonstrated that SF isolated from RA patients are NPC2-deficient (1). In the current study, we elucidated a molecular mechanism for NPC2-dependent suppression of inflammatory mediators in human fibroblasts.

Methods: NPC2-null human skin fibroblasts were derived from patients with NPC2 disease (1). DNA microarray and real-time RT-PCR analyses of NPC2-null cells were performed as described (1). Arachidonic acid (AA) metabolome profiling was performed by the liquid chromatography (LC) electrospray ionization tandem mass spectrometry (LC/MS/MS) (2). Suppression of cytosolic phospholipase A2 (cPLA2) activity and lysophosphatidic acid (LPA) signaling was achieved by using their respective specific inhibitors, Calbiochem 525543 and Ki 16245. All cell manipulations and measurements were performed under unstimulated conditions.

Results: In order to elucidate a molecular mechanism responsible for the increased production of interleukins 1B (IL-1B) and 6 (IL-6) in NPC2-null cells (1), we probed the cPLA2 metabolic pathway. DNA microarray and real-time RT-PCR data demonstrated upregulation of cPLA2 (*PLA24GA*), phospholipase D3 (*PLD3*), prostaglandin-endoperoxide synthase 2 (*PTGS2*),

and prostaglandin E synthase (*PTGES*) mRNAs by respectively ~60-fold, 3-fold, 150-fold, and 10-fold. The LPA receptor EDG2 (*LPA1*) and the prostaglandin E2 receptor *EP4* were induced by ~2-fold and ~3-fold, respectively. Inhibition of cPLA2 led to suppression of *IL-1B* and *IL-6* mRNA levels by ~ 90%. Blocking EDG2 signaling resulted in ~75% suppression of *IL-1B* and *IL-6* mRNAs. Because LPA was implicated in the induction of a key RA inflammatory mediator, prostaglandin E2 (PGE2), we examined PGE2 production by NPC2-null fibroblasts using LC/MS/MS. The data showed more than 10-fold upregulation of PGE2 production and secretion by NPC2-null cells as compared to control. More importantly, AA metabolome profiling by LC/MS/MS revealed the very specific nature of PGE2 up-regulation as the other analyzed AA metabolites were mostly down-regulated (Fig. 1).



Conclusion: This work identifies NPC2 protein as an important negative regulator of the cPLA2 metabolic pathway which drives production of both the inflammatory cytokines and PGE2 in activated human fibroblasts. Given the crucial role of these mediators in RA, we envision NPC2 protein or its signaling pathway as a potentially novel and multifaceted therapeutic tool to target activated SF in RA.

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1675

A Novel CR3 Agonist Attenuates Pro-Inflammatory Signaling in Subjects with Common and Variant ITGAM Polymorphism, rs1143679.

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Background/Purpose: The mechanism underlying initiation and perpetuation of inflammation—with eventual end organ injury—in Systemic Lupus Erythematosus (SLE) is not yet defined. Equally unclear are mechanisms to attenuate such inflammation. An important candidate for initiation and perpetuation of the inflammatory response may be the chronic stimulation of resident leukocytes through toll like receptors (TLR). Complement Receptor 3 (CR3), a heterodimeric receptor on the surface of various types of leucocytes, is known to decrease pro-inflammatory signals by dendritic cells when ligated to iC3b. The goal of this study was to evaluate whether a TLR-mediated pro-inflammatory stimulus is attenuated by a novel iC3b mimetic specific for CR3—known as LA1—on other cells expressing CR3: macrophages and neutrophils. ITGAM polymorphism rs1143679, encoding for a non-conserved R77H substitution in the CD11b alpha chain of CR3, is known to be associated with SLE across various ethnic groups. While the polymorphism is theorized to affect ligand binding to CR3, its functional significance is unknown. A sub-goal was to evaluate if rs1143679 carrier status attenuated the effect of LA1.

Methods: The effect of LA1 on basal and stimulated responses by macrophages and neutrophils of human subjects (twenty healthy donors) was evaluated. Rs1143679 carrier status of subjects was determined by allelic discrimination. Macrophages derived from CD14+ monocytes of healthy human donors were treated with R848 (a specific TLR7 ligand, 1 uM), with and without LA1 (a recently described CR3 agonist, 15 uM). Quantification of TNF-α secretion, the readout of TLR7 activation, was assessed by ELISA. Neutrophils derived from healthy subjects were evaluated for superoxide anion production after stimulation with FMLP (.1 uM) in the absence and presence of LA1 (15 uM). Neutrophils were also evaluated for adhesion to a fibrinogen-coated surface in the presence of LA1.

Results: Treatment of macrophages with R848 significantly stimulated TNF-α release compared with macrophages alone (1265 $\pm$ 297 pg/ml versus 26 $\pm$ 30 pg/ml, respectively, $p = 0.006$, $n = 7$). Pre-exposure to LA1 followed by treatment with R848 impaired TNF-α secretion from macrophages (R848 + LA1: 700 $\pm$ 249 pg/ml, $p=0.015$). Exposure of macrophages to LA1 in absence of R848 had no effect on cellular morphology, and did not induce TNF-α over 24 hrs. The % inhibition by LA1 of TNF-α in rs1143679 non-carriers was 63% ($n=5$) vs. 17% ($n=2$) in rs1143679 carriers (heterozygous). The addition of LA1 to neutrophils 15 min before FMLP resulted in the inhibition of O° production (13 nmol O*/5 min vs 7 nmol O*/5 min). As expected, pretreatment with LA1 alone stimulated the adherence of neutrophils to fibrinogen-coated surface (8$\pm$10 PMNs baseline, 5,930 $\pm$ 250 PMNs, LAI, 15 uM).

Conclusion: As previously shown in dendritic cells, inflammatory responses in macrophages and neutrophils are able to be attenuated in a CR3-specific fashion—in this case, by novel agonist LA1. These results also suggest significant cross-talk between CR3 and other pro-inflammatory pathways, such as TLR7. A novel functional difference in immune response to iC3b mimetic LA1, based on carrier-status of the rs1143679 polymorphism, is suggested.

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Musculoskeletal Inflammation and Estrogens: T-Cell Leukemia 1A (*TCL1A*) Gene-Dependent Regulation of Inflammatory Cytokines.

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Background/Purpose: Arthralgia, myalgia and inflammatory arthritis occur in up to 50% of women who receive inhibitors of estrogen synthesis (aromatase inhibitors, AIs) for the treatment of breast cancer. In a recent genome-wide association study (GWAS), we identified 4 SNPs on chromosome 14, one of which created an estrogen response element, that were associated with musculoskeletal adverse events (MS-AEs) in women who participated in an adjuvant therapy trial (NCIC-CTG MA.27, Ingle et al. J Clin Oncol 2010;28:4674) using AIs to treat early breast cancer. Those SNPs mapped near the 3'-end of the T-Cell Leukemia 1A (*TCL1A*) gene. Therefore, we set out to study the possible role of TCL1A in mediating MS-AEs during AI therapy.

Methods: Functional genomic studies in pursuit of this GWAS SNP signal included characterization of TCL1A and inflammatory cytokine and cytokine receptor expression in response to estrogen using qRT-PCR in a sarcoma cell line (U2OS) stably transfected with ERα. We assayed cytokine expression changes after TCL1A knockdown and over-expression, as well as NF-kB transcriptional activity. In order to characterize the impact of the SNPs identified during the GWAS on NF-kB activity, we also used lymphoblastoid cell lines (LCLs) stably with known SNP genotypes transfected with ERα to perform selected experiments.

Results: We showed that TCL1A expression was increased by estradiol (E2) and that it significantly decreased expression of IL-17RA, increased IL-17, IL-12, IL-12RB2 and IL-1R2 expression as well as NF-kB transcriptional activity. Increased TCL1A expression was associated with variant SNP genotypes in E2-treated LCLs stably transfected with ERα. Finally, exposure of these LCLs to E2, followed by ERα blockade with ICI-182,780, resulted in greatly increased NF-kB transcriptional activity for variant SNP genotypes. These studies have linked variant SNP sequences near *TCL1A* to AI-dependent musculoskeletal pain, to enhanced E2-dependent TCL1A expression and to downstream alterations in cytokine and cytokine receptor expression.

Conclusion: Our recent case-control GWAS of DNA samples from a large AI clinical trial identified SNPs near the 3′-end of *TCL1A* that were associated with AI-dependent MS-AEs. In the present studies, we found that E2 induces TCL1A expression that, in turn, alters IL-17RA, IL-17, IL-12, IL-12RB2, and IL-1R2 expression as well as NF-kB transcriptional activity. These results provide a novel pharmacogenomic explanation for a clinically important adverse drug reaction, as well as insight into a novel estrogen-dependant mechanism for the regulation of cytokine and cytokine receptor expression.

ACR Concurrent Abstract Session
Genetics, Genomics, and Proteomics
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An International Collaboration for the Genetic Fine Mapping of 8,000 Rheumatoid Arthritis Cases and 12,000 Controls Refines Associations to Known Loci, Indicates Multiple Independent Affects and Reveals Novel Associations. Stephen Eyre[1], John Bowes[2], Anne Barton[3], Soumya Raychaudhuri[4], Christopher Amos[5], Dorothee Diogo[4], Annette T. Lee[6], Lars Klareskog[7], Leonid Padyukov[8], Eli A. Stahl[4], Peter K. Gregersen[9], Robert M. Plenge[4] and Jane Worthington[1]. [1]University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [4]Brigham and Women's Hospital, Boston, MA, [5]Houston, TX, [6]Feinstein Institute Med Rsch, Manhasset, NY, [7]Karolinska Institutet, Stockholm, Sweden, [8]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [9]Feinstein Institute Medical Reschearch, Manhasset, NY

Background/Purpose: Genome wide association studies (GWAS) have been tremendously successful in identifying loci associated with a range of traits and disorders. Indeed, there are over 240 confirmed susceptibility loci reported for nine autoimmune diseases alone. One task now is to take these findings and translate them into clinical utility. The first step in this is to elucidate the genetic architecture of the loci in each disease with fine mapping experiments. These are expected to localise the association signal, indicate whether multiple, independent genetic affects are present and may point to the casual gene.

Methods: The aim of this study was to fine map loci significantly associated with autoimmune disease in a large cohort of 10,000 rheumatoid arthritis (RA) cases and 14,000 controls using the custom Illumina Immunochip. The Immunochip was designed by a consortium of researchers investigating 12 autoimmune diseases and represents all known genetic variation from dbSNP, 1kG and sequencing projects for approximately 200 validated loci.The genotyping for the RA samples was performed in multiple centres and therefore all raw genotyping data was collated centrally for combined clustering and analysis. The data was first re-clustered and after applying strict QC metrics (98% SNP and 98% sample) the samples were subjected to further pruning for relatedness and ancestral outliers.

Results: In the initial analysis we have examples of re-focusing of the strongest association signal (e.g. 2q11), evidence for multiple independent associations within a locus (e.g. *PADI4, PTPN22*) and associations to previously unconfirmed RA loci (e.g. *IRAK1, IRF8*).Within the 2q11 locus the peak of associations has moved 76kb to now lie within the *AFF3* gene. The *PADI4* gene has, for the first time, been robustly associated with RA in a Caucasian population ($p = 7\times10^{-8}$). There is also evidence for two independent affects in this region, one of which is correlated with the variant previously reported to be associated with RA in Japanese populations. In addition we have preliminary evidence that there may be 2 independent associations around the *PTPN22* locus. The second affect is centred on the RSBN1/PHTF1 genes, a region previously implicated with PsA. We also have preliminary evidence of genome-wide significant ($p<5\times10^{-8}$) associations to *IRF8*, a gene previously associated with Multiple Sclerosis, and to a region on ChrX incorporating *IRAK1*, a loci previously associated with systemic lupus erythematosus. This is the first evidence of a significant association with a locus on ChrX with RA.

Conclusion: Although GWAS studies have underpinned a dramatic advance in our understanding of the genetic architecture of rheumatoid arthritis it is clear that large scale fine mapping efforts, such as this, will be necessary to better interpret the complexity of the results and translate the findings into clinicsal utility.

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Genome-Wide Association Study of Dermatomyositis Reveals Shared Genetic Risk Factors with Other Autoimmune Diseases. Frederick W. Miller[1], Robert G. Cooper[2], Jiri Vencovsky[3], Lisa G. Rider[4], Katalin Danko[5], Lucy R. Wedderburn[6], Ingrid E. Lundberg[7], Lauren M. Pachman[8], Ann M. Reed[9], Steven R. Ytterberg[9], Leonid Padyukov[10], Albert Selva O'Callaghan[11], Timothy Radstake[12], David A. Isenberg[13], Hector Chinoy[14], William E. Ollier[15], Terrance O'Hanlon[16], Bo Peng[17], Paul Scheet[17], Annette T. Lee[18], Janine Lamb[14], Wei Chen[17], Christopher Amos[17], Peter K. Gregersen[19] and Myositis Genetics Consortium[20]. [1]NIH/NIEHS NIH Bldg 10 4–2330, Bethesda, MD, [2]Hope Hospital, Salford, United Kingdom, [3]Institute of Rheumatology, Prague 2, Czech Republic, [4]NIEHS NIH, Bethesda, MD, [5]University of Debrecen, Debrecen, Hungary, Debrecan, Hungary, [6]University College London (UCL), United Kingdom, [7]Karolinska Institutet, Stockholm, Sweden, [8]Northwestern University Feinberg School of Medicine, Chicago, IL, [9]Mayo Clinic, Rochester, MN, [10]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [11]Hospital Universitari General Vall d'Hebron, Barcelona, Spain, [12]Geert Groote Plein 8, Nymegen, Netherlands, [13]University College London, London WC1E 6JF, United Kingdom, [14]Manchester, United Kingdom, [15]Univ of Manchester Med School, Manchester, United Kingdom, [16]NIH, Bethesda, MD, [17]Houston, TX, [18]Feinstein Institute Med Rsch, Manhasset, NY, [19]Feinstein Institute Medical Reschearch, Manhasset, NY, [20]Bethesda

Background/Purpose: Genetic risk factors for adult dermatomyositis (DM) and juvenile DM outside of the major histocompatibility complex (MHC) have been difficult to identify, although family studies have suggested that DM shares genetic risk factors with other autoimmune diseases.

Methods: We performed a genome-wide association study (GWAS) on adult DM and juvenile DM subjects of European ancestry meeting probable or definite Bohan and Peter criteria using the Illumina platform. DM cases (n=1178: 705 with adult DM and 473 with juvenile DM) were compared to geographically- and race-matched controls (n=4724). Ingenuity Systems Pathway Analyses were performed based on the genes identified by GWAS.

Results: As expected, we observed a strong signal in the MHC locus across the class II region (maximum $p=2.79\times10^{-29}$) but no other locus reached genome-wide significance in this dataset. To assess for possible shared genes with other autoimmune diseases, however, we examined the association signals in 140 non-MHC loci that have been associated with autoimmune diseases. Strikingly, seven SNPs from six genes had p values $\leq$ 0.01, thus substantially exceeding expectation. These included: B lymphocyte kinase (*BLK*: rs2736340, $p=6.53\times10^{-5}$); chemokine (C-C motif) ligand 21 (*CCL21*: rs2492358, $p=2.10\times10^{-4}$; and rs951005, $p=3.17\times10^{-5}$); protein tyrosine phosphatase non-receptor type 2 (*PTPN2*: rs1893217, p=0.0029); signal transducer and activator of transcription 4 (*STAT4*: rs7574865, p=0.0050); interleukin 2 receptor alpha (*IL2RA*: rs7072793, p=0.0073); and a gene encoding a 153–amino acid protein with four putative transmembrane domains (*ORMDL3:* rs2290400, p=0.0010). Based on the associated genes from the entire GWAS, canonical pathways that seemed particularly important in DM were those relating to antigen presentation ($p=9.49\times10^{-23}$), cytotoxic T cell-mediated apoptosis of target cells ($p=1.44\times10^{-17}$), allograft rejection signaling ($p=1.44\times10^{-17}$), the OX40 (CD134) signaling pathway ($p=5.9\times10^{-17}$) and autoimmune thyroid disease signaling ($p=5.0\times10^{-13}$).

Conclusion: Our findings indicate that DM shares many genetic features and canonical pathways with other autoimmune diseases. This first identification of these common autoimmune disease genetic predispositions that promote the development of DM suggests potential novel therapeutic approaches for this disorder.

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Genome Wide Association Study of Quantitative Anti-CCP Level in Rheumatoid Arthritis Identified New Risk Variants. Jing Cui[1], Kimberly E. Taylor[2], Henrik Kallberg[3], Michael E. Weinblatt[4], Lars Klareskog[3], Lindsey A. Criswell[5], Nancy A. Shadick[4], Robert M. Plenge[6] and Elizabeth W. Karlson[6]. [1]Brigham and Womens Hospital, Boston, MA, [2]University of California, San Francisco, San Francisco, CA, [3]Karolinska Institutet, Stockholm, Sweden, [4]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [5]University of California San Francisco, San Francisco, CA, [6]Brigham and Women's Hospital, Boston, MA

Background/Purpose: Anti-cyclic citrullinated peptide (anti-CCP) antibody is a proxy for disease activity of rheumatoid arthritis (RA). We conducted a study to test if anti-CCP level is a heritable trait. We then carried out a genome wide association study (GWAS) meta-analysis using more than 2 million SNPs in 2031 anti-CCP+ RA patients from 3 large cohorts of European American RA patients,

Brigham Rheumatoid Arthritis Sequential Study (BRASS), North American Rheumatoid Arthritis Consortium (NARAC), and Epidemiological Investigation of RA (EIRA) to identify SNPs that influence quantitative anti-CCP level in RA patients.

Methods: Anti-CCP was measured using the second generation ELISA assay for all 3 cohorts. Genotyping platforms Affymetrix 6.0, Illumina 550K and 317K were used for BRASS, NARAC and EIRA samples, respectively. Anti-CCP measures were normalized by taking the inverse normal of the rank. A mixed linear model analysis was used to estimate the proportion of variance that explained by genotyped SNPs from the whole genome, so called heritability. Association between SNPs and anti-CCP level was tested assuming a genetic additive model adjusting for the first three principal component values in each cohort. Inverse variance weighted meta-analysis was used to combine statistics from the 3 cohorts. Polygenic risk scores of additive, beta weighted risk allele counts at independent SNPs were conducted assuming thousands of genetic variants that have small impact on anti-CCP level.

Results: 483 BRASS, 868 NARAC and 680 EIRA samples that passed all quality control filters were included. Heritability analysis estimated that 38% of anti-CCP variation was attributable to all SNPs genome wide. Meta GWAS analysis showed the human leukocyte antigen (HLA) region was the top hit with p-value of 8.8E-12 for rs3117097 (near BTNL2 gene). There were 65 SNPs in this region that exceeded the genome-wide significance threshold of 5E-8. The SNPs were in linkage disequilibrium (LD) with the HLA-DR3 allele with LD r^2 in range of (0.25–0.89). Suggestive novel associations outside of HLA were also observed. The top SNP was rs8063248 with p-value of 6E-7. The top 10 findings are listed in the table. None of known RA risk alleles (~45 loci) were associated with anti-CCP level except for HLA. Using SNPs at p-value <0.05, polygenic analysis excluding the HLA region revealed that polygenic risk scores (N= 14498 SNPs) were associated with quantitative anti-CCP level and explained ~1.5% total variance.

Table. Top 10 SNPs associations with anti-CCP level outside HLA

Chr	rs	gene	Base pair	Allele A	Minor allele frequency	Meta Beta	Meta p value
16	rs8063248	GP2	20166228	A	0.08	−0.27	6.1E–07
4	rs10489063	LDB2	15993700	A	0.08	−0.25	4.42E–06
5	rs3805698	PCDHGC5	140801305	G	0.07	−0.27	5.54E–06
1	rs17160351	PRKAB2	144230912	C	0.03	−0.42	6.67E–06
17	rs8067785	MAP2K4	11871706	G	0.15	−0.19	6.82E–06
16	rs12595857	ADCY9	4002593	A	0.47	−0.14	7.83E–06
5	rs10066407	PROP1	177437627	C	0.24	−0.15	9.72E–06
2	rs155124	ITGA4	182133444	G	0.04	−0.40	1.02E–05
3	rs12485750	OSBPL10	31392045	A	0.46	−0.25	1.06E–05
1	rs906265	LMX1A	162017692	A	0.07	−0.26	1.15E–05

Conclusion: We show that anti-CCP level is a heritable trait and genetic factors explain ~38% of the phenotypic variance. We confirmed that the HLA region is associated with anti-CCP level. There are suggestive genetic effects outside the HLA region that influence anti-CCP level. GWAS results explain a small percent of the variance and other techniques such as next generation sequencing should be pursued.

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Genome-Wide Association Study of African Americans Implicates Multiple Lung and Inflammatory Disease-Associated Loci in Sarcoidosis Susceptibility. Indra Adrianto[1], Chee Paul Lin[1], Jessica J. Hale[1], Albert M. Levin[2], Indrani Datta[2], Ryan Parker[1], Adam Adler[1], Jennifer A. Kelly[1], Kenneth M. Kaufman[3], Christopher J. Lessard[1], Kathy L. Moser[4], Michael C. Iannuzzi[5], Benjamin A. Rybicki[2] and Courtney G. Montgomery[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Henry Ford Health System, Detroit, MI, [3]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation and US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [4]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]SUNY Upstate Medical University, Syracuse, NY

Background/Purpose: Sarcoidosis is a systemic inflammatory disease, characterized by the formation of granulomas primarily in the lungs, but the disease can also affect other organ systems including the bones, joints, muscles, spleen, lymph, liver, glands, brain, skin, and heart. While the etiology of this disease remains elusive, the causal chain likely involves a dysregulated immune in response to an environmental agent in a genetically susceptible host. Despite its higher prevalence and morbidity in African Americans (AAs), to date, genome-wide association studies (GWASs) of this disease have focused only on non-African populations. We present here the first GWAS of sarcoidosis in a population of African origin.

Methods: We genotyped 1487 AA sarcoidosis cases and 1504 AA family members and independent controls using the Illumina HumanOmni1-Quad platform for 1.1 million single-nucleotide polymorphisms (SNPs) across the genome. After applying sample and SNP quality control, the final set comprised 2,918 samples (1,273 cases and 1,645 controls) including 180 HapMap YRI and ASW controls from the Illumina iControlDB and 887,296 SNPs. We assessed single SNP association to sarcoidosis using the Efficient Mixed-Model Association eXpedited (EMMAX) software that simultaneously controls for both pairwise genetic relatedness between individuals and population stratification under the additive model. Regions associated at a suggestive level of $p < 1 \times 10^{-4}$ were imputed using IMPUTE2 program and the 1000 Genomes Project haplotypes as reference panels.

Results: We identify two novel sarcoidosis effects reaching genome-wide significance ($p < 5 \times 10^{-8}$) at *NOTCH4* ($p = 4.30 \times 10^{-9}$) and *HLA-DQA1* ($p = 1.04 \times 10^{-11}$). We also replicated previous sarcoidosis Caucasian GWAS hits of *RAB23* ($p = 9.47 \times 10^{-5}$) and *BTNL2* ($p = 6.10 \times 10^{-6}$) and confirmed association in 12 regions shown to be involved in other lung or inflammatory diseases, including *TGM3* ($p = 5.60 \times 10^{-6}$) and *DMBT1* ($p = 8.70 \times 10^{-5}$), associated with celiac and Chrohn's disease, respectively. Pathway-based analyses suggested involvement of inflammation regulation and apoptosis ($p < 0.001$) pathways and an effect-specific heritability estimation analyses suggested the existence of rare genetic effects in sarcoidosis.

Conclusion: We completed the first GWAS for sarcoidosis in AAs. The novel, replication and confirmatory findings of this study highlight both the usefulness of and need for genetic studies of sarcoidosis in the understudied but greatly affected AA population. Future replication and sequencing studies are required to further elucidate the functional variants that may underlie these novel associations.

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Variation in the *ICAM1-ICAM4-ICAM5* Locus Is Associated with Systemic Lupus Erythematosus Susceptibility in Multiple Ancestry Populations. Kwangwoo Kim*[1], and Elizabeth E. Brown* on behalf of PROFILE[2], Chan-Bum Choi[3], Marta E. Alarcon-Riquelme on behalf of BIOLUPUS[4], Jennifer A. Kelly[5], Kenneth M. Kaufman[5], So-Young Bang[3], Hye-Soon Lee[3], Taehyeung Kim[1], Swapan Nath[5], Betty P. Tsao[6], Amr H. Sawalha[5], Bernardo Pons-Estel on behalf of GENLES[7], Timothy J. Vyse on behalf of SLEGEN[8], Patrick M. Gaffney on behalf of LLAS2[5], Carl D. Langefeld[9], John B. Harley[10], Changwon Kang[1], Robert P. Kimberly[2] and Sang-Cheol Bae on behalf of Korean Investigators[3]. [1]Korea Advanced Institute of Science and Technology, Daejeon, South Korea, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [4]Pfizer-University of Granada-Junta de Andalucía, Grranada, Spain, [5]Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [7]Sanatorio Parque, Rosario, Argentina, [8]King's College London, Guy's Hospital, London, United Kingdom, [9]Wake Forest School of Medicine, Winston-Salem, NC, [10]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH

Background/Purpose: Systemic lupus erythematosus (SLE, OMIM 152700) is a chronic autoimmune disease with etiology that includes genetic and environmental factors. *ITGAM*, integrin alpha M (complement component 3 receptor 3 subunit), a ligand for intracellular adhesion molecule (ICAM) proteins, is an established SLE susceptibility locus. However, the independent and joint effects of common variation in the genes that encode ITGAM and ICAM have not been previously evaluated.

Methods: We examined 12 directly typed and 58 imputed loci in the *ICAM1-ICAM4-ICAM5* locus spanning ~22 kb on chromosome 19p13, a single locus in *ITGAM* and 347 ancestry informative markers using customized arrays based on the Illumina iSelect platform in a total of 17,481 unrelated SLE affecteds and controls from four divergent ancestry backgrounds (European, African, Hispanic, Asian). All participants were of self-reported sex and race/ethnicity. Affecteds had a minimum of four of eleven 1997 American College of Rheumatology revised criteria for the classification of SLE. We estimated allele frequencies in SLE affecteds relative to controls using logistic regression based on additive models and adjusted for population substructure.

Results: The A-allele of *ICAM1-ICAM4-ICAM5* rs3093030, associated with elevated plasma levels of soluble ICAM-1, showed the strongest association with increased SLE susceptibility in each of the ancestry populations and the trans-ancestry meta-analysis (OR_{meta}=1.16, 95% CI 1.11–1.22; P=4.8×10^{-10}) as did the *ITGAM* rs11436679-A allele (OR_{meta}=1.67, 95% CI 1.55–1.79; P=3.32×10^{-46}). Carriers of both *ICAM* rs30930330-AA and *ITGAM* rs1143679-AA were significantly more likely to develop SLE compared to

carriers without at-risk alleles at both loci (OR=4.08, 95% CI 2.09–7.98; $P=3.91\times10^{-5}$), supporting a synergistic receptor-ligand interaction.

Conclusion: These findings are the first to provide evidence to support the contribution of the ICAM locus alone and an ICAM-integrin mediated pathway to SLE susceptibility.

* These authors contributed equally to this work.

1682

Major Histocompatibility Complex Association to Rheumatoid Arthritis Is Explained by Polymorphic Amino Acids In the Binding Grooves of *HLA-DRB1*, *HLA-B*, and *HLA-DPB1*. Soumya Raychaudhuri[1], Eli A. Stahl[1], Xiaoming Jia[1], Lars Alfredsson[2], Leonid Padyukov[3], Katherine A. Siminovitch[4], Lars Klareskog[5], Jane Worthington[6], Robert M. Plenge[1], Peter K. Gregersen[7] and Paul de Bakker[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Institute of Environmental Medicine, Unit of Cardiovascular Epidemiology, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [4]Mount Sinai Hospital, Toronto, ON, [5]Karolinska Institutet, Stockholm, Sweden, [6]University of Manchester, Manchester, United Kingdom, [7]Feinstein Institute Medical Reschearch, Manhasset, NY

Background/Purpose: Rheumatoid arthritis (RA) is a common autoimmune disease that affects up to 1% of the general adult population worldwide. While the RA association at the major histocompatibility complex (MHC) has been noted for >20 years, there has been controversy about other associations outside DRB1, and the causal alleles within DRB1 itself.

Methods: In order to fine-map the MHC association, we used a strategy previously described (Pereyra *et al*., Science, 2010) to impute classical types and amino acid polymorphisms for the classical *HLA-A*, *HLA -B*, *HLA-C*, *DPA1*, *DPB1*, *DQA1*, *DQB1*, and *DRB1* loci along with 2,537 SNPs across the MHC in 5,018 anti-CCP+ cases and 14,974 controls from 6 GWAS data sets (Stahl *et al*., Nature Genetics, 2010). Using logistic regression across all 6 data sets jointly, we performed conditional analyses to identify independent variants, correcting for 5 principal components in each GWAS.

Results: We compared imputed classical alleles to *DRB1* 4-digit genotypes for 1150 overlapping individuals from two cohorts; the imputation was 96.5% and 85.4% accurate for 2-digit and 4-digit types, respectively. We also observed that classical *DRB1* associations were identical to previously reported effect sizes. The strongest signal mapped to the presence of a valine or leucine in position 11 of *DRB1* (OR=3.7, $p<10^{-500}$), accounting in itself for 9% of the phenotypic variance. With conditional haplotype analysis we found that most of the *DRB1* signal can be parsimoniously explained by 3 amino acid positions within DRB1 (11, 71, 74), refining the "shared epitope" hypothesis to include position 11, located at the floor of the binding groove, but to exclude positions 70, 72, and 73. We also confirmed an independent effect due to a single amino acid polymorphism in *HLA-B* (OR=2.1; $p=2\times10^{-38}$, Asp at position 9), corresponding to *HLA-B*08*, and identified a novel independent effect at *HLA-DPB1* (OR=1.3; $p=5\times10^{-22}$, Phe at position 9). Controlling for all of these variants leaves no additional significant associations within the MHC ($p>10^{-6}$).

Conclusion: In each case, the amino acid residues at these positions point into the binding groove of the HLA molecule, highlighting the importance of these residues in presenting auto-antigens to the immune system. In aggregate, these independent variants account for almost all of the known MHC signal in RA, and explain ~15% of the phenotypic variance, a significant increase relative to the most recent genome-wide meta-analysis in RA.

ACR Concurrent Abstract Session
Pediatric Rheumatology - Pathogenesis
Monday, November 7, 2011, 4:30 PM–6:00 PM

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IL-10 Mainly Derived From Activated Hepatic T-Cells Suppresses Toll-Like Receptor 9-Mediated Macrophage Activation Syndrome Independent of Effects on the Pathogenic IL-12/Interferon-γ Axis. Scott W. Canna[1], Michele E. Paessler[1], Portia Kreiger[2], Katharine Slade[1], Sheila Rao[1] and Edward M. Behrens[1]. [1]Childrens Hospital of Philadelphia, Philadelphia, PA, [2]A.I. DuPont Hospital for Children, Wilmington, DE

Background/Purpose: Macrophage Activation Syndrome (MAS) is a potentially fatal cytokine storm syndrome that complicates multiple rheumatic illnesses. We have recently shown the critical role of IL-10 as a regulator of MAS in an infection-free murine model. The current study dissects the mechanisms by which IL-10 exerts this profound regulatory effect.

Methods: As previously described, the Toll-like Receptor 9 (TLR9) agonist CpG1826 was injected repeatedly to induce MAS. Cellular IL-10 production was assessed by means of both intracellular flow cytometry and a YFP reporter system. Signaling of IL-10 and IL-12 were inhibited by monoclonal antibodies to IL10R1 and IL-12 (1B1.3A & C17.8), respectively. Transgenic mice and dendritic cell (DC)-depleted mice were utilized as detailed.

Results: As shown previously, CpG given during IL-10R blockade resulted in fulminant MAS, complete with excess hemophagocytosis. Additionally, serum IFNγ, IL-10, IL-6 and IL-12 levels in IL-10R blocked mice were dramatically elevated compared to IL-10 sufficient mice. Investigating the source of this protective IL-10, we found that CpG resulted in induction of IL-10 by a variety of hematopoietic cells, particularly activated ($CD44^{hi}CD69^{hi}CD62L^{lo}$) hepatic T-cells. Both Rag−/− and DC-deficient mice developed enhanced MAS in response to CpG, correlating with reduced IL-10. These data are consistent with DC/T-cell interactions as a possible mechanism for IL-10 induction.

Earlier studies showed that IFNγ is critical for driving MAS, and thus we tested whether the fulminant MAS seen in IL-10R blocked mice was due to enhanced IFNγ production. CpG given to IFNγ−/− mice during IL-10R blockade resulted in fulminant MAS indistinguishable from WT mice. IL-12 was elevated above WT levels in IL-10R blocked IFNγ−/− mice, and thus we tested whether IL-12 might be driving an IFNγ independent mechanism. Interestingly, coadministration of an IL-12 blocking antibody with CpG prevented MAS in IL-10 sufficient mice, but still led to severe disease in IL10R blocked mice. IFNγ levels were depressed regardless of IL-10R blockade, suggesting IFNγ induction is IL-12 dependent.

Conclusion: While TLR9-induced MAS appears to be predominantly dependent on the IL-12/IFNγ axis in IL-10 sufficient mice, IL-10R blockade reveals other mechanisms by which TLR9 stimulation can cause severe MAS. Further studies will elucidate pathogenic mechanisms not reliant on IL-12 or IFNγ, specify the nature of DC/T-cell interactions in driving T-cell IL-10 production, clarify the function of these cells, and discern which cells and tissues must respond to IL-10 in order to prevent severe disease. These studies support the critical role of IL-10 in prevention of fulminant MAS, explicate an important pathogenic axis in this disease, and continue to identify targetable cell populations and pathways for treating MAS patients.

1684

Reduction of Annexin A5 Anticoagulant Activity in Children with Systemic Lupus Erythematosus. Dawn M. Wahezi[1], Norman T. Ilowite[1], Xiao Xuan Wu[2], Bas de Laat[3], Jacob H. Rand[2] and the APPLE Investigators[4]. [1]Children's Hospital Montefiore, Bronx, NY, [2]Montefiore Medical Center, Bronx, NY, [3]Maastricht University Medical Center, The Netherlands, [4]Varies by Investigator

Background/Purpose: Children with systemic lupus erythematosus (SLE) have a high prevalence of antiphospholipid (aPL) antibodies and are at increased risk of aPL-related thrombosis. In adults, reports have implicated domain one (D1) of β2-glycoprotein I (β2GPI) as the major antigenic target for thrombogenic aPL antibodies. In addition, evidence has evolved suggesting that the antibody-mediated disruption of an annexin A5 anticoagulant shield may play a role in the pathogenesis of aPL-related thrombosis. We investigated the association between anti-D1 antibodies and annexin A5 anticoagulant activity in a cohort of children with SLE.

Methods: Using plasma samples collected during the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial, we evaluated 183 children with SLE (mean age: 15.6 years) for resistance to the anticoagulant effects of annexin A5, using the annexin A5 resistance (A5R) assay. This assay measures coagulation times in the presence and absence of annexin A5 and resistance is expressed as a reduction in this ratio. Mean A5R levels were compared with pediatric controls (mean age: 12.4 years) without known autoimmune or thrombophilic disorders. In children with SLE, plasma samples were additionally screened for the presence of anti-D1 antibodies and available data regarding lupus anticoagulant (LA) and anti-cardiolipin (aCL) antibodies were examined.

Results: Overall, children with SLE had significantly reduced mean A5R levels (i.e. greater resistance to annexin A5 anticoagulant activity) compared to healthy pediatric controls: mean A5R = 172 ± 30 % versus

243 ± 30 % ($p<0.0001$) (Figure 1). The association between mean A5R levels with LA (n=87) and aCL antibodies (n=19) are presented in Table 1. In children with SLE, 46 (25.1 %) patients had positive anti-D1 antibodies and significantly lower mean A5R levels as compared to the rest of the cohort: mean A5R = 155 ± 24 % versus 177 ± 30 % ($p<0.0001$).

Figure 1: Annexin A5 Resistance in Pediatric SLE Patients versus Controls

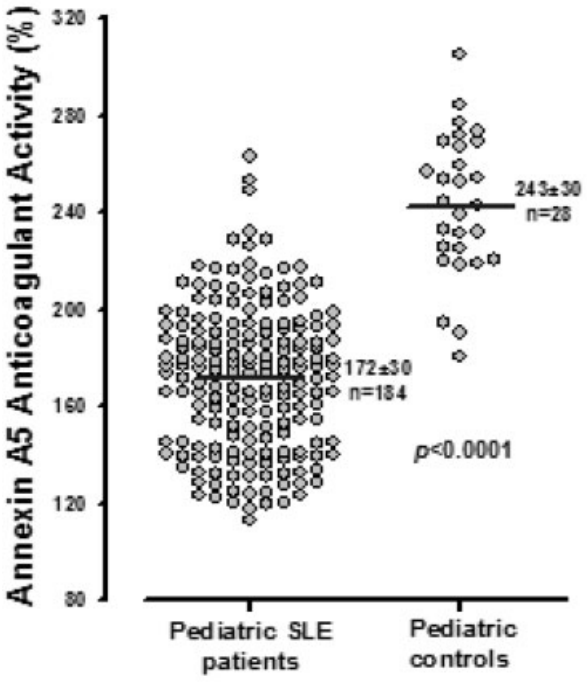


Table 1. Mean A5R (%) in relation to the presence aPL antibodies in a cohort of children with SLE (n=183)

	Positive	Borderline/Negative	p-value
Lupus anticoagulant (n=87)*	150 ± 24	169 ± 30	**0.021**
aCL antibodies (n=19)*	157 ± 25	179 ± 27	0.285
Anti-D1 antibodies (n=183)	155 ± 24	177 ± 30	**<0.0001**

* Data not available on the remainder of the cohort

Conclusion: Children with SLE have markedly reduced annexin A5 anticoagulant activity as compared to pediatric controls. Additionally, the presence of aPL antibodies, including anti-D1 antibodies, led to further reduction in A5R. Future examination of the clinical implications of annexin A5 resistance and antibody specificity for D1 in children with SLE is warranted.

1685

A Markedly Low-Level of Interferon-Induced Gene Expression Distinguishes Active Systemic Juvenile Idiopathic Arthritis Synovium From the Oligoarticular Subtype; A Difference That Cannot Be Attributed to Monocytic Hypo-Responsiveness to Interferon-γ. Keith A. Sikora, Ndate Fall, Sherry Thornton and Alexei A. Grom. Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA) is an autoinflammatory syndrome where IL-1β and IL-6 play a pivotal role. SJIA is strongly associated with the macrophage activation syndrome (MAS), a hemophagocytic syndrome where inflammatory macrophages are believed to be driven by interferon-γ (IFN-γ). However, recent gene expression studies have failed to demonstrate the presence of an IFN-induced signature in fresh peripheral blood mononuclear cells (PBMCs) from active SJIA/MAS patients, while the status of this signature has not been adequately studied within affected tissues. An altered responsiveness to IFN-γ, perhaps due to cross-talk between IL-1β and IFN-induced signaling pathways, has been suggested as a possible explanation. The main goals of this study were to determine the presence of an IFN-induced signature within affected synovial tissue and to gauge IFN-induced signaling pathways in freshly isolated monocytes from active SJIA patients by measuring STAT1 phosphorylation (STAT1-P), as well as IFN-induced gene expression, at baseline and upon stimulation with IFN-γ.

Methods: To detect a possible IFN-induced signature within affected synovium, total mRNA was extracted from frozen synovial biopsies from 12 active SJIA and 9 active oligoarticular JIA patients as a control. Real-time PCR was then used to quantify IP-10, MIG, and I-TAC mRNA levels. To determine potential IFN-responsiveness, fresh PBMCs were collected from 3 active SJIA patients and 3 healthy controls (HCs). CD14+ PBMCs were isolated and treated with and without 100 units IFN-γ for 1 hour. STAT1-P levels were then quantified via intracellular FACS. Finally, to gauge transcriptional responsiveness to IFN-γ, fresh CD14+ PBMCs from 4 active SJIA patients and 7 HCs were isolated and then incubated with and without 100 units IFN-g for 3 hours. Total mRNA was then extracted and real-time PCR was used to quantify IP-10, MIG, and STAT1 mRNA levels.

Results: We detected a markedly lower level of IFN-induced mRNA levels in SJIA synovium compared to oligoarticular JIA; on average, IP-10 levels were 4.5x lower, MIG levels were 15.8x lower, and I-TAC levels were 3.6x lower. In regards to STAT1-P, baseline STAT1-P levels in CD14+ PBMCs from SJIA patients were mildly increased over HCs. Upon stimulation with IFN-γ, the amount of STAT1-P in SJIA patients increased by a greater magnitude compared to HCs. Lastly, CD14+ PBMCs from active SJIA patients displayed a significantly lower baseline level of MIG and STAT1 mRNA, while baseline IP-10 was comparable to HCs. However, upon stimulation of these cells with IFN-γ, the increase in MIG mRNA was significantly greater than HCs and while not statistically significant, the increase in IP-10 and STAT1 mRNA levels trended towards being greater.

Conclusion: A markedly low-level of IFN-induced gene expression distinguishes active SJIA synovium from active oligoarticular JIA synovium. In CD14+ PBMCs, this signature appears altogether absent, but this is not likely due to a hypo-responsiveness to IFN-γ. In contrast, SJIA PBMCs appear to have an *increased* responsiveness compared to HC cells. The impact of this apparent difference on terminal macrophage differentiation in SJIA is an area that deserves much attention.

1686

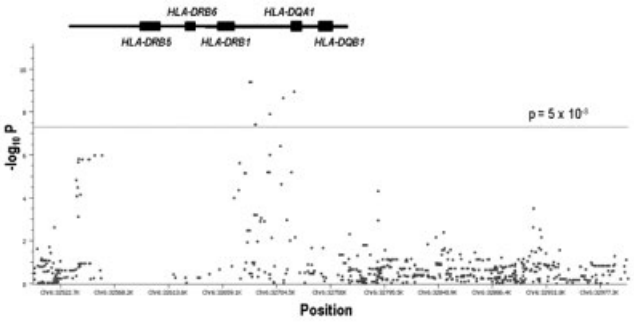
Major Histocompatibility Complex Class II Gene Cluster Harbors Systemic Juvenile Idiopathic Arthritis Susceptibility Locus. Michael J. Ombrello[1], Elaine Remmers[1], Alexei A. Grom[2], Wendy Thomson[3], Alberto Martini[4], Marco Gattorno[5], Seza Ozen[6], Ahmet Gul[7], John F. Bohnsack[8], Sampath Prahalad[9], Andrew S. Zeft[8], Elizabeth D. Mellins[10], Colleen Satorius[1], Jane L. Park[10], Carl D. Langefeld[11], Eleftheria Zeggini[12], David N. Glass[2], Susan D. Thompson[2], Daniel L. Kastner[1], Patricia Woo[13] and International Childhood Arthritis Genetics Consortium[14]. [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]University of Manchester Medical School, Manchester, United Kingdom, [4]IRCCS G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [5]Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genova, Italy, [6]Hacettepe University Faculty of Medicine, Ankara, Turkey, [7]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [8]University of Utah, Salt Lake City, UT, [9]Emory Children's Center, Atlanta, GA, [10]Stanford University Medical Center, Stanford, CA, [11]Wake Forest School of Medicine, Winston-Salem, NC, [12]The Wellcome Trust Sanger Institute, Cambridge, United Kingdom, [13]University College London Medical School, London, United Kingdom, [14]Manchester, United Kingdom

Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA) is a systemic inflammatory disease whose etiology remains unknown. The inflammatory features of sJIA clearly distinguish it from other subtypes of JIA, and immunologically, sJIA patients demonstrate innate immune activation not seen in other JIA subtypes. sJIA is a rare, complex genetic trait, and the discovery of sJIA susceptibility genes has been hindered by sampling bias, population stratification, and genetic heterogeneity. In this study, we used genome wide SNP genotyping to address these obstacles in a large patient collection as we sought to identify sJIA susceptibility loci.

Methods: We performed SNP genotyping on 576 children fulfilling ILAR criteria for sJIA and 366 healthy subjects with Illumina Omni1M Quad beadchips and an iScan platform. Samples (cases/controls) were obtained from Cincinnati Children's Hospital Medical Center (205/210), University of Manchester (188/0), Genoa University (56/60), Hacettepe University (54/0), University of Utah (42/0), Stanford University (34/0), and Istanbul University (0/96). Additionally, Omni1M Quad genotypes from 60 unrelated HapMap CEU individuals were obtained from the Illumina iControl database for use

in the genome-wide analysis. SNPs with call rates < 95 %, minor allele frequencies < 0.05, or Hardy-Weinberg Equilibrium p < 1E-5 were excluded. Using MaCH imputation software, we assembled a chromosome 6 SNP set that included 1594 additional controls from the 1958 U.K. Birth Cohort. We used principal components (PC) analysis to exclude genetically dissimilar individuals and to correct association testing. PC analysis, association testing, and logistic regression analysis were performed using SVS7, and haplotypes were analyzed using Haploview. Two-digit *HLA-DRB1* data were available for 231 cases and 1752 controls in our PC-matched collection.

Results: Genome-wide association testing revealed 12 SNPs within the MHC Class II region whose associations exceeded the threshold for genome-wide significance (p < 5E-8). Analysis of the MaCH-imputed chromosome 6 SNP set identified 7 additional SNPs with p < 5E-8, and logistic regression identified rs615672 as responsible for the regional association. Further, we identified a 203 Kb sJIA-associated SNP haplotype (p = 5.33E-12; OR = 2.184, 95 CI 1.74, 2.74) which included *HLA-DRB1, -DQA1,* and *-DQB1*. This extended haplotype had a greater effect size and a stronger association than any individual SNP. We also found that *HLA-DRB1*11* was associated with sJIA (p = 1.31E-6, OR = 2.09 [95% CI = 1.55–2.81]).



SNP Associations within the Major Histocompatibility Complex Class II Gene Cluster sJIA. Displayed is a plot of the PC-corrected $-\log_{10}$ p values of association for the MHC Class II cluster. The horizontal line at y=7.3 represents the genome-wide significance threshold of p < 5E-8.

Conclusion: We have identified an association of sJIA with genetic variants in the MHC Class II gene cluster, closest to *HLA-DRB1* and *HLA-DQA1*. This suggests that although innate immune activation has been reported in sJIA, adaptive immune mechanisms may also influence its pathogenesis.

1687

Serum Follistatin-Like Protein 1 Is Elevated in Systemic Juvenile Idiopathic Arthritis and Is a Biomarker for Macrophage Activation Syndrome. Mark Gorelik[1], Ndate Fall[2], Susan D. Thompson[2], Alexei A. Grom[2] and Raphael Hirsch[3]. [1]Univ of Pittsburgh Med Ctr Children's Hospital, Pittsburgh, PA, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA) can be complicated by macrophage activation syndrome (MAS), an often fatal disorder characterized by multisystem organ failure. IL-1b and IL-6 are key inflammatory mediators in SJIA and blockade of these cytokines can ameliorate disease activity in a subset of patients. We have recently demonstrated that follistatin-like protein 1 (FSTL-1) can increase secretion of IL-1b and IL-6 from monocytes and mesenchymal stromal cells (MSC). This study was performed to determine how FSTL-1 levels correlate with measures of clinical disease activity and development of MAS.

Methods: FSTL-1 serum levels were measured by ELISA in 27 patients with sJIA, including 6 patients who developed MAS, as well as in 15 normal controls. Levels were correlated with CD163 and sIL2Ra expression. Peripheral blood mononuclear cells (PBMC) were separated on Ficoll gradients, and RNA was analyzed to evaluate differential gene expression.

Results: FSTL-1 serum levels are elevated at the time of initial diagnosis of sJIA, as compared to controls (mean of 216.3 ng/ml vs. 156.1 ng/ml, p=0.01). FSTL-1 levels decreased during the course of treatment (mean of 132.5 ng/ml after 24 months, p = 0.001). Especially high levels of FSTL-1 were present in patients during acute MAS (mean of 231.5 ng/ml). In 3 patients for whom paired samples were available pre- and post-treatment for MAS, FSTL-1 levels changed from a mean of 289.5 ng/ml to a mean of 124.0 ng/ml, p=0.08. Patients with elevated FSTL-1 levels showed increased expression of markers previously associated with MAS, including CD163. PBMC from these patients also showed a 2-fold or greater increase in expression levels of IL-1 receptor, Lipocalin 2, MMP-8, MMP-9, IL-18, as well as other genes associated with TLR4/IL1R signaling (p <0.05).

Conclusion: Serum FSTL-1 is elevated in clinically active sJIA and may represent a biomarker for development of MAS. Patients with elevated levels of FSTL-1 had increased expression of Interleukin-1 and TLR4 related genes, and may represent a subgroup with more severe disease.

1688

Analysis of the Immunochip in a Large Cohort of Oligo- and Polyarthritis Juvenile Idiopathic Arthritis Cases Confirms Previous and Identifies Novel Associations. Joanna Cobb[1], Anne Hinks[1], John Bowes[1], Marc Sudman[2], Miranda C. Marion[3], Mehdi Keddache[4], Lucy R. Wedderburn[5], Johannes Peter Haas[6], David N. Glass[2], Carl D. Langefeld[3], Wendy Thomson[1] and Susan D. Thompson[2]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Wake Forest School of Medicine, Winston-Salem, NC, [4]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]University College London (UCL), United Kingdom, [6]German Centre for Rheumatology in Children and Young People, Garmisch-Partenkirchen, Germany

Background/Purpose: Genome wide association studies (GWAS) have been hugely successful in the identification of susceptibility loci for autoimmune diseases. One interesting outcome of these studies is the observation that many of the loci are shared across these diseases. The regions identified now require more detailed fine-mapping to localize the association signal, identify potential pleiotropic effects and identify putative functional variants. To this end the Immunochip consortium was established to pool confirmed loci from 12 diseases to include on a custom genotyping chip. The Immunochip, based on the Illumina Infinium platform, investigates ~200 established autoimmune susceptibility loci. For each locus, all known genetic variation from dbSNP, 1000 Genome and other sequencing projects was included. Juvenile idiopathic arthritis (JIA) is the most common arthritic disease of childhood. Candidate gene and GWAS have identified a number of common autoimmune genes that confer susceptibility to JIA. However, JIA has been less well studied using GWAS approaches and thus genotyping using the Immunochip has the potential for not only fine-mapping previously associated regions but also to identify novel loci for JIA.

Methods: Genotyping was performed using the Immunochip, in a large cohort from the UK, US and Germany comprising 1749 JIA oligoarthritis and RF negative polyarthritis cases and 8854 controls. All raw genotyping data was combined for clustering and QC. SNPs failed QC based on a call rate <98% and/or cluster separation score <0.4. Samples failed QC based on a call rate <98%. Outliers of mean heterozygosity, related individuals and ancestral outliers were removed. Final sample size after QC was 1614 cases and 7153 controls. Analysis was performed using logistic regression adjusting for the top 5 principal components in PLINK vers1.07.

Results: Initial analysis has not only confirmed previously associated JIA loci (*PTPN22*, *IL2RA, IL2, STAT4, PTPN2* and *SH2B3/ATXN2)* but has strengthened their association, such that all now reach genome-wide significance. A number of novel loci have been identified, some of which showed weak evidence previously, such as *IL7R* and *IRF1,* and others which have never been associated with JIA to date, such as *REV3L* and *TYK2*. These will require validation in independent cohorts.

Conclusion: The Immunochip project enables cost-effective fine-mapping of autoimmune loci in diseases such as JIA. This preliminary analysis has confirmed and strengthened the association of a number of previously associated genes as well as the identification of novel susceptibility loci for JIA. Further analysis of this data will help characterise all associated variants and identify the likely causal variants for future functional studies.

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1689

Questionable Relevance of Subclinical Synovitis: First Degree Ultrasound Findings Are Not Associated with Pain, Swelling or Power Doppler Findings in Rheumatoid Arthritis (RA). Matthias Witt, Felix Mueller, Axel Nigg, Christiane Reindl, Nicola Stein, Stefan Mayer, Christina Gebhardt, Ariane Hammitzsch, Claudia Dechant, Hendrik Schulze-Koops and Mathias Grunke. University of Munich, Munich, Germany

Background/Purpose: Several ultrasound scores have been developed for the assessment of patients with RA. Most of these are using a semiquantitative grading system with scores between 0 and 3 for greyscale (GS) and power doppler (PD) scoring. Borderline results are often scored as grade 1 and are usually counted as synovitic joints. As treatment decisions are increasingly based on US findings, this work investigated the relevance of grade 1 GS findings in regard to their association with pain, swelling and PD findings.

Methods: The three small joint regions of metacarpophalangeal (MCP-), proximal interphalangeal (PIP-) and metatarsophalangeal (MTP-) joints of 63 patients with RA were assessed clinically for tenderness and swelling according to the EULAR examination technique. All joints were then independently evaluated by ultrasound GS and PD mode with an 18 MHz high resolution device for capsule swelling and synovial hyperperfusion. The MCP-, PIP- and MTP- joints of 20 healthy individuals were examined by ultrasound and served as controls. Joints with grade 1 GS findings were identified and evaluated for their association with swelling, pain and power Doppler findings.

Results: 633 MCP-, 641 PIP- and 628-MTP joints of 63 patients with rheumatoid arthritis were assessed. 160 (25,3%), 100 (20,5%) and 100 (18,3%) grade 1 GS findings were identified for all MCP-, PIP- and MTP-joints, respectively. With exception of MCP4 and MTP5 all joints were affected similarly on the single joint level. When compared to healthy controls, significantly more grade 1 GS findings were found in the RA group for the PIP- and MTP-joints but not for the MCP-joints. In the presence of grade 1 findings, no association with swelling, pain or PD findings was observed ("subclinical synovitis"). In contrast, in the presence of grade 2 or 3 GS findings, significant association of swelling, pain and PD findings was noted.

Conclusion: Grade 1 GS findings in joints of RA patients are a frequent finding in the individual RA joint and coined the term of "subclinical synovitis". In general, these findings show a homogenous distribution across the three joint regions examined in this study. Notably, there was no significant difference between RA patients and healthy controls in regard to grade 1 findings in the MCP joints. Together with the lack of association with swelling, pain and PD findings, this data suggests a questionable clinical relevance of grade 1 GS findings especially in regard to treatment decisions. Longitudinal observation of these joints is underway to clarify their susceptibility for inflammatory exacerbation and development of erosive disease.

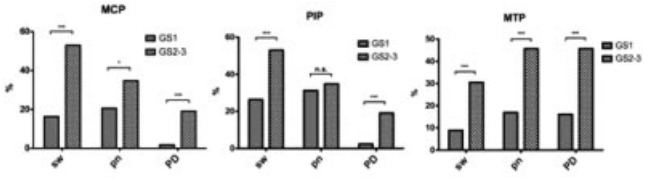


Figure 4. Significant associations of swelling, pain and PD findings in grade 2 or 3 GS findings versus grade 1 GS findings.

1690

Patient Reported Outcome Measures: Its Impact on Disease Activity and Adherence to Therapy in Inflammatory Arthritis. Yasser M. El Miedany[1], Deborah Palmer[1] and Maha El Gaafary[2]. [1]Darent Valley Hospital, Dartford, United Kingdom, [2]Ain Shams University, Cairo, Egypt

Background/Purpose: To assess the impact of the patient reported outcome measures, recorded in the standard clinical practice, on the disease activity as well as the patients' adherence to anti-rheumatic drug therapy in patients with inflammatory arthritis.

Methods: This was a double-blind randomized controlled study. 127 patients diagnosed to have inflammatory arthritis according to the ACR criteria were included in this work. All patients received DMARDs / Biologic therapy and were monitored over the period of 1-year. Every patient completed a copy of the multidimensional patient reported outcome measures (PROMs) questionnaire. By the 6th month of treatment, the patients were randomly allocated to an active group (64 patients) who were able to view the scores recorded of their former self-reported outcome measures as well as discuss the changes in their reported disease activity parameters, functional disability and quality of life; and a control group (63 patients) who continued their treatment and management based on the view of their presentation and clinical assessment on that particular clinic visit. The patients were assessed at 3 monthly intervals for another 6 months. Before every assessment in the clinic every patient in both groups completed a copy of the PROMs questionnaire. Primary outcome was the patients' adherence to their medications; change in disease activity score (DAS-28) and PROMs disease activity parameters. Secondary outcome was the results of a survey completed by every patient in both the active group and control group (using VAS) by the end of 1-year of management, to rate the patient's perspective regarding their condition and treatment.

Results: Viewing of the PROMs scores before and after treatment led to a significant greater reduction of disease activity parameters, DAS-28 score, as well as improvement of the patients' adherence to anti-rheumatic therapy ($p<0.01$). Stopping the DMARDs therapy because of intolerance was significantly less in the active group ($p< 0.01$). The improvement of disease activity parameters was associated with improvement in functional disability and quality of life scores. Initially, the mean changes in disease activity parameters showed no significant differences at 3 and 6 months of therapy but differences were statistically significant at 12 months follow up ($p< 0.01$). Medication compliance was significantly correlated with changes in all measured disease activity parameters. Analysis of the patients' answers to the survey revealed that the active group were more likely to adhere to their medication, less likely to stop their medication because of intolerance, more able to cope with their activities of daily living, and have less concern about their future.

Conclusion: By monitoring PROMs and viewing these changes in the standard clinical practice, a new experience has been created. This has enabled the patients to see how they are doing regarding their disease activity and helped to optimize their adherence to their treatment. PROMs had a positive and significant impact on the disease activity control.

1691

Influence of Autonomic Nervous Modulation on Rheumatoid Arthritis. Olga Malysheva, Petra Baum, Anke Esber and Christoph G. Baerwald. University Hospital, Leipzig, Germany

Background/Purpose: Growing evidence supports the hypothesis that alteration of the interaction between the autonomic nervous system (ANS) and the immune system contributes to the pathogenesis of rheumatoid arthritis (RA). To further characterize neuroimmune interactions common variants of the beta2-adrenergic receptors (beta2R) and functional stress pattern responses were studied in RA patients and controls.

Methods: An allele-specific polymerase chain reaction was used to determine the common variants of the beta2R at position 16, 27, and 164 in patients with RA (n = 310) and ethnically matched healthy controls (n = 305). In a subgroup of RA patients (n = 100) the autonomic response upon various standardized stressors was performed by utilizing the heart rate variability (HRV) test (ProSciCard III, Version 2.2a, Medi-Syst GmbH, Germany) and compared to 40 age and sex matched osteoarthritis patients. HRV measures including frequency domain analysis (employing rapid processing of a 5 minute ECG rhythm strip) yielding measures of parasympathetic and sympathetic activity as well as the total power of ANS influence on various parameters: high frequency (HF), low frequency (LF), and very low frequency index of HRV and square root of the mean of the squares of successive R-R interval differences (RMSSD).

Results: There was a highly significant distortion in the distribution of beta2R polymorphisms at codon 16 between RA patients and controls. Arginine (Arg) at codon 16 was present in 278 RA patients (89.7 %) compared to 202 controls (66.2%; OR 4.43, 95 % CI 2.81 to 7.02, p = 0.00001). Interestingly, HRV at baseline in RA patients was characterized by reduced power of the ANS in general as well as a decreased parasympathetic activity compared to OA patients (HRV index: 7.81 ±

0.3 vs. 9.23 ± 0.6, p < 0.05; RMSSD: 25.46 ± 1.2 ms vs. 33.84 ± 3.2 ms, p < 0.03). Otherwise, sympathetic stress response was reduced under the mental stress test (MST) in RA patients compared to OA patients (LF HRV: 1.69 ± 0.21 Hz vs. 3.05 ± 1.0 Hz, and LF/HF HRV: 1.1 ± 0.09 vs. 1.34 ± 0.06, p < 0.05, respectively). Stratifying RA patients for the genetic at position 16 revealed a statistically significant decrease of parasympathetic activity, in particular for the deep breathing test, in patients with homozygosity for Glycine (Gly) 16 compared to RA patients with heterozygosity (Arg16Gly). However, RA patients with homozygosity for Glycine 16 showed a normalisation of the sympathetic reactivity upon MST. Interestingly, all patients exhibiting parasympathetic hyperactivity at baseline (RMSSD >50 ms) were in remission (DAS 1.4 ± 0.4).

Conclusion: Polymorphisms of the beta2AR contribute to the genetic background of RA and is associated with disturbed functional autonomic stress reactivity in RA patients. In particular parasympathetic reactivity might be used as an indicator of RA remission. Further studies are warranted to determine the role of the ANS in the disease process of RA.

1692

Low Persistence of Serotype Specific Antibodies 1.5 Years After Vaccination with 7-Valent Pneumococcal Conjugate Vaccine in Patients with Established Arthritis. Meliha C. Kapetanovic[1], Tore Saxne[2], Göran Jönsson[3], Lennart T. Truedsson[4] and Pierre Geborek[2]. [1]Dept of Clinical Sciences Lund, Lund, Sweden, [2]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden, [3]Dept of Clinical Sciences Lund, Section of Infectious Diseases, Lund, Sweden, [4]Dept of Clinical Sciences Lund, Section of Microbiology, Immunology and Glycobiology, Lund, Sweden

Background/Purpose: To study the persistence of antibodies 1.5 years after vaccination using 7-valent pneumococcal conjugate vaccine in patients with established rheumatoid arthritis (RA) and spondylarthropathy (SpA).

Methods: Of 505 patients initially recruited, data on current antirheumatic treatment and blood samples were obtained from 399 (79%) subjects after mean (SD) 1.4 (0.03) years. Antibody levels against pneumococcal serotypes 23F and 6B were analyzed by ELISA. Original treatment groups were RA on methotrexate (MTX), RA on anti-TNF as monotherapy, RA on anti-TNF+ MTX, SpA on anti-TNF as monotherapy, SpA on anti-TNF+MTX, and SpA on NSAID/analgesics (controls).

Results: At follow up 300 (75.2%) patients had unchanged medication. Geometric mean levels (GML; 95% CI) and proportion (%) of patients with putative protective antibody levels ≥1 mg/L for both serotypes calculated in different treatment groups were compared to results 4–6 weeks after vaccination (Table). GML for each serotype were significantly lower in all groups at 1.5 years follow up (p-value 0.035 to <0.001; paired sample T-test) as were proportion of patients with protective antibody levels for both serotypes (p<0.001; Chi2 test).

Table. GML (95%CI) in mg/L and percentage of patients with protective antibody levels for 23F and 6B in different treatment groups at 4–6 weeks and 1.5 years follow up

	RA on methotrexate	RA on anti-TNF as monotheraphy	RA on anti-TNF + MTX	SpA on anti-TNF as monotherapy	SpA on anti-TNF+MTX	SpA on NSAID/ analgesics
No of patients at vaccination	85	79	89	83	83	86
GML (95% CI) for 23F 4–6 weeks after vaccination	1.9 (1.3–2.6)	1.9 (1.3–2.7)	1.4 (1.1–1.9)	3.1 (2.2–4.5)	2.5 (1.8–3.5)	6.4 (4.5–9.1)
GML (95% CI) for 6B 4–6 weeks after vaccination	3.5 (2.5–4.9)	3.6 (2.5–5.3)	2.3 (1.7–3.2)	4.8 (3.3–6.9)	3.0 (22.1–4.4)	9.5 (6.7–13.6)
% of patients with protective antibody levels for both 23F and 6B 4–6 weeks after vaccination	**63.5%**	**59.5%**	**53.9%**	**77.1%**	**65.1%**	**84.9%**
No of patients (%) at 1.5 years	57 (67.1%)	50 (63.3%)	55 (61.8%)	47 (46.7%)	49 (59.0%)	42 (48.8%)
GML (95% CI) for 23F at 1.5 years	0.6 (0.4–0.8)	0.5 (0.4–0.8)	0.4 (0.3–0.5)	1.0 (0.6–1.6)	0.8 (0.5–1.3)	1.9 (1.2–3.0)
GML (95% CI) for 6B at 1.5 years	1.2 (0.7–1.9)	1.0 (0.6–1.7)	0.6 (0.4–1.0)	1.4 (0.9–2.1)	1.0 (0.6–1.6)	2.7 (1.6–4.4)
% of patients with protective antibody levels for both 23F and 6B at 1.5 years	**40.6%**	**32.0%**	**20.0%**	**59.6%**	**49.0%**	**69.0%**
Relative Ratio of protective antibody at 1.5 years compared to 4–6 weeks	**0.64**	**0.54**	**0.37**	**0.77**	**0.75**	**0.81**

Conclusion: Postvaccination antibody levels were significantly lower 1.5 years after pneumococcal vaccination compared to levels 4–6 weeks after vaccination. Persistence of protective immunity against the serotypes tested was shorter than reported in healthy individuals (Musher et al, JID, 2010). Revaccination earlier than recommended for healthy persons may be needed in patients with arthritis.

1693

Inverse Relationship Between 25-Hydroxyvitamin D and Parathyroid Hormone Observed in the General Population but Not Among Rheumatoid Arthritis Patients. Anna R. Broder[1], Amy Skversky[2], Michal L. Melamed[3], Jonathan N. Tobin[4], John A. Hardin[5] and Chaim Putterman[3]. [1]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [2]Montefiore Medical Center, Bronx, NY, [3]Albert Einstein College of Medicine, Bronx, NY, [4]Albert Einstein College of Medicine/CDN Network, New York, NY, [5]Albert Einstein Coll of Med, Bronx, NY

Background/Purpose: Vitamin D deficiency and insufficiency are defined as 25-hydroxyvitamin D (25OHD) levels below 20 ng/ml and 30 ng/ml, respectively, based on data from the general population demonstrating that parathyroid hormone (PTH) levels normalize (below 65 pg/ml) at 25OHD concentrations above 30 ng/ml. Our hypothesis is that the relationship between 25OHD and PTH is altered in rheumatoid arthritis (RA) due to chronic inflammation and corticosteroid use. We studied the relationship between 25OHD and PTH using both the National Health and Nutrition Examination Surveys (NHANES) 2003–2006 and RA patients from a large tertiary care center.

Methods: For the NHANES cohort and for the tertiary care center cohort we included all adult participants with recorded values for 25OHD and PTH. Participants from both cohorts were excluded if their estimated glomerular filtration rate was < 50 ml/min/1.73 m2, because of the known altered relationship between 25OHD and PTH in chronic kidney disease. In the NHANES we compared participants with RA and participants without arthritis, based on self-report. Linear regression adjusted for age, gender, race/ethnicity and body mass index (BMI) was used for the NHANES cohort within each 25OHD interval (< 10, 10 to 20, 20 to 30, and >30 ng/ml). We constructed Kernel-weighted local polynomial smoothing curves for the RA cohort from our center.

Results: In the NHANES cohort, there were 363 participants with RA, and 5995 without arthritis. In the no-arthritis group the relationship between PTH and 25OHD within each stratum of 25OHD was similar to what was previously described in the general population. However, there was no statistically significant relationship between PTH and 25OHD in any of the strata among RA participants (Table 1). Similarly, among 47 RA patients from the tertiary care center who satisfied the inclusion criteria, PTH levels normalized at 25OHD levels slightly above 10 ng/ml and remained fairly constant at all 25OHD levels (Figure 1).

Table 1. Linear regression model showing the change in PTH (95% CI) per 1 ng/ml change in 25OHD within each 25OHD interval (ng/ml): < 10, 10 to 20, 20 to 30, and >30, adjusted for age, gender, race/ethnicity, and BMI

	RA (363 observations, subpopulation 4460045)	No arthritis (5995 observations, subpopulation size 91951415)
For 25OHD < 10 ng/ml, change in PTH, pg/ml (95% CI)	0.08 (−4.3, 4.4)	−2.9 (−5.1, −0.7)
p-value	0.969	0.011
For 25OHD ≥ 10 ng/ml and < 20 ng/ml, change in PTH, pg/ml (95% CI)	−1.2 (−3.0, −0.5)	−0.8 (−1.3, 0.3)
p-value	0.154	0.003
For 25OHD ≥ 20 ng/ml and < 30 ng/ml, change in PTH, pg/ml (95% CI)	−0.1 (−1.0, 0.77)	−0.1 (−0.5, 0.2)
p-value	0.796	0.5
For 25OHD ≥ 30 ng/ml, change in PTH, pg/ml (95% CI)	−0.3 (−0.9, 0.2)	−0.2 (−0.3, −0.1)
p-value	0.19	0.003

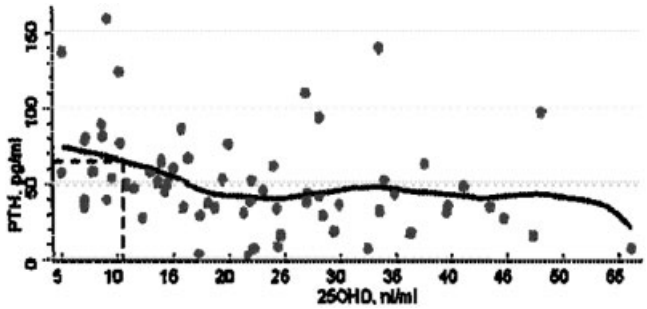


Figure 1. Polynomial curve for RA from a large tertiary care center (n=47)

Conclusion: The relationship between PTH and 25OHD is altered in RA compared with the general population. This finding has important implications for future clinical trials and for optimizing vitamin D replacement in RA.

1694

Do Rheumatoid Arthritis Patients Expect Less From Total Knee Arthroplasty? Hassan Ghomrawi[1], Lisa A. Mandl[2], Beverly Johnson[2], Michael Alexiades[2] and Susan M. Goodman[2]. [1]Weil-Cornell Medical College, NYC, NY, [2]Hospital for Special Surgery, New York, NY

Background/Purpose: RA patients undergoing TKA often do not achieve the same functional results as osteoarthritis (OA) patients, yet are surprisingly satisfied. Satisfaction is determined not just by absolute improvements in pain and function, but also by fulfillment of pre-operative expectations. It is unknown if RA patients have different expectations compared to similar OA patients.

Methods: RA patients undergoing TKA were compared to OA patients matched for age, gender, and lower extremity activity (LEAS) score. All were drawn from a prospective institutional registry, patients with previous arthroplasties were excluded. Expectations were assessed using the validated Hospital for Special Surgery Expectations Survey (see Table 1). A composite score is calculated; range: 0–100; 100=highest expectations. Preoperative data collection also included level of education, living situation, WOMAC, VAS for pain, ED-5Q, SF-36. Wilcoxon Signed Ranks test with Bonferroni correction was used to compare individual expectation items and T-test for mean expectations score.

Table 1. Comparisons of Pre-operative Expectations in OA vs. RA

	OA Controls	Wilcoxon Signed Ranks Test
Knee Expectations Items		**P-value**
Relief of pain	Higher	0.127
Improve ability to walk short distance (indoors, 1 block)	Higher	0.036
Improve ability to walk medium distance (take a walk, < 1 mile)	Higher	0.097
Improve ability to walk long distance (> 1 mile)	Higher	0.254
Remove the need for a cane, crutch or walker	Higher	0.012
Make knee or leg straight	Higher	0.015
Improve ability to go up stairs	Higher	0.007
Improve ability to go down stairs	Higher	0.012
Improve ability to kneel	Higher	0.503
Improve ability to squat	Higher	0.083
Improve ability to use public transportation, drive	Higher	0.006
Be employed for monetary reimbursement	Higher	0.489
Improve ability to participate in recreation (e.g. dancing, pleasure travel)	Higher	0.071
Improve ability to perform daily activities (e.g., household chores, daily routine)	Higher	**<0.0026**
Improve ability to exercise or participate in sports	Higher	0.015
Improve ability to change position (e.g. go from sitting to standing or from standing to sitting)	Higher	0.003
Improve ability to interact with others (for example, take care of someone, play with children)	Higher	**<0.0026**
Improve sexual activity	Higher	0.036
Improve psychological well-being	Higher	0.003

Bonferroni corrected significant P-value <0.0026

Results: 62 RA patients were identified and matched to 124 OA controls. 87.1% were women, average age was 64.7±9.7 years, and average LEAS was 8.7±3.1 (range 2–17), which corresponds to being able to walk around the house and for several blocks without assistance. Other differences were statistically but unlikely clinically significant (see Table 2). There was no difference in living status or education. RA patients had a significantly lower expectations score than OA patients (mean 73.7 vs. 79.8 (p-value=0.03); a difference >6 is clinically meaningful. Scores on multiple individual expectations items were also lower for RA patients, but with a Bonferroni correction only statistically significant for two (see Table 2). In addition, RA patients had lower ED-5Q scale scores suggesting RA patients place a lower value on their current health state.

Table 2. Pre-Operative Data

Variable	RA Cases N=62	OA Controls N=124	P-value
Expectations score	73.7 ± 18.5	79.8 ± 17.1	0.030
WOMAC Pain	10.8 ± 2.8	9.8 ± 3.3	0.040
WOMAC Stiffness	5.1 ± 1.5	4.7 ± 1.6	0.188
WOMAC Function	38.6 ± 11.2	34.7 ± 11.9	0.048
SF-36 PCS	29.3 ± 7.7	32.5 ± 7.8	0.009
SF-36 MCS	45.4 ± 13.1	48.2 ± 13.1	0.190
EQ5D scale	62.9 ± 21.6	71.1 ± 20.4	0.017
EQ5D score	0.6 ± 0.2	0.6 ± 0.2	0.279

Conclusion: Compared to matched OA patients, RA patients had clinically meaningful differences in overall expectations prior to TKA. They also had lower expectations for multiple individual items, and also placed lower value on their pre-operative heath state. This may explain the discrepancy between higher satisfaction and lower functional outcomes in RA patients. In the anti-TNF era, RA patients may be inappropriately accepting poorer outcomes. This raises the possibility they may not be optimizing their post-surgical outcomes.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Existing Disease-Modifying Antirheumatic Drugs - Tight Control, Induction and Drug Withdrawal Trials

Monday, November 7, 2011, 4:30 PM–6:00 PM

1695

Double-Blind Randomized CAMERA-II Trial: Better Control of Disease and Erosive Joint Damage with Inclusion of Low-Dose Prednisone Into a MTX-Based Tight Control Strategy for Early Rheumatoid Arthritis. Marije F. Bakker[1], Johannes W.G. Jacobs[1], Paco M.J. Welsing[1], Suzanne M.M. Verstappen[1], Janneke Tekstra[1], Evelien Ton[1], Monique A.W. Geurts[2], Jacobine H. van der Werf[3], G.A. van Albada-Kuipers[4], Z.N. Jahangier[5], Maaike J. van der Veen[6], C.M. Verhoef[7], Floris P.J.G. Lafeber[1] and Johannes W.J. Bijlsma[1]. [1]UMC Utrecht, Utrecht, Netherlands, [2]St. Antonius hospital, Nieuwegein, Netherlands, [3]Diakonessenhuis, Utrecht, Netherlands, [4]Meander Medical Center, Amersfoort, Netherlands, [5]Tergooi hospital, Hilversum, Netherlands, [6]St. Jansdal hospital, Harderwijk, Netherlands, [7]Flevohospital, Almere, Netherlands

Background/Purpose: Tight control treatment strategies for early rheumatoid arthritis (RA) are highly effective, but leave room for improvement. This study investigated whether including 10 mg/day prednisone from the start of treatment to a methotrexate (MTX) based tight control strategy for early RA is more effective than this strategy without prednisone, regarding disease activity and radiographic outcome, i.e. erosive joint damage.

Methods: Patients with early RA (<1 year) were enrolled in the two-year prospective randomized, placebo-controlled, double-blind, multi-centre MTX-based tight control step-up trial CAMERA-II (Computer Assisted Management in Early RA-II). Patients were randomized to a MTX-based tight control strategy with either prednisone (MTX-pred) or placebo (MTX-plac). MTX treatment was tailored to the individual patient at monthly visits, based on predefined response criteria, aiming for remission. If remission was not achieved at the maximum (tolerable) dose of MTX, a biological was added to the regimen. Primary endpoint was radiographic erosive joint damage after two years. Secondary endpoints included response criteria, remission, and the need of a biological during the trial.

Results: Respectively 117 and 119 patients were randomized to MTX-pred and MTX-plac. Erosive joint damage at the end of the trial was less in the MTX-pred than in the MTX-plac group (median (IQR); 0 (0–0) vs. 0

(0–2), p=0.04). The strategy with MTX-pred was also more effective in reducing disease activity and disability (p≤0.03). A higher proportion of patients in the MTX-pred group achieved sustained remission (72% vs. 61%, p=0.09) and a lower proportion needed biological treatment (14% vs. 36%, p<0.001), compared to the proportions in the MTX-plac group. In the MTX-pred group 29% of patients experienced adverse events compared to 35% in the MTX-plac group.

Conclusion: Inclusion of low-dose prednisone from the start into a two-year MTX-based tight control treatment strategy for early RA increases both effectiveness (i.e. disease activity variables) and outcome (i.e. erosive joint damage) without increasing toxicity. It also reduces the need for (early) treatment with biologicals.

1696

Validation of Methotrexate First Strategy in Early Rheumatoid Arthritis: A Randomized, Double-Blind, 2-Year Trial. James R. O'Dell[1], Jeffrey R. Curtis[2], Stacey Cofield[3], S. Louis Bridges Jr.[4], Ted R. Mikuls[5] and Larry W. Moreland[6]. [1]Univ of Nebraska Med Ctr, Omaha, NE, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]Univ of Alabama at Birmingham,, Birmingham, AL, [4]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [5]Omaha VA and University of Nebraska, Omaha, NE, [6]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: MTX is recommended by both ACR and EULAR guidelines as the initial DMARD for RA. However, there are no data from blinded randomized trials about this approach compared to initial combination therapy or importantly of the consequences of delaying combination therapy and giving it only to those who fail MTX.

Methods: The TEAR trial was an investigator initiated trial in early (mean duration 3.6 months) poor prognosis RA that randomized 755 patients to initial MTX (n=379) versus immediate combination therapy (MTX/etanercept or MTX/SSA/HCQ). MTX only patients stepped-up to combinations at 24 weeks if they failed to achieve low disease activity (DAS28 < 3.2). This design allows the unique opportunity to examine the strategy of using MTX monotherapy as the first intervention in RA.

Results: In the MTX only group, 28% achieved low disease activity and did not step-up to combination therapy. The mean DAS28 for patients remaining on MTX monotherapy at week 102 was 2.7± 1.1 indicating a durable response. This DAS28 was nominally lower than patients treated with immediate combinations (DAS28 3.0±1.4 [P=0.15] see Figure). Further, the MTX group had nominally less radiographic progression compared to immediate combination therapy (TSS 0.1±1.0 vs 1.1±6.; P=0.10). Patients who stepped-up had DAS28 similar DAS28 and radiographic progression to those on combo from the beginning by 12 weeks after step-up through 102 weeks. Results with both immediate combination approaches were similar.

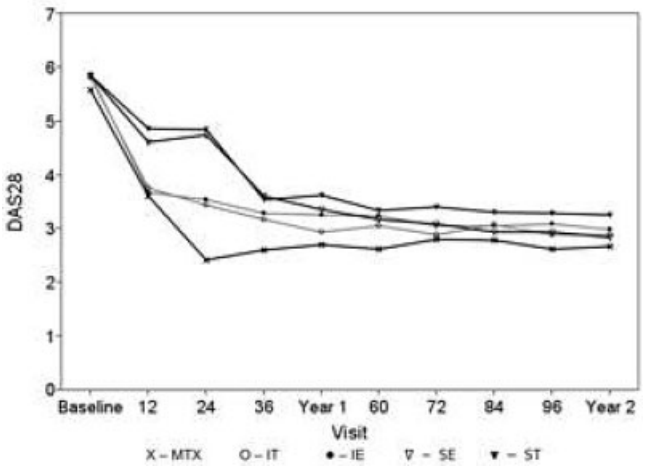


Figure. Observed DAS28 for MTX only, Immediate and Step-up Therapies

Conclusion: These data from a randomized blinded trial in patients with early, DMARD naïve, poor prognosis RA have for the first time validated the oft recommended strategy of starting with MTX mono-therapy. If this is done, approximately 30% of patients will not need combination therapy and the 70% who need add-on therapy will be clinically indistinguishable from those that received immediate combination therapy 3 months after step-up and importantly radiographically indistinguishable at 2 years.

1697

Efficacy of An Induction Therapy with Adalimumab Plus Methotrexate Versus Methotrexate Monotherapy in Recent Onset Rheumatoid Arthritis—An Investigator Initiated Randomized Controlled Trial. Jacqueline Detert[1], Hans Bastian[1], Joachim Listing[2], Anja Weiss[2], Siegfried Wassenberg[3], Anke Liebhaber[4], Karin Rockwitz[5], Rieke Alten[6], Klaus Krüger[7], Rolf Rau[8], Christina Simon[1], Eva Gremmelsbacher[1], Tanja Braun[1], Bettina Marsmann[2], Vera Höhne-Zimmer[1], Karl Egerer[1], Frank Buttgereit[1] and Gerd R. Burmester[1]. [1]Charité-Universitätsmedizin Berlin, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Evangelisches Fachkrankenhaus, Ratingen, Germany, [4]Rheumatologic Practice, Halle, Germany, [5]Rheumatologic Practice, Goslar, Germany, [6]Rheumatology Schlossparkklinik, Berlin, Germany, [7]Practice Center, München, Germany, [8]Düsseldorf, Germany

Background/Purpose: The effectiveness of an early induction therapy within the window of opportunity in patients with early rheumatoid arthritis (RA) is unclear. The present study (designated HIT HARD, funded by the German Ministry of Science) investigated whether disease activity of DMARD naïve patients with early RA benefits long term from induction therapy with adalimumab (ADA) plus methotrexate (MTX).

Methods: In a double-blinded, controlled multicenter trial, DMARD naïve RA patients (active disease ≥6 swollen, ≥6 tender joints, CRP≥10mg/l, disease duration of ≤12 months) were randomized into two groups. During the first 24 weeks (w), group A (n=87): MTX s.c. plus 40mg ADA eow; group B (n=85) 15 mg/w MTX s.c. plus placebo. After w24, both groups were treated only with MTX. Primary outcome was the DAS28 at w48. Secondary outcomes were the proportions of patients in remission (DAS28<2.6), ACR50 response, HAQ, and radiographic progression. Statistical analysis was based on the intention-to-treat population. To improve power, analysis of covariance (ANCOVA) with baseline status as covariable was applied to compare DAS28, HAQ scores between groups. Non-parametric ANCOVA was used to compare van der Heijde modified Sharp (Sharp vdH) scores. Multiple imputation method was used to replace missing data.

Results: Tables 1 and 2 show the baseline characteristics of patients, the outcome parameters at the end of the induction phase (w24) and at the end of follow-up (w48) in both treatment groups. 87% had disease duration of ≤3 months.

Table 1. Baseline characteristics

	ADA/MTX	Placebo/MTX
Age	47.2 ± 12.1	52.5 ± 14.3
Disease duration (months)	1.8 ± 2.1	1.6 ± 1.7
Rheumatoid factor positive	68 %	69 %
ACPA positive	54 %	52 %
DAS28	6.2 ± 0.8	6.3 ± 0.9
HAQ	1.4 ± 0.6	1.3 ± 0.6
Sharp vdH total score	2.3	4.6

Table 2. Outcome parameters at the end of the induction phase (w24) and at the end of follow-up (w48)

	w24 ADA/MTX	w24 Placebo/MTX	w24 p	w48 MTX mono (ADA-group)	w48 MTX mono (Placebo-group)	w48 p
DAS28	3.0 (1.2)	3.5 (1.4)	0.013	3.2 (1.4)	3.4 (1.6)	0.49
Remission (%)	47.0	30.6	0.035	43.8	36.8	0.42
ACR50 response (%)	65.5	49.4	0.033	54.0	48.2	0.45
ACR70 response (%)	47.1	35.3	0.007	41.4	35.3	0.41
HAQ	0.49 (0.6)	0.72 (0.6)	0.001	0.60 (0.6)	0.65 (0.6)	0.28
Sharp vdH total score				6.3 (5.0)	11.4 (14.8)	0.03

During the induction phase, combination therapy of ADA plus MTX reduced disease activity to a significantly greater extent than MTX plus placebo (tab. 2). After termination of ADA or placebo treatment and continuation with MTX alone, the differences between both groups in clinical outcome parameters (DAS28, remission, ACR50 response HAQ) decreased and did not reach statistical significance at w48. Nevertheless, combination therapy significantly reduced radiographic progression compared to MTX alone when analyzed after w48 (implying w24 after discontinuation) of ADA.

Conclusion: Combination therapy with ADA and MTX was significantly superior to MTX alone during the initial treatment phase of w24. A reduction of radiographic progression was observed at w48 indicating a sustained effect of combination treatment that was not found regarding for the primary endpoint, which was the reduction in disease activity. The numerical increase in the clinical outcome parameters of the ADA/MTX group from w40 onwards may reflect the loss of response after removal of ADA.

1698

Treating Rheumatoid Arthritis to Target: Outcomes and Predictors in Early Rheumatoid Arthritis Patients Treated with Adalimumab Plus Methotrexate, Methotrexate Alone, or Methotrexate Plus Subsequent Adalimumab. Josef Smolen[1], Roy M. Fleischmann[2], Paul Emery[3], Ronald F. van Vollenhoven[4], Benoit Guerette[5], Sourav Santra[6], Hartmut Kupper[7], Laura Redden[6], Benjamin Wolfe[6] and Arthur Kavanaugh[8]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]MCRC, University of Texas, Dallas, TX, [3]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [4]The Karolinska Institute, Stockholm, Sweden, [5]Abbott, Rungis, France, [6]Abbott, Abbott Park, IL, [7]Abbott GmbH & Co KG, Ludwigshafen, Germany, [8]University of California San Diego, San Diego, CA

Background/Purpose: The goals of these analyses were to evaluate 1) the optimal strategy for treating patients (pts) with early rheumatoid arthritis (RA) by comparing 78-wk outcomes in pts who continued methotrexate (MTX) or adalimumab (ADA)+MTX after reaching a stable target of DAS28 <3.2 (LDA) at wks 22 & 26 (responders, R), and 2) open-label (OL) ADA+MTX in MTX-pts who did not achieve the wk 22 & 26 target (inadequate responders, IR) in the OPTIMA trial.

Methods: MTX-naïve pts ≥18 years with RA <1 year, active disease [DAS28(CRP) >3.2, ESR ≥28 mm/hr or CRP ≥1.5 mg/dL], and either >1 erosion, RF+, or anti-CCP+ were randomized to ADA+MTX (n=515) or PBO+MTX (n=517) for 26 wks (Period 1, P1). Pts identified as R continued original treatment [ADA+MTX(R)→ADA+MTX and PBO+MTX(R)→PBO+MTX] for an additional 52 wks (P2) and were assessed for the primary composite outcome of DAS28 <3.2 and radiographic non-progression (ΔmTSS ≤0.5) at wk 78. PBO+MTX(IR) pts received OL ADA+MTX after wk 26 [PBO+MTX(IR)→ADA+MTX]. Responses after 26 wks of OL ADA+MTX were compared with those observed for ADA+MTX in P1. Regression analysis examined associations of variables at baseline (BL) and wk 12 with wk 26 rapid radiographic progression (RRP, ΔmTSS >1.5). Pts receiving ≥1 dose of ADA were monitored for adverse events (AEs).

Results: After 26 wks, significantly more ADA+MTX (44%) than PBO+MTX (24%, P <0.01) pts achieved the stable target. Although PBO+MTX(R)→PBO+MTX pts maintained robust clinical responses over 78 wks, significantly more ADA+MTX(R)→ADA+MTX pts achieved high levels of response (**Table**). Overall joint damage was persistently low (mean ΔmTSS: 0.4, PBO+MTX(R)→PBO+MTX; 0.1, ADA+MTX(R)→ADA+MTX); however, more PBO+MTX(R)→PBO+MTX pts had radiographic progression at wk 78 when compared with ADA+MTX(R)→ADA+MTX.

Table. Clinical, Functional, and Radiographic Outcomes at Wk 78

Treatment Group	DAS28 <3.2 and ΔmTSS ≤0.5[a], %	ACR 20/50/70, %	DAS28 <3.2, %	DAS28 <2.6, %	HAQ-DI <0.5, %	ΔmTSS ≤0.5[b], %
ADA+MTX(R)→ADA+MTX	70	95/89/77	91	86	67	89
PBO+MTX(R)→PBO+MTX	55	91/77/62	81	68	64	78
P value	.02	.23/.03/.01	.03	.002	.71	.02

All outcomes are LOCF, unless otherwise indicated.
[a]Primary endpoint of study; non-responder imputation.
[b]Multiple imputation.
Abbreviations: Wk, week; DAS28, 28-joint disease activity score; mTSS, modified total Sharp score; ACR, American College of Rheumatology; HAQ-DI, disability index of the health assessment questionnaire; ADA, adalimumab; MTX, methotrexate; R, responder; PBO, placebo.

PBO+MTX(IR)→OL ADA+MTX pts showed comparable clinical and functional responses with pts initiated on ADA+MTX in P1 but had more radiographic progression (mean ΔmTSS 1.2 vs. 0.15); importantly, OL ADA addition halted radiographic progression in P2. Regression analysis indicated that CRP, anti-CCP, and erosions at BL, and pt global at wk 12 were predictive of RRP at 26 wks (P <.001) among PBO+MTX(IR). AEs [n (%)] observed in 863 pts after any exposure to ADA included: serious AEs, 106 (12.3); serious infections, 35 (4.1); malignancies, 11 (1.3) including nonmelanoma skin cancer, 4 (0.5); opportunistic infections (excluding TB), 8 (0.9); confirmed TB, 4 (0.5); deaths, 9 (1.0).

Conclusion: Achieving a stable LDA target defined pts with good prognosis upon continuation of respective therapies. For PBO+MTX(IR), adding ADA after 26 wks halted radiographic progression and yielded outcomes comparable with naïve pts initiated on ADA+MTX, suggesting that rapid adjustment of therapy in early RA may be comparable with early initiation of ADA+MTX. However, pts with high levels of CRP, anti-CCP, and existing erosions at BL may benefit from earlier use of ADA+MTX.

1699

Withdrawal of Adalimumab in Early Rheumatoid Arthritis Patients Who Attained Stable Low Disease Activity with Adalimumab Plus Methotrexate: Results of a Phase 4, Double-Blind, Placebo-Controlled Trial. Arthur Kavanaugh[1], P. Emery[2], Roy Fleischmann[3], Ronald F. van Vollenhoven[4], Karel Pavelka[5], Patrick Durez[6], Benoit Guerette[7], Sourav Santra[8], Laura Redden[8], Hartmut Kupper[9], Theresa Peterson[8] and Josef Smolen[10]. [1]University of California San Diego, La Jolla, CA, [2]Leeds Teaching Hospital, Leeds, United Kingdom, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]The Karolinska Institute, Stockholm, Sweden, [5]1Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [6]Université Catholique de Louvain, Brussels, Belgium, [7]Abbott, Rungis, France, [8]Abbott, Abbott Park, IL, [9]Abbott, Ludwigshafen, Germany, [10]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: While treatment with adalimumab (ADA) plus methotrexate (MTX) has been shown to be effective in inducing low disease activity (LDA) or remission in early, active, MTX-naïve RA pts, it is not clear if subsequent withdrawal of ADA will allow maintenance of response. In this study, outcomes after 52 weeks of double-blind withdrawal or continuation of ADA were assessed in early RA pts who achieved a stable LDA target of DAS28 <3.2 at wks 22 & 26 with initial ADA+MTX.

Methods: MTX-naïve pts ≥18 years old with RA <1 year and active disease (DAS28[CRP] >3.2, ESR ≥28 mm/hr or CRP ≥1.5 mg/dL), and either >1 erosion, RF+, or anti-CCP+ were randomized to ADA+MTX (n=515) or PBO+MTX (n=517) for 26 wks (Period 1, P1). Pts who achieved the stable LDA target were re-randomized to continue ADA+MTX treatment [ADA+MTX(R)→ADA+MTX] or have ADA withdrawn [ADA+MTX(R)→PBO+MTX] for an additional 52 wks during P2. Clinical, radiographic, and functional outcomes were evaluated through P2. Logistic regression was used to determine study baseline (BL) predictors of stable composite outcomes (DAS28 <2.6 or SDAI ≤3.3, *and* HAQ <0.5, *and* ΔmTSS ≤0.5 from wks 52 to 78) in ADA+MTX(R)→PBO+MTX pts. Pts receiving ≥1 dose of ADA were monitored for adverse events (AEs).

Results: Of the 466 ADA+MTX pts completing P1, 207 pts (44%) achieved the stable LDA target and were re-randomized to ADA+MTX(R)→PBO+MTX (n=102) or ADA+MTX(R)→ADA+MTX (n=105). BL characteristics were similar, with a mean RA duration of 3.9 mos, mean DAS28 of 5.9/5.7, CRP of 28.4/23.5 mg/L, TJC68 of 25.5/23.3, SJC66 of 16.4/15.4, and mTSS of 12.2/10.8 for the two groups. Through wk 78, clinical, radiographic, and functional outcomes were generally comparable for both groups, although significantly more ADA+MTX(R)→ADA+MTX pts achieved higher measures of disease control (ACR70, DAS28 <3.2, and DAS28 <2.6), and numerically fewer pts exhibited radiographic progression at wk 78 (**Table**).

Table. Outcomes at Week 78 (LOCF unless otherwise specified)

Treatment group	ACR20/50/70, %	DAS28 <3.2, %	DAS28 <2.6, %	SDAI ≤ 11, %	SDAI ≤ 3.3, %	ΔmTSS ≤ 0.5, %*	mean ΔmTSS*	mean HAQ‡
ADA + MTX(R)→ PBO + MTX	94/80/65	81	66	84	51	89	0.3	0.35
ADA + MTX(R)→ ADA + MTX	95/89/77	91	86	92	62	81	0.1	0.33
P value	0.72/0.11/0.05	0.04	0.001	0.07	0.1	0.06	0.69	0.66

* multiple imputation; ‡ BL HAQ, ADA+MTX(R) → PBO+MTX: 1.62; ADA+MTX(R) → ADA+MTX: 1.39

Lower HAQ at BL predicted achieving stable composite outcomes from wks 52 to 78 (P <.01) in the ADA+MTX(R)→PBO+MTX group.

Other variables did not predict these outcomes. AEs [n (%)] observed in 863 pts after any ADA exposure included serious AEs, 106 (12.3); serious infections, 35 (4.1); malignancies, 11 (1.3) including nonmelanoma skin cancer, 4 (0.5); opportunistic infections (excluding TB), 8 (0.9); confirmed TB, 4 (0.5); deaths, 9 (1.0).

Conclusion: Most MTX-naïve pts with early, active RA who achieved a stable LDA after 26 wks of ADA+MTX treatment maintained good clinical, radiographic, and functional responses through wk 78 upon removal of ADA. Lower HAQ at BL predicted stable disease remission, normal function, and no radiographic progression. More pts who remained on ADA+MTX achieved higher levels of disease control compared with pts who had ADA removed, suggesting that certain pts may benefit from continued ADA+MTX therapy.

1700

Successful Dose De-Escalation of Infliximab in Rheumatoid Arthritis Patients with Stable Low Disease Activity and Treatment. Aatke van der Maas[1], Alfons den Broeder[1], Frank H.J. van den Hoogen[2], Piet Van Riel[3] and Bart J.F. van den Bemt[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [3]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Optimal dosing of DMARDs and biologics in patients with rheumatoid arthritis (RA) requires maximum effect and minimum cost and side effects. Using step down strategies, frequent monitoring of disease activity, setting goals and adjusting therapy if the goal isn't reached are more effective than routine care, but can lead to overtreatment. This is also true for infliximab.

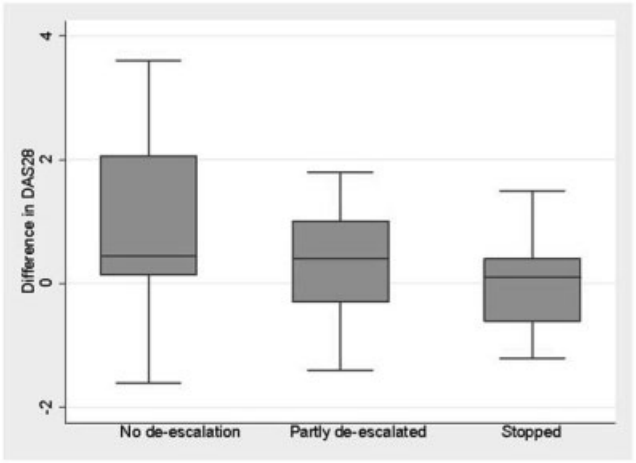
De-escalation or stopping infliximab in RA patients in remission has proven to be feasible in a part of the patients. Therefore our local treatment protocol includes tapering down infliximab dose until discontinuation in RA patients with stable low disease activity and treatment. The goal of this observational study is to describe the prevalence of successful de-escalation.

Methods: According to local treatment protocol infliximab dose was de-escalated with 25% of the original dose (3mg/kg) every 8–12 weeks without interval change in all RA patients with stable low DAS28 and treatment for at least 6 months. The dose was tapered until discontinuation or flare, defined as > 1.2 DAS28 increase, or >0.6 if DAS28 >3.2 on 2 subsequent visits. During 1 year DAS28 and medication changes were recorded. Descriptive statistics were used: percentage of patients de-escalated/stopped, infliximab dose and DAS28 difference before and after de-escalation with T-test and mean DAS28 difference with nonparametric tests.

Results: In 51 RA patients infliximab was de-escalated according to protocol (table 1). In 16% (95% confidence interval(CI) 6–26) and 45% (95%CI 31–59) respectively infliximab was stopped or de-escalated. In 39% (95%CI 26–53) no de-escalation was possible. Mean infliximab dose at start (224mg (95%CI 212–236mg) was significantly lower after 1 year (130 mg, 95%CI 105–154mg), which would imply a cost reduction of approximately € 645,-/infusion and yearly € 5.463/patient. Median DAS28 increased from 2.5 (p25–75=2.0–2.9) to 2.8 (2.2–3.6) after 1 year. This was most noticeable in patients in whom infliximab couldn't be de-escalated, however differences between groups (discontinued, de-escalated and not de-escalated) weren't significant (figure 1). During follow up extra corticosteroids were given in 6% of all 421 visits. DMARDs were seldom changed.

Table 1. Baseline characteristics

Number of patients	51
Age, years (sd*)	59 (11.2)
Female, N° (%)	29 (57)
Weight, kg (sd)	75 (13)
Disease duration in years, median [p25-p75]	12 [9-18]
RF positive, N° (%)	42 (82)
Anti-CCP positive, N° (%)	37 (73)
Erosive disease, N° (%)	39 (76)
DAS29 at inclusion (sd)	2.5 (0.8)
Duration of infliximab therapy, years (sd)	5.6 (2.6)
Interval duration at start, median [p25-p75]	8 [6-8]
Infliximab dose at start, mg (sd)	223 (41)
No of previous DMARDs, median [p25-p75]	3 [2-3]
Previous MTX, N° (%)	49 (96)
Previous anti-TNF-alpha therapy, N° (%)	5 (10)
Concomitant DMARD use, N° (%)	41 (80)
Concomitant MTX use, N° (%)	35 (68)
Concomitant corticosteroid use, N° (%)	2 (4)



Conclusion: In the majority of patients with stable low disease activity and treatment infliximab can be de-escalated or stopped. Mean DAS28 after 1 year is somewhat higher in patients who couldn't de-escalate, which might be partly explained by regression to the mean. Predictors for successful de-escalation are warranted however.

ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis - Pathogenesis, Etiology
Monday, November 7, 2011, 4:30 PM–6:00 PM

1701

A Reverse Interferon-γ Signature Is Shared by CD103+CD4+ Dendritic Cells From HLA-B27 Transgenic Rat and Macrophages From Ankylosing Spondylitis Patients. Ingrid Fert[1], Nicolas Cagnard[1], Simon Glatigny[1], Franck Letourneur[1], Sebastien Jacques[1], Luiza Krause[1], Robert A. Colbert[2], Gilles Chiocchia[1] and Maxime A. Breban[3]. [1]Institut Cochin, 75014 Paris, France, [2]NIAMS NIH, Bethesda, MD, [3]Hopital Ambroise Pare, Boulogne, France

Background/Purpose: In HLA-B27/human β_2-microglobulin transgenic rat, the spontaneous development of an ankylosing spondylitis-like disease (AS) is strongly correlated with high levels of transgene expression and with abnormal function of dendritic cells (DCs). In this study, we investigated the factors implicated in HLA-B27 DC dysfunction by analysing their transcriptome. We further compared our results with those reported on monocyte-derived macrophages from AS patients (*Arthritis Rheum* 2008;58:1640).

Methods: RNA extraction and amplification was performed on $CD103^+CD4^+$DC samples purified from 3 groups of age-matched male rat spleens: 8 different pools of HLA-B27, 6 of HLA-B7 and 7 of nontransgenic rats, using magnetic cell sorting. Affymetrix Rat230_2 GeneChip (a genome-wide array with 31,100 probe sets) was used for the transcriptome assay. Gene expression levels were normalized using GC-RMA and flags were computed using MAS5. Quality assessment of the chips was performed with affyQCReport R package. Inter-group comparisons were done using Student's *t* test. We filtered the p-values at 5% and we only conserved expression fold changes ≥ 1.5. Data were submitted to Ingenuity Pathway Analysis to infer relevant biological pathways.

A meta-analysis was further performed, as previously described (*Immunity* 2010; 33(3): 375), between the rat data and published gene expression analysis performed on macrophages from 8 AS patients and 9 healthy controls: human data extraction, normalization and analysis were performed with the same method as for the rat study, in order to unveil possible correspondences between both species. The human and rat data were merged and submitted to hierarchical clustering.

Results: Rat microarray analysis revealed significant differential expression of 178 genes in HLA-B27 DCs, as compared with both HLA-B7 and nontransgenic DCs. Hierarchical clustering readily separated HLA-B27 from controls DCs. Among the differentially expressed genes, 45 (25.3%) were interferon-γ-regulated (IFNγ), among which 30 IFNγ–up-regulated described genes were underexpressed in HLA-B27 DCs, indicating a "reverse" IFNγ signature (fold

changes: 0.02–0.66). In contrast, several genes involved in antimicrobial peptides pathway were overexpressed in HLA-B27 DCs (fold changes: 7–209).

The combined rat/human hierarchical clustering, performed with 251 ortholog genes, strikingly separated all (n = 17) patient and HLA-B27 rat samples from most (n = 19/22) human and rat controls. The meta-analysis between rat and human data revealed 9 differentially expressed genes shared by AS patients and HLA-B27 rat, as compared to controls. Among these, 5 were indicative of a reverse IFNγ signature: IRF1, STAT1, CXCL9, CXCL10 and IFIT3.

Conclusion: This study reveals consistent differences in gene expression patterns between DCs from HLA-B27 rats vs. controls and AS patients vs. controls, with evidence for a "reverse" IFNγ signature shared with AS patients. Together with an overexpression of genes involved in antimicrobial peptides pathway, these results suggest that expression of HLA-B27 may lead to a defect in IFNγ signaling, with regulatory consequences and implications for disease pathogenesis.

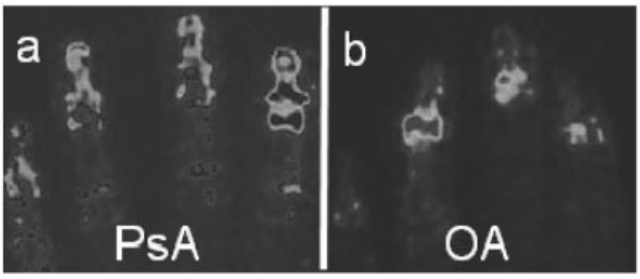
1702

Regional Differences in Bone Metabolism in the DIP Joint in Psoriatic Arthritis Compared to Osteoarthritis Support the Concept of An Integrated Bone-Enthesis Nail Apparatus—A High-Resolution ^{18}F-fluoride Positron Emission Tomography Study. Ai Lyn Tan[1], Steven Tanner[2], Michael Waller[3], Elizabeth Hensor[4], Alison Burns[3], Alan Jeavons[2], Robert Bury[3], Paul Emery[5] and Dennis McGonagle[1]. [1]University of Leeds and Leeds Teaching Hospitals, Leeds, United Kingdom, [2]University of Leeds, Leeds, United Kingdom, [3]Leeds Teaching Hospitals, Leeds, United Kingdom, [4]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [5]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom

Background/Purpose: Bone involvement of the DIP joint including new bone formation and osteolysis are common in psoriatic arthritis (PsA) but are poorly understood in relationship to the nail. This study used high resolution positron emission tomography (hrPET) and ^{18}F-fluoride to explore bone metabolism in the DIP joints in PsA, osteoarthritis (OA) and in healthy controls (HC). The aim was to test the hypothesis that in PsA, the nail is functionally integrated with the bone.

Methods: 234 DIP joints were scanned in 30 subjects (10 PsA, 10 OA and 10 HC) using the QuadHIDAC nano PET scanner. ^{18}F-fluoride uptake intensity was normalised to a region in the mid shaft of a proximal phalanx in each hand. The images were assessed blinded to diagnosis and symptoms (VAS 0–10) for site and intensity (score 0–3) of increased isotope uptake.

Results: At the DIP joints, the uptake of ^{18}F-fluoride in the distal phalanx (DP) was strong relative to the intermediate phalanx in both PsA and OA. In PsA, uptake often occurred in a diffuse pattern involving most of the DP adjacent to the nail (43% of PsA joints, 19% of OA joints, p=0.01) (Fig a). There was also greater isotope uptake at the enthesis, the periosteum, and at the tufts of the DP of PsA compared to OA, which may explain the commonly seen bony phenotype of PsA ranging from periostitis (periosteal pattern of uptake) to end-stage osteolysis or whittling of DPs (diffuse and tuftal patterns of uptake). In contrast, in OA uptake was greatest in the peri-articular/sub-chondral region of the joint adjacent to known sites of osteophytosis and bone erosions (Fig b).



Of the 3 groups, the PsA joints showed an overall greater intensity of ^{18}F-fluoride uptake. Compared to the asymptomatic PsA DIP joints, there was greater intensity of isotope uptake in the symptomatic joints (median [range] intensity 2 [1–3] in symptomatic joints, 1 [0–2] in asymptomatic joints), and a greater proportion of symptomatic PsA DIP joints had DP isotope uptake at the subchondral bone and the periosteum, where there are large concentrations of enthesis attachments including attachments from the nail, suggesting that events taking place within bone may be major determinants of symptoms in PsA. The asymptomatic PsA joints had a greater degree of isotope uptake in the DPs compared to the HC asymptomatic joints (median [range] intensity in PsA 1 [0–2], normal 0 [0–1], p=0.001) supporting the established view of a large burden of asymptomatic subclinical disease in PsA.

Conclusion: This is the first reported study showing that hrPET can be used to study human arthritis and demonstrates diffuse increased bone metabolism involving the entire DP, periostium and entheses, especially in PsA. The subchondral bone and periosteum at the DP have large concentrations of enthesis attachments including attachments from the nail supporting the concept of an integrated nail and joint apparatus leading to a wide area of abnormal bone metabolism in PsA.

1703

Evidence That HLA-B27-Induced Endoplasmic Reticulum (ER) Stress Produces Pro- and Anti-Osteoclastogenic Cytokines in Rats with Spondyloarthritis-Like Disease. Gerlinde Layh-Schmitt, Eva Yang and Robert A. Colbert. NIAMS NIH, Bethesda, MD

Background/Purpose: Spondyloarthritis (SpA) is an immune-mediated inflammatory disease that can result in both systemic bone loss and aberrant bone formation. HLA-B27 (B27) is a major genetic risk factor, and in B27/human β_2m transgenic (B27-Tg) rats that develop SpA-like disease, B27 misfolding and generation of ER stress activates the unfolded protein response (UPR). This promotes IFN-β and IL-23 expression, and is associated with expansion and activation of CD4+ Th17 T cells, and IL-17 and TNF-α overexpression in the colon. IL-23 induction provides a plausible mechanism for the development of colitis, and suggests an 'upstream' role for B27 in promoting inflammation. Since HLA class I molecules are expressed in many different cell types, including those involved in bone homeostasis, we hypothesized that B27 may also have 'downstream' effects that alter cell behavior in response to pro-inflammatory cytokines. Thus, we examined whether B27 expression affects the development of osteoclasts from bone marrow (BM) precursors under the influence of TNF-α or RANKL.

Methods: BM monocytes (BMMo) were obtained from healthy wild type (WT) and B27-Tg rats, and treated for five days with M-CSF and either RANKL (10–100 ng/ml) or TNF-α (7.5–30 ng/ml) to induce osteoclast formation. Osteoclasts were quantified by counting TRAP (tartrate tesistant acid phosphatase)-positive cells with >3 nuclei. Expression levels of B27 and UPR-target genes (BiP and XBP1s) were examined by RT-PCR, western blot, and immunofluorescence. Neutralizing antibodies against IL-1α and IFN-β were used to block autocrine effects of these cytokines.

Results: BMMo from B27-Tg rats treated with TNF-α form 2–3-fold more osteoclasts than BMMos from wild type (WT) animals (n=6 experiments, 2.5-fold, 95% CI=2.16–2.94). In contrast, RANKL stimulated the formation of the same number of osteoclasts in B27-Tg and WT BMMos. TNF-α upregulated B27 expression, exacerbated misfolding, and activated the UPR in B27-Tg cells, but no UPR activation was seen in WT cells. In contrast, RANKL had no effect on B27 expression, and UPR activation was not seen in either B27-Tg or WT BMMos. Neutralization of IL-1α completely blocked the increase in osteoclast formation in B27-expressing BMMos, while IFN-β neutralization further promoted TNF-α-induced osteoclast formation in B27-Tg cells (2-fold). In WT cells neither antibody had a significant effect on osteoclast formation.

Conclusion: Our results indicate that osteoclast precursors from rats expressing HLA-B27 produce at least two activities in response to TNF-α most likely as a consequence of B27 misfolding and UPR activation; one activity (IL-1α) promotes osteoclastogenesis, while a second (IFN-β) inhibits osteoclastogenesis. Although the net result in this system is pro-osteoclastogenic and may contribute to the bone loss observed in these rats, other factors that further induce IFN-β could shift this balance towards a net anti-osteoclastognic effect. These results are of considerable interest given the bone phenotype of ankylosing spondylitis where aberrant bone formation is frequently juxtaposed with bone loss in the axial skeleton.

1704

Identification of a Unique Subset DC-STAMP+ (Dendritic Cell-Specific Transmembrane Protein) T Cells with a Th17 Signature in Psoriatic Arthritis (PsA) Patients. Yahui Grace Chiu, Edward M. Schwarz, Wojciech Wojciechowski, Ben Panepento, Igor Kuzin, Tim Bushnell, Sharon Moorehead, Rick Barrett and Christopher Ritchlin. University of Rochester, Rochester, NY

Background/Purpose: The contribution of Th17 cells to disease pathogenesis in psoriatic arthritis (PsA) is not well understood. We previously demonstrated that the expression of DC-STAMP (Dendritic Cell-Specific Transmembrane Protein), a 7-pass transmembrane protein required for monocyte fusion during osteoclast (OC) development, is increased in freshly isolated monocytes from PsA patients and may be a marker of osteoclast precursors. We also noted that a subset of CD3+/CD4+ T cells expressed DC-STAMP. Herein, we examined if DC-STAMP+/CD3+/CD4+ cells have a Th17 cell signature.

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from PsA patients and healthy controls (HC), stained with an antibody cocktail composed of Th17-specific antibodies including IL-23R, CD161, CCR4, CCR6, and 1A2, a monoclonal antibody to DC-STAMP. The intracellular expression of IL-17, IFN-γ and IL-4 was also examined. A portion of PBMC was cultured in the presence of Th17-promoting cytokines and examined by the same antibody cocktail after 8 days in culture. IL-17 concentration in culture supernatants was evaluated by ELISA and the expression of Th17-specific genes was analyzed by real-time PCR (RT-PCR). Cellular localization of DC-STAMP on DC-STAMP+/CD3+/CD4+ T cells and DC-STAMP+/CD14+ monocytes was visualized and compared by Amnis ImageStream.

Results: Analysis of flow data from PsA patients (n=32) revealed a positive correlation between the percentage of DC-STAMP+ and DC-STAMP+/CD3+ cells (Pearson correlation=0.506, p=0.003). We identified a unique subset of CD3+/CD4+/DC-STAMP+ cells with a Th17 cell signature (CCR4+/CCR6+/IL23R+/IL17A+/CD161+). These cells expressed low levels of intracellular IL-4 and IFN-γ. Importantly, this subset was detected in PsA patients but not in HC. After 8-day culture in Th17-promoting conditions, the percentage of DC-STAMP+ cells was increased 2-fold and the Th17 phenotype was greatly enhanced. These cells secreted increased levels of IL-17 compared to unstimulated cells. RT-PCR analysis revealed an increase in CCR4, CCR6, IL23R and RORgammaT gene expression, which was associated with an elevated DC-STAMP signal after culture. DC-STAMP+/CD3+ cells from tonsil were distinct from those in PBMC and did not have Th17 signature. DC-STAMP was mainly expressed on the cell surface of DC-STAMP+/CD14+ monocytes but was found evenly distributed in the cytoplasm of DC-STAMP+/CD3+/CD4+ T cells.

Conclusion: A novel CD3+/CD4+/DC-STAMP+ cell population with a distinct Th17 cell signature was identified in a subset of PsA patients. This T cell phenotype was enhanced in the presence of Th17-promoting cytokines *in vitro* and was associated with increased secretion of IL-17. The intracellular localization of DC-STAMP on CD3+/CD4+ T cells suggests internalization of receptor/antibody complexes, a phenomenon commonly observed in chemokine receptors. Distinct cellular localization of DC-STAMP in CD14+ monocytes and CD3+/CD4+ T cells suggests divergent biological functions of DC-STAMP in these 2 cell lineages. Future studies on this unique DC-STAMP+ T cell subset may provide new insights into the mechanisms of inflammation and bone destruction regulated by T cells in PsA.

1705

The Role of Gut Microflora and Autoreactive CD4+ T Cells in the Development of Spondyloarthritis and Inflammatory Bowel Disease in Beta-Glucan-Treated SKG Mice. Merja Ruutu[1], Jared Velasco[1], Daniel Aguirre[2], Helen Benham[1], Mark Morrison[2], Michael McGuckin[3] and Ranjeny Thomas[1]. [1]Univ of Queensland, Brisbane, Australia, [2]CSIRO, Brisbane, Australia, [3]Mater Medical Research Institute, Brisbane, Australia

Background/Purpose: Although spondyloarthritis and inflammatory bowel disease (IBD) co-exist in human spondyloarthropathies (SpA) the mechanism is unclear. Despite shared genetic associations, only a subset of patients develops spondyloarthritis and IBD, and either may present first. Autoimmune cross-reactivity towards joint and gut antigens may occur. Alternatively there may be coincident or sequential development of joint and gut autoreactivity driven by common innate mechanisms, potentially triggered by infection. The SKG ZAP-70^{W163C} mutation of the BALB/c strain reduces T cell receptor signaling, altering sensitivity of developing thymocytes to negative and positive selection, and enriching the peripheral repertoire with IL-17-skewed autoreactive T cells. When otherwise healthy SKG mice are housed in microbially clean (spf) conditions, systemic administration of 1,3-D beta-glucan (curdlan) triggers arthritis of wrists and ankles, spondylitis of tail and lumbar spine, Crohn's-like ileitis and unilateral anterior uveitis. To elucidate the mechanism underlying the involvement of multiple organs after a single trigger, we sought the contribution of the gut microflora, and of CD4+ autoreactive T cells to arthritis, spondylitis and ileitis in this model.

Methods: SKG mice housed in spf or rederived to germ free conditions were injected i.p. once with 3 ug curdlan. Arthritis, general appearance and weight loss were scored for 10 weeks. Organ pathology was determined by H&E staining of paraffin-embedded tissue sections at sacrifice between 1 and 10 weeks after injection of curdlan. Sera were analyzed for autoantibodies. $CD4^+$ T cells were transferred from lymph nodes and spleen of SKG mice treated 1 week previously with curdlan, to immunodeficient mice.

Results: Under spf conditions, histological analysis of tissues showed that arthritis and spondylitis developed simultaneously and progressively from 1 week after curdlan injection, associated with the development of anti-proteoglycan and anti-collagen type II autoantibodies. In contrast, there was no histological evidence of ileitis until 6–10 weeks after curdlan injection. All recipients of $CD4^+$ T cells from SKG mice treated 1 week previously with curdlan developed arthritis and spondylitis but not ileitis. However, immunodeficient recipients of $CD4^+$ T cells also developed colitis. Under germ free conditions, arthritis and spondylitis were markedly attenuated.

Conclusion: After systemic exposure to beta-glucan, SKG mice develop sequential features of SpA. Arthritis and spondylitis, transferable with CD4+ T cells and associated with autoimmunity to cartilage antigens, develops first, followed by ileitis. The failure of CD4+ T cells to transfer ileitis early in disease argues against T cell cross-reactivity towards joint and small intestinal autoantigens. The lack of arthritis in germ free conditions suggests, however, that gut microflora mediate systemic effects of curdlan, potentially through adjuvant effects on joint autoantigen presentation.

1706

Transcriptomic Analysis of Monocytes and Monocyte-Derived Dendritic Cells (MD-DCs) Reveals Several Genes Differentially Regulated Between Ankylosing Spondylitis (AS) Patients and Healthy Controls. Alice Talpin[1], Nelly Bonilla[1], Félicie Costantino[2], Franck Letourneur[1], Sebastien Jacques[1], Florent Dumont[1], Henri-Jean Garchon[2], Maxime A. Breban[3] and Gilles Chiocchia[1]. [1]Institut Cochin, 75014 Paris, France, [2]Institut Cochin, Paris, France, [3]Hopital Ambroise Pare, Boulogne, France

Background/Purpose: As originally shown in an HLA-B27 transgenic rat model, abnormal regulation of antigen-presenting cells is a characteristic feature of AS. Indeed, monocytes-derived DCs from AS patients exhibit a weaker stimulatory efficiency of CD4+ T cells than control DCs (*Arthritis Rheum.* 2009;60:1432). Consequently, it is of first importance to analyze the gene expression profile in DCs from AS patients.

Objectives: To identify genes differentially expressed in monocytes and MD-DCs from AS patients, as compared to healthy controls.

Methods: Monocytes were purified from 9 HLA-B27+ AS patients and 10 healthy controls PBMCs using anti-CD14-coupled immunomagnetic beads and either RNA directly extracted or cells were further cultured with IL-4 and GM-CSF for 7 days. MD-DCs were then stimulated with LPS for 6 and 24 hours. RNAs were extracted and copied into cRNA. Transcriptomic study was performed with Affymetrix HuGene 1.0 ST microarrays (23,021 genes) on monocytes and on unstimulated and stimulated MD-DCs. Data were analyzed with Bioconductor. Following normalization, gene expression levels in patients and in controls were compared using a multivariate design under a linear model (LIMMA). Bonferroni correction was applied. Analysis of signaling pathway-linked genes was done with Ingenuity Pathway Assist Software.

Results: Transcriptomic analysis identified 41 and 53 genes differentially expressed between AS and controls, in monocytes (0.18%) and in MD-DCs (0.23%), respectively. Highest statistical significance was observed for early growth response-2 (*EGR2*) and sphingomyelin synthase 2 (*SGMS2*) genes (Pcorr = 2.2×10^{-5} and 1.5×10^{-4}, respectively) in monocytes; and for metallopeptidase with thrombospondin type 1 motif 15 (*ADAMTS15*) and tumor necrosis factor superfamily, member 13B (*TNFSF13B/BAFF*) (Pcorr= 2×10^{-2} and 4×10^{-2}, respectively) in MD-DCs. IL-17 and IL-6 signaling canonical pathways were detected as

differentially regulated in monocytes between AS and controls. In MD-DCs, genes related to inducible T-cell co-stimulator (ICOS) signaling appeared differentially expressed. Validation by q-PCR of the most significant genes is underway.

Conclusion: This transcriptomic study reveals striking differences in the gene expression patterns of monocytes and MD-DCs between AS and controls. Several differentially expressed genes suggest interesting biological relevance, such as *EGR2* which is regulated by dectin and *BAFF* which may correlate with disease activity in psoriatic arthritis. Conversely, other genes, such as SGMS2, are unforeseen by previous works and may reveal new pathogenetic pathways.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects: General
Monday, November 7, 2011, 4:30 PM–6:00 PM

1707

Favorable Prognosis in a Large, Prospective Multicenter Study of Lupus Pregnancies. Jill P. Buyon[1], Lamya Garabet[2], Mimi Kim[3], Emily R. Reeves[2], Marta M. Guerra[2], Michael D. Lockshin[4], Carl A. Laskin[5], Ware Branch[6], Lisa R. Sammaritano[2], Michelle Petri[7], Joan T. Merrill[8], Allen D. Sawitzke[9] and Jane E. Salmon[10]. [1]New York University School of Medicine, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Albert Einstein College of Medicine, Bronx, NY, [4]Barbara Volcker Center for Women and Rheumatic Diseases: Hospital for Special Surgery, New York, NY, [5]University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON, [6]Univ of Utah, Salt Lake City, UT, [7]Johns Hopkins University School of Medicine, Baltimore, MD, [8]Oklahoma Medical Research Foundation, Oklahoma City, OK, [9]University of Utah Medical Ctr, Salt Lake City, UT, [10]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

Background/Purpose: Accurate prediction of fetal and maternal outcomes of pregnancies complicated by lupus is required to plan treatment. The frequency of adverse outcomes and associated clinical and laboratory variables were evaluated in a large, prospective multicenter, multiethnic study.

Methods: The PROMISSE Study (**P**redictors of p**R**egnancy **O**utcome: Bio**M**arkers **I**n antiphospholipid antibody **S**yndrome and **S**ystemic Lupus **E**rythematosus) evaluated 333 pregnant women each month with ≥4 ACR SLE criteria enrolled in the first trimester. Exclusion criteria were multi-fetal pregnancy, prednisone >20mg/d, proteinuria >1gm/24hr, and/or creatinine >1.2 mg/dL. An adverse pregnancy outcome was at least one of the following: fetal/neonatal death, birth <36 weeks due to placental insufficiency, hypertension, or preeclampsia, and small for gestational age <5th percentile (SGA). Mild/moderate and severe flares were defined by SLEPDAI Index (**SL**E **P**regnancy **D**isease **A**ctivity **I**ndex), which excludes physiologic changes of pregnancy but incorporates the components of the SELENA-SLEDAI score as well as changes in clinical parameters and medications, and physician's global assessment (PGA). Subjects were: 56.8% Caucasian, 19.8% Black, 10.2% Asian, 13.2% mixed or other races; overall 16.0% Hispanic by ethnicity. Thirty-one percent had previous renal disease. At enrollment 38% were anti-dsDNA positive; 60% took HCQ, 41% prednisone, and 18% azathioprine. Mean SLEPDAI was 2.6 ± 2.8.

Results: Adverse pregnancy outcome occurred in 63 (19%) patients: 19 had fetal/neonatal death and 30 each had birth <36 weeks or SGA infants. The following baseline variables associated with poor outcome: SLEPDAI ≥4 (p=.02), high titer aPL (LAC + or IgG aCL > 40, p<.0001), higher median uric acid levels (3.4±1.4 vs. 3.0±2.2 mg/dL, p=.01), as was an increase over baseline in SLEPDAI ≥3 at 20 or 32 wks (p =.03) and an increase in PGA ≥0.3. None of the following influenced pregnancy outcomes: Hispanic ethnicity, prior renal disease or use of cylophosphamide, or at entry, proteinuria ≥2+ or 500–1000mg/d, positive anti-dsDNA, initial C3 or C4 level, HCQ, prednisone, or azathioprine. Ten percent of patients developed preeclampsia. Mild/moderate flares occurred in 10.2% at 20 wks and 7.8% at 32 weeks. Severe flares occurred in 2.1% at 20 wks and 2.4% at 32 weeks. Of the 15 patients with severe flares: 4 were renal, 5 pleuritis, 1 thrombocytopenia, 1 CNS, 2 arthritis, 1 myositis and 1 pericarditis. Neither the initial mean C3 or C4 nor presence of anti-dsDNA associated with flare.

Conclusion: Eighty percent of patients have a favorable pregnancy outcome. Adverse outcome was associated with an increase in lupus activity during pregnancy, high titer aPL antibody, and higher levels of uric acid at baseline. Mild/moderate and severe flares were infrequent in patients clinically stable at baseline despite anti-dsDNA antibodies or past history of renal disease. This large, prospective study provides reassurances for patients with stable lupus contemplating pregnancy and suggests parameters that merit caution for the minority at risk of adverse outcome.

1708

Derivation and Validation of Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus. Michelle Petri[1], Ana-Maria Orbai[1], Graciela S. Alarcón[2], Caroline Gordon[3], Joan T. Merrill[4], Paul R. Fortin[5], Ian N. Bruce[6], David A. Isenberg[7], Daniel J. Wallace[8], Ola Nived[9], Gunnar K. Sturfelt[10], Rosalind Ramsey-Goldman[11], Sang-Cheol Bae[12], John G. Hanly[13], Jorge Sanchez-Guerrero[14], Ann E. Clarke[15], Cynthia Aranow[16], Susan Manzi[17], Murray B. Urowitz[18], Dafna D. Gladman[19], Kenneth C. Kalunian[20], Melissa I. Costner[21], Hong Fang[1], Systemic Lupus International Collaborating Clinics (SLICC)[22] and Laurence S. Magder[23]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Birmingham, Birmingham, United Kingdom, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Toronto Western Hospital, Toronto, ON, [6]The University of Manchester, Manchester, United Kingdom, [7]University College London, London WC1E 6JF, United Kingdom, [8]Cedars-Sinai/UCLA, Los Angeles, CA, [9]University Hospital, Lund, Sweden, [10]University Hospital Lund, Lund, Sweden, [11]Northwestern University, Chicago, IL, [12]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [13]Nova Scotia Rehabilitation Center, Halifax, NS, [14]University Health Network/Mount Sinai Hospital, Toronto, ON, [15]Research Institute of the McGill Univ. Health, Montreal, QC, [16]Feinstein Institute for Medical Research, Manhasset, NY, [17]Allegheny Singer Research Institute, Pittsburgh, PA, [18]Toronto Western Hospital and University of Toronto, Toronto, ON, [19]Toronto Western Research Institute, University of Toronto, University Health Network, Toronto, ON, [20]UCSD School of Medicine, La Jolla, CA, [21]North Dallas Dermatology Assoc, Dallas, TX, [22]Chicago, [23]University of Maryland, Baltimore, MD

Background/Purpose: The Systemic Lupus International Collaborating Clinics (SLICC) revised the American College of Rheumatology (ACR) SLE classification criteria and then validated the new criteria in order to improve clinical relevance, meet more stringent methodology requirements and incorporate new knowledge in SLE immunology since 1982.

Methods: The new classification criteria were derived from a set of 702 expert-rated patient scenarios. Recursive partitioning and logistic regression were used to derive an initial rule that was simplified and refined based on SLICC physician consensus. The SLICC classification rule was validated in a new sample of 690 SLE patients and controls.

Results: The SLICC criteria rule for SLE classification requires: 1) Four criteria, with at least one clinical criterion AND one immunologic criterion OR 2) Lupus nephritis alone in the presence of ANA or anti-dsDNA antibodies. In the derivation set, the SLICC classification rule resulted in fewer misclassifications than the current ACR classification rule (49 compared to 70, p=0.0082), had greater sensitivity (94% versus 86%, p<0.0001) and equal specificity (92% versus 93%, p=0.39). In the validation set, the SLICC classification rule resulted in fewer misclassifications (66 compared to 74, p=0.43), had greater sensitivity (97% versus 83%, p<0.0001) but less specificity (84% versus 96%, p<0.0001).

Conclusion: The new SLICC classification criteria performed well on a large set of patient scenarios rated by experts. In particular, the new criteria provide updated and more inclusive definitions for each criterion.

Importantly, they require that at least one clinical criterion and one immunologic criterion be present to have a classification of SLE. Under the new SLICC classification lupus nephritis by biopsy (in the presence of SLE autoantibodies) is sufficient for classification.

Table. Clinical and Immunologic Criteria Used in the Classification Rule

Clinical Criteria

1. Acute cutaneous lupus
   including lupus malar rash (do not count if malar discoid)
   bullous lupus
   toxic epidermal necrolysis variant of SLE
   maculopapular lupus rash
   photosensitive lupus rash
   in the absence of dermatomyositis or subacute cutaneous lupus
   (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias).
2. Chronic cutaneous lupus
   including classical discoid rash
   localized (above the neck)
   generalized (above and below the neck)
   hypertrophic (verrucous) lupus
   lupus panniculitis (profundus)
   mucosal lupus
   lupus erythematosus tumidus
   chilblains lupus
   discoid lupus/lichen planus overlap
3. Oral ulcers: palate
   buccal
   tongue
   or nasal ulcers
   in the absence of other causes, such as vasculitis, Behcets, infection (herpes), inflammatory bowel disease, reactive arthritis, acidic foods
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) *in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia*
5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness.
6. Serositis
   typical pleurisy for more than 1 day
   or pleural effusions
   or pleural rub
   typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
   or pericardial effusion
   or pericardial rub
   or pericarditis by EKG
   in the absence of other causes, such as infection, uremia, and Dressler's pericarditis
7. Renal
   Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein/24 hr
   or
   Red blood cell casts
8. Neurologic
   seizures
   psychosis
   mononeuritis multiplex
   in the absence of other known causes such as primary vasculitis myelitis
   peripheral or cranial neuropathy
   in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
   acute confusional state
   in the absence of other causes, including toxic-metabolic, uremia, drugs
9. Hemolytic anemia
10. Leukopenia (< 4000/mm^3 at least once)
    in the absence of other known causes such as Felty's, drugs, portal hypertension
    OR
    Lymphopenia (< 1000/mm^3 at least once)
    in the absence of other known causes such as corticosteroids, drugs and infection
11. Thrombocytopenia (<100,000/mm^3) at least once *in the absence of other known causes such as drugs, portal hypertension, TTP*

Immunological Criteria

1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range
3. Anti-Sm
4. Antiphospholipid antibody: any of the following
   lupus anticoagulant
   false-positive RPR
   medium or high titer anticardiolipin
   anti-b2 glycoprotein I
5. Low complement
   low C3
   low C4
   low CH50
6. Direct Coombs test in the absence of hemolytic anemia

1709

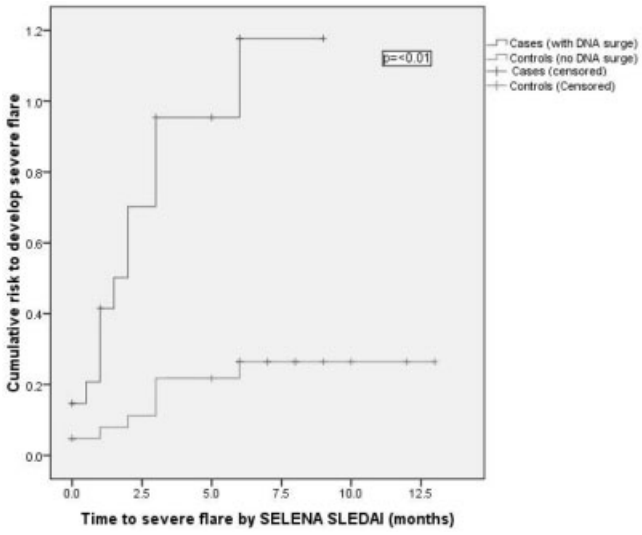
Rapid Surges of Anti-dsDNA Titers Predict Severe Clinical Flares in Systemic Lupus Erythematosus. Nancy Pan[1], Isabelle Amigues[2], Rolando Duculan[3], Faiza Aziz[4], Stephen L. Lyman[1], Mary K. Crow[1] and Kyriakos A. Kirou[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital Saint Joseph Saint Luc, Paris, France, [3]Mary Kirkland Center for Lupus Research-Hospital for Special Surgery, New York, NY, [4]Interfaith Medical Center, Brooklyn, NY

Background/Purpose: Autoantibodies to double stranded (ds) DNA (anti-DNA) are very specific for the diagnosis of systemic lupus erythematosus (SLE). Anti-DNA titers are used by 76% of US rheumatologists to monitor disease activity, though there are conflicting reports as to its utility. Studies have shown increased anti-DNA titers with no clinical activity, and conversely, increased disease activity with low or absent anti-DNA titers. We hypothesized that a rapid and dramatic increase in anti-DNA titers ("anti-DNA surge") may herald a severe SLE flare.

Methods: A matched case-control study was conducted to assess the association between a preceding anti-DNA surge and a subsequent clinical flare in patients with SLE. The study protocol was approved by the institutional review board. All patients were identified from the Hospital for Special Surgery (HSS) SLE Registry and met the American College of Rheumatology 1982 revised classification criteria for SLE. Cases had to have a surge of anti-DNA, defined as an increase of anti-DNA titer by the *Crithidia luciliae* assay from 0 to 3+/4+, or from 1+ to 4+, within a period of less than 12 months. The date of the anti-DNA surge was defined as Day 0. Two control SLE patients were identified through the HSS registry for each case and were matched for age, sex and race, and Day 0 (visit date closest to corresponding date for case), but without an anti-DNA surge.

The primary outcome was Severe Flare by SELENA SLEDAI within 6 months of an anti-DNA surge. Secondary outcomes were a Renal Flare (by BILAG Renal A or B) within 6 months, occurrence of a Mild/Moderate Clinical Flare (by SELENA SLEDAI), and mild, moderate or severe flare by the mSFI (Modified SELENA Flare Index) within 6 months. Chi square analysis and logistic regression were used to detect associations of anti-DNA surges with clinical SLE flares, age, sex, race, and complement levels.

Results: Twenty-three cases and 45 controls were identified. A higher proportion of cases, compared to controls, experienced a Severe Flare within 6 months of Day 0 (OR 6.3, p=0.02, CI 2–19). The cumulative risk of having a severe flare was significantly higher in cases (see figure). Anti-DNA surges also were associated with an increased risk for a severe or moderate flare by mSFI (OR 3.3, p=0.03, CI 1.1–9.5). An anti-DNA surge was not predictive of a Renal flare. Race, Hispanic ethnicity, and sex were not predictive of a severe SELENA flare. More dramatic anti-DNA surges (increase of titers from 0–4+) had a higher risk for a severe SELENA flare (OR 7.9, p=0.002) than less dramatic anti-DNA increases (OR 4.475, p=0.1).



Conclusion: A rapid, dramatic rise in anti-DNA titer was strongly associated with the development of a severe clinical SLE flare by SELENA SLEDAI within 6 months. We believe that clinicians should intensify follow-up for such patients and treat aggressively as soon as a clinical flare occurs.

1710

The Resting State and Task Based Functional Magnetic Resonance Imaging Study in Non-Neuropsychiatric Systemic Lupus Erythematosus. Yongfei Fang and Qinghua Zou. Chongqing Southwest Hospital, Shapingba, China

Background/Purpose: To find evidence for occult cerebral functional damage resides prior to clinical symptoms by using resting state and task based functional magnetic resonance imaging(fMRI) in systemic lupus erythematosus (SLE) patients without neuropsychological symptoms.

Methods: 41 non-neuropsychiatric systemic lupus erythematosus (non-NPSLE) patients and 28 similar control participants were enrolled, performed paced visual serial addition test (PVSAT), and performed both resting state and PVSAT task based fMRI scanning. Data were processed and analysed by SPM8 software package, resting state data were post processed with method called regional homogeneity (ReHo). Difference of ReHo values between patients and controls were compared by independent t test. The activated brain areas of PVASAT tasks were compared in SPM8, and functional connectivity of these areas were tested in resting state data.

Results: During resting state, compared to the controls, non-NPSLE subjects displayed significantly decreased ReHo values in multiple areas including the bilateral posterior lobes of the cerebellum (predominantly in crus I and II of the neocerebellum), the vermis, left inferior frontal gyrus, left precuneus, right limbic lobe and cingulate gyrus; ReHo was increased in bilateral cuneus and in the calcarine gyrus. Both groups had no significant difference in PVSAT test. In PVSAT task based fMRI, in control subjects, the activations were situated in left superior and inferior parietal lobe, and left inferior frontal gyrus. While for non-NPSLE patients, significantly extended activations were found in left hemisphere in superior and inferior parietal lobe, superior, middle and inferior frontal gyrus. Brain areas activated in healthy controls were selected as regions of interest (ROIs) to test for the functional connectivity strength between patients and controls. Compared with controls, non-NPSLE patients exhibited a significantly higher magnitude of connectivity strength between areas activated during working memory task.

Conclusion: During resting state, non-NPSLE patients exhibited alteration of major areas of default mode network; while significantly expanded areas of activation in task based fMRI, both resutls demonstrated that cerebral damage existed prior to the presentation of any neuropsychological symptoms.

1711

The Intrathecal Production of IL-6, IL-8, IP-10, MCP-1 and G-CSF Increases More Highly Than the Serum Production in Patients with Central Neuropsychiatric Lupus Erythematosus. Taku Yoshio[1], Hiroshi Okamoto[2], Kazuhiro Kurasawa[3], Yoshiaki Dei[4], Shunsei Hirohata[5] and Seiji Minota[6]. [1]Jichi Medical University, School of Medicine, Shimotsuke-shi, Tochigi-ken, Japan, [2]Minami-Otsuka Clinic, Tokyo, Japan, [3]Dokkyo Medical University, Mibu-machi, Tochigi-ken, Japan, [4]Saiseikai Utsunomiya Hospital, Utsunomiya-shi, Tochigi-ken, Japan, [5]Kitasato University School of Medicine, Sagamihara, Japan, [6]Jichi Medical University, Tochigi, Japan

Background/Purpose: To determine whether the intrathecal concentrations of cytokines/chemokines are associated with, or influenced by serum concentrations in patients with central neuropsychiatric SLE (NPSLE), and whether the increased production of cytokines/chemokines intrathecally relative to serum levels is associated with the presence of central NPSLE.

Methods: Fifty-two SLE patients, of whom the CSF and serum samples were obtained at the same time, were enrolled. Of the 52 SLE patients enrolled, 30 exhibited central NPSLE while the reminding 22 were non-NPSLE. The concentrations of IL-6, IL-8, TNF-α, IP-10, MCP-1, IFN-γ, IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-7, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, Eotaxin, FGF basic, G-CSF, GM-CSF, MIP-1α, MIP-1β, PDGF, RANTES and VEGF in the CSF and serum samples were measured by Bio-Plex Pro Assays. IFN-α in the CSF and serum samples were measured by ELISA.

Results: No significant positive correlation was observed between CSF concentration and serum concentration of each cytokine/chemokine in the 52 SLE patients. For each of the 30 NPSLE patients, the mean concentration of IL-6, IL-8, IP-10, MCP-1 and G-CSF was higher in the CSF than in the sera, (Table 1). Especially, the mean concentration of MCP-1 in the CSF was significantly higher than in the sera. The prevalence of higher IL-6, IP-10, and G-CSF concentrations in the CSF than in the sera were significantly greater in the 30 patients with NPSLE than in the 22 with non-NPSLE ($p = 0.00015$, $p = 0.036$ and $p = 0.0077$, Fisher's 2 tailed exact test, respectively). Furthermore, the concentrations of IL-6, IL-8, IP-10, MCP-1 and G-CSF in the CSF of the 30 patients with NPSLE were significantly higher than in the 22 patients with non-NPSLE, respectively (Table 2). Importantly, the largest differences occurred in CSF IL-6 concentrations. In each patient cohort, the mean concentration of RANTES 1 and IFN-α in the CSF was lower than those in the sera, respectively (Table 1).

Table 1. Comparison of cytokine/chemokine concentrations in the CSF and the sera of 30 patients with central NPSLE.

	Central NPSLE positive patients (n = 30)		
	CSF	Sera	P
IL-6 (pg/ml)	490.0 ± 1144.0	98.5 ± 133.5	0.668
IL-8 (pg/ml)	1993.0 ± 8665.4	62.0 ± 60.9	0.129
IP-10 (pg/ml)	9256.8 ± 15484.3	6259.3 ± 3884.9	0.211
MCP-1 (pg/ml)	2036.9 ± 7957.0	225.3 ± 511.8	0.00019
G-CSF (pg/ml)	176.8 ± 683.5	75.6 ± 53.7	0.00019
RANTES 1 (pg/ml)	15.4 ± 20.9	3978.6 ± 1729.1	2.87×10^{-11}
IFN-α (pg/ml)	13.1 ± 57.9	17.8 ± 32.7	0.0022

Table 2. Comparison of cytokine/chemokine concentrations in the CSF of 30 patients with central NPSLE and 22 patients with non-NPSLE.

	Central NPSLE		
	Positive (n = 30)	Negative (n = 22)	P
CSF IL-6 (pg/ml)	490.0 ± 1144.0	5.72 ± 5.63	6.82×10^{-5}
CSF IL-8 (pg/ml)	1993.0 ± 8665.4	31.6 ± 27.7	0.00037
CSF IP-10 (pg/ml)	9256.8 ± 15484.3	2096.4 ± 3390.3	0.0028
CSF MCP-1 (pg/ml)	2036.9 ± 7957.0	250.7 ± 163.5	0.00065
CSF G-CSF (pg/ml)	176.8 ± 683.5	5.70 ± 8.71	0.00010

Conclusion: In central NPSLE, the intrathecal concentrations of cytokines/chemokines are not influenced by the serum concentrations, indicating that the production of IL-6, IL-8, IP-10, MCP-1 and G-CSF might take place in CNS. These increased CSF cytokines/chemokines might be associated with the pathogenesis and appearance of central NPSLE. The measurement of these cytokines/chemokines, especially IL-6 might be useful for the diagnosis of central NPSLE.

1712

Systemic Lupus Erythematosus Disease Activity During a 12-Month Period and Risk of New Onset Organ System Damage and/or Death: Observations in a Single US Academic Medical Center. Deanna Hill[1], Peter Egger[2], Qinggong Fu[1], Hong Fang[3] and Michelle Petri[3]. [1]GlaxoSmithKline, Collegeville, PA, [2]GlaxoSmithKline, Stockley Park, United Kingdom, [3]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: The association between disease activity over a short period and subsequent risk of new onset organ system damage or death has not been well-studied. Our objective was to investigate whether the pattern of SLE disease activity during a 12-month period (i.e. observation period; OP) was predictive of new onset organ system damage accrual or death in the subsequent follow-up period (FP) for patients with mild-to-moderate disease activity at cohort entry.

Methods: A prospective cohort of 1168 adult SLE patients were seen quarterly, or more often if clinically indicated, during 1987–2010. Individuals with a SLICC/ACR Damage Index (SDI) score ≥3, ESRD, history of organ transplant or malignant neoplasm at cohort entry were excluded from the analysis. The standardized protocol included measurement of disease activity using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at every visit and organ system damage (SDI)

annually. To describe disease activity over time, adjusted mean SLEDAI (AMS) was the main exposure variable and the index date was 12 months after cohort entry. New onset damage was defined as ≥1-unit increase in SDI score between the OP and last recorded FP visit. Cox proportional hazard ratio (HR) models estimated the risk of new onset damage and death adjusted for age, gender, race, SLE duration, overall SDI score at start of the FP and ever prescribed oral prednisone dosage >7.5 mg/day during the OP.

Results: Women comprised 93% of the cohort. At cohort entry median age was 36 years, disease duration was 6 years, and SLEDAI score was 2. During the 12-month OP, 80% of patients had clinical manifestations in ≥1 organ system and median SDI score of 1. Fifty-percent of patients were prescribed oral prednisone in the OP and 60% of exposed patients were prescribed >7.5 mg/day. During the FP, 92 cohort patients died (8%). After restricting the analysis to patients without recorded damage at the start of the FP in the organ system of interest, 40% of patients had new onset damage in any organ system, 7% cardiovascular and 3% renal system damage (SDI≥1). In adjusted models, AMS and plaquenil use in the OP were significant predictors of death (HR=1.23, 95% CI: 1.14, 1.33; HR=0.46, 95% CI: 0.30, 0.73, respectively) and new onset renal damage (HR=1.24, 95% CI: 1.08, 1.42; HR=0.30, 95% CI: 0.13, 0.68, respectively). AMS and NSAID use in the OP were associated with increased risk of new onset cardiovascular damage (HR=1.18, 95% CI: 1.08, 1.30; HR=1.66, 95% CI: 1.04, 2.63, respectively) in the adjusted model. AMS in the OP was not a significant predictor of new onset overall damage (HR=1.05, 95% CI: 1.00, 1.11), after adjustment for other covariates.

Conclusion: A one-unit increase in AMS during a 12 month-period was significantly associated with a 23% increased risk of death and 18 to 24% increased risk of new onset cardiovascular and renal damage accrual in the FP, respectively, after adjustment for other covariates. Plaquenil use in OP was associated with a 54 to 70% reduction in risk of death and renal damage in the FP, respectively, while NSAID use in OP increased the risk of cardiovascular damage by 66% in patients with mild-to-moderate SLE at cohort entry. (Study number: WEUKBRE4566)

ACR Concurrent Abstract Session
Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics II
Monday, November 7, 2011, 4:30 PM–6:00 PM

1713

A Clinicopathologic Study of Retroperitoneal Fibrosis and Its Association with Immunoglobulin G4-Related Disease. Arezou Khosroshahi, Robert P. Hasserjian, Nisha I. Sainani, Vikram Deshpande and John H. Stone. Massachusetts General Hospital, Boston, MA

Background/Purpose: Retroperitoneal fibrosis (RPF) can be divided into idiopathic and secondary cases. Small studies have suggested that idiopathic RPF can be classified into cases that are associated with histopathologic features of IgG4-related disease (IgG4-RD) and those that are not. We analyzed 23 previously unclassified cases of RPF to evaluate clinicopathological differences between those associated with pathological features of IgG4-RD and those not associated with such features.

Methods: We searched our pathology service database to identify all patients with RPF diagnosed since 1990. Pathology blocks were available for immunohistochemical analysis on 23 patients. We subclassified RPF cases following chart review into either the idiopathic or secondary categories on the basis of clinical features, and performed immunohistochemical analysis for IgG4 and IgG. RPF cases were classified as IgG4-related if they had IgG4/IgG-positive plasma cell ratios >30%. Histologic features, age, sex, clinical symptoms, location of the fibrosis, and presence or absence of fibrosing lesions at other locations were compared between patients with IgG4-related and non-IgG4-related RPF. The statistical analysis was performed using Fisher's exact test. A probability of $P<0.05$ was considered statistically significant.

Results: Nineteen cases were categorized as idiopathic, and four as secondary. Twelve of 19 (63%) idiopathic cases were classified as IgG4-related and 7 (36%) as non-IgG4-related. The clinicopathologic features of these cases are summarized in Table 1. Compared with non-IgG4-related RPF, IgG4-related RPF was more likely to show periaortic involvement and more frequently showed storiform-type fibrosis and eosinophil infiltration. In the IgG4-related cases, the overall mean number of IgG4-positive plasma cells per high-power field (hpf) was 13, a figure much lower than that generally observed in other organs involved with IgG4-RD. The mean IgG4/IgG ratio, however, was 78%.

Table 1. Clinicopathologic features of IgG4-related with non-IgG4-related idiopathic RPF

	IgG4-related (n=12)	Non-IgG4-related (n=7)	Statistical comparison
Gender (M:F)	10:2	4:3	NS
Age, median (range)	58 y (38–71)	64 y (37–72)	NS
Periaortic involvement	10/12 (83%)	2/7 (28%)	p=0.02
Hydronephrosis	5/12 (41%)	5/7 (71%)	NS
Aortitis	2/12 (17%)	1/7 (14%)	NS
Storiform-type fibrosis	10/12 (83%)	2/7 (28%)	p=0.02
Eosinophils >5/hpf	10/12 (83%)	0/7 (0%)	p<0.001

Conclusion: IgG4-RD accounts for a sizeable subset of patients with RPF. Both histological features and IgG4 immunostaining are critical to the diagnosis of IgG4-RD. Findings of plasma cell infiltration, tissue eosinophilia, and storiform fibrosis should lead pathologists to perform IgG4 immunostains. The IgG4/IgG ratio may be more important in diagnosis than the absolute number of IgG4-positive plasma cells/HPF, particularly when extensive fibrosis is the paramount finding.

1714

Developing a Disease Activity and Therapeutic Response Index in Connective Tissue Disease Related Interstitial Lung Disease: Initial Results of a Delphi Exercise. Lesley Ann Saketkoo[1], Doerte Huscher[2], Dinesh Khanna[3], Paul F. Dellaripa[4], Kevin Flaherty[3], Eric L. Matteson[5], Chester V. Oddis[6], Kristine Phillips[7], Athol U. Wells[8], Christopher P. Denton[9], Oliver Distler[10], Otylia M. Kowal-Bielecka[11], David Pittrow[12], Romy Christmann[13], Nora Sandorfi[14], Vibeke Strand[15], Kevin K. Brown[16] and James R. Seibold[17]. [1]LSU Health Science Center, New Orleans, LA, [2]Charité Universitaetsmedizin, Dept of Rheumatology and Clinical Immunology and The German Rheumatism Research Centre, Berlin, Germany, [3]University of Michigan, Ann Arbor, MI, [4]Brigham & Womens Hospital, Boston, MA, [5]Mayo Clinic, Rochester, MN, [6]University of Pittsburgh, Pittsburgh, PA, [7]University of Michigan Medical School, Ann Arbor, MI, [8]Royal Brompton Hospital, United Kingdom, [9]UCL Medical School, London, United Kingdom, [10]University Hospital Zurich, Zurich, Switzerland, [11]Medical Univ in Bialystok, Bialystok, Poland, [12]Institute of Clinical Pharmacology - University of Dresden, Dresden, Germany, [13]Boston University, Boston, MA, [14]Thomas Jefferson Univ Med Coll, Philadelphia, PA, [15]Stanford University, Palo Alto, CA, [16]National Jewish Hospital, Denver, CO, [17]Scleroderma Research Consultants LLC, Avon, CT

Background/Purpose: The lack of accepted and validated measures of disease activity and clinical response in patients with connective tissue disease (CTD)-related interstitial lung disease (ILD) makes clinical trial design difficult. We report a multi-tiered investigation to develop consensus on provisional criteria for disease activity and therapeutic responses in both CTD-ILD and Idiopathic Pulmonary Fibrosis (IPF). Within the OMERACT framework, 270 experts identified 23 "domains" and 616 "instruments" preparatory for a 3-tiered Delphi exercise. We report the results of Tier 1 expert voting.

Methods: Using a custom-designed secure web-site, participants in Tier 1 rated 23 domains and 616 instruments for IPF and CTD-ILD (1278 combined ratings) anchored in degree of usefulness of instruments on a 9-point Likert scale with "insufficiently familiar" as an additional voting option. A cut-off median <4 was applied to the results. Final review demanded 100% consensus agreement for item dismissal based on: 1. Lack of face validity, 2. Content validity more suited to diagnostic, demographic, or inclusion criteria and 3. Lack of feasibility.

Results: 90% of invited experts participated including 137 pulmonary, 102 rheumatology and 4 cardiology specialists from 32 countries/6 continents. 74% and 69% of participants considered 'ILD' and 'rheumatologic lung disease' respectively as a primary field of research or clinical interest. After statistical analysis, 20 domains and 96 instruments "survived" for inclusion in Tier 2.

Table 1. Results of Tier 1 Analysis

COUGH	**PHYSICIAN GLOBAL ASSESSMENT - DISEASE ACTIVITY**
Cough Severity by Visual Analogue Scale is the only surviving item	Only Visual Analogue Scale survives
DYSPNEA	**EXTRA-PULMONARY CTD FEATURES**
9 Instruments survive that measure dyspnea	5 Instruments survive
HEALTH RELATED QUALITY of LIFE (HRQoL)	**GASTRO ESOPHAGEAL REFLUX (GERD)**
3 Generic HRQoL instruments survive 2 Respiratory disease specific instruments survive	2 Instruments survive that measure GERD
	MEDICATIONS
FATIGUE	2 Items that measure medication use survive
6 Instruments survive that measure fatigue	
	BIOMARKERS
SLEEP	6 Serologic markers survive
4 Instruments survive that measure sleep quality	
	LUNG IMAGING
MENTAL HEALTH	6 Instruments related to HRCT survive
5 Items survive that measure anxiety & depression	
	LUNG PHYSIOLOGY / FUNCTION
PATIENT GLOBAL ASSESSMENT OF DISEASE ACTIVITY	7 Instruments related to 6MWT survive
Only Visual Analogue Scale survives	5 Items survive related to quantifying oxygenation
	4 Instruments survive related to spirometry
PHYSICAL FUNCTION	**COMPOSITE SCORES**
5 Items survive measuring physical function & ability	Only Composite Physiologic Index (CPI) survives
PARTICIPATION and PRODUCTIVITY	
No single item survived to measure participation; However; 'multi-dimensional' functioning is captured in generic HRQoL instruments	**LUNG VASCULAR** 2 instruments remain; both use RHC
	CARDIAC FUNCITON
2 Instruments survive that measure productivity (remunerative work, imminent job loss due to illness & work in the home)	2 Instruments survive measuring cardiac function
	SURVIVAL
	11 Items remain for survival or its surrogates

Conclusion: Development of clinically meaningful outcome measures that assess disease progression and therapeutic response is essential for performing clinical trials in CTD-ILD. This is the first comprehensive, multi-disciplinary and international effort to assess domains and instruments in the study of ILD. Experts identified a group of core set measures focused on radiographic, physiologic and patient-reported outcomes, culled from a large number of candidate instruments. A research agenda focused on candidate biomarkers will be developed. The high degree of participation in this Delphi process from a multidisciplinary ILD research community reflects the perceived need in this area.

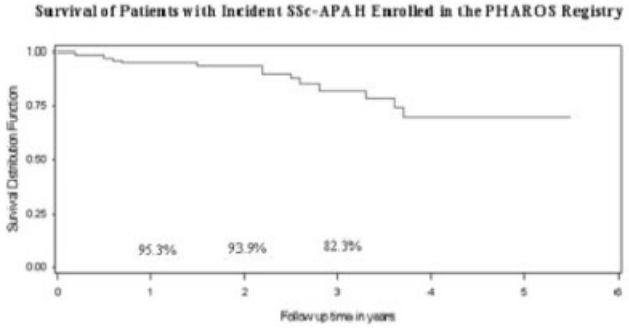
1715

Better Survival in Systemic Sclerosis-Associated Pulmonary Arterial Hypertension Patients Enrolled in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry. Lorinda Chung[1], Robyn T. Domsic[2], Bharathi Lingala[3], Virginia D. Steen[4] and PHAROS Investigators[5]. [1]Stanford Univ Medical Center, Palo Alto, CA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Stanford, [4]Georgetown Univ Medical Center, Washington, DC, [5]Washington, DC

Background/Purpose: Patients with systemic sclerosis-associated pulmonary arterial hypertension (SSc-APAH) experience poorer outcomes than patients with idiopathic PAH and other forms of connective tissue disease-APAH. We sought to assess cumulative survival rates and identify independent predictors of 1-year mortality in patients with incident SSc-APAH from the PHAROS registry.

Methods: Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a multi-center prospective registry of SSc patients at high risk for PAH or with definite PH diagnosed by right heart catheterization (RHC) within 6 months of enrollment. Only patients with World Health Organization Group I PAH (mean pulmonary artery pressure (mPAP)≥25 mmHg and pulmonary capillary wedge pressure≤15 mmHg without significant interstitial lung disease) were included in these analyses. Kaplan-Meier curves were estimated for survival from the time of the diagnostic RHC. Differences in outcomes between subgroups were assessed by the log-rank test. Univariate and multivariate Cox regression models were used to identify significant predictors of 1-year mortality. Backward selection was used to determine the final model retaining only variables with $p<0.05$.

Results: 125 patients with incident PAH had a mean age of 60.4±10.5 years and disease duration from first non-Raynaud symptom of 10.2±9.4 years. 85% were female, 82% Caucasian, 70% had limited cutaneous disease, and 34% were anti-centromere antibody positive. Mean 6 minute walk distance (6MWD) was 337±131 m, diffusing capacity of carbon monoxide 42±16% predicted, mPAP 36.7±10.3, pulmonary vascular resistance (PVR) 5.5±3.1 WU, and creatinine 1.0±0.6. 34% had a pericardial effusion; 57% were functional class (FC) I or II; and 5.6% were FC IV. Only 14 (11%) patients died over a mean follow-up of 1.8±1.3 years. 1-, 2-, and 3-year survival was 95.3%, 93.9%, and 82.4% in the overall cohort. The following variables were significant predictors of 1-year mortality in univariate analyses: FC IV (HR 5.8, 95% CI 1.3–27.2), 6MWD<165 m (HR 3.4, 95%CI 1.0–11.5), and PVR>4.6 WU (HR 5.8, 95% CI 1.3–25.6). Age>60, presence of a pericardial effusion, DLCO<32% predicted, mPAP>35 mmHg, and creatinine did not predict death. On multivariate analysis (N=77), FC IV (HR 7.9, 95% CI 1.5–41.3, p=0.01) remained the only significant predictor of mortality.



Conclusion: The 82.4% 3-year survival of SSc patients with incident PAH followed at scleroderma centers involved in the PHAROS registry was higher than other recently described cohorts. Not unexpectedly, those who are FC IV at the time of diagnosis have a high risk for death at 1 year.

1716

Clinical and Hemodynamic Features of Scleroderma Patients with Pulmonary Venous Hypertension Versus Pulmonary Arterial Hypertension. Jessica K. Gordon[1], Kamini Doobay[2], Evelyn Horn[3], Marcy B. Bolster[4], Lee S. Shapiro[5], Dinesh Khanna[6], Tracy M. Frech[7], Kara Fields[2], Chris T. Derk[8], Laura K. Hummers[9], Maureen D. Mayes[10], Virginia D. Steen[11] and PHAROS Investigators[12]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, [3]Weill-Cornell Medical College, New York, NY, [4]Medical Univ of South Carolina, Charleston, SC, [5]Albany, NY, [6]University of Michigan, Ann Arbor, MI, [7]University of Utah School of Medicine, SLC, UT, [8]Jefferson Medical College, Philadelphia, PA, [9]Johns Hopkins University, Baltimore, MD, [10]University of Texas Health Science Center at Houston, Houston, TX, [11]Georgetown Univ Medical Center, Washington, DC, [12]Washington

Background/Purpose: Pulmonary hypertension (PH) is a leading cause of death in patients (pts) with Systemic Sclerosis (SSc). The World Health Organization (WHO) classifies PH into groups: PAH (WHO group 1), most common in SSc, is characterized by a mean pulmonary artery pressure (mPAP)≥25 mmHg and a pulmonary capillary wedge pressure (PCWP) <15 mmHg. WHO Group 2 is PH secondary to left heart dysfunction or pulmonary venous hypertension (PVH.) WHO Group 3 is PH secondary to pulmonary disease. Here we describe the differences between SSc pts with PAH versus PVH as well as the overlap between the groups.

Methods: Pts in the PHAROS database with PH were categorized by WHO criteria. A PCWP<15 mmHg on initial right heart catheterization (RHC) differentiated Group 1 and 2 pts. Pts with ILD as defined by a forced vital capacity (FVC) <65% predicted and/or significant fibrosis on chest CT with a normal PCWP were included in group 3, and are not included in this analysis. Univariate analysis with Mann-Whitney and Fischer-Exact tests was performed.

Results: There are 197 pts with PH in the PHAROS database: PAH-127, PVH–32, and PH-ILD–38. Pts with PVH were more likely to be African-

American, younger, male, and have diffuse cutaneous (dc)SSc. 20% of PVH pts were anti-Scl70 positive vs 6.7% of PAH pts, (p=0.036). There was no difference with respect to disease duration based on time since first non-Raynaud's symptom. Although the systolic PAP was lower in PVH patients on echo, the mPAP on RHC was not significantly different. The pulmonary vascular resistance (PVR) was significantly lower in the PVH pts. The BNP and NT-BNP were increased in both groups but not significantly different. On PFTs, there was more restrictive disease with a lower FVC in PVH patients, but there was no difference in the DLCO, with both groups very low. The FVC to DLCO ratio was significantly higher in the PAH group.

Some PAH pts had evidence of PVH on either exercise RHC or on repeat RHC. An increased PCWP on repeat RHC was seen in 8.7% of PAH pts, and in 8 of 22 PAH pts undergoing exercise RHC (36.4%) the PCWP was ≥18. Unlike most other pts with PVH, the left atrial diameter (LAD) was not always increased, and in 39.3% of PAH pts, the LAD was > 4.0 cm on echo. There was no correlation between the LAD and PCWP or PCWP and BNP.

	PAH (n= 127)	PVH (n=32)	P-Value
Age (median, range)	61.00 (34, 84)	55.50 (35, 78)	0.015
Disease Duration (median, range)	7.32 (0.02, 43.2)	6.9 (0.2, 19.2)	0.47
Gender (% female)	84%	70%	0.045
Ethnicity (%)	83% Caucasian	60% Caucasian	0.019
Ethnicity (%)	9% Black	27% Black	
Ethnicity (%)	8% Other	13% Other	
SSc Subtype (%)	72% Limited	41% Limited	0.003
SSc Subtype (%)	24% Diffuse	50% Diffuse	
ECHO DATA			
Systolic PAP - mmHg	60 (31, 46)	49 (17, 38)	0.005
Ejection Fraction-%	60 (45, 82)	60 (25, 77)	0.49
Left Atrial Diameter–cm	3.7 (2.4, 6.3)	4.1 (2.1, 5.2)	0.50
PFT DATA			
Forced Vital Capacity-% pred, median (range)	81.7 (43, 123)	65.4 (27, 99)	<0.001
Diffusion Capacity-% pred, median (range)	38.9 (14, 98)	36.5 (13, 97)	0.40
FVC/DLCO Ratio	2.02 (0.95, 6.08)	1.69 (0.46, 2.96)	0.03
RHC DATA			
Pulmonary Artery Systolic Pressure–mmHg	55 (30, 119)	46 (36, 87)	0.004
Mean PAP–mmHg	35 (25, 75)	32.5 (26, 60)	0.11
PCWP–mmHg	10 (2, 17)	21 (16, 35)	<0.0001
PVR–dyn·s·cm^{-5}	368 (106, 999)	189.3 (56, 828)	<0.0001

Conclusion: In SSc, an increased PAP is not always PAH. PVH pts differ from PAH pts in several ways. They are more likely to be African American, younger, male, have dcSSc, and be anti-Scl70 positive. The RHC is critical in making this diagnosis since the echo can not determine the PCWP. The PVR is useful in distinguishing the groups. An exercise or fluid challenge may be helpful in determining a propensity for an increased PCWP under a stressor. Furthermore, in SSc there is evidence for some degree of PVH in a significant percentage of pts with PAH. How these categorizations affect the prognosis of PH pts will be further studied in the long-term follow-up of the PHAROS cohort.

1717

Validation of Potential Classification Criteria for Systemic Sclerosis. Sindhu R. Johnson[1], Jaap Fransen[2], Dinesh Khanna[3], Thomas A. Medsger[4], Christine A. Peschken[5], Patricia Carreira[6], Gabriela Riemekasten[7], Alan G. Tyndall[8], Marco Matucci-Cerinic[9], Murray Baron[10], Frank Van den Hoogen[11] and Janet E. Pope[12]. [1]Toronto Western and Mt. Sinai Hospitals, University of Toronto, Toronto, ON, [2]The Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]University of Michigan, Ann Arbor, MI, [4]Univ of Pittsburgh, Pittsburgh, PA, [5]University of Manitoba, Winnipeg, MB, [6]Hospital Universitario 12 de Octubre, Madrid, Spain, [7]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [8]University of Basel, Basel, Switzerland, [9]University of Florence, Firenze, Italy, [10]Jewish General Hospital, Montreal, QC, [11]Nijmegen, Netherlands, [12]St. Joseph's Health Care, University of Western Ontario, London, ON

Background/Purpose: Classification criteria for systemic sclerosis (SSc) are being updated jointly by EULAR and ACR. Potential items for classification were reduced to 23 using Delphi and Nominal Group Techniques. We evaluated the face, discriminant and construct validity of the items to be further studied as potential criteria.

Methods: Face validity was evaluated using the frequency of items in patients sampled from the Canadian Scleroderma Research Group, 1000 Faces of Lupus, the Pittsburgh, Toronto, Madrid and Berlin CTD databases. SSc (n=783) were compared to 1071 patients with diseases similar to SSc (mimickers): SLE (n=499), myositis (n=171), Sjögren syndrome (n=95), Raynaud's syndrome (n=228), MCTD (n=29), and idiopathic PAH (n=49). Discriminant validity was evaluated using odds ratios (OR). For construct validity, empiric ranking was compared to expert ranking.

Results: Compared to mimickers, SSc are more likely to have skin thickening (OR 427), telangiectasias (OR 91), anti-RNA polymerase III antibody (OR 75), puffy fingers (OR 35), finger flexion contractures (OR 29), tendon/bursal friction rubs (OR 27), anti-topoisomerase-I antibody (OR 25), Raynaud's phenomenon (OR 24), finger tip ulcers/pitting scars (OR 19), anti-centromere antibody(OR 14), abnormal nailfold capillaries (OR 10), GERD symptoms (OR 8), and ANA, calcinosis, dysphagia, esophageal dilation (all OR=6), interstitial lung disease/pulmonary fibrosis (OR 5), PM-Scl antibody (OR 2), reduced DLCO (OR 1.5), PAH (OR 1.2), and reduced FVC (OR 0.9). Renal crisis and digital pulp loss/acro-osteolysis did not occur in SSc mimickers (OR not estimated). Empiric and expert ranking were correlated (Spearman rho 0.53, p=0.01).

Conclusion: The candidate items have good face, discriminant and construct validity. Further item reduction will be evaluated in prospective SSc and mimicker cases.

1718

Ultrasonographic Hand Features in Systemic Sclerosis and Correlates with Clinical, Biological and Radiographic Findings. Muriel Elhai[1], Henri Guerini[2], Ramin Bazeli[2], Jerome Avouac[1], Veronique Freire[2], Jean-Luc Drape[3], Andre Kahan[1] and Yannick Allanore[1]. [1]Rheumatology A, Paris Descartes University, Cochin Hospital, APHP, Paris, France, Paris, France, [2]Radiology B, Paris Descartes University, Cochin Hospital, APHP, Paris, France, Paris, France, [3]Paris Descartes University, Radiology B Department, Cochin Hospital, Paris, France

Background/Purpose: Articular involvement is a common feature of systemic sclerosis (SSc) with major impact on quality of life. However assessment is frequently difficult, as clinical assessment is limited by concomitant skin involvement and X-ray cannot capture tendon damages. Therefore, the prevalence and characteristics of joint involvement are imperfectly known. Ultrasonography (US) has demonstrated its major input in other rheumatic conditions but only scarce data are available in SSc. Therefore, we set out to investigate ultrasonographic hand and wrists features in consecutive SSc patients and their relationships with clinical examination, biological and radiographic data.

Methods: 52 consecutive SSc were included in a cross-sectional observational study and in addition 24 patients with rheumatoid arthritis were enrolled as controls. All the patients underwent clinical examination. Global disability was assessed using the Health Assessment Questionnaire and the Duruoz Hand Index. US was performed on joints of both hands, both wrists and fingers. The following predefined features were searched for: synovitis, tenosynovitis, acro-osteolysis, calcinosis, power Doppler in the nail bed and in the pulp. Radiographies of the hands and wrists were also performed. Data were statistically analyzed using chi-square tests and the Student's t-test. A multivariate stepwise logistic regression analysis was also performed for all variables identified with $p \leq 0.10$. $P < 0.05$ was considered statistically significant.

Results: The characteristics of SSc-patients were: mean age: 56.3 (± 14.1) years, 75% were women, mean disease duration: 8.6 (± 8.6) years, 40% fulfilled diffuse cutaneous subtype. Prevalences of US abnormalities in SSc-patients were as follow: synovitis in 46%, tenosynovitis in 27%, calcifications in 40%, acroosteolysis in 19% and impairment in the distal microvascularisation in 44%. Synovitis were in 57% of cases mildly inflammatory (Doppler grade 1), whereas tenosynovitis showed a mixed pattern associating both inflammatory and fibrotic changes. As compared to RA patients, US hand features specific to SSc were "sclerosing" tenosynovitis (p<0.01), soft-tissue calcifications (p=0.01) and impairment in the distal microvascularisation (p<0.01). US detected 31% and 21% more patients with synovitis and tenosynovitis, respectively, than clinical examination. In multivariate analysis, a CRP level superior to 10mg/L was associated with inflammatory activity at power Doppler assessment (p=0.03). Disability did not correlate with synovitis or tenosynovitis. However, patients with at least 4 synovitis and/or tenosynovitis had a higher Duruoz Hand index than patients with less than 4 US abnormalities (p=0.006).

Conclusion: Our study confirms that articular involvement in SSc is frequent. It is associated with disability in cases of polyarticular disease and under-estimated by clinical examination. It is characterized by mild inflammatory damages associated with biological inflammatory syndrome and with US sclerosing findings for tenosynovitis. Further prospective studies are warranted to evaluate the predictive value of these findings.

1719

Effectiveness of Facet Joint Infiltration in Low Back Pain. Luiza H. C. Ribeiro, Rita V. Furtado, Monique Konai, Andre Rosenfeld, Ana B. Andreo and Jamil Natour. Universidade Federal de Sao Paulo, Sao Paulo, Brazil

Background/Purpose: Lumbar facet joints are a well recognized source of low back pain. Studies have shown the prevalence of lumbar facet joint pain in 30% to 40% of the patients with chronic low back pain. Facet joint interventions, including intra-articular injections, medial branch nerve blocks, and neurotomy by radiofrequency are used to manage chronic facet-mediated spinal pain. Several studies have been evaluated the effectiveness of these interventions. Results of facet joint infiltration, however, are conflicting.The aim of this study is to evaluate the effectiveness of facet joint infiltration with corticosteroids in patients with facet joint syndrome.

Methods: Sixty subjects with diagnostic of facet joint syndrome were enrolled in the study. They were randomized into experimental and control groups. The experimental group was submitted to intra-articular infiltration of six facet joints (L3/L4;L4/L5;L5/S1 bilaterally) with triamcinolone hexacetonide. The control group was submitted to triamcinolone acetonide intramuscular injection of six lumbar paravertebral points. After the randomization, all subjects were assessed by an investigator blinded to the groups. The assessment were taken just before the interventions (T0) and them 7, 30, 90 and 180 days after the interventions. The following assessment instruments were used: pain visual analogical scale (VAS) (0–10cm), pain visual analogical scale during extension of the spine (VAS E) (0–10cm), Likert scale for improving (0–5), percentage scale of subjective improving perception(0–100%), Rolland-Morris questionnaire (0–24), short health survey questionnaire (SF36), accountability of medications taken for back pain: analgesics and non-steroidal antiinflamatories (NSAIDs). Statistical analysis: the homogeneity of the sample was tested using Student's T, Pearson's Chi- Square and Mann-Whitney tests. ANOVA with repeated measures was performed to evaluate inter- and intra-group differences. A 5% significance level was used for all variables and tests.

Results: There were no significant differences in the baseline characteristics between the two groups. The experimental group showed a significant improvement in the physical aspects domain, assessed by SF-36. At visit 7 the experimental group showed a better response of improving (much better) assessed by the Likert scale. However in the following visits both groups had similar results. The consumption of NSAIDs were significantly lower in the experimental group at the last visit (T180).

Conclusion: Facet joint infiltration had a weak effectiveness. The improvement was observed in few aspects of quality of life and self-assessment of improving. However it provided a reduction in NSAIDs intake.

1720

Health Outcomes From a Residential Multidisciplinary Rehabilitation Program for Musculoskeletal Conditions: A Ten Year Observational Study. Peter B. B. Jones[1] and Peter Sharplin[2]. [1]Waikato Clinical School, Waikato Hospital, Hamilton, New Zealand, [2]QE Health, Rotorua, New Zealand

Background/Purpose: In an era of increasingly technological approaches to arthritis care, intensive rehabilation has a lower priority for provision. There is a relative lack of outcomes data for such treatment. QE Health has an established intensive rehabilitation program for people disabled by chronic musculoskeletal conditions including inflammatory arthritis, degenerative conditions, and pain syndromes. The aim was to evaluate change in health outcome in these groups over a ten year period.

Methods: Patients accessed the program on referral from a specialist or general practitioner and were diagnosed with a musculoskeletal condition. Medical therapy was optimised prior to entry into the program. Govenrment funding was provided by third party purchasers. Demographic and disease data were gathered at admission, together with the following outcome measures at admission and on discharge: McGill Pain Questionnaire (MPQ); Wellness 10cm Visual Analog Scale (WVAS); EQ-5D; Stanford Health Assessment Disability Questionnaire (HAQ); 6-minute walk test (6MW). In addition a validated measure of holistic health status, the QE Health Scale (QEHS) was applied. The intervention was a 3 week residential program comprising medical, physiotherapy, occupational therapy, nursing and counselling interventions. Assistive devices, splints or orthoses were dispensed as required. Data was analysed for patients admitted between January 2001 and December 2010. Multivariate analysis was used using linear models to test for confounding effects from the following variables: age, gender, occupation, diagnosis, race, baseline values.

Results: There were 3214 admissions in the period comprising 2624 patients; recidivism was 16%. Mean age 59, mode 74; 26% employed, 38% retired. Chronic spinal pain (25%), osteoarthritis (21%), rheumatoid arthritis (15%) and fibromyalgia (13%) dominated the diagnostic categories. 83% were of NZ European ethnicity and 13% were Maori (indigenous); 72% were female. Complete data were available for 89.7% of care episodes. Overall, 82.9% of patients recorded improvements that exceeded the minimal clinically important difference in two or more measures. For each measure, significant and clinically meaningful improvements were observed (baseline, change, $p<0.0001$ for all): MPQ (22.6, −6.4); WVAS (4.9, 2.2); EQ5D (47.7, 25.4); HAQ (1.41,-0.32); 6MW (364.9, 62.2); QEHS (96.1, 19.5). Those with poorer baseline health status and Maori patients showed greater improvements. Age and gender showed significant but inconsistent effects.

Conclusion: In a large patient database, consistent, clinically meaningful and significant improvements in health status were observed during an intensive residential multidisciplinary rehabilitation program regardless of gender, race or diagnosis. Those with the lowest baseline scores showed the greatest improvements. Intensive multidisciplinary rehabilitation offers meaningful health change for people living with chronic disabling musculoskeletal conditions.

1721

Risk Factors for Restricting Back Pain in Community-Living Older Persons. Una E. Makris[1], Liana Fraenkel[2], Ling Han[3], Linda Leo-Summers[3] and Thomas M. Gill[4]. [1]Yale, New Haven, CT, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, [3]Yale University School of Medicine, New Haven, CT, [4]Yale University School of Medicine, New Haven

Background/Purpose: Back pain is a common and costly condition among older persons. We recently demonstrated that back pain, severe enough to restrict activity (hereafter referred to as restricting back pain), is often recurrent. Few longitudinal studies have evaluated the risk factors for restricting back pain. Our objective was to identify risk factors for restricting back pain in community-living older persons.

Methods: We evaluated the 733 participants (mean age 78.4 years, 65% women) of the Precipitating Events Project, a longitudinal study of community-living persons, aged 70+ years, who completed monthly telephone assessments of restricting back pain, defined as staying in bed for at least half a day and/or cutting down on one's usual activities due to back pain, for over 10 years. Candidate risk factors were measured from five domains (demographic, cognitive-psychosocial, health related, habitual, physical capacity) during comprehensive home-based assessments that were completed every 18 months for up to 108 months. Restricting back pain was assessed monthly for up to 126 months. In participants who did not report restricting back pain at the start of an 18-month interval, incident episodes of two distinct restricting back pain outcomes were determined during the subsequent 18-months: (1) short-term (one episode lasting one month) and (2) persistent (one episode lasting two or more months) or recurrent (two or more episodes of any duration). The cumulative incidence proportions of these two restricting back pain outcomes were estimated during the total follow-up period using a Generalized Estimation Equation binomial model. A multivariate Cox model was used to evaluate the adjusted associations between each candidate risk factor (eligible to enter the final model) and the two outcomes of interest.

Results: The cumulative incidence was 17.8% (95% CI: 16.5, 19.3) for the short-term outcome and 17.9% (16.1, 19.9) for the persistent or recurrent outcome. Table 1 shows the multivariate results; factors from each domain were independently associated with a higher risk of developing persistent or recurrent restricting back pain. Female sex (26% increased risk) and poor grip strength (33%) were the only factors associated with an increased likelihood of short-term restricting back pain. In contrast, female sex (47%), depressive symptoms (82%), BMI ≥25 (33%), arthritis (63%), greater than two chronic conditions (29%), and poor grip strength (33%) conferred a higher risk of persistent or recurrent restricting back pain.

Table 1. Factors Associated in Multivariable Analysis with Short-Term and Persistent/Recurrent Restricting Back Pain in 733 Community-Living Older Persons

Factor	Hazard Ratio (95% Confidence Interval) Short-Term	P-value	Persistent or Recurrent	P-value
Demographic				
Aged ≥ 85	1.04 (0.84–1.29)	0.69	0.81 (0.63–1.04)	0.09
Female	1.26 (1.03–1.54)	0.02	1.47 (1.11–1.95)	0.008
Not currently married	0.99 (0.82–1.19)	0.90	1.10 (0.85–1.42)	0.47
Cognitive-Psychosocial				
High depressive symptoms	1.21 (0.98–1.50)	0.07	1.82 (1.42–2.32)	<0.001
Low social support	0.95 (0.76–1.18)	0.63	0.92 (0.71–1.21)	0.57
Health Related				
No. chronic conditions (≥2)	1.16 (0.96–1.39)	0.13	1.29 (1.00–1.67)	0.05
Arthritis	1.08 (0.90–1.29)	0.43	1.63 (1.29–2.05)	<0.001
Weight loss ≥ 10 pounds in past year	1.08 (0.88–1.33)	0.46	1.02 (0.80–1.31)	0.87
Habitual				
Overweight (Body Mass Index: ˜25)	1.06 (0.88–1.28)	0.55	1.33 (1.05–1.70)	0.02
Physical Capacity				
Short Physical Performance Battery (per each point)	1.03 (0.82–1.29)	0.81	1.15 (0.87–1.52)	0.33
Poor grip strength	1.33 (1.09–1.62)	0.006	1.33 (1.02–1.75)	0.038
Hip weakness	1.19 (0.96–1.48)	0.11	1.20 (0.92–1.55)	0.175

Conclusion: In this longitudinal study, several factors were independently associated with clinically significant restricting back pain, including three (depressive symptoms, BMI ≥25, poor grip strength) that may be amenable to interventions designed to prevent the occurrence, persistence or recurrence of this common disorder in older persons.

1722

The Effectiveness of Exercise with and without Manual Therapy for Hip Osteoarthritis: A Multi-Centre Randomised Controlled Trial. Helen P. French[1], Tara Cusack[2], Aisling Brennan[3], Aoife Caffrey[4], Vanessa Cuddy[5], Martina Fitzpatrick[4], Oliver M. FitzGerald[6], Clare Gilsenan[5], David Kane[3], Paul G. O'Connell[5], Breon White[7] and G M. McCarthy[7]. [1]Royal College of Surgeons in Ireland, Dublin 2, Ireland, [2]University College Dublin, Dublin, Ireland, [3]Adelaide, Meath hospital Dublin (incorporating the National Children's hospital), Dublin 24, Ireland, [4]St. Vincent's University Hospital, Dublin 4, Ireland, [5]Beaumont Hospital, Dublin 9, Ireland, [6]St. Vincent's University Hospital, Dublin, Ireland, [7]Mater Misericordiae University Hospital, Dublin 7, Ireland

Background/Purpose: Although exercise therapy (ET) is recommended in the management of hip OA, research to date shows small effects for reduction in pain and improvement of physical function. Manual therapy (MT), which comprises joint mobilisations and other hands-on techniques is commonly used by physiotherapists as an adjunct to ET for hip OA but lacks evidence of efficacy. This RCT was undertaken to primarily determine the clinical effectiveness of physiotherapy-based ET with and without MT for hip OA. A secondary aim was to ascertain the impact of an 8-week waiting period for physiotherapy on clinical outcomes.

Methods: 131 people with hip OA recruited from four hospitals were initially randomised to one of three groups: ET (n=45), ET+MT (n=43) and wait-list control (n=43). Both intervention groups received treatment for 8 weeks, control group participants remained on the waiting list (8 weeks) and were subsequently randomised into the ET or ET+MT group. Their data were pooled with original treatment group data: ET (n=66) and ET+MT (n=65). All participants were assessed post-treatment (9 weeks) and at 18 weeks. The primary outcome was the WOMAC physical function (PF) subscale and secondary outcomes included physical performance tests, pain severity, hip range of motion (HROM), anxiety/depression, quality of life, pain medication usage, patient-perceived change and patient satisfaction. Ethical approval was obtained at all sites. Intention-to-treat analyses were used to determine between–group differences for the three groups at baseline and 9 weeks (prior to re-randomisation), and the two treatment groups (including re-randomised control group) at baseline, 9 and 18 weeks.

Results: There was no significant difference in WOMAC PF between ET and ET+MT groups at 9 weeks (mean diff −0.91; 95%CI −6.28, 4.44) or 18 weeks (mean diff −1.41; 95%CI −7.12, 4.29). 'Patient satisfaction with outcome' was greater for ET+MT group (p=0.02). There was no significant difference between groups in other outcomes. Results for the three groups (secondary aim) showed significant improvement in WOMAC PF in the ET (mean change from baseline 4.60 (SD=8.76)) and ET+MT (mean change from baseline 4.68 (SD= 15.31)) groups compared to the control group (mean change from baseline −3.82 (SD=8.97)). Similar trends were observed in HROM, pain severity and patient-perceived change. There was no significant difference between the three groups in remaining outcomes.

Conclusion: ET demonstrated improvements in self-report function, pain, HROM and patient-perceived change for hip OA. MT had no further benefit as an adjunct to ET, although patients who received additional MT reported greater satisfaction with outcome. Patients deteriorated in pain, function and HROM measures while waiting for physiotherapy. These findings have implications for clinicians who can use treatment time more efficiently and enhance self-management principles for those with hip OA, and for those managing waiting lists to develop initiatives to minimise waiting times for physiotherapy.

1723

Exercise Training Reverts Chronotropic Incompetence and Improves Heart Rate Recovery After Exercise in Women with Systemic Lupus Erythematosus. Danilo M. L. Prado[1], Renata Miossi[2], Thalita Dassouki[1], Luiz A. Perandini[1], Fernanda R. Lima[1], Bruno Gualano[3], Ana Lucia S. Pinto[1], Eloisa Bonfa[4] and Hamilton Roschel[3]. [1]University of Sao Paulo, Rheumatology Division, LACRE, Sao Paulo, Brazil, [2]University of Sao Paulo, Rheumatology Division, Sao Paulo, Brazil, [3]University of Sao Paulo, School of Physical Education and Sport, Sao Paulo, Brazil, [4]Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil

Background/Purpose: We recently observed that patients with systemic lupus erythematosus (SLE) may present chronotropic incompetence and lower heart rate recovery (HRR) after maximal graded exercise, both suggesting autonomic dysfunction. Previous studies have shown in several diseases that aerobic exercise training attenuates autonomic dysfunction by increasing vagal tone and decreasing sympathetic activity. However, whether exercise training ameliorates chronotropic reserve and HRR after graded exercise in SLE remains unclear. Our purpose was to evaluate the effect of an exercise training program on chronotropic reserve and HRR in SLE woman.

Methods: Eighteen consecutive SLE women (age: 31.0 ± 1.3 years; BMI = 23.4 ± 0.7 kg/m^2; SLEDAI score = 1.0 ± 2.3) without cardiopulmonary involvement were divided into two groups: exercise training (n=10) and control group (n=8). A treadmill cardiorespiratory test was performed and heart rate response during exercise was evaluated. HRR at both one minute (ΔHRR1) and two minutes (ΔHRR2) were defined as the difference between heart rate at peak of exercise and at 1 and 2 minutes post-exercise, respectively. The supervised exercise program consisted of combined resistance and aerobic training exercises at moderate intensity, 60 min per session, twice-a-week, throughout 12 weeks.

Results: Exercise training resulted in significant improvements in chronotropic reserve and heart rate recovery (Table 1). Body weight, BMI and maximal oxygen consumption (VO_{2max}) were unchanged. Importantly, chronotropic incompetence was completely reversed.

	Exercise training		Control	
	pre	*post*	*pre*	*post*
CR	69.9 ± 5.0	101.1 ± 2.5*†	76.3 ± 5.2	77.0 ± 7.7
ΔHRR1	20.9 ± 3.0	39.4 ± 2.5*†	23.6 ± 3.0	22.8 ± 2.2
ΔHRR2	36.9 ± 4.0	57.0 ± 3.1*†	38.6 ± 3.5	38.3 ± 5.4

* p< 0.05 vs. pre; † p<0.05 vs. control. Repeated measures two-way ANOVA.

Conclusion: These findings indicate improvement in both chronotropic reserve and heart rate recovery in woman with SLE following a supervised exercise training program. Altogether, these data reinforce the compelling therapeutic relevance of exercise training in attenuating autonomic dysfunction in SLE.

1724

Is Knee Pain Relevant for Meeting Physical Activity Guidelines Among People with Knee Osteoarthritis Who Can Walk Already Walk At a Moderate Intensity? the Multicenter Osteoarthritis Study. Daniel K. White[1], David T. Felson[1], Yuqing Zhang[1], K. Douglas Gross[2], Jingbo Niu[1], Michael C. Nevitt[3], C.E. Lewis[4], James Torner[5] and Tuhina Neogi[6]. [1]Boston University School of Medicine, Boston, MA, [2]MGH Institute of Health Professions, Boston, MA, [3]University of California-San Francisco, San Francisco, CA, [4]University of Alabama, Birmingham City, AL, [5]University of Iowa, Iowa City, Iowa City, IA, [6]Boston University, Boston, MA

Background/Purpose: Knee pain precludes the ability to walk at a moderate intensity in knee osteoarthritis (OA), which is necessary to meet the Department

of Health and Human Services (DHHS) Physical Activity Guidelines. However, it is not known if knee pain is still relevant for meeting Physical Activity Guidelines among those who can already walk at a moderate intensity. Furthermore, it is not known if other modifiable factors, such as strength, walking speed, BMI, or depressive symptoms are relevant as well. Thus, we evaluated the association of knee pain along with other modifiable factors with meeting Physical Activity Guidelines among people with or at high risk of knee OA who could already walk at a moderate intensity.

Methods: MOST is an NIH funded study of people who have or are at high risk for knee OA. We selected subjects who were able to walk at a moderate intensity, defined as walking at a step frequency of at least 100 steps per minute during a 20-meter walk. Subjects wore an accelerometer-enabled pedometer (Stepwatch) to record steps taken over 7 days. Using Stepwatch data, we defined meeting Physical Activity Guidelines as walking 150 minutes at a moderate intensity (step frequency of at least 100 steps per minute) in at least 10 continuous minute bouts. We defined knee pain as pain on average in the last 30 days using a 0–100 visual analogue scale. We examined the association of knee pain along with isokinetic knee extensor strength, walking at a community speed (≥ 1.22 m/s), BMI, and depressive symptoms with meeting Physical Activity Guidelines adjusted for potential confounders using logistic regression.

		% (n/N) or Mean (sd)	Mutually adjusted* OR [95% CI]
Knee Pain [10 unit increments on 0-100 VAS scale]		1.5 (2.0)	1.0 [0.8, 1.1]
Strength [Tertiles]			
	Weakest	2 (7/303)	1.0 Reference
		5 (19/369)	1.6 [0.6, 4.3]
	Strongest	13 (50/379)	2.8 [1.3, 5.8]
Pedestrian Walk Speed [m/s]			
	<1.2	3 (17/543)	1.0 Reference
	>1.2	9 (64/714)	2.8 [1.3, 5.8]
BMI [kg/m^2]			
<25 'healthy weight'	<25	14 (29/201)	6.8 [1.5, 30.8]
25-30 'overweight'	25-30	7 (34/472)	4.2 [1.0, 18.6]
30-35 'obese class I'	30-35	4 (15/364)	2.6 [0.6, 12.1]
>35 'obese class II - III'	>35	1 (3/220)	1.0 Reference
Depressive Symptoms [CES-D > 16]			
	Absent	7 (77/1173)	1.0 Reference
	Present	5 (4/83)	0.9 [0.2, 3.0]

* Adjusted for age, sex, comorbidity, race, living situation, education, and study site. Higher OR indicates higher odds of meeting Physical Activity Guidelines.

Results: Of the 1380 subjects who had 7 days of monitoring (Age 67 ± 8 yrs, BMI 31 ± 6 kg/m^2, female 60%) 91% (1257/1380) were able to walk at a moderate intensity. Among these subjects, 6.4% (81/1257) met Physical Activity Guidelines. Greater knee pain severity was not associated with meeting Physical Activity Guidelines (OR = 1.0, 95% CI [0.8, 1.1]). In contrast, subjects with a BMI of 25 or less had 6.8 times the odds of meeting guidelines compared with those with a BMI 35 or greater (OR = 6.8 95%CI [1.5, 30.8]). Subjects walking at least a community speed (1.22 m/s) had 2.8 times the odds of meeting guidelines compared with those not walking a community speed (2.8 [1.3, 5.8]). Lastly, those in the highest strength tertile were 2.9 times as likely to meet guidelines compared with those in the lowest strength tertile (2.9 [1.1, 7.6]). Depressive symptoms were not associated with meeting guidelines.

Conclusion: We found BMI, walking speed, and knee strength but not knee pain or depressive symptoms to be associated with meeting guidelines among people who have the ability to walk at a moderate intensity. Targeting strength, walking speed, and BMI may be more promising than treating pain to increase physical activity among people who already have the ability to walk at a moderate intensity assessed in the clinic.

ACR REF Special Session

ACR REF Marshall J. Schiff, MD, Memorial Lectureship: Multicenter Orthopaedic Outcomes Network - A Prospective Longitudinal Cohort of ACL Reconstruction Outcomes

Monday, November 7, 2011, 4:30 PM–6:00 PM

1725

In Vivo Effect of Bone-Specific EphB4 Overexpression In Mice On Subchondral Bone and Cartilage During Osteoarthritis. Johanne M. Pelletier. Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC

Background/Purpose: In humans, evidence suggests the subchondral bone to be an active component of the osteoarthritis (OA) process. Some members of the ephrin system, including the receptor EphB4 and its specific ligand, ephrin-B2, were found to be involved in bone biology. Recently, our group showed that *in vitro* ephrin-B2 activation of the EphB4 receptor inhibits the resorptive activity of human OA subchondral bone osteoblasts. We further investigated, in mice, the *in vivo* effect of bone-specific EphB4 overexpression on OA development.

Methods: Morphological evaluations were performed on postnatal day 5 (P5) mouse skeletons with alizarin red/alcian blue staining and on 10-week-old adult mice radiographically. On the induced OA knee, histology (OARSI grading), cartilage collagen meshwork disorganization grading (sirius red staining), and micro-computed tomography scans (microCT) were performed on the medial compartment.

Results: Homozygous conditional type I collagen EphB4 overexpressing mice and wild type (WT) were used. Morphometric analysis and skeletal staining at P5 showed no obvious phenotypic difference in bone development between EphB4 and WT mice. Although 10-week-old WT and EphB4 mice had similar body size and bone length, EphB4 mice demonstrated increased bone density. OA was induced, using the partial medial meniscectomy (DMM) model, in the 10-week-old mice. Eight and 12 weeks after surgery, histology revealed that EphB4 mice had significantly less articular alterations than the WT in both medial condyle and tibia at 8 (4.9 ± 0.1 vs. 3.1 ± 0.4, $p<0.008$; 3.4 ± 0.3 vs. 2.1 ± 0.3, $p<0.0009$, respectively) and 12 weeks (3.4 ± 0.3 vs. 2.4 ± 0.30, $p<0.04$; 4.5 ± 0.3 vs. 3.3 ± 0.4, $p<0.04$) post-surgery. Evaluation of collagen fibril revealed significantly higher levels of disorganization in the WT mice compared with the EphB4 mice in the tibia at 8 (2.4 ± 0.4 vs. 1.1 ± 0.2, $p<0.0007$) and 12 weeks (2.3 ± 0.2 vs. 1.1 ± 0.1, $p<0.0003$) post-surgery. In addition, microCT of the medial tibia performed 12 weeks after surgery demonstrated a significant reduction in sclerotic subchondral bone volume as well as the trabecular thickness ($p\leq0.04$) in the EphB4 mice compared to the WT.

Conclusion: This study is the first to provide *in vivo* evidence that bone-specific EphB4 receptor overexpression exerts a protective effect on structural changes that occur in OA articular cartilage and subchondral bone. These data also support the notion that this system could be targeted as a specific therapeutic approach for OA.

1726

Lysyl Hydroxylase 2b Is Strongly Induced During Experimental Osteoarthritis and the Potential Cause of Persistent Synovial Fibrosis. Dennis F.G. Remst, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Fibrosis contributes to stiffness in osteoarthritis (OA) and is associated with joint pain. Lysyl hydroxylase 2b (LH2b) increases pyridinoline cross-links during collagen synthesis, which are harder to degrade than "normal" cross-links and are increased in fibrosis. In previous studies we found a relationship between LH2b and irreversible fibrosis after TGF-β exposure in murine synovium. TGF-β induced LH2b expression in human synovial OA fibroblasts (hSF). In this study we examined whether LH2b is actually induced in experimental OA. Thereafter we investigated which TGF-β signaling route is involved in up regulation of LH2b expression and whether gene expression also translates into LH2 protein production by TGF-β in hSF.

Methods: We induced OA by i.a. injection of collagenase into the right knee joint of C57BL/6 mice. The mice were sacrificed after 7, 21 and 42 days. mRNA was isolated from the synovium for Q-PCR. Human synovium fibroblast were isolated from knee joints of OA patients undergoing arthroplasties. The hSF were transduced with Ad-TGF-β, Ad-CTGF or Ad-Luc to determine whether LH2b induction is TGF-β specific. Thereafter, hSF were stimulated with TGF-β with and without ALK5 or ALK1 kinase inhibitor, SB-505124 (SB) or dorsomorphin (DM) respectively. In addition, hSF were transduced with constitutive active ALK1 or ALK5 to determine whether LH2b expression is ALK1 or ALK5 specific. mRNA was isolated and the gene expression for LH1, 2 and −3, lysyl oxidase (LOX), collagen type 1A1 (COL 1A1), and CTGF were analyzed with RT-PCR. LH2 protein level was determined with Western Blot analysis.

Results: In murine experimental OA there was a significant and long-lasting increase of LH2b gene expression in the synovium on day 7, 21 and 42 compared to the control knee joints. In hSF Ad-TGF-β induced LH2b gene expression whereas Ad-CTGF did not, comparable to our observations in murine synovium. TGF-β stimulation induced LH2b, CTGF, COL1A1 and LOX gene expression as well as LH2 protein. No major changes in LH1 and LH3 gene expression were found. Ad-caALK5 but not Ad-caALK1 significantly induced LH2b. This was confirmed by SB completely blocking TGF-β induced LH2b, while DM only

slightly decreased LH2b. Identical results were observed for all five primary fibroblast cell cultures.

Conclusion: In this study we have shown that LH2b is strongly induced in an experimental OA model that is accompanied by synovial fibrosis. Furthermore, we showed that both LH2b gene expression and LH2 protein are induced by TGF-β in hSF. Overexpressing caALK5, the canonical TGF-β type I receptor, induced LH2b, whereas blocking ALK5 kinase activity prevented TGF-β induced LH2b. The overexpression of caALK1 did not alter LH2b gene expression, indicating TGF-β-induced LH2b relies on ALK5 signaling alone. During OA, TGF-β is elevated causing enhanced LH2b expression. LH2b increases pyridinoline cross-links in collagen. We therefore propose that LH2b will be responsible for the persistence of fibrosis during OA. Selective blocking of LH2b in OA may prevent the formation of the pyridinoline cross-links, and therefore the formation of persistent fibrosis. Thus LH2b is a highly interesting new target to treat OA-related fibrosis.

ARHP Concurrent Abstract Session
ARHP Health Services Research
Monday, November 7, 2011, 4:30 PM–6:00 PM

1727

Organization of Care Delivery for People with Arthritis: Models and Processes. A. M. Davis[1], C. Cott[2], L. Li[3], M. Landry[4], A. Jones[5], R. Wong[6], C. Frank[7], L. Bergeron[8], R. Birtwhistle[9] and E. M. Badley[10]. [1]Health Care and Outcomes Research, Toronto Western Research Institute; Departments of Rehabilitation Science and Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, [2]Health Care and Outcomes Research, Toronto Western Research Institute; Departments of Physical Therapy and Rehabilitation Science, University of Toronto, Toronto, ON, [3]Arthritis Centre of Canada and Department of Physical Therapy, University of British Columbia, Vancouver, BC, [4]Departments of Physical Therapy and Rehabilitation Science, University of Toronto, Toronto, ON, [5]Departments of Physical Therapy and School of Public Health, University of Alberta, Edmonton, AB, [6]Health Care and Outcomes Research, Toronto Western Research Institute, Toronto, ON, [7]Alberta Bone and Joint Institute and Department of Surgery, University of Calgary, Calgary, AB, [8]Canadian Arthritis Patient Alliance, Ottawa, ON, [9]Centre for Studies in Primary Care and Family Medicine and Community Health and Epidemiology, Queen's University, Kingston, ON, [10]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background/Purpose: The substantial burden of arthritis has resulted in significant gaps in care such that there is a need to optimize access to and care for people with arthritis. The benefits of early diagnosis and treatment of inflammatory arthritis, wait times for joint replacement and limited health human resources have resulted in the development of alternative models of care delivery to address these care gaps. This study identified models of arthritis care and determined how care was organized within the models.

Methods: One-on-one interviews were conducted with program managers and care providers in British Columbia (BC), Alberta (AB) and Ontario (ON), Canada to determine how care was organized for people with arthritis. We also asked about the profession, role and skill set of those providing care. Interviews were transcribed verbatim and analyzed thematically using content analysis.

Results: 53 interviews were conducted, 17 in BC, 11 in AB and 25 in ON. Five overarching models were identified: 1) a community-based model that usually includes a single health professional or multiple health professions working independently with patients; 2) a traditional model where primary care physicians refer to specialists; 3) a multi-professional model; 4) an inter-professional model; and, 5) an inter-professional model where care is provided both by individuals and in a group format. Multi-professional models and inter-professional models were developed in the context of specialist care and rarely were situated in primary care. Rarely were models developed and implemented for people with arthritis in general. Additionally, some models had formalized linkages with community providers, particularly related to chronic disease management including exercise programs. None of the models addressed the entire continuum of care.

Some models include health professionals working in alternative ways, e.g. enhancement with extended roles or substitution where roles are delegated. Processes to enhance access for specific subgroups of people with arthritis including triage processes for people with suspected inflammatory arthritis for rheumatology consultation and for people who were likely candidates for joint replacement were most common.

Conclusion: Innovative care models have been developed to improve access to care for people with arthritis but these models mainly have focused on inflammatory arthritis and total joint replacement. Most models do not or in only a limited way address conservative management for people with the most common type of arthritis, osteoarthritis. It appears that current models of care are most organized at the level of specialist care, but not in primary care which is the gateway to early diagnosis, treatment and health promotion. Given the increasing prevalence of arthritis and that published data show that only a small proportion of arthritis care is specialist care, addressing this public health concern and provision of timely, appropriate care requires the development, implementation and evaluation of models of care for people with arthritis in general across the continuum of care.

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Capturing the Patient Experience: Patient Advisory Committee at Rush University Rheumatologists. Laura Wright[1] and John O'Toole[2]. [1]RUSH University Medical Center, Chicago, IL, [2]RUSH, Chicago, IL

Background/Purpose: The broad objective is to improve patient satisfaction. The purpose of this study is to determine if creating a Patient Advisory Committee (PAC) will lead to increased patient satisfaction which is measured quarterly via Press Ganey Medical Practice Report scores. Press Ganey (PG) produces the industry standard for measuring customer service satisfaction in healthcare. Our goal is to initiate changes in our Rush Rheumatology clinic based on the problems/solutions discussed during PAC meetings.

Methods: Distribute patient satisfaction survey to each patient prior to quarterly PAC meeting; Ask about interest in PAC; Create agenda; Hold quarterly meetings; Record patient input; Initiate changes based on patient input; Analyze effect of changes made based on PG scores

Results: *First PAC Meeting (3/1/11):* Patients can't get parking discount booklets sold in the medical center (accessibility); Met with parking administrator and received permission to sell the discount booklets at our front desk.

Patients want staff and physicians to more clearly identify their title and role; Met with faculty and staff to discuss titles and roles of providers, perceptions of patients.

Patients like that our physicians have latest information/technology, wash their hands in exam room, and take time to break down medical information; Relayed information to faculty/staff at meeting and via email summarizing the PAC meetings.

Patients want physicians to follow through with what they have said they will do such as calling back, sending information, sharing results (timely); Section Director discussed with faculty at weekly meeting and physicians discussed how to improve.

Patients would like administrative and clinical staff to participate in the PAC meetings; Administrative and clinical staff attended 2nd PAC meeting.

Patient expressed frustration with phone tree, difficulty reaching employees at front desk; Changed phone tree message and access to allow option to choose front desk staff.

Meeting End:Informed patients that RUSH is implementing EPIC electronic medical system, asked patients to notice any affect on their interaction with medical staff & comment at next visit.

Second PAC meeting (6/1/11): Patients like the After Visit Summary that is now printed at the end of their visit (Epic EMR implemented 4/5/11) and like that they don't have to request records. Feel more confident now that all of their providers can access their entire medical record; Shared information with faculty and staff and via email summarizing the PAC meetings.

Patients would like staff to call them to obtain information regarding past medical history and list of medications rather than taking up appointment time; Certified Medical Assistants testing in a very limited pilot program.

Conclusion: PG scores (to date) do not support initial improvement in "very good" responses via questionnaires. Many positive and enthusiastic patient comments about changes that have been made due to suggestions of patient advisory committee. Almost double the number of patients attended the second meeting. Patients are very appreciative of being "listened to" and included.

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The Impact of Advanced Clinician Practitioner in Arthritis Care Program-Trained Extended Role Practitioners on Health Care Delivery: A Two Year Prospective Study. Carol Kennedy[1], Kelly Warmington[1], Leslie J. Soever[2], Laura A. Passalent[3], Sydney C. Lineker[4], Katie Lundon[1], Rachel Shupak[1] and Rayfel Schneider[5]. [1]St. Michael's Hospital, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]University Health Network, Toronto, ON, [4]The Arthritis Society, Toronto, ON, [5]Hospital for Sick Children, University of Toronto, Toronto, ON

Background/Purpose: The Advanced Clinician Practitioner in Arthritis Care (ACPAC) program is an innovative, clinical and academic, post-licensure program for experienced physical and occupational therapists. The program focuses on assessment, diagnosis, triage and independent management of selected musculoskeletal and arthritis-related disorders. In order to improve arthritis care through the implementation of a new clinical role, it is imperative to evaluate the extent to which ACPAC program graduates are delivering integrated and timely healthcare.

This study aimed to evaluate the impact of the Advanced Clinician Practitioner in Arthritis Care (ACPAC) program-trained extended role practitioner with respect to health care delivery. The research objectives were: 1) to measure access to ACPAC program-trained practitioners in Ontario, 2) to describe the role utilization of the ACPAC program-trained practitioner, and 3) to explore integration with internal/external services and other resources.

Methods: ACPAC program-trained practitioners (n=30) were recruited from 15 healthcare institutions across the province of Ontario, Canada. These included urban, rural, academic, non-academic, adult and paediatric settings. A longitudinal survey was completed at the end of each fiscal quarter in 2009 and 2010. Questions relating to system impact were developed through peer consensus. Descriptive statistics were used to summarize the data.

Results: The response rate varied from 83–97% over the 8 fiscal quarters of 2009 and 2010. The mean wait time from referral to initial assessment by an ACPAC program-trained practitioner varied from 14 to 26 days. Most respondents were working in an extended practice role (range 84–93%). These practitioners referred patients to a wide range of services (expressed as % of total patients seen in fiscal year 2009 [n=13407] and 2010 [n=14546]): 10% referred to internal services (publicly funded, privately funded but within); 18–20% to external/community services; 12–14% to medical doctors (general practitioners or specialists); 47–73% to other services (e.g. lab, imaging); and 22–24% to educational resources. Most ACPAC graduates (58–79%) reported acting under the auspices of medical directives to support their extended practice role. Most respondents ordered X-rays (82–88%), lab tests (64–74%) and diagnostic ultrasounds (43–55%). 70–80% reported recommending medication/dosage changes and 4–14% made these changes independently. 93–96% reported recommending joint injections and 8–18% were performing them.

Conclusion: Most ACPAC program-trained practitioners are working in extended practice roles and are performing tasks that have potential to improve access to care for patients with arthritis. Future evaluations will monitor the evolution of the graduates' extended roles and assess the impact of their care on patient outcomes.

The ACPAC therapist can potentially improve wait times for care and provide an interprofessional approach to managing patients with arthritis and other musculoskeletal disorders. This new human health resource may be an effective strategy to address the progressive decline in the number of arthritis care specialists.

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Patient Satisfaction with a New Healthcare Provider: Advanced Clinician Practitioner in Arthritis Care Program-Trained Clinicians. Kelly Warmington[1], Carol Kennedy[1], Sydney C. Lineker[2], Leslie J. Soever[3], Laura A. Passalent[4], Katie Lundon[1], Rachel Shupak[1] and Rayfel Schneider[5]. [1]St. Michael's Hospital, Toronto, ON, [2]The Arthritis Society, Toronto, ON, [3]Mount Sinai Hospital, Toronto, ON, [4]University Health Network, Toronto, ON, [5]Hospital for Sick Children, University of Toronto, Toronto, ON

Background/Purpose: In an effort to provide more appropriate and timely arthritis care, patients are being presented with new models of care and disease management. The Advanced Clinician Practitioner in Arthritis Care (ACPAC) Program is an innovative, clinical and academic education program for licensed physical therapists and occupational therapists. It focuses on the assessment, diagnosis and independent management of selected musculoskeletal and arthritis-related disorders.

As stakeholders in their own care, it is important to give patients a voice in determining the value of their care provider. Our objectives were to evaluate patients' satisfaction with the care received from ACPAC Program graduates and to explore factors associated with levels of satisfaction.

Methods: The patients (N=325) of 27 ACPAC program-trained therapists, seen during a face-to-face visit, were recruited from15 healthcare institutions across Ontario, Canada.

This was a cross-sectional study utilizing a self-report survey. The primary outcome measure was the Patient-Doctor Interaction Scale, modified to reflect patient-therapist interaction (PTIS). The PTIS subscales included: Providing Information (PI), Rapport (R), Meeting Patient Needs (PN). Secondary outcomes included satisfaction with services received (8 items from GHAA Consumer Satisfaction Survey); acceptability of wait times; overall satisfaction, and comparison with arthritis care received from other healthcare professionals.

Analyses included descriptive statistics and logistic regression methods. In the latter, the dependent variable was the PTIS (satisfied vs not satisfied). Fourteen independent factors were considered.

Results: The respondent mean age was 54 years (3–75), with most respondents female (72%), adult (82%) and living in urban areas (79%). The majority of respondents were not working (51%) and most had a diagnosis of an inflammatory (52%) or non-inflammatory (33%) condition.

The PTIS subscale scores [mean (sd); 1–5, 5=very satisfied] were high. PI: 4.5 (0.6), R: 4.6 (0.5), PN: 4.6 (0.5). Satisfaction with services received [1–5, 5=very satisfied]: item means ranged from 4.1–4.6. Wait time was acceptable: from referral (88% agree/strongly agree), and in clinic (87% agree/strongly agree). Overall satisfaction was high [1–5, 5=excellent]: 4.4 (0.7). The majority felt the arthritis care they received was comparable to (37%) or better than (61%) that provided by other healthcare professionals.

Higher levels of satisfaction were associated with acceptable wait times. A number of other factors were also associated with satisfaction across one or two subscales.

Conclusion: Patients seen by ACPAC program-trained practitioners were consistently satisfied across all PTIS subscales and secondary outcomes including access to care. Given the added involvement of this new human health resource in their arthritis management, patients are highly satisfied with the graduates' abilities and feel that their needs are being well addressed. Future work should focus on how the ACPAC program-trained therapists are improving patient care and filling gaps in this area of the healthcare system.

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Evaluation of Interprofessional Patient-Centred Collaborative Practice Behaviour and Perceptions Following An Intensive Continuing Education Development Initiative in Arthritis Care. Katie Lundon[1], Carol Kennedy[1], Kelly Warmington[1], Linda Rozmovits[2], Leslie J. Soever[3], Laura A. Passalent[4], Sydney C. Lineker[5], Rachel Shupak[6], Rayfel Schneider[7] and Lynne Sinclair[8]. [1]St. Michael's Hospital, Toronto, ON, [2]Consultant, Toronto, ON, [3]Mount Sinai Hospital, Toronto, ON, [4]University Health Network, Toronto, ON, [5]The Arthritis Society, Toronto, ON, [6]St. Michaels Hospital, Toronto, ON, [7]Hospital for Sick Children, University of Toronto, Toronto, ON, [8]Toronto Rehabiltation Institute, Toronto, ON

Background/Purpose: The Advanced Clinician Practitioner in Arthritis Care (ACPAC) program is an intensive one-year, academic and clinical training program offered to experienced physical and occupational therapists practising in diverse clinical settings across Ontario, Canada. These extended role practitioners both anticipate and are expected to work in the context of Interprofessional Patient-Centred Collaboration (IPC). This is motivated by the growing consensus that IPC practice improves patient care, access to care, patient safety and satisfaction. Purpose: To evaluate the IPC practice behaviour and perceptions amongst ACPAC program-trained practitioners and their teams.

Methods: This study used a mixed-method approach. Qualitative: Focus groups (n=3) for ACPAC practitioners (n=20 participated); Interviews (n=18) for their clinical colleagues and administrators. These were digitally audio-recorded for verbatim transcription, entered into HyperResearch software for textual data analysis. Transcripts were coded for anticipated and emergent themes using the method of constant comparison including searches for disconfirming evidence. Themes related to IPC were identified using components of Barr et al (2005) evaluation of interprofessional education (IPE) initiatives framework to evaluate behavior and modification of attitudes and perceptions, readiness for change in organizational practice and any benefit to patient. Quantitative survey completed by ACPAC practitioners (n=24): Bruyère Clinical Team Self-Assessment on Interprofessional Practice and a single-item rating of team's readiness for IPC practice. Descriptive statistics were used.

Results: Interviews and focus groups with ACPAC graduates and their clinical colleagues and administrators suggest these practitioners are generally effective at promoting and contributing to IPC within arthritis care settings. Varying degrees of IPC exist within their arthritis care teams. Barriers such as institution-specific lack of medical directives, remuneration conflicts, and role recognition issues were identified to impede role implementation. Quantitative survey: Seventy percent felt their team was actively working in an IPC practice model while just over 25% felt it was in the precontemplation (never thought about it) or contemplation phase (thinking about it), and the remaining 5% were prepared for action (making plans). Mean Bruyère subjective subscale scores were high (all >3, scale range 1–5=better perception of teams IPC practice) and lower (mean 4.6, scale range 0–9=more team practices associated with IPC) on the objective scale.

Conclusion: ACPAC program graduates are effective participants of, and contributors to IPC care at select sites. Their presence appears to both promote organizational change and impart general benefit to the collaborative care of patients with arthritis. However, ACPAC graduates are working on teams that are at varying stages of readiness for IPC practice. They appear to understand what is needed for IPC while fewer actual IPC team practices are in place. Intensive IPC components were recently added to the ACPAC curriculum to address this gap.

Key Words: *evaluation, advanced practice, arthritis care, IPC*

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An Overview of Clinical Performance by Advanced Clinician Practitioner in Arthritis Care Program-Trained Therapists: A Two-Year Prospective Study. Laura A. Passalent[1], Carol Kennedy[2], Leslie J. Soever[3], Kelly Warmington[2], Sydney C. Lineker[4], Katie Lundon[2], Rachel Shupak[5] and Rayfel Schneider[6]. [1]University Health Network, Toronto, ON, [2]St. Michael's Hospital, Toronto, ON, [3]Mount Sinai Hospital, Toronto, ON, [4]The Arthritis Society, Toronto, ON, [5]St. Michaels Hospital, Toronto, ON, [6]Hospital for Sick Children, University of Toronto, Toronto, ON

Background/Purpose: The Advanced Clinician Practitioner in Arthritis Care (ACPAC) Program is an innovative clinical and academic training program focused on assessment, diagnosis, triage and independent management of selected musculoskeletal and arthritis disorders. The aim of the program is to prepare experienced physical and occupational therapists for extended practice roles and to develop innovative models of arthritis care across diverse clinical settings. It is now critical and timely to evaluate the ACPAC program graduates' clinical performance. The specific objectives of this study were to examine the clinical performance of ACPAC program-trained therapists with respect to the following indicators: 1) referral source; 2) patient volumes and 3) patient diagnoses.

Methods: A longitudinal survey was administered to 30 ACPAC graduates working at 15 healthcare institutions across the Canadian province of Ontario. These included urban, rural, academic, non-academic, adult and paediatric settings. An electronic questionnaire was sent each quarter for the 2009 and 2010 fiscal years. Questions relating to clinical performance were established through peer consensus and were tested for face validity. Descriptive statistics were used to summarize the data.

Results: The mean response rate per quarter was 91.3% (range = 83.3% – 96.7%). ACPAC graduates saw a total of 13407 patients during the 2009 fiscal year and 14546 patients during the 2010 fiscal year. In 2009, the majority of patients were referred by a family physician (43.9%), followed by 35.8% of patients referred by a specialist. In contrast, 51.5% of patients were referred by a specialist in the 2010 fiscal year, followed by 37.3% referred by a family physician. Over the two-year period, new consults constituted 24.9% of all patients seen, of which 7.3% were paediatric. Just over half (55.6%) of patients seen by ACPAC program-trained therapist were for follow-up, with 17.5% of follow-ups specific to the paediatric population. The remaining patients underwent triage by ACPAC program-trained therapists. Approximately half (51.6%) of the patients seen had a diagnosis of osteoarthritis (OA), followed by rheumatoid arthritis (RA) (14.7%), juvenile idiopathic arthritis (11.1%) and the remainder having diagnoses related to various inflammatory and non-inflammatory arthropathies.

Conclusion: ACPAC program-trained therapists working in the province of Ontario are primarily seeing patients with OA or RA in a follow-up capacity, with most patients being referred by either a family physician or specialist. The above evaluation provides a snapshot of the clinical performance of the ACPAC program-trained therapist in terms of volumes, referral sources and diagnoses and identifies an evolving role in the triage of patients, which may improve access to care. The increase in referrals from specialists may reflect their growing awareness of the potential triage role offered by extended role practitioners. Knowing the clinical performance of this unique human health resource can help to shape strategic planning for health care clinical utilization and delivery of care.

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Reduced Imprints of Receptor Editing At the Immunologlobulin κ and λ Light Chain Loci During Rituximab Treatment. Khalid Muhammad[1], Arumugam Palanichamy[1], Petra Roll[1], Stefan Kleinert[1], Thomas Dörner[2] and Hans-Peter Tony[1]. [1]University of Würzburg, Würzburg, Germany, [2]Charite Universitätsmedizin Berlin and DRFZ, Berlin, Germany

Background/Purpose: Transient B cell depletion by rituximab (RTX) has gained more importance in the treatment of rheumatoid arthritis (RA) in recent years. Although phenotypic reports on repopulation kinetics of B cell subsets are increasing, precise molecular analysis of the reconstituting immunoglobulin (Ig) genes are sparse. Detailed gene and mutational investigations are demanding to better understand the influence of RTX on Ig genes.

Methods: 708 individual CD19+CD27+ (memory) and CD19+CD27- (naive) B cells were analyzed from 2 RA patients at baseline and 7 months after RTX at B cell repopulation. Ig light chain variable kappa (Vκ) and lambda (Vλ) light chain gene rearrangements were amplified, sequenced and analyzed with a focus on receptor editing.

Results: The naïve as well as the memory repertoire repopulated polyclonally with a diverse use of variable light chain gene families and minigenes. In general, reemerging CD27+ Ig light chain genes displayed substantially higher mutations compared to baseline ($P<0.0001$ prior to RTX versus during reconstitution).. During reconstitution phase, B cells used significantly fewer Jκ distal Vκ genes (P=0.0006) together with a higher frequency of somatic hypermutation of rearrangements employing Jk5 compared to baseline in memory B cells. The use of Vλ rearrangements in regenerating B cells was also biased towards use of Vλ genes of the proximal cassette.

Conclusion: The data indicate that RTX therapy leads to the generation of distinct Vκ/Jκ and Vλ/Jλ gene repertoires consistent with replenishment of antigen-experienced B cells by germinal centers. At baseline, the imprints of receptor editing appeared to be more striking which indicates that a defect of receptor editing is not characteristic of RA and can be normalized by RTX.

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The Levels of Memory B-Cells with a Plasmablast-Like Phenotype Are Associated with Response to Anti-CD20 Treatment in Rheumatoid Arthritis. Gururaj Arumugakani[1], Andrew Rawstron[2], Reuben Tooze[1], Paul Emery[3] and Dennis McGonagle[4]. [1]University of Leeds, Leeds, United Kingdom, [2]NIHR Leeds Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [4]University of Leeds and Leeds Teaching Hospitals, Leeds, United Kingdom

Background/Purpose: The advent of B-cell depletion therapy has significantly improved outcome of various autoimmune conditions including Rheumatoid Arthritis (RA), Lupus, Wegner's etc. The extent of B-cell depletion determined by high sensitivity flow cytometry is a key predictor of response and outcome. The pattern of B-cell reconstitution also appears to be important as clinical relapse does not occur in individuals with sustained B-cell depletion, and recovery of plasmablasts in the absence of other B-cell subsets predicts imminent relapse. Individuals with recovery of multiple B-cell subsets have a variable clinical course but those with a high proportion of memory cells within the reconstituting B-cell pool may have an increased risk of relapse. (Dass et al Arthritis Rheum. 2008 Oct;58(10):2993–9) The aim of this study was to identify the characteristics of B-cell subsets which contribute to relapse.

Methods: 79 samples from patients with autoimmune disorders and 28 disease controls were analysed by 10-parameter flow cytometry. An antibody backbone of CD19 and CD20 CD27, and CD38 were used to identify naïve,B-cells memory B-cells and plasmablasts in the backbone to define the initial subsets. 34 additional surface markers known to be expressed by B-cells were evaluated on selected RA cases and controls to identify the most informative subsets. Final assessment of the B-cell subset distribution was performed on 7 individuals prior to first anti-CD20 treatment and 6 individuals with relapsed disease prior to re-treatment.

Results: An iterative approach was used to select markers for further investigation, with an initial stage to detect markers with heterogeneous expression followed by further stages to identify combinations of markers which were complementary in the delineation of different B-cell subsets. Distinct populations could be identified by differential expression of 9 markers, 5/9 of these identified a population of CD38-negative memory B-cells which were otherwise phenotypically similar to plasmablasts. The proportions of these plasmablast-like memory B-cells were relatively low in control cases (median 18% of total memory B-cells, range 7–29%) but were more prevalent in rheumatoid cases prior to anti-CD20 treatment (median 26% of total memory B-cells, range 20–52%) although this difference did not reach statistical significance (Mann Whitney P=0.22). Individuals with relapsed disease requiring re-treatment had variable numbers of naïve B-cells but showed a highly significant increase in the proportion of plasmablast-like memory B-cells (median 55%, range 39–65%, Mann-Whitney P=0.007).

Conclusion: Extensive analysis of B-cell subsets in rheumatoid patients demonstrates heavy skewing of the memory B-cell pool in individuals relapsing after anti-CD20 treatment. Poor or unsustained response to anti-CD20 treatment is associated with the persistence and/or skewed reconstitution by both plasmablasts and plasmablast-like memory B-cells during and after anti-CD20 treatment.

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B Cell Depletion Therapy After Multiple Cycles of Rituximab in Patients with Rheumatoid Arthritis: B Cell and Plasma Cell Dynamics Measured Using Serology. Geraldine Cambridge[1], Maria J. Leandro[1], Jonathan CW Edwards[1], Harvey M. Parsons[1], Marion C. Dickson[2] and Hayley Perry[2]. [1]UCL, London, United Kingdom, [2]GSK, Stevenage

Background/Purpose: Pharmacokinetic studies of rituximab-based B cell depletion in RA, allows analysis of elements important for clinical response and relapse. B cell return is mandatory for relapse but in up to 50% of patients, disease flare only occurs several months (or years) after B cell return. Whether Concordant or Discordant with B cell return, relapse is coincident with rises in serum autoantibodies and maturation of B cells into memory cells. Patterns of response and relapse are usually consistent over cycles in individual patients suggesting qualitative as well as quantitative differences in pathogenic B cell selection and maturation. The aim of this study was to use serological markers to identify relationships between maturation of B cells into memory and plasma cells at key points in repeat cycles (median 3, range 2–4) of treatment with rituximab in 24 patients with RA.

Methods: Analytes were tested at 4 time points within each cycle of therapy: baseline, depletion (CD19+Bcell <5cells/μl), repopulation (CD19+Bcell ≥ 5cells/μl) and relapse. Soluble CD23 (sCD23) was used as a measure of B cell maturation into (CD27+) memory cells and serum free light chains as a measure of plasmablast/plasma cell activity. Levels of isotypes of autoantibodies, RF and anti-CCP, of protective antibodies, and of BAFF over the same cycles of treatment were measured. Mann Whitney U and Wilcoxon tests were performed for independent and paired parameters.

Results: After Cycle 1, all analytes decreased significantly from baseline ($p<0.01$) except TT and PCP antibodies. When divided into Concordant and Discordant patients however, IgG and IgA anti-CCP and IgA-RF did not decrease significantly in the Discordant group. These patterns were repeated in the second cycle. When paired samples taken pre-rituximab and at relapse after 3 cycles were compared, significant decreases were found for IgM-RhF and IgM-CCP ($p=0.004$; $p=0.02$ respectively) and for IgG-CCP ($p=0.04$) and sCD23 ($p=0.05$) with a highly significant increase in BAFF levels ($p=0.008$); the drop in CRP approached significance ($p=0.055$). Linear regression analyses of Cycles 1 and 2 showed that IgM-, IgA- and IgG-CCP antibodies were strongly correlated at relapses in the Concordant patient group, whereas IgA and IgM classes of CCP and of RF were strongly correlated at relapses in the Discordant group ($R^2 > 0.72$). There was a statistically significant association between the log transformed sCD23 as time dependent covariate and time to relapse in Cycles 2 and 3 but not in Cycle 1.

Conclusion: The findings of these studies suggest that a critical level of maturation of different autoreactive B cell clones must be reached for relapse to occur. This is largely independent of BAFF levels. Differences were also found between the response of B cell clones in Concordant and Discordant patients during depletion and also at relapse. The temporal relationship between sCD23 and relapse further supports the concept that maturation of B cells into memory phenotype is linked to relapse, but the dissociation between B cell repopulation and relapse suggests that the specificity of maturing clones is also important.

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Value of Predictive B Cell Markers for EULAR Response to RITUXIMAB in Patients with Rheumatoid Arthritis (FIRST). Hans-Peter Tony[1], Petra Roll[1], Henrik Mei[2], Lara Gnuegge[3], Monika Kobialko[3], Thomas Dörner[4] and FIRST study team[5]. [1]University of Würzburg, Würzburg, Germany, [2]Charite Universitätsmedizin Berlin and DRFZ,, 10117 Berlin, Germany, [3]Roche Pharma AG, 79639 Grenzach-Wyhlen, Germany, [4]Charite Universitätsmedizin Berlin and DRFZ,, Berlin,, Germany, [5]Würzburg

Background/Purpose: FIRST is an exploratory, multi-center, open label, uncontrolled phase IIIb study evaluating the efficacy of Rituximab (RTX) in RA after inadequate response to a single TNFα inhibitor (TNFi). 302 patients were treated with 1000 mg RTX on days 1 and 15 and observed up to 2 years. In a substudy, it was intended to investigate B cell markers and to identify B cell populations predictive of response at week 16.

Methods: In the substudy (n=154) rheumatoid factor (RF), RF-isotypes, peripheral CD19+ B cells and CD19+ B cell subpopulations using marker combinations of IgD, CD10, CD38, CD27 and CD20 were determined. Their impact on EULAR response rates (ER) was analysed univariately and multivariately. Stepwise forward logistic regression including the significant ($p<0.1$) B cell markers (logarithms) was used with entry and stay criterion of 10%. Odds ratios (OR) and their 95% confidence intervals [in brackets] were determined for the final model.

Results: Baseline characteristics: n=154, age [mean ± s.d.] = 54.9 ± 9.9 years, female 77.9%, RF+ 71.4%, RFIgA 103.9 ± 118.7 [IU/mL]. At week 16 112 patients (72.7%) achieved ER (good response 26.6%). DAS28 changed from initial 5.8 ± 1.0 to 4.0 ± 1.2 (week 16). About half of the patients (49.4%) showed an improvement in ACR 20, 18.8% in ACR 50 and 6.5% in ACR 70. According to predictors identified, the observed ER were: for RF+ patients 80.0%, RF- 56.1%, RFIgA+ 81.4%, RFIgA- 63.5%, for normal or above normal CD19 B cells [%] (CD19+) 75.7%, for low CD19 [%] (CD19-) 62.2%.

Multivariate analysis (MVA) yielded higher ER for RFIgA+ ($p = 0.0154$, OR=2.576 [1.198, 5.540]) and for CD19+ [%] ($p = 0.0517$, OR=2.186 [0.994, 4.807]). Observed ER were 83.9% (RFIgA+/CD19+), 73.1% (RFIgA+/CD19-), 69.0% (RFIgA-/CD19+) and 47.4% (RFIgA-/CD19-). Further MVA intending to differentiate specific B cell subpopulations yielded that ER is influenced by "double negative" CD27-IgD- B cells (27-D-) ($p=0.0174$, OR=1.989 [1.129, 3.506]). Observed ER for CD27-IgD- B cells ($\geq 5/\mu L$) were 81.8% and for low CD27-IgD- B cells ($<5/\mu L$) 62.9%. Combining RF and CD27-IgD- B cells resulted in ER for RF+ patients with 90.9% (RF+/27-D-(≥ 5) and 72.5% (RF+/27-D-(<5)). In RF negative patients the RF-/27-D-(≥ 5) group achieved 61.9% and the RF-/27-D-(<5) group 41.2% ER.

Conclusion: Among the different B cell markers in addition to RF positivity, normal or high values of B cells (CD19) and higher values of "double negative" CD27-IgD- B cells proved to be predictive of better EULAR responses to a first course of RTX+MTX. This was true among RF+ as well as among RF- patients. Particularly in RF negative patients the determination of CD19+ or "double negative" CD27-IgD- B cells may prove useful to select responding patients.

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B Cell Activating Factor (BAFF) Binding Receptors (BBR) on B Cells: Characterization in Patients with Rheumatoid Arthritis (RA) Receiving B Cell Depletion Therapy (BCDT) Based on Rituximab (Rtx). Elena Becerra-Fernandez[1], Inmaculada de la Torre[2], Lara Valor[2], Maria J. Leandro[1] and Geraldine Cambridge[1]. [1]UCL, London, United Kingdom, [2]Gregorio Marañón Hospital, Madrid, Spain

Background/Purpose: Two pattern of response/relapse in patients with RA after Rtx have been identified: *Concordant* between B cell return and clinical relapse *(C-R)* and *discordant* between B cells return *(D-NR)* and clinical relapse *(D-R)*. **Aim:** To investigate BBR expression in relation to B cell return after depletion and relation to clinical relapse

Methods: Phenotype analyses of BAFF-R, TACI and BCMA expression on PBMC were performed using combinations of CD19, CD27, CD38 and IgD (% and mean fluorescence intensity-MFI) in normal controls (NC) (n: 5) and patients pre (n: 11) and after Rtx, classified as C-R at B cell repopulation (n: 11), D-R > 3 months after repopulation (n: 11) or D-NR after B cell return (n: 11).

Results: BAFF-R, TACI expression in patients with RA pre and after Rtx compared to NC: Mean % of naïve and memory B cells subsets expressing BAFF-R and TACI (as well as MFI) was lower for patients with RA compared to NC. Lower BAFF-R expression on naive B cell pool for C-R patients was related to relapse closer to B cell return. Main differences between D-R or D-NR was BAFF-R expression on the post-Germinal Center (GC) B cells. **BAFFR/BCMA ratio before and after Rtx:** Inverse correlation between BAFF-R and BCMA seem to be preserved before Rtx, but after Rtx:1) D-NR patients, still inactive, presented with higher BCMA expression and lower BAFF-R on their naive B cells, 2) C-R patients, active after Rtx, in whom their naive B cells presented with lower BAFF-R expression, but normal BCMA expression. **Phenotype pattern in RA patients pre and after Rtx**: C-R patients presented with lower % of naïve mature B cells when compared to D-R or -NR patients (54.15% vs 79.13% and 79.78%, $p=0.01$ and $p=0.02$, respectively) and also with higher % of plasmablasts (15.4% vs 2.3% and 0.77%, $p=0.07$, $p=0.03$, respectively). D-NR patients showed a tendency through lower % of plasmablast when compared to pre-treatment patients (0.7% vs. 3.9%, $p=0.07$). % of post GC B cell was uniformly decreased after Rtx when compared to pre-treatment patients. However, D-NR patients showed a tendency through lower % of post GC when compared to D-R patients (0.04% vs. 1.7%, $p=0.08$).

Conclusion: Patients C-R repopulated with higher % of plasmablasts, and their naïve B cell pool presented with lower BAFF-R. Patients D at B cell return, repopulated with higher naïve B cells, and although BAFF-R could be lower in their naïve population, there is a tendency through higher BCMA. D-R patients presented with higher post GC B cells than D-NR. TACI was uniformly low after Rtx. Different preferential survival for C-R though plasmablast and antibody production may explain shorter clinical response after B cell return in those patients vs. the D ones. TACI low expression + BAFF-R/BCMA deregulation may be related to delayed acquisition of memory B cell and low Igs after Rtx.

Post hoc results for normalized quadriceps femoris muscle strength. At 3 months following total knee arthroplasty (TKA), the muscle in the involved limb was weaker than that in the uninvolved limb ($P<.001$). By 1 year, strength in the involved limb improved ($P=.016$), but this limb continued to be weaker than the uninvolved limb ($P=.015$). Compared with control subjects, subjects 3 months following TKA had a weaker muscle in the involved limb ($P=.001$) but not in the uninvolved limb ($P=.092$). At 1 year following TKA, there were no differences (involved limb, $P=.096$; uninvolved limb, $P=.408$). Abbreviations: 3 mo=3 months following TKA, 1 y=1 year following TKA, NON=noninvolved (not surgically treated) limb, OP=involved (surgically treated) limb, BMI=body mass index, MVC=maximal voluntary contraction.

1738

No Expression of An Alternative CD20 Transcript Variant in B Cells From Patients with Rheumatoid Arthritis. Marina Deschamp[1], Béatrice Gaugler[1], Philippe Saas[1], Christophe Ferrand[1] and Eric Toussirot[2]. [1]INSERM UMR645 - IFR 133, Besançon, [2]Rheumatology and CIC Biotherapy 506 and EA 4266 Pathogens and Inflammation, Besançon, France

Background/Purpose: Targeting B cells is an effective therapy in rheumatoid arthritis (RA). Rituximab (RTX) is a chimeric monoclonal antibody directed against the membrane CD20 protein present on B cells. Predictive factors for good response to RTX therapy in RA have been identified and included the presence of rheumatoid factors and anti -CCP antibodies. Recently, a spliced mRNA transcript of CD20 (ΔCD20) has been identified in B cell lines from patients with lymphoma and leukaemia (ref). This transcript is coding for a non anchored membrane protein and its expression is associated with resistance to RTX in patients with haematological malignancies. Objectives: to determine whether ΔCD20 is expressed by circulating B cells from patients with RA and whether it could be a factor for non response to RTX therapy.

Methods: 23 RA patients (17 F, age [mean ± SEM]: 60.1 ± 2.7 years; disease duration: 13.3 ± 1.7 years, positive rheumatoid factors: 19/23; positive anti-CCP antibodies: 19/23) and 20 healthy controls (15 F, age: 59.6 ± 2.5 years) were evaluated. Patients were under DMARDs, low corticosteroids (< 10 mg/j) or anti TNFa agents but none received or had received RTX. CD20 mRNA expression study was performed using RT-PCR assay allowing first to discriminate full length CD20 (membrane CD20) from ΔCD20 transcripts. A more sensitive RT-PCR assay, using a specific primer spanning the splice fusion area was then used to detect specifically only the ΔCD20 transcript.

Results: RA patients had mild active disease (DAS28 score: 3.3 ± 0.3; CRP levels: 6.8 ± 1.9 mg/l). Number of circulating B cells per μl was not different between RA patients and controls (mean ± SEM, range: 184± 22, 18–437 *vs* 211± 27, 63–408, respectively). Among all the 23 RA samples, although full length CD20 expression was always detected, we were unable

to detect ΔCD20, even with the more sensitive RT-PCR assay permitting to identify the spliced transcript form.

Conclusion: The present study showed that, on the contrary of leukemic or lymphoma B cells, RA B-cells do not express ΔCD20, suggesting that this transcript may be a molecular marker of malignancies rather than of auto-immune diseases like RA. Study of RTX-non responders or -escaping RA patients may be relevant to know if ΔCD20 expression may be detected under the pressure of RTX therapy.

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1739

B Cell Function and Cytokine Secretion After B Cell Depletion Therapy in SLE and Rheumatoid Arthritis. Arumugam Palanichamy, James Roger, Wensheng Wang, Jennifer Barnard, Jamie Biear, Chungwen Wei, Iñaki Sanz and Jennifer H. Anolik. University of Rochester, Rochester, NY

Background/Purpose: The physiological complexity of B cell subsets and functions has been highlighted by the variable success of rituximab (anti-CD20) based B cell depletion therapy (BCDT) in multiple autoimmune diseases including systemic lupus (SLE) and rheumatoid arthritis (RA). We have previously described that a B cell reconstitution with transitional cells is associated with sustained clinical remission while a quick resurgence of memory cells portends a poor outcome. One critical question that remains to be addressed is whether the benefit of BCDT is directly mediated by the expanded transitional cells, a putative regulatory subset, or instead reflects the absence of effector B cells or a combination of both.

Methods: B cells from SLE (n=11) and RA patients (n11) were analyzed by multi-color flow cytometry at various times after BCDT or in untreated subjects. An additional 10 subjects were studied at baseline, 2 month, 4 month, and q4 months after BCD. Expression of CXCR3, CD21, CD95, and anchor markers (IgD, CD19, CD27, CD38, CD24 and live/dead/T-cell exclusions) were used to subset memory B cells. Expression of MitoTracker Green extrusion, CD10, IgM, CD23 and anchor markers were used to subset transitional B cells. Cytokine expression in distinct B cell subsets was examined by flow cytometry after 48 hours CpG stimulation (5 ug/ml) and 5 hr culture with PMA and ionomycin (both 500 ng/ml).

Results: Early after BCD (<6 month) residual B cells were detectable and consisted predominantly of memory B cell populations: switched CD27+IgD- memory, CD27-IgD- memory, and plasma cells. The residual memory B cells displayed a high fraction of CD95+ and CD21- compared to pre-depletion suggesting some resistance of these activated populations to anti-CD20. In patients who had previously received rituximab but were being re-treated because of disease relapse, memory B cells were overwhelmingly CD95+, CD21-, suggesting that disease is driven by these effector memory populations. In previously rituximab naïve patients, reconstitution occurred with a variable distribution of transitional, naïve, and memory B cells, with a memory dominant profile more common in SLE and associated with a less robust clinical response. In memory vs. transitional dominant patients, there was a significantly higher fraction of activated, effector B cell populations (CD21– 51.2+21.9 vs. 12.5+7.6%; CD24– 58.5+9.7 vs. 20.5+15.9%, CD95+ 76.9+24.4 vs. 17.6+7.2%, CXCR3+ 17.2+4.8 vs. 6.6+4.5%, $p<0.05$). In RA the predominant IL10 producing B cell populations were naïve/transitional, but the unswitched memory had the highest relative content of IL10+ cells. In untreated SLE IL10 production shifted to include more memory B cell populations, whereas the naïve/transitional compartment became the predominant IL10 producer after BCD. IL10 production in the unswitched memory compartment also increased after BCD in this group (4.7+3.3 vs. 1.2+1.1, $p=0.03$).

Conclusion: Our results support the hypothesis that the clinical and immunological outcome of BCDT depends on the relative balance of protective and pathogenic B cell subsets established after BCD and upon B cell repopulation.

1740

Rituximab for the Treatment of IgG4-Related Disease:Lessons From Ten Consecutive Patients. Arezou Khosroshahi, Mollie Carruthers, Vikram Deshpande, Sebastian Unizony, Donald B. Bloch and John H. Stone. Massachusetts General Hospital, Boston, MA

Background/Purpose: Patients with IgG4-related disease (IgG4-RD) share histopathological features that are similar across affected organs and typically have elevated serum concentrations of IgG4. IgG4-RD patients frequently require prolonged treatment with glucocorticoids. Traditional disease-modifying antirheumatic drugs (DMARDs) are generally ineffective. We assessed the clinical and serologic responses to B lymphocyte depletion therapy in ten consecutive patients with glucocorticoid- and DMARD-refractory IgG4-RD.

Methods: Ten patients with IgG4-RD were treated with rituximab (RTX) (1000 mg times two, 15 days apart). Clinical improvement was assessed by monitoring patients' ability to taper prednisone to discontinuation and to stop DMARDs; by serial measurements of total IgG and IgG subclasses; and by follow-up radiologic assessments guided by the patients' particular patterns of organ involvement. We also applied a prototype of the IgG4-RD Disease Activity Index and Flare Tool to these cases retrospectively.

Results: The patients' organ involvement included the pancreas, biliary tree, aorta, salivary glands (submandibular and parotid), lacrimal glands, lymph nodes, thyroid gland, and retroperitoneum. Nine of the 10 patients demonstrated striking clinical improvement within one month of starting RTX. One patient with advanced thyroid fibrosis associated with Riedel's thyroiditis and a history of disease in multiple other organ systems did not have improvement in her thyroid gland but her disease did not progress to involve new organs. All ten patients discontinued prednisone and DMARDs following RTX therapy. Significant decreases in IgG concentrations were observed for the IgG4 subclass only (Figure). Four patients were re-treated with RTX after 6 months because of either symptom recurrence and increasing IgG4 concentration at the time of peripheral B cell reconstitution (n = 2) or because of physician discretion (n=2). Repeated courses of RTX maintained their effectiveness, and serial RTX courses led to steadily lower IgG4 concentrations. Serum IgG4 concentrations appeared to be a reliable surrogate of disease activity for patients in whom they were increased at baseline.

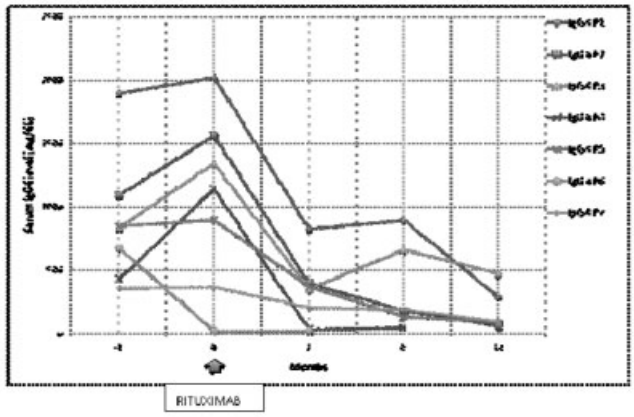

Figure. The graph is showing the serum IgG4 concentrations of 7 out of 10 patients with IgG4-RD who had elevated serum IgG4 levels at baseline 2 month prior to rituximab treatment to 12 months after treatment.

Conclusion: Treatment of IgG4-RD with RTX led to prompt clinical and serologic improvement in refractory IgG4-RD in all patients with active inflammation. Serial treatments with RTX may lead to progressive declines in serum IgG4 concentrations and better disease control. Serum IgG4 concentrations may remain low and clinical disease activity may remain quiescent even after B cell reconstitution in a significant proportion of patients.

1741

Antibody Secreting Cells Arising After Vaccination From Anti-Cardiolipin Positive Individuals Can Produce Antibodies Which Are Bi-Specific and Bind to Both Cardiolipin and the Vaccinating Antigen. Kenneth Smith[1], Jennifer Muther[1], Angie Duke[1], Emily McKee[1], Patrick C. Wilson[2] and Judith A. James[3]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Chicago, Chicago, IL, [3]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: While it is well known that certain bacterial infections may cause the presence of serum anti-cardiolipin antibodies in healthy controls, no one has previously dissected the presence of such antibodies on a 'per-antibody' basis. To this end, we have made antibodies from a serum anti-cardiolipin (aCl) positive, but otherwise healthy individual

after three separate vaccinations. These antibodies bind to the vaccinating agent as expected, however, several also bind to cardiolipin.

Methods: The OMRF Human Antibody Core Facility has developed a technology that allows us to make fully human monoclonal antibodies from any antigen currently approved as a vaccination in humans. This allows us to make large numbers of fully human full-length monoclonal antibodies which are highly specific to the vaccine antigen(s). This technology is based on the discovery of a population of B cells (ASCs), which arise 7 days after vaccination and produce antibody that is specific for the vaccine antigen. These cells can be sorted and their antibody genes cloned to express the antigen-specific antibody from each ASC.

Results: From this donor, we have characterized 49 antibodies to *Streptococcus pneumoniae* polysaccharides after vaccination with Pneumovax®23, 11 antibodies to S-OIV after vaccination with the monovalent swine flu vaccine, and 9 antibodies to VZV after vaccination with Zostavax®. Of the S. pneumoniae antibodies, two clonally related antibodies to cell wall polysaccharide, as well as an impressive clonal family of 7 antibodies to serotype 18C bind to cardiolipin (18%). Only one S-OIV antibody also binds to cardiolipin (9%), however it has a remarkable affinity of 8×10^{-9}M. Three VZV antibodies also bind to cardiolipin (33%).

All of the cardiolipin positive antibodies from this donor were also characterized using β2-GPI and qualitative ELISAs to other APS antigens (AESKU APS-Profil-GM kit). Although this donor's serum is not positive for β2-GPI antibodies, two VZV antibodies are weakly positive for β2-GPI. One of these two antibodies also showed clear binding to phosphatidylethanolamine.

Conclusion: The ability to analyze the immune response of a serum aCl positive individual on a 'per-antibody' basis indicates that it is possible in "healthy" and likely autoimmune patients for antigen specific antibodies to also bind to auto-antigen and such antibodies may arise after immune responses to a variety of immunogens.

1742

Epratuzumab Inhibits Upstream B Cell Receptor Signaling and Modulates Ca^{2+} Flux Upon Activation. N. Sieger[1], K. Reiter[1], H.E. Mei[1], T. Shock[2], C. Daridon[1] and T. Dörner[1]. [1]Charité University Medicine Berlin, Berlin, Germany, [2]UCB, Slough, United Kingdom

Background/Purpose: CD22 is a surface molecule exclusively expressed on B lymphocytes that is involved in adhesion and B cell receptor (BCR) signaling. By recruiting a tyrosine phosphatase to its intracellular tail, it acts as an inhibitory co-receptor of the BCR via dephosphorylation of signaling molecules such as spleen tyrosine kinase (Syk). Phosphorylation of Syk is essential upon BCR engagement and is upstream of BCR-triggered Ca^{2+} flux. Epratuzumab, a humanized anti-CD22 monoclonal antibody, is currently being investigated in phase III clinical trials in systemic lupus erythematosus (SLE) patients. Although recent data show that the antibody affects B cell proliferation[1] as well as the expression of adhesion molecules and B cell migration,[2] its potential impact on intracellular signaling events has not been delineated. Therefore, the current study investigated the influence of epratuzumab on downstream kinases and BCR-induced Ca^{2+} flux in human B cells.

Methods: The *in vitro* effects of epratuzumab on BCR-induced Ca^{2+} signaling were evaluated by Ca^{2+} flux assays. Purified human B cells were pre-incubated with $F(ab')_2$-epratuzumab or medium alone for 60 min and were subsequently stimulated with anti-$F(ab')_2$ IgM and IgG. Intracellular Ca^{2+} concentrations were monitored by flow cytometry in B cells pre-loaded with Indo-1AM for a period of 10 min after activation. Additionally, the influence of epratuzumab on the phosphorylation of the BCR signaling molecules Syk and PLC-γ2 linked to Ca^{2+} flux was studied *in vitro* by flow cytometry.

Results: BCR activation induced an initial peak of Ca^{2+} flux within the first 10 s. Pre-incubation with epratuzumab moderately increased this initial peak. Notably, after the initial period, pre-incubation with epratuzumab strongly reduced Ca^{2+} flux in B cells, compared with controls treated with medium alone, which exhibited increased Ca^{2+}flux during BCR triggering over 10 min. At corresponding time points used to monitor Ca^{2+} flux, the phosphorylation status of Syk and PLC-g2 after BCR stimulation was measured. Pre-treatment with epratuzumab led to substantial reductions in the phosphorylation of Syk and PLC-g2 8 min after BCR stimulation, compared with controls. These differences in Syk and PLC-g2 were not found during the initial Ca^{2+}-peak at 10 s or after 1 min, consistent with the notion that they were not yet fully activated. Notably, effects on the phosphorylation of Syk and PLC-g2 were observed in $CD27^-$ naive and $CD27^+$ memory B cells.

Conclusion: These data indicate that epratuzumab exerts inhibitory effects on BCR signaling by reducing Ca^{2+} flux and Syk and PLC-g2 phosphorylation after BCR engagement. They are therefore consistent with the concept that targeting CD22 may reduce the characteristic B cell hyper-reactivity in SLE.

References:

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1743

PTPN22 Risk Allele Interferes with the Removal of Developing Autoreactive B Cells in Humans. David Saadoun[1], Laurence Menard[2], Isabelle Isnardi[2], Yen-shing Ng[3], Greta Meyers[2], Clara Abraham[4], Roja Moyaghedi[5], Jane Buckner[6], Peter K. Gregersen[7] and Eric Meffre[8]. [1]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06511, USA;, New haven, [3]Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06511, USA;, New Haven, [4]Department of Medicine, Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT 06509, USA,, New Haven, [5]Department of Pediatrics, Weill Medical College of Cornell University, New York, NY 10021, USA,, New York, [6]Translational Research Program, Benaroya Research Institute, Seattle, WA 98101, USA,, Seattle, [7]Feinstein Institute Medical Reschearch, Manhasset, NY, [8]Yale University School of Medicine, New Haven, CT

Background/Purpose: Protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) gene polymorphisms associate with many autoimmune diseases; the major risk allele encodes an R620W amino acid change that alters B cell receptor (BCR) signaling involved in the regulation of central B cell tolerance.

Methods: To assess whether the *PTPN22* riskallele affects the removal of developing autoreactive B cells, we tested by ELISA the reactivity of recombinant antibodies isolated from single B cells from asymptomatic healthy individuals carrying one or two *PTPN22* risk allele(s).

Results: We found that new emigrant/transitional and mature naive B cells from *PTPN22* risk allele carriers contained high frequencies of autoreactive clones compared to non-carrier donors, revealing defective central and peripheral B cell tolerance checkpoints. Hence, a single *PTPN22* risk allele has a dominant effect on altering autoreactive B cell counterselection before any onset of autoimmunity. In addition, gene array experiments analyzing mature naïve B cells displaying *PTPN22* risk allele(s) revealed that the association strength of *PTPN22* for autoimmunity may not only be due to the impaired removal of autoreactive B cells but also to the upregulation of genes such as *CD40, TRAF1* and *IRF5*, which promote B cell activation and have been identified as susceptibility genes associated with autoimmune diseases.

Conclusion: We demonstrated that the *PTPN22* risk allele interferes with the removal of developing autoreactive B cells and allows the accumulation of large numbers of self-reactive mature naïve B cells in the periphery.

1744

Syk Inhibition with Fostamatinib Leads to Transitional B Lymphocyte Depletion. Chungwen Wei, Paul M. Barr, Julia Schaefer-Cutillo, John Jung, James Roger, Jennifer L. Kelly, Alex Rosenberg, Jonathan W. Friedberg and Iñaki Sanz. University of Rochester, Rochester, NY

Background/Purpose: The protein tyrosine kinase syk (spleen tyrosine kinase) is a critical component of B cell receptor (BCR) signaling, and plays an important role in both the maturation and survival of the B cell lineage. Syk deficient murine models demonstrate a developmental block at the transitional B cell stage and an absence of B cells in peripheral lymphoid organs. Promising results have been generated using an orally administered small molecule inhibitor of syk, fostamatinib, in the treatment of lymphoid malignancies as well as autoimmune diseases such as rheumatoid arthritis and immune thrombocytopenic purpura. However, the mechanism of action of syk inhibition in alleviating the symptoms of autoimmune diseases and its effects on B cell homeostasis remains to be elucidated.

Methods: Patients were obtained from a prospective phase 1/2 clinical trial with support from Rigel Pharmaceuticals, and blood samples were collected at baseline, 1 month and 2 months after treatment with fostamatinib. PBMCs from eleven patients, all with relapsed or refractory B-cell lymphoid malignancies [7 diffuse large B cell lymphoma (DLBCL), 2 follicular lymphoma (FL), 2 mantle cell lymphoma (MCL)], were analyzed by

multi-color flow cytometry. Mitotracker Green extrusion and the staining of CD19, IgD, CD27, CD38, CD24 as well as CD3/live/dead exclusion allow the identification of B cell subsets defined by the expression of IgD and CD27 and the fine discrimination of naïve and transitional B cells. P-values were calculated using the non-parametric Wilcoxon signed rank test for paired samples. To account for the 8 independent hypotheses tested, a Bonferroni adjusted threshold was used for statistical significance ($p<0.006$).

Results: In these patients, $CD19^+$ B cells remained unaffected after 2 months of treatment with fostamatinib. In addition, the fractions of the four core subsets defined by IgD/CD27 within the B cell population remained relatively stable. However, the early transitional (T1/T2) cells were rapidly depleted within the first month of treatment ($p=0.0029$) and continued to decline over the second month ($p=0.0039$). There was also a significant but lesser magnitude decrease in the late transitional (T3) cells at 2 months ($p=0.02$), with a concomitant increase in the naïve population ($p=0.0059$). The decrease in the T1/T2 population was also observed when absolute cell counts for the B cell subsets were calculated ($p=0.0039$). No association was identified between infections or clinical responses and the degree of transitional B cell depletion.

Conclusion: We demonstrate that short-term use of fostamatinib impairs B lymphocyte development at the transitional B cell stage without affecting mature B cell populations. These results provide mechanistic insights of action of syk inhibition in autoimmune diseases. Further, it suggests that prolonged administration may impair development of mature B cells and ultimately functioning of the humoral immune system. As development of syk inhibitors and other agents targeting molecules downstream of the B cell receptor proceeds, careful monitoring for infectious complications is warranted.

1745

Carbamoylation of Vimentin in Patients with Rheumatoid Arthritis: Identification of a Novel Protein Modification with a Possible Link to Disease Pathogenesis. Holger Bang[1], Karl Egerer[2], Anette Krämer[1], Eugen Feist[2] and Gerd R. Burmester[2]. [1]Orgentec Diagnostika GmbH, Mainz, Germany, [2]Charité - Universitätsmedizin Berlin, Berlin, Germany

Background/Purpose: The pathogenesis of rheumatoid arthritis (RA) is believed to result from a multistep process, in which - based on a particular genetic background—environmental triggers initiate or modify specific immune reactions including anti-citrullinated peptide/protein antibodies (ACPA) generation. Especially, smoking has been identified as an important environmental factor potentially leading to protein modification resulting in an autoimmune response in the setting of a disturbed immune system. The aim of the current study was to investigate the possible role of a newly identified modification process, the carbamoylation of vimentin, in causing autoantibody production and immune responses in patients and animal models.

Methods: Human vimentin was carbamoylated and/or citrullinated by non-enzymatic and enzymatic posttranslational modifications. Corresponding ELISA assays were established and sera from human healthy individuals, RA patients in different stages of disease and with different DMARD treatments and disease controls (systemic autoimmune diseases such as SLE and Sjören′ syndrome) were analyzed. Rabbits were immunized with carbamoylated vimentin and mutated citrullinated vimentin (MCV), and antisera were tested for binding to cyclic citrullinated peptides (CCP), vimentin and its modified analogs. Induction of rheumatoid factor in treated animals was characterized as well. Cell models were used to identify pathways for induction of modified vimentin under inflammatory conditions.

Results: Carbamoylated vimentin (carbVim) shows a > 90% homocitrulline content in double mass spectrometry and sequencing analysis. Rabbits immunized with carbVim produced high affinity antibodies against carbVim and, to a lesser extent, against MCV. These antisera also bound human IgG and to a low extent immunoglobulin from other animal species. In 110 RA patients, sensitivities of 86,8 % and 69,2 % were calculated for the anti-MCV and anti-carbVim assays, respectively. Sera from healthy persons and disease control groups showed a comparable specificity for both assays (anti-MCV 97% and anti-carbVim 91%) and none had anti-vimentin abs. A significant correlation of ACPA positivity lacking rheumatoid factor with presence of anti-carbVim abs was documented in early RA patients (91 %). In cell models, modified vimentin was generated among inflammatory (TNF or IFN) or environment stress (hydrogen peroxide) conditions and cross react with abs from RA-patients or immunized animals.

Conclusion: Environmental triggers such as smoking together with inflammatory conditions involving destructive enzymes may result in carbamoylation of vimentin with a possible impact on its function as stress fiber, cell homing or adhesion protein. Anti-homocitrulline responses develop in the early stages of RA, where carbamoylated vimentin represents a major target of autoantibodies in RA patients. These results also suggest a critical reevaluation of the polyclonal immune response of RA patients, so far described as exclusively citrulline specific and may provide diagnostic options for the early detection of patients even before clinical onset of RA.

1746

Early Rheumatoid Arthritis (ERA) Has Lower Levels of Plasmablasts and Memory B Cells Compared to Long-Standing Rheumatoid Arthritis (LSRA) and Responds to Conventional Therapy with a Normalization of B Cell Subsets Abnormalities. Anna Laura Fedele, Barbara Tolusso, Silvia L. Bosello, Silvia Canestri, Elisa Gremese and Gianfranco Ferraccioli. Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: B cells have been shown to be important players in RA chronicity and B cell depletion has been shown to be effective in RF seropositive patients. The aim of the study was to evaluate B cells subpopulations distribution in ERA and LSRA patients and their possible association with clinical or immunological data at baseline or with response to conventional therapy (ERA).

Methods: 53 ERA (88.7% females; mean age 53.2±15.1 years; 62% anti-CCP positive) and 49 LSRA, along with 30 healthy controls were studied. Baseline clinical and immunological characteristics and inflammatory status were assessed. Peripheral blood samples were analyzed by flow cytometry for the distribution of circulating B cell subsets by staining with surface markers CD19, CD45, CD38, CD27 and IgD and intracellular marker ZAP70. Plasma levels of IL-6 and BAFF were also determined with ELISAs. 22 ERA patients were followed for 6 months: they were treated with MTX (n=14) and MTX + TNF blockers (n=8).

Results: ERA patients showed an higher percentage of Bm2+Bm2' cells (48.8±20.9%) compared to LSRA patients (33.8±17.8%, *p=0.001*) and a lower percentage of eBm5 (10.0±7.3%) compared to LSRA (14.1±8.6%, *p=0.004*) and controls (16.0±7.1%, *p<0.001*). The percentage of CD19+/IgD-CD27- cells (7.5±4.8%) and CD19+/CD38+CD27+ cells (3.0±4.4%) was lower in ERA compared to LRSA (13.7±7.8%, *p<0.001*; 8.2±5.2%, *p<0.001*, respectively) and controls (16.2±9.1%, *p<0.001*; 8.0±3.5%, *p<0.001*, respectively). The percentage of CD19+/ZAP70+ cells (6.0±7.1%) was higher in ERA patients compared with controls (2.2±1.4%, *p=0.01*), while no difference was seen between ERA and LSRA. There were no differences in the distribution of B cell subpopulations between patients RF and anti-CCP positive and negative. ERA patients with baseline high DAS (>3.7) showed an higher percentage of CD19+/CD27+CD38+ cells compared to subjects with moderate DAS (*p=0.01*). The percentage of CD19+/ZAP70+ cells was higher in ERA patients with baseline plasma levels of BAFF>780 pg/ml (mean±2 SD of controls) (8.0±8.5%) compared to patients with levels of BAFF <780 pg/ml (3.0±2.3%, *p=0.08*). Plasma levels of BAFF correlated positively with percentage of CD19+/ZAP70+ cells (r=0.41, *p=0.002*) and of CD19+/IgD-CD27- cells (r=0.26, *p=0.05*). In ERA patients followed for 6 months, we observed DAS falling from 3.4 to 1.6 (*p<0.001*), an increased percentage of Bm1 cells (T0=21.4±17.8% vs T6=32.5±19.2%, *p=0.005*) and a fall in the percentage of eBm5 (T0=9.9±3.8% vs T6=6.5±4.7%, *p=0.01*) and of CD19+/ZAP70+ cells (T0=6.7±5.6% vs T6=3.8±3.1%, *p=0.02*), irrespectively of the type of therapy administered.

Conclusion: ERA differs from LSRA for higher levels of naive preswitch B cells, lower levels of memory B cells and plasmablasts. After six months of conventional treatment, a fall of memory B cells and ZAP70+ B cells and an increase of naïve B cells were observed. These results suggest that changing the inflammatory milieu in the early phases of the disease, leads to substantial changes in B cell subsets. Further studies are needed to define the molecular events linked to these effects. Early RA represents the best opportunity to normalize the immunological setting.

1747

Identification of Autoantibody Profiles by Monitoring Autoantibody Biomarkers in Rheumatoid Arthritis with Microarray Surface Plasmon Resonance Imaging. Joyce J.B.C. Van Beers[1], Angelique M.C. Segbers-Lokate[1], Wilma T.M. Vree Egberts[1], Richard B.M. Schasfoort[2] and Ger J.M. Pruijn[1]. [1]Radboud University Nijmegen, Nijmegen, Netherlands, [2]University of Twente and IBIS Technologies BV, Enschede, Netherlands

Background/Purpose: Autoantibodies against citrullinated proteins (ACPA) are specifically found in approximately 75% of rheumatoid arthritis (RA) patients. Citrullination is the post-translational conversion

of peptidylarginine into peptidylcitrulline, which is catalyzed by peptidylarginine deiminase (PAD) in a calcium-dependent manner. Several citrullinated antigens have been identified in the inflamed joints of RA patients. These include fibrinogen, alpha-enolase, vimentin and collagen type II. Accumulating evidence suggests a role of citrullinated proteins and ACPA in the pathophysiology of RA. The results of many studies indicate that the ACPA response is highly heterogeneous with diverse patterns of reactivity to distinct citrullinated epitopes. This study aimed to identify clinically meaningful ACPA profiles in RA patients using a microarray containing different citrullinated peptides in combination with surface plasmon resonance imaging (*i*SPR).

Methods: Several pairs of synthetic peptides (citrullinated and the corresponding non-citrullinated control) derived from known ACPA targets (e.g. fibrinogen, alpha-enolase, vimentin) as well as peptides isolated from synthetic citrullinated peptide libraries were used to generate ACPA target arrays. ACPA in RA patient sera were monitored by *i*SPR, which allows the simultaneous detection of autoantibody-peptide interactions in real-time. The present study was started using a 24-spot microarray and currently peptides are spotted using a continuous flow microspotter resulting in a 48-spot microarray.

Results: Using the 24-spot microarray, a total of 94 RA and 46 control sera were analyzed. The results confirmed the heterogeneous nature of ACPA in RA sera. RA patients displayed different patterns of co-occurrence of autoantibodies directed to distinct citrullinated peptides. The recognition of one peptide was very specific for RA and was observed in 62% of the anti-CCP2 positive RA patients. No reactivity was observed in the anti-CCP2 negative patients and a weak reactivity (2%) was observed in control patients. Another peptide showed reactivity in 68% of the RA patients, both anti-CCP2 positive (74%) as anti-CCP2 negative (54%) patients, whereas patients with other autoimmune diseases showed far less reactivity (13%).The median number of citrullinated peptides recognized by anti-CCP2 positive RA patients (4) was significantly higher than that of anti-CCP2 negative RA patients (1) and disease controls (1). The use of continuous flow microspotting instead of non-contact spotting is being optimized to increase the array size and to improve the quality and reproducibility of the microarrays.

Conclusion: Using microarray-iSPR we have shown that RA sera recognize various citrullinated peptides more frequently than other autoimmune disease sera. Sera from different RA patients frequently recognize different citrullinated peptides. Our data are consistent with the existence of different ACPA profiles that may have diagnostic and/or prognostic value. Microarray-*i*SPR represents a suitable system for multiplex autoantibody monitoring and allows the identification ACPA profiles.

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Development of a High-Throughput, Multiplex Assay for Profiling the Autoantibody Fine Specificity in Rheumatoid Arthritis. Xiaoyan Zhao[1], P. Scott Eastman[1], Ferhan Qureshi[1], William C. Manning[1], William Robinson[2] and Lyndal K. Hesterberg[1]. [1]Crescendo Bioscience, Inc., South San Francisco, CA, [2]Stanford Univ School of Med, Stanford, CA

Background/Purpose: Rheumatoid Arthritis (RA) is an aggressive autoimmune disease that progressively destroys affected joints with frequent systemic complications. Production of autoantibodies, especially those against citrullinated proteins and peptides, is a hallmark of RA. The causal relationship between the development of autoantibodies and radiographic joint damage to this point remains unclear. To better understand this relationship, we developed autoantibody assays in a multiplex format against a panel of common and novel RA epitopes and applied the assays for profiling the fine specificity of these autoantibodies in RA.

Methods: Individual serum samples from 35 RA patients with different disease activities were evaluated for the presence of autoantibodies. Anti-cyclic citrullinated peptide (CCP) reactivity and rheumatoid factor (RF) status were assessed with commercial kits from Euro Diagnostica (CCP 2) and TheraTest Labs (RF). The reactivity of a panel of peptides derived from multiple proteins including both well known and novel antigens was also evaluated. Nine peptides were printed in a 3×3 grid on the bottom of a 96-well plate (Quansys Bioscience) and probed with RA patient samples. HRP-conjugated secondary antibody against human IgG, IgM or IgA was used to measure autoantibodies to specific peptides in a chemiluminescent format.

Results: The levels of anti-CCP antibodies ranged from >5,000 to below the cutoff (<25 arbitrary units) for CCP and from ~600 to 3 units for RF-IgA, suggesting a range of disease. Not surprisingly, levels of autoantibodies, when detected by anti-human IgG, reflected anti-CCP levels, predominantly to citrullinated fibrinogen and citrullinated filaggrin peptides. However, a wide range of anti-IgM/A responses were observed regardless of whether anti-CCP levels were high, intermediate or low. Interestingly, when anti-human IgA or IgM was used as detection, CCP negative and low CCP RA subjects frequently demonstrated strong positive reactivity to epitopes derived from citrullinated apoliporotein, citrullinated biglycan, native histone and/or native fibromodulin. While several of the IgM/A peptide reactivities overlapped with the IgG, in many instances the IgM and/or the IgA profiles demonstrated unique response patterns.

Conclusion: A high-throughput, multiplex assay has been developed to investigate the fine specificity of autoantibody reactivity against a broad variety of RA antigens including both citrullinated and native peptides. While anti-human IgG profiles reflected CCP levels, diverse levels of response were observed with anti-IgM and/or anti-IgA, including at low and intermediate CCP levels. Most studies to date have employed the CCP 2 assay, which uses a mixture of peptides, with mixed results. We observed that profiles of individual peptides may be different with different immunoglobulin isotypes. Thus evaluation of individual peptides in the context of immunoglobulin subtypes may provide insight into disease progression.

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Anti-hnRNP Autoantibodies Detected in Inflammatory Rheumatic Diseases in Use to Close the Sensitivity gap left by Rheumatoid Factor and Anti CCP in Early Rheumatoid Arthritis. Bianka Marklein[1], Zoltan Konthur[2], Gerd-Rüdiger Burmester[3] and Karl Skriner[1]. [1]Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Max Planck Institute for Molecular Genetics, Berlin, Germany, [3]Charité - University Medicine Berlin, Berlin, Germany

Background/Purpose: Autoantigens are produced in bacteria ex-pressed purified using His-tag and Cm-sepharose under native and denaturated conditions. Bacterially expressed recombinant hnRNPs proteins were used in Elisa for confirming the data obtained by macroarray and immunoblotting. Anti-hnRNP-A/B and hnRNP D proteins were detected in a newly developed Elisa with patient sera and sera from animal model of SLE and RA

Methods: Autoantigens are produced in bacteria ex-pressed purified using His-tag and Cm-sepharose under native and denaturated conditions. Bacterially expressed recombinant hnRNPs proteins were used in Elisa for confirming the data obtained by macroarray and immunoblotting. Anti-hnRNP-A/B and hnRNP D proteins were detected in a newly developed Elisa with patient sera and sera from animal model of SLE and RA.

Results: Using a combination of three hnRNPs A2/D/DL, 76% of RA, 84% of SLE sera and 87% SKG mice which spontaneously develop chronic autoimmune arthritis, can be detected. Moreover hnRNP A2/A3/D/DL identified epitopes as well as identified citrullinated peptides (deduced citrullinated peptides thereof) were used to identify patterns associated with disease severity. No crossreactivity could be detected between the affinity purified anti-hnRNPDL and the highly related hnRNPD. A unique sequenz only found in hnRNP DL between aminoacid 81–120 was identified as indistinguishable for autoantibody binding. With citrullinated peptides out of a mutated form of hnRNPA3 and hnRNPA2/D/DL, 94 % out of 130 early RA sera can be identified but only in <10% of osteoarthritis and healthy control patients. With a combination of citrullinated forms of three hnRNPs (A2, D, DL) 98 % of the sera were tested positive in a cohort of 92 early RA patients (<12month). The hnRNP auoantibody response is dependent on Mod88, Tir8 and both TLR 7 and TLR9 costimulation tested with sera from TLR7, TLR9 deficient and double-deficient mice with an MRL-lpr/lpr background.

Conclusion: The hnRNP antibody response is Myd88, Toll 7 and 9 dependent generated. A combination of hnRNPs (A3/A2/DL/D) can be used to predict disease severity and partially close the sensitivity gap left by rheumatoid factor and anti CCP antibodies in early RA patients.

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Substantial Influence of Rheumatoid Factor Positivity On the Peripheral Memory B Cells and Its Modulation by TNF Inhibition In Rheumatoid Arthritis. Petra Roll[1], Khalid Muhammad[1], Mathias Schumann[1], Stefan Kleinert[2] and Hans-Peter Tony[1]. [1]University of Würzburg, Würzburg, Germany, [2]Rheumatology, University of Würzburg, Würzburg, Germany

Background/Purpose: The role of B cells has been appreciated with the advent of B cell targeted therapies in patients with rheumatoid arthritis. However, alterations of peripheral B cell subsets have been described also under TNF inhibition. In this study, we focused on the influence of

rheumatoid factor positivity on the anti-TNF induced modulation of the peripheral B cell compartment.

Methods: Twenty six RA patients with inadequate response to methotrexate were included in a prospective study of weekly etanercept treatment. Immunphenotyping was performed at baseline, week 12 and 24.

Results: At baseline, rheumatoid factor (RF) negative patients had a significant higher percentage of overall CD27+ memory B cells compared to healthy controls (n=21) and RF positive patients. In detail, RF negative patients had 68.9% (25.6–86.6%) CD27+ B cells vs. 31.3% (12.9–56.9%, p=0.01) in HC and 28.8% (19–73.3%, p=0.02) in RF positive patients respectively. Within the CD27+ B cells compartment particularly pre-switch (CD27+/IgD+) memory B cells were significantly increased to 29.8% (15.8–51.1%) in RF negative patients compared to 14.9% (4.1–27.3%, p=0.0012) in HC and 10.4% (6–25.2%, p=0.001) in RF positive patients, respectively. Interestingly, relative and absolute numbers of CD27+ memory B cells increased significantly during anti-TNF therapy only in RF negative patients. Relative numbers increased from 68.9% (25.6–86.6%) to 73% (31.3–75.8%) at week 24 (p=0.03). Absolute numbers of CD27+ memory B cells showed a significant increase from baseline 49.3/μl (31.5–125.1/μl) to 77.1/μl (63.6–174.3/μl) at week 24 (p=0.01).

Conclusion: Peripheral accumulation of memory B cells, particularly pre-switch memory B cells, was observed in RF negative patients. Anti-TNF therapy leads significantly to increased memory B cells only in RF negative patients suggesting the peripheral memory B cell compartment being more amenable to TNF inhibition in these patients.

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Dynamic Evolution of a Public Clonotypic Autoantibody Specific for Ro60: Perpetuating Humoral Autoimmunity Through Clonotypic Shift. Rhianna Lindop[1], Georgia Arentz[1], Tim, K. Chataway[2], Lauren A. Thurgood[1], Michael W. Jackson[1] and Tom P. Gordon[1]. [1]Flinders Medical Centre and Flinders University, Adelaide, Australia, [2]Flinders University, Adelaide, Australia

Background/Purpose: We have recently discovered a public Ro60-reactive clonotypic autoantibody specified by a unique V_H3–23/V_K3–20 chain pairing, by using positive epitope selection of human sera with anti-Ro/La responses and *de novo* sequencing of the purified autoantibody proteome (Lindop et al, Arthritis Rheum, in press). In the present longitudinal study, we use this unique clonotypic signature to trace the evolution of humoral autoimmunity directed against a member of the ENA family in human systemic autoimmunity.

Methods: Clonotypic V_H3–23/V_K3–20 IgGs specific for the immunodominant Ro60peg determinant (amino acids 193–236) were purified by epitope-specific affinity chromatography from serial serum samples of 5 patients with primary Sjögren's syndrome (ranges from 1 to 10 years apart). Direct variable (V)-region sequencing of heavy and light chains was performed by high-resolution *de novo* orbitrap mass spectrometric sequencing. Relative anti-Ro60peg binding affinities were compared by the KCSN elution method.

Results: Patient sera tested at each time point expressed a dominant Ro60peg-specific monoclonal IgG1 kappa species with a characteristic V_H3–23/V_K3–20 gene rearrangement signature, consistent with a common clonal origin for each patient. However, near full-length protein sequencing of serial samples from individual patients revealed that each clonotypic autoantibody, irrespective of the duration of disease, was subtly different from its predecessor, being specified by a unique pattern of somatic V-region mutations. Relative affinities of anti-Ro60peg clonotypic autoantibody variants were remarkably constant over years and even decades in the face of ongoing clonotypic shift, explained by preservation of key amino acid replacement mutations in the CDR regions critical for antibody binding.

Conclusion: Analysis of the autoantibody proteome has demonstrated for the first time a dynamic process of clonal evolution in systemic humoral autoimmunity, characterised by serial replacement of existing clonotypes with somatically mutated variants that presumably have a survival advantage over their predecessors. The selection pressures driving this process are not based solely on affinity for the autoepitope since the response reaches an affinity ceiling early in disease. The perpetual clonotypic shifts allow this secreted autoantibody to keep one step ahead of B-cell tolerogenic censuring mechanisms, resulting in life-long production of potentially pathogenic anti-Ro60 autoantibodies in patients with lupus and primary Sjögren's syndrome.

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APRIL and BAFF Levels After Rituximab Treatment in Patients with Primary Sjögren's Syndrome: A Placebo-Controlled Clinical Trial. Rodney Pollard, Wayel H. Abdulahad, Minke G. Huitema, Annie Visser, Jiska Meijer, Hans Burgerhof, Fred Spijkervet, Cees GM Kallenberg, Arjan Vissink, Frans Kroese and Hendrika Bootsma. University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by infiltrates of B- and T-cells in salivary and lacrimal glands, eventually leading to destruction of these glands. B-cell activating factor (BAFF) and proliferation-inducing ligand (APRIL), members of the tumor necrosis factor (TNF)-ligand family, are essential for development, maturation and survival of B-cells. To assess the effect of rituximab (anti-CD20) treatment on BAFF and APRIL levels in patients with pSS

Methods: In a randomised double-blinded placebo-controlled trial, pSS patients were treated on day 1 and 15 with either rituximab (n= 20) or placebo (n= 10). To minimise side effects (infusion reactions, serum sickness), all patients were pre-medicated with methylprednisolone and oral prednisone. Fresh blood samples were collected at various time points (before, 5, 12, 36 and 48 weeks following treatment). Age- and sex-matched blood samples were collected from healthy controls (n=10). In addition, paired incisional parotid biopsies were taken in 10 patients (5 rituximab, 5 placebo) before and 12 weeks after rituximab/placebo treatment. Percentages and numbers of B cell subsets were examined by four-color cytometry. BAFF and APRIL levels were assessed by enzyme-linked immunosorbent assay. BAFF expression in salivary glands was revealed by immunohistochemistry of parotid gland sections.

Results: Complete depletion of B-cells in serum was observed in the rituximab treated group, while B-cell levels remained unchanged after placebo treatment. B-cells reappeared in the rituximab treated group within 24 to 48 weeks after treatment. At baseline, both BAFF and APRIL serum levels were significantly ($p<0.01$) increased in pSS-patients in comparison to healthy controls. Strikingly, long-term elevated serum levels of BAFF (3.0–4.0 fold, $p<0.05$) were observed up to 36 weeks following rituximab treatment followed by a complete return to baseline levels by week 48. In contrast, BAFF serum levels were almost unchanged in the placebo group, except for a slight (0.5 fold, $p<0.05$) increase in BAFF levels at week 5 after treatment, likely due to methylprednisolone administration. APRIL levels in serum were hardly affected by the rituximab treatment, although there was a slight increase (0.25 fold, $p<0.05$) at 12 weeks after treatment, followed by a rapid return to baseline levels. Furthermore, at least 3 out of 5 pSS showed an increase in BAFF expression in parotid glands after rituximab treatment at tissue level.

Conclusion: These data show that both BAFF and APRIL levels are increased in serum of pSS patients, indicating that both cytokines could be involved in the pathogenesis of pSS, possibly by triggering the activation and differentiation of self-antigen-driven autoimmune B-cells. Importantly, we also demonstrate that there is a significant increase of BAFF in blood and salivary glands after rituximab therapy, whereas APRIL levels are almost unaffected by the treatment and remain elevated during the entire study period. This observation might be important for treatment strategies with biologicals affecting BAFF, T-cell co-stimulation and/or B-cell depletion. Extended data are in progress and will be presented at the ACR meeting.

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Expansion of Functionally Anergic Autoreactive CD21$^{-/Low}$ Marginal Zone B Cell Clones in Hepatitis C Virus Infection-Related Autoimmunity. Benjamin Terrier[1], Florence Joly[2], Philippe Benech[2], Michelle Rosenzwajg[3], Wassila Carpentier[4], Pascale Ghillani-Dalbin[5], David Klatzmann[3], Patrice Cacoub[5] and David Saadoun[6]. [1]Pitié-Salpêtrière Hospital, Paris, France, [2]Prediguard, Marseille, France, [3]Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Paris, France, [4]Plateforme génomique P3S, Paris, France, [5]CHU Pitié-Salpêtrière, Paris, France, [6]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France

Background/Purpose: Homeostasis of peripheral B cell subsets is disturbed during chronic hepatitis C virus (HCV) infection, leading to the

occurrence of autoimmunity and B-cell lymphoproliferation. However, mechanisms by which HCV causes lymphoproliferation remain controversial.

Methods: 38 patients with HCV-related mixed cryoglobulinemia vasculitis (MC) and 35 patients with HCV infection without MC, before the initiation of therapy, and 20 healthy donors (HD) were included in the present study. Phenotypic analysis of B cells from peripheral blood using flow cytometry and sequencing and repertoire analysis using single-cell analysis were performed. Functional analysis of B cells, assessing B cell activation, calcium flux, proliferation and survival, was performed. Microarray gene expression profile analysis of clonal B cells compared to conventional B cells was performed on Illumina whole human genome chips.

Results: We report on significant elevated proportion of clonal $CD21^{-/low}$ marginal zone (MZ) B cells in the peripheral blood of HCV patients that correlates with the presence of autoimmunity and lymphoproliferation (24.3% in HCV-MC patients vs. 5.4% in HCV patients vs. 1.8% in HD; $p<0,0001$ each). We found an increase use in autoreactive BCRs using V_H1–69 and V_H4–34 genes in $CD21^{-/low}$ MZ B cells. $CD21^{-/low}$ MZ B cells showed impaired calcium-mediated signaling, did not up-regulate activation markers, and did not proliferate in response to B-cell receptor triggering using F(ab′)2 anti-IgM. $CD21^{-/low}$ MZ B cells were also prone to dye faster than their $CD21^{+}$ counterparts, suggesting that these autoreactive B cells were anergic. $CD21^{-/low}$ MZ B cells, in contrast, remained responsive to TLR9 stimulation. Gene array analyses comparing $CD21^{-/low}$ MZ B cells and conventional $CD21^{+}$ MZ B cells revealed the critical role of EGR2 and Cbl-b in the induction of anergy.

Conclusion: HCV infected patients who display high frequencies of autoreactive and unresponsive $CD21^{-/low}$ MZ B cells are more susceptible to develop autoimmunity and/or lymphoproliferation. These cells remain in peripheral blood controlled by functional anergy instead of being eliminated. Chronic antigenic stimulation through TLR stimulation may create a favorable environment for breaking tolerance and activating these cells in order to produce cryoglobulinemia and cause vasculitis and/or lymphoma.

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The Sympathetic Neurotransmitter Norepinephrine Inhibits Proinflammatory IL-7-Receptor Alpha Positive B Cells in Arthritis. Georg Pongratz, Judith Anthofer, Madlen Melzer and Rainer H. Straub. University Hospital Regensburg, Regensburg, Germany

Background/Purpose: Recent data show higher concentrations of IL-7 in synovial fluid of patients with rheumatoid arthritis (RA) as compared to osteoarthritis (OA). Among other cells in the inflamed synovium, IL-7 receptor (IL-7R) is expressed on synovial B cells but the role of these cells in arthritis is unclear.

Methods: Collagen type II induced arthritis (CIA) in DBA1 mice. ELISA to determine specific anti-CII antibodies. Isolation of naïve splenic B cells and in vitro culture. FACS analysis to determine IL-7R+ cells and intracellular pSTAT5. Immunohistochemistry to show pSTAT5+ and IL-7R+ B cells in RA and OA synovial tissue.

Results: Activation of naïve splenic murine B cells with CD40L and IL-4 in vitro increases IL-7R expression. To determine the role of IL-7R+ B cells in arthritis we treated arthritic mice with B cells that have been activated and stimulated with IL-7. Mice treated with IL-7 stimulated B cells developed more severe arthritis than controls. We also show that human RA and OA tissue contains IL-7R+ and pSTAT5+ B cells in synovial tissue. We know from former experiments that norepinephrine treated B cells show anti-inflammatory potential in arthritis. Therefore, B cells were activated in the presence of norepinehphrine and then stimulated with IL-7. Treatment of mice with these B cells did not show different severity of arthritis as compared to controls. As possible explanation for this observation we show that proper IL-7R signaling via STAT5 is inhibited in B cells pretreated with norepinephrine.

Conclusion: Taken together, these data indicate that IL7R+ B cells have a proinflammatory role in arthritis, which can be inhibited by the sympathetic neurotransmitter norepinephrine via inhibition of IL-7R signaling.

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Arthritogenic T Cells Regulate the Homeostatic Expansion of Antigen-Specific B Cells, and These B Cells or Antibodies Are Essential for the Development of Arthritis. Katalin Kis-Toth[1], Marianna Radacs[2], Tamas Kobezda[3], Willem van Eden[4], Katalin Mikecz[3] and Tibor T. Glant[3]. [1]Boston, MA, [2]Szegedi Tudomany Egyetem: JGYPK, Szeged, Hungary, [3]Rush University Medical Center, Chicago, IL, [4]Utrecht,, Netherlands

Background/Purpose: The original goals of this study were to prove whether the arthritogenic epitope-specific T cell receptor transgenic (TCR-Tg) $CD4^{+}$ T cell can transfer arthritis, and if so, what other 'costimulatory' components (e.g., B cells or antibodies) can contribute to an earlier onset or more severe arthritis. Unexpectedly, these highly specific arthritogenic TCR-Tg $CD4^{+}$ T cells were unable to transfer the disease alone, but supported the reconstitution of arthritogenic proteoglycan (PG)-specific B cell homeostasis, which appeared to be critical for arthritis induction.

Methods: PG (arthritogenic epitope)-specific TCR-Tg mice were generated earlier and their basic functions tested both *in vitro* and *in vivo*. $CD4^{+}$ T cells were separated from spleen of wild-type (WT) and TCR-Tg BALB/c (arthritic or non-arthritic) mice using the Pan T Cell Isolation Kit and B Cell Isolation Kit for negative selection. The purity and viability of $CD3^{+}/CD4^{+}$ T cells and $CD19^{+}/B220^{+}$ B cells were at least 98%. $CD4^{+}$ T cells (5×10^{6} cells in 200 μl PBS) were injected intraperitoneally into syngeneic BALB/c^{SCID} mice without or with PG antigen (100 μg with the first transfer), followed by a second transfer of (i) T cells from arthritic or non-arthritic WT or TCR-Tg mice, (ii) B cells from naïve, non-arthritic or arthritic BALB/c mice, or (iii) with IgGs purified from sera of arthritic or naïve animals. Two transfers were given at 7–10-day intervals. In reciprocal experiments, (i-iii) were injected first, which was followed by purified $CD4^{+}$ T cells from naïve or arthritic WT or TCR-Tg mice. Mice were scored for arthritis, and sacrificed 21–24 days after the second transfer for characterization of T and B cell markers, antigen-specific T cell responses, serum auto-antibodies (Abs) and cytokines.

Results: Neither PG-specific T or B cells, nor anti-PG Abs alone were sufficient for arthritis induction. In contrast, purified $CD4^{+}$ T cells (>98% purity) from TCR-Tg mice, if injected together with arthritogenic epitope-containing PG, induced arthritis in recipient SCID mice, but the onset and severity seemed to be dependent on selective proliferation of PG-specific autoAb-producing B cells. To further analyze the critical role of autoAbs in the development of arthritis, T cell transfer was followed by transfers of autoAb-producing B cells or autoAbs. TCR-Tg $CD4^{+}$ T cells controlled a highly selective homeostatic proliferation of autoAb-producing B cells, which their presence was critical for disease induction.

Conclusion: Anti-PG autoAbs bound to cartilage surface and co-localized with complement C3, might thus activate the complement cascade. They might also react with either intact or citrullinated G1 domain of PG, a domain structure which contains 12 potential sites of citrullination, and the G1 domain of human PG (injected together with the first transfer) heavily citrullinated in an age-dependent manner in human cartilage. At this moment, it remains an open question whether the homeostatic anti-PG B cell proliferation has been controlled primarily by highly specific TCR-Tg $CD4^{+}$ T cells, or the citrullinated G1 domain injected together with the first cell transfer, or both.

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$FasL^{+}$ Regulatory B Cells Are Expanded by Interleukin-5 and Induce Apoptosis in $CD4^{+}$ T Cells Via Cell-Cell Contact and Secretion of $FasL^{+}$ Exosomes. Matthew W. Klinker. Brian Alzua, Tamra Reed, Campbell Shaw, David A. Fox and Steven K. Lundy, University of Michigan, Ann Arbor, MI

Background/Purpose: We previously identified a subset of B cells that express the apoptosis-inducing molecule Fas ligand (FasL). Since little is known about $FasL^{+}$ B cells, we sought to characterize their surface phenotype, identify potential growth factors, and demonstrate their ability to directly induce apoptosis in $CD4^{+}$ T cells.

Methods: $CD19^{+}FasL^{+}$ murine splenocytes were assayed for expression of B cell markers and cytokine receptors by flow cytometry. The effects of cytokines on the expansion of $FasL^{+}$ B cells were tested *in vitro*. To measure the apoptosis-inducing function of $FasL^{+}$ B cells, they were cultured with TCR-transgenic $CD4^{+}$ T cells and T cell apoptosis was assayed via Annexin-V staining. A panel of human B cell-derived lymphoblastoid cell lines (LCLs) from RA patients and healthy controls was tested for FasL expression by immunoblot. A bead-based flow cytometry assay was used to test LCL culture supernatants for the presence of $MHCII^{+}FasL^{+}$ exosomes, and the ability of these exosomes to induce apoptosis in $CD4^{+}$ T cells isolated from peripheral blood was tested. A similar technique was used to analyze B cell-derived $FasL^{+}$ exosomes among murine splenic exosomes.

Results: $FasL^{+}$ B cells have the surface phenotype $IgM^{high}CD21^{high}$ $CD23^{+}CD5^{+}CD1d^{high}$, similar to that of IL-10-producing marginal zone precursor (MZP) B cells. In addition, $FasL^{+}$ B cells expressed high levels of the IL-5 receptor and *in vitro* culture of splenic B cells with IL-5 induced expansion of $FasL^{+}$ B cells and secretion of IL-10. These IL-5-stimulated B cells induced apoptosis in TCR-transgenic $CD4^{+}$ splenocytes, and this effect was greatly increased in the presence of the relevant antigen. In studies of

human B cells, it was found that all LCLs constitutively expressed FasL and secreted MHCII$^+$FasL$^+$ exosomes. LCL-derived exosomes induced apoptosis in autologous CD4$^+$ T cells in the presence of a superantigen. Finally, we found IgM$^+$FasL$^+$ exosomes in murine spleen extracts, suggesting that B cells secrete FasL$^+$ exosomes *in vivo*.

Conclusion: These data demonstrate that B cells can induce apoptosis in CD4$^+$ T cells, both by direct cell-cell contact and through the secretion of FasL$^+$ exosomes. The apoptosis-inducing properties of exosomes could extend the range of tissue compartments susceptible to the immunosuppressive effects of regulatory B cells. The ability to experimentally expand FasL$^+$ B cells through generation of LCLs and culture with IL-5 has many therapeutic implications in the treatment of rheumatoid arthritis and other T cell-mediated autoimmune diseases.

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Translational Medicine of a Selective Inhibitor of Btk in Rheumatic Diseases: Pharmacology and Early Clinical Development. Erica Evans, Richland Tester. Sharon Aslanian, Prasoon Chaturvedi, Russell Karp, Matt Labenski, Hormoz Mazdiyasni, Mariana Nacht, Michael Sheets, Kathryn Stiede, Steve Witowski, Heather Lounsbury, Russ Petter, Juswinder Singh and William Westlin, Avila Therapeutics, Waltham, MA

Background/Purpose: Dysregulated B cell activation and function has been demonstrated to be a critical component of the disease process in rheumatoid arthritis. The activity of Bruton's tyrosine kinase (Btk) is required for activation of B lymphocytes through the B Cell Receptor (BCR) signaling network. Due to a highly restricted expression pattern in humans (B cells, myeloid cells, mast cells), Btk is an exceptional target for a novel RA therapeutic. AVL-292 is a highly selective, orally active small molecule inhibitor of Btk in clinical development. This presentation summarizes therapeutic activity of AVL-292, including efficacy in preclinical models of RA and the results of a unique translational Phase 1a study that establishes the relationship between dose level administered, plasma drug concentration, and Btk molecular target engagement.

Methods: An ELISA assay has been developed to quantitatively determine the degree of AVL-292-Btk occupancy. In vivo activity of AVL-292 was evaluated in several models of RA including Collagen-Induced Arthritis in DBA1 male mice. AVL-292 was administered to healthy adult subjects in a Phase 1 clinical trial to assess the safety, pharmacokinetics, and Btk target occupancy in a double-blind, placebo controlled, single ascending dose study.

Results: AVL-292 covalently bonds to Cys481 on Btk and potently inhibited Btk in vitro in biochemical ($IC_{50} < 0.5$nM) and cellular assays ($EC_{50} \sim 3$nM) including isolated human B cells. The extent of Btk target occupancy directly correlated with inhibition of Btk enzyme activity and substrate phosphorylation. AVL-292 was disease-modifying in animal models of RA with 75% inhibition of the clinical score at an oral dose of 3 mg/kg that correlated directly with 75% Btk target occupancy. Complete inhibition of disease correlated with complete target occupancy at 10 mg/kg. In healthy human subjects, AVL-292 was found to be safe and well tolerated following oral administration at dose levels ranging from 0.5–7.0 mg/kg. All subjects that received an oral dose of 1.0 mg/kg of AVL-292 achieved >80% Btk occupancy. Mean peak plasma levels (Cmax 365 ng/mL) of AVL-292 were rapidly achieved (Tmax median 40 min) at this dose level. By 8 hours, plasma levels of AVL-292 ranged from 2.9–8.1ng/mL, whereas Btk occupancy was sustained at >73% in all subjects. 5 of the 6 subjects administered AVL-292 at 2.0 mg/kg achieved complete Btk occupancy. Cmax plasma levels in this dose level cohort (542ng/mL) were achieved at a Tmax of 60 min post dose administration. Btk occupancy was sustained through 24 hours even after plasma levels of AVL-292 had declined demonstrating that covalent inhibition of Btk with AVL-292 enables continued activity without requiring persistence of circulating drug.

Conclusion: Using this unique translational medicine approach the relationship between dose, plasma AVL-292 concentrations, and Btk molecular target occupancy has been established in humans. AVL-292 covalently bonds to Btk in a selective and potent manner leading to sustained inhibition of Btk that has the potential to translate to substantial clinical benefit for patients with RA and other autoimmune diseases characterized by aberrant B cell activation.

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A Bruton's Tyrosine Kinase Inhibitor Prevents Antigen-Driven B Cell Activation *In Vivo*. Micah Benson[1], Varenka A. Rodriguez[1], Tatyana Andreyeva[1], Sean Keegan[1], John R. Springer[2], Mark E. Schnute[2], Kyri Dunussi-Joannopoulos[1], Cheryl L. Nickerson-Nutter[1], Andrew L. Rankin[1], Melanie Ruzek[1] and John Douhan III[1]. [1]Pfizer, Cambridge, MA, [2]Pfizer, Inc, Cambridge, MA

Background/Purpose: Therapeutic targeting of B cells has proven effective for a multitude of human autoimmune indications. Most investigative and approved therapies are injected monoclonal antibodies that either deplete or inactivate B cells by targeting B cell surface moieties directly or by inactivating B cell modulating cytokines, with orally-available B cell modulating treatments currently lacking. Proximal to the intracellular signaling components of the B cell receptor (BCR) resides a network of adaptor proteins and protein tyrosine kinases that include the Tec family kinase Bruton's Tyrosine Kinase (BTK). The kinase activity of BTK is critical for transmitting signals received through the BCR to downstream signaling pathways that direct B cell activation. In this study, we assessed the ability of an orally-accessible BTK inhibitor to prevent antigen-driven B cell activation *in vivo*.

Methods: C57BL/6 mice were dosed orally with either vehicle alone or vehicle with BTK inhibitor at 10, 3, 1, or 0.3 mgs/kg as indicated. For the anti-IgD model, either 100mg of agonistic anti-CD40 (clone 1C10) or 200ml of goat-anti-mouse anti-IgD antisera (Ebioscience) were injected intraperitoneally (i.p) two hours after dosing. Mice were sacrificed between 4–18 hours later and splenic B cells analyzed. For mRNA transcript analysis, mature B220$^+$CD23$^+$ B cells were enriched to >93% purity by B cell negative selection followed by CD23 positive selection by antibody-coupled microbeads. Purified RNA was analyzed for mRNA transcript levels. To analyze the induction of B cell surface activation markers, B220$^+$ B cells were analyzed by FACS for CD86 expression levels. For the NP-Ficoll model, 100mg of NP-Ficoll were injected i.p. the day after dosing with either vehicle alone or vehicle with BTK inhibitor. BTK inhibitor was dosed daily for the duration of the experiment until day 7, whereupon anti-NP serum IgM and IgG3 titers were quantified by ELISA.

Results: We report that dosing with a BTK inhibitor suppressed, in a dose dependent manner, both anti-IgD driven B cell activation and NP-Ficoll elicited anti-NP IgM and IgG3 antibody titers in vivo. The suppression of anti-IgD driven B cell activation was manifested by suppression of the surface activation markers CD86 as well as suppression of mRNA transcripts (e.g. c-Myc, Bcl-xL, CCL3, CD98, EBI2, EGR1, EGR2 and IRF4), all markers otherwise rapidly induced upon engagement of the BCR with antigen. BTK inhibition had no impact on agonistic anti-CD40 driven B cell activation, indicating the specificity of the BTK inhibitor used in this study for the BCR signaling pathway. Lastly, inhibition of BTK prevented, in a dose-dependent manner, the generation of anti-NP IgM and IgG3antibodies upon immunization with NP-Ficoll.

Conclusion: Our results provide mechanistic insight into the role of BTK inhibition in a mouse model of in vivo BCR-driven B cell activation and support the concept that BTK kinase inhibitors represent a promising therapeutic approach for patients with B cell-dependent autoimmune disorders.

1759

IL-10-Producing Regulatory B Cells (B10 cells) Inhibit Intestinal Injury In Mice. Koichi Yanaba and Shinichi Sato. The University of Tokyo, Tokyo, Japan

Background/Purpose: Ulcerative colitis (UC) is an inflammatory bowel disease characterized by pathologic mucosal damage and ulceration, which can involve the rectum and extend proximally. Although the etiology and pathogenesis of UC have not yet been identified, an inappropriate activation of the mucosal immune system has been found to play an important role in the pathogenesis of mucosal inflammation. Oral administration of dextran sulfate sodium (DSS) solution to rodents is widely employed as a model of human UC, because it can cause acute inflammatory reaction and ulceration in the entire colon similar to that observed in patients with UC.

B cells mediate multiple functions that influence immune and inflammatory responses. Recently, it has been demonstrated that B cells and specific B cell subsets can also negatively regulate immune responses in mice, validating the existence of regulatory B cells. A potent subset of regulatory B cells with a phenotype of CD1d^{hi}CD5$^+$ was recently found to regulate contact hypersensitivity and experimental autoimmune encephalomyelitis in an IL-10-dependent manner. This regulatory B cell subset is called B10 cells to distinguish them from other regulatory B cell subsets that may exist and to identify them as the

predominant source of B cell IL-10 production. B10 cell subset is found within the spleen of naïve wild-type mice at 1–2% of the total B cell count, whereas CD19-deficient ($CD19^{-/-}$) mice have few, if any, B10 cells. At present, the contribution of regulatory B cells to DSS-induced colitis is unclear.

We examined the importance of regulatory B cells in DSS-induced colitis in $CD19^{-/-}$ and wild-type mice.

Methods: We treated $CD19^{-/-}$ and wild-type mice with 3% DSS for 7 days and quantitatively evaluated the severity of colitis.

Results: $CD19^{-/-}$ mice developed more severe colitis, both clinically and pathologically, than wild-type mice. Splenic B cell IL-10 expression was enhanced in wild-type mice during DSS-induced colitis and the enhanced IL-10 expression was restricted to the $CD1d^{hi}CD5^{+}$ B10 cell subset. By contrast, B cell IL-10 expression in mesenteric lymph nodes, Peyer's patches, and intestinal lamina propria did not change during DSS-induced colitis in wild-type or $CD19^{-/-}$ mice. Furthermore, blocking IL-10 receptor function enhanced the severity of DSS-induced colitis. Remarkably, the adoptive transfer of spleen $CD1d^{hi}CD5^{+}$ B cells from wild-type mice ameliorated DSS-induced colitis, whereas either splenic $CD1d^{hi}CD5^{+}$ B cells from $IL\text{-}10^{-/-}$ mice or non-$CD1d^{hi}CD5^{+}$ B cells from wild-type mice were without effect.

Conclusion: IL-10 production from $CD1d^{hi}CD5^{+}$ B10 cells regulated DSS-induced colitis. Further studies are needed to determine the precise mechanisms by which regulatory B cells attenuate the severity of colitis. Nonetheless, the current results may provide new insights and therapeutic approaches for treating UC.

1760

B Cell Depletion Enhances T Regulatory Activity Essential in the Suppression of Arthritis. Susan Ashaye, Keith Hamel, Yanxia Cao, Yumei Wang, Tibor T. Glant and Alison Finnegan. Rush University Medical Center, Chicago, IL

Background/Purpose: B cell depletion is an effective therapy in Rheumatoid arthritis (RA), however, the mechanism responsible for suppression of disease is not clear. Autoantibodies are decreased in B cell depleted patients but the decrease does not necessarily correlate with clinical outcome suggesting that other mechanism may be effective. In a previous reported, we showed that in a murine model of arthritis proteoglycan-induced arthritis (PGIA) that B cell depletion inhibits autoreactive T cell responses. Recent studies of B cell depletion therapy also indicate a role for B cells in suppressing regulatory mechanisms. Here we tested where B cells inhibited both the expansion and the function of T regulatory (Treg) cells in PGIA.

Methods: B cells were depleted using in mice with PGIA an anti-CD20 mAb and Treg cell determined by Treg phenotype as $CD4^{+}$ $CD25^{+}$ $Foxp3^{+}$ by flow cytometry. T cell responses were measured by T cell proliferation and cytokine secretion.

Results: Treg cell percentages were elevated in B cell-depleted mice in comparison to control Ab treated. $CD4^{+}CD25^{+}$ cells from B cell depleted mice expressed increased amounts of Foxp3 and were significantly more suppressive than those from control Ab-treated mice. The depletion of Treg cells with an anti-CD25 mAb concurrent with B cell depletion therapy restored the severity of PGIA to levels equal to untreated mice. $CD4^{+}$ T cell recall responses to the immunizing antigen returned as measured by T proliferation and cytokine production.

Conclusion: These studies demonstrate B cells contribute to inflammation by inhibiting Treg cell expansion and function. B cell may inhibit T reg cells directly or indirectly by promoting preferential differentiation of naïve $CD4^{+}$ T cells towards a proinflammatory effector phenotypes rather than Tregs. Alternatively, the B cells act as APCs may expand the pool of autoreactive Teffs beyond the control of a Treg response. Further elucidation of the mechanisms utilized by B cells to suppress Tregs will have a major impact on the development of new therapies for the treatment of diseases.

1761

Efficient Depletion of Autoreactive Plasma Cells within the Nephritic Kidneys in a Murine Model of SLE by Bortezomib. Charlotte M. Starke[1], Vilma Urbonaviciute[1], Silke Frey[1], Georg Schett[2] and Reinhard E. Voll[3]. [1]Clinical Research Group, Nikolaus-Fiebiger Center of Molecular Medicine, Erlangen, Germany, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]Dept. of Rheumatology and Centre of Chronic Immunodeficiency, University of Freiburg, Freiburg, Germany

Background/Purpose: In autoimmune disorders such as systemic lupus erythematosus (SLE) self-reactive plasma cells (PCs) are known to contribute by diverse effector functions, for instance production of autoantibodies, to lupus pathogenicity. Glomerular deposits of immune complexes which are mainly composed of autoantibodies directed against nuclear components cause lupus nephritis, a severe manifestation of SLE-patients. Recently, we have shown that pathogenic autoantibodies are produced *in situ* within nephritic kidneys of lupus prone mice and that both short- and even more long-lived PCs are located in the renal tissue, indicating that a long-term production of renal autoantibodies is maintained by long-lived PCs. In contrast to short-lived PCs, the long-lived ones are extremely resistant to therapy. Therefore, novel therapeutic strategies targeting both short- and long-lived PCs are of particular importance.

Methods: NZB/W F1 lupus mice, displaying high titers of anti-double-stranded-DNA (dsDNA) antibodies and increased proteinuria, were treated short-term with either bortezomib (Bz) or Dexamethason (Dex) to evaluate possible depleting effects on specific leukocyte subsets within the nephritic kidneys by flow cytometry. To determine long-term effects, mice were analyzed after four weeks of initial therapy. Short- and long-lived PCs were differentiated using *in vivo* bromodeoxyuridine (BrdU)-labeling. ELISPOT assays were performed to quantify renal ASCs directed against antigen-specificities as dsDNA, histones and nucleosomes.

Results: We found a significant decrease of $CD138^{+}$ / intracellular κ/λ-L $chain^{+}$ PCs in renal tissue of Bz treated NZB/W F1 mice whereas treatment with Dex shows only a moderate depleting effect. Importantly, both short- and long-lived PCs as well as T lymphocytes were efficiently reduced after proteasome inhibition with Bz in the inflamed kidneys. In comparison, treatment with Dex solely depleted renal short-lived PCs and T leukocytes. Moreover, Bz short-term treatment markedly decreased not only renal IgG-antibody secreting cells (ASCs) but also potentially pathogenic anti-dsDNA, anti-histone and anti-nucleosome ASCs located in the nephritic tissue. Four weeks after initial therapy with Bz and subsequently a further therapy with Dex lupus mice showed beneficial effects in terms of the PC reconstitution in the kidneys. Interestingly, we observed that the IgG-secretion rate was significantly increased in renal IgG-ASCs when compared to IgG-secreting cells in spleen and BM.

Conclusion: Short- and long-lived PCs within the nephritic kidneys of NZB/W F1 lupus mice and can be efficiently depleted by treatment with Bz. Hence, the elimination of renal autoantibody-secreting cells by proteasome inhibition may critically contribute to beneficial effects in SLE-patients with lupus nephritis.

1762

TLR7 Overexpression Promotes Accumulation of Autoreactive CD19+ CD11c+ B Cells. Alice Wiedeman and Keith B. Elkon. University of Washington, Seattle, WA

Background/Purpose: 90% of patients with SLE are females yet the reasons for gender bias are incompletely understood. Recently, a novel CD11c+ B cell population was described that is expanded in older female mice (Age-Dependent B cells, or ABCs) and implicated in autoantibody production. Significantly, TLR7 appeared to be necessary for the generation of these cells since accumulation of ABCs was not observed in TLR7 deficient female mice. Since TLR7 has been strongly implicated in both mouse and human SLE, we asked what the effect of TLR7 overexpression would be on the numbers of ABC in male and female mice. We also asked whether type 1 interferon (T1-IFN) was responsible for driving expansion of these cells since TLR7 drives T1-IFN production and females have been shown to have increased type 1 interferon (T1-IFN) response to TLR7 ligands. Finally, we addressed whether the autoantigen (RNA) was responsible for driving the expansion of ABC in TLR7 Tg B cells.

Methods: Knock-in B6 mice that overexpressed TLR7 were kindly provided by S. Bolland. These mice were crossed to IFNaR knockout mice (to remove the effects of interferon-alpha signaling) or to RNAse transgenic mice (to diminish the source of antigen that is presumed to activate TLR7). ABCs were quantified by staining splenic B cells with anti-CD19 and CD11c mAbs by flow cytometry. Anti-RNA autoantibodies were quantified by ELISA.

Results: In wild-type B6 mice, an increased proportion of ABC was observed in female mice older than 6 months (2.70 vs 1.03%, $p<0.02$) confirming previous findings. However, in TLR7 transgenic mice, significantly more ABCs were observed in both female (4.52 vs 2.70%, $p<0.002$) as well as male (4.14 vs 1.03%, $p<0.004$) mice. Furthermore, these increases were markedly accelerated in time, being observed in mice as young as 3 months of age. Although TLR7 drives T1-IFN and this cytokine has a powerful effect on B cell activation, TLR7 transgenic mice deficient in IFNaR had only a modest reduction in ABC accumulation (4.53 vs 3.37%, $p< 0.04$). The % ABCs also correlated with levels of anti-RNA autoantibodies ($R^2=0.37$, $p<0.008$). When TLR7 transgenic mice were crossed to RNAse transgenic mice there was a partial reduction in the proportion of ABCs (4.53 vs 2.94%, $p<0.07$).

Conclusion: TLR7 overexpression in a non-autoimmune background accelerates the expansion of an unusual CD11c+ B cell population (ABC) in both male and female mice. These results suggest that gender specific factors act in concert with TLR7 pathways to promote the production of ABCs that are closely associated with autoantibody production. However, when TLR7 levels are increased by other mechanisms, the requirement for female hormones or other gender factors are not necessary. Since the expansion of ABC is only partially interferon-alpha-dependent, other mechanisms relevant to TLR7 activation or signaling also play a role. Since overexpression of RNAse in TLR7 transgenic mice reduced the proportion of ABC, and anti-RNA autoantibody levels correlated with the proportion of ABCs, the expansion of ABCs appears to be autoantigen driven. ABCs should be considered as a potential target for therapy to reduce autoantibody production.

1763

Anti-DNA Antibody Production Is Restricted by the Germline Composition of DH Genes. Aaron Silva-Sanchez[1], Cunren Liu[1], Pratibha Kapoor[1], Yingxin Zhuang[1], Trenton R. Schoeb[1] and Harry W. Schroeder Jr.[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama-Birmingham, Birmingham, AL

Background/Purpose: Diversity genes (D_H genes) have a critical role in determining BCR specificity since they encode most of the CDR-H3 loop which is structurally located at the center of the antigen-binding site. The relevance of D_H genes has been overlooked due to the presumption that repertoire is randomly generated and only shaped by somatic events occurring during B cell maturation. D_H preferential use of reading frame (RF) 1, limited D-J recombination by inversion and presence of stop codons in RF3 contribute to narrow the physicochemical features of the mature BCR repertoire. One crucial feature of the WT repertoire is the poor representation of highly charged (R, K) amino acids. A probable explanation is that conserved DH sequences decrease the probability to produce potentially harmful self-reactive BCRs, e.g. anti-DNA BCRs containing CDR-H3s rich in arginine. In this work we hypothesized that D_H sequences encoding charged amino acids will favor the production of anti-DNA antibodies.

Methods: To test this hypothesis we used transgenic BALB/c mice with a single D_H gene encoding (in RF1) charged amino acids (DiD mice), mice with a single WT D_H gene (DFL16.1 gene, DFL mice), WT x DiD F1 ($DiD^{+/WT}$), WT x DFL F1 ($DFL^{+/WT}$), and WT BALB/c mice (considered to be resistant to anti-DNA antibody production). Cohorts of 9–16 female mice were followed for a period of ten months (2–12 months of age). Serum was obtained monthly and stored at −70°C until analysis. 1 year old mice were euthanized and the kidneys were collected for histological analysis. Total IgM, total IgG, anti-ssDNA and anti-dsDNA IgM and IgG was determined by ELISA. DNA reactivity was confirmed by Crithidia luciliae Immunofluorescence (CLIF) assay. Kidney sections were HE and PASH stained for histology analysis.

Results: At 12 months of age, sera from all groups showed similar concentration of anti-DNA IgM. Only mice containing the DiD allele had increased production of anti-DNA IgG. The increased production of anti-dsDNA IgG ranged from 3 to 8 fold increase when compared with WT average concentration, and the differences between $DiD^{+/+}$ and $DFL^{+/+}$ or $DFL^{+/WT}$ were statistically significant. Notably, DiD allele had increased anti-DNA IgG as soon as 5 months of age. Strains that do not contain the DiD allele have similar and homogeneous concentrations of anti-DNA IgG and IgM. A deleterious or additive effect of the DFL or DiD allele on the antibody production was discarded since the concentrations of total IgM and IgG showed no statistical differences among groups. DNA reactivity in $DiD^{+/+}$ and $DiD^{+/WT}$ samples was confirmed with the CLIF assay. Kidney histology did not revealed considerable alterations and most of the samples showed mild segmental sclerosis tipical of C57BL/6 mice.

Conclusion: These results show that D_H germline sequence shape preimmune BCR repertoire and this is reflected in B cell function. Importantly, tolerance mechanism in BALB/c mice acting on the BCR repertoire can be overcome by altering the D_H germline sequence. Also, our results suggest that the conserved D_H germline sequences have been selected to limit potentially auto-reactive BCRs and open the possibility to find new susceptibility genes in humans with D_H sequences encoding charged amino acids.

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A Novel Method to Evaluate Autoreactivity by Inducing Antibodies Secretion Allows the Study of Tolerance In Mice. Emiliano Marasco[1], Nataly Manjarrez Orduño[1], Peter K. Gregersen[2] and Betty Diamond[3]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]Feinstein Institute Medical Reschearch, Manhasset, NY, [3]Feinstein Institute Med Rsch, Manhasset, NY

Background/Purpose: During maturation, B cells rearrange their V(D)J segments to produce functional immunoglobulins. Along the development pathway, there are checkpoints to censor B cells bearing autoreactive antibodies thus avoiding potential tissue damage. In systemic lupus erythematosus, the censoring at these tolerance checkpoints is not effective and autoreactive B cells enter the mature B cell pool, where they can be activated and induced to secrete pathogenic autoantibodies. Many transgenic models bearing autoreactive receptors have been developed to study the process of B cell tolerance and the pathogenesis of autoimmune diseases. However these manipulations can perturb the physiology of the system, leading us to build a model that might not fully apply to unmanipulated organisms. Here we present a different approach to study autoreactivity and censoring checkpoints of a native B cell repertoire in murine models of human autoimmune diseases.

Methods: B cells subpopulations in spleen and peritoneal cavity were sorted from BALB/c and NZB/W F1 mice and activated with a cocktail of TLR agonists and cytokines to induce the secretion of antibodies. After four days of culture, cells were harvested and seeded for ELISpot analysis. ELISpots were performed to evaluate the percentage of cells induced to secrete antibodies and the fraction of cells that secrete anti-DNA antibodies in each of the subpopulations. Finally, the percentage of autoreactive cells was normalized to the number of antibody secreting cells (ASC).

Results: Over 80% of each B cell subset was induced to secrete antibody. As reported in other models, we observe that autoreactivity decreases during development from the transitional to the mature follicular stage, while a large amount of autoreactivity can still be found in the marginal zone (MZ) and B1 cell pools. As expected B cells from NZB/W F1 mice, at every stage of development, contain a higher percentage of DNA reactive cells when compared to BALB/c mice, highlighting the altered censoring checkpoints present in this murine model of SLE.

Conclusion: To date, tolerance and autoreactivity checkpoints have been studied mainly through genetically modified mice. Here, we propose this method as a tool for the analysis of autoreactivity directly ex vivo. Our method allows us to measure the reactivity of antibodies to biologically and pathologically meaningful antigens in genetically unaltered animals within a reasonable timeframe. Consequently we propose this method to expand the knowledge acquired from transgenic models, and overcome the limitation of studying tolerance one B cell receptor at a time.

1765

Subtoxic Dose of Mercury Reduces Splenic Marginal Zone B Cells, Resulting in the Increase in Autoantibodies in Murine Mercury-Induced Autoimmunity. Takaji Matsutani[1], Miho Murakami[1], Hooi-Ming Lee[2], Hidehiko Sugino[2] and Norihiro Nishimoto[1]. [1]Wakayama Medical University, Ibaraki, Japan, [2]Osaka University, Suita, Japan

Background/Purpose: Mercury is one of the most abundant heavy-metal in the environment. It has been reported that high levels of serum anti-nuclear or anti-nucleolar autoantibodies were observed in peoples exposed to mercury in gold-mining area of Brazil. In rodent, *in vivo* administration of subtoxic dose of inorganic mercury ($HgCl_2$) can induce autoantibody production in susceptible strains of mice (Hg-induced autoimmune mouse model, HgIA). It is considered that the autoantibody production is T cell dependent and associated with particular MHC class II haplotype ($H\text{-}2^s$). However, it remain little known about the mechanism of autoantibody production by subtoxic mercury.

Methods: SJL mice ($H\text{-}2^s$) were treated with 10 ppm of $HgCl_2$ drinking water *ad libitum* for 4 weeks. Anti-nuclear or anti-nucleolar antibodies were measured with indirect immunofluorescence assay with Hep-2 slides. T cell subsets, CD4/CD8 ratio, activation markers ($CD69^+$, $CD62L^{low}$, $CD25^+$), and T cell receptor repertoires were analyzed in thymuses, spleens and LNs. Furthermore, splenocytes were surface stained with anti-CD19, IgM, IgD, IgG, CD21 and CD23, and analyzed with FACScalibur. Lymphoid follicle formation was evaluated with Immunohistochemical staining with anti-IgM and anti-MOMA-1 antibodies.

Results: Elevated numbers of B cells expressing surface IgG and increased levels of plasma IgG1-type anti-nucleolar antibodies were observed in HgIA mice. However, mercury administration had little impact on T cell profiles and repertoires *in vivo*. Interestingly, we found that mercury administration reduced splenic $CD21^{high}CD23^{low}$ marginal zone (MZ) B cells but not $CD21^{high}CD23^+$ follicular (FO) B cells. Such effects were not observed in resistant strains of mice. Immunohistochemcal staining confirmed the decrease of splenic MZ B cells localized in marginal zone of lymphoid follicle distinct from T cell area. Given T cell profiles were not altered in HgIA mice, it is possible that mercury can directly act on MZ B cells in a T cell-independent manner.

Conclusion: *In vivo* administration of subtoxic dose of mercury reduced splenic MZ B cells in HgIA mice. This suggests the possibility that mercury act directly on MZ B cells in a T cell-independent fashion, provoking B cells to produce autoantibody.

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Induction of Regulatory B Cells in Healthy Individuals and Patients with Systemic Lupus Erythematosus. Shun-ichiro Ota, Hiroaki Niiro, Naoko Ueki, Hirofumi Tsuzuki, Siamak Jabbarzadeh-Tabrizi, Yasushi Inoue, Yojiro Arinobu and Koichi Akashi. Kyushu University, Fukuoka, Japan

Background/Purpose: Recent evidence from B-cell depletion studies highlights the importance of antibody-independent roles for B cells in autoimmune diseases. In this respect, B cells can negatively regulate the disease process via production of an anti-inflammatory cytokine, IL-10, and thus is termed regulatory B cells (Bregs). The nature of human Bregs, however, remains somewhat elusive, due to a few conflicting previous results.

Methods: IL-10 expression in B cells was evaluated using real-time quantitative PCR and ELISA.

Results: We first determined IL-10 expression in $CD19^+$ B cells from healthy controls following stimulation of surface receptors for BCR, CD40, and TLR9, and found that CpG, a TLR9 ligand, is the most potent for Breg induction. Combined stimulation with BCR and CpG exerted synergistic effects on IL-10 production in B cells. Both naïve and memory B cells exhibited comparable levels of CpG-induced IL-10 expression. We next evaluated the effects of various chemical inhibitors of signaling pathways on CpG-induced Bregs. Among them, the inhibitors of the ERK, p38 MAPK, PI3K and STAT3 pathways significantly abrogated Breg induction. Combined stimulation with CpG and STAT3-activating cytokines induced higher levels of IL-10 production in B cells. We finally determined Breg induction in patients with systemic lupus erythematosus (SLE), and found that CpG-induced IL-10 production is significantly impaired in memory B cell subsets as compared with healthy controls. Intriguingly, sustained calcium signaling in B cells from healthy controls abrogated Breg induction in particularly memory B cells, which is reminiscent of SLE memory B cells. We are currently working on further underlying mechanisms of impaired induction of Bregs in SLE patients.

Conclusion: Our current findings could help to better understand a role of human Bregs in the pathogenesis of autoimmune diseases as well as to provide a novel clue to manipulate the generation of human Bregs for therapeutic application in the future.

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The Comprehensive B Cell Profiling Analysis of a Multicenter SLE Cohort. John Jung[1], Jamie Biear[1], Youqun Huang[1], Bridget Neary[1], Elides Marin[1], Jennifer Hossler[1], Elise Palmer[1], Sharleen Smith[1], Ehtisham Akhter[2], Tracey Sanford[1], Jie Xu[2], Michelle Petri[2], Alex Rosenberg[1], Jennifer H. Anolik[1], Chungwen Wei[1] and Iñaki Sanz[1]. [1]University of Rochester, Rochester, NY, [2]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: B cell abnormalities in Systemic Lupus Erythematosus (SLE) are well-established contributors to disease pathogenesis. Past limitations such as pauci-color flow cytometry have limited a full characterization of this multifactorial disease. This study utilizes several multicolored flow cytometry panels to render a high-resolution footprint of the B cell profiles linked with comprehensive clinical parameters to identify distinct B cell signatures in SLE.

Methods: PBMCs were isolated and analyzed by flow cytometry from Healthy Controls (HC) (n=36) and SLE patients (n=161). B cell subsets were identified using the following markers: IgD, CD19, CD27, CD38, CD24, CXCR3, CD21, CD24, CD95, MitoTracker Green, CD10, IgM, CD23. SLE patients met ACR criteria for the classification of SLE, and were sub-categorized based on primary clinical manifestation. Disease activity and flares were measured by SELENA-SLEDAI and physician global assessment. All clinical and experimental data were imported into a customized database where multivariate methods were used to seek natural divisions based on the B cell profiles and relationship to clinical parameters.

Results: Our initial analyses show pronounced heterogeneity in SLE subjects. Multidimensional analysis of our multicolor panels can identify a total of 330 B cell subsets of which 132 demonstrate abnormal behavior with significantly different frequencies found between HC, SLElow (SLEDAI<=4), and SLEhi (SLEDAI>4) disease activity ($p<0.05$). SLE patients have a significant expansion of CD27- memory B cells and a contraction of unswitched memory subsets relative to HC subjects ($p<0.05$). Further characterization of memory B cells reveals additional signatures of active disease characterized by expansions of CD21low, CD24low, CXCR3hi, and CD95hi that correlate with higher number of autoantibodies, lower C3/C4 levels, higher disease activity, and flares ($p<0.0005$). Detailed analysis of the IgD+CD27- subsets show B cell subset shifts where overall the true naïve B cells contract and the transitional B cell compartments expand when compared to healthy controls ($p<0.005$). High dimensional multi-parameter analysis identifies multiple clusters of SLE subjects that can be sub-classified based on their B cell profiles and show similar clinical features. Further novel-analysis tools including heat-map displays and Principle Component Analysis confirm the added value of refined B cell phenotyping for superior segregation of HC and SLE subclasses.

Conclusion: Collectively, this study demonstrates that while SLE patients have variable B cell profiles, immune-profiling has the ability to identify clusters of SLE. Two year longitudinal studies of these subjects are currently under way to clarify whether the signatures corresponding to the different disease clusters have subset-specific changes to disease activity and predictive of disease progression. These profiles will be useful in understanding disease. Careful immunological studies of patients with SLE will increase our understanding of multiple aspects of human B cell biology and will be critical to providing the framework for the design and evaluation of current and future B cell targeted therapies.

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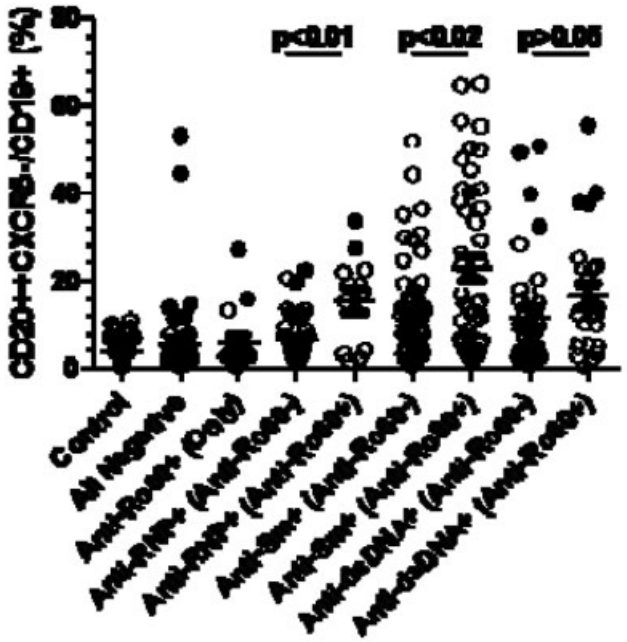
A Novel Circulating CXCR5-CD20++ B Cell Compartment in Patients with Systemic Lupus Erythematosus. Eric S. Sobel, Edward Butfiloski, James Hunt, Mark Segal, Laurence Morel, Westley H. Reeves and Minoru Satoh. University of Florida, Gainesville, FL

Background/Purpose: Alterations in B cell homeostasis have been identified in patients with SLE and typically correlate with disease activity. Here, we describe a novel B cell compartment in our SLE cohort more related to autoantibody specificity.

Methods: A total of 131 patients with SLE were studied by 7- or 8-color flow cytometry, 81 of whom had two or more samples at least one year apart and 33 with multiple samples over a two to three year interval. A total of 47 controls were also studied. Clinical and serological data, including autoantibody characterization by immunoprecipitation, were available for all patients.

Results: In a subset of patients with lupus, there was a striking increase in a subset of CD19+ B cells that had the phenotype of CD20++CXCR5−. The mean percentage and standard deviation was $3.7\pm2.3\%$ for controls and was 12.8 ± 19.7 for all SLE samples. While there was a correlation between the percentage of this subset with disease activity ($9.4\pm11.3\%$ for SLEDAI <4 vs. $16.0\pm14.8\%$ for SLEDAI ≥4; $p<0.001$), a closer examination showed that there was a stronger correlation with autoantibody specificity (Figure). In patients negative for the specificities commonly available in clinical laboratories (anti-dsDNA, anti-Sm/RNP, anti-RNP, and anti-Ro60), the average percent of CD20++CXCR5− B cells was unchanged from the control population ($p>0.05$ by ANOVA). The outliers (shown in filled circles) were positive for either Ku or ribosomal P antibodies. In one case, the patient had seven unidentified bands. The presence of anti-RNP alone did not affect this population, but it doubled in the presence of anti-Ro60. In contrast, anti-Ro60 alone had only a minimal impact that did not achieve statistical significance. The few outliers also had additional known specificities (La, PCNA). The presence of anti-Sm characteristically had the biggest impact ($p<0.01$ by ANOVA compared to all negative) and this too was augmented by the co-presence of anti-Ro60 antibodies. The effect of anti-dsDNA was less clear. Although statistically significant ($p<0.05$ by ANOVA), most of the high positives had other specificities (primarily anti-Ku and anti-RNA helicase A), and the impact of anti-Ro60 was even less clear and did not reach statistical significance. Because of the striking similarity of our findings of specificity to the recently described novel class-switched IgD-CD27− memory B cell population, we examined the percent of these cells within our CD20++CXCR5−population. In patients with initial high levels of CD20++CXCR5- B cells, the IgD-CD27− B cells comprised a varying but substantial percentage (range 20–70%). This percentage fluctuated, but the overall trend indicated it was increasing over time.



Conclusion: Taken together, these findings suggest that this novel population is driven by TLR7-dependent pathways, and that the class-switched CD27- population may be the final product.

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Effect of Mycophenolat Mofetil (MMF) on Clinical and Paraclinical Parameters in Systemic Lupus Erythematosus (SLE). Sebastian Eickenberg, Elisabeth Jung, Eva Mickholz and Annett M. Jacobi. University Hospital Münster, Münster, Germany

Background/Purpose: Although efficacy and safety of MMF were investigated thoroughly in SLE and experts consider MMF to be a therapeutic standard in lupus nephritis, few attempts have been undertaken to further delineate its mechanism of action in SLE—a disease characterized by enhanced B cell activation.

Methods: This consecutive investigation of our outpatients with SLE has been conducted for one year. During this time period 39 patients on MMF, 30 patients on aza and 38 patients currently not taking immunosuppressive drugs other than prednisolone and hydroxychloroquine (controls) were seen. Disease activity and manifestations, serologic and cellular parameters were recorded. To further delineate the effect of mycophenolic acid on naïve and memory B cells, *in vitro* assays were performed.

Results: Most Patients treated with MMF had a LN (90%, 57% in remission) compared to 2/3 of the aza-treated patients (45% in remission) and 38% (54% in remission) of the controls. Patients taking aza flared more frequently (47%, 71% LN) and showed a higher mean disease activity (SLEDAI: 7.1±5.5) than patients on MMF (23%, 44% LN, mean SLEDAI: 4.9±3.4) or controls (32%, 50% LN, mean SLEDAI: 5.6±5.6). These differences did not reach statistical significance and the three patient cohorts did not differ significantly with regard to all clinical manifestations recorded. However we observed a number of significant differences investigating paraclinical parameters suggesting that MMF has a favorable and distinct mechanism of action compared to other immunosuppressive drugs used in lupus patients. White blood cell count ($p<0.03$), B cell frequency ($p<0.005$) and B cell number ($p<0.002$) were significantly higher in patients taking MMF compared to those on aza. However B cell subset analysis revealed significantly lower numbers and frequencies of plasmablasts in patients taking MMF compared to those on aza ($p>0.0001$ und 0.001, respectively) or controls ($p=0.0002$ und <0.0001, respectively). On the contrary, MMF treatment was associated with a significantly higher frequency and number of transitional/regulatory B cells ($p<0.0001$ and <0.0001) as well as naïve B cells ($p<0.001$ and <0.0005) compared to treatment with aza. T cell subsets did not differ between patient groups. In line with these data, the results of our *in vitro* assays supported a preferential inhibition of B cells activated by CPG (Figure 1) or anti-CD40+IL-21.

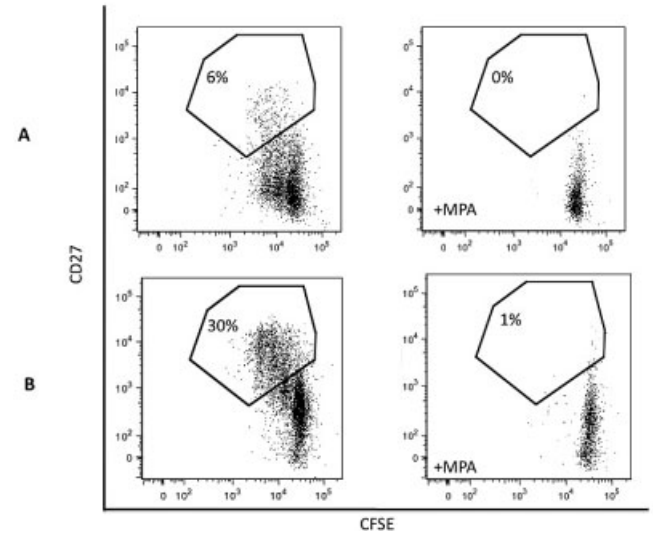

Figure 1. Naïve (A) and memory (B) B cells were isolated from the peripheral blood of healthy individuals and stimulated with CPG for 3 days with (right) or without mycophenolic acid (MPA, left). MPA abolished B cell division and plasmablast formation completely.

Conclusion: The specific inhibition of activated B cell subsets observed in this study might explain the favorable outcomes of previous clinical trials, since enhanced B cell activation is a common finding in patients with SLE.

ACR/ARHP Poster Session C
Biology and Pathology of Bone and Joint: Inflammation and Osteoarthritis
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

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Simultaneous Targeting of IL-1α and IL-1β by a Dual-Variable-Domain Immunoglobulin (DVD-Ig™) Prevents Cartilage Degradation In Preclinical Models of Osteoarthritis. Rajesh Kamath. Abbott Research Center, Worcester, MA

Background/Purpose: Interleukin-1 (IL-1) plays a major role in the development and progression of osteoarthritis (OA). IL-1α and IL-1β are two distinct cytokines that bind to the same receptor and are expressed in synovial membranes, cartilage, and synovial fluid of patients with OA. IL-1 induces structural changes (cartilage degradation, bone sclerosis & synovial proliferation) by inducing proteases and proinflammatory cytokines from all tissues (cartilage, bone and synovium) of the joint. The purpose of the study is to demonstrate a) blockade of both IL-1a and IL-1b with a combination of anti-mouse IL-1a and IL-1b monoclonal antibodies (mAbs) is efficacious compared to treatment with single mAbs in mouse models of OA, and b) to demonstrate that anti-IL-1a/b dual variable domain –Ig (DVD-Ig) produces similar efficacy as the combination of anti-mouse IL-1a and IL-1b mAbs.

Methods: The joint instability model (JIM) and destabilization of medial meniscus (DMM) model of OA were used to evaluate efficacy of IL-1 treatment. For JIM model, male Swiss Webster mice had anterior cruciate ligament (ACL) trauma on day 0 to transect the ACL and induce OA lesions. For DMM model, male sv129 mice were anesthetized on day 0 and then medial meniscotibial ligament which anchors the medial meniscus to the tibial plateau was transected to induce OA. Intraperitoneal (ip) treatments with IL-1 neutralizing antibodies [mouse anti-mouse IL-1α mAb, mouse anti-mouse IL-1β mAb alone, in combination, or anti-IL-1a/b DVD-Ig were initiated the day of the surgery and continued twice a week for either 3 weeks in JIM or 8 weeks in DMM models. Knees were harvested and histopathologic alterations were scored and characterized.

Results: In both JIM and DMM model, cartilage degeneration in animals treated with either anti-IL-1a (6 mg/kg) or IL-1b mAbs (6 mg/kg) was similar to vehicle control knees. However, a combination therapy with both antibodies (6 mg/kg each significantly decreased cartilage degeneration scores. We have recently reported on a novel dual-specific biologics approach, termed

DVD-Ig™ that can convert two pre-existing mAbs into a dual targeting agent by combining the variable domains of two mAbs via naturally occurring linkers. Anti–mIL-1α/β DVD-Ig (6 mg/kg) also significantly inhibited the progression of OA with comparable efficacy to the combination of the parental mAbs.

Conclusion: Our preclinical data demonstrate that combination of mouse anti-mouse-IL-1a and anti-mouse-IL-1b mAb as well as anti-mouse-IL-1a/b DVD-Ig™ molecules had significant beneficial effects on histopathological parameters of mouse OA. These preclinical proof of concept studies with anti-IL-1a/b DVD-Ig™ molecules form the basis for further investigation of therapeutic IL-1a/b DVD-Ig™ molecules in human OA patients.

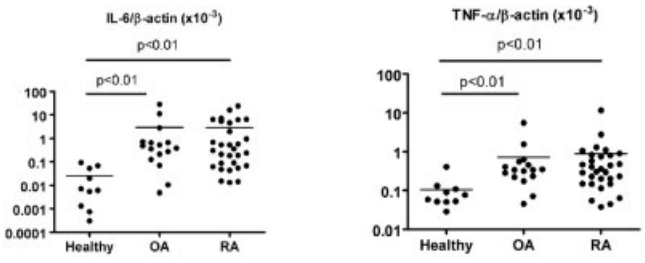
1771

Enhanced Expression of mRNA for Interleukin 6 and Tumor Necrosis Factor-Alpha In CD34+ Cells of the Bone Marrow In Osteoarthritis. Shunsei Hirohata[1], Tamiko Yanagida[2], Tetsuya Tomita[3] and Hideki Yoshikawa[4]. [1]Kitasato Univ School of Med, Kanagawa, Japan, [2]Teikyo University School of Medicine, Tokyo, Japan, [3]Osaka University Med School, Suita Osaka, Japan, [4]Osaka University Graduate School of Medicine, Osaka, Japan

Background/Purpose: Recent studies have disclosed that bone marrow lesions also play an important role in the pathogenesis of osteosrthritis (OA). Thus, bone marrow lesions have been consistently associated with an increased prevalence and severity of cartilage defects and metaphyseal expansion, both characteristics of the increasing severity of knee OA. Moreover, the development of new bone marrow lesions was associated with progressive knee cartilage pathology in asymptomatic middle-aged adults. However, the nature of bone marrow abnormalities in OA has not been determined. The current studies were therefore undertaken to explore the expression of mRNA for interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in bone marrow CD34+ cells in OA.

Methods: Bone marrow samples obtained from 16 patients with established OA (2 males and 14 females; mean age, 70.9 years) and from 30 patients with rheumatoid arthritis (RA) (5 males and 25 females: mean age, 59.4 years), who gave informed consent, during joint operations via aspiration from the iliac crest. CD34+ cells were purified from the bone marrow mononuclear cells by positive selection with magnetic beads. CD34+ cells from healthy individuals were also purchased from Bio-Whittaker, Walkersville, MD (8 males and 2 females: mean age, 24.9 years). The expression of mRNA for IL-6, TNF-α, NFkB1, FK506 binding protein 5, and Kruppel-like factor 5 in the CD34+ cells was examined by quantitative RT-PCR, and is evaluated as the ratio of the copy numbers to those of β-actin mRNA.

Results: The expression of mRNA for IL-6 and TNF-α in bone marrow CD34+ cells was significantly elevated in OA patients as well as in RA patients compared with that in healthy individuals (Figure). There was no significant difference in the expression of mRNA for IL-6 and TNF-α between OA bone marrow CD34+ cells and RA bone marrow CD34+ cells, although the expression of mRNA for several genes, including NFkB1, FK506 binding protein 5, and Kruppel-like factor 5, was significantly higher in RA bone marrow CD34+ cells.



Conclusion: These results demonstrate that bone marrow CD34+ cells in OA display the enhanced expression of mRNA for IL-6 and TNF-α, which might be a common sequela of inflammation of joints. The data also suggest that primary abnormalities in bone marrow CD34+ cells that lead to the enhanced mRNA expression for several genes other than these inflammatory cytokines might be a unique feature in RA.

1772

Transcriptome Analysis Reveals a Robust Profile In Osteoarthritis Synovial Fibroblasts. Manuel J. Del Rey[1], Alicia Usategui[1], Elena Izquierdo[1], Vanessa Miranda[1], Juan D. Cañete[2], Francisco J. Blanco Sr.[3], Gabriel Criado[1] and Jose L. Pablos[1]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain, [3]INIBIC-CHUAC, La Coruna, Spain

Background/Purpose: Gene expression profiling in rheumatoid arthritis synovial fibroblasts (RASF) has not consistently demonstrated a unique phenotype and shows great heterogeneity. RASF gene expression changes have been usually defined by comparison to osteoarthritis SF (OASF) rather than healthy SF (HSF). The aim of this study was to analyze the transcriptome of OASF compared to both RASF and HSF.

Methods: Total RNA was extracted from 9 RASF, 11 OASF and 11 HSF lines (n=31) and cRNA was hybridized in Agilent G4112F platform (Whole Human Genome Microarray 44k). ANOVA with Benjamini and Hochberg multiple testing correction was used to determine the statistical significance of the differences in gene expression. Tukey post-hoc test was used to compare the three possible pairs after ANOVA. Cluster analysis was also performed with Cluster 3.0 software. Validation of microarray data was performed by quantitative RT-PCR of selected genes. Differentially expressed genes were analyzed to identify potential functional pathways using the Database for Annotation, Visualization and Integrated Discovery (DAVID).

Results: ANOVA showed 345 transcripts significantly different (down- or up-regulated) between the three different groups. Tukey post-hoc test identified the largest number of significant differences in OASF compared RASF or HSF (325/323 respectively), whereas only 39 transcripts were different in RASF compared to HSF. Cluster analysis of the 31 SF lines by similarity on gene expression patterns identified a single cluster including all OASF lines, whereas RASF clustered together with HSF into several clusters. The set of genes statistically different between OASF and HSF included several categories significantly different to the DAVID database, remarkably: genes related to cell-cell or cell-ECM adhesion and actin cytoskeleton regulation, growth factor and cytokine activities, synapse or neuroactive elements, and GTPase activity.

Conclusion: Cultured OASF display a more robust transcriptomic profile than RASF when compared to HSF which supports a role of SF in the pathogenesis of OA. These data also advise against the use of OASF as controls for SF studies.

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Destabilization of the Medial Meniscus As a Model to Study the Relationship Between Joint Degeneration and Pain. Rachel E. Miller, Phuong Tran, Nayereh Ghoreishi-Haack, Rosalina Das and Anne-Marie Malfait. Rush University Medical Center, Chicago, IL

Background/Purpose: Pain is the major symptom in osteoarthritis (OA), yet how this pain develops remains unknown. Our long-term goal is to quantitatively measure pain and dissect molecular pathways involved in pain generation in a mouse model of OA. We chose destabilization of the medial meniscus (DMM) in C57BL/6 mice because, unlike in other rodent OA models, the joint pathology in this model is slowly progressive over 16 weeks. Previous studies in our lab have found that mice receiving DMM surgery develop progressive mechanical allodynia in the ipsilateral hindpaw, as early as 2 weeks and progressing over 8 weeks post DMM (but not sham) surgery.

Methods: DMM or sham surgery was performed in the right knee of 10-week old male C57BL/6 mice. At 8 and 16 weeks post surgery, histopathology of the knees was evaluated according to OARSI recommendations. Additionally, at 4 and 8 weeks after surgery, whole knee joints were collected for protein extraction and ELISA. The LABORAS system (Metris, NL) was used to measure locomotor activity at 4, 8, and 16 weeks post surgery. At the same time points, innervating dorsal root ganglia (DRG), L3-L5, from DMM or sham-operated mice and age-matched naïve mice were collected for mRNA extraction for quantitative RT-PCR of nerve growth factor (NGF), monocyte chemoattractant protein (MCP)-1 and its receptor CCR2, and stromal cell-derived factor (SDF)-1. Finally, at 8 weeks post surgery, the response of DRG neurons to chemokines was recorded though intracellular Ca^{2+}-imaging, following standard protocols. In brief, DRG neurons were acutely isolated, plated on coverslips, cultured for 3–4 days, and loaded with a calcium indicator dye. The number of cells responding to chemokines was counted.

Results: Following DMM (but not sham) surgery, C57BL/6 mice developed cartilage degeneration and osteophyte formation by 8 weeks in the ipsilateral knee only, with progressive cartilage deterioration occurring up to 16 weeks. At 4 weeks post DMM, protein levels of MCP-1 and NGF were elevated in total joint extracts from the operated knee compared to naïve age-matched controls; by 8 weeks post DMM, levels of both proteins had returned to baseline. Additionally, locomotor activity (measured as total distance traveled) was relatively constant over the first 8 weeks, but was decreased in DMM mice at 16 weeks post surgery compared to age-matched naïve mice.

mRNA levels of NGF, MCP-1, CCR2, and SDF-1 in the innervating DRG were upregulated compared to naïve and sham age-matched controls, peaking at 8 weeks post surgery. Exposing isolated DRG neurons from DMM mice at 8 weeks post surgery to MCP-1 or to SDF-1 (200 or 500 ng/mL, respectively) resulted in an increased calcium response compared to naïve age-matched controls, indicating an upregulation of their respective receptors, CCR2 and CXCR4, on these cells.

Conclusion: Time-course experiments in the murine DMM model of OA enable us to quantify pain at different stages of disease. The upregulation of CCR2 and CXCR4 signaling pathways indicate that they likely play a central role in mediating painful osteoarthritis, similar to what has been reported in other neuropathic disease models; future work will address whether these pathways may serve as useful therapeutic targets.

1774

IL-1beta Inhibits TNF-Mediated Differentiation of Human Osteoclast Precursors Grown in Presence of Fibroblast-Like Synoviocytes. Bohdan P. Harvey, Farhan A. Syed and Zehra Kaymakcalan. Abbott Laboratories, Worcester, MA

Background/Purpose: Inflammatory cytokines such as TNF-alpha (TNFa), IL-1beta (IL-1b) and IL-6 have been shown to contribute to osteoclastogenesis independently or in conjunction with M-CSF or RANKL, two key cytokines involved in osteoclast development. However, the role of TNFa as well as the other inflammatory cytokines in promoting the expression of these key osteoclastogenic factors in synovial tissue and the concomitant induction of osteoclast differentiation is poorly understood. In this study, we sought to determine whether TNFa, IL-1b or IL-6, separately or in combination, could induce human osteoclast differentiation directly in the presence of fibroblast-like synoviocytes (FLS).

Methods: Primary human osteoblasts or FLS from healthy or rheumatoid arthritis (RA) donors, were pre-treated with various combinations of TNFa, IL-1b, IL-6, soluble IL-6 receptor (sIL-6R), M-CSF and RANKL for 24 hr in the absence or presence of osteoprotegerin (OPG), a natural inhibitor of RANKL. Human osteoclast precursor cells were then added, and the co-cultures were continued for 7 days. Western blot analysis was performed on RA-FLS to evaluate RANKL protein expression. Osteoclast differentiation was determined by the appearance of large multinucleated cells staining positive for tartrate-resistant acid phosphatase (TRAP) and by bone-specific TRAP5b activity within culture supernatants.

Results: RA-FLS were found to express RANKL protein in response to either TNFa or IL-1b. Pre-treatment of osteoblasts or RA-FLS with a combination of TNF and M-CSF led to the appearance of TRAP+ multinucleated cells and an increase in TRAP5b activity; whereas, the combination of TNF and RANKL was ineffective in inducing osteoclasts, suggesting that TNF could substitute for exogenous RANKL but not M-CSF. Osteoclast differentiation was observed with FLS from healthy and RA donors and was found to increase in a TNF dose dependent manner. Addition of the RANKL inhibitor OPG caused a significant reduction in TRAP+ multinucleated cells without altering the level of TRAP5b activity. A greater degree of inhibition was observed with the addition of IL-1b alone or in combination with IL-6 and sIL-6R, since the generation of both TRAP+ multinucleated cells and TRAP5b were significantly reduced even in the presence of exogenous RANKL.

Conclusion: These findings suggest that in a co-culture system with FLS, TNFa can induce an early stage of osteoclast differentiation independent of RANKL as indicated by the expression of TRAP5b in the presence of OPG. This finding is in agreement with the literature describing TRAP5b as a marker of an immature osteoclast. However, the generation of multinucleated cells requires TNF-induced RANKL expression from the FLS since the number of TRAP+ multinucleated cells was reduced with OPG treatment. Surprisingly, IL-1b prevented both the expression of TRAP5b and the generation of TRAP+ multinucleated cells that was induced by either TNF or RANKL, suggesting that this pro-inflammatory cytokine can inhibit osteoclast development at an early stage.

1775

Norepinephrine (NE) Affects Mesenchymal Stem Cell (MSCs) Chondrogenesis and Accordingly the Self-Regeneration Capacity of Cartilage. Zsuzsa Jenei-Lanzl[1], Peter Angele[2] and Rainer H. Straub[3]. [1]Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine, University Hospital Regensburg, Regensburg, Germany, [2]Department of Trauma Surgery, University Hospital Regensburg, Germany, Regensburg, Germany, [3]University Hospital Regensburg, Regensburg, Germany

Background/Purpose: It is known that sympathetic nerve fibers are present in healthy and osteoarthritic (OA) synovium and that the sympathetic nervous system mediates numerous effects on adult skeletal system. The presence of mesenchymal stem cells (MSCs) in healthy or arthritic cartilage has also been confirmed. In addition, MSCs migrating from synovium into the cartilage and differentiating into chondrocytes has been described. This might be the reason for increased MSC number in OA. The aim of this study was to investigate the effects of the most important sympathetic neurotransmitter norepinephrine (NE) on MSC chondrogenesis.

Methods: Human bone marrow derived MSCs were expanded in serum containing medium. After achieving confluence, 3D aggregates were formed and chondrogenesis was initiated by the use of a specific serum-free chondrogenic medium. Parallel to control conditions, aggregates were incubated with different concentrations of NE (10^{-9} to 10^{-6} M). Based on the first results aggregates were treated with specific β-adrenoceptor agonist (isoproterenol) or antagonist (nadolol). After 21 days, the quality of aggregate chondrogenesis was evaluated macroscopically, histologically and biochemically. Furthermore, specific adrenoceptors (α1 and β2) were detected.

Results: Aggregates treated with high NE concentrations (10^{-7} to 10^{-6}M) or with isoproterenol were smaller, showed a weaker staining of cartilaginous matrix and significantly reduced type II collagen synthesis than control aggregates or aggregates treated with lower NE concentrations or nadolol alone. Nadolol reversed the effects of NE and isoproterenol. In addition, acceleration of chondrocyte hypertrophy (increased MMP13 and type X collagen expression) was observed after NE and isoproterenol addition, which was reversed by nadolol. Presence of specific adrenoceptors (α1 and β2) was shown in the aggregates undergoing chondrogenesis.

Conclusion: The suppression of chondrogenesis by high NE or isoproterenol suggests that the β-adrenoceptors mediate this effect. This pathway might influence existing or migrating MSCs and play a role in OA development and manifestation. Further experiments are required to discover underlying signalling pathways, which might help to develop therapy options for the regeneration of injured or osteoarthritic cartilage tissue.

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Adiponectin Is Associated with Joint Inflammation and Cartilage Degradation in Osteoarthritis. Anna Koskinen[1], Sami Juslin[1], Katriina Vuolteenaho[1], Riina Nieminen[1], Teemu Moilanen[2] and Eeva Moilanen[1]. [1]The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland, [2]The Immunopharmacology Research Group, University of Tampere School of Medicine, Tampere University Hospital, and Coxa Hospital for Joint Replacement, Tampere, Finland

Background/Purpose: Adipocytokine adiponectin is known to regulate insulin sensitivity, energy metabolism and appetite. Recently, it has also been related to inflammation and arthritis. The aim of the present study was to investigate the association and effects of adiponectin on inflammation and cartilage destruction in osteoarthritic joints.

Methods: Blood and cartilage samples were collected from 35 male patients with OA undergoing total knee replacement surgery. Preoperative radiographs were evaluated according to the Ahlbäck grading scale for knee osteoarhtritis. Plasma concentrations of adiponectin and biomarkers of cartilage degradation, i.e. COMP (cartilage oligometric matrix protein)

and MMP-3 (matrix metalloproteinase 3) were measured by immunoassay. Cartilage samples were cultured for 42h, and amounts of adiponectin released into the culture media were measured and correlated to NO (nitric oxide), IL-6 (interleukin-6), MMP-1 and MMP-3 production. The effects of adiponectin on NO, IL-6, and MMP production in cartilage were studied in cell and tissue culture experiments.

Results: Plasma adiponectin concentrations correlated positively with biomarkers of cartilage degradation, i.e. with COMP (Pearson r=0.54, p<0.001, ln transformation) and with MMP-3 (r=0.34, p=0.046). Patients with the most severe radiographic findings (Ahlbäck grades IV-V) had higher circulating adiponectin concentrations as compared to patients with milder OA (grades I-III; p=0.012). OA cartilage was found to produce adiponectin and the amount of adiponectin released by cultured cartilage was also higher in samples from patients with the most severe radiographic findings (grades I-III vs. grades IV-V; p<0.001). In addition, adiponectin amounts released by cartilage in culture correlated positively with production of NO (r=0.34, p=0.049), IL-6 (r=0.39, p=0.021, ln transformation) and MMP-3 (r=0.36, p=0.037, ln transformation). Exogenous adiponectin, when added into the culture, enhanced production of NO, IL-6, MMP-1 and MMP-3 in primary human chondrocytes and in OA cartilage *in vitro* by a p38 MAP kinase dependent manner.

Conclusion: Adiponectin was found to correlate with OA biomarkers, with radiographic severity of OA and with production of catabolic/ inflammatory factors by cartilage *ex vivo*. In addition, adiponectin enhanced production of catabolic and inflammatory factors in OA cartilage and chondrocytes. These findings suggest that adiponectin is involved in the pathogenesis of joint inflammation and cartilage destruction in osteoarthritis and may be a target for disease-modifying drug development.

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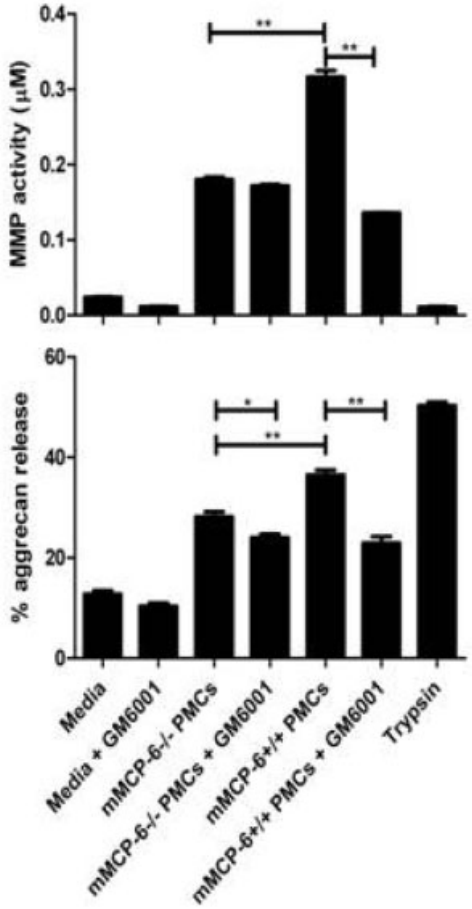
Mast Cell-Restricted, Tetramer-Forming Tryptases Are Novel Mediators of Articular Cartilage Aggrecanolysis by Activating Matrix Metalloprotease Zymogens. Natalia Magarinos[1], Katherine J. Bryant[1], Amanda J. Fosang[2], Richard L. Stevens[3] and H. Patrick McNeil[1]. [1]University of New South Wales, Sydney, Australia, [2]University of Melbourne, Melbourne, Australia, [3]Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Background/Purpose: The mast cells (MCs) in human and mouse synovium express hTryptase-β and its ortholog mouse mast cell protease (mMCP)-6, respectively. During experimental inflammatory arthritis, more aggrecan proteoglycan is lost from cartilage of mMCP-6-null C57BL/6 mice than wild-type C57BL/6 mice. We therefore used *ex vivo* cultures of mouse femoral head explants to explore the mechanism(s) of tryptase-mediated aggrecanolysis.

Methods: Mouse femoral head cartilage explants were freeze-thawed to devitalise chondrocytes, then cultured in the presence or absence of recombinant hTryptase-β or granule protein from peritoneal MCs (PMCs) isolated from mMCP-6$^{+/+}$ or mMCP-6$^{-/-}$ mice. Cartilage-derived aggrecan fragments in the media were measured using a glycosaminoglycan (GAG) dye-binding assay. Aggrecan degradation products were characterised by immunoblotting using antibodies that recognize the DIPEN neoepitope formed during matrix metalloprotease (MMP)-dependent aggrecanolysis. A fluorimetric assay was used to quantitate MMP activity in the cartilage explants. Activation of recombinant human proMMP-3 by hTryptase-β was determined by immunoblotting.

Results: Human and mouse MC tryptases induced significant release of aggrecan fragments from freeze-thawed femoral heads, indicating living chondrocytes were not required for tryptase-mediated aggrecanolysis. The finding that hTryptase-β and mMCP-6 failed to cleave purified aggrecan efficiently suggested that their aggrecanolysis activities were a result of activation of an aggrecan-degrading protease zymogen constitutively present in cartilage. In support of this conclusion, incubation of proMMP-3 with hTryptase-β *in vitro* resulted in conversion of the zymogen into its enzymatically active form. hTryptase-β caused release of 28% of aggrecan from articular cartilage within 24 h compared to 14% release from cartilage cultured in media alone (P<0.001). Similarly, the granule protein from mMCP-6$^{+/+}$ PMCs induced significantly greater release of GAGs (37%) compared to that obtained with the granule protein from mMCP-6$^{-/-}$ PMCs (28%) (P<0.01). Aggrecan fragments released into the media by hTryptase-β or mMCP-6$^{+/+}$ PMC granules possessed the DIPEN neoepitope, consistent with MMP-dependent proteolysis of aggrecan. Incubation of femoral heads with hTryptase-β or mMCP-6$^{+/+}$ PMC granules resulted in increased MMP enzymatic activity. Finally, the abilities of hTryptase-β and mMCP-6$^{+/+}$ PMC granules to induce aggrecanolysis were significantly inhibited by 72% and 57%, respectively, when cartilage explants were co-incubated with the MMP-inhibitor GM6001 (P<0.01).



Conclusion: The accumulated data suggest that tetramer-forming human and mouse tryptases participate in the early-stages of cartilage destruction in arthritis, in part, by activating latent MMPs that are constitutively present in cartilage's extracellular matrix.

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Calcium Mineral Deposition In the Cultures of Fibroblast-Like Synoviocytes. Yubo Sun, David Mauerhan, Atiya Franklin, Andrew Sun, Natalia Zinchenko, H. Norton, Edward Hanley Jr. and Helen Gruber. Carolinas Medical Center, Charlotte, NC

Background/Purpose: Calcium crystals are present in synovial fluid of ~75% of patients with osteoarthritis (OA) and up to 26% of patients with rheumatoid arthritis (RA). Recent findings, however, demonstrate that calcium crystals are present in all articular cartilage of patients with OA. Recent findings also demonstrate that more calcium deposits or crystals were formed in the monolayer culture of OA articular chondrocytes and OA meniscal cells than in the monolayer culture of those corresponding cells derived from control subjects. These newer findings indicate that pathological calcification occurs in all cases of OA and that pathological calcification is a cell-mediated process. In this study we hypothesized that fibroblast-like synoviocyte (FLS) also play a role in the formation and deposition of synovial calcium crystals.

Methods: Selected genes implicated in biomineral formation in hTERT-OA 13A FLS and hTERT-RA 516 FLS were examined for their expression using real-time RT-PCR. Calcium deposition in monolayer cultures of OA FLS and RA FLS was investigated using an ATP-induced ^{45}calcium deposition assay. Inhibition of calcium deposition by phosphocitrate, a calcification inhibitor, was also investigated using the ATP-induced ^{45}calcium deposition assay. Calcium mineral formation in monolayer cultures and micromass cultures of hTERT-OA 13A FLS and hTERT-RA 516 FLS grown under conditions promoting chondrogenesis (micromass formation) were examined with alizarin red staining.

Results: Several genes involved in biomineral formation, including ankylosis progressive homolog and ectonucleotide pyrophosphatase 1, were upregulated in hTERT-OA 13A FLS compared to hTERT-RA 516 FLS. Calcium deposition in monolayer cultures of OA FLS was significantly greater than that in monolayer cultures of RA FLS. Calcium minerals were detected in micromass cultures of hTERT-OA 13A FLS, but not in hTERT-RA 516 FLS. Examination using polarized microscope indicated that the majority of calcium minerals were basic calcium phosphate (BCP) crystal aggregates. Phosphocitrate, a calcification inhibitor, was found to potently inhibit OA FLS-mediated calcium deposition at concentrations of 0.1 to 0.5 mM.

Conclusion: OA FLS is not a passive bystander and may play an active role in the formation of synovial calcium crystals. Therefore, OA FLS may be valid target for OA intervention. Phosphocitrate may have other unidentified molecular targets whose identification may provide information important for the development of new novel drugs for OA therapy, and valuable for a better understanding of the disease mechanisms of OA.

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Infliximab Does Reverse Cytokine - Mediated Anti-Apoptotic Effects In CD14 $^{+}$/CD11b^{+} Circulating Monocytes - Implications for Osteoclastogenesis. Michael Seitz, Daniel Aeberli, Richard K. Kamgang, Willy Hofstetter, Deepak Balani and Peter M. Villiger. University Hospital, Bern, Switzerland

Background/Purpose: To study apoptosis in circulating CD14^{+}/CD11b^{+} monocytes treated with the chimeric TNFa antibody infliximab *in vitro* and *ex vivo*.

Methods: The induction of apoptosis in circulating CD14^{+}/CD11b^{+} monocytes from peripheral blood was investigated *in vitro* in cells from 16 healthy subjects and *ex vivo* in cells from 6 patients with ankylosing spondylitis (AS) that were treated with infliximab. The monocytes from healthy donors were exposed *in vitro* to interferon-g (IFNg) and tumor necrosis factor—a (TNFa) in the presence or absence of subsequent infliximab. Induction of apoptosis was detected by staining with annexinV and propidium iodide (PI). Osteoclastogenic potential of monocytes was tested *in vitro* by growing cells on dentin wafers.

Results: Treatment of monocytes from healthy donors with IFNg or TNFa caused a decrease in the number of CD14^{+}/CD11b^{+}/ annexinV^{+} monocytes ($p = 0.03$) and of CD14^{+}/CD11b^{+}/PI^{+} monocytes after TNFa exposure ($p=0.03$). This effect which was reversed by infliximab. Correspondingly, 2 days after the first infliximab infusion in AS patients, the numbers of CD14^{+}/ CD11b^{+}/annexinV^{+} and CD14^{+}/CD11b^{+}/PI^{+} monocytes increased, a change which was accompanied by a depletion of circulating monocytes. Based on their bone resorbing activity CD14^{+}/CD11b^{+} monocytes were further characterized as osteoclast precursor cells (OPC).

Conclusion: The findings of this study suggest that the anti-bone resorptive effects of infliximab are mediated by a rapid induction of apoptosis in OPC in patients with chronic inflammatory diseases.

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New Alginate-Chitosan Hydrogel Beads with Anti-Inflammatory and Anabolic Effects on Human Chondrocytes. Frédéric Oprenyeszk[1], Christelle Sanchez[1], Jean-Emile Dubuc[2], Véronique Maquet[3] and Yves Henrotin[4]. [1]University of Liège, Liège, Belgium, [2]Clinical University Saint Luc, Bruxelles, Belgium, [3]KitoZyme SA, Herstal, Belgium, [4]Univ of Liege/ Pathology Inst, Liege, Belgium

Background/Purpose: Today there is no treatment to cure osteoarthritis (OA) or to delay effectively its progression. Current treatments are mainly based on the alleviation of painful symptoms but are unable to restore the cartilage. The development of new scaffolds for tissue engineering is a promising approach. Herein, we report the effects of alginate-chitosan hydrogel (AC) beads on the metabolism of chondrocytes.

Methods: Human chondrocytes were isolated from OA cartilage and then cultured either in AC beads or in alginate (A) beads. AC beads were prepared using ultra-pure chitosan (KiOmedine-CsU, KitoZyme, Herstal, Belgium) with molecular weight of 40 K (AC40) or 20 K (AC20) and alginate (Sigma Aldrich, Bornem, Belgium). The two polymer solutions were prepared separately before being mixed together. Cells were added to the polymer mixture and the cell-containing beads prepared by precipitation in a calcium chloride solution. The chondrocytes embedded in the beads (0.5 to 1×10^5 cells/bead) were then cultured in a well defined culture medium for 21 days. Cell viability was determined by quantifying the amount of lactate deshydrogenase (LDH) released in the culture medium. Interleukin (IL)-6 and −8, Matrix Metalloproteinase (MMP)-3 and aggrecan (AGG) were measured by specific sandwich enzyme-linked immunoabsorbent assays (ELISA). A spectrophotometric method based upon the Griess reaction was used to quantify nitric oxide (NO) product.

Results: Histological analysis of AC beads showed a homogeneous distribution of chitosan trabeculae in the alginate matrix and the presence of chondrocytes in contact with chitosan trabeculae. LDH level remained below the limit of detection over the culture duration suggesting that the AC had no cytotoxic effect. By comparison with cells cultured in A beads, chondrocytes cultured in AC40 or AC20 beads produced significantly higher amounts of AGG but lower levels of MMP-3, NO, IL-6 and IL-8 factors (Table 1).

Table 1. AGG, MMP-3, NO, IL-6 and IL-8 production of chondrocyte in AC40 and AC20 beads.

	AGG	MMP-3	NO	IL-6	IL-8
AC40	217.68 ± 72.24***	59.04 ± 30.04**	46.82 ± 6.21***	19.17 ± 14.8***	17.16 ± 3.37***
AC20	154.27 ± 15.23**	21.69 ± 16.64***	42.12 ± 20.20***	12.67 ± 2.58***	6.12 ± 3.37***

Results were represented as % of production of chondrocytes in A beads. Results were expressed as mean ± SEM (n=9). Comparison of mean values was performed by Student t parametric analysis. *** $p < 0.001$, ** $p < 0.01$ production of cells in AC beads was significantly different than production of cells in A beads.

Conclusion: AC beads reduce the production of inflammatory and catabolic mediators by OA chondrocytes and promote the synthesis of cartilage-specific matrix components. These particular effects indicate that AC beads are potential carriers for cell transplantation, and particularly to repair cartilage defects.

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Activation of Adenosine A_{2A} Receptors Prevents Wear Particle-Induced Osteolysis. Aranzazu Mediero[1], Sally Frenkel[2], Tuere Wilder[1] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]Hospital for Joint Disease, New York, NY, [3]New York Univ Medical Center, New York, NY

Background/Purpose: Prosthesis loosening is a common cause for joint prosthesis failure and necessitates further restorative surgery. Aseptic failure of cemented prostheses is associated with wear particle-induced inflammation and bone destruction mediated by osteoclasts. Adenosine A_{2A} receptors ($A_{2A}R$) mediate potent anti-inflammatory effects in many tissues and prevent osteoclast differentiation. We therefore tested the hypothesis that the selective $A_{2A}R$ agonist CGS21680 prevents osteoclast-mediated bone resorption at sites of prosthesis wear in a calvaria model of wear particle-induced bone resorption.

Methods: 52 C57Bl/6 (WT) and 18 A_{2A}KO mice age 6–8 weeks were anesthetized and a 1cm midline sagittal incision was made over the calvaria. 12 WT and 6 A_{2A}KO mice received no particles (Control), and the rest received 3mg of polyethylene particles (UHMWPE). 9 WT and 6 A_{2A}KO mice received 20μl of saline 0.9% at the surgical site, and the rest received 20μl of CGS21680 (1μM-1nM) every day. Animals were sacrificed after 14 days and calvaria were prepared for microCT, histological studies and cytokine assay.

Results: MicroCT analysis demonstrated pitting and increased porosity in untreated particle-exposed mice but treatment with CGS21680 significantly reduced the area of resorption in a dose-dependent manner (by as much as 41±11% of control resorption, $IC_{50} = 8.9$ nM, $p<0.05$). In CGS21680-treated mice the reduction in cortical bone was significantly less than in untreated-particle-exposed mice ($p<0.01$) and CGS21680-treated calvaria had significantly greater mean bone volume than did the untreated-group ($p<0.0005$). Histological examination of calvaria demonstrated a lymphohistiocytic infiltration in both particle-exposed groups that was significantly diminished by CGS21680 in a dose-dependent manner ($IC_{50} = 10$ nM). In contrast, CGS21680 did not affect inflammation or osteoclast-mediated bone resorption in A_{2A}RKO mice (p=NS for all measures above) Immunohistochemistry for RANK, RANKL, Cathepsin K, CD163, TNFα and Osteopontin revealed a marked increased in expression of these proteins in particle-exposed groups that was diminished by treatment with CGS21680. Similarly, CGS21680 treatment reduced TRAP+ osteoclasts in a dose-dependent manner ($IC_{50} = 10$ nM). There were decreased concentrations of IL-1β and TNFα in CGS21680 treated animals (Il-1β: Control: 168±11 pg/ml, Particle/Saline: 256±10 pg/ml, CGS21680: 101±7 pg/ml, $p<0.01$ respectively: TNFα: Control 85±8 pg/ml, Particle/Saline: 158±5 pg/ml, CGS21680: 111±3 pg/ml, $p<0.01$ and $p<0.05$ respectively).

Conclusion: Adenosine $A_{2A}R$ activation reduces inflammation and osteoclast-mediated bone destruction due to prosthetic wear particles in a dose-dependent manner. This suggests that site-specific delivery of the $A_{2A}R$-agonist could enhance implant survival, delaying or eliminating the need for revision arthroplastic surgery.

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Heme Oxygenase-1 Lentiviral Transduction of Human Osteoarthritic Osteoblasts Down-Regulates Inflammatory, Degradative and Senescence Markers. Maria Isabel Guillen[1], Victoria Clerigues[1], Miguel Angel Castejon[2], Francisco Gomar[3] and Maria Jose Alcaraz[1]. [1]University of Valencia, Burjasot, Valencia, Spain, [2]La Ribera Hospital, Alzira, Valencia, Spain, [3]University of Valencia and University Hospital, Valencia, Spain

Background/Purpose: In previous works we demonstrated that the antioxidant enzyme heme oxygenase-1 (HO-1) protects against inflammatory and degenerative effects of IL-1β in osteoarthritic (OA) chondrocytes and synoviocytes. Osteoblasts play an important role in remodelling processes in OA. In this work we studied HO-1 effects on inflammatory, degradative and senescence markers in OA osteoblasts stimulated with IL-1β. Overexpression of HO-1 was performed by infection of these cells with lentiviral vectors.

Methods: The knee specimens were obtained from 46 patients with the diagnosis of advanced OA (71.5±7.1 years, mean ± S.E.M.) undergoing total knee joint replacement. The pieces of trabecular bone were obtained from the femoral condyles and tibial plateau, and cells were isolated after collagenase digestion. Osteoblasts were cultured in osteogenic medium and used at third passage. Lentiviral vector stocks were generated in HEK293T cells by calcium phosphate-mediated transient transfection of psPAX2, pMD2G and pWXL plasmids for 24 and 48h. The titers of lentiviral stocks were in the range of $3–5 \times 10^5$ IU/ml as determined by immunocytochemical analysis of HEK293T-infected cells. Osteoblasts culture was infected with LV-HO-1 flag or control empty vector, LV(−) for 24 h. After infection and culture in osteogenic medium for 2 days, osteoblasts were stimulated with IL-1β (10 ng/ml) for 24 h. HO-1 expression was measured by immunofluorescence using an anti-flag monoclonal antibody. PGE_2 was evaluated by RIA, IL-6, TNF-α, IL-10, matrix metalloproteinases (MMPs) and transcription factors NF-κB and AP-1 by ELISA, COX-2, mPGES-1, osteocalcin (OCN), osteopontin (OPN), collagen 1A1, collagen 1A2, osteoprotegerin (OPG), RANKL, and senescence markers (hTERT, caveolin and p21) by real-time PCR.

Results: Lentiviral vectors showed not toxicity on OA osteoblasts, evaluated by trypan blue exclusion test. The results showed that IL-b decreased HO-1 expression in cells treated with IL-1β and transfected with LV(−). However, in LV-HO-1 flag-transfected cells, IL-b did not alter the expression of HO-1. These effects were observed at protein and mRNA levels. IL-1β significantly increased the production of PGE_2, COX-2, mPGES-1, IL-6, TNF-α, MMP- 1, 2 and 3, with respect to basal conditions. In LV-HO-1 flag cells, all these mediators were significantly reduced. In contrast, HO-1 overexpression increased the production of IL-10, OCN, OPN, collagen 1A1, and the ratio OPG/RANKL, with respect to IL-1β control cells. The evaluation of senescence parameters showed that in cells transfected with LV-HO-1 flag hTERT was enhanced and caveolin decreased. The analysis of transcription factors showed HO-1 overexpression significantly reduced NF-κB activation in osteoblasts stimulated with IL-1β.

Conclusion: In this study we have demonstrated that HO-1 down-regulates the inflammatory response and cellular senescence besides exerting a positive effect on osteoblastic markers. HO-1 may be a novel therapeutic target in inflammatory and degradative processes in OA bone

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Human End-Stage Osteoarthritic Cartilage is Responsive to Transforming Growth Factor Beta and Contains a Population of Cells That Expresses SMAD2/3P and SMAD1/5/8P. Arjan P. M. van Caam, Esmeralda N. Blaney Davidson, Elly L. Vitters, Wim B. van den Berg and Peter M. van der Kraan. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Joint diseases such as osteoarthritis (OA) result in destruction of articular cartilage. Transforming Growth factor beta is considered as a protective factor in young cartilage while this function is lost upon aging. In chondrocytes, TGF beta can signal via phosphorylation of SMAD2/3 (via ALK5) or SMAD1/5/8 (via ALK1). In earlier studies we have found that in young healthy human cartilage (age < 10 years) only SMAD2/3 phosphorylation (SMAD2/3P) occurs and no SMAD1/5/8 phosphorylation (SMAD1/5/8P). Moreover, in human OA cartilage we showed a significant correlation between ALK1 and MMP13 expression. Our goal was to study the expression of SMAD2/3P and SMAD1/5/8P in chondrocyte populations in end-stage human OA cartilage and whether addition of exogenous TGF beta modulates the expression of MMP13 and ALK5 and ALK1 in this cartilage.

Methods: Human OA articular cartilage was obtained during knee joint replacement (n=20). Cartilage sections were stained for SMAD2/3P and SMAD1/5/8P using specific antibodies. In addition, human OA cartilage was incubated with 10 ng/ml TGF beta for 24h. Part of the cartilage explants were pre-incubated with the ALK5 inhibitor SB-505124 (50μM) for 6 hours. Expression of MMP13, ALK5 and ALK1 was analyzed by quantitative PCR.

Results: Staining for both SMAD2/3P and SMAD1/5/8P was observed in human OA cartilage. Strikingly, SMAD2/3P staining was mostly negative in histological intact cartilage areas while cells in damaged areas, mainly in chondrocyte clusters, were often strongly positive. Also staining for SMAD1/5/8P was most intense in cells surrounding damaged regions and chondrocyte clusters. Incubation of human OA cartilage with TGF beta significantly down regulated MMP13 expression. This effect was totally abolished by the ALK5 inhibitor SB-505124. TGF beta also significantly elevated ALK5 expression, and decreased ALK1 expression, and both these effects were completely blocked by pre-incubation with SB-505124.

Conclusion: Stimulation of human end-stage OA cartilage with high TGF beta concentrations down regulates MMP13 expression and modulates TGF beta type I receptors, increasing the ALK5/ALK1 ratio. These effects all run via SMAD2/3 (ALK5). We propose, based on these results and earlier findings, that during aging TGF beta loses its protective role by a loss of SMAD2/3 signaling in articular chondrocytes. This loss plays a role in the initiation of cartilage degradation. In end-stage OA cartilage the majority of cells does not display either SMAD2/3P or SMAD1/5/8P. However, neighboring severely damaged cartilage a population of chondrocytes is present, most probably involved in (unsuccessful) repair, that expresses SMAD2/3P and SMAD1/5/8P.

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A Single Injection of Adipose-Derived Stem Cells Protects Against Cartilage Damage and Lowers Synovial Activation in Experimental Osteoarthritis. Menno C. ter Huurne[1], Peter L.E.M. van Lent[1], Arjen B. Blom[1], Roxane Blattes[2], Yannick Jeanson[2], Louis Casteilla[2], Christian Jorgensen[3] and Wim B. van den Berg[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]INSERM U1031, Toulouse, France, [3]Hospital Lapeyronie, Montpellier, France

Background/Purpose: Synovial activation is evident in a substantial subpopulation of patients with early osteoarthritis (OA) and has been associated with pathophysiology and clinical symptoms of OA. Previous studies have shown that synovial activation is involved in mediating cartilage destruction during experimental OA. Recently it has been shown that Adipose-derived Stroma/Stem Cells (ASCs) express immunosuppressive characteristics. The aim of our study was to explore the effect of intra-articular injection of ASCs on synovial activation and cartilage destruction during experimental OA.

Methods: ASCs were isolated from inguinal fat surrounding the popliteal lymph nodes and cultured for two weeks according to standard procedures. Experimental OA was induced by injection of collagenase into murine knee joints, which causes instability and cartilage destruction. Collagenase-induced OA is characterized by thickening and activation of the synovial lining layer. ASCs were injected into knee joints at various time-points after induction of OA. OA phenotypes were measured within 8 weeks after induction. Total knee joints were isolated and processed for histology. Synovial activation was measured using an arbitrary scale (0 to 3) and cartilage destruction was measured in 4 different layers of the knee joint (medial and lateral tibia and femur) according to the scoring method of Pritzker et al.. Damage to the cruciate ligaments was scored using an arbitrary scale (0 to 5). Moreover, cartilage formation was assessed by quantification of proteoglycans in Safranin O stained sections, using an arbitrary scale (0 to 5).

Results: A single dose of ASCs (20×10^3 in mouse serum) was injected into the knee joint of mice, 7 days after induction of osteoarthritis. Histology showed that synovial activation was significantly inhibited at day 14 (9%) and day 42 (35%) when compared to serum treated joints. Destruction of cartilage was also significantly inhibited at day 14 (54%) and at day 42 (35%). Inhibition of cartilage destruction was particularly found in the medial tibia. Interestingly, ASC-treatment had a protective effect on the cruciate ligaments. At day 42, damage to the ligaments was reduced by nearly 50% in the ASC treated joints when compared to

controls. In line with that, 88% of the serum injected animals showed a dislocation of the knee joint, in contrast to only 25% of the ASC treated animals. Strikingly, new formation of cartilage was 50% lower in the ASC treated animals. In contrast to early treatment, injection of the same dose of ASCs, 14 days after induction of OA only showed a small inhibiting effect (11%) on synovial activation when measured at day 42. Although cartilage destruction diminished with 28%, these values did not reach significance at that time-point.

Conclusion: Our study indicates that a single injection of ASCs into the knee joints of mice with collagenase-induced osteoarthritis gives protection of synovial activation and cartilage destruction when given shortly (day 7) after induction of experimental OA, probably by protecting cruciate ligament destruction.

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Chondrocytes in a Subset of Osteo-Arthritic Patients with Reduced Nuclear FactorkappaB-p65 Levels Are Vulnerable to Apoptosis Induced by Tumor Necrosis Factor Alpha, Which Could Be Released by the Synovium. Onno J. Arntz, Eline A. Vermeij, Esmeralda N. Blaney Davidson, Shahla Abdollahi-Roodsaz, Miranda B. Bennink, Peter M. van der Kraan, Wim B. van den Berg and Fons Van De Loo. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Chondrocytes play a central role in cartilage pathology as seen in rheumatoid arthritis (RA) and osteoarthritis (OA) patients by a deranged synthesis of extracellular matrix (ECM) components and the enhanced release of ECM destructive metalloproteinases (MMPs). Nuclear factor-kappaB (NF-kappaB) is an important transcription factor in the regulation of MMPs, but is also regarded as a survival factor in cells. We studied the levels of NFkappaB-p65(P65) in articular chondrocytes of osteoarthritis(OA), rheumatoid arthritis(RA), and mouse models and study the biological consequence regarding cell viability.

Methods: Levels of P65 were detected by immunohistochemistry and RT-qPCR levels in human cartilage of RA and OA patients, in murine cartilage of the spontaneous osteoarthritis mouse model (STR/ort) and cartilage from young (14 weeks) and old (>12 months) C57Black/6 mice. To study the functional consequences of decreased level of P65 in chondrocytes the murine H4 chondrocyte-cell line was stably transduced with a lentivirus expressing a short-hairpin RNA against P65 to reduce the P65 protein levels by a RNA interference approach. We selected several cell lines that expressed different amounts of P65 protein. To study the biological consequences, IL-1β, TNFα or conditioned medium of OA synovium was added to the murine chondrocyte-cell line with the lowest P65 level. Cell death was measured by Facs analysis of 7-AAD positive cells. In conditioned medium of OA synovium, levels of TNFα were measured by Luminex. P65 and an apoptotic marker (Caspase-3 active form) were detected by immunohistochemistry in serial paraffin sections of human OA cartilage explants from 6 different patients (4–10 section each patient). To study a relation between P65 in chondrocytes, synovial TNFα production and chondrocyte cell death, in 6 OA patients levels were detected in the same joint.

Results: A subset of OA patients showed low P65 levels (5 out of 10) compared to RA. In STR/ort mice levels were diminished more than 75% when joints became affected. Levels of P65 in normal young and old mice were equal. *In vitro*, adding TNFα to selected chondrocyte cell lines caused only cell death in the cell-line with low levels of P65. IL-1 had no effect on cell viability. Challenging the cell line with low P65 levels with conditioned medium from synovial tissue resulted in more than 60% chondrocyte death in 3 of the 5 OA patients. Synovial TNFα production was detected in the same samples that caused cell death. In human OA cartilage, chondrocyte P65 showed a significant negative correlation with Caspase-3 (an apoptotic marker) staining. Analyzing all parameters of a single joint in 6 OA patients showed that the combination of low endogenous P65 levels in cartilage and synovial TNF production caused chondrocyte cell death.

Conclusion: This study clearly demonstrated that low levels of P65 makes chondrocytes more vulnerable for TNFα, a cytokine which can be produced by the synovial tissue during OA, and that this transcription factor is downregulated in chondrocytes in murine OA and a considerable portion of OA patients.

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Adipokines Leptin and Adiponectin Correlate with Matrix Metalloproteinases and Interleukin-6 in Synovial Fluid From Osteoarthritis Patients and Enhance Their Production in Osteoarthritic Cartilage *Ex Vivo*. Katriina Vuolteenaho[1], Anna Koskinen[1], Sami Juslin[1], Riina Nieminen[1], Teemu Moilanen[2] and Eeva Moilanen[1]. [1]The Immunopharmacology Research Group, University of Tampere School of Medicine, and Tampere University Hospital, Tampere, Finland, [2]Coxa Hospital for Joint Replacement, Tampere, Finland

Background/Purpose: Adipokines leptin and adiponectin were first discovered to be produced by adipose tissue and to regulate energy metabolism and apetite. Interestingly, they have recently been found also in inflamed joints and related to the regulation of inflammatory responses. In arthritis, proteolytic degradation of cartilage is mediated by matrix metalloproteinases (MMPs) and interleukin-6 (IL-6) contributes to joint inflammation. In the present study, we investigated the effects of leptin and adiponectin on human OA cartilage, and further, assessed the association of leptin and adiponectin to MMPs and IL-6 in synovial fluid from osteoarthritis patients.

Methods: Cartilage samples for tissue culture were collected from OA patients undergoing total knee replacement surgery. The effects of leptin and adiponectin on MMP and IL-6 production in cartilage were studied in tissue culture experiments and in primary OA chondrocytes and the signaling pathways involved were studied by pharmacological means. Synovial fluid samples were obtained from 100 OA patients (62 females, BMI 30.8±0.6kg/m2, age 70.0±1.0 years; mean±SEM), and concentrations of leptin, adiponectin, MMPs and IL-6 were measured by immunoassay.

Results: Leptin and adiponectin enhanced production of MMPs and IL-6 in OA cartilage and in primary OA chondrocytes in vitro. Leptin-induced MMP-1, −3 and −13 and IL-6 productions were dependent on activation of MAP kinase JNK. In addition, p38 was involved in the leptin-induced MMP-1 and MMP-13 production and ERK1/2 pathway in MMP-1 production. Adiponectin enhanced IL-6, MMP-1 and MMP-3 production in OA cartilage culture was mediated by p38. In addition, Erk1/2 and JNK mediated adiponectin-induced production of IL-6 while contribution of these pathways to MMP-1 and MMP-3 production was smaller and did not reach statistical significance.

To evaluate if the stimulatory effect of these adipokines on IL-6 and MMPs in OA cartilage *ex vivo* could be translated *in vivo*, the concentrations of leptin, adiponectin, MMPs and IL-6 were determined in synovial fluid from OA patients. Synovial fluid leptin correlated positively with MMP-1 ($r=0.41$, $p<0.001$) and MMP-3 ($r=0.51$, $p<0.001$) as well as with IL-6 ($r=0.33$, $p=0.002$). There was also an association between adiponectin and IL-6 ($r=0.39$, $p<0.001$), MMP-1 ($r=0.31$, $p=0.004$) and MMP-3 ($r=0.27$, $p=0.011$).

Conclusion: The findings support the idea of leptin and adiponectin as catabolic and proinflammatory factors in the pathogenesis of OA, and as possible link between obesity and osteoarthritis.

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Adenosine A1 Receptor Blockade Inhibits Osteoclast Formation of Mouse Bone Marrow Cells by Downregulation RANKL Signaling. Wenjie He[1] and Bruce N. Cronstein[2]. [1]NYU, New York, NY, [2]New York Univ Medical Center, New York, NY

Background/Purpose: Adenosine is a purine molecule necessary for normal cell metabolism and growth. Previous work from our laboratory has uncovered a critical role for adenosine A1 receptors (A1R) in RANKL-stimulated osteoclast formation both in vivo and in vitro. In this study, we examined the effect of A1R blockade on RANKL-RANK signaling in osteoclast formation.

Methods: Osteoclasts were generated from bone marrow cells extracted from the femurs and tibiae of 4–6-week-old female C57BL/6 mice by exposure to macrophage colony-stimulating factor (M-CSF) and RANKL. The A1R specific antagonist, DPCPX, was added to bone marrow macrophages (BMMs) with RANKL for 5 days.

Results: A1R blockade inhibits the differentiation of BMMs into TRAP+ multinucleated cells by as much as 51% ($p<0.001$, $n=3$; $IC_{50}= 0.1\mu M$). Both western blot analysis of nuclear extracts and ELISA showed that A1R blockade markedly inhibits NF-kappa B activation: p65 nuclear translocation and p65 transcription activity ($p<0.05$, $n=4$). TRAF6, an adaptor protein that regulates RANKL signaling, was immunoprecipitated from BMMs and immunoblotted for TAK1, a serine/threonine kinase that, on activation, forms a complex with TRAF6 and subsequently activates NF-kappaB activity. A1R blockade by DPCPX diminishes TAK1 association with TRAF6 by 44.1% ($p<0.05$, $n=4$).

Conclusion: These results are consistent with the hypothesis that endogenously released adenosine, acting at A1 receptors, provides critical intracellular signals required for downstream activation of NF-κB, an event required for osteoclastogenesis. This study further supports the notion that adenosine A1 receptors may represent a novel therapeutic target to control bone resorption associated with postmenopausal osteoporosis or such pathologic conditions as Rheumatoid Arthritis.

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MAPK-Activated Protein Kinase-2 (MK2) Regulates Bone Homeostasis. Tobias Braun[1], Johannes Lepper[1], Gisela Ruiz Heiland[1], Georg Schett[1] and Jochen Zwerina[2]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Hanusch Hospital, Vienna, Austria

Background/Purpose: Mitogen-activated protein kinase (MAPK)-activated protein kinase 2 (MK2) is an intracellular signal transduction molecule mediating inflammatory signals. Recent data indicate a strong link between the immune system and regulation of bone homeostasis. The aim of our study is to determine whether MK2 contributes to the regulation of osteoclastogenesis and bone turnover.

Methods: Osteoblasts and osteoclasts were generated from wildtype and $MK2^{-/-}$ mice ex vivo. Gene expression of osteoblast- and osteoclast- associated genes was determined by real-time PCR. Bone turnover was analysed by determination of serum levels of RANKL, OPG, CrossLaps and osteocalcin. Bone histomorphometry and μCT were used to determine bone turnover in vivo in wildtype and $MK2^{-/-}$ mice. A four-p point-bending test was used to evaluate bone quality of tibiae from wildtype and MK2- deficient mice. Finally, ovariectomy was performed in wildtype and MK2- deficient mice.

Results: MK2- deficient osteoclast precursor cells showed impaired differentiation capacity ex vivo and expression of osteoclast- specific genes was reduced. MK2- deficient osteoblasts showed an increased expression of OPG in vitro. Bone histomorphometry and μCT analysis revealed an increased bone mineral density in MK2- deficient mice. Moreover, four point bending tests demonstrated a higher mechanical stability of MK2- deficient bones. In vivo, the number of osteoclasts was reduced in $MK2^{-/-}$ mice while there was no difference in the number of osteoblasts. Serum osteocalcin and CrossLaps levels were reduced MK2 deficient mice further indicating a low bone turnover. Moreover, serum levels of OPG but not RANKL were increased in $MK2^{-/-}$ mice. Loss of MK2 partially protected mice from ovariectomy- induced bone loss.

Conclusion: MK2- deficient mice have increased bone mineral density associated with impaired osteoclast- differentiation. Further, MK2 is involved in estrogen- related bone loss. Thus, MK2 plays an important role in bone homeostasis.

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Human MSCs Ameliorate Bone Erosion in TNF-Alpha Transgenic Mice. Joy M. Whitbred[1], Robert M. Lowe[2], Donald P. Lennon[3], Joseph Molter[4], Chris A. Flask[4], Tracey L. Bonfield[2], Arnold I. Caplan[3] and Nora G. Singer[1]. [1]Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, [2]Department of Pediatrics, Case Western Reserve University, Cleveland, OH, [3]Skeletal Research Center, Case Western Reserve University, Cleveland, OH, [4]Department of Radiology, Case Western Reserve University, Cleveland, OH

Background/Purpose: Human Mesenchymal Stem Cells (hMSCs) are promising immune modulators with therapeutic potential to treat a wide variety autoimmune diseases. Pleiotropic hMSCs have shown tremendous promise as immunomodulatory therapeutic agents in mouse models of asthma, inflammatory bowel disease (IBD) and multiple sclerosis (MS). However, their role in modulating bone erosions in a mouse model with excess TNF-alpha driven arthritis (TNF-alpha Tg) has not been explored. The purpose of these studies was to quantify the effects of hMSCs on disease progression in TNF-alpha Tg mice using a sensitive imaging technique prior to the onset of clinically apparent symptoms and correlate with immunological and histological outcomes.

Methods: Interperitoneal (IP) injections of 1×10^6 hMSCs or PBS (sham injection) in TNF-alpha Tg or non-Tg control mice were administered every two weeks beginning at age 6.5 weeks and for 8 weeks thereafter. Isosurface CT renderings, joint measurements and clinical scores were recorded. Mice were sacrificed at age 14.5 weeks and histological analysis of joints was performed.

Results: Joint erosion was first detected using isosurface CT at age 8.5 weeks in TNF-alpha Tg compared with non-Tg and C57BL/6 controls. Differential disease progression was observed by CT at age 12.5 weeks in TNF-alpha Tg mice treated with hMSCs versus those that were sham-injected. Untreated 16 week old TNF-alpha Tg mice showed extensive bone erosions compared to controls using isosurface CT. As might be anticipated in the presence of constitutively expressed TNF-alpha, TNF-alpha Tg mice had some progression of arthritis despite hMSC treatment, as evidenced by joint measurements and clinical scores. Sham-treated TNF-alpha Tg mice had enhanced erythema and reduced range of motion at 14.5 weeks compared to those treated with hMSCs. Histologically, TNF-alpha Tg mice treated with hMSCs had an immature pannus development, with little or no infiltration of joint space and insignificant cartilage and bone erosions compared to sham-treated TNF-alpha Tg mice, where loss of proteoglycan, loss of joint architecture, and highly developed mature pannus was observed.

Conclusion: hMSC treatment attenuates bone erosion and joint damage in the TNF-alpha Tg model of arthritis. Isosurface CT imaging is useful to detect and quantify bone erosion at very early stages in TNF-alpha-driven arthritis. These studies provide proof of concept of the potential therapeutic efficacy of hMSC therapy in inflammatory arthritis. These data suggest that hMSCs could modulate the immune-mediated destruction of joints in early RA.

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The Role of Mir-29 in the Chondrogenic Differentiation of Mesenchymal Stem Cells. D. Guerit[1], D. Philipot[2], P. Chuchana[1], JM Brondello[2], Christian Jorgensen[3] and Daniele Noel[2]. [1]INSERM U844, Montpellier, France, [2]UM1, Montpellier, France, [3]CHU Lapeyronie, Montpellier, France

Background/Purpose: Mesenchymal stem or stromal cells (MSC) are multipotent cells that can differentiate into different lineages, particularly osteoblasts and chondrocytes. The differentiation process of MSC is regulated by various molecules among which Sox9 and Runx2 are key transcription factors leading, respectively to chondrogenesis or osteogenesis. Recently, a new class of regulating factors, namely microRNAs (miRs), has been shown to be important for differentiation processes but few data are available on the identity of miRNAs regulating chondrogenesis. The objective of my PhD project is therefore to identify microRNAs involved in the chondrogenic differentiation of MSC.

Methods: We performed the analysis of miRNA arrays obtained from samples of MSC (day 0) and MSC-derived pre-chondrocytes (day 3). We then compared the expression of the modulated miRNAs to that of mRNAs originating from another transcriptomic analysis from similar samples at identical time points. Using prediction software, we observed that a little number of transcription factors can regulate the majority of miRNAs. Among transcription factors, the master gene of chondrogenesis Sox9 and also YY1, which is known to negatively regulate chondromodulin during chondrogenesis, might bind to 71 out of 75 miRNAs. In particular, Sox9 and YY1 putatively bind to the promoter region of miR-29 which is down regulated at day 3.

Results: We confirmed by real-time RT-PCR that the expression level of miR-29 continuously decreases until the end of the differentiation (day 21). Transfection of Sox9 or YY1 in the Stro-1A MSC cell line significantly reduced the expression of miR-29. Moreover, transfection of both factors almost abolished its expression suggesting that they negatively regulate miR-29 after binding to the promoter region. The effect of gain- and loss-of-function of miR-29 during the chondrogenic differentiation of MSCs by transfecting pre-miRs or antago-miRs confirms the role of miR-29 during chondrogenesis.

Conclusion: Our preliminary data show that, during chondrogenesis, miR-29 expression is down-regulated, probably through the interaction of Sox9 and YY1 on the miR promoter region. Because miR-29 has been described to regulate different targets (DKK1, sFRP2, Kremen2 and CDK6 whose expression decreases during differentiation), future experiments will investigate whether these target genes are modulated by miR-29.

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Activation of AMP-Activated Protein Kinase (AMPK) Alleviates Endoplasmic Reticulum (ER) Stress and Inhibits Catabolic Responses to Biomechanical Injury in Chondrocytes. Freyr Petursson[1], Xianling Zhao[1], Robert Terkeltaub[2] and Ru L. Bryan[1]. [1]UCSD/VAMC, San Diego, CA, [2]VA Medical Ctr, San Diego, CA

Background/Purpose: Many cell stresses trigger protein misfolding in the ER, and the consequent unfolded protein response (UPR) can either trigger redox stress, inflammation, and apoptosis, or, if successful, restores ER homeostasis by upregulation of chaperones and protein folding catalysts.

AMP-activated protein kinase (AMPK) is a master regulator of energy homeostasis and cellular metabolism. AMPK activity is decreased in osteoarthritic (OA) and aged chondrocytes/cartilage, and drops in chondrocytes stimulated by IL-1b and TNFa; conversely, activation of AMPK inhibits chondrocyte catabolic responses to IL-1b and TNFa (Arthritis Rheum 2011, epub). Here, we tested the hypothesis that activation of AMPK alleviates ER stress and catabolic responses in articular chondrocytes in response to inflammation and biomechanical injury.

Methods: Primary human and/or bovine knee articular chondrocytes were pre-treated with AMPK activators AICAR (0.5–1 mM) or A769662 (0.25–0.5 mM), or the AMPK inhibitor Compound C (10 mM) for 2 h before stimulation with IL-1b (10 ng/ml), TNFa (10 ng/ml), and the ER stress positive control inducer tunicamycin (TM, 2.5 mg/ml) for 18 h. Also, chondrocytes embedded in alginate molds were subjected to sublethal biomechanical injury (22% maximum axial compression, 12% amplitude, 0.5 Hz) for 16 hours. Knockdown of AMPKa1/2 in primary human knee chondrocytes was achieved via siRNA. The cell lysates from each condition were analyzed for protein expression of the UPR activation markers GRP78 and CHOP, and MMP-3 by SDS-PAGE/Western blot. The conditioned media was assayed for release of nitric oxide (NO) and sulfated GAG by Greiss reaction and dimethylmethylene blue (DMMB) assay, respectively.

Results: IL-1b and TNFa modestly induced GRP78, whereas TM strongly induced both GRP78 and CHOP protein expression in chondrocytes. These effects were blunted by AICAR and A-769662, but significantly enhanced by Compound C. Knockdown of AMPKa1/2 enhanced induction of expression of GRP78 and CHOP by TM in chondrocytes. Last, biomechanical injury rapidly induced GRP78 and CHOP in chondrocytes, and this response was inhibited by AICAR and A-769662. Under these conditions, AMPK activators blunted catabolic responses of chondrocytes (including induction of NO and GAG release and MMP-3 expression).

Conclusion: Activation of AMPK alleviates ER stress and inhibits catabolic responses in articular chondrocytes subjected to inflammatory stress and biomechanical injury. Targeted activation of AMPK by pharmacological means has therapeutic potential to protect chondrocytes from excessive catabolic responses in part by successfully alleviating ER stress.

1792

Apolipoprotein E and Undercarboxylated Osteocalcin Are Associated with Bone Fragility but Not with Bone Mineral Density in Osteoarthritis Patients. Ana M. Rodrigues[1], Joana Caetano-Lopes[2], Ana Lopes[3], Ana Catarina Vale[4], Inês Aleixo[3], Inês P. Perpétuo[2], Ana Sofia Pena[3], Alexandra Faustino[3], Alexandre Sepriano[3], Joaquim Polido-Pereira[5], Elsa Vieira-Sousa[6], Bruno Vidal[7], JC Romeu[8], PM Amaral[4], Luis G. Rosa[4], José A. Pereira da Silva[9], Jacinto Monteiro[10], Maria Fátima Vaz[4], J. E. Fonseca[5] and Helena Canhão[5]. [1]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisbon, Portugal, [2]Rheumatology Research Unit, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [3]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [4]Department of Mechanical Engineering, Instituto Superior Técnico, ICEMS, Lisbon, Portugal, [5]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisboa, Portugal, [6]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [7]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal., Lisbon, Portugal, [8]Hospital de Santa Maria, Lisbon, Portugal, [9]Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisbon, Portugal, [10]Orthopaedics Department, Hospital de Santa Maria, Lisbon, Portugal

Background/Purpose: Apolipoprotein E (apoE) gene polymorphisms and undercarboxylated osteocalcin (ucOC) and vitamin K have been associated with fragility fractures and low BMD in general population. The aim of this work was to study whether the effect of apoE gene polymorphisms, seric apoE levels and ucOC influence trabecular bone biomechanics and bone mineral density (BMD) in patients submitted to hip replacement surgery due to advanced primary osteoarthritis.

Methods: Patients were evaluated for established clinical risk factors for fracture. A dual X-ray absorptiometry (DXA) was performed. ApoE genotyping was performed at positions rs429358 and rs7412. Fasting blood samples were collected at the time of surgery to assess the following parameters: seric apoE, ucOC, Vitamin K, LDL cholesterol, triglycerides and bone turnover markers. Femoral epiphyses were collected and trabecular bone cylinders were drilled in order to perform compression mechanical tests and analyze bone strength and stiffness.

Results: Forty-four patients were studied (median 70 years of age, 55% women and 90% postmenopausal, BMI of 27.2 Kg/m2). 6.8% had prevalent fragility fractures, 36% had normal BMD and 64% were osteopenic. The apoE genotype distribution was in accordance with Hardy-Weinberg equilibrium and the E4 allele, previously documented as the risk allele, was present in 16% of the patients. This allele was significantly associated with lower trabecular strength ($p=0.004$) and stiffness ($p=0.070$), adjusted for age and gender, but not with BMD. Moreover, E4 allele was associated with higher levels of markers of bone formation: ALP ($p=0.067$), BSALP ($p=0.085$) and P1NP ($p=0.062$). We also found that ucOC was negatively correlated with strength ($p=0.077$) and stiffness ($p=0.047$), regardless of patients gender, age or vitamin K, but not with BMD. ApoE levels were also associated with strength ($p=0.056$; $R=-0.322$) and stiffness ($p=0.001$; $R=-0.513$).

Conclusion: Other studies have shown that advanced hip osteoarthritis can be associated with a higher BMD, but is not a protective factor for fragility fractures. Our observations suggest that in osteoarthritis patients apoE4 allele, seric apoE and ucOC are biologic risk factors for bone fragility in a more independent way from BMD than in the general population.

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Alarmins s100a8 and s100a9 Elicit a Higher Catabolic Response in Osteoarthritic Chondrocytes Compared to Normal Chondrocytes That Is Toll Like Receptor 4 Dependent. Rik Schelbergen[1], Arjen B. Blom[1], Martijn H.J. van den Bosch[1], Annet Sloetjes[1], Thomas Vogl[2], Johannes Roth[2], Wim B. van den Berg[1] and Peter L.E.M. van Lent[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]University of Muenster, Munster, Germany

Background/Purpose: S100A8 and S100A9 are classified as damage associated molecular patterns (DAMPs) or alarmins and are found in high amounts in the synovial fluid of rheumatoid arthritis (RA) and osteoarthritis (OA) patients. Previously, we found that S100A8 and S100A9 are associated with cartilage degradation in murine collagenase-induced OA. We also showed that S100A8 and S100A9 stimulate expression and activity of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines in murine chondrocytes.

In the current study, we investigated whether and via which receptor S100A8 and/or S100A9 can have a catabolic effect on chondrocytes from OA patients. Furthermore, we compared the S100-effect on OA chondrocytes with non-OA chondrocytes.

Methods: In cartilage from end stage OA, we stained for S100A8 and S100A9 protein, MMP-1 and −3 and a cartilage breakdown epitope specific for MMPs (VDIPEN) using immunohistochemistry. Isolated chondrocytes from OA and non-OA donors were stimulated with S100A8 and S100A9 protein. mRNA levels of MMPs, cytokines and cartilage matrix molecules were determined with RT-qPCR, protein levels of MMPs and cytokines with Luminex. For receptor blocking studies, specific inhibitors for Toll-like receptor 4 (TLR4) (intracellular TAK242) and RAGE and carboxylated glycans (blocking antibodies) were used.

Results: In cartilage of OA patients, localisation of S100A8 and S100A9 protein was found close to chondrocytes and was associated with proteoglycan (PG) depletion, MMP1 and −3 and VDIPEN expression.

Stimulation of OA chondrocytes with S100A8 and S100A9 caused a significant upregulation of MMP1, −3, −9 and −13 at the mRNA level (5.7, 5.0, 4.0, and 3.1-fold respectively). The upregulation was confirmed on protein level for MMP-1, −3 and −13 (2.3, 3.1 and 3.6-fold respectively). Moreover, S100A8 and S100A9 caused a huge increase in cytokine and chemokine expression. IL-6, IL-8 and MCP-1 were all greatly increased by S100A8 and S100A9 at both the mRNA (15.1, 24.0 and 3.7-fold respectively) as well as the protein level (29.1, 49.7 and 7.7-fold respectively). Moreover, the expression of anabolic markers (aggrecan and collagen type II) was significantly reduced at the mRNA level (2.7 and 2.7-fold decrease respectively).

Blocking TLR4 almost completely inhibited the upregulation of MMP-3, IL-6, IL-8, MCP-1 and collagen type II by S100A9 in OA chondrocytes. In contrast, blocking of carboxylated glycans and RAGE did not alter the S100-effects.

Finally, the catabolic effect of S100A8 and S100A9 was significantly more pronounced in chondrocytes from OA patients when compared to non-OA. TLR4 mRNA expression was enhanced in OA chondrocytes, which might explain the increased sensitivity.

Conclusion: S100A8 and S100A9 have a catabolic effect on human chondrocytes that is dependent on TLR4. OA chondrocytes are more sensitive for S100-stimulation than normal chondrocytes.

This study underlines the potential of S100A8 and S100A9 as mediators of cartilage damage during OA.

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Periostin, An Osteoblast Stimulating Factor, Regulates Cartilage Metabolism Via MMP-13 Activation. Mukundan Attur[1], Glyn Palmer[1], Yuki Tachida[2], Seiichiro Kumakura[2], Kohei Shimada[2] and Steven B. Abramson[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Daiichi-Sankyo Co. Ltd.,, Tokyo, Japan

Background/Purpose: Periostin (POSTN), a gamma-carboxylated extracellular matrix protein originally identified as an osteoblast stimulating factor. This study investigates its expression in OA cartilage and regulation of chondrocyte metabolism.

Methods: Cartilage slices were obtained from the advanced OA patients (age 45–80 years) undergoing knee replacement surgery. Non-arthritic knee cartilages were obtained from autopsy patients within 24h (NDRI, Philadelphia). Predesigned TaqMan PCR primers were purchased from Applied Biosystems. Lentiviral shRNA targeting POSTN were purchased from Sigma. Matrix metalloproteinases proMMP-1 and proMMP-13 ELISA kits were from R&D Systems. Degradation products of type II collagen was measured using CTX II -based assay kit.

Results: We studied the expression of POSTN in pools (n=10) of OA and age-matched non-diseased cartilage using U133 Affymetrix microarray. POSTN was overexpressed 2–4 fold in OA cartilage ($p<0.035$) compared to non-diseased controls. Verification by real-time PCR confirmed POSTN upregulation. Surgical-induction of OA in rats by anterior cruciate ligament transection (ACLT) and destabilization of the medial meniscus (DMM) models also significantly increased POSTN (3–11 fold) from 2–8 weeks after surgery. In OA chondrocytes isolated from human tibial cartilage, POSTN mRNA levels, determined by qPCR, were inhibited 3-fold in the presence of inflammatory cytokines IL-1β and TNFα. In contrast, TGFβ-1 (2 ng/ml) significantly increased POSTN expression (2–40-fold). In functional assays, exogenously added (1–30 ug/ml) or overexpression of POSTN significantly increased MMP-13 expression and activity ($p<0.02$) in primary human OA, rat and bovine chondrocytes. Conversely; knock down of endogenous POSTN using targeted lentiviral shRNAs significantly decreased MMP-13 expression in the presence of TGF-β1. In OA cartilage explants cultures, PSTN increased cartilage degeneration, evidenced by increased release of collagen (C1, 2C) and GAG fragments in culture supernatants. To determine whether PSTN is a hypertrophic marker of chondrocytes we examined its expression in chondrogenesis assays using human bone marrow-derived MSCs and immature murine costal chondrocytes undergoing maturation. In both assays PSTN expression was upregulated in a time-dependent manner, and expression coincided with MMP-13, Alkaline Phosphatase and F-spondin. These findings suggest that PSTN expression is associated with chondrocyte terminal differentiation.

Conclusion: Together, these studies indicate that PSTN is a marker of OA cartilage and chondrocyte hypertrophy. In OA, PSTN may contribute to disease pathogenesis by promoting cartilage degradation via induction of MMP-13.

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Sirt1 Deficient Mice Exhibit An Altered Cartilage Phenotype. Odile H. Gabay Engel[1], Christelle Sanchez[2], Mona dvir-Ginzberg[3], Viktoria Gagarina[1], Eun Jin Lee[1], Kristien J. Zaal[1], Michael McBurney[4] and David J. Hall[1]. [1]NIH, Bethesda, MD, [2]Bone and Cartilage Research Unit, Liege, Belgium, [3]Hebrew University- Hadassah Ein Kerem, Jerusalem, Israel, [4]Ottawa Hospital, Ottawa, ON

Background/Purpose: Cartilage degenerative diseases such as osteoarthritis, are age-related. The histone deacetylase Sirt 1 has been shown as an anti-aging protein. We previously demonstrated that Sirt 1 regulates apoptosis and cartilage-specific gene expression in human chondrocytes. Sirt 1 is also a potent inhibitor of the matrix metalloproteinases. To determine if Sirt 1 plays a protective role on cartilage homeostasis *in vivo*, we investigated Sirt1 KO mice to characterize their cartilage and try to understand the mechanisms underlying a phenotype, such as cartilage breakdown or apoptosis.

Methods: Articular cartilage was harvested form hind paws and knees of 1-week to 6-month old mice carrying wildtype, null or point mutations affecting the Sirt1 gene. The cartilage was processed for histology, immunohistochemistry, or used to establish cultures of chondrocytes.

Results: We found that articular cartilage tissue sections from Sirt1 KO mice at any age exhibited low levels of type 2 collagen, aggrecan and glycosaminoglycans. In contrast, protein levels of MMP-8, MMP-9 and MMP-13, were elevated in the SirT1 KO mice, leading to an increase of cartilage breakdown. The apoptotic process was shown to be elevated in these mice. Moreover, PTP1b, protein tyrosine phosphatase b, a chondrocyte proapoptotic protein elevated in OA, was elevated in the Sirt 1 KO mice.

Conclusion: The findings from this animal model demonstrate that Sirt1 KO mice present an altered cartilage phenotype: The apoptotic process and the cartilage breakdown were elevated in these mice.

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Rac1 and NADPH Oxidase Regulate NFκB Activity and MMP-13 Expression in Chondrocytes in Response to Integrin Activation. Richard F. Loeser, Elizabeth A. Erickson and David A. Long. Wake Forest University, Winston-Salem, NC

Background/Purpose: Matrix fragments, including fibronectin fragments (FN-f) that signal through the $\alpha5\beta1$ integrin, accumulate in the matrix during the development of OA stimulating chondrocyte cytokine, chemokine and MMP production. The signaling pathways activated by FN-f require generation of reactive oxygen species (ROS) as second messengers. The small GTPase Rac1 can mediate ROS generation through regulation of the NADPH oxidase (NOX) complex. We tested the hypothesis that Rac1 and NOX are required for FN-f stimulation of MMP-13 expression by articular chondrocytes and determined the mechanisms involved.

Methods: Human articular chondrocytes, isolated from normal ankle cartilage obtained from adult tissue donors or OA knee cartilage removed during joint replacement, were cultured in primary high density monolayers or in alginate beads. Serum-free cultures were treated with a recombinant FN-f that activates the $\alpha5\beta1$ integrin. Rac1 was inhibited with the specific inhibitor NSC23766 (100μM) or knocked-down by use of siRNA and NOX was inhibited with VAS 2870 (25μM). Rac 1 activity was increased using an adenoviral construct expressing constitutively active (CA) Rac 1. MMP-13 protein was measured by immunoblotting or ELISA of conditioned media and expression by real-time PCR. ROS production was quantified by detection of DCFDA fluorescence, a reactive oxygen species sensitive dye. MAP kinase activation was measured by immunoblotting with phospho-specific antibodies and NFkB activity using a promoter-reporter assay and immunoblotting for p65 translocation into the nucleus. Rac activity was measured by an activity-based ELISA kit and using a specific antibody that recognizes active (GTP bound) Rac.

Results: Chemical inhibition of Rac1 or transfection with Rac1 siRNA significantly reduced basal and FN-f stimulated ROS production by normal chondrocytes. The Rac inhibitor, the NOX inhibitor and Rac siRNA each blocked FN-f stimulated MMP-13 expression and production, while expression of CA Rac1 increased MMP-13 production. The Rac inhibitor also significantly reduced basal MMP-13 production by OA chondrocytes and blocked FN-f stimulation of MMP-13 production by cells cultured in alginate. Confocal microscopy revealed active Rac1 in a perinuclear distribution. Neither NOX or Rac inhibition had an affect on FN-f stimulation of MAP kinase phosphorylation. However, NOX inhibition blocked FN-f stimulated p65 phosphorylation. Both Rac and NOX inhibition blocked p65 translocation into the nucleus and reduced NFkB promoter-reporter activity. The basal activation of Rac1 was higher in OA chondrocytes than normal chondrocytes and immunocytochemistry revealed active Rac1 in OA but not normal cartilage in situ.

Conclusion: These results demonstrate for the first time that Rac1 and NOX regulate MMP-13 expression in response to integrin activation by FN-f. The findings are consistent with a role for NOX in NFκB activation via p65 phosphorylation followed by translocation to the nucleus which required Rac1 activity. The presence of activated Rac1 in OA but not normal cartilage together with the findings that Rac1 can positively regulate NFκB and MMP-13 suggests Rac1 may be an important mediator of matrix destruction in OA.

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Disease-Specific Induction of Fibroblast Activation Protein Alpha in Rheumatoid Arthritis. Christina Wunrau[1], Marianne Heitzmann[1], Corinna Wehmeyer[1], George Kollias[2], Thomas Pap[1] and Berno Dankbar[1]. [1]University Hospital Muenster, Muenster, Germany, [2]Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece

Background/Purpose: The progressive destruction of articular cartilage and bones are hallmarks of rheumatoid arthritis (RA) and osteoclast differentiation and migration constitutes critically to process. The Fibroblast Activation Protein alpha (FAPa) is an integral membrane serine protease that plays a major role in cell migration, wound healing, and metastasis. Based on recent studies that have implicated membrane- bound serine proteases in osteoclast migration, we sought to study the expression of FAPa in RA as well as in tumor necrosis factor alpha transgenic (hTNFtg) mice and analyze its role in osteoclastogenesis under inflammatory conditions.

Methods: The *in vivo* expression of FAPa was determined by immunohistochemistry in human synovial tissues of RA and osteoarthritis (OA) patients as well as in hind paws of hTNFtg mice, which develop an RA-like destructive arthritis. The *in vitro* expression of FAPa was analyzed in freshly differentiated osteoclasts cocultured with osteoblasts, RA or OA fibroblast like synoviocytes (FLS) by PCR. Osteoclast differentiation was verified by tartrate-resistant acid phosphatase (TRAP) staining. The *in vitro* collagenolytic activity of preosteoclasts was evaluated by western blot analyses of degraded collagen type I.

Results: RA synovial tissues demonstrated a high expression of FAPa throughout the tissues whereas in OA samples FAPa was expressed only in the lining layer. *In vitro*, no expression of FAPa was found in differentiated preosteoclasts and osteoclasts, but coculture experiments showed that RA FLS, but not OA SF or osteoblasts, induce the expression of FAPa in preosteoclasts and osteoclasts. Consistent with the selective induction of FAPa in osteoclasts by RA-FLS, FAPa expression was detected in osteoclasts at the invasion front of the hyperplastic synovial tissues in the joints of hTNFtg mice. FAPa expressing preosteoclasts showed an MMP independent cleavage of native collagen type I.

Conclusion: The disease-dependent expression pattern of FAPa by osteoclasts in human RA and TNFtg mice suggest a role for FAPa in bone erosion in RA. The selective induction of FAPa in preosteoclasts and osteoclasts by RA-FLS indicate that FAPa may be regulated through the interaction with the pannus tissue. Furthermore, the collagenolytic activity of the FAPa expressing preosteoclasts point to a possible additional role of this serine protease in osteoclast precursor migration.

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Theragnostic Nanosomes for Detection and Treatment of Early Osteoarthritis and Cartilage Damage. Karen A. Hasty[1], Hongsik Cho[2], Eugene Pinkhassik[3] and John M. Stuart[4]. [1]University of Tennessee Health Science Center, VA Medical Center, Memphis, TN, [2]University of Tennessee Health Science Center, Memphis, TN, [3]University of Memphis, Memphis, TN, [4]VA Medical Center, University of Tennessee Health Science Center, Memphis, TN

Background/Purpose: Osteoarthritis (OA) is a common condition with few preventive therapies. One obstacle to developing therapies is a reliable method of detecting and measuring progression in the early stages of disease when intervention may prove more beneficial. This application uses fluorescent, targeted nanosomes (200 nm liposomes) developed as a theragnostic delivery system. The nanosomes incorporate a monoclonal antibody (Mab) to native type II collagen (CII) and a near infrared emitting fluorescent dye (NIF) that can be quantitatively visualized *in vivo*. CII in normal cartilage is not available for binding and is only unmasked when the surface of the cartilage is damaged. We show targeted nanosomes selectively bind exposed CII and can be quantitated using an external imaging system in both inflammatory and degenerative arthritis.

Methods: Animal All animal studies were approved IACUC protocols at the University of Tennessee Center for the Health Sciences. Dunkin-Hartley guinea pigs ranging in age 3–24 month were obtained from The Jackson Laboratory. To induce inflammatory arthritis in mice, DBA/1J mice were immunized with CII in complete Freund's adjuvant and observed until the onset of inflammation. Two months after inflammation subsided, mice were injected with NIF-MabCII nanosomes or control NIF-MabCon nanosomes.

Results: *In vivo* imaging was done at 24 hours post-injection using a Lumina II, In Vivo Imaging System (IVIS), (Caliper Life Sciences, MA) with an Indocyanine Green (ICG) Filter set (excitation 710–760nm, emission 810–875 nm). With imaging, older guinea pigs showed a significant difference between intraarticularly injected nanosomes with MabCII and those bound to control Mab. The NIF-MabCII showed a high degree of binding and exhibited fluorescence corresponding to joint degradation. This binding is proportional to the histopathological stage of cartilage damage in the joint. The administered nanosomes conjugated to a control antibody showed minimal binding. A minimal amount of binding was also observed in the young guinea pig for both control and experimental nanosomes. IVIS imaging of the dissected joint tissue surrounding the joint in both young and old samples showed no soft tissue fluorescence. Dissection showed binding of the NIF-MabCII-nanosomes was principally to the medial condyle. Histopathology of the joint showed the young joint had limited degradation while older joints displayed osteoarthritis with characteristic cartilage damage. IVIS imaging showed that nanosomes labeled with NIF-MabCII targeted directly to knee joints of animals that had previously shown evidence of CIA, when injected intravascularly or intraarticularly. Controls were negative.

Conclusion: Specific binding of nanosomes conjugated to type II collagen antibodies in joints with spontaneous OA and those damaged by CIA was seen. Collected data indicated the amount of nanosome binding is proportional to the level of cartilage damage. Adding drugs or cytokines inside the nanosomes may offer a method for diagnosis and treatmetn of early OA before clinical presentation of the disease.

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Sclerostin Levels in Rheumatoid Arthritis and Its Relationship to Disease Activity and Radiographic Joint Damage. M. Vis[1], K. Britsemmer[2], A.C. Heijboer[1], N. Bravenboer[1], D. van Schaardenburg[2] and W. F. Lems[1]. [1]VU University medical center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute / Reade, Amsterdam, Netherlands

Background/Purpose: Joint erosions are the hallmark of rheumatoid arthritis (RA). They are caused by an increased bone resorption. However there in no increased bone formation to prevent or heal these erosions. The Wnt pathway is important in the control of bone formation through regulation of osteoblast activity. Sclerostin is an important regulator of the Wnt pathway by blocking Wnt binding to its receptor and thereby inhibiting bone formation.

In this study we investigated whether sclerostin levels are increased in RA patients compared to healthy controls and whether there is an association with disease activity and radiographic damage.

Methods: Female patients from the Amsterdam Early Arthritis Cohort (EAC) were studied. Data and samples at 1 year after inclusion were used in this study. Consecutive patients were selected from the database on the basis of high or low disease activity (DAS-28 $<$ or $>$ 3.2) until both groups consisted of 25 patients. Ten healthy female students and 10 healthy postmenopausal women served as healthy controls. Sclerostin was measured using ELISA (Biomedica, Wien, Austria).

Results: In the 50 RA patients, mean age was 57 ($\pm$13), mean disease duration 6 months ($\pm$4), median Sharp van der Heijde score 2.5 (0–110) and mean DAS-28 3.6 ($\pm$1.2). Sclerostin levels were 28.7 pmol/l (12.1) in all RA patients, 30.7 pmol/l (12.9) in post menopausal women and 9.6 pmol/l (5.9) in healthy female students, which was significantly lower than the other 2 groups. ($p < 0.001$) In the RA patients sclerostin levels were significantly correlated with age (r 0.29, $p<0.05$) and inversely with DAS-28 (-0.28, $r<0.05$). No correlation was found between Sharp van der Heijde scores and sclerostin levels ($p=0.453$).

Conclusion: Sclerostin levels are low in healthy pre-menopausal women compared to healthy postmenopausal women and female RA patients.In female RA patients sclerostin levels are associated with age and inversely with disease activity. These data indicate that the decreased bone formation in active RA is not caused by increased sclerostin levels.

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A Novel Method of Basic Calcium Phosphate Crystal Quantification in Synovial Fluid Using a Tetracycline Binding Assay. Jonathan Kushi[1], Claudia Gohr[1], Brian Jubeck[1], Peter A. Simkin[2] and Ann K. Rosenthal[1]. [1]Medical College of Wisconsin, Milwaukee, WI, [2]University of Washington, Seattle, WA

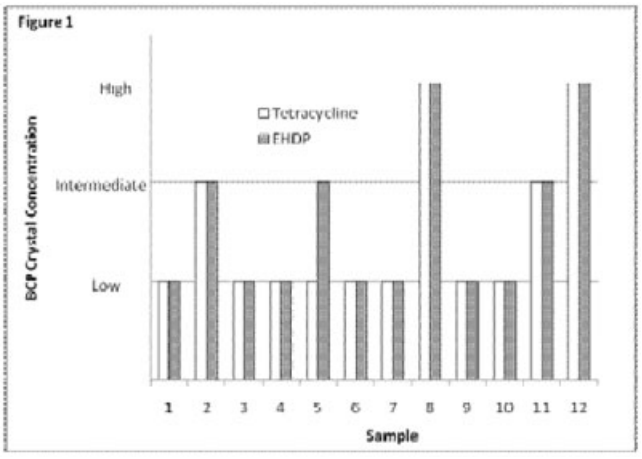
Background/Purpose: Basic calcium phosphate (BCP) crystals are known to play an important role in osteoarthritis; however, analysis of these crystals has been previously limited by difficulties with detection. Tetracycline, which is known to bind hydroxyapatite, has also been shown to qualitatively identify BCP crystals using fluorescence microscopy. We have developed an assay to quantify BCP crystal concentration in synovial fluid using tetracycline binding. This assay was run in parallel with the well

established Carbon-14 labeled etidronate (EHDP) binding assay as a basis for comparison.

Methods: Synovial fluid was collected from osteoarthritis patients and screened for visible crystals under polarizing microscopy. Crystal-negative samples were treated with hyaluronidase and trypsin and spun down. Pellets were divided equally to be run in both the tetracycline and EHDP assays. The first sample portion was incubated with oxytetracycline for 60 minutes at 37°C. Fluorescence of the fluid was measured using an excitation spectrum of 450/50 nm and emission spectrum of 540/35 nm. Synthetic BCP crystals at known concentrations were also measured for fluorescence to derive a comparative standard curve. The remaining sample portion was incubated with C-14 EHDP using established methods and measured in the scintillation counter to estimate percentage bound. A standard curve for the EHDP assay using synthetic BCP crystal was also generated.

Results: The tetracycline binding assay produced a linear standard curve with an r^2 value of 0.99 using BCP concentrations from 25–250 mg/ml. This standard curve was consistently reproducible with similar correlation coefficients. Twelve fluid samples were measured and an estimated BCP concentration was derived from the tetracycline standard curve. Fluorescence values within the upper tertile of the standard curve were determined to be of high concentration, the lower tertile of low concentration and the middle tertile of intermediate concentration. Samples from the EHDP assay were also stratified and assigned high, low and intermediate concentrations based on percent bound values.

In the tetracycline binding assay, 2 samples were of high concentration, 8 were of low concentration and 2 were intermediate. The EHDP assay demonstrated similar results in 11 of the 12 samples with stratification into identical tertiles as the tetracycline assay (2 high, 7 low and 2 intermediate). One sample did not correlate, measuring low concentration in the tetracycline assay, but intermediate in the EHDP assay (Figure 1).



Conclusion: Tetracycline binding can be used to estimate BCP crystal concentration in synovial fluid. This method is reproducible and comparable to an existing standard, C-14 EHDP binding. Tetracycline has advantages over EHDP in that it is both non-radioactive and readily available.

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Revisiting Chemical and Morphological Diversity of Calcium-Containing Crystals in Human Osteoarthritic Menisci. Christelle Nguyen[1], Frédéric Lioté[1], Didier Hannouche[2], Valérie Bousson[3], Frédéric Velard[1], Michel Daudon[4], Dominique Bazin[5] and Hang-Korng Ea[1]. [1]UMR-S 606, INSERM & Paris Diderot University; PRES Sorbonne Paris-Cité; Lariboisière Hospital, Paris, France, [2]Orthopaedic Surgery Department; Lariboisière Hospital (AP-HP); Univ. Paris Diderot, Sorbonne Paris-Cité, Paris, France, [3]Radiology Department; Lariboisière Hospital (AP-HP); University Paris Diderot, Paris, France, [4]Service de Biochimie A; Necker Hospital (AP-HP), Paris, France, [5]Laboratoire de Physique des Solides; Paris Sud University, Orsay, France

Background/Purpose: Calcium-containing crystals (CC), including basic calcium phosphate crystals (BCPs) and calcium pyrophosphate crystals (CPPs) are associated with destructive forms of osteoarthritis (OA). Mineralization of several joint structures, including articular cartilage and menisci, is an indissociable process of end-stage OA, that occurs independently of ageing. We aimed to assess prevalence and biochemical composition of mineral phases in human OA menisci, and to determine their morphological aspects.

Methods: Fourteen patients (12 females and 2 males) who underwent total knee replacement (TKR) surgery for primary OA were prospectively included. A 24-year-old woman who underwent TKR for chondrosarcoma, and a 28-year-old man who had meniscectomy for medial meniscus tear served as non-OA control subjects. Clinical data and preoperative knee plain radiographs were retrieved from clinical charts. Specimen included lateral meniscus and medial meniscus, when this latter was available. For each meniscus, 2 samples were collected, consisting in 1-mm-thick slices. Slices were cut tangentially to the surface of the meniscus center part, within its superficial and deep layers, respectively. Menisci calcifications prevalence and semi-quantification were obtained using digital contact radiography (DCR). Biochemical composition was assessed using Fourier-transform infra-red (FTIR), while morphological aspects were determined using scanning electron microscopy (SEM).

Results: Mean age and body mass index at the time of TKR were 73.7 (8.6) years, and 29.3 (7.4) kg/m^2, respectively. Preoperative X-rays, available for 9 patients, found uni-, bi- or tricompartmental knee OA in 3 (33.3%), 5 (55.5%) and 1 (11.1%) cases, respectively. In all cases, the compartment mainly affected was medial femoro-tibial, and mean Kellgren and Lawrence score was 3.7 ± 0.5. Overall, 19 menisci (14 lateral and 5 medial) were harvested and analysed. Visual assessment found macroscopic menisci calcifications in 10 OA out of 14 patients (71.4%). Using DCR, CC were detected in all 19 OA menisci, whereas CC were not detected in non-OA control menisci. The mean overall mineral content represented $9.0\pm5.3\%$ of total volume (range 3.2–24%). FTIR analysis confirmed the presence CC in all 19 OA menisci specimens. CC were identified as CPPs only in 10 menisci (52.6%), as BCPs only in 6 (31.6%) and as both BCPs and CCPs in 3 (5.2%). Mean overall CPPs content represented $12.1\pm16.3\%$ and mean overall BCPs content represented $2.9\pm5.4\%$. In all cases, identified BCPs were characterized as carbonated apatite. Finally, by SEM, 2 different morphological aspects were identified: 1/spherical structures, typical of biological apatite, resulting from an agglomeration of nm-scale cristallites surrounded by proteins, in the BCPs-containing samples; 2/ acicular or cubic structures of different sizes, in the CPPs-containing samples.

Conclusion: CC are constantly found in human OA menisci at the time of knee joint replacement. Cartilage calcifications in human OA menisci are mainly identified as CPPs. Furthermore, CC morphological aspects are specific to the crystal type.

1802

Inhibition of p38 Signaling Negatively Affects Chondrogenesis *in Vitro*, but Does Not Inhibit Ankylosis in a Model of Ankylosing Spondylitis. Kirsten Braem, Frank P. Luyten and Rik Lories. KU Leuven, Leuven, Belgium

Background/Purpose: Mitogen activated protein kinases (MAPKs) convert various extracellular stimuli onto different cellular responses and mediate distinct effects on a wide array of biological processes. Among the various MAPKs subfamilies, p38 plays an important role in bone formation, but it is also involved in the catabolic actions of pro-inflammatory cytokines interleukin 1 (IL1) and tumor necrosis factor α (TNFα). Ankylosing spondylitis (AS) is characterized by chronic inflammation of the spine and joints as well as progressive ankylosis leading to loss of function and disability. In spite of increasingly successful control of inflammation with TNFα inhibitory agents, structural progression of disease appears not to be affected by these drugs, suggesting that the processes of inflammation and ankylosis are at least partially independent. Bone morphogenetic proteins (BMP) have been identified as key players in onset and progression of ankylosis. BMP associated intracellular signaling cascades (SMAD and p38 MAPK signaling) play a role during chondrogenesis and osteogenesis *in vitro* and *in vivo* . Here, we studied the inhibition of p38 on chondrogenesis *in vitro* and *in vivo* with specific attention to its potential role in ankylosing enthesitis.

Methods: Male DBA/1 mice from different litters were caged together at the age of 8 weeks. From week 10 onwards to week 17, mice were injected daily with SB203580 (50 μg/g body weight) or DMSO vehicle control. In a second set of experiments, mice were injected daily with SB203580 or DMSO after the first symptoms appeared in each mouse and sacrificed 3 weeks later. Mice were evaluated for prospective signs of arthritis and toe joints were analyzed by histology to assess disease severity. For *in vitro* experiments, human periosteum-derived progenitor cells were cultured in pellets and stimulated with BMP2 or TGFβ1 in the presence or absence of

SB203580, IL1 or TNF. Chondrogenic differentiation was evaluated at day 7 using quantitative PCR marker analysis. Canonical SMAD and alternative MAPK signaling were studied by performing western blot analysis.

Results: p38 inhibition by SB203580 downregulated chondrogenic markers (*COL2*, *COL10*, *ACAN*) in periosteal progenitor cell pellet cultures stimulated by TGFβ1 or BMP2. This inhibition was also found with pro-inflammatory cytokines IL1 and TNF. In contrast, the *in vivo* experiments resulted in an increased clinical incidence of peripheral arthritis and pathology severity score in mice receiving SB203580, reflecting progression towards ankylosis.

Conclusion: p38 activation occurs both downstream of pro-inflammatory cytokines and TGFβ superfamily members. *In vitro* inhibition of p38 negatively affects chondrogenesis, demonstrating that not only the SMAD signaling pathways but also the alternative activation of MAPKs including p38 contribute to chondrogenesis. In a mouse model of ankylosing spondylitis, such an inhibitory effect is not found. Additionally, increased incidence and disease severity in preventive experiments as well as shifts in disease stages in a therapeutical experimental setup suggests that p38 inhibition may have deleterious rather than beneficial effects.

1803

Human Chondrocyte Behaviour During In Vitro Over Expression of Normal and Mutated HFE, the Hemochromatosis Gene. Vanessa Martelli[1], John A. Di Battista[1], Pantelis Panopalis[1], John Antoniou[2], Michael Sebag[1], Brian Gilfix[1] and Henri A. Ménard[1]. [1]McGill University Health Center, Montreal, QC, [2]Jewish General Hospital, Montreal, QC

Background/Purpose: Clinical hereditary hemochromatosis type I (HH-I) is defined as the progressive accumulation of iron in organs and is caused by missense mutations in the HFE gene. In population studies, there are two prevalent mutations the C282Y and the H63D. Rheumatic complaints of the osteoarthritis (HHOA) phenotype are the leading clinical manifestations of HH-I. Yet, little is known about the expression in chondrocytes of proteins regulating iron metabolism. Our study verified their presence and explored variations of OA-related biomarkers in normal vs. HFE-mutation-carrying cultured human chondrocytes and, in normal chondrocytes transfected with normal or mutated HFE under basal conditions or cytokine stimulations in a variable culture medium/serum iron environment.

Methods: Cultured chondrocytes were derived from tissues obtained at total knee replacement (TKR) of patients not carrying (OA) or carrying mutations (HHOA).Levels of MMP-1, MMP-3, MMP-13, iNOS and COX-2 (referred to as an "activation profile") were measured in normal chondrocytes transfected with plasmids containing normal or mutated HFE.

Results: Ferroportin, Divalent Metal Transporter 1, ferritin and transferrin receptor 1 were all identified by PCR in human chondrocytes. In vivo mutated chondrocytes spontaneously expressed in vitro, significantly higher levels of the "activation profile" compared with cells obtained from age-matched patients with idiopathic primary OA. The in vitro transfection of a construct expressing the wild type (normal) HFE gene into normal donor-derived chondrocytes had similar effects on basal or cytokine-induced MMP-13 or COX-2 expression as cells transfected with an empty vector or under mock transfection conditions. However, transfecting plasmids with HFE containing the mutations, generated through site directed mutagenesis, resulted in a 3 to 7-fold increase in MMP-1/MMP-13/COX-2/iNOS expression levels under basal and cytokine-induced conditions. Those effects were similar in the presence of normal vs. elevated iron concentrations in the culture medium.

Conclusion: These data albeit preliminary, constitute the first attempt to define in chondrocytes the molecular mechanisms driving the characteristic HHOA and the role that HFE mutant genotypes may play in this regard. Our companion clinical observations as well as published population-based data suggest that many patients with the so-called "silent" H63D HFE mutation have early rheumatic symptoms while presenting a normal biochemical phenotype. It follows that given its high frequency that mutation may be a major, still insufficiently recognized, genetic risk factor for OA. We are currrently trying to repair in vitro the HHOA phenotype of the chondrocytes using normal HFE gene therapy.

1804

Blockade of Delta-like1 Suppresses Osteoclastgenesis and Arthritis. Chiyoko Sekine[1], Akemi Koyanagi[1], Noriko Koyama[1], Katsuto Hozumi[2], Shigeru Chiba[3] and Hideo Yagita[1]. [1]Juntendo University School of Medicine, Tokyo, Japan, [2]Tokai University School of Medicine, Japan, [3]University of Tsukuba, Tsukuba, Japan

Background/Purpose: Osteoclastogenesis plays an important role in the bone erosion of rheumatoid arthritis (RA). Recently, Notch receptors have been implicated in the development of osteoclasts. However, the responsible Notch ligands have not been identified yet. This study was undertaken to determine the role of individual Notch receptors and ligands in osteoclastogenesis.

Methods: Mouse bone marrow-derived macrophages or human peripheral blood monocytes were used as osteoclast precursors and cultured with RANKL and M-CSF to induce osteoclasts. Osteoclasts were detected by tartrate-resistant acid phosphatase (TRAP) staining. K/BxN serum-induced arthritic mice were treated with anti-mouse Delta-like 1 (Dll1) blocking monoclonal antibody (mAb).

Results: Blockade of a Notch ligand Dll1 with mAb inhibited osteoclastogenesis and, conversely, immobilized Dll1-Fc fusion protein enhanced it in both mice and humans. In contrast, blockade of a Notch ligand Jagged1 enhanced osteoclastogenesis and immobilized Jagged1-Fc suppressed it. Enhancement of osteoclastogenesis by agonistic anti-Notch2 mAb suggested that Dll1 promoted osteoclastogenesis via Notch2, while suppression by agonistic anti-Notch1 mAb suggested that Jagged1 suppressed osteoclastogenesis via Notch1. Inhibition of Notch signaling by a γ–secretase inhibitor suppressed osteoclastogenesis, implying that Notch2/Dll1-mediated enhancement was dominant. Actually, blockade of Dll1 ameliorated arthritis induced by K/BxN serum transfer and reduced the number of osteoclasts in the affected joints.

Conclusion: The differential regulation of osteoclastogenesis by Notch2/Dll1 and Notch1/Jagged1 axes may be a novel target for amelioration of bone erosion in RA patients.

ACR/ARHP Poster Session C
Cytokines, Mediators, and Gene Regulation II
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

1805

Induction of Tyrosine Hydroxylase (TH) and Modulation of Cytokine Release by Hypoxia in Mixed Synovial Cells of Patients with Rheumatoid Arthritis and Osteoarthritis. Silvia Capellino[1], Zsuzsa Jenei-Lanzl[1] and Rainer H. Straub[2]. [1]1Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine, University Hospital Regensburg, Regensburg, Germany, [2]University Hospital Regensburg, Regensburg, Germany

Background/Purpose: It is known that the microenvironment of inflamed joints is hypoxic and that hypoxia induces tyrosine hydroxylase (TH) *in vivo* . Furthermore, in previous studies we have shown that TH-positive, catecholamine-producing cells are present in inflamed synovial tissue. Therefore, the aim of our study was to investigate whether hypoxia is responsible for TH expression and how hypoxia-induced catecholamines influence the inflammatory response in arthritis.

Methods: Synovial tissue was obtained from rheumatoid arthritis (RA) and osteoarthritis (OA) patients. Synovial cells were isolated by enzymatic digestion and cultivated under normal or hypoxic conditions. After 24 hours, cells were stained for TH. In order to determine effects caused by TH, cells were incubated with the competitive TH-inhibitor alpha-methyl-p-tyrosine (αMPT). In addition, different concentrations of catecholamine receptor (α- and b-adrenergic, D1/D5, D2,D3,D4 dopamine) or adenosine (A1aR, A2aR) receptor antagonists were applied. After 24 hours, supernatants were collected and cytokine (TNF, IL-6, IL-8, IL-10) concentrations were determined.

Results: Hypoxia increased the number of TH positive cells compared to cells cultured under normoxia. Compared to normoxic conditions, hypoxia exhibited inhibitory effects on IL-6, IL-8, and IL-10, whereas TNF was unaffected in OA. In contrast, hypoxia increased IL-6 and IL-8, but inhibited IL-10 and TNF in RA. These effects are partly dependent on locally produced catecholamines. Thus, TH blockade by αMPT reversed hypoxia-induced inhibition of IL-6 and upregulation of IL-8 in OA cells. In RA cells, αMPT reversed hypoxia-induced upregulation of IL-8. Moreover, specific catecholamine receptor antagonists were able to reverse hypoxia-induced influences on IL-8 and TNF in both OA and RA cells. Interestingly hypoxia-induced IL-8 increase was reversed by D1/D5 blockade.

Conclusion: This study demonstrates that hypoxia induces TH production in synovial cells, especially in RA patients. In addition, our results show that IL-6 and IL-8 are stimulated in RA by hypoxia. This is probably due to the activation of catecholamine pathway, especially of dopamine, as the blockade of dopamine D1/D5 receptors reverses IL-8 upregulation. In summary, these results suggest that hypoxia influences the inflammatory response in RA synovial cells by modulating local production of catecholamines.

1806

Synovial Tissue Cytokine Expression in Rheumatoid Arthritis and Associations with Lymphoid Neogenesis, Disease Activity and the European League Against Rheumatism Response. Juan D. Canete[1], Raquel Celis[2], Julio Ramirez[1], Sara Marsal[3], Gabriel Avila[3], Raimon Sanmarti[2] and Jose L. Pablos[4]. [1]Hospital Clinic, Barcelona, Spain, [2]Clinic Hospital, Barcelona, Spain, [3]Hospital Vall de Hebró, Grup de Recerca de Reumatologia, Barcelona, Spain, [4]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain

Background/Purpose: We analized wether LN is associated with specific patterns of inflammatory cytokine expression in synovial tissue (ST), and the potential association of cytokine expression with disease activity and response to therapy.

Methods: ST samples were obtained by arthroscopy from the inflamed knee of 62 RA patients, In twenty-one patients which started TNF blockers a second biopsy was obtained after a mean of 8+5 months of treatment. ST samples were immunostained with CD3 (T cell), CD20 (B cell), and MECA-79 (high endothelial vessels). Total ST mRNA was extracted and gene expression of CCR7, LT-beta, IL-7, IL-10, IL-17A, IL-21, IL-22, IL-23, TNF-alpha, IL-1b, and IL-6 was measured by quantitative real-time PCR. Clinical and biological data were collected at inclusion and after a median of 2.3 years of follow-up.

Results: 28 out of 62 patients (45.2%) had LN, which correlated with a significantly-higher expression of three key molecular markers of LN, CCR7, IL-7 and LT-beta ($p<0.037$, $p<0.038$, and $p=0.009$, respectively). LN-positive patients also had higher IL-23 ($p=0.035$) and higher DAS28 score, both at inclusion and at the end of follow-up ($p=0.055$ and $p=0.037$, respectively). In the group of patients with ST before and after TNF blockers, EULAR good response was associated with IL-10 reduction ($p=0.035$). In the entire group EULAR response correlated with IL-1b expression ($P=0.014$).

Conclusion: RA patients with LN are characterized by higher expression of key molecular markers of LN, IL-23 and higher disease activity. Significant reduction in IL-10 expression after therapy with TNF-blockers is associated with good EULAR response.

1807

Mucocutaneous Flares As Opposed to Flares From Other Organs Have the Strongest Association with High Type I Interferon Levels in Patents with Systemic Lupus Erythematosus. Elzbieta E. Jacek[1], Mikhail Olferiev[2], Vinicius Domingues[3], Rolando Duculan[1], Nancy Pan[4], Mary K. Crow[4] and Kyriakos A. Kirou[5]. [1]Mary Kirkland Center for Lupus Research-Hospital for Special Surgery, New York, NY, [2]Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, NY, [3]Estacio de Sá University, Rio de Janeiro, Brazil, [4]Hospital for Special Surgery, New York, NY, [5]Mary Kirkland Center for Lupus Care, Hospital for Special Surgery, New York, NY

Background/Purpose: Patients with Systemic Lupus Erythematosus (SLE) have elevated levels of type I Interferon (IFN-I) in their sera and in cross-sectional studies these levels correlate with disease activity. Here, we studied whether IFN-I levels correlate with any specific organ flares in a longitudinally followed cohort of SLE patients.

Methods: There were 30 patients in our study: 83% female, 56% Caucasian, 26% African/American, mean age of 29± 8.8. We collected serum from all visits of each patient and used it to stimulate reporter cells (WISH cells) which are sensitive to IFN-I, and relative expression of two IFN-I-inducible genes, IFIT1 and IFI44, was quantified using real-time RT-PCR. The IFN-I score was calculated by converting relative expression values to IFN units, using a standard curve acquired from dose response stimulations of WISH cells with 1–100 units of recombinant IFN-α. The IFN score was reported as median and Interquartile Range (IQ). Flares of the disease were identified using the SELENA-SLEDAI instrument, and organ involvement was determined by BILAG. The median IFN-I levels during patient visits with mucocutaneous, musculoskeletal, renal, general and all flares were compared to the median IFN-I levels during non-flaring visits. Analyses were performed using Nonparametric Wilcoxon matched-pairs signed rank test (for comparison of visits within the same patient) and Mann-Whitney test when assessing collective differences between flares of particular organs among all patients.

Results:

Paired analysis of visits within same patients	IFN Score (IQ Range)	p-value
All flares (n=30)	4.81 (1.41–18.31)	0.0027
No flare (n=30)	2.41 (1.03–6.31)	
Flares with mucocutaneous involvement (n=11)	5.19 (2.17–16.44)	0.0098
No flare (n=11)	2.53 (1.22–2.86)	
Pure mucocutaneous flares (n=10)	10.83 (3.74–19.42)	0.0039
No flare (n=10)	2.54 (1.03–2.99)	
Pure mucocutaneous flares (n=9)	10.96 (6.6–36.19)	0.039
Flares without mucocutaneous involvement (n=9)	7.68 (2.97–14.99)	
Flares with musculoskeletal involvement (n=7)	3.97 (2.26–16.05)	0.067
No flare (n=7)	1.58 (0.99–03.59)	
Pure musculoskeletal flares (n=7)	2.5 (1.55–10.34)	0.21
No flare (n=7)	1.26 (0.86–3.26)	
Renal flare (n=7)	2.18 (1.56–8.23)	0.46
No flare (n=7)	2.54 (1.16–4.60)	
Nonpaired analysis of all visits		
All flares (n=106)	3.95 (1.62–12.97)	0.0009
No flare (n=247)	1.56 (0.75–3.63)	
Pure mucocutaneous flares (n=12)	11.12 (2.1–26.33)	0.006
No flare (n=247)	1.56 (0.77–3.65)	
Pure mucocutaneous flares (n=12)	11.12 (2.1–26.33)	0.16
Flares without mucocutaneous involvement (n=84)	3.36 (1.57–9.79)	

Conclusion: IFN-I levels vary within SLE patients during the course of their disease and roughly correlate with flares of disease. Interestingly, IFN-I levels are highest with mucocutaneous flares but much less so with musculoskeletal and especially renal flares.These results indicate a special role of IFN-I in the pathogenesis of mucocutaneous flares in SLE patients.

1808

Atherogenic Properties of Rheumatoid Arthritis and SLE Plasma Are Attenuated by Interferon-γ Depletion. Allison B. Reiss, Iryna Voloshyna, Michael J. Littlefield, Elise Belilos, Kristina B. Belostocki, Lois A. Bonetti, Gary C. Rosenblum and Steven E. Carsons. Winthrop University Hospital, Mineola, NY

Background/Purpose: The risk of cardiovascular (CV) morbidity and mortality is profoundly increased in patients with SLE and RA, resulting in a significantly shortened lifespan. It is likely that immunologic derangements contribute to CV disease in these patients. We have discovered that SLE and RA patients manifest a pattern of disturbance in expression of cholesterol transport genes that is atheroma-promoting. Exposure of monocytes/macrophages to human RA or SLE plasma suppresses the cholesterol efflux proteins 27-hydroxylase (27-OHase) and ATP binding cassette transporter (ABC)A1, while the scavenger receptor CD36 that facilitates cholesterol uptake is augmented. As a result, plasma from RA and SLE patients severely disrupts cholesterol balance, leading to excess lipid accumulation and foam cell formation (FCF). We have shown that IFN-γ, a pro-atherogenic, pro-inflammatory cytokine, lessens ABCA1 and 27-OHase and enhances CD36 expression and FCF. This study examines whether depletion of IFN-γ from SLE and RA patient plasma alters the atherogenic properties of the plasma.

Methods: 27-OHase, ABCA1, and CD36 expression were evaluated in THP-1 human monocytes/macrophages, a pertinent model of atherosclerosis. Cells were incubated for 18h in medium containing 10% SLE, RA or control human plasma (CHP) or 10% of the same plasma after depletion of IFN-γ. IFN-γ depletion was accomplished by immunoprecipitation with human IFN-γ antibody overnight at 4°C. Following incubation, mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative PCR using specific primers for each gene. PCR results were normalized to the housekeeping gene GAPDH. Cellular extracts were prepared for Western immunoblotting.

Results: Pooled plasma from SLE and RA patients was compared to CHP (CHP expression set at 100%). In THP-1 macrophages, 10% SLE and RA plasma decreased 27-OHase message by 36.2 ± 12.8% and 49.1 ± 14.7% (n=3, $P<0.01$) below CHP, respectively and ABCA1 fell by 58.3 ± 15.5% (n=3, $P<0.001$) and 48.3 ± 18.7% (n=3, $P<0.01$) below CHP, respectively. CD36 message level rose to 223.8 ± 98.0% and 176.7 ± 53.6% (n=3, $P<0.01$) of CHP, respectively. These same SLE and RA plasma samples, when depleted of IFN-γ, lost their ability to affect 27-OHase and ABCA1 so that levels did not significantly differ from those seen in CHP-exposed cells.

However, CD36 message remained elevated compared to CHP and was the same as with the undepleted RA and SLE plasma.

Conclusion: This study demonstrates pro-atherogenic properties of SLE and RA plasma that may promote atherosclerosis by interfering with cholesterol transport, leading to lipid overload. Removal of IFN-γ from the autoimmune plasma improves cholesterol homeostasis by restoring efflux proteins, but does not change the scavenger receptor CD36. This provides further evidence of the involvement of the immune system in atherogenesis. Novel therapeutic approaches to increased CV risk in patients with autoimmune disorders may be directed toward improved cholesterol balance by targeting IFN-γ or its receptor. This line of research is particularly urgent in light of studies showing little effect of statins, mainstay drugs in CV treatment, on subclinical atherosclerosis in SLE.

1809

Potentiation of TNF-Induced T Cell Chemokine Expression by Type I Interferon in Fibroblast-Like Synoviocytes: Target for JAK Inhibition. Sanna Rosengren, Gary S. Firestein and David L. Boyle. UCSD School of Medicine, La Jolla, CA

Background/Purpose: Interferon-beta (IFNβ) was recently evaluated in clinical trials for treatment of rheumatoid arthritis (RA). Although effective in some animal arthritis models, IFNβ therapy has limited benefit in RA. In fibroblast-like synoviocytes (FLS), IFNβ inhibits IL1β-induced MMP secretion. In contrast, we recently showed that IFNβ acts as an autocrine intermediate in TNF-induced expression of chemokines such as IP10, RANTES, and MCP1 by FLS. To reconcile these apparently contradictory findings, we systematically examined the effect of type I IFN on cytokine-induced gene expression in FLS and the effect of JAK inhibition.

Methods: RA FLS were isolated from arthroplasty tissue, cultured, and serum-starved prior to stimulation. Message levels were determined by qPCR, and protein levels in supernatants determined by ELISA or multiplex bead assay. qPCR results are expressed in relative expression units (REU).

Results: IFNβ (25000 U/ml) significantly decreased IL1β-induced MMP3, IL6, and IL8 expression at 18h. In contrast, when combined with TNF, IFNβ had no effect on IL8 expression, but potentiated IL6 expression and secretion (3.3±0.5 and 2.2±0.5 fold levels of those induced by TNF alone, respectively, p=0.001 and 0.04). In addition, a substantial synergistic effect of IFNβ was observed on TNF-induced IP10, RANTES, and MCP1 expression. For example, IP10 expression after TNF alone was 89±2 REU, IFNβ alone 8.7±1.3, and TNF+IFNβ 1140±170 (n=6, p<0.0001 for TNF+IFNβ compared to the summed values for each). IL1β-induced IP10 and RANTES expression was also potentiated by IFNβ. Similar results were observed at the protein level, and with another member of the type I IFN family, IFNa2 (5000 U/ml). The only gene product studied that was induced by TNF and inhibited by IFNβ was MMP3, whose expression after TNF alone was 10.6±5.8, IFNβ alone 0.03±0.01, and TNF+IFNβ 5.4±3.5 (p=0.02). The type I IFN chemokine and IL6 synergy was reversed by tofacitinib. For example, IFNa2+TNF-induced IP10 levels in medium were 18±4 fold compared to TNF alone, an effect that was inhibited 78±4% by tofacitinib. Of note, the inhibition of TNF-induced MMP3 expression by IFNa2 was not reversed by tofacitinib. MMP3 levels in tofacitinib-treated FLS were 0.56±0.08 and 0.57±0.08 fold that of TNF+vehicle after TNF and TNF+IFNa2 treatment, respectively (p=0.96).

Conclusion: Type I IFN differentially affects IL1β- versus TNF-induced gene expression in FLS. Several genes including IL6 are inhibited by IFNβ in IL1β-stimulated FLS, but only MMP3 is suppressed in FLS activated by TNF. On the other hand, synergy is observed with type I IFN on TNF-induced T cell chemokines and IL6. These findings might explain the anti-inflammatory effects by IFNβ in some animal models where IL1β plays a key pathogenic role and the lack of efficacy of IFNβ treatment in clinical trials in RA where TNF is more important. The Jak inhibitor, tofacitinib significantly reverses this synergy but does not alter the inhibitory effect by IFN on MMP3 suggesting additional therapeutic effects of JAK/STAT pathway blockade in RA.

1810

IL-6 and TNF-α Enhance the Expression of U1C and Affect the Splicing of Functional Defective Angiopoietin-1 (*Ang1*) Gene Mediated by Anti-U1C Antibody in the Patients with MCTD. Tatsuki Okuyama[1], Yuka Kosugi[1], Koichiro Komai[1], Akira Hashiramoto[2], Kazuko Shiozawa[3] and Shunichi Shiozawa[2]. [1]Graduate School of Health Sciences, Kobe Univ., Kobe, Japan, [2]Graduate School of Health Sciences and Medicine, Kobe Univ. / The Center for Rheumatic Diseases, Kobe Univ., Hosp., Kobe, Japan, [3]Rheumatic Diseases Center, Konan Kakogawa Hospital, Kakogawa, Japan

Background/Purpose: Angiopoietin-1 (*Ang1*), the ligand of endothelial tyrosine kinase receptor Tie2, which induces cell proliferation *via* ERK and resistance for apoptosis-induction *via* Akt (Arth. & Rheum. 57 (7): 2170, '07). *Ang1* is strongly up-regulated in the lung of patients with mixed connective tissue disease (MCTD) accompanied by pulmonary hypertension (PH), indicating that *Ang1* may play a key role in the pathogenesis of PH associated with MCTD. We previously showed that the frequency of the splicing variant of *Ang1* mRNA with nt805GGT insertion (*Ang1*/ins) encoding 269Gly was significantly increased in the Japanese patients with MCTD and those with PH as compared with *Ang1*/del with nt805GGT deletion (Arth. & Rheum. 52 (9): S283, '05). We also found that *Ang1*/ins facilitated proliferation of pulmonary endothelial cells and potentially induced hyperplasia of smooth muscle cells as compared with *Ang1*/del (Arth. & Rheum. 58 (9): S659, '08 and 60 (10): S8, '09). On the other hand, *Ang1*/ins variant was relatively increased when anti-U1C or U1–70K Ab was introduced into human pulmonary artery smooth muscle cells (HPASMC) in the presence of IL-6 and TNF-α (Arth. & Rheum. 62 (10): S370, '10), while it was not in cases without cytokine stimulation. We here investigated the mechanism how IL-6 or TNF-α interferes with the splicing of *Ang1*.

Methods: Anti-U1A, U1C, and U1–70K Abs (LifeSpan Biosc. and Bio Acad.) were labeled with Alexa Fluor 488 (invitrogen) and introduced into HPASMC by using protein delivery reagentPolyplus transfection) and cultivated with 20ng/ml of IL-6 or TNF-α for 24 h. Intracellular localization of introduced fluorescein labeled Abs was observed by using fluorescence microscope and the amount of introduced Abs was determined by using FACS. In order to quantify U1RNP mRNA, total RNA of cytokine-stimulated HPASMC was extracted and amounts of U1A, U1C, U1–70K mRNA were quantified by real-time TaqMan® PCR. The nuclear protein extracted from cytokine-stimulated HPASMC was analyzed by Western blotting using specific Abs for U1RNP proteins. We also examined the concentration of IL-6 and TNF-α in the sera of patients with MCTD (n=12) by using ELISA (R&D systems).

Results: Features of intracellular localization and amounts of introduced Abs appeared to be similar between the cases with or without IL-6 and TNF-α, however, the expression of mRNA and the amount of U1C protein were both significantly increased in HPASMC under the stimulation with IL-6 and TNF-α ($P < 0.05$). The serum concentrations of IL-6 and TNF-α in the patients having *Ang1* /ins dominantly (average±1SD) was 17.47±3.88 pg/ml, which showed significant increase as compared with 10.55±2.05 pg/ml in the patients having *Ang1* /del dominantly ($P < 0.005$). "dominant" represents that *Ang1* /del or *Ang1* /ins expressed higher than twice of the other one.

Conclusion: IL-6 and TNF-α interfere with the expression of U1C, thereby increasing the potential for intracellular-introduction of anti-U1C Ab. The anti-U1RNP antibody found in the sera of patients with MCTD or MCTD with PH may interfere with the splicing of *Ang1* to increase *Ang1* /ins variants.

1811

Chemerin/ChemR23 Expression and Pro-Inflammatory Effects in Synovitis of Patients with Rheumatoid Arthritis. Hirahito Endo, Makoto Kabraki, Yoshie Kusunoki, Natsuko Kusunoki and Shinichi Kawai. Toho University School of Medicine, Tokyo, Japan

Background/Purpose: Chemerin is an adipokine that stimulates chemotaxis of cells of the innate immune system. To evaluate the role of chemerin, and its G protein - coupled receptor ChemR23 in inflammatory arthritis such as rheumatoid arthritis(RA) and Osteoarthritis(OA) we analyzed using synovial tissues and osteoclastogenesis system.

Methods: Level of Chemerin in synovial fluids and plasma from 52 patients with RA and 20 patients with OA were measured by an specific ELISA. Reverse transcription-polymerase chain reaction (RT-PCR), real-time quantitative PCR, and *in situ* hybridization were performed to detect mRNA for ChemR23 in 30 patients with RA and 10 patients with OA. Chemerin measured by immunohistochemical methods in synovium of RA and OA. The effects of chemerin/chemR23 on matorix metalloproteanases (MMP) synthesis in cultured synovial cells were measured. Effect of active chemerin on osteoclastgenesis, osteoblastgenesis from murine bone marrow cells and monocyte-linageRAW264.7 were also examined.

Results: Chemerin showed significantly higher levels in RA synovial fluids (378.8±185.2 ng/ml) than OA synovial fluids (102.5±74.8 ng/ml). Expression of ChemR23mRNA were stronger in RA synovium than OA synovium (RA 27.3±2.6 AU, OA 8.6±3.8 AU, p<0.05). *In situ* hybridization for ChemR23 mRNA expressed in macrophage and fibroblast-like cells from lining layer of RA synovium. Plasma chemerin levels of RA were not

higher than that of OA (RA 89±16.7ng/ml, OA 100.2±15.8ng/ml). Expression of Chemerin induced by interleukin-1 from cultured synovial cells in a dose dependent and time dependent manner. Chemerin induced MMP1 and MMP3 synthesis in cultured RA synovial cells via ChemR23. Chemerin/ChemR23 also induced osteoclastogenesis via active extracellular signal regulated kinase(ERK)1/2 in receptor activator of NF-kB ligand(RANKL)-stimulated bone marrow monocyte and macrophage-linage cells. Chemerin induced tartrate acid phosphatase(TRAP) mRNA and MMP-9 in these cells. Chemerin suppressed osteoblastogenetic differentiation accompanied with adipogenesis from progenitor cells in murine bone marrow system. Chemerin/ChemR23 also promoted resorption capacities of RANKL stimulated macrophage-linage cells on calcium phosphate-coated culture plates.

Conclusion: ChemR23 is an important target of chemerin in synovial tissues of patients with RA. Chemerin in inflammatory synovitis produce locally in inflammatory arthritis such as RA. Chemerin/ChemR23 might be modulate the bone resorption via osteoclast differentiation in RA. These findings could leads to the development of new therapeutic approach for inflammatory arthritis such as RA.

1812

Functional Characterization of An Allosteric Enhancer of the Adenosine A_{2a} Receptor That Inhibits Pro-Inflammatory Cytokine Production. Ajith A. Welihinda and Edward P. Amento. Molecular Medicine Research Institute, Sunnyvale, CA

Background/Purpose: Adenosine, an endogenous nucleoside, is produced at high levels at inflamed sites as a by-product of cellular activation and breakdown. Adenosine, mediates its immune suppressive activity primarily through the adenosine A_{2a} receptor ($A_{2a}R$), a member of the G-protein coupled receptor family of transmembrane receptors. High affinity $A_{2a}R$ agonists have demonstrated anti-inflammatory efficacy, however, their therapeutic utility is hindered by lack of adenosine receptor subtype selectivity upon systemic exposure. We sought to harness the inherent immune suppressive effects of adenosine by enhancing the responsiveness of $A_{2a}R$ to endogenously produced adenosine. Using a mutually exclusive array of cell-based assays, we examined a series of compounds originally derived from plant sources to identify potential $A_{2a}R$ allosteric enhancers. The present study describes allosteric properties of a representative compound.

Methods: Compounds that inhibited inflammatory cytokines by mononuclear cells without affecting known anti-inflammatory pathways were screened for the enhancement of $A_{2a}R$-mediated cAMP production in cells over-expressing the receptor. $A_{2a}R$ deficient $CD4^+$ T cells were used to identify those compounds whose anti-inflammatory activity depended solely upon the intact receptor. Binding affinity of $A_{2a}R$ was determined using [^{14}C]CGS21680. $A_{2a}R$-mediated G-protein activation was evaluated using [^{35}S]GTP-γS binding to $A_{2a}R$ membranes. Human monocytes were isolated from PBMCs by depleting other cell types. $CD4^+$ T cells were isolated from splenocytes by negative selection. Cytokine levels in culture media and intracellular cAMP levels were quantitated by ELISA.

Results: A subset of compounds potentiated cAMP production by CHO cells stably expressing the human $A_{2a}R$ only in the presence of adenosine. A representative compound, AEA061, was chosen to establish allosteric modulation as the basis of the activity. AEA061 enhanced both the potency and efficacy of adenosine at the $A_{2a}R$. Binding studies demonstrated that the compound increased the affinity as well as the B_{max} of the $hA_{2a}R$ to agonists. In addition, AEA061 elevated agonist-mediated G-protein activation as shown by increased [^{35}S]GTP-γS incorporation into $A_{2a}R$ expressing cell membranes. Consistent with the immunomodulatory role of the $A_{2a}R$, AEA061-dependent activation of the receptor attenuated TNF-α production stimulated by distinctly different signaling pathways in monocytes/macrophages. Moreover, AEA061 attenuated IFN-γ production by anti-CD3-stimulated wild-type $CD4^+$ T cells but not by $A_{2a}R$ deficient $CD4^+$ T cells.

Conclusion: Our observations support the hypothesis that AEA061 and its analogs allosterically modulate the $A_{2a}R$ to potentiate cAMP production. The allosteric enhancement of $A_{2a}R$ leads to inhibition of pro-inflammatory cytokines. The potential to enhance natural immune suppression through the adenosine-$A_{2a}R$ pathway may provide a means to focus anti-inflammatory activity at disease sites where adenosine is abundant. Allosteric modulation of A2aR presents a novel and unique approach for the treatment of RA and associated inflammatory conditions.

1813

Mechanism of Fractalkine/CX3CL1 Synthesis and Shedding in Rheumatoid Arthritis Synovial Fibroblasts. Brian Jones, Maria Beamer, Ayesha Rahman, Wissam Ali Aboualaiwi and Salahuddin Ahmed. Department of Pharmacology, University of Toledo College of Pharmacy & Pharmaceutical Sciences, Toledo, OH

Background/Purpose: Tumor necrosis factor (TNF)-α and interferon (IFN)-γ together induce the production of fractalkine/CX3CL1 (FKN), a well known chemoattractant and cell adhesion chemokine, in rheumatoid arthritis(RA) synovial fibroblasts by an unknown mechanism. The present study was undertaken to determine the cellular mechanisms governing RA synovial fibroblast FKN synthesis and shedding so that highly targeted therapeutic approaches against it may be developed for RA.

Methods: Effect of TNF-α and IFN-γ, alone or in combination, on human RA synovial fibroblast FKN synthesis and shedding was determined over 6–72 hours by immunostaining, quantitative RT-PCR, and Western blotting methods. The role of enzymes ADAM17, ADAM10 and caspase-3, the signaling mediators such as mitogen-activated protein kinases (MAPK) and nuclear factor-κB (NF-κB) pathways were evaluated using signaling inhibitors. 20S Proteasome activity in the treated samples and the DNA-binding activity of NF-κB in the nuclear fractions were evaluated using the commercially available ELISA kits.

Results: In RA synovial fibroblasts, the combination of TNF-α/IFN-γ induced the cellular expression of FKN that peaked as early as 24 hours ($P<0.05$; $n=3$). Activation of ADAM17 expression, but not ADAM10, enhanced the proteolytic shedding of FKN, resulting in the release of soluble FKN (sFKN) that peaked around 48–72 hours of stimulation. TNF-α/IFN-γ-induced FKN expression and sFKN release were markedly inhibited in RA synovial fibroblasts by the pretreatment of GM6001 (an inhibitor of ADAM17) or MG132 (a proteasome inhibitor), but not Z-DEVD-FMK (an inhibitor of caspase-3), suggesting an important role of ADAM17 in the proteolytic shedding of sFKN. This observation was further supported by an increase in the proteasome activity by 40% in the samples treated with TNF-α/IFN-γ as compared to the untreated samples ($P<0.001$; $n=3$). Evaluation of the signaling pathways revealed that MG132 and SB203580 (a p38-MAPK inhibitor) selectively inhibited TNF-α/IFN-γ-induced sFKN production in RA synovial fibroblasts ($p<0.05$; $n=3$), suggesting the clinical importance of these pathways in mediating the synthesis and proteolytic processing of FKN. Importantly, we also observed a rapid phosphorylation and proteasomal degradation of IκBα and an activation of phospho-p38 expression within 1–5 minutes of TNF-α/IFN-γ stimulation, which further correlated with the increased DNA-binding activity of NF-κB in the nuclear fractions of the similarly treated RA synovial fibroblasts.

Conclusion: Our results provide the evidence of the role of ADAM17, p38-MAPK, and proteasome pathway in regulating TNF-α/IFN-γ-induced synthesis and proteolytic shedding of FKN. Selective inhibition of these molecular targets may be one of the potential therapeutic approaches to limit the pathological role of FKN in RA synovial fibroblast mediated inflammation and tissue destruction.

1814

Comparison of Anti-Interleukin-6 and Anti-Interleukin-6 Receptor Antibodies Using *In Vivo* Functional Systems. Stevan Shaw, Diane Marshall, Helen Neale, Kosmas Kretsos, Tim Bourne and Alastair Lawson. UCB, Slough, United Kingdom

Background/Purpose: The multi-step assembly of the interleukin-6 (IL-6) signaling complex offers the potential for several therapeutic points of intervention in the treatment of rheumatoid arthritis; for example, targeting the cytokine IL-6, the IL-6 receptor (IL-6R; gp80), or gp130. The objective of this study was to compare affinity-matched anti-murine monoclonal antibodies (mAbs) that target either the cytokine or the receptor in a range of *in vivo* assays.

Methods: Affinity-matched anti-murine reagents 54E07 mAb (anti-IL-6) and 440-1 mAb (anti-IL-6R; gp80) were evaluated for their ability to inhibit either murine IL-6 or CFA-induced serum amyloid A (SAA). IL-6 is also known to have a significant role in B-cell function; therefore, these antibodies (Abs) were evaluated for their ability to inhibit dinitrophenyl (DNP)-specific Ab production. Furthermore, these Abs were dosed to steady state and their capacity to inhibit collagen-induced arthritis (CIA) in DBA-1 mice was evaluated.

Results: 54E07 mAb produced a ≥90% reduction in the SAA response to both IL-6 and CFA at a dose of 0.1 mg/kg ($p < 0.01$ and $p < 0.001$, respectively). In contrast, doses of at least 1 mg/kg and 3 mg/kg of 440-1 mAb were required to significantly reduce the SAA response ($p < 0.001$ for both doses). *In vivo* inhibition of IL-6 by 54E07 mAb significantly reduced the DNP-specific IgG response by 72% at doses as low as 0.3 mg/kg s.c. ($p < 0.05$), whereas 440-1 mAb only achieved a significant reduction (80%) in DNP-specific Ab titer at a dose of 10 mg/kg s.c. ($p < 0.05$). In the murine CIA model, both 54E07 mAb and 440-1 mAb achieved a similar reduction (≥97%) in the clinical arthritis score at the same high dose exposure; however, at the same low dose exposure, only 54E07 mAb caused a significant reduction (67%) in clinical score versus controls.

Conclusion: These murine *in vivo* studies strongly suggest that targeting IL-6 cytokine rather than the IL-6 receptor is the more efficient therapeutic approach for the treatment of autoimmune diseases such as rheumatoid arthritis.

1815

Oncostatin M Is a Potent Regulator of Interleukin-6 and RANKL Expression in Mouse Synovial Fibroblasts and Synergises with Interleukin-1. Benoit Le Goff, Brett A. Tonkin, Sofie Singbrant, T. John Martin, Evange Romas, Natalie A. Sims and Nicole C. Walsh. St Vincent's Institute of Medical Research, Melbourne, Australia

Background/Purpose: Oncostatin M (OSM) is a multipotent cytokine expressed in the synovium of rheumatoid arthritis (RA) patients. OSM alone, or in concert with pro-inflammatory cytokines like IL-1, can stimulate expression of genes that promote inflammation and joint destruction. This study determined the acute effects of OSM, IL-1, and their combination on expression of IL-6 and RANKL in synovial fibroblasts (SFs).

Methods: SFs were isolated from non-arthritic mouse hind paws from wild type and OSMR knockout (OSMR−/−) mice, and stimulated with mouse OSM (2 ng/mL), mouse IL-1 (10 ng/mL), or their combination for 1, 6 and 24 hours. Gene expression was assessed by quantitative RT-PCR. IL-6 protein expression was determined using ELISA, and flow cytometry was performed to identify receptor expression. To identify protein expression in vivo, immunohistochemistry was performed on paraffin sections of non-arthritic and arthritic knee joints from mice induced with antigen-induced arthritis.

Results: In wild type SFs, OSM and IL-1 both increased IL-6 mRNA expression, with induction by OSM being more rapid and sustained compared with induction by IL-1: 179 fold vs. 40-fold at 24 hrs. Profound synergistic upregulation of IL-6 mRNA expression was observed when submaximal doses of OSM and IL-1 were combined (>1000-fold at 6 and 24 hrs). At the maximum cytokine doses the combination of OSM and IL-1 resulted in the release of approximately 10ng/mL IL-6 protein into the culture supernatant after 24 hrs of treatment (>1200 fold increase compared to control). Both OSM and IL-1 increased RANKL mRNA expression by 6 hrs (9-fold and 4-fold, respectively) but only OSM further increased RANKL expression at 24 hrs (23-fold). Combining submaximal doses of OSM and IL-1 significantly enhanced RANKL expression by 24 hrs (up to 100-fold). Importantly cells lacking OSMR expression (OSMR−/−) showed no induction of IL-6 or RANKL mRNA expression in response to OSM treatment, but did respond to IL-1 treatment in a similar manner to matched wild type SFs. In wild type SFs, OSM stimulated expression of its co-receptors (OSMR, 6-fold at 6 and 24 hrs, and gp130, 3-fold at 24 hrs). Furthermore, OSM increased IL-1 receptor mRNA expression at 6 and 24 hrs (5-fold) and increased IL-1 receptor protein expression at 24 hrs as determined by flow cytometry. Finally, immunostaining showed protein expression of OSM and its co-receptors in the synovium in normal mouse knee joints; this expression was increased in antigen-induced arthritis.

Conclusion: Together our data shows that OSM, acting alone or in synergy with IL-1, is a potent regulator of IL-6 mRNA and protein expression in SFs. Furthermore this cytokine combination can act together to increase RANKL expression in these cells. The ability of OSM to increase expression of IL-1R at both the gene and protein level may contribute in part to its synergistic effects with IL-1 on SFs. The results highlight the potential for OSM, acting through OSMR, to significantly contribute to inflammation and bone destruction in arthritic joints. OSM signaling via OSMR is therefore a potential therapeutic target in the treatment of RA.

1816

Late Apoptotic Bodies Mediates Sterile Inflammation in Vitro and In Vivo Via IL-1alpha. Yael Berda-Haddad[1], Stéphane Robert[1], Paul Salers[1], Leila Zekraoui[2], Catherine Farnarier[3], Charles A. Dinarello[4], Françoise Dignat-George[1] and Gilles Kaplanski[1]. [1]INSERM U608, Marseille, France, [2]Faculté de Médecine-Timone, Marseille, France, [3]Hopital de la Conception, Marseille, France, [4]Denver, CO

Background/Purpose: A common paradigm is that apoptotic bodies (AB) are rapidly cleared from the circulation by macrophage phagocytosis delivering an anti-inflammatory signal. During systemic lupus erythematosus, due to a defect of macrophage-mediated phagocytosis, AB persist in the circulation becoming late AB leading to anti-nucleosome and anti-DNA antibodies appearance. We asked whether late AB may also mediate a pro-inflammatory signal.

Methods: AB were prepared in vitro using serial centrifugations from the supernatant of apoptotic human umbilical vein endothelial cells (HUVEC) induced by combination of serum starvation and TNF-alpha stimulation. The presence of IL-1alpha was studied by ELISA, FACS, immuno-gold electronic microscopy, Western blot (WB) analysis. The pro-inflammatory function of late AB was studied in vitro through their ability to induce endothelial chemokine secretion in co-culture with normal HUVEC and in vivo by intra-peritoneal injection in mice.

Results: AB were isolated from the supernatant of apoptotic HUVEC using their size (1–3 microns), co-labelling with annexinV and propidium iodide and the detection of histones. In vitro, in the absence of macrophages, these AB becomes late AB. IL-1alpha was detected by ELISA in AB lysates, FACS analysis on permeabilized AB and electronic microscopy. WB analysis on AB lysates identified both the 31 kDA IL-1alpha precursor and its 17 kDa mature form. During in vitro co-culture with HUVEC, late AB were able to induce IL-8 and MCP-1 which were completely inhibited by addition of anti-IL-1alpha and IL-1receptor antagonist (IL-1ra) but not by anti-TNFalpha or anti-IL-1beta. Mice intra-peritoneal injection of late AB induced increased production of neutrophilic chemokine and a neutrophilic inflammation which was completely prevented by treatment with IL-1ra.

Conclusion: During cell necrosis, cytoplasmic IL-1alpha is released though the porous cell membrane and induces sterile inflammation. On the contrary, during apoptosis IL-1alpha remains associated within the nucleus preventing its pro-inflammatory effects. We observed that IL-1alpha is associated within AB and maybe released from late AB to induce sterile inflammation, suggesting that IL-1alpha may play a pathogenic role in the inflammation of auto-immune diseases.

1817

Fatty Acid-Binding Protein (FABP)-4 Is Increased in Patients with Rheumatoid Arthritis and Correlates with Metabolic Rather Than with Disease Activity Status. Lucie Andrés Cerezo[1], Hana Hulejová[1], Zdenka Vernerová[2], Markéta Kuklová[1], Ondrej Pecha[3], Vlasta Pesáková[1], Karel Pavelka[1], Jiri Vencovsky[1] and Ladislav Senolt[1]. [1]Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]Department of Pathology, 3rd Medical Faculty, Charles Universityin Prague, Prague, Czech Republic, [3]Institute of Biophysics and Informatics, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic

Background/Purpose: FABP4 protein belongs to the family of fatty acid binding proteins (FABPs) which are known to bind fatty acids and are believed to coordinate lipid response in cells. FABP4 was initially detected in mature adipocytes and linked to metabolic disorders; however, recently FABP4 has been identified in macrophages and shown to modulate inflammatory cytokines production. The purpose of this study was to assess FABP4 expression pattern in synovial tissues, serum and synovial fluid from patients with rheumatoid arthritis (RA) and osteoarthritis (OA), and to study relationship between FABP4, disease activity and metabolic status.

Methods: Synovial tissues were obtained from patients with established RA (n=5) and from patients with osteoarthritis (OA) (n=5). Immunohistochemical analysis of synovial tissues was used to determine the expression of FABP4 protein. FABP4 levels in serum and synovial fluid were determined by ELISA (Biovendor, Czech Republic) in 40 patients with RA and 40 control patients with OA. Patients with RA were assessed for disease activity (CRP, DAS28) and autoantibodies (ACPA and IgM-RF). Serum lipids including triglycerides (TG), total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein cholesterol were measured.

Results: We found an increased expression of FABP4 protein in RA

compared with OA synovial membrane, particularly in inflammatory infiltrates. Similar patterns of FABP4 staining intensity were detected in endothelial cells and adipose tissues in RA and OA synovial membranes. The levels of FABP4 were higher in serum (29.22±2.69 vs. 19.61±1.33 ng/ml; p=0.002) and synovial fluid (23.96±1.91 vs. 18.04±0.99 ng/ml; p=0.008) of patients with RA than in patients with OA, even when adjusted to age, sex and BMI (p= 0.001 and p=0.005). The levels of FABP4 significantly correlated between serum and synovial fluid in RA as well as in OA patients. In addition, FABP4 was higher in females than in males and its serum (r=0.343, p=0.03) and synovial fluid (r=0.447, p=0.004) levels significantly correlated with BMI in patients with RA, but not with OA. When adjusted to age, sex and BMI, serum and synovial fluid FABP4 levels significantly correlated with total cholesterol (r=0.302, p=0.07 and r=0.383, p=0.02, respectively) and LDL cholesterol (r=0.357, p=0.045 and r=0.412, p=0.019, respectively) in patients with RA, but not with OA. On the other hand, there were not found any associations between FABP4 levels and clinical or laboratory markers of RA.

Conclusion: Increased FABP4 in RA synovial membrane, synovial fluid and blood circulation and its positive correlation with BMI, total and LDL cholesterol suggests that FABP-4 may be related to metabolic abnormalities rather than to disease activity in patients with RA.

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1818

Role of Liver X Receptors In the Regulation of Effector Functions of Fibroblast-Like Synoviocytes In Rheumatoid Arthritis. M.Teresa Arce-Franco[1], M. Jesus Dominguez-Luis[2], Ana Diaz-Martin[2], Ada Herrera-Garcia[3], Maria Eugenia Miranda-Carus[4], Sagrario Bustabad-Reyes[3], Antonio Castrillo[5] and Federico Diaz-Gonzalez[1]. [1]Rheumatology Service, La Laguna, Spain, [2]Hospital Universitario de Canarias, La Laguna, Spain, [3]Hospital Universitario de Canarias, La Laguna. Tenerife, Spain, [4]La Paz Hospital. IdiPaz, Madrid, Spain, [5]University of Las Palmas de Gran Canaria (ULPGC), Canary Islands, Las Palmas (Gran Canaria), Spain

Background/Purpose: Fibroblast-like synoviocytes (FLS) play an essential role as effector cells in the pathogenesis of rheumatoid arthritis (RA) through the proliferation, production of metalloproteinases (MMPs) and invasion of joint structures. However, until now none therapeutic approach has been designed to target FLS in RA. The liver X receptors (LXR) isoforms, α and β are members of the nuclear receptor superfamily of transcription factors activated by ligand. LXR-induced genes were mainly identified as genes involved in reverse cholesterol transport but several evidences suggest that they are also involved in the modulation of the inflammatory response. The main objective of this work was to study the presence of LXR subtypes and the implication of LXR agonists in the migration, proliferation and MMPs production by FLS from RA patients.

Methods: Six FLS cell lines were isolated by enzymatic dispersion of synovial membrane and cultured in DMEM high glucose from 6 RA patients undergoing knee replacement prosthesis. The presence of LXR isoforms on cultured FLS was studied by RT-PCR and Western Blot. Quantitative RT-PCR of ATP binding cassette A1 (ABCA1) and ABCG1, two LXR target genes, was used to determine the functional capability of LXR on FLS in response to the LXR synthetic agonists: T1317 and GW3965. The role of LXR in FLS chemotaxis was determined by two-compartment transwell assay. Cell growth was measured by a fluorescence-based proliferation assay. Collagenase activity was determined by a fibril degradation assay.

Results: FLS from patients with RA expressed in basal conditions both mRNA and protein of a and b isoforms of LXR. The LXR synthetic agonists T1317 and GW3965 induced ABCA1 and ABCG1 genes in FLS by qRT-PCR. FLS cultured in the presence of both LXR agonists showed a reduction in their proliferative capacity of 40±5% respect to the absence of agonists with or without TNF-α. In transwell experiments using SDF-1 as chemoattractant, both LXR agonists significantly inhibited in 40±7% the migration of cells. FLS cultured with TNF-α in the presence of LXR agonists showed a reduction in the expression of MMP-1 and MMP-9 of 2.5 and 12 times, respectively ((-$\Delta\Delta$Ct) method). Similarly, the collagenase activity induced by TNF-α in FLS supernatant decreased significantly (65±10%) by the presence of GW3965 respect to basal conditions.

Conclusion: FLS from RA patients express constitutively functional LXR. Agonists of these receptors show antiproliferative activity, reduce migration and MMP production in FLS. Taken together, these data suggest that LXR may be a potential therapeutic target for the control of synovitis in patients with RA.

1819

Poly I:C, a Ligand for TLR3, Abrogates Stimulation of Fibrotic Response Induced by Transforming Growth Factor-β. Feng Fang[1], Kohtaro Ooka[2], Swati Bhattacharyya[3] and John Varga[3]. [1]Northwestern University, Chicago, IL, [2]Northwestern University, [3]Northwestern Univ Med School, Chicago, IL

Background/Purpose: Transforming growth factor β (TGF-β) is a potent inducer of collagen synthesis, myofibroblast differentiation and epithelial-mesenchymal transition (EMT), and is implicated in fibrosis. Toll-like receptors (TLRs) mediate immune cell responses to endogenous danger signals generated during tissue injury. Aberrant TLR signaling is implicated in chronic inflammation and autoimmunity, but its role in fibrosis is not understood.

Methods: TLR3 expression on skin and lung fibroblasts was determined by real-time qPCR and immunofluorescence microscopy. Regulation of collagen and α-smooth muscle actin (α-SMA) gene expression and TGF-β signaling by Poly I:C, a TLR3 ligand, were examined by real-time qPCR, Western blot, immunofluorescence microscopy and transient transfection assays. Gene expression changes induced by Poly I:C were examined at the genomewide level using Illumina microarrays.

Results: Poly I:C caused inhibition of collagen and α-SMA gene expression in a dose- and time-dependent manner, while the expression of TLR3 was substantially enhanced. Microarray analysis revealed that many genes related to TGF-β signaling pathway were down-regulated by poly I: C. In TGF-β-activated fibroblasts, poly I:C abrogated the stimulation of fibrotic responses, and attenuated Smad2/3 phosphorylation and Smad-dependent transcription. These effects were largely TLR3-independent. Gene expression profiling showed that poly I:C significantly up-regulated the expression of Type I interferon (IFN), and 291 IFN-regulated genes. Type I IFN was required for mediating the antagonistic effect of Poly I:C on TGF-β-inducible responses.

Conclusion: Poly I:C, a TLR3 ligand mimicking the effects of nucleic acids generated at sites of tissue injury, abrogated Smad-dependent fibrotic TGF-β responses through a TLR3-independent Type I IFN-dependent manner. IFN-inducible genes stimulated by Poly I:C might underlie the repression of collagen and α-SMA, while up-regulating many inflammatory gene (IL-6, IL-8 CXCL10). The nature of Poly I:C signaling in fibroblasts, and mechanism underlying the antagonistic cross-talk between the IFN and TGF-β/Smad signaling pathways, are currently under study.

1820

Visfatin and B-Cell Activating Factor of the TNF Family Serum Levels Correlate with Disease Activity in Anti-Jo-1 Positive Patients with Idiopathic Inflammatory Myopathies. Hana Hulejová[1], Olga Kryštufková[1], Klára Kuncová[2], Josef Zámecník[2], Herman F. Mann[1], Ladislav Senolt[1] and Jiri Vencovsky[1]. [1]Institute of Rheumatology,1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]2nd Medical School and University Hospital Motol, Charles University, Prague, Czech Republic, Prague, Czech Republic

Background/Purpose: Visfatin (PBEF, pre-B-cell colony-enhancing factor) is an adipocytokine that supports B-lymphocyte precursor maturation, and besides other functions, takes part in regulation of inflammation. Anti-histidyl-tRNA syntethase antibodies (anti-Jo-1) are the most frequent autoantibodies in polymyositis (PM) and dermatomyositis (DM). Recently we showed increased serum levels of B-cell activating factor of the TNF family (BAFF) in anti-Jo-1+ PM/DM patients and its association with disease activity. The aim of this work was to evaluate serum levels of visfatin in anti-Jo-1+ PM/DM, expression of visfatin in muscle tissue and investigate potential relation between visfatin, BAFF and disease activity.

Methods: Visfatin was detected by immunohistochemistry in muscle tissues of PM/DM patients (n=5/5) and compared with non-inflammatory control muscle tissues from patients with myasthenia gravis (n=5). ELISA was used for detection of serum levels of visfatin (BioVision), BAFF (R&D) and anti-Jo-1 (Orgentec) in 38 patients with PM (n=27) or DM (n=11) and in 25 age and sex matched healthy controls. 16 patients had paired serum samples from different time points available (median interval 13.4 months; min 7–max 73.6). Disease activity was evaluated by myositis disease activity assessment visual analogue scales (MYOACT) and by serum levels of CK, ALT, AST, LDH and myoglobin.

Results: Visfatin expression was increased in muscle tissues from patients with PM/DM compared with that in controls and the expression was particularly associated with endomysial and perimysial inflammatory cell

infiltration. Serum visfatin levels were significantly higher in myositis patients compared to healthy controls (1.94 [range 0.13–9.9] vs. 1.31 [0.1–5.2] ng/ml; $p<0.02$). Both visfatin and BAFF levels were associated with clinical muscle activity ($rs=0.39$ and 0.34, $p<0.02$ and $p=0.04$) and there was a trend for correlation with the global disease activity ($rs=0.28$ and 0.33, $p=0.09$ and 0.05). Visfatin significantly correlated with LDH ($rs=0.39$, $p<0.02$), whereas BAFF correlated with CK ($rs=0.51$, $p=0.001$), myoglobin ($rs=0.57$, $p=0.002$) and AST ($p=0.39$, $p=0.01$). Serum levels of visfatin were positively correlated with BAFF in myositis patients ($rs=0.44$, $p=0.006$), but negatively in healthy controls ($rs=-0.54$, $p=0.005$). No association of visfatin with anti-Jo-1 autoantibody levels was found while BAFF correlated with levels of anti-Jo-1 positively ($rs=0.85$, $p=0.001$). Visfatin levels decreased significantly (from 2.12 [0.7–9.4] to 1.16 [0.6–4.45] ng/ml; $p=0.01$) over time while the decrease of BAFF was not significant (from 1.69 [0.6–10.9] to 1.11 [0.7–4.8] ng/ml; $p=0.09$).

Conclusion: These results demonstrate that the serum levels of visfatin, similarly to BAFF, associate with disease activity in patients with myositis. Increased visfatin levels and expression in inflamed muscle tissues support its possible role in the pathogenesis of idiopathic inflammatory myopathies.

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1821

FMS-Like Tyrosine Kinase 3 Ligand/CD135 in Arthritis: A New Inflammatory System in Rheumatoid Arthritis? Maria I. Martins Ramos, Saïda Aarrass, Lisa G.M. van Baarsen, Danielle M. Gerlag, PP. Tak and Maria C. Lebre. Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Fms-like tyrosine kinase 3 ligand (Flt3L) is a potent endogenous growth factor for myeloid dendritic cells (mDC) and plasmacytoid dendritic cells (pDC). Its administration to mice and humans leads to dramatic increases of various DC subsets while Flt3L−/− mice show reduced DC numbers. Flt3L and its receptor (CD135) have been poorly studied in the setting of autoimmune diseases in general. Typically, CD135 is expressed on early myeloid and lymphoid progenitors and is activated by its soluble ligand, Flt3L.The highly differentiated cellular pattern in rheumatoid arthritis (RA) synovium made us hypothesise that Flt3L, with its ability to induce proliferation and differentiation, could be of importance in induction and/or progression of arthritis. This research aims to directly determine the functional role of FLT3/Flt3L in RA.

Methods: Patients with active RA, psoriatic arthritis (PsA), spondyloarthritis (SpA), osteoarthritis (OA), gout and healthydonors (HD) were included in this study. Soluble (s)Flt3L levels in synovial fluid (SF) and serum were determined by ELISA. Expression of membrane-bound (m)Flt3L and Flt3L receptor (CD135) in peripheral blood mononuclear cells PBMC) and SFMC were assessed by FACS. In addition, immunohistochemical analysis of Flt3L and CD135 was performed in RA, PsA, gout, OA and HD synovial tissues.

Results: SF levels of Flt3L in RA ($n=103$), PsA ($n=33$), and SpA ($n=32$), OA ($n=8$) and gout ($n=43$) were significantly higher compared to paired serum. In addition, Flt3L levels were significantly higher in RA, PsA and SpA SFs compared to gout SF. In peripheral blood (PB) monocytes, B cells and mDC the expression of mFlt3L in RA was higher compared to HD. Flt3L receptor expression was confined to monocytes and mDC and higher in RA SF compared to PB. Immunohistochemistry and immunofluorescence data showed the presence of Flt3L and CD135 in RA ST. Interestingly, microarray data of RA synovial tissue showed that CD135 expression is increased in patients with high inflammatory gene profile compared to low inflammatory gene profile. There is no different in Flt3L expression between RA and OA confirming the ELISA data. In addition, prednisone treatment reduced Flt3L serum levels in RA patients, and changes in Flt3L serum levels correlate with changes in DAS28.

Conclusion: The data presented in this study point to inflammatory role for Flt3L/CD135 system. Moreover, as the Flt3L/CD135 system is implicated in the generation of DC and B cells, inflammatory cells important in RA pathogenesis, this system might be of importance in RA. Achieving a detailed understanding of Flt3L function(s) in arthritis may lead to the development of novel immunotherapies for RA and other immune-mediated inflammatory diseases.

1822

Efficacy of Influenza and Meningococcal Vaccinations in Healthy Subjects Exposed to Secukinumab 150 Mg: Preliminary Study Results. Andrea Chioato. Novartis, Basel, Switzerland

Background/Purpose: AIN457 (secukinumab) is a high-affinity, anti-human interleukin-17A antibody in trials for inflammatory conditions. IL-17A is produced by memory effectors CD4+ and CD8+ T lymphocytes and the IL-23-Th17 cell pathway is critical for protective immunity against bacterial infections[1]. As this compound will be used in rheumatic conditions, we wanted to determine whether the interference with the IL17 cytokine could influence the response to antigens in frequently used vaccinations. The objective of this study was to evaluate immune response in subjects treated with secukinumab after 2 vaccines, aimed to protect against influenza and meningococcal infection.

Methods: This was an open-label, parallel group, randomized, single-center study in healthy subjects (age 18–55 years, body weight: ≥50 kg, BMI 18–29 kg/m^2). Main exclusion criteria included previous vaccinations and history of significant systemic diseases. After measurement of antibody (Ab) titers at baseline, subjects were randomized to a single secukinumab 150 mg s.c. dose or no treatment (control group), followed two weeks later by influenza or meningococcal vaccinations. The primary efficacy were the responses to influenza (≥4-fold increase in Ab titer in ≥2/3 serotypes) and meningococcal vaccines (also ≥4-fold increase) at 4 weeks.

With a total of 50 subjects (25 in each group), the study had an overall power of >85% to demonstrate non-inferiority for both influenza and meningococcal vaccinations.

Results: 50 out of 112 subjects screened were randomized (1:1) to secukinumab or control groups. All subjects completed the study. Mean age was 31.5 years, mean weight 68.1 Kg. Response to influenza vaccination (≥4-fold in ≥2/3 serotypes) at 4 weeks was seen in 20/25 subjects (80 %) in both groups. Both treatments induced a comparable response to meningococcal vaccine, with 19/25 subjects (76%) generating titers with ≥4 fold increase from baseline at 4 weeks in the secukinumab group compared to 18/25 subjects (72%) in the control group (difference 4%, 90% CI −16%,24%). These results support the non-inferiority of secukinumab compared to control.

Conclusion: Blockade of IL-17 by secukinumab does not appear to interfere with the efficacy of influenza and meningococcal vaccinations, as assessed by the achievement of antibody protective levels after vaccination. A protective (≥4 fold) immune response to influenza and meningococcal vaccinations at 4 weeks was achieved in 76 to 80% of subjects exposed to secukinumab. Further studies may be needed to replicate the results in patients with long term exposure to secukinumab.

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1823

Adiponectin Isoforms Differentially Affect Gene Expression, Signaling Transduction and Migration of Rheumatoid Arthritis Synovial Fibroblasts. Klaus Frommer[1], Rosel Engel[1], Andreas Schäffler[2], Christa Büchler[2], Jürgen Steinmeyer[3], Markus Rickert[3], Stefan Rehart[4], Fabia Brentano[5], Steffen Gay[6], Ulf Müller-Ladner[1] and Elena Neumann[1]. [1]Justus-Liebig-University of Gieβen, Bad Nauheim, Germany, [2]University of Regensburg, Regensburg, Germany, [3]University Hospital Gieβen and Marburg, Gieβen, Germany, [4]Markus-Hospital, Frankfurt, Germany, [5]University Hospital Zürich, [6]University Hospital of Zürich, Zürich, Switzerland

Background/Purpose: The pathogenesis of rheumatoid (RA) arthritis is determined by numerous factors. A new group of such factors are the so-called adipo(cyto)kines, proteins with cytokine-like properties, which are predominantly found in adipose tissue. Adiponectin (AdQ), the most abundant adipokine in human serum, is elevated in the synovial fluid of RA patients and positively correlates with RA disease severity. Adiponectin exists in several isoforms, which can induce different effects. We therefore analyzed the effects of adiponectin isoforms on gene expression, signal transduction and migration of RA synovial fibroblasts (SF).

Methods: Human RASF were stimulated with different AdQ isoforms and analyzed for changes in gene expression by Affymetrix® oligonucleotide microarrays and protein arrays. Real-time PCR and immunoassays were used to quantify mRNA expression and protein secretion, respectively. Media from AdQ-stimulated RASF were analyzed for their chemoattractive potential on

RASF using a two chamber migration system. Human phospho-kinase signaling arrays were used to examine signaling molecule phosphorylation after stimulation of RASF with four AdQ isoforms: full-length AdQ containing all isoforms (fl-AdQ), globular (g-AdQ), high-molecular/middle-molecular weight-enriched (HMW/MMW-AdQ), and trimeric (t-AdQ) AdQ.

Results: The individual adiponectin isoforms induced various molecules with a known or potential role in the pathogenesis of RA, but to a notably different extent: the least potent isoform was the trimer, while the most potent isoforms were g-AdQ and HMW/MMW-AdQ. We observed a variably increased expression of cytokines (e.g. mRNA: IL-11-fl-AdQ, 24.3-fold/ HMW/MMW AdQ, 441-fold), chemokines (e.g. protein: ENA-78-fl-AdQ, 22.5-fold/t-AdQ, 9.9-fold), proinflammatory molecules (e.g. mRNA: PTGS2-t-AdQ, 7.1-fold/g-AdQ, 26.1-fold), growth factors (e.g. mRNA: FGF10-fl-AdQ, 5.0-fold/t-AdQ, no change), proteins involved in bone-, and matrix-remodeling (e.g. protein: pro-MMP1-HMW/MMW AdQ, 35.2/ t-AdQ, 11.6). We further confirmed that the secretion of chemokines induced by AdQ in RASF increases the migration of RASF: up to 177% by fl-AdQ, 208% by HMW/MMW AdQ, 127% by t-AdQ and 212% by g-AdQ. Of note, AdQ itself did not act as a chemoattractant. Signaling array analysis revealed differential AdQ-induced signaling molecule phosphorylation (fl- / HMW/ MMW- / t- / g-AdQ), e.g. for p27 (T198) (3.4/3.4/1.5/6.3), paxillin (5.0/1.6/ −1.9/3.9), eNOS (1.6/1.8/−1.4/2.1), and Pyk2 (4.4/1.3/−2.1/5.5).

Conclusion: The data support the hypothesis that AdQ contributes to RA activity by inducing the secretion of proinflammatory molecules, matrix-degrading enzymes, and chemokines in RASF, which in turn most likely promotes the additional influx of RASF to sites of inflammation and cartilage degradation. The adiponectin isoforms have different potencies for eliciting these effects as well as for activating signaling molecules, which suggests that targeting specific isoforms or inhibiting the receptor binding of isoforms may be more promising for therapeutic approaches than inhibiting AdQ in general.

1824

F-Spondin Mediates Catabolic Effects on Articular Chondrocytes Via Its Thrombospondin Repeat Domain. James Liu[1], Glyn Palmer[1], Yang Qing[2], Daniel Rifkin[2], Mukundan Attur[1] and Steven B. Abramson[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]New York University School of Medicine, New York, NY

Background/Purpose: We have previously shown that the thrombospondin-related, extracellular matrix protein, F-spondin, is upregulated in osteoarthritis (OA), and induces the production of catabolic mediators, PGE2 and MMP-13 in cartilage explants in a TGF-b dependent manner. In this study, we characterize the role of individual protein domains of F-spondin in modulating its catabolic effects in chondrocytes.

Methods: OA chondrocytes were harvested from tibial cartilage obtained from OA patients with end-stage disease undergoing knee replacement surgery. Transient transfections were performed using TransIT-LT1 reagent (Mirus) and cDNAs encoding full length (FS1) or a truncated C-terminal (FS7) portion of F-spondin coding sequence. Levels of TGF-b1 (R&D systems) and PGE2 (Cayman Chemical) were determined by ELISA, MMP-13 expression was measured by qRT-PCR (Applied Biosystems). TGF-b activity was also measured in conditioned media supernatants by incubation with mink lung epithelial cells (MLEC) expressing a TGF-b-responsive luciferase reporter.

Results: Consistent with our previous observations of the effects of intact F-spondin in cartilage explants, overexpression of FS1 in cultured OA chondrocytes from 3 patients increased expression levels of MMP-13 ~100 % compared to mock-transfected controls. Similarly, FS1 also increased PGE2 levels by 25 % ($p<0.05$). Both effects could be mimicked by transfection with a construct encoding only the c-terminal TSR repeat domain FS7; MMP-13 and PGE2 levels were elevated by FS7 above control vector transfected cultures, ~50 % ($p<0.005$) and 71% ($p<0.05$), respectively. Since the F-spondin TSR domain harbors consensus sequences for latent TGF-b activation (WxxW and KRFK), we tested whether this domain mediates TGF-b activation in cultured chondrocytes. In OA chondrocytes, TGF-b levels in culture supernatants were increased 30% by FS1 and 70% by FS7 compared to controls. Similarly, measurement of active TGF-b using MLEC reporter cells showed that FS1 and FS7-transfected culture media supernatants stimulated luciferase activity 30% and 100%, respectively ($p<0.05$). Conversely, FS3 and FS5 constructs, which both contain TSR-domain deletions, did not stimulate TGF-b activity in MLEC cells. Evidence of enhanced activation of TGF-b was also demonstrated by increased SMAD signaling. Immunoblot of FS treated chondrocytes showed increased phosphorylation of SMAD 1, 5, 8 relative to mock transfected cells. Similarly, both FS1 and FS7 stimulated expression of a SMAD-luciferase reporter in OA chondrocytes.

Conclusion: Our data provide evidence that F-spondin, via its TSR domain, can act as a latent TGF-b-activating protein and enhance the catabolic activity of chondrocytes via induction of MMP-13 and PGE2. The TSR domain of F-spondin may therefore represent a novel therapeutic target for slowing cartilage breakdown in OA.

1825

Adipokine Expression in Osteoarthritis Osteophytes. Susann Junker[1], Klaus Frommer[1], Grit Krumbholz[1], Angela Lehr[2], Stefan Rehart[2], Markus Rickert[3], Jürgen Steinmeyer[3], Georg Schett[4], Ulf Müller-Ladner[1] and Elena Neumann[1]. [1]Justus-Liebig-University of Gieβen, Bad Nauheim, Germany, [2]Markus-Hospital, Frankfurt, Germany, [3]University Hospital Gieβen and Marburg, Gieβen, Germany, [4]University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Obesity is a recognized risk factor in osteoarthritis (OA) but little is known about the interaction between adipose tissue derived factors and bone formation. Adipocytes produce a variety of cytokine-like proteins, such as adiponectin, visfatin or resistin. While it is known that these adipokines are associated with the pathogenesis of rheumatoid arthritis and can be produced by other cell types such as fibroblasts, osteoblasts and osteoclasts, their role in osteophyte formation in OA has not been studied. Despite the mostly unknown mechanisms of osteophyte formation, there is growing evidence that inflammation and local stress contribute to this process. In this study, the expression of adipokines in osteophytes and their co-localization with cells of bone remodeling was analyzed.

Methods: Osteophyte tissue and cartilage was obtained from OA patients during joint replacement surgery. Serial sections of decalcified and deparaffinized osteophyte tissue were prepared. For histological overview, hematoxylin/eosin and Masson trichrome stainings were performed. Using these stainings, the osteophytes were scored and divided into grade one (early, small osteophyte, no ossification) to four (ossified osteophyte with cartilage). Immunohistochemistry was performed to identify sites and localization of adipokines using antibodies against alkaline phosphatase, vimentin, collagen type I, type II, adiponectin, visfatin, and resistin. TRAP stainings were performed to identify osteoclasts. Immunoassay analyses for visfatin were done with cartilage and isolated primary chondrocyte lysates.

Results: Adiponectin, visfatin and resistin were detectable in all osteophytes of OA patients (grade 1–4). Adiponectin was localized around blood vessels as well as in some fibroblasts in the connective tissue of non-ossified osteophytes (25% of fibroblasts). In ossified osteophytes (grade 2–3), resistin and visfatin showed a co-localization with osteoblasts at the border of newly formed, non-mineralized bone tissue and with osteoblasts and osteoclasts at sites of bone resorption. In osteophytes without ossification (no detectable osteoblasts and osteoclasts, grade 1), visfatin and resistin were detectable only in single cells. Quantitatively, more visfatin than resistin expressing cells could be observed (resistin: 10% vs. visfatin: 25% of cells). ELISA using chondrocytes and cartilage confirmed the visfatin expression in these cells on the protein level.

Conclusion: The co-localization of visfatin and resistin with osteoblasts and osteoclasts in advanced osteophyte formation (grade 2–3) suggests that they may be involved in bone neo-formation and remodeling of OA osteophytes. In contrast, adiponectin was lower in advanced stages of osteophyte formation (grade 2–3) but present in early osteophytes that mainly consist of connective tissue (grade 1). These results indicate that visfatin, resistin and adiponectin may be involved in osteophyte formation at different stages and most likely affect different cell types of cartilage and bone formation during these processes.

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1826

Increasing Serum IL-17F Levels in Pediatric Localized Scleroderma As Disease Enters Remission. Kathryn S. Torok[1], Katherine Kurzinski[1], Christina Kelsey[1] and Carol A. Feghali-Bostwick[2]. [1]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: A predominant lymphocytic infiltrate has been identified in scleroderma skin specimens, both localized scleroderma (LS) and systemic sclerosis (SSc). CD4+T cell staining in affected skin supports potential involvement of T-helper cell associated cytokines in the pathogenesis of scleroderma. SSc studies have supported the role of Th1, Th2 and

more recently Th17 cell lineages, finding their associated cytokines in the serum, and expressed in PBMCs and skin specimens. However, there is limited data regarding pediatric LS.This study was designed to evaluate the Th17 serum profile of pediatric LS patients longitudinally as their disease was treated and transitioned to remission.

Methods: Serum samples were obtained from 23 pediatric LS patients with 3 or more specimens with concurrent clinical outcome measures of disease activity, mLoSSI (modified Localized Scleroderma Severity Index) and PGA-A (Physician Global Assessment of Disease Activity). All patients had active disease at the time of first sample collection, defined clinically by the presence of new, expanding, and/or erythematous lesions. They were also naïve to systemic therapy at first visit. All patients clinically improved and entered remission during follow-up serum and clinical data collection. Ten pediatric healthy controls were used as comparison. A luminex panel evaluating Th17 associated cytokines IL-17A, −17F, −22, −23, −27 was performed. Nonparametric analyses were performed to compare cytokine levels between LS and healthy groups and between time points for the LS patients ($p < 0.05$).

Results: Serum levels of IL-17A, −21 and −23 at the baseline visit were significantly lower in the LS group compared to healthy controls (p-values 0.005 – 0.01). IL-17F and IL-22 were not significantly different between controls and LS group at baseline; however, as LS patients clinically improved with systemic treatment, IL-17F levels increased significantly from their previous visits and in comparison to controls. A smaller proportion of LS patients exhibited increasing levels of IL-22 and IL-27 over time. The disease activity scores decreased significantly from baseline to timepoint 2 (median 4.36 mos from baseline) and timepoint 3 (median 11.6 mos from baseline), signifying disease improvement and remission.

	IL-17F (pg/ml)		mLoSSI		PGA-A	
Group	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Peds LS Baseline visit	232.9	79.5–456.6	8	(4–12)	45	(33–68)
Peds LS Timepoint 2	336.8	177.3–556.0	0	(0–0)	0	(0–0)
Peds LS Timepoint 3	452.9	271.5–539.5	0	(0–0)	0	(0–2)
Healthy Control	133.3	68.0–232.0	.	.	.	.

Conclusion: Th-17 associated cytokines of LS patients at baseline, when the disease was most active, were either not significantly different or lower than pediatric healthy controls. As systemic treatment was initiated and the patients improved clinically, mirrored by significant improvement in validated clinical outcome measures of disease activity, the IL-17F serum levels increased in the majority of patients and IL-22 and IL-27 increased in a smaller portion of patients. This may represent Th-17 cell lineage as an important factor in disease remission. Further studies analyzing PBMC and skin expression of Th-17 associated cytokines is warranted.

1827

TWEAKing Cutaneous Manifestations In MRL-Lpr/Lpr Lupus Prone mice. Yumin Xia[1], Karin Blecher[1], Jing Wen[1], Jennifer S. Michaelson[2], Linda C. Burkly[2], Adam Friedman[1] and Chaim Putterman[3]. [1]Albert Einstein College of Med, Bronx, NY, [2]Biogen Idec, Cambridge, MA, [3]Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: TWEAK, a TNF superfamily cytokine, is synthesized as a membrane bound protein and processed into a soluble form that circulates to bind to its sole signaling receptor Fn14. The TWEAK/Fn14 pathway is upregulated in the context of injury and inflammatory disease, and has a variety of functions including the stimulation of inflammatory mediators, angiogenesis, and modulation of cell survival. Both keratinocytes and dermal fibroblasts express Fn14 and respond to TWEAK, as shown by the production of inflammatory mediators implicated in cutaneous lupus. In addition, TWEAK acts with other cytokines to induce keratinocyte death. On the basis of these studies, we hypothesized that TWEAK may be involved in the pathogenesis of cutaneous manifestations in the MRL-lpr/lpr (MRL/lpr) spontaneous mouse SLE model.

Methods: 129 Fn14 knockout mice were backcrossed 8 generations onto MRL-lpr/lpr (MRL/lpr) mice to generate MRL-lpr, Fn14 deficient mice (Fn14 KO). The development of cutaneous lesions in MRL/lpr Fn14KO mice was compared to MRL/lpr wild type (Fn14 WT) mice, and to the control strain MRL/+. Lesion scoring was based on erythema, scaling, alopecia, lesion thickness, and percent of body surface area involved, with the total score comprised of a weighted combination of the scores of each of these features. Skin biopsies were obtained for histology and immunohistochemistry.

Results: We evaluated cutaneous disease in age matched cohorts of MRL-lpr Fn14 WT and KO mice (30 weeks of age) in a blinded assessment. Lesional skin in MRL/lpr WT mice was found predominantly on the head and upper trunk, with erythematous plaques displaying crusted erosions and scarring alopecia. Eight of 11 MRL/lpr Fn14WT mice displayed signs of cutaneous disease, as compared to only 2/8 MRL-lpr Fn14KO mice and 1/10 MRL/+ mice that exhibited skin lesions (**Figure 1**). Cutaneous involvement in MRL/lpr Fn14WT mice was also significantly more severe as compared to MRL/lpr Fn14KO mice (lesion score of 4.4±1.4 in WT vs. 0.9±0.7 in KO; $p<0.03$), with no significant difference between MRL/lpr Fn14 KO and control MRL/+ mice ($p=0.35$). Skin histology in the MRL/lpr Fn14WT mice demonstrated parakeratosis and serous crust in the stratum corneum, epidermal acanthosis with necrotic keratinocytes, and infiltration of the dermis with lymphocytes and histiocytes, associated with thickened collagen and follicular plugging. In contrast, MRL/lpr Fn14KO and MRL/+ mice demonstrated no atypia with normal basketweaving of the stratum corneum, a 2–3 cell thick epidermis, and healthy dermal collagen. Immunohistochemistry confirmed T cell and macrophage infiltration of the skin in MRL/lpr Fn14WT but not Fn14KO mice.

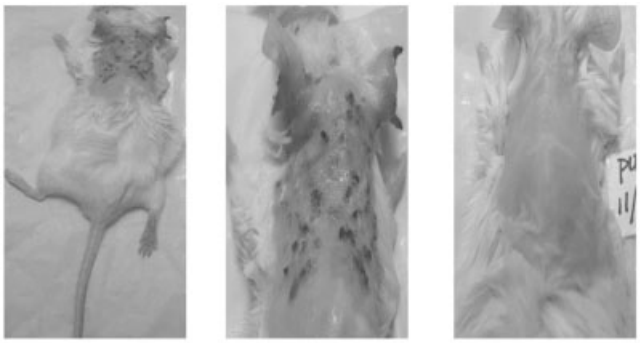


Figure 1.

Conclusion: Our data implicate the TWEAK/Fn14 pathway in the pathogenesis of cutaneous lesions in MRL/lpr mice, suggesting that targeting the TWEAK pathway may be a novel approach to treat cutaneous disease in lupus.

1828

Pro-Inflammatory Cytokine Measurement in Whole Blood Cultures Stimulated with Lipopolysaccharide Predicts Treatment Outcomes of Patients with Rheumatoid Arthritis Treated with Biologics. Ken Kayakabe[1], Takashi Kuroiwa[2], Noriyuki Sakurai[1], Hidekazu Ikeuchi[1], Anastasie K.T.[1], Toru Sakairi[1], Akito Maeshima[1], Keiju Hiromura[1] and Yoshihisa Nojima[1]. [1]Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [2]Jichi Medical University, Saitama Medical Center, Saitama, Japan

Background/Purpose: Although biological therapies targeting tumor necrosis factor (TNF)-α or interleukin (IL)-6 are highly effective for rheumatoid arthritis (RA), they are expensive and occasionally associated with severe side effects. Therefore, it is important to identify patients who respond or do not respond to the biologics. Possibility exists that such response is associated with each patient's capacity of pro-inflammatory cytokine production. Whole blood culture with lipopolysaccharide (LPS) stimulation is a valid low-cost method to measure cytokine synthesis in monocytes. To find predictors of response to biologics, we examined pro-inflammatory cytokine production in whole blood culture.

Methods: Whole blood was obtained from biologics-naïve patients with RA (n=41) before starting biologics (infliximab 13, etanercept 26, and adalimumab 2). At 6 months after initiation of biologics, whole blood was again drawn from 14 out of 41patients. Blood from 12 healthy volunteers were used as controls. We measured the concentration of TNF-α, IL-1β and IL-6 in supernatants of LPS-stimulated (at 1ng/ml, for 24 hrs) whole blood culture. Disease activity score (DAS28) was evaluated at baseline and 6 months after the therapy. Response to the therapy was defined by EULAR response criteria.

Results: The mean age of the patients was 55.9 yrs and 87.8% of them were female. The median of disease duration was 44.0 months. The mean DAS28 at baseline was 4.48. Rheumatoid factor and anti-citrullinated peptide antibodies were positive in 70.0% and 84.2%, respectively. The patients treated with methotrexate were 78.0% (mean 7.0 mg/week). Among patients examined, 32 were responders (good 14/moderate 18), and 9 were non-responders. All cytokines measured were significantly lower in RA patients than in healthy controls (the median and [interquartile range] of TNF-α: 30.4 [9.6, 149] vs. 256 [172, 406] pg/ml p=0.002, IL-1β: 6.9 [2.9, 75] vs. 256 [229, 371] pg/ml p<0.001, IL-6: 358 [65.3, 1975] vs. 1933 [1320, 2984] pg/ml p=0.004). In RA patients, IL-1β production before therapy was significantly lower in non-responders than in responders (3.48 [1.51, 9.41] vs. 10.0 [5.21, 93.1] pg/ml p=0.048). TNF-α and IL-6 were also lower in non-responders than in responders, but statistical significance was not observed (TNF-α: 23.0 [2.23, 66.5] vs. 31.5 [11.0, 224] pg/ml p=0.393, IL-6: 185 [45.3, 1257] vs. 366 [76.1, 2333] pg/ml, p=0.546). The area under the curve (AUC) from a receiver operating characteristic (ROC) curve analysis for the prediction of response using IL-1β was 0.717 (95% CI; 0.520 – 0.914). The sensitivity and specificity of IL-1β (cut-off value of 4.84pg/ml) were 78.1% and 77.8%, respectively. All cytokines were significantly higher after 6 month later of biologic therapy as compared with the respective baselines (TNF-α: 142 [38.0, 431] vs. 16.8 [7.45, 24.8] pg/ml p=0.004, IL-1β: 30.9 [7.11, 84.5] vs. 5.86 [1.02, 10.6] pg/ml p=0.001, IL-6: 1061 [385, 2286] vs. 122 [50.6, 275] pg/ml p=0.001).

Conclusion: This preliminary study suggests that IL-1β production in whole blood culture predicts the response to the biologic therapy. Cytokine production capacity is up-regulated by the biologic therapy. Larger studies to prove this concept are warranted.

1829

Mitochondrial Mutagenesis Correlates with the Local Inflammatory Environment in Arthritis. Leonard C. Harty[1], Monika Biniecka[1], Edward Fox[2], Jacintha N. O'Sullivan[3], Ursula Fearon[1] and Douglas J. Veale[1]. [1]Translation Rheumatology Research Group, Dublin, Ireland, [2]University of Washington, Seattle, WA, [3]Trinity University, Dublin, Ireland

Background/Purpose: To examine the association between levels of mitochondrial mutagenesis and the pro-inflammatory micro-environment in patients with inflammatory arthritis.

Methods: Fifty patients with inflammatory arthritis underwent arthroscopy and synovial tissue biopsies, synovial fluid and clinical assessment were obtained. A subgroup of patients (n=15) pre/post TNFi were also recruited. Normal synovial biopsies were obtained from 10 subjects undergoing interventional arthroscopy. Macroscopic synovitis/vascularity was measured by visual analogue scale (VAS). Cell specific markers CD3 (T cells), CD68 (macrophages) and lining layer thickness were quantified by immunohistology. TNFa, IL-6, IFNg, IL-1b and IL-8 were measured in paired synovial fluid by MSD multiplex assays. Synovial tissue mitochondrial mutagenesis was quantified using a mitochondrial random mutation capture assay (RMC). The direct effect of TNFa on oxidative stress and mitochondrial function was also assessed in primary RA synovial fibroblast cultures and mitochondrial mutagenesis, reactive oxygen species (ROS), mitochondrial membrane potential (MMP) and mitochondrial mass (MM) were quantified using the RMC assay and specific cell fluorescent probes.

Results: A significant increase in mtDNA mutation frequency was demonstrated in inflamed synovial tissue compared to control synovial tissue (p<0.05), an effect that was independent of age. mtDNA mutations positively correlated with macroscopic synovitis (r=0.52, p<0.01) and vascularity (r=0.54, p<0.01) and with sub-lining expression of CD3 (r=.46, p=0.046) and CD68 (r=.508, p=0.026). mtDNA mutation positively correlated with synovial fluid TNFa (r=0.74, p<0.01), IL-1b (r=0.65, p<0.05) and IFNg (r=0.72, p<0.05). mtDNA mutation frequency post TNFi therapy were significantly lower in patients with a DAS<3.2 (p<0.05). *In vitro* TNFa treatment significantly induced mtDNA mutations, ROS, MM and MMP in RASFCs (all p<0.05).

Conclusion: High mitochondrial mutations are strongly associated with synovial inflammation showing a direct link between mitochondrial mutations and key pro-inflammatory pathways.

1830

Relationship of Serum Tumor Necrosis Factor α, Tumor Necrosis Factor α Receptors and Tumor Necrosis Factor—Weak Inducer of Apoptosis to Clinical Parameters and Therapeutic Response in Rheumatoid Arthritis Patients Treated with Etanercept. Gunther Neeck[1], Helmut Dotzlaw[2] and Martin Schulz[2]. [1]Rheumazentrum Bad Doberan, Bad Doberan, Germany, [2]Center for Rheumatology, Bad Doberan, Germany

Background/Purpose: TWEAK has been shown to be a potent arthritogenic cytokine in the mouse model of collagen-induced arthritis. Serum levels of TWEAK increase in this model during the course of disease development, and treatment with an anti-TWEAK neutralizing monoclonal antibody reduces overall disease severity. It has been shown that TWEAK induces the expression of TNF α and that TWEAK-stimulated cell death is an indirect effect that is mediated by TNF α/TNF α receptor interactions. Our objective was to determine what relationships exist between the serum levels of TNF α, the TNF α receptors TNF-R1/-R2 and TWEAK with clinical response and disease biomarkers in a cohort of RA patients during the course of treatment with Etanercept.

Methods: Twenty patients with active rheumatoid arthritis according to the classification criteria of the American College of Rheumatology (ACR) that started Etanercept therapy due to an inadequate response to the treatment with conventional DMARDs were enrolled in the study. Patients received Etanercept 50 mg subcutaneously weekly during the course of the study. Clinical and laboratory assessments were conducted prior to injection at baseline and at 4 and 12 weeks into therapy with Etanercept. Quantification of sTNF-R1, sTNF-R2, sTWEAK, IL-6 and sTNF α in serum samples was performed using ELISA kits (R&D Systems, Wiesbaden, Germany) following the manufacturer's protocol.

Results: Etanercept therapy resulted in no sustainable effects on serum TNF-R1 and TWEAK levels during the observation period. A correlation between TNF-R2 concentrations was found with age and TNF-R1 prior to treatment with Etanercept, indicating a physiological relationship between the serum levels of TNF receptors 1 and 2. Circulating TNF α and TNF-R2 as measured using ELISA increased significantly during treatment with Etanercept. We could show that our anti-TNF-R2 assay was able to detect circulating Etanercept in serum.

Conclusion: We found no correlations between disease activity as measured using DAS28 and the levels of serum TNF-R1, TNF α and TWEAK at any of the time points during the course of treatment with Etanercept, suggesting that the levels of these factors had little measureable influence on the response to the treatment in this group of patients. The increase of serum TNF α during the course of treatment is related to the presence of high levels of TNF-R2 as measured using ELISA, since elevated TNF α is found in all patients except in two where no increased TNF-R2 was detected. The fact that patients with elevated levels of TNF α respond favorably to Etanercept suggests that this TNF α is biologically inactive, and is probably complexed with Etanercept in the serum. Interestingly, the two RA patients in which no increase in TNF α or TNF-R2 (Etanercept) could be measured during the course of treatment showed no reduction in the DAS28 after 12 weeks of therapy, suggesting that the measurement of TNF α / TNF-R2 might be useful in monitoring for compliance or for individual clearance times for serum Etanercept.

1831

The Role of IL-17 in Systemic Lupus Erythematosus. Gil Amarilyo[1], Elaine Lourenco[2] and Antonio La Cava[3]. [1]University of California, Los Angeles, Los Angeles, CA, [2]UCLA David Geffen School of Medicine, Los Angeles, CA, [3]Univ of California Los Angeles, Los Angeles, CA

Background/Purpose: T helper 17 cells (Th17), named after their signature cytokine IL-17, favor the development and progression of autoimmune diseases such as rheumatoid arthritis, Crohn's disease and multiple sclerosis. A role for Th17 cells in systemic lupus erythematosus (SLE) has been suggested by the finding that sera from lupus patients had abnormally elevated levels of IL-17 that correlated with disease activity, and by the observation that IL-17-producing T cells were present in kidney infiltrates of murine models as well as patients with lupus nephritis. Here we studied the role of IL-17 in the development of lupus-like disease induced by pristane in mice.

Methods: IL-17 knockout mice (on the B6 background) were compared with wild-type B6 mice (WT) for the development of lupus-like disease after intraperitoneal injection of the hydrocarbon oil pristane (which induces a

lupus-like disease characterized by the development of lupus-associated autoantibodies and glomerulonephritis). Total and percentage numbers of peripheral CD4, CD8 and related subsets including CD4+CD25+Foxp3+ regulatory T cells (Treg) were monitored ex vivo by flow cytometry at time 0, 3 weeks, 3 months, 5 months and 8 moths after disease induction in IL-17 knockout mice as compared to WT control mice.

Results: IL-17 deficient mice treated with pristane had reduced hypergammaglobulinemia and lower levels of anti-ssDNA and anti-chromatin antibodies in comparison with WT mice treated with pristane. The onset and the extent of glomerulonephritis were also delayed in the IL-17-deficient mice. Although IL-17 deficient mice had similar levels of CD4 and CD8 when compared to pristane injected wild type mice, they had significantly higher numbers of Treg by three months after pristane injection ($p<0.003$), and this number subsequently declined.

Conclusion: IL-17 deficiency reduced the development of lupus-like disease induced by pristane. These findings suggest a direct role of Il-17 in the SLE pathogenesis and may point towards a new drug therapy pathway for this disease.

1832

A Specific Microrna Pattern Discriminates Synovial Macrophages From Rheumatoid Arthritis and Osteoarthritis Patients. Andrea Diaz-Alderete[1], Vanessa Miranda[2], Ignacio Caballero[1], Manuel Tardaguila[1], Alberto Pascual-Montano[1], Jose L. Pablos[2] and Santos Mañes[1]. [1]Centro Nacional de Biotecnología- CSIC, Madrid, Spain, [2]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain

Background/Purpose: Osteoarthritis (OA) and rheumatoid arthritis (RA) are chronic inflammatory diseases that can lead to joint destruction. OA is a degenerative disease of cartilage, RA is an autoimmune disease. Many pathological alterations in RA and OA are a consequence of aberrant hyperactivation of macrophages in the inflamed synovial membrane, and inhibition of their effector functions is a therapeutic strategy in both diseases. Little is known, however, about the specific genetic circuits that are differentially deregulated in RA and OA macrophages. microRNAs (miRNA) are a class of small, non-coding RNA molecules involved in fine-tuning gene expression at the post-transcriptional level. Deregulation of specific miRNA is associated with the onset or progression of human disease. We compared miRNA expression in macrophages from RA and OA patients to identify activation circuits specific for each pathological condition.

Methods: Synovial macrophages were obtained by centrifugation of synovial fluid of RA patients on Ficoll, or by collagenase I digestion of the synovial membrane of OA patients, followed by magnetic separation of CD14+ cells. The miRNA expression profile was initially evaluated in 3 RA and 3 OA samples using miRCURY LNA microRNA arrays; the miRNA identified were validated by real-time quantitative PCR (RT-qPCR) with specific probes in an independent set of samples. For bioinformatic analysis, we used 15 databases for predicted and observed miRNA targets. A statistical scoring system was applied to sort the most relevant pairs. A list of 215 high-confidence potential targets was selected and functional pathway analysis conducted on Ingenuity Pathway Analysis. Target expression was validated by RT-qPCR in purified macrophages and by immunohistochemistry in synovial membranes from RA and OA patients. Statistical analyses were performed with the Mann-Whitney U-test.

Results: Microarray analyses detected 19 differentially expressed miRNA (defined as 3.5-fold change; $p<0.02$) in macrophages from RA compared to OA patients. Of these, two up- and seven downregulated miRNA were validated by RT-qPCR in macrophages from 11 RA and 13 OA patients ($p<0.05$). Bioinformatics analysis was used to determine and prioritize potential miRNA-mRNA target pairs based on relevant biological context. A total of 215 high-confidence potential targets was selected, which defined a set of signaling pathways associated with the miRNA. Among them, the NF-kB ($p = 1.4 \times 10^{-15}$), IL-6 ($p = 1.2 \times 10^{-13}$), JAK/STAT ($p = 1.2 \times 10^{-9}$) and TNFR1 ($p = 9.3 \times 10^{-7}$) pathways were present. Finally, we validated the differential regulation of the NF-kB pathway in RA vs. OA macrophages. mRNA expression of IKKa (IkappaB kinase alpha; CHUK) was significantly lower in macrophages purified from RA compared to OA samples ($p<0.05$). Immunohistochemistry showed expression of IKKa protein in $CD68^+$ macrophages from RA and OA patients.

Conclusion: We identified a differential expression pattern of miRNA in synovial macrophages from RA compared to OA samples. This profile might be used to identify new targets and signaling pathways involved in each disease condition.

1833

The Influence of Interleukin-32γ on Osteoclastogenesis, with a Focus on Fusion-Related Genes. Bon San Koo, Yong-Gil Kim, Min Wook So, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Background/Purpose: We previously reported that interleukin-32γ (IL-32γ) has a direct effect on osteoclast differentiation and activation in vitro in the context of receptor activator of NF-κB ligand (RANKL) co-stimulation. However, the stage of osteoclast differentiation at which IL-32γ exerts its effect was not determined. We investigated the stage of osteoclast differentiation at which IL-32γ exerts this action, focusing on its effects on the fusion-related genes, dendritic cell-specific transmembrane protein (DC-STAMP) and the d2 isoform of vacuolar (H^+) ATPase (v-ATPase) Vo domain (Atp6v0d2).

Methods: Bone marrow-derived macrophages (BMMs) were isolated from mouse (C57BL/6J) femurs and tibiae. To determine the effects of IL-32γ and identify the most appropriate concentration for inducing osteoclast differentiation, we treated BMMs with different concentrations of IL-32γ (0, 12.5, 25, and 50 ng/ml) and then cultured them with M-CSF (30 ng/ml) and RANKL (50 ng/ml) for 4 d. To investigate whether IL-32γ affected the expression of NFATc1 and the fusion related-genes, DC-STAMP and ATP6v0d2, we performed RT-PCR from cells incubated in the absence or presence of IL-32γ. Lastly, to further investigate the stage of osteoclast differentiation during which IL-32γ acts, we added IL-32γ to our culture system at various times and incubated for 24 h.

Results: IL-32γ significantly increased osteoclast counts at concentrations of 25 and 50 ng/ml, producing the most effective induction of osteoclastogenesis at 25 ng/ml. We demonstrated that IL-32γ plays an important role in the fusion of preosteoclasts to yield multinuclear osteoclasts-particularly large osteoclasts (≥ 5 nuclei). The synergistic effect of IL-32γ on RANKL-induced formation of multinuclear osteoclasts was readily apparent when cells were treated with IL-32γ at days 1 and 2, considered to be the fusion stage of osteoclast differentiation. In addition, compared with controls, cells stimulated with IL-32γ highly expressed DC-STAMP on days 2 and 3, and NFATc1 was highly expressed on day 2.

Conclusion: On the basis of these results, we suggest that IL-32γ is a potent cytokine capable of promoting the differentiation of large osteoclasts in the context of co-stimulation with RANKL in a murine model. These effects could be related to up-regulation of the fusion-enhancing gene DC-STAMP via NFATc1 in the early stage of differentiation.

1834

Identification of Activated Cytokine Pathways in the Blood of Systemic Lupus Erythematosus, Myositis, Rheumatoid Arthritis, and Scleroderma Patients. Brandon W. Higgs[1], Wei Zhu[1], Laura Richman[1], David Fiorentino[2], Steven A. Greenberg[3], Bahija Jallal[1] and Yihong Yao[1]. [1]MedImmune, Gaithersburg, MD, [2]Stanford, Stanford, CA, [3]Brigham Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: To develop genomic signatures of seven cytokines involved in the pathogenesis of rheumatic diseases such as systemic lupus erythematosus (SLE), dermatomyositis (DM), polymyositis (PM), rheumatoid arthritis (RA), or systemic sclerosis (SSc) that could potentially help to identify patients likely to benefit from therapies that target these individual cytokines.

Methods: Over-expressed transcripts in the whole blood (WB) were identified from 262 SLE, 44 DM, 33 PM, 38 SSc and 89 RA subjects and compared to 24 healthy subjects using Affymetrix arrays. Cytokine-inducible gene signatures such as type I IFN, TNF-α, IL1β, IL-10, IL-13, IL-17, and GM-CSF were assessed in the WB of these subjects to identify subpopulations showing activation of specific cytokine pathways.

Results: Significant activation of the type I IFN pathway in a population of 5 diseases studied was universally observed. The TNF-α and IL-1β pathways were activated in subgroups of PM and RA subjects, respectively, with another subgroup of RA subjects showing activation of the IL-13 pathway. The GM-CSF pathway was activated in a subgroup of SSc subjects and the IL-17 pathway was activated in subgroups of all diseases except SLE.

Conclusion: A novel gene expression measurement of activated cytokines in five different rheumatic diseases is presented. Characterizing the cytokine pathways most activated in specific patient subpopulations has the potential to help to target the appropriate patient populations for corresponding anti-cytokine therapies.

1835

Systemic Lupus Erythematosus, Myositis, Rheumatoid Arthritis, and Scleroderma Patients Share Activation of a Common Type I Interferon Pathway. Brandon W. Higgs[1], Zheng Liu[1], Barbara White[1], Wei Zhu[1], Wendy White[1], Chris Morehouse[1], Philip Brohawn[1], Peter Kiener[1], Laura Richman[1], David Fiorentino[2], Steven A. Greenberg[3], Bahija Jallal[1] and Yihong Yao[1]. [1]MedImmune, Gaithersburg, MD, [2]Stanford, Stanford, CA, [3]Brigham Women's Hospital, Harvard Medical School, Boston, MA

Background/Purpose: To characterize the type I IFN pathway activation across systemic lupus erythematosus (SLE), dermatomyositis (DM), polymyositis (PM), rheumatoid arthritis (RA), and systemic scleroderma (SSc) subjects and evaluate the potential to develop a molecular diagnostic from the peripheral blood that reflects this activation in disease-affected tissues.

Methods: Over-expressed transcripts were identified in the whole blood (WB) of 262 SLE, 44 DM, 33 PM, 28 SSc and 89 RA subjects and compared to 24 healthy subjects using Affymetrix microarrays. A 5 gene type I IFN signature was assessed in these subjects to: 1) identify subpopulations showing both activation and concordance of the type I IFN pathway in the peripheral blood and disease-affected tissues of each disease, and 2) correlate this pathway activation in the WB with clinical measurements.

Results: A common set of 36 type I IFN-inducible transcripts were identified among the most over-expressed in the WB of all subjects. Significant activation of the type I IFN pathway in subgroups of each of the 5 diseases studied was observed. Baseline disease activity measurements correlated with a type I IFN gene signature in the WB of subjects with SLE, PM, and SSc, as did various serum autoantibody levels in SLE or DM subjects. This signature was also well correlated between disease-affected tissue and WB in subjects with SLE, DM, PM, or SSc.

Conclusion: The results indicate that in patient subsets of 5 rheumatic diseases, the IFN pathway is activated and identification of these subsets could play an important role in future therapies.

1836

Extracellular 14-3-3η: A Novel Mediator of Inflammation Associated with Selective Activation of Intracellular Pathways. Anthony Marotta[1], Yuan Gui[1], Aziz Ghahary[2], Ruhangiz Kilani[2] and Walter P. Maksymowych[3]. [1]Augurex Life Sciences Corp, North Vancouver, BC, [2]University of British Columbia, Vancover, BC, [3]University of Alberta, Edmonton, AB

Background/Purpose: Rheumatoid arthritis (RA) results from the interaction and convergence of mediators that contribute to pathological processes. The 14-3-3 family members are ubiquitously expressed intracellular chaperones. We previously demonstrated that the η isoform is specifically present extracellularly in the synovial fluid and matched serum of patients with inflammatory arthritis and that its expression significantly correlated with levels of MMP-1 and MMP-3. Recent data also indicates that serum 14-3-3η is highly specific for RA. We aimed to examine the role of extracellular 14-3-3η in the pathogenesis of RA by investigating its effects on 1) the activation of RA-relevant signaling cascades, 2) induction of pro-inflammatory mediators and 3) the effects of selectively targeting 14-3-3η with monoclonal antibodies.

Methods: Cells of the monocytic lineage (THP-1) were stimulated with 12.5ng/ml of recombinant human 14-3-3η and activation of relevant signaling targets was assessed by immunoblot analysis using phosphospecific antibodies. Activation of HL-60, PCS-201-010, Jurkat and Daudi cells was assessed by evaluating the phosphorylation status of MAPK/ERK following 15 minutes of stimulation with 12.5ng/ml. mRNA levels of IL-1β, IL-6, IL-8, CCL2/MCP-1, CCL4/MIP-1β, MMP-1, MMP-9, TNFα, RANKL were assessed in THP-1 cells following 18h incubation with a dose range of 0.10 to 100ng/ml of recombinant human 14-3-3η reflecting in vivo concentrations. For antibody targeting studies, recombinant human 14-3-3η was co-incubated with antibody (0.2 to 20mg/ml) for 18h and levels of transcripts were assessed.

Results: Stimulation assays showed that while monocytic, myeloid, and fibroblast cell lines were activated in response to 14-3-3η, T and B cell lines were not. Extracellular 14-3-3η, at concentrations found in RA patient serum (median 1.12ng/ml and range of 0.12 to 20ng/ml) activated key intracellular signalling cascades that regulate cell proliferation (MAPK/ERK), survival (AKT), inflammation (JAK-STAT), and tissue remodelling (SAPK/JNK). These cell stimulatory effects were specific yet distinct from other reported endokines/extracellular factors since neither the activation of p38MAPK nor NFκB was not observed with 14-3-3η stimulation. Furthermore, extracellular 14-3-3η at levels approximating median serum levels behaved as a potent inducer of IL-1β, IL-8, CCL2/MCP-1, CCL4/MIP-1β, MMP-1, MMP-9 and RANKL transcripts. Higher levels of 14-3-3η, though within the range found in vivo, were required for induction of IL-6 and TNFα. Targeting 14-3-3η with monoclonal antibody compounds attenuated these effects.

Conclusion: Extracellular 14-3-3η is a novel mediator that induces expression of several factors associated with the pathogenesis of RA. In contrast to other endokines that activate both p38MAPK and NFkB as well as up-regulate pro-inflammatory factors, 14-3-3η acts through alternate signalling pathways. Targeting 14-3-3η with monoclonal antibody compounds attenuates its inducing effects underscoring its novelty as a potential therapeutic target.

1837

Serum Galectin-3 Level in Patients with Scleroderma. Metin Ozgen[1], Suleyman Serdar Koca[1], Fatma Akbas[1], Nevin Ilhan[2], Baris Gundogdu[1] and Ahmet Isik[1]. [1]Department of Rheumatology, Faculty of Medicine, Firat University, Elazig, Turkey, [2]Department of Biochemistry, Faculty of Medicine, Firat University, Elazig, Turkey

Background/Purpose: Scleroderma (systemic sclerosis [SSc]) is an autoimmune disease of unknown etiology characterized by progressive multiorgan fibrosis. Activated fibroblasts are mainly responsible for fibrosis in SSc. Galectin-3, a β-galactoside binding lectin, plays many important regulatory roles in both physiological and pathological processes including proliferation, apoptosis, inflammation and fibrosis. Previous studies have demonstrated that galectin-3 contributes significantly to fibroblast activation and the development of fibrosis.

The purpose of this study was to asses the serum galectin-3 level and its association with disease activity and severity indexes in patients with SSc.

Methods: Thirty seven SSc patients, 23 systemic lupus erythematosus (SLE) patients (serving as patient control group) and 28 healthy volunteers were enrolled in this study. Disease activity and severity scores were detected with Valentini disease activity index and Medsger disease severity scale in the SSc group, and SLE Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics/American Collage of Rheumatology (SLICC/ACR) damage index in the SLE group. The serum levels of galectin-3, vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β and interleukin (IL)-6 were determined.

Results: Compared with the control group, the galectin-3 levels were higher (Table) in the SSc and SLE groups. The galectin-3 levels were not correlated with the disease activity and severity indexes in both patient groups. But, the serum galectin-3 levels were higher in the active SSc and SLE subgroups than in the inactive SSc (4.6 ng/mL vs. 1.3 ng/mL p=0.015) and SLE (17.4 ng/mL vs. 6.5 ng/mL p=0.019) subgroups.

Table. Demographics and laboratory data in the study groups

	SSc	SLE	HC	P
Age (years)	46 ± 13	37 ± 10	42 ± 14	0.110*
Gender (Female/Male)	32/5	21/2	22/6	0.302**
BMI (kg/m^2)	24.2/5.1	25.2 ± 4.1	26.9 ± 4.8	0.980*
Disease duration (years)	4.19 ± 4.57	5.13 ± 4.38	—	0.079*
ESR (mm/h)	26 ± 20[b]	32 ± 26[c]	9 ± 4	0.001*
CRP (mg/L)	12 ± 20	6 ± 6	3 ± 0	0.056*
IL-6 (pg/mL)	11.4 ± 5.6	18.5 ± 20.4	14.9 ± 26.1	0.116*
TGF-β (ng/mL)	42.7 ± 14.8	32.8 ± 11.7	35.5 ± 12.2	0.085*
VEGF (pg/mL)	337 ± 242	210 ± 175[a]	330 ± 195	0.023*
Galectin-3 (ng/mL)	3.5 ± 4.9[a,d]	14.0 ± 11.6[c]	1.25 ± 1.08	0.001*

Data were presented as mean ± standard deviation. SSc: Systemic sclerosis, SLE: Systemic lupus erythematosus, HC: Healthy control, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, IL: Interleukin, TGF: Transforming growth factor, VEGF: Vascular endothelial growth factor.
* ANOVA and ** Chi-square p value; Compared with control group: [a] p<0.05, [b] p<0.01, [c] p<0.001; Compared with SLE group: [d] p<0.001.

Conclusion: These results suggest that galectin-3 is involved in the pathogenesis of SSc characterized by fibrosis and SLE characterized by inflammation. Galectin-3, which is proposed as biomarker of fibrosis and inflammation by previous studies, may be a novel biomarker for activities of SSc and SLE.

1838

Atherogenic Effect of Inflammatory Cytokines in Chronic Inflammatory Diseases. Misato Hashizume and Masahiko Mihara. Chugai Pharmaceutical Co., Ltd., Gotemba, Shizuoka, Japan

Background/Purpose: In patients with chronic inflammatory diseases such as rheumatoid arthritis (RA), the risk of cardiovascular disease (CVD) is increased. Inflammatory cytokines are considered of fundamental importance to atherogenesis. It was reported that high level scavenger receptor-A (SR-A) gene expression is associated with an increased incidence of cardiovascular events in acute coronary syndrome. SR-A is expressed on macrophages and facilitates the intracellular accumulation of oxidized LDL (oxLDL), resulting in the formation of atherosclerotic plaque. To explore whether inflammatory cytokines promote atherogenesis, we examined their effects on SR-A expression oxLDL accumulation.

Methods: THP-1 cells were induced to differentiate into macrophage-like cells (THP-1/macrophages) by culture with phorbol myristate acetate for 4 days. THP-1/macrophages were then stimulated for 24 h by serum from RA patients or healthy subjects, and IL-6 and TNF-α in the presence or absence of anti-IL-6 receptor antibody (tocilizumab, TCZ) or TNF-α receptor (p75)-Fc (etanercept, ETN). The level of SR-A mRNA was measured by real-time PCR. Cells were further incubated with oxLDL for a specific time. Intracellular accumulation of oxLDL was measured by Oil Red O staining and fluorescence.

Results: First, we determined the effect of TNF-α and IL-6 on the expression of SR-A and formation of atherosclerotic plaque. Either cytokine induced SR-A mRNA expression and increased intracellular oxLDL accumulation by THP-1/macrophages. ETN inhibited the induction of SR-A by TNF-α. Interestingly, TCZ inhibited SR-A induction by IL-6 as well as TNF-α because IL-6 induced by TNF-α increased SR-A expression. To test whether SR-A expression and the accumulation of oxLDL were induced by blood, THP-1/macrophages were cultured in the presence of serum from healthy subjects or RA patients. Serum from the latter but not the former induced expression of SR-A. Moreover, RA patients′ serum augmented the accumulation of oxLDL by THP-1/macrophages. Finally, in order to examine the effect of TNF-α and IL-6 on the induction of SR-A expression and the accumulation of oxLDL by RA serum, the sera were incubated with ETN or TCZ. Both agents were found to partially or completely inhibit the induction of SR-A expression and the accumulation of oxLDL stimulated by RA serum.

Conclusion: Inflammatory cytokines, TNF-α and IL-6 induce the expression of SR-A and accumulation of oxLDL. These cytokines are directly implicated in atherosclerotic plaque formation and progression. Our findings indicate that blockade of TNF-α and IL-6 has therapeutic potential for reducing CVD in chronic inflammatory diseases. We are now examining the expression of SR-A and plaque formation using macrophages from patients with chronic inflammatory diseases.

1839

Follistatin-Like Protein 1 Promotes Arthritis by Enhancing Cytokine/Chemokine Gene Expression. Yury Chaly[1], Anthony Marinov[1], Leif Oxburgh[2], Daniel Bushnell[1] and Raphael Hirsch[1]. [1]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Maine Medical Center Research Institute, Scarborough, ME

Background/Purpose: Follistatin-like protein 1 (FSTL-1) is a secreted glycoprotein that is over-expressed in the synovium of rheumatoid arthritis (RA) patients. We have previously shown that serum levels of FSTL-1 correlate with active disease in children with systemic juvenile idiopathic arthritis. We also demonstrated that over-expression of FSTL-1 exacerbated murine collagen-induced arthritis (CIA) while its neutralization suppressed CIA. The aim of the current study was to determine the mechanism by which FSTL-1 promotes arthritis focusing on FSTL-1 as a putative mediator of pro-inflammatory cytokine and chemokine synthesis.

Methods: CIA was induced in mice hypomorphic for FSTL-1 that were generated using a genetrap technique, resulting in a significant reduction of FSTL-1 protein expression. Arthritis was assessed by measuring paw swelling and using a qualitative arthritic index. Mesenchymal stromal cells (MSC) were isolated from the bone marrow of wild type and hypomorphic mice. To suppress FSTL-1 expression, mouse stromal ST2 cells were transduced with a lentivirus encoding mouse FSTL-1 short hairpin RNA. MSC and ST2 cells were stimulated with IL-1β, TNF-α and IL-17. Monocytic U937 cells, which do not normally express FSTL-1, were transfected with FSTL-1 and stimulated with phorbol myristate acetate (PMA) and lipopolysaccharide (LPS). The levels of FSTL-1, IL-6, IL-8 and monocyte chemotactic protein-1 (MCP-1) were assessed by ELISA.

Results: In CIA, a significant correlation was found between serum FSTL-1 levels and both paw swelling and the arthritic index ($r=0.399$, $p<0.01$; $r=0.496$, $p<0.05$, respectively). FSTL-1 up-regulated IL-6, IL-8 and MCP-1 production in PMA- and LPS-stimulated U937 cells. Knockdown of endogenous FSTL-1 expression suppressed IL-6 and MCP-1 production by stimulated stromal ST2 cells and MSC. FSTL-1 protein could be induced in vivo after treatment of mice with LPS.

Conclusion: These findings demonstrate that FSTL-1 directly up-regulates pro-inflammatory mediators important in the pathogenesis of arthritis and that serum levels of FSTL-1 correlate with severity of arthritis. Thus, FSTL-1 might be a useful biomarker of arthritis and a novel therapeutic target in chronic inflammatory diseases such as RA.

1840

Decreased Interleukin-22 in Pulmonary Fibrosis: Potential Role As a Regulatory Cytokine. Minrui Liang[1], Xiangjun Chen[2], Jiu-Cun Wang[3], Min Guan[2], Haiyan Chu[4] and Hejian Zou[5]. [1]Huashan Hospital,Fudan University,Shanghai, Shanghai, China, [2]Huashan Hospital, Fudan University, Shanghai, China, [3]Fudan University, Shanghai, China, [4]School of Life Science, Fudan University, China, [5]Huashan Hospital, Shanghai, China

Background/Purpose: Idiopathic pulmonary fibrosis (IPF) is clinically characterized of pulmonary inflammation, fibrosis and loss of lung function. IPF is one of the major causes for mortality in most connective tissue diseases. Recent studies have demonstrated that Interleukin(IL)-22 has both proinflammatory and tissue-protective properties in certain inflammatory milieu. To better understand the pathogenesis of IPF with alveolar epithelial to mesenchymal cell transition (EMT) and excessive collagen deposition, we used bleomycin(BLM)-induced pulmonary fibrosis mouse models to explore a critical regulatory role for IL-22.

Methods: BLM-induced pulmonary inflammation and fibrosis was confirmed by hematoxylin and eosin(H&E) and Masson Trichrome staining. The relative expression of *collagen1a2, collagen3al, mmp2, mmp9, tgf-*β was determined by real-time RT-PCR. The expressions of α-SMA, E-cadherin (E-cad) and IL-22 in the lung tissues were meanwhile measured by immunohistochemisty(IHC) and western-blot. The secreting IL-22 in alveolar lavage fluid was quantitated by ELISA. The effects of recombinant IL-22 (rIL-22) on BLM treated A549 cells, with regard to the proliferation of A549 and production of α-SMA, were examined by CCK-8 and western-blot analysis.

Results: Pulmonary inflammation and fibrosis were observed by H&E and Masson Trichrome stainings in BLM-induced C57BL/6 mice, researching the peak at the third week. BLM induced mice then, undergo EMT, which was accompanied by the upregulation of myofibroblast phenotypic markersα-SMA and the downregulation of the epithelial phenotype marker E-cad. Our data showed that *collagen1a2, collagen3a1, mmp2, mmp9, tgf-*β in the lung of BLM induced mice increased, with significantly diminished IL-22 in the alveolar lavage fluid and lung tissue. In vitro, alvealor epithelial cell expressing IL-22R1 but not fibroblasts was determined as the main IL-22 target cell; IL-22 could induce the phosphorylation of STAT3, up-regulate the viability of A549 cell line and down-regulate the level of α-SMA induced by BLM.

Conclusion: Our study indicates a protective pathway during the pulmonary fibrosis possibly through inhibiting EMT regulated by IL-22.

1841

Bridging ELISA As a Screening Assay to Monitor Immunogenicity in Routine Clinical Practice. Sandra Garcês[1], Jocelyne Demengeot[2], J. Canas da Silva[3] and L. Aarden[4]. [1]Instituto Gulbenkian Ciência; Hospital Garcia de Orta, Oeiras, Portugal, [2]Instituto Gulbenkian Ciência, Oeiras, Portugal, [3]Hospital Garcia de Orta, Almada, Portugal, [4]Sanquin Research and Landsteiner Laboratory, Amsterdam, Netherlands

Background/Purpose: Drug immunogenicity can be a significant problem in the treatment of patients with therapeutic antibodies, such as TNF alpha inhibitors. The clinical and scientific relevance of monitoring immunogenicity in clinical practice have been recognized and recommended by the European Agency of Medicine (EMEA). However, its assessment is technically challenging and no consensus exists about the way immunogenicity can be monitored. Newly developed fluid-phase radio-immuno assays (RIA) have been presented as a kind of "gold standard" method to assess immunogenicity. However, RIA requires high doses of radioactivity and special conditions,

preventing its use as a routine assay. By contrast, enzyme-linked immunoassay (ELISA) it's a simple and cheap method, ideal candidate to be used as a high-throughput screening assay. Bridging ELISA has increased specificity over the conventional ELISAs methods. Several optimizations of this method were made so that it can become a good screening assay to monitor drug immunogenicity. We aim to test, in a same cohort of patients receiving infliximab, this bridging ELISA in comparison with a fluid-phase antigen-binding RIA to quantify anti-infliximab antibodies.

Methods: A total of 82 consecutive patients were evaluated (38 rheumatoid arthritis patients, 27 ankylosing spondylitis, 9 psoriatic arthritis and 18 patients with inflammatory bowel disease), 61 females, with a mean age of 41 (4.2) years, that were receiving Infliximab (3–5mg/Kg every 6 or 8 weeks) for a mean period of 3.5 (2.0) years. Blood samples were collected immediately before the next infliximab infusion. Anti-infliximab antibodies were quantified by 1) Bridging ELISA where the antibodies bind to the infliximab coated in a solid phase and revealed by the addition of biotinylated infliximab and by 2) fluid-phase RIA-ABA that uses a sepharose-immobilized protein A, IgG total and IgG4-specific, to bind IgGs in the patient's serum. Anti-infliximab specific IgGs are revealed by the addition of ^{125}I-labeled infliximab F(ab')2. A simple ELISA method was used to quantify serum infliximab levels., Therapeutic response was assessed according to validated criteria established for each disease.

Results: A total of 22 (27%) were tested positive for the presence of anti-infliximab abs using RIA, coinciding with the samples that were also positives in Bridging ELISA. Bridging ELISA cannot detect monovalent IgG4. No samples testing exclusively IgG4 specific anti-infliximab were detected. All patients (100%) with detectable anti-infliximab antibodies had undetectable serum trough drug levels and were not able to sustain the therapeutic response.

Conclusion: Bridging ELISA was able to detect the same positive samples as RIA. The presence of IgG4-specific antibodies did not alter the assay's ability in detecting positive samples, since exclusively IgG4-specific antibodies are unlikely to occur. By its simplicity Bridging ELISA is a suitable test to be implemented in routine clinical practice as a screening assay to monitor drug immunogenicity.

1842

In Vivo Gene Transfer of IL-17A Induces Osteoclast Formation in a RANKL-Dependent Manner, Exacerbates Collagen-Induced Arthritis and Induces Epidermal Hyperplasia. Iannis E. Adamopoulos[1], Cheng-Chi Chao[2] and Eddie P. Bowman[3]. [1]UC Davis, Sacramento, CA, [2]Merck, Palo Alto, CA, [3]Merck, Palo Alto

Background/Purpose: Rheumatoid arthritis is an autoimmune disease where the interaction between the activated immune system and the skeletal system results in bone loss. We have previously shown that IL-17A upregulates the receptor RANK on human osteoclast precursors to increase their responsiveness to RANKL leading to increased bone loss *in vitro*.

Methods: In this study, we used minicircle-mediated gene transfer to evaluate the *in vivo* interplay between IL-17A and RANKL on bone metabolism.

Results: Chronic systemic IL-17A exposure induces neutrophilia *in vivo*, but was not sufficient to drive synovial inflammation in a naïve C57Bl/6 mouse. Systemic IL-17A exposure *in vivo* sensitized osteoclast precursors to sub-optimal RANKL levels resulting in elevated serum TRAP levels. The serum TRAP induction was independent of arthritis development. Moreover, systemic IL-17A exposure prior to collagen-induced arthritis sensitization severely exacerbated arthritis and bone loss, and led to epidermal hyperplasia.

Conclusion: Collectively our data suggest that IL-17A may play distinct roles in bone loss, joint inflammation and psoriasis making it a suitable candidate to combat psoriatic arthritis.

1843

FMS-Like Tyrosine Kinase 3 Receptor Inhibition Leads to Decreased Production of Interleukin 6 by Synovial Biopsies, Fibroblast-Like Synoviocytes and Monocytic Cells From Arthritic Patients. Maria I. Martins Ramos, Saïda Aarrass, Danielle M. Gerlag, PP. Tak and Maria C. Lebre. Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is characterized by inflammation of the synovial membrane and synovial lining hyperplasia, which results in erosion of cartilage and bone. Fibroblast-like synoviocytes (FLS) and macrophages play critical roles in this destructive process by producing inflammatory cytokines. Interleukin 6 (IL-6) is a key inflammatory cytokine in the pathobiology of RA and biological therapies targeting the IL-6 receptor have shown clinical benefit. Fms-like tyrosine kinase 3 ligand (FLT3L) plays a major role in dendritic cell (DC) biology. Flt3L can be detected in RA synovial fluid (SF) and serum and we have shown that Flt3L and its receptor are also expressed in other arthritic diseases. This axis exerts both pro-inflammatory and tissue destructive properties once in the joint cavity. Therefore we examined the effect(s) of a specific Flt3 inhibitor on IL-6 production by synovial biopsies from arthritic patients, cultured FLS and monocytic cells.

Methods: Synovial tissue biopsy specimens were obtained by arthroscopy and cultured in the absence or in the presence of a Flt3 specific inhibitor (50–100 nM, CEP-701) for 4 days. Monocytes were isolated from peripheral blood mononuclear cells (PBMC) by Ficoll gradient followed by Percoll gradient. Macrophages and DC were generated by culturing monocytes with GM-CSF or GM-CSF+IL-4, respectively. FLS and monocytic cells were cultured in the absence or in the presence of CEP-701 (50–100 nM). After 24h (monocytic cells and FLS) or after 4 days (synovial biopsies) IL-6 production was measured by ELISA.

Results: CEP-701 efficiently suppressed spontaneous production of IL-6 by synovial biopsies. As the main producers of IL-6 in the inflamed joint are synovial fibroblasts and macrophages we investigated the production of this inflammatory cytokine by these cells. Indeed, CEP-701 treatment blocked IL-6 levels in both FLS and monocytic cells.

Conclusion: Our findings suggest that therapies targeting Flt3L/Flt3 activity may be useful in suppressing inflammation in RA and other rheumatic diseases

1844

Anti-Inflammatory Activity of Apremilast Against T Cells, Chondrocytes, and Rheumatoid Arthritis Synovial Fibroblasts in Vitro. Lori Capone, Audry Rogovitz, Anita Gandhi and Peter Schafer. Celgene Corporation, Summit, NJ

Background/Purpose: Apremilast (APR) is a novel, orally available small molecule that specifically targets phosphodiesterase 4 (PDE4), thereby modulating multiple pro-inflammatory and anti-inflammatory mediators in both immune and non-immune cells. T cells secrete various cytokines and chemokines that play a role in RA and spondylarthritis. In addition, cytokines produced by chondrocytes and synoviocytes contribute to inflammatory joint diseases such as arthritis and in bone damage, and are increased in synovial fluid of spondylarthritis and RA patients.

Methods: To explore the modulation of various cellular responses involved in arthritis and joint damage, the effect of APR on inflammatory responses of primary human T cells, chondrocytes, and RA patient synovial fibroblasts was examined, and compared with that of other anti-rheumatic agents etanercept (ETAN), cyclosporine A (CsA), methotrexate (MTX), and prednisolone (PRED). Human peripheral blood total T cells from healthy donors were stimulated with anti-CD3 antibody. Total peripheral blood mononuclear cells were stimulated with Staphylococcal Enterotoxin B. Cytokine and chemokine protein levels were analyzed by cytometric bead array. Normal primary human chondrocytes and RA synovial fibroblasts were stimulated with IL-1β, IL-6 and IL-6R. IL-7 mRNA was measured by qRT-PCR.

Results: In T cells, APR inhibited production of all T cell cytokines and chemokines measured (IL-2, IL-4, IL-13, IFN-gamma, TNF-alpha, CXCL10, CCL3, and CCL4) with 50% inhibitory concentrations (IC50s) of 15–360 ng/mL. CsA also inhibited all analytes, with IC50s of 4.7–140 ng/mL. In contrast, ETAN potently inhibited TNF-alpha (IC50=1.5 ng/mL), and to a lesser degree IL-13 and IP-10 (16–62 ng/mL), but IC50s for all other analytes were >1600 ng/mL. Notably, ETAN and CsA inhibited TNF-α by 90–95%, while APR inhibited TNF-α by a maximum of 70%. In chondrocytes, APR significantly inhibited IL-7 gene expression (IC50=140 ng/mL) to a greater degree than ETAN or MTX, while IL-7 inhibition by PRED was greatest. APR showed a trend of inhibition of $\alpha v\beta 3$ integrin, ICAM-1 expression, and production of IL-8, MMP-3, and MMP-13 by chondrocytes. In stimulated RA synovial fibroblasts, APR inhibited IL-7 gene expression (IC50=1800 ng/mL), while PRED, MTX, and ETAN had no significant effect.

Conclusion: Treatment of human T cells with APR resulted in inhibition of IL-2, IL-4, IL-13, IFN-gamma, TNF-alpha, CXCL10, CCL3, and CCL4, with a predominant pattern of partial inhibition. In chondrocytes and RA synovial fibroblasts, APR inhibited IL-7 gene expression. These results illustrate the distinct pattern of modulation of inflammatory responses by PDE4 inhibition, compared to other classes of drugs.

1845

C5orf30 a Candidate Susceptibility Gene in Rheumatoid Arthritis. Sachin Khetan[1], Munitta Muthana[1] and A. G. Wilson[2]. [1]Dr, Sheffield, United Kingdom, [2]Sheffield Uni /Medical School, Sheffield, United Kingdom

Background/Purpose: A recent genome wide associations study identified SNP rs26232 with risk of developing rheumatoid arthritis (RA) (1), in addition a recent study has reported association with radiological damage (2). The SNP rs26232 is located at chromosome 5q21 within the intron of a predicted gene *C5orf30* . The aim of this study is to determine the pattern of expression of *C5orf30* in rheumatoid synovium and cultured synovial cells.

Methods: Fresh synovial biopsies obtained from RA patients were used to isolate fibroblast-like synovial cells (FLS) following digestion with collagenase-1. Real time PCR was used to determine *C5orf30* transcript levels in FLS (stimulated with TNF, LPS & hypoxia) and in peripheral blood mononuclear cells (PBMC) isolated from RA patients and healthy individuals. *C5orf30* gene expression was also assessed in a panel of other cell types. To study protein expression we stained paraffin-embedded athroscopy sections with anti-*C5orf30*.

Results: The expression of *C5orf30* was confirmed at the mRNA level in many cell types including macrophages, keratinocytes, thymus and cancer cells including lung, breast, prostate and melanoma. *C5orf30* was also expressed in joint FLS and was found to be up-regulated following treatment with bacterial LPS (22 fold), hypoxia (26-fold) but not TNF-a (0.9 fold) when compared to untreated FLS. Interestingly, expression of *C5orf30* was detected at lower levels in PBMCs of patients than controls. Indeed, in some RA patients (14/23) this was undetectable. Immunohistochemistry, staining of patient arthroscopies revealed that *C5orf30* was strongly expressed in both the nuclear and cytoplasmic compartment of synovial lining cells.

Conclusion: *C5orf30* is expressed at both the transcript & protein level in synovial cells but not in circulating PBMC obtained from RA patients, suggesting that *C5orf30* is expressed in a tissue-specific manner. We are currently performing confocal microscopy to determine the subcellular localization of *C5orf30* expression in RA joints and mass spectrometry to work out the biology of this important marker in the pathogenesis and severity of RA.

Reference:

Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, *et al* (2010). Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nat Genet. 42(6):508–14.

Wilson AG, Teare M, van der Helm-van AH, Moore D, Knevel R, Kleszcz A, Huizinga T (2011). Identification and validation of a novel marker for radiological severity in RA. Abstract N° OP0229. EULAR.

ACR/ARHP Poster Session C

Epidemiology and Health Services Research III: Connective Tissue Diseases/Vasculitis/Inflammatory Arthritis

Tuesday, November 8, 2011, 9:00 AM–6:00 PM

1846

Adult Prevalence of Systemic Autoimmune Rheumatic Diseases (SARDs) in British Columbia, Canada. J. Antonio Avina-Zubieta[1], Eric C. Sayre[1], Sasha Bernatsky[2], Allen J. Lehman[1], Kamran Shojania[1], John Esdaile[3] and Diane Lacaille[1]. [1]Arthritis Research Centre of Canada/ University of British Columbia, Vancouver, BC, [2]McGill UHC/RVH, Montreal, QC, [3]University of Calgary, Calgary, AB

Background/Purpose: There is a growing interest in the use of administrative health data to estimate the incidence and prevalence of systemic autoimmune rheumatic disorders (SARDs) such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's disease (SjD), and poly/dermatomyositis (PM/DM) [collectively called as connective tissue diseases CTD]; and, systemic vasculitides (polyarteritis nodosa, Wegener's disease, giant cell arteritis and Takayasu's disease). We estimated the prevalence and incidence rates of SARDs as a group and as individual diseases by sex in age 20+ years in the province of British Columbia (BC), Canada (population 3.3 million) using physician billing and hospitalization databases.

Methods: Our data included all visits to health professionals and hospital admissions covered by the comprehensive provincial medical services plan from January 1, 1990 until December 31, 2007 for all individuals > 18 years of age. SARDs was defined as: **(a)** ≥ 2 ICD-9/10 codes for SARDs ≥ 2 months apart but within a two-year period by any physician other than rheumatologists or **(b)** one ICD-9/10 code for SARDs by a rheumatologist (at any time), or **(c)** >1 hospitalization diagnostic code of SARDs. To improve specificity of our algorithm, we excluded individuals with at least two visits ≥ 2 months apart subsequent to the first SARD visit (second for a non-rheumatologist) with diagnoses of other non-SARDs inflammatory arthritides (e.g. rheumatoid arthritis, psoriatic arthritis, spondyloarthropathy) and those where a diagnosis of SARDs by a non-rheumatologist was non confirmed when seen by a rheumatologist. The prevalence estimates were calculated for the year 2007, based on the number of cases that had been identified during the study period (1996–2007) who remained alive as of December 31, 2007, with the denominator being the total number of BC residents at that time. SARDs cases were identified as incident cases for 1996–2007 if they had no prior visit for SARDs since 1990.

Results: The overall prevalence of CTD and systemic vasculitides in 2007 were 0.39% and 0.03%, respectively. The BC prevalence rates of CTD by sex and age are similar to those reported previously using Bayesian models (*males:* 176.3 versus 221.3 and *females*: 591.9 versus 605.9, for BC and Canada, respectively). The prevalence and incidence rates per 100,000 by disease, and sex in age 20+ are shown in the table below.

SARD DISEASE	Prevalence per 100K Males 20+	Prevalence per 100K Females 20+	Prevalence per 100K Total 20+	Incidence per 100K PY Males 20+	Incidence per 100K PY Females 20+	Incidence per 100K PY Total 20+
CONNECTIVE TISSUE DISEASES	176.3	591.9	388.6	20.1	67.5	44.3
SLE	30.4	193.9	113.9	3.6	24.2	14.1
SSc	6.4	35.6	21.3	1.5	5.6	3.6
SjD	5.5	36.4	21.3	1.7	6.8	4.3
DM	3.2	7.5	5.4	0.4	1.6	1.0
PM	8.0	10.3	9.2	1.1	1.8	1.4
SYSTEMIC VASCULITIDES	21.1	42.2	31.9	3.7	6.9	5.3
Polyarteritis nodosa	3.0	5.0	4.0	0.4	0.8	0.6
Wegener's disease	10.0	10.7	10.3	2.0	2.5	2.2
Giant cell arteritis	8.5	25.6	17.3	1.6	3.8	2.7
Takayasu's disease	0.6	2.8	1.7	0.2	0.5	0.4

Conclusion: CTD and systemic vasculitis rates in this study are comparable with epidemiologic studies on SARDs. Administrative data are a valuable source to study the epidemiology and surveillance of SARDs.

1847

The Georgia Lupus Registry: Differences in Age-Specific Incidence Rates Between Black and White Females with SLE. Cristina M. Drenkard[1], Gaobin Bao[1], Charles G. Helmick[2], C. Gordon[3], Rana Bayakly[4] and S. Sam Lim[1]. [1]Emory University, Atlanta, GA, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]University of Birmingham, Birmingham, United Kingdom, [4]Georgia Department of Public Health, Atlanta, GA

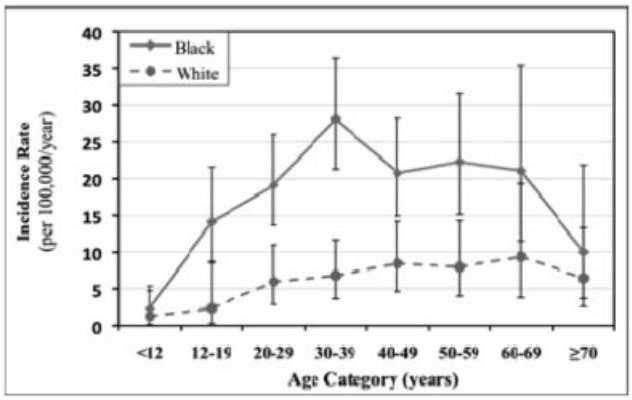
Background/Purpose: Although it is considered that SLE most often strikes women in their childbearing-ages, European studies have reported peak incidence among White women to occur above age 50. US studies have shown increased risk among younger Black females compared with Whites. However, age-specific risks by race in American women have been estimated from populations with relatively small number of Blacks. We aimed to describe age-specific incidence rates of SLE in Black and White females from a large population-based registry.

Methods: The Georgia Lupus Registry is a population-based registry designed to estimate the incidence and prevalence of SLE in Atlanta, GA. The state HIPAA exemption for surveillance allowed health care providers and facilities to provide access to protected health information without written patient consent. Sources of cases included hospitals (20), rheumatologists (35), nephrologists (10), dermatologists (20), commercial labs, and population databases. Trained abstractors reviewed >8,000 medical records. The catchment area was the two main counties (Fulton and DeKalb) that include Atlanta. Denominators were derived from the 2000 US Census Bureau Vintage 2009, for the period 2002–2004. The total population in the target counties for the period at risk was 4,742,264, of

whom 1,082,131 were White females (WF) and 1,239,819 Black females (BF). Average annual age-specific incidence rates per 100,000 and exact 95% confidence intervals assuming a Poisson distribution were calculated. BF and WF cases that were either definite (≥4 ACR Criteria) or probable (3 ACR Criteria with Final Diagnosis by Rheumatologist) were included in the analysis.

Results: Among a total of 332 incident cases, 215 were BF and 66 WF. The mean age at diagnosis was 39.4 and 46.3 years in BF and WF, respectively (p=0.009). The average annual incidence rate was 17.3/100,000 (95% CI 15.1, 19.8) for BF and 6.1 (95% CI 4.7, 7.8) for WF.

Average Annual Age-Specific Incidence Rates for females by race



Note: Vertical lines represent 95% CI

Conclusion: Our data support that Black females develop SLE at a younger age compared to White females. Incidence rates are similar at the extreme ages where female hormones are potentially less involved. However, the rates in Black females increase more dramatically at puberty and peak at 28/100,000/year between ages 30–39. White female rates have a more gradual increase and peak at 9.4/100,000/year between ages 60–69. Although SLE is often considered to be a disease that affects women in their reproductive years, these findings suggest that female hormones may be associated with lower threshold levels for the development of SLE in Blacks as compared to Whites. The development of lupus is likely to be influenced by both genetic and environmental factors that interact. More research into the mechanisms underpinning the racial disparities in susceptibility is warranted.

1848

Epidemiology of Systemic Lupus Erythematosus in a Large United States Managed Care Population. Daniel E. Furst[1], Ann Clarke[2], Ancilla Fernandes[3], Tim Bancroft[4], Warren Greth[3] and Serban R. Iorga[4]. [1]UCLA Medical School, Los Angeles, CA, [2]Montreal General Hospital, Montreal, QC, [3]MedImmune LLC, Gaithersburg, MD, [4]Innovus, Eden Prairie, MN

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by multiorgan involvement including skin, joints, kidney, heart, lungs and brain. Accurate data on the current incidence and prevalence of SLE are largely lacking, with ranges for incidence in the United States from 1.8–5.6 per 100,000 persons and prevalence from 53–150 per 100,000 persons. We investigated the incidence and prevalence of SLE in a large US managed care population by examining medical claims.

Methods: We conducted a retrospective study of SLE in a large US managed care database. Patients were included in the incidence cohort if they had a medical claim with SLE (ICD-9-CM diagnosis code of 710.0x) and an index date from 2003–2008 that satisfied the following criteria: 1) at least 1 inpatient claim or ≥2 office or ER visits at least 30 days apart with a diagnosis code for SLE; 2) ≥18 years of age on the index date; 3) continuously enrolled for 12 months before and after the index date; and 4) no SLE claims 12 months prior to index date. Patients were identified for the prevalence cohort using the same criteria, with the exception of requirement 4. Overall and annual incidence for the duration of 2003–2008 was estimated and age and gender adjusted to the US 2000 census population. Annual prevalence was calculated for each year from 2003 to 2008. Patients contributed to annual incidence only once (the earliest service date that met the above criteria was set as the index date), but could contribute to prevalence in multiple years. Sensitivity analyses were performed using select clinical characteristics (presence of a rheumatologist/dermatologist/nephrologists/neurologist visit) and/or treatments (presence of antimalarials/systemic corticosteroids/immunosuppressants).

Results: A total of 7301 patients were included in the incidence cohort (88% female, median age=48). During the period from 2003–2008, the overall age- and gender-adjusted SLE incidence rate was 24.06 cases per 100,000 person-years (95% CI, 23.36–24.75). The adjusted annual incidence of SLE ranged from 23.55 per 100,000 persons in 2003 to 29.19 per 100,000 persons in 2008. In the sensitivity analysis using clinical and treatment characteristics, the overall adjusted incidence rate was 21.69 cases per 100,000 person-years (95% CI, 21.04–22.35). A total of 15,396 patients were included in the prevalence cohort (90% female, median age=46). The annual prevalence of SLE (per 100,000 persons) varied from 81.07 in 2003 to 102.94 in 2008. The annual SLE prevalence was slightly lower in sensitivity analyses using clinical characteristics, and ranged between 67.90 in 2003 to 89.35 in 2008 per 100,000 persons.

Conclusion: While the prevalence of SLE in the US managed care population evaluated in this analysis was within the previously reported range for the United States, the incidence was several-fold higher. Due to the limitations inherent in claims analysis, such as possible miscoding and plan turnover, results should be interpreted with caution. Future research should also examine causes for the increased incidence observed in this population.

1849

Population-Based Incidence Estimates for Systemic Lupus Erythematosus in the USA, 2002–2005: Results From the Michigan Lupus Epidemiology and Surveillance (MILES) Program. Emily C. Somers[1], Wendy Marder[1], Patricia C. Cagnoli[1], Emily E. Lewis[1], Peter DeGuire[2], Caroline Gordon[3], Charles G. Helmick[4], Lu Wang[1], Jeffrey J. Wing[1], J. Patricia Dhar[5], James C. Leisen[6], W. Joseph McCune[1] and MILES Group[7]. [1]University of Michigan, Ann Arbor, MI, [2]MI Dept of Community Health, Lansing, MI, [3]University of Birmingham, Birmingham, United Kingdom, [4]Centers for Disease Control and Prevention, Atlanta, GA, [5]Wayne State University, Detroit, MI, [6]Henry Ford Hospital, Detroit, MI, [7]Ann Arbor, MI

Background/Purpose: The epidemiology of lupus in the USA has been characterized predominantly using homogenous populations from the tertiary care setting. We conducted this public health surveillance project to estimate systemic lupus erythematosus (SLE) incidence in a diverse population in Southeastern Michigan (source population ~2.3 million).

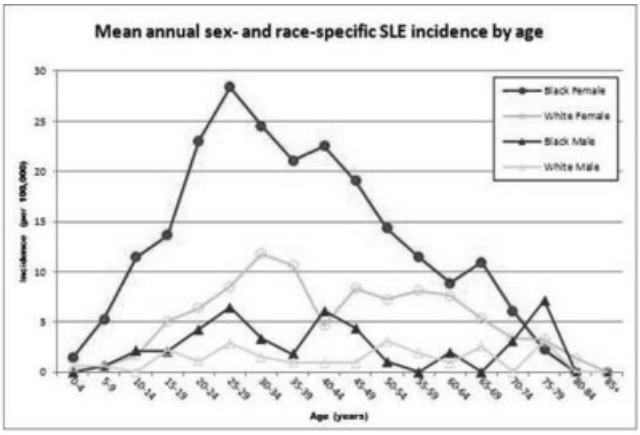
Methods: MILES is a population-based, active SLE surveillance program utilizing multiple sources of case-finding (eg, hospitals, private practice physicians, laboratories, etc) to identify SLE cases in the catchment area of Washtenaw (includes Ann Arbor) & Wayne (includes Detroit) Counties (2002–2005). Detailed record reviews are performed for all potential SLE cases meeting eligibility criteria. We recently completed case-finding and review activities, and final data cleaning steps are underway. The case definition for this analysis is: persons with a new diagnosis of SLE meeting ACR classification criteria (≥4) during 2002–2005, and who were residents of Washtenaw or Wayne Counties. Age-, sex- and race-specific denominators by county in Michigan were based on US Census data ("vintage 2009 bridged-race population files"). Mean annual incidence estimates and exact 95% CIs were calculated using SAS 9.2. Age standardization was performed using the 2000 US standard population.

Results: Among >13,000 records screened, 2482 cases met ACR classification criteria (≥4) for SLE: 2250 (90.7%) female; 944 (38%) white, 1410 (57%) black, 128 (5%) other race. Of these cases, 565 were newly diagnosed during the 4-year surveillance period. Incidence estimates are presented below (expressed per 100,000). Age-standardized mean annual incidence rates were 6.0 overall, 9.9 female, and 1.9 male. Peak incidence occurred at age 25–29 for black females and 30–34 for white females. Among males, due to the small sample size, age-specific patterns are less clear but appear more constant across ages.

Table 1. Mean annual SLE incidence per 100,000 (95% CIs) for Washtenaw and Wayne Counties, 2002–2005

Age	Average annual no. new cases	Overall population	Female	Male
0–4	1	0.6 (0.3, 1.1)	0.9 (0.3, 2.8)	0.3 (0.1, 0.9)
5–9	3	1.7 (1.0, 3.1)	2.9 (1.6, 5.5)	0.6 (0.2, 1.7)
10–14	8	4 (2.8, 5.8)	6.9 (4.7, 10.2)	1.3 (0.5, 3.1)
15–19	11	6.3 (4.7, 8.5)	10.4 (7.5, 14.5)	2.3 (1.2, 4.7)
20–24	14	8.5 (6.5, 11.1)	14.5 (10.9, 19.3)	2.5 (1.3, 5.0)
25–29	18	11.4 (9.0, 14.4)	18.5 (14.3, 23.9)	4.0 (2.2, 7.0)
30–34	18	10.2 (8.0, 12.8)	17.6 (13.8, 22.6)	2.3 (1.2, 4.7)
35–39	15	8.3 (6.4, 10.7)	15.1 (11.6, 19.8)	1.2 (0.4, 3.1)
40–44	13	7.1 (5.4, 9.3)	11.4 (8.4, 15.4)	2.6 (1.3, 4.9)
45–49	13	7.5 (5.7, 9.8)	12.5 (9.4, 16.7)	2.0 (1.0, 4.3)
50–54	11	6.9 (5.1, 9.2)	10.4 (7.4, 14.5)	3.0 (1.6, 5.7)
55–59	7	5.4 (3.7, 7.8)	9.1 (6.1, 13.6)	1.3 (0.4, 3.9)
60–64	4	4.7 (2.9, 7.6)	7.8 (4.7, 13.0)	1.2 (0.3, 4.7)
65–69	3	4.8 (2.8, 8.3)	7.2 (4.0, 13.1)	1.7 (0.4, 6.8)
70–74	2	3.3 (1.6, 6.6)	4.9 (2.3, 10.3)	1.0 (0.1, 7.1)
75–79	2	3.9 (2.0, 7.4)	3.6 (1.5, 8.7)	4.2 (1.6, 11.3)
80–84	0	0.6 (0.1, 4.2)	0.9 (0.1, 6.6)	0 (—)
85+	0	0 (—)	0 (—)	0 (—)
Total crude	***141***	***6.0 (5.7, 6.2)***	***9.8 (9.1, 10.7)***	***1.9 (1.7, 2.0)***
Total ASR*	***141***	***6.0 (5.9, 6.1)***	***9.9 (9.8, 10.0)***	***1.9 (1.8, 1.9)***

* ASR=age-standardized rate



Conclusion: SLE incidence in the diverse source population of Southeastern MI is estimated to be at the upper range of previously reported North American estimates, and slightly higher than previous European estimates. In contrast to recent European studies describing peak incidence among females around age of menopause, peak incidence in this population occurs during the reproductive years.Black females have highest risk of SLE, and the youngest peak age of incidence.

1850

Impact of Autoimmune Diseases on Health Status and Health Care Utilization. Pamela Shea Poynter, Kyoung-Suk Lee, Heather Bush and Leslie J. Crofford. University of Kentucky, Lexington, KY

Background/Purpose: Patients with autoimmune diseases are known to have reductions in health status and increased health care utilization compared with a healthy population. Few studies have compared patients with different autoimmune diseases and patients with other chronic diseases to determine the factors that drive these observations. The purpose of this study was to evaluate the impact of autoimmune diagnosis compared with other chronic diseases on self-report health perception and health care consumption.

Methods: This was a cross-sectional case-control study of participants in the Kentucky Women's Health Registry, a self-report longitudinal survey containing information on demographic variables, health behaviors, health care utilization, medical diagnoses, and health symptoms. The sample consisted of 10,684 women with different autoimmune disease diagnoses [n=794; rheumatoid arthritis (RA)=490; connective tissue diseases (CTD)=141; multiple sclerosis/myasthenia gravis (MS/MG)=80; inflammatory bowel disease (IBD)=83], asthma (n=1,664), hypertension (n=2097), and healthy controls (n=6,124). All analyses were performed using SAS Version 9.2. Univariate analyses were performed for all variables followed by multivariable logistic regression anlyses. Confounding factors in multivariable analyses included age, education, race, Appalachian residence, employment status, smoking status, marital status, insurance, social support, depression, anxiety, sedentary lifestyle, body mass index, and medical co-morbidities.

Results: Patients with autoimmune diseases had significantly poorer global health perception compared with the healthy control group with an adjusted odds ratio (aOR) of 4.49 (95%CI: 3.43, 5.88) versus an aOR of 1.71 (1.36, 2.16) for asthma and 1.77 (1.42, 2.21) for hypertension. There were striking increases in chronic fatigue [aOR 4.46 (3.54, 5.62)] and chronic pain [aOR 3.28 (2.65, 4.06)] in patients with an autoimmune diagnosis versus controls that were much more pronounced than with other chronic diseases. Furthermore, patients with autoimmune diseases were greater consumers of health care as measured by doctor visits [aOR 2.97 (2.43, 2.63) and ER visits [aOR 1.81 (1.43, 2.28) over the past 12 months. There were significant differences in health symptoms among the different autoimmune diseases. Notable findings were an increase in chronic fatigue among patients with MS/MG [aOR 2.28 (1.17, 4.45)] and a decrease in chronic fatigue among patients with IBD [aOR 0.44 (0.22, 0.87)] compared with RA patients. Patients with IBD also had a significantly lower risk for chronic pain [aOR 0.23 (0.12, 0.44)] than RA patients.

Conclusion: Autoimmune diseases have adverse effects on health status and health care utilization compared with other chronic diseases. The high prevalence of chronic fatigue and chronic pain appear to be important drivers of these effects. Among the autoimmune diseases, chronic pain in RA and chronic fatigue in MS/MG are the most important symptoms. Addressing these symptoms may provide important benefits to improve health status and reduce health care expenditures in patients with RA and other autoimmune diseases.

1851

Racial Disparities In Treatment Preferences Among Lupus Patients In An Urban Academic Center. Ernest R. Vina, Christopher M. Masi, Stephanie L. Green and Tammy O. Utset. University of Chicago, Chicago, IL

Background/Purpose: African American, compared to white, Systemic Lupus Erythematosus (SLE) patients have worse health outcomes. While racial differences in patient preferences for treatment decisions have been documented in other diseases, this phenomenon has not been explored in SLE. The objectives of this study are: 1) to determine whether there are differences between African American & white SLE patients' willingness to a) receive an immunosuppressive medication (i.e. cyclophosphamide, CTX) when indicated and b) participate in clinical trials involving novel, experimental medications; and 2) to determine whether demographic, psychosocial and clinical characteristics explain racial differences in either measure of medical management.

Methods: Data from 120 African American & 62 white lupus patients were evaluated. Structured telephone interviews were conducted to determine treatment preferences, as well as characteristics and beliefs that may affect these preferences. Chart reviews were conducted to evaluate clinical characteristics (SLE disease activity, damage index). Serial hierarchical multivariate logistic regression analyses were performed and their deviances from a saturated model were calculated.

Results: Compared to white SLE patients, African American SLE patients were less willing to receive CTX (84.9% vs. 67.0%, p=0.001). They were also less likely to have high income (p<0.005) and private insurance (p<0.005), and more likely to believe in prayer affecting health (p<0.005). Lupus patients willing to receive CTX were more likely to have private insurance (p=0.026), be married (p=0.011) and perceive CTX to be effective (p<0.001) and low risk (p=0.049). Multivariate logistic regression showed that white race (OR = 3.50, p=0.017), physician trust (OR = 1.05, p=0.071) and perception of effectiveness of treatment (OR = 1.40, p<0.005) were significant predictors of willingness to receive CTX. After adjustment for socioeconomic variables, the effect of race on willingness to receive CTX was no longer significant (OR 1.69, 95% CI 0.62–4.65)

In contrast, racial differences were observed in willingness to participate in a clinical trial but did not reach statistical significance (80.7% whites vs. 68.7% African Americans, p=0.096). A logistic regression model showed that internal health locus of control (OR 0.92, p=0.022), physician partici-

patory decision-making style (OR 1.03, $p<0.005$), lack of physician race preference (OR 2.28, $p=0.002$), marital status (OR 128.5, $p=0.012$), and the interaction between marital status & physician race preference (OR 0.39, $p=0.030$) were significant predictors of willingness to participate.

Conclusion: African American and white SLE patients did not differ in willingness to participate in a clinical trial. However, we found a decreased likelihood of accepting CTX in African American compared to white lupus patients. After controlling for socioeconomic factors, this racial disparity was no longer significant. Nevertheless, willingness to receive CTX was also associated with belief in its efficacy and trust in physicians, suggesting that education and improved trust can influence decision-making among SLE patients.

1852

Effort-Reward Imbalance in Patients with Systemic Lupus Erythematodes? Jutta G. Richter, Thomas Muth, Birthe Koerbl, Nicole Hoffmann, Tobias Koch, Johannes Siegrist and Matthias Schneider. Heinrich-Heine-University, Duesseldorf, Germany

Background/Purpose: Working life factors influence patients' (life) satisfaction and their well being. Effort at work is spent as part of a 'social contract' that reciprocates effort by adequate reward. Components of work-related rewards have been shown to matter for health. Research on ERI might contribute to the understanding of social and psychological factors related to the well-being of SLE patients (pts) with systemic lupus erythematosus (SLE). We studied psychosocial stress levels at work measured by the ERI model.

Methods: Within a cross sectional nationwide study a set of standardized self-administered questionnaires was applied to SLE pts. The ERI questionnaire assessed the effort-reward imbalance in SLE pts capable for work. Effort-reward ratio (ERR) scores >1 and the upper tertile scores of overcommitment (OCS) reflect relevant values. Data were analyzed in comparison to controls (c) not suffering from a rheumatic disease and recruited by the pts. Ethics committee approval had been obtained.

Results: 267 pts (95.9% female (f)) and 178 c (90.8% f) answered the questionnaires. Pts' mean age was 39.9 ± 9.5 (c 42.8 ± 9.8) years, mean disease duration 10.4 ± 7.3 years, 81.3% self-reported at least one comorbidity (range 1–10). 70.0% received at least one immunosuppressive medication (DMARD, range 1–3). 41.6% were on steroids $\leq$7.5mg and 15.7% on steroids $>$7.5mg. 33.0% took NSAIDS. Occupational status and self-categorized occupation groups (scog) did not significantly differ between pts and c.

77.8% of the pts (c 5.4%;$p<0.0001$) showed an ERR$>$1, significantly more female pts had an ERR$>$1 ($p<0.05$). Age, disease duration, functional capacity, number of DMARDs, steroid dosages, education, marital status, and scog did not significantly differ to those with ERR$\leq$1.

The OCS showed relevant values in 40.2% pts (f 40.0%, male 45.5%; c 25.2% (both p-values$>$0.05). Age, disease duration, functional capacity, number of DMARDs, steroid dosages, education, marital status, and scog were not significantly different to those with OCS in the lower tertiles.

Table 1. Effort & reward and overcommitment scores, ERR$>$1 and OCS upper tertil in pts and c

	Effort mean ± SD	Reward mean ± SD	ERR > 1 %	Overcommittment mean ± SD	OCS upper tertile %
Pts	15.5 ± 4.9	22.1 ± 9.9	77.8	14.4 ± 4.0	40.2
Female	15.6 ± 4.9	21.9 ± 9.8	79.2	14.4 ± 4.0	40.0
Male	14.0 ± 6.5	26.6 ± 11.7	37.5	13.5 ± 4.0	45.5
Controls	14.2 ± 4.1	46.8 ± 6.6	5.4	12.8 ± 3.9	25.2
Female	14.0 ± 4.0	47.0 ± 6.5	4.1	12.6 ± 3.8	23.2
Male	16.9 ± 3.9	43.8 ± 7.4	18.8	14.3 ± 4.1	43.8

Conclusion: This is the first study investigating the ERI in SLE pts. Compared to controls a significantly higher proportion of pts reported a relevant ERI. Analysis on direct and indirect mechanisms potentially involved in the relation between psychosocial work characteristics and SLE need further evaluations. However, although no cause and effect relationship can be established a reduction of stressful experiences in the framework of the worksites for SLE pts seems reasonable.

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Missed Work Days In Systemic Lupus Erythematosus. Jie Xu, Hong Fang and Michelle Petri. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: SLE has a profound effect on work productivity that is not captured in most analyses of medical care costs. We quantified the frequency and clinical associations of missed work days in SLE patients.

Methods: A medical resource use questionnaire that covered the last 3 months was distributed to 240 SLE patients. They were 89% female, 58% Caucasian, 32% African American. Exclusion criteria were diagnosis with SLE less than 6 months, age younger than 18 or older than 75, pregnant at baseline, and active HIV patients.

Results: 35.8% (86/240) had missed work days. The mean missed work days was 0.9 (range: 0–30) per month.

Table 1. Patient Characteristics Associated with Missed Work Days

Variable	No missed work days (%, N=154)	1–5 missed work days (%, N=55)	5+ missed work days (%, N=31)	P-value
Age at visit (years)				
≤3	24.68	40.00	32.26	0.092
>35	75.32	60.00	67.74	
Race				
African-American	28.57	30.91	48.39	0.18
Caucasian	60.39	61.82	38.71	
Other	11.04	7.27	12.90	
Education (years)				
≤12	20.78	25.45	25.81	0.69
>12	79.22	74.55	74.19	
Income ($)				
≤50K	36.36	41.82	58.06	0.08
>50K	63.64	58.18	41.94	
Smoking	5.19	12.73	16.13	0.054
Anti-dsDNA	71.43	60.00	45.16	0.012
Low C3	67.53	47.27	41.94	0.0032
Diabetes	3.25	10.91	16.13	0.01
Physical global assessment >1 (0 to 3 VAS)	9.09	12.73	29.03	0.009
SLEDAI '4	19.48	14.55	32.26	0.14
BMI>30	28.57	25.45	51.61	0.025
Vitamin D <15	3.90	7.27	16.13	0.035
Prednisone (mg)				
0	68.18	58.18	51.61	0.0008
1–9	27.27	27.27	19.35	
10+	4.55	14.55	29.03	

Conclusion: About one third of SLE patients had missed work days. Age, race, education, and income were not associated with missed work days. The physician global assessment of disease activity (but not SLEDAI) and prednisone $\geq$ 10 mg were associated with missed work days. Serologic measures (anti-DNA, low complement) were associated with missed work, but in a counterintuitive way (patients with no missed work were more likely to have high anti-dsDNA and low complement). A low vitamin D was somewhat associated. These data suggest that both control of disease activity and reduction in prednisone would reduce loss of work and indirect medical care costs.

1854

Life and Job Satisfaction in Patients with Systemic Lupus Erythematosus. Jutta G. Richter, Thomas Muth, Birthe Koerbl, Mia Vidakovic, Tobias Koch and Matthias Schneider. Heinrich-Heine-University, Duesseldorf, Germany

Background/Purpose: Life satisfaction (LS) is a psychological construct that has become an increasingly important outcome measure in healthcare and is a relevant indicator of job satisfaction. The objectives of the study were to investigate life and job satisfaction in patients (pts) with systemic lupus erythematosus (SLE) capable for work.

Methods: Within a cross sectional nationwide study a set of standardized self-administered questionnaires was applied to SLE pts. The questionnaire on life satisfaction (FLZ) measures ten domains of satisfaction (health, finances, job and profession, friends and relatives, leisure, home, partner/relationship, sexuality, children, self), the total score values general LS. According to questionnaire's analysis scores are expressed as age and sex standardized stanines (a method of scaling test scores on a normalized nine-point standard scale (1–9) with a mean of 5 and a standard deviation of 2). Data were analyzed in comparison to controls (c) not suffering from a rheumatic disease. Ethics committee approval had been obtained.

Results: 267 pts (95.9% female (f)) and 178 c (90.8% f) answered the questionnaires. Pts' mean age was 39.9±9.5 (c 42.8±9.8) years, mean disease duration 10.4±7.3 years, 81.3% self-reported at least one comorbidity (range 1–10). 70.0% received at least one immunosuppressive medication (DMARD, range 1–3). 41.6% were on steroids ≤7.5mg and 15.7% on steroids >7.5mg. 33.0% took NSAIDS. Occupational status and self-categorized occupation groups (scog) did not significantly differ between pts and c.

Compared to c significantly higher proportions of pts reported lower satisfaction in the domains health, job and profession, friends and relatives, leisure, sexuality, self and in the total score reflecting general LS (see table 1). Age, disease duration, number of DMARDs, steroid dosages, education, marital status, or scog were not significantly different in pts' general LS stanines (p-values>0.05). However, functional capacity differed significantly in stanines for general LS ($p<0.05$): more pts with stanines 1–4 had lower functional capacity.

Table 1. FLZ stanines in ten domains and for general LS

	SLE pts			Controls			
	Stanines 1–3% of pts (expected 23%*)	Stanines 4–6% of pts (expected 54%*)	Stanines 7–9% of pts (expected 23%*)	Stanines 1–3% of c (expected 23%*)	Stanines 4–6% of c (expected 54%*)	Stanines 7–9% of c (expected 23%*)	P values Pts vs C
Health	73.5	23.1	3.4	20.5	57.8	21.7	<0.01
Finances	26.7	52.5	20.8	20.5	52.8	26.7	n.s.
Job and profession	27.8	53.5	18.7	16.2	56.3	27.5	<0.05
Friends and relatives	31.5	46.6	21.9	20.0	53.8	26.2	<0.05
Leisure	37.5	47.7	14.8	22.2	58.6	19.2	<0.01
Home	14.0	56.8	29.2	11.2	48.8	40.0	<0.1
Partner/relationship	26.6	47.8	25.6	22.6	47.5	29.9	n.s.
Sexuality	43.0	44.3	12.7	21.1	52.6	26.3	<0.01
Children	31.6	41.9	26.5	20.9	39.6	39.5	<0.1
Self	35.7	47.9	16.4	19.2	60.9	19.9	<0.01
General LS (FLZ total score)	43.8	41.9	14.3	13.7	58.9	27.4	<0.01

*Expected from stanines' normal distribution, n.s. not significant

Conclusion: This first study of FLZ in SLE pts revealed significant less life, job and self satisfaction as well as satisfaction in other social domains. These domains are potentially modifiable by interventions that should predominantly target social and job related issues. Besides from already established assessments (e.g. HAQ, SF36) further clinical studies might gain from the additional assessment of LS as an outcome parameter.

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Impact of Systemic Lupus Erythematosus on Employment and Work Productivity in the US. Ellen Sulcs[1], Mechele Lee[2], Cindy P. Garris[3] and Priti M. Jhingran[3]. [1]Harris Interactive Inc., New York, NY, [2]Harris Interactive Inc., New York, [3]GlaxoSmithKline R&D, Research Triangle Park, NC

Background/Purpose: SLE is a complex, chronic autoimmune disorder characterized by fluctuating periods of disease activity affecting multiple organ systems. SLE patients experience a wide variety of symptoms including fatigue, rash, joint pain, kidney disease, central nervous system disease, and heart involvement. This study was conducted to evaluate the impact of SLE on patients' employment and productivity.

Methods: A cross-sectional cohort of employed and unemployed patients with SLE in the US, recruited through a patient advocacy association and the Harris Chronic Illness Panel, was surveyed online (IRB approved) between Dec 2010 and Mar 2011. Inclusion criteria were ≥18 years old, self-reported SLE diagnosis, and ≥1 SLE flare in prior 3 months requiring medical attention (taking medications, calling or visiting a physician, or going to the ER or hospital). A control group of employed patients without SLE recruited from HarrisPollOnline (HPOL) were demographically matched (age, sex, race, income, and education) to the employed SLE cohort. Controls met the above inclusion criteria excluding the SLE related criteria and were also surveyed online. Questions for the SLE cohort included perceived flare activity (a flare was defined as any time a patient perceived that their SLE symptoms intensified, whether mildly or severely), symptoms and impact of SLE on employment and work productivity. The control group answered similar questions about the impact of any health conditions on work. Impact on work productivity/daily activities was assessed over the past 7 days using a 10-point scale; anchors are at 0 (SLE/health conditions had no effect on my work/ regular daily activities) and 10 (SLE/health conditions completely prevented me from working/doing my regular daily activities). Employed and unemployed SLE patients were compared to controls by dependent sample T-tests.

Results: 546 SLE patients (281 employed, 265 unemployed) and 300 employed controls completed the survey; of the 300 control group respondents, 69% reported having ≥1 health condition(s). The unemployed SLE cohort was older than both the employed SLE group and control group (mean age 45.4 vs. 39.8 and 41.1, respectively; $p<0.05$). Of all surveyed respondents, 96% were female and 79% were Caucasian (no significant differences across groups). Of unemployed SLE patients, 75% attributed their unemployment to SLE, and 59% reported receiving disability benefits. Unemployed SLE patients reported experiencing a mean of 8.9 flares over 3 months compared with 5.7 flares for employed SLE patients ($p<0.05$). The employed SLE cohort reported more lost work hours per week due to SLE (6.9 hours) than the employed control group due to any health condition (1.6 hours)($p<0.05$). Mean work productivity rating was 4.5 for the SLE employed cohort vs. 1.3 for the control group ($p<0.05$). Likewise, mean daily activity rating was higher for both SLE cohorts (employed 5.6, unemployed 6.6) compared with the control group (1.8) ($p<0.05$).

Conclusion: Patients with SLE reported significantly reduced ability to work, work productivity, and daily activities. Further research is needed to quantify the economic impact of impaired work productivity due to SLE for patients, employers and society.

1856

Association of Body Mass Index, Race/Ethnicity and Gender in a Cohort of Systemic Lupus Erythematosus Patients with Diabetes and/or Hypertension. Jonea Lim[1], Nasir Mushtaq[2], Rachna Aggarwal[3] and R. Hal Scofield[4]. [1]Harold Hamm Oklahoma Diabetes Center, University of Oklahoma Health Science Center, Oklahoma City, OK, [2]University of Oklahoma Health Science Center College of Public Health, Oklahoma City, OK, [3]University of Oklahoma Health Science Center; Oklahoma Medical Research Foundation, OK, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: To determine the prevalence of diabetes mellitus (DM) and/or hypertension (HTN) in systemic lupus erythematosus (SLE) patients and its association with body mass index (BMI). To determine racial/ethnic and gender differences among SLE patients having DM and/or HTN.

Methods: In a large cohort of 2044 SLE patients we explored BMI, race/ethnicity and gender as risk factors for development of DM and HTN. All SLE patients met at least four 1982 American College of Rheumatology classification criteria. Chi square and regression techniques were used for this analysis. Statistical analysis was performed on 991 patients for whom we could confirm the diagnosis of DM and HTN after review of medical records of these patients. SAS version 9.1 was used for statistical analysis.

Results: Results of the descriptive analysis showed that 80% (n=789) had HTN, 7% (n=74) DM, and 13% (n=128) had both DM and HTN. Most of the participants (87%) were woman and the majority of them were White (44%) followed by African American (35%). The mean BMI of the sample was 28.93 (SD = 7.85) kg/m^2. Table 1 summarizes characteristics of the SLE patients participating in the study. Results of the univariate logistic regression models indicated that there was no statistically significant association of DM with gender or race as compared to those having HTN.

Table 1. Characteristics of the 991 SLE patients participating in the study

Variable	Overall	Diabetes	Hypertension	Both
Gender *n(%)*				
Female	860 (86.78)	68 (91.89)	686 (86.95)	106 (82.81)
Male	131 (13.22)	6 (8.11)	103 (13.05)	22 (17.19)
Race *n(%)*				
White	437 (44.10)	28 (37.84)	359 (45.50)	50 (39.06)
African American	344 (34.71)	22 (29.73)	271 (34.35)	51 (39.84)
AI/AN	40 (4.04)	6 (8.11)	31 (3.93)	3 (2.34)
Others	170 (17.15)	18 (24.32)	128 (16.22)	24 (18.75)
BMI *mean (sd)*	28.93 (7.85)	28.99 (7.91)	28.34 (7.61)	32.65 (8.35)

Comparison of exclusive DM and exclusive HTN did not show significant association with BMI, however when we compared all DM patients (exclusive DM and both DM and HTN) with exclusive HTN patients there was an association with BMI. SLE patients with higher BMI had increased odds (OR

1.045, 95%CI: 1.025–1.065) of having DM. There was no interaction between these variables and the results of the multiple logistic regression analysis showed similar estimates.

Crude and adjusted odds ratios suggested a statistically significant association between BMI and having both DM and HTN. SLE patients having higher BMI were 1.063 (95% CI: 1.040–1.087) times more likely to have both DM and HTN when adjusted for gender and race.

Results of analysis of variance indicated that the SLE patients having both DM and HTN had higher mean BMI than those who exclusively had DM (Mean difference = 3.659, 95%CI: 0.942–6.377) or HTN (mean difference = 4.314, 95%CI: 2.532, 6.097).

Conclusion: The impact of higher body mass index dominates race/ethnicity and gender association in developing DM and HTN among SLE patients.

1857

Everyday Stress, C-Reactive Protein, and Systemic Lupus Erythematosus. Amanda Eudy[1], Anissa I. Vines[1], Charles Poole[1], Carolina Lupus Study Investigators[2] and Christine G. Parks[3]. [1]University of North Carolina, Chapel Hill, NC, [2]USA, [3]NIH/NIEHS, Research Triangle Park, NC

Background/Purpose: Racial/ethnic and socioeconomic disparities in systemic lupus erythematous (SLE) are well described but not well understood. Psychosocial stress has known effects on immune function and may influence disease course in SLE. Elevated C-reactive protein (CRP), an inflammatory biomarker associated with psychosocial stress, has been seen in individuals of lower socioeconomic status (SES) and nonwhite race. We examined the relationship of self-reported disease activity in SLE with daily stress, squelched anger, and CRP, exploring potential differences by race or SES.

Methods: Data included of 72 Caucasian and 115 African American SLE patients diagnosed between 1995 and 1999, and enrolled in the Carolina Lupus Study (75% of the cases in the full cohort). CRP and self-reported disease activity were collected at baseline. Questions on day-to-day stress, squelched anger, recent flares (in past 3 months) and hospitalizations were asked at a 2001 follow-up interview. Age, sex, race and education adjusted logistic regression models estimated odds ratios (OR) and 95% confidence intervals (CI) for the associations of stress and anger with flare and hospitalization in the past 12 months. Student's t and ANOVA tests were used to compare log-transformed CRP by disease activity and hospitalization. We also considered factors associated with baseline CRP in linear regression models adjusted for age, sex, race and education. Stratified analyses explored modification by race and education (≤12 high school, >high school).

Results: Feeling the need to squelch anger was more common in both African Americans (26% vs. 10% Caucasians) and the less educated (28% vs. 14% >high school). Recent flare was reported by 58% (61% African American and 54% Caucasians). Overall, patients reporting a recent flare had higher daily stress (OR=1.8; 95%CI 1.0, 3.3) and felt the need to squelch anger more frequently (OR=1.8; 95% CI 1.0, 3.3). These associations did not differ by race and education, and the association of African-American race and anger squelching (OR=2.0; 95%CI 1.0, 3.3) persisted after adjusting for flare. Recent hospitalization was not associated with daily stress or squelched anger overall. Recent hospitalization was also associated with daily stress in Caucasians (OR=1.9; 95%CI 0.5, 6.4), but not in African-Americans (OR=0.6; 95%CI 0.1, 2.3). Higher baseline CRP was associated with recent flare, especially in African Americans and those with less education, and was associated with recent hospitalization in all groups.

Conclusion: Our findings support the idea that SLE disease activity may be related to stress and anger. They provide some evidence of racial/ethnic and socioeconomic differences in the experiences of daily stressors in SLE patients, though small sample size limited power for statistical comparisons. These data cannot directly address the role of stress as a cause or consequence of inflammation, but the observations support the need to better understand the interrelationships of anger, stress, and CRP levels as potential sources of socioeconomic health disparities in SLE.

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Stressful Life Experiences and Inflammation in the Carolina Lupus Study: An Open-Ended Query on Stress. Christine G. Parks[1], Anissa I. Vines[2], Amanda Eudy[3] and Carolina Lupus Study Investigators[4]. [1]NIH/NIEHS, Research Triangle Park, NC, [2]University of North Carolina, Chapel Hill, NC, [3]UNC Chapel Hill, Chapel Hill, NC, [4]USA

Background/Purpose: Psychosocial stress has been associated with disease activity in systemic lupus erythematosus (SLE), but knowledge is limited on biologic pathways relating stress to racial and socioeconomic health disparities in SLE. Here we describe open-ended reports of stressful experiences in a population-based study of participants in the Carolina Lupus Study. We also explore the association of the stressful experiences with C-reactive protein (CRP), an inflammatory biomarker previously related to SLE, stress, non-white race and low socioeconomic status (SES)

Methods: Participants included SLE patients (n=249; 64% African-American, 90% women; median age 37 years and 13 months since diagnosis) in North Carolina and South Carolina, and age, sex, and state-matched controls (n=329). In person interviews collected detailed participant characteristics and a blood specimen. Using an open-ended format, participants were asked to describe *up to* three stressful times in their lives and the age(s) of these experiences. Verbatim responses were later grouped by thematic subgroups of life events or chronic stressors. High sensitivity serum CRP was measured by ELISA. Odds ratios (OR) and 95% confidence intervals (CI) for reported stressful experiences in relation to SLE were estimated in regression models, adjusting for age, sex, state, race and education. In patients, we examined stress reporting in relation to log-transformed CRP, adjusted for age, sex, race, education, smoking, and recent flare. All analyses were also stratified to explore differences by race and education.

Results: Only 15% of participants (patients and controls) reported no stressors, but nearly 3-times as many African-American patients reported no stressors (17% vs. 6% in whites, p=0.01). The most common stressors were: death/major loss; relationship; health (cases); and job stressors. Caucasian patients reported more trauma, abuse, or accidents (p=0.02) versus African American patients, while higher education was related to job stress in all participant sub-groups. No other differences were seen in specific stressors by race or SES. Among Caucasians, SLE was associated with reporting at least one stressful experience (OR=3.4; 95%CI 1.3, 9.1). Among African Americans who reported stressors, patients described more health-stress than controls (OR=3.2; 95%CI 1.4, 7.0). In patients, higher CRP was associated with reporting at least one stressor (p=0.004) and more stressors reported p=0.03), independent of other risk factors (older age, African-American race, and low education). The association of patient-CRP levels with reporting at least one stressor was most apparent in African Americans, while higher CRP in Caucasians was associated with financial stress and lower education.

Conclusion: SLE patients may be more likely to report psychosocial stressors in general. Our results suggest stress may be related to inflammation in patients, but a causal role cannot be determined in these cross-sectional analyses. Observed racial differences in stress reporting and associations highlight a need for culturally-appropriate methods to assess stress in studies of SLE disparities.

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LupusPRO: Cross Cultural Validation Study for Lupus in the Philippines. S. Navarra[1], Rachel A. Mikolaitis[2], Joel A. Block[2] and Meenakshi Jolly[2]. [1]University of Santo Tomas Hospital, Manila, Philippines, [2]Rush University Medical Center, Chicago, IL

Background/Purpose: LupusPRO is a disease-targeted Patient Reported Outcome measure that was developed and validated from and among US patients with systemic lupus erythematosus (SLE). We herein report the results of the cross-cultural validation study of the English language version of LupusPRO among SLE patients in the Philippines.

Methods: The 43-item LupusPRO was pretested in 15 SLE individuals. It was then self administered to 106 SLE patients meeting ACR classification criteria (T1), along with generic tools SF36 and EQ5D visual analogue scale. A mail/drop back LupusPRO and change in health status item survey were given to the patients to be completed within 2–3 days (T2). Data on demographics, clinical and serological characteristics were collected. Disease activity was measured using Physician Global Assessment (PGA), SELENA-SLEDAI and LFA Flare (yes/no and severity of flare). Disease damage was determined using SLICC-ACR SLE damage index (SDI). Internal consistency reliability (ICR), test-retest reliability (TRT), convergent validity (corresponding SF36 domains), and criterion validity (against various general health and disease activity measures) were tested. All reported p values are two tailed.

Results: 121 SLE subjects (95% women) with at least high school level of English instruction medium education participated. Mean age ± SD was 34.7 ± 10.7 yrs and mean ± SD disease duration 6.2 ±4.9 yrs; 97% Asians, 75 % had more than high school education, and 42% were currently married. Mean ± SD PGA 0.81 ± 1.1, mean ± SD SLEDAI 5.3 ± 7.6 and mean ± SD SDI 0.8 ± 1.2. Table 1 outlines the psychometric properties. ICR and TRT were fair to excellent. Convergent validity ranged from moderate to strong. Criterion validity

was established against general health and/or disease activity measures on most domains. The tool was well received by the patients.

Table 1. Psychometric properties of LupusPRO among SLE patients in the Philippines

LupusPRO Domain	ICR	TRT	Convergent Validity (correlation coefficient r, p value)	Criterion Validity (p value)
Lupus Symptoms	0.66	0.95		LFA Flare (p 0.001), Flare severity (0.001), Patient-Change in Health (0.04), PGA (0.0001), SLEDAI (0.007), EQ5D VAS (0.001)
Cognition	0.79	0.95		Patient-Change in Health (0.03)
Lupus Medications	0.72	0.86		
Physical Health	0.88	0.90	Physical Function (0.35, 0.001), Role Physical (0.21, 0.02)	LFA Flare (0.04), Flare severity (0.01), Patient-Change in Health (0.0001), SF36-Overall Health (0.03),PGA (0.07), SLEDAI (0.0001), PGA (0.09)
Pain-Vitality	0.85	0.91	Bodily Pain (0.69, 0.001), Vitality (0.48, 0.001)	LFA Flare (0.05), Flare severity (0.09), Patient-Change in Health (0.0001),SF36-Overall Health (0.006), SLEDAI (0.004), PGA (0.03), EQ5D VAS (0.002)
Body Image	0.88	0.96		Flare severity (0.07), Patient-Change in Health (0.06), SF36-Overall Health (0.02), PGA (0.02), EQ5D VAS (0.02)
Emotional Health	0.88	0.93	Mental Health (0.46, 0.001), Role Emotional (0.33, 0.001)	Patient-Change in Health (0.06), EQ5D VAS (0.08)
Procreation	0.82	0.94		PGA (0.006), Patient-Change in Health (0.05)
Desires-Goals	0.86	0.89		Patient-Change in Health (0.01), SF36-Overall Health (0.04)
Social Support	0.80	0.95		SLEDAI (0.09), Patient-Change in Health (0.01)
Cope	0.72	0.91		SF36-Overall Health (0.006), EQ5D VAS (0.002)
Satisfaction Med Care	0.91	0.96		

Conclusion: English LupusPRO has fair psychometric properties among SLE patients in the Philippines. Validation studies on a Filipino version of LupusPRO are being planned.

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Spanish LupusPRO: Cross Cultural Validation Study for Lupus. Meenakshi Jolly[1], Joel A. Block[1], Rachel A. Mikolaitis[1], Daniel Wallace[2], Sergio Duran-Barragán[3], Ana M. Bertoli[4], Sergio Toloza[5], Ivana Blazevic[6], Luis M. Vila[7], Dilrukshie Cooray[8], Emmanuel P. Katsaros[9], Karina Marianne D. Torralba[10], Michael H. Weisman[11] and Graciela S. Alarcon[12]. [1]Rush University Medical Center, Chicago, IL, [2]Cedars-Sinai/UCLA, Los Angeles, CA, [3]UIECD, Guadalajara, Mexico, Guadalajara, Mexico, [4]Instituto Reumatológico Strusberg, Cordoba, Cordoba, Argentina, [5]Hospital San Juan Bautista, Catamarca, Argentina, [6]University of Buenos Aires, Buenos Aries, Argentina, [7]University of PuertoRico Medical Sciences Campus, San Juan, PR, [8]Harbor UCLA Medical Center, Torrance, CA, [9]Loma Linda Univ, Loma Linda, CA, [10]USC Keck Schl of Medicine, Los Angeles, CA, [11]Cedars Sinai Med Ctr, Los Angeles, CA, [12]University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: LupusPRO is a disease targeted Patient Reported Outcome measure that was developed and validated from and among US patients with Systemic Lupus Erythematosus (SLE). We herein report the results of the cross-cultural validation study of the Spanish translated version of the LupusPRO.

Methods: Forward and back translations of the 43 item English LupusPRO were undertaken and pretested in five individuals. The finalized Spanish version was applied to the SLE patients meeting ACR classification criteria of Hispanic ancestry from the US and Latin America. Demographic, clinical and serological characteristics were obtained and the SF-36 (Spanish) and Spanish LupusPRO (T1) administered. Disease activity was ascertained using the physician Global Assessment (PGA), SELENA-SLEDAI and LFA defined Flare (Yes/No). Disease damage was assessed using the SLICC-ACR SDI. A mail back Spanish LupusPRO to be completed within 2–3 days (T2) was also given. Internal consistency reliability (ICR), test-retest reliability (TRT), criterion validity (against measures of disease activity or health status) and convergent validity (corresponding domains of the SF36) were all tested. All reported p values are two tailed.

Results: 211 SLE subjects (90% women) were enrolled. Sixty-four percent had upto High School education, and 46% were currently married. The mean ± SD age (yrs) and disease duration were 38 ± 12 and 8.8 ±7.6. The mean ± SD PGA and SLEDAI were 0.78 ±0.76 and 3.9 ±4.4. The mean ± SD SDI were 0.61 ± 1.1. Psychometric properties are shown in the table.

Table. Psychometric Properties of Spanish LupusPRO

Domain	ICR T1	ICR T2	TRT	Conv. Validity (corr r, p)	Criterion Validity (p value)
Lupus Symptoms	0.67	0.73	0.94		LFA Flare (p 0.001), Flare severity (0.007), Patient-Change in Health (0.01), SF36-Overall Health (0.0001), PGA (0.0001), SLEDAI (0.01)
Cognition	0.91	0.93	0.9		LFA Flare (0.01), Flare severity (0.06), Patient-Change in Health (0.03), SF36-Overall Health (0.0001), PGA (0.0001),SLEDAI (0.04)
Lupus Medications	0.74	0.74	0.89		LFA Flare (0.04), SF36-Overall Health (0.001),PGA (0.002), SLEDAI (0.03)
Physical Health	0.87	0.93	0.95	SDI (−0.15, 0.04), PF (0.64, 0.001), RP(0.61, 0.001)	LFA Flare (0.001), Flare severity (0.01), Patient-Change in Health (0.0001), SF36-Overall Health (0.0001),PGA (0.0001), SLEDAI (0.0001)
Pain-Vitality	0.94	0.95	0.96	BP (0.78, 0.001), VT (0.73, 0.001)	LFA Flare (0.002), Flare severity (0.003), Patient-Change in Health (0.0001),SF36-Overall Health (0.0001), PGA (0.0001), SLEDAI (0.003)
Body Image	0.95	0.96	0.96		LFA Flare (0.001), Flare severity (0.002), Patient-Change in Health (0.06), SF36-Overall Health (0.0001), PGA (0.0001), SLEDAI (0.008)
Emotional Health	0.93	0.95	0.97	EH (0.67, 0.001), RE (0.64, 0.001)	LFA Flare (0.002), Flare severity (0.006), SF36-Overall Health (0.0001),PGA (0.001), SLEDAI (0.03)
Procreation	0.59	0.81	0.92		PGA (0.05)
Desires-Goals	0.88	0.93	0.93		LFA Flare (0.01), Flare severity (0.07), Patient-Change in Health (0.01), SF36-Overall Health (0.0001), PGA (0.001), SLEDAI (0.001)
Social Support	0.79	0.84	0.8		
Cope	0.71	0.6	0.88		
Satisfaction Med Care	0.86	0.5	0.8		

Conclusion: The Spanish LupusPRO has fair psychometric properties and is now available to be included in Latino-American clinical trials and in longitudinal studies for testing of responsiveness to change.

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Epidemiology of Systemic Sclerosis in a Large United States Managed Care Population. Daniel E. Furst[1], Ancilla Fernandes[2], Serban R. Iorga[3], Warren Greth[2] and Tim Bancroft[3]. [1]UCLA Medical School, Los Angeles, CA, [2]MedImmune LLC, Gaithersburg, MD, [3]Innovus, Eden Prairie, MN

Background/Purpose: Previous epidemiologic studies of systemic sclerosis (SSc) in the United States have reported an annual incidence of slightly fewer than 2 per 100,000 persons and a prevalence of 24–28 per 100,000 persons. As most prior studies of SSc epidemiology in the United States relied on data from about 10 years ago (or longer), an updated description of disease characteristics may help increase awareness among healthcare providers of this rare condition.

Methods: We conducted a retrospective study of SSc in a large US managed care database. Patients were included in the incidence cohort if they had a medical claim with an SSc ICD-9-CM code of 710.1x and an index date from 2003–2008 that satisfied the following criteria: 1) at least 1 inpatient claim *or* ≥2 office or ER visits at least 30 days apart with a diagnosis code for SSc; 2) ≥18 years of age on the index date; 3) continuously enrolled for 12 months before and after the index date; and 4) no SSc claims 12 months prior to index date. Patients were identified for the prevalence cohort using the same criteria, with the exception of requirement 4. Overall and annual incidence for the duration of 2003–2008 was estimated and age-gender adjusted to the US 2000 census population. Annual prevalence was calculated for each year from 2003 to 2008. Patients contributed to annual incidence only once (the earliest service date that met the above criteria was set as the index date) but could contribute to prevalence in multiple years. Sensitivity analyses were performed using select clinical characteristics (presence of rheumatologist / dermatologist / nephrologist visit) and treatments (presence of systemic corticosteroids / immunosuppressants use).

Results: A total of 1,529 patients were included in the incidence cohort (85% female, median age=52) and 2,739 were included in the prevalence

cohort (86% female, median age=52). From 2003–2008, the overall crude incidence rate for SSc was 4.57 cases per 100,000 person-years (95% CI, 4.34−4.80), and the overall adjusted incidence rate was 5.61 cases per 100,000 person-years (95% CI, 5.24–5.98). The adjusted annual incidence of SSc ranged from 5.37 per 100,000 persons in 2003 to 5.95 per 100,000 persons in 2008. In sensitivity analyses using clinical and treatment characteristics, the overall adjusted incidence rate was 4.74 cases per 100,000 person-years (95% CI, 4.40–5.07). The annual prevalence of SSc ranged from 13.47 in 2003 to 18.38 in 2008 per 100,000 persons. In sensitivity analyses using clinical characteristics, the annual prevalence was slightly lower, ranging between 11.17 in 2003 to 15.95 in 2008 per 100,000 persons.

Conclusion: These results suggest a higher SSc incidence and a lower prevalence in the managed care population evaluated in this study compared with other epidemiologic studies of SSc in the United States. Due to the limitations inherent in claims analysis, such as possible miscoding and plan turnover, results should be interpreted with caution. Future research should also examine causes for any observed difference in the epidemiology of SSc.

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Population-Based Prevalence Estimates of Myositis in First Nations Relative to Non-First Nations Canadians. Cheryl CM Barnabe[1], Lawrence Joseph[2], Patrick Belisle[2], Jeremy Labrecque[3], Lawrence W. Svenson[1], Steven M. Edworthy[1], Susan G. Barr[1], Marvin J. Fritzler[1], Christine A. Peschken[4], Brenda Hemmelgarn[1] and Sasha Bernatsky[3]. [1]University of Calgary, Calgary, AB, [2]McGill University Health Centre, Montreal, QC, [3]McGill UHC/RVH, Montreal, QC, [4]University of Manitoba, Winnipeg, MB

Background/Purpose: Canada's First Nations (FN) population has higher prevalence of rheumatoid arthritis, osteoarthritis, lupus and scleroderma relative to the non-First Nations (non-FN) population. Population-based prevalence estimates for autoimmune inflammatory myopathies considering race have not been previously reported. In addition, we examined the effect of demographic factors which may affect our estimates, given that they influence access to health services and thus identification of affected individuals in administrative healthcare databases.

Methods: Physician billing claims and hospitalization data (years 1994–2007), coded according to the International Classification of Diseases (ICD) system, were used to ascertain cases of polymyositis and dermatomyositis, using three case definitions: i) ≥1 billing code by a rheumatologist; ii) ≥2 billing codes by any physician, ≥8 weeks apart but within 2 years; or iii) one hospitalization diagnosis. A latent class Bayesian hierarchical regression model was employed to account for the imperfect sensitivity and specificity of these data sources in case ascertainment. We accounted for demographic factors, estimating prevalence for FN and non-FN populations by sex, age group, and location of residence (urban versus rural). FN status was determined by methodology derived by the provincial steward for health data to identify individuals registered with the Department of Indian and Northern Affairs of the Government of Canada.

Results: Contrary to other rheumatic diseases, the overall prevalence point estimate for myositis was lower in the FN population, at 25.0 per 100,000 persons, with a relatively wide credible interval (CrI) (95% CrI 13.4–49.0), compared to 33.8 per 100,000 (95% CrI 28.9–39.6) in the non-FN population. Except for rural FN females <45 years of age, all prevalence point estimates were higher in the non-FN population (Table 1), although the credible intervals overlapped. In non-FN we demonstrated higher prevalence estimates for females and older individuals, with similar trends in FN individuals. Trends were seen for higher myositis prevalence in rural locations.

Table 1. Myositis Prevalence Estimates (95% credible interval) for First Nations and non-First Nations Populations, per 100,000 people

	Females		Males	
	First Nations	Non-First Nations	First Nations	Non-First Nations
<45 years old				
Rural	27.7 (10.0–67.2)	19.2 (13.3–27.1)	2.1 (0.1–13.4)	5.7 (3.0–9.6)
Urban	4.5 (0.1–35.8)	13.4 (9.6–18.7)	4.8 (0.5–23.7)	4.2 (2.4–7.2)
>45 years old				
Rural	137.3 (55.9–345.6)	124.5 (97.5–161.9)	12.7 (1.1–54.7)	58.7 (43.5–78.9)
Urban	87.3 (4.8–415.9)	86.7 (70.6–107.6)	17.4 (0.2–153.9)	37.6 (28.5–49.5)

Conclusion: Female sex and older age were associated with higher myositis prevalence. We did not find higher myositis prevalence estimates in FN individuals, but our estimates are limited by the inability to capture Métis and non-treaty individuals of FN descent. There was an interesting trend for higher prevalence in rural areas, which raises potential hypotheses about genetic risk pools and/or environmental factors that might be triggers for autoimmune disease (e.g. pesticides, zoonotic pathogens, respirable silica etc.) as well as physician diagnosis and referral patterns. Further work is required to address these issues.

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Development and Content Validity of the Hand Disability in Systemic Sclerosis—Digital Ulcers (HDISS-DU) Scale. Dinesh Khanna[1], Serge Poiraudeau[2], Heather Gelhorn[3], Elke Hunsche[4], Kelly Papadakis[4], Loic Perchenet[4], Maria Stoeckl Mattera[5], Margaret Vernon[5] and Luc Mouthon[2]. [1]University of Michigan, Ann Arbor, MI, [2]Hopital Cochin, Paris, France, [3]United BioSource Corporation, Golden, CO, [4]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, [5]United BioSource Corporation, Bethseda, Bethesda, US., MD

Background/Purpose: Digital ulcers (DU) are common, painful, debilitating manifestations of systemic sclerosis (SSc); they adversely affect hand function in daily activities. The Cochin Hand Function Scale (CHFS), originally developed for use in rheumatoid arthritis, is a self-administered hand functional disability questionnaire, containing 18 items related to daily activities. The objective of this research was to evaluate the content validity of the CHFS in patients with SSc and active DU, and to modify the instrument as needed.

Methods: A cross-sectional qualitative interview study was conducted in the US. Eligibility included a diagnosis of SSc and at least one recent, visible, active ischemic DU, for which the patient had seen a physician within the past 8 weeks. The study had 2 phases: Phase I consisted of 20 face-to-face semi-structured interviews, which focused on 2 parts: a) elicitation of emergent concepts relevant and important to DU-related hand function and b) cognitive debriefing of the CHFS. Based on findings and after having reached saturation of concepts, the original CHFS was modified and then cognitively debriefed in further qualitative interviews (Phase II, n=16) to confirm changes and the content validity of the modified instrument. IRB approval was obtained and all participants provided written informed consent. Interviews were recorded, transcribed, and analyzed using Atlas.ti (qualitative analysis software).

Results: The 36 patients had a mean age of 52.5 years (range: 18–73); 81% were female, and 83% Caucasian. Among the 35 participants with clinician-documented data, the mean number of active ulcers was 2.7; 89% and 71% had DU(s) on the dominant hand and submissive hand, respectively. Examples of commonly reported limitations due to DUs (in Phase I) included: activities using fingertips (e.g., using keyboard), washing dishes, cleaning, dressing, fitness activities, bathing/ showering, and grooming. Items in the original CHFS were modified and new items were added to cover the types of limitations patients reported in Phase I; specifically, 13 items were added, 4 items were deleted, and 12 items were modified and/or clarified to be more relevant to DU-related hand functioning. The revised instrument was called the Hand Disability in Systemic Sclerosis—Digital Ulcers (HDISS-DU) questionnaire. In Phase II, in which the HDISS-DU was cognitively debriefed, participants confirmed the clarity and relevance of the items, and the appropriateness of the recall period and response scales of the revised instrument. Only limited additional modifications to the instructions and response options were required; one item was deleted. The current version of the HDISS-DU assesses the impact of DUs on hand functioning through 26-items; patients are asked to rate their ability to complete common activities over the past 7 days.

Conclusion: The qualitative interview study suggests that the draft version of the HDISS-DU is a comprehensive, content valid instrument assessing the impact of DUs on hand functioning in patients with SSc. Future studies will be conducted for additional item reduction (if required) and assessment of psychometric properties of the HDISS-DU.

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Epidemiology of Idiopathic Inflammatory Myopathy in a Large United States Managed Care Population. Daniel E. Furst[1], Anthony A. Amato[2], Serban R. Iorga[3], Kavita Gajria[4] and Ancilla Fernandes[4]. [1]UCLA Medical School, Los Angeles, CA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Innovus, Eden Prairie, MN, [4]MedImmune LLC, Gaithersburg, MD

Background/Purpose: Prior studies have reported low incidence (0.1–1 per 100,000 persons) and prevalence (0.55–6 per 100,000 persons) of idiopathic inflammatory myopathies (IIMs) in the United States. However, updated estimates on the incidence and prevalence of IIMs have not been easily available.

Methods: We conducted a retrospective study of IIMs in a large US managed care database. Subjects were included in the incidence cohort if they had a medical claim with a myositis diagnosis (ICD-9-CM 710.3 [dermatomyositis/DM], 710.4 [polymyositis/PM], 728.81 [interstitial myositis]) and an index date from 2003–2008 that satisfied the following: 1) at least 1 inpatient claim or ≥2 office or ER visits at least 30 days apart with a diagnosis code for myositis; 2) ≥18 years of age on the index date; 3) continuously enrolled for 12 months before and after the index date; and 4) no myositis claims 12 months prior to index date. Subjects were identified for the prevalence cohort using the same criteria, with the exception of requirement 4. Overall and annual incidence for the duration of 2003–2008 was estimated and age-gender adjusted to the US 2000 census population. Annual prevalence was calculated for each year from 2003 to 2008. Subjects contributed to annual incidence once (the earliest service date that met the above criteria was set as the index date), but could contribute to prevalence in multiple years. Sensitivity analyses were performed using select clinical characteristics (presence of muscle biopsy or rheumatologist/neurologist/dermatologist visit) and treatments (presence of medications used to treat IIMs).

Results: A total of 1941 subjects were included in the incidence cohort (65% female, median age=49). For the duration of 2003–2008, the overall adjusted incidence rate for myositis was 6.57 cases (95% CI, 6.20–6.94) per 100,000 person-years. Similarly, the overall adjusted rates for PM, DM, and interstitial myositis were 3.79, 1.38, and 1.69 per 100,000 person-years, respectively. The adjusted annual incidence of myositis ranged from 5.81 to 7.89 per 100,000 persons from 2003 to 2008. From sensitivity analyses (using clinical/treatment characteristics), the overall adjusted incidence rate was 5.07 cases per 100,000 person-years (95% CI, 4.73–5.40). A total of 3112 subjects were included in the prevalence cohort (67% female, median age=49). The annual prevalence of myositis ranged from 13.99 in 2003 to 17.37 in 2008 per 100,000 persons. In sensitivity analyses (using clinical characteristics), the annual prevalence decreased slightly to range between 9.59 in 2003 to 13.61 in 2008 per 100,000 persons.

Conclusion: Our findings suggest that the incidence and prevalence of IIMs in the managed care database are higher than those previously reported. Due to the limitations inherent in claims analysis, such as plan turnover, additional research is needed to substantiate these results. Understanding the epidemiology of these rare conditions may help increase the awareness of healthcare providers and eventually contribute to early diagnosis and treatment of these debilitating conditions.

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Descriptive Epidemiology of Granulomatosis with Polyangitis (Wegener's), Microscopic Polyangitis, Polyarteritis Nodosa and Goodpasture's Syndrome in the United States. Martin M. Crane[1], Vincent X. Rabatin[2] and Alfred Mahr[3]. [1]GlaxoSmithKline, Research Triangle, NC, [2]GlaxoSmithKline, Research Triangle Park, NC, [3]Hospital Saint-Louis, Paris, France

Background/Purpose: Population-based registries for vasculitides in Europe have provided robust estimates for granulomatosis with polyangitis (Wegener's) (GPA), microscopic polyangitis (MPA), polyarteritis nodosa (PAN) and Churg-Strauss (CSS) syndrome but none for Goodpasture's syndrome (GS) are known to us. Contemporary estimates for the United States have been lacking. Herein we report incidence and prevalence rates for all but CSS based on an administrative claims database.

Methods: The HIPPA-compliant Thomson-Reuters Marketscan Commercial Claims and Encounters and the Medicare Supplemental and COB databases contain information (in-and out-patient encounters, prescription drugs, other services) for approximately 86 million (2.1 years mean follow-up) insured employees and their dependents covered by employer-sponsored plans and for Medicare-eligible and employer-paid supplemental insured individuals. The study population was defined as all subjects ≥ 20 years old having medical information for the entire 12 months of 2007 (N=17.2 million individuals). Prevalent disease in 2008–09 was defined as having at least two visits ≥30 days apart with the occurrence of a relevant ICD9 code (GPA [446.4]; MPA [446.20, 446.29]; PAN [446.0] and GS [446.21]) prior to the end of 2009. Incident cases were required to have at least two visits ≥30 days apart within the 2008–2009 time frame and no occurrences prior to 2008. Incidence is expressed as cases per million person-years at risk and prevalence as cases per million individuals. CSS could not be studied because of the lack of a well-defined ICD9 code and the code for PAN potentially includes other vasculitis entities.

Results: Unadjusted incidence of GPA, MPA, PAN and GS were 15.6/million (95%CI: 14.2, 17.1), 13.4/million (95%CI: 12.1,.14.8), 6.9/million (95%CI: 6.1, 8.0) and 1.6/million person-years (95%CI: 1.2, 2.1) based on 472, 405, 209 and 48 cases, respectively, and 30.2 million person-years of observation. Age-standardized incidence rates were slightly lower for GPA (14.9/million) and MPA (12.2/million) but virtually unchanged for PAN and GS. Gender-specific rates were higher in females for all diseases except GS (female-to-male ratio: 0.68); the highest female preponderance was observed for MPA (female-to-male ratio: 2.43). Incidence peaked in the 8th decade for GPA (38.9/million), the 6th decade for MPA (18.1/million), and the 8th and 9th decades for PAN (21.1/million) and GS (5.1/million). The year 2008–2009 prevalence rates were 123/million (95%CI: 118, 128) for GPA, 78.3/million (95%CI: 74, 83) for MPA, 51.0/million (95%CI: 47.7, 54.7) for PAN and 8.8/million (95%CI: 7.5, 10.4) for GS; respectively, based on 2113, 1346, 876 and 152 cases.

Conclusion: The incidence and prevalence of GPA and MPA in this US claims database were in the upper range of those reported for European populations. These data lend further support to the concept that rates of GPA and MPA have continued to increase in recent years, perhaps due to increased diagnostic awareness. Findings for the PAN group need probably to be viewed as a combination of several vasculitic entities. To the best of our knowledge, this is the first estimate of the frequency of GS from a large population.

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Prevalence of ANCA Associated Vasculitis and Polyarteritis Nodosa in Southern Sweden-Revisited 2010. Aladdin Mohammad[1] and Mårten Segelmark[2]. [1]Skåne University Hospital, Lund, Sweden, [2]Linköping University, Linköping, Sweden

Background/Purpose: Epidemiological studies have reported increasing incidence and prevalence of ANCA Associated Vasculitis [AAV: Granulomatosis with Polyangiitis (Wegener's) (GPA), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS)] and polyarteritis nodosa (PAN) during the last two decades. In 2003 we found the highest prevalence ever reported (299/million)[1]. In the present investigation we have studied the development over the last 7 years.

Methods: The study area is a health care district in southern Sweden with a total population of 313,000 inhabitants (January 2010). Women made up 50.4% of the population. Patients with AAV and PAN who were living within the study area at the date of prevalence estimates were identified using hospital records (ICD-10) and a serology ANCA database. Diagnosis was verified by case records review. Patients were classified using the EMEA classification algorithm[2]. The date of point prevalence estimate was January, 1, 2010. The prevalence was calculated using the total number of patients fulfilled the study criteria as the numerator and the total population in the area as the denominator. The diagnosis delay was defined as time elapsed in months from the first possible symptoms of vasculitis to the date of diagnosis.

Results: Ninety-nine patients (48 female) with a median age of 67 years (range 21–90) fulfilled the study criteria and were alive at the date of point prevalence (Table 1). There were 51 patients with GPA; 38 with MPA; 6 with CSS and 4 with PAN. The point prevalence/million inhabitants was estimated to be 163 (95% confidence interval 118–208) for GPA, 121 (83–160) for MPA, 19 (4–34) for CSS, and 13 (0–25) for PAN. The prevalence was slightly higher in men than women (326 vs. 306/million).

Table 1.

	All n=99	GPA n=51	MPA n=38	CSS n=6	PAN n=4
Prevalence/million (95% CI)	316 (254–378)	163 (118–208)	121 (83–160)	19 (4–34)	13 (0–25)
Sex F/M	48/51	21/30	19/19	4/2	4/0
Age at diagnosis, median (range), yrs	57 (15–88)	55 (18–88)	60 (15–85)	60 (37–66)	60.5 (44–71)
Age at prevalence date, median (range), yrs	67 (21–90)	65 (21–89)	68 (33–90)	65 (52–70)	79 (63–83)
Time of follow-up, median (range), yrs	10 (0–43)	10 (0–26)	6 (0–43)	6.5 (2–16)	12 (8–34)
Diagnosis delay, median (range), months	3 (0–96)	3 (0–96)	2 (0–18)	3 (0.5–6)	5.5 (4–8)

Conclusion: The overall prevalence of AAV and PAN in southern Sweden is high (316/million) but has increased only marginally since the estimate in 2003 (299/million). For individual disease, the prevalence was stable for GPA and CSS, while decreasing for patients with PAN. However, the major difference was a 28% increases in the prevalence rate of MPA.

[1]Rheumatology (Oxford). 2007; 46 (8):1329–37
[2]Ann Rheum Dis. 2007;66:222–7

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Informed Consent for Treatment of ANCA-Associated Vasculitis. Raluca Cozmuta[1], Peter A. Merkel[2] and Liana Fraenkel[3]. [1]St. Vincent Medical Center, Bridgeport, CT, [2]Boston University School of Medicine, Boston, MA, [3]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT

Background/Purpose: Treatment for ANCA-associated vasculitis (AAV) now frequently involves a choice between rituximab and cyclophosphamide. The decision can be extremely difficult and informed consent discussions between physicians and patients should rely on clear and consistent communication of the risks and benefits associated with each treatment option. To date, there are insufficient data fully describing the magnitude of risks associated with each of these treatments and no guidelines describing what experts consider as important to disclose to their patients. The objective of this study was to obtain expert ratings of 1) the risks associated with available treatment options for AAV and 2) the importance of disclosing specific adverse events (AEs).

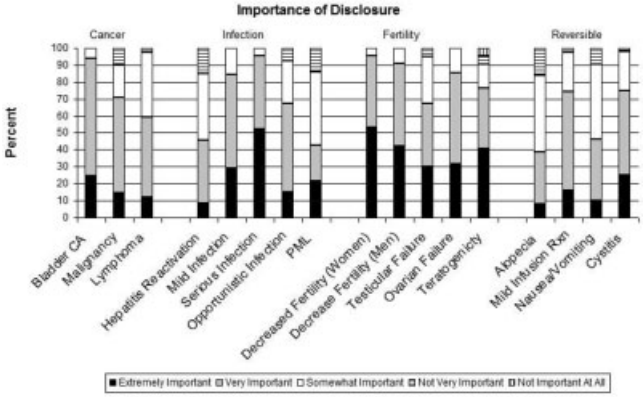
Methods: We created a web survey in which we asked vasculitis experts (defined as physicians whose practices focus on vasculitis and physicians engaged in research in vasculitis) to rate the magnitude of risk for a list of AEs using prespecified response options ranging from 50% risk to 0% risk for rituximab and IV cyclophosphamide. Respondents were also asked to rate the importance of disclosing each AE on a 5-point scale.

Results: The survey was emailed to 167 vasculitis experts. Of these, 145 were successfully delivered. The survey was opened by 94 subjects and completed by 50. 77% were male, 49% were rheumatologists, and 39% were nephrologists. 90% were attending physicians and 4% were trainees. 67% reported spending the majority of their time in clinical practice, 31% in clinical research and 2% in basic research. 71% worked in a University hospital setting. 24% were from the US and 61% were from Europe. 80% reported seeing more than 10 patients with AAV in the previous year, 12% saw between 6 and 10 patients, and 8% saw between 1 and 5 patients. Experts' ratings of the probabilities of specific AEs varied significantly and are provided in the Table. The importance of disclosing these AEs according to the surveyed experts is illustrated in the Figure. The majority (75% or greater) of the experts surveyed felt that it was very or extremely important to disclose half of the AEs listed.

Table. Experts' Rating of Risks Associated with IV Cyclophosphamide (CTX) and Rituximab (RTX)

	30%+		20%–25%		10%–15%		5%		1%		1 in 500		1 in 1,000		1 in 10,000		1 in 100,000		0 (no risk)	
Adverse Event	**CTX**	**RTX**	**CTX**	**RTX**	**CTX**	**RTX**	**CTX**	**RTX**	**CTX**	**RTX**	**CTX**	**RTX**	**CTX**	**RTX**	**CTX**	**RTX**	**CTX**	**RTX**	**CTX**	**RTX**
Cancer																				
Bladder Cancer	0%	0%	0%	0%	10%	2%	16%	0%	**37%**	0%	14%	6%	14%	2%	6%	10%	0%	10%	2%	**69%**
Malignancy (Other)	0%	0%	2%	0%	10%	5%	27%	8%	**32%**	**33%**	12%	15%	7%	10%	10%	10%	0%	8%	0%	13%
Lymphoma/Leukemia	2%	0%	0%	2%	5%	2%	5%	0%	**36%**	16%	26%	5%	17%	16%	10%	9%	0%	9%	0%	**40%**
Infection																				
Hepatitis Reactivation	2%	7%	9%	7%	17%	20%	17%	**20%**	**28%**	17%	9%	13%	9%	7%	4%	7%	2%	0%	2%	4%
Infections - Mild	31%	22%	**36%**	27%	25%	**29%**	9%	9%	0%	11%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%
Infections - Serious	2%	0%	11%	13%	**39%**	22%	30%	33%	15%	28%	2%	0%	0%	2%	0%	0%	0%	0%	0%	2%
Opportunistic Infection	2%	0%	0%	0%	21%	10%	**31%**	29%	26%	**41%**	14%	104%	5%	5%	0%	0%	0%	0%	0%	2%
PML	0%	0%	0%	0%	0%	2%	0%	0%	7%	12%	5%	9%	10%	16%	36%	**42%**	26%	16%	17%	2%
Fertility																				
Decreased Female Fertility	33%	0%	**29%**	0%	24%	2%	9%	0%	4%	9%	0%	9%	0%	4%	0%	0%	0%	4%	0%	**71%**
Decreased Male Fertility	20%	0%	13%	0%	**36%**	0%	13%	0%	16%	11%	2%	11%	0%	2%	0%	2%	0%	4%	0%	**69%**
Testicular Failure	3%	0%	13%	0%	13%	0%	23%	0%	**28%**	5%	18%	5%	0%	5%	5%	8%	0%	8%	0%	**70%**
Ovarian Failure	17%	0%	15%	0%	20%	0%	**24%**	0%	20%	10%	5%	8%	0%	0%	0%	5%	0%	8%	0%	**70%**
Teratogenicity	**37%**	0%	7%	0%	15%	5%	7%	11%	10%	21%	7%	8%	12%	11%	5%	16%	0%	5%	0%	**24%**
Reversible																				
Alopecia	**22%**	0%	12%	0%	24%	4%	18%	4%	16%	18%	8%	2%	0%	4%	0%	2%	0%	2%	0%	**63%**
Infusion Reaction	0%	11%	5%	16%	16%	**46%**	**36%**	18%	25%	5%	5%	0%	9%	2%	0%	0%	2%	0%	2%	2%
Nausea/Vomiting	**49%**	0%	15%	2%	22%	15%	7%	24%	7%	**27%**	0%	7%	0%	5%	0%	2%	0%	0%	0%	17%
Cystitis	2%	0%	0%	0%	17%	0%	15%	0%	**46%**	2%	15%	4%	4%	2%	0%	0%	0%	4%	2%	**88%**

Most frequent responses per AE are bolded for both medications.



Conclusion: Experts vary significantly in the magnitude of risk they assign to AEs associated with treatment options for AAV. Further efforts are needed to develop consistent risk communication strategies for patients with AAV. There is currently fair agreement, however, on which risks are very or extremely important to disclose to patients.

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Increased Prevalence of Metabolic Syndrome and Higher Serum Leptin Levels in Patients with Psoriatic Arthritis. Devy Zisman[1], S. Nissan[1], Lihi Eder[1], J. Feld[1], M.A Rahat[1], Muna Elias[1], D. Rimar[1], A. Laor[1] and H. Bitterman[2]. [1]Carmel Medical Center, Haifa, Israel, [2]Carmel Medical Center, The Ruth and Bruce Rappaport Faculty of Medicine Technion, Haifa, Israel

Background/Purpose: To evaluate the prevalence of metabolic syndrome (MeS) in patients with psoriatic arthritis (PsA) compared to the general population and to determine its association with clinical biomarkers of inflammation and serum levels of pro- and anti-atherogenic adipokines.

Methods: Patients with PsA from a rheumatology clinic who met the CASPAR criteria were compared to control subjects without psoriasis and inflammatory rheumatic diseases, all of who were followed in a community clinic. All patients were interviewed regarding demographic data, concomitant diseases, medical treatment, smoking, physical activity and alcohol consumption. Blood pressure, body mass index (BMI), waist circumference and disease activity parameters were measured. Laboratory evaluation included fasting blood glucose level and lipid profile. The presence of MeS was determined according to the definition of the International Diabetes Federation criteria. Serum adiponectin and leptin levels were analyzed in 32 individuals in each group by ELISA. Continuous variables were compared by t-test, and a Chi square test was used for comparing discrete variables. Multivariate regression models compared the association of MeS, leptin and adiponectin with PsA in comparison to controls, after adjusting for potential confounders.

Results: 74 patients with PsA (average age of 57.6 years) were compared to 82 controls. The groups were comparable with regard to age, gender, smoking status, alcohol consumption, and physical activity, as well as personal and family history of atherosclerotic heart disease, hypertension, diabetes mellitus and hyperlipidemia. BMI was higher in PsA patients compared to the control group (29.6 vs. 27.8, $p=0.04$).

The prevalence of MeS was higher in PsA patients compared to the control group (54.8% vs. 36.6%, $p=0.02$). The difference remained statistically significant after adjustment for age, gender, ethnicity and smoking status (Odds Ratio=2.33, 95% confidence interval 1.16–4.69). No association was found between the occurrence of MeS and parameters of articular disease activity, severity of skin manifestation or treatment (anti TNFα agents, classical Disease Modifying Anti Rheumatic Drugs, steroids and non-steroidal anti inflammatory agents).

Leptin levels and leptin/adiponectin ratio were higher in PsA patients compared to controls (83.4 ng/ml vs. 51.7 ng/ml, $p=0.001$ and 6.3×10^{-3} vs. 4.1×10^{-3}, $p=0.015$, respectively). These differences remained statistically significant after adjustment for age and gender.

Conclusion: A higher prevalence of MeS was found in patients with PsA compared to the general population, accompanied by an increase in plasma concentration of leptin, the pro-atherogenic factor and the leptin/adiponectin ratio, thus pointing to an increased risk of vascular morbidity in PsA patients.

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Quantifying the Harmful Effects of Psoriatic Diseases on Quality of Life Outcomes—COMPASS III Study. Deepan Dalal[1], Yih Chang Lin[1], Danielle Brennan[1], Katherine Wolski[1], Neil Borkar[2], Neil J. Korman[2], Diane Dylinski[1] and M. Elaine Husni[1]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]University Hospitals—Case Medical Center, Cleveland, OH

Background/Purpose: Up to 30% of patients with Psoriasis (PsO) may suffer from concurrent Psoriatic Arthritis (PsA). Both, PsO and PsA have worse Quality of Life (QoL) outcomes compared to the general population, however, there is limited literature comparing the QoL outcomes between these diseases. We seek to investigate the differences in QoL outcomes between these 2 groups and its treatment implications.

Methods: The current study is a cross-sectional analysis of a cohort of 252 patients with PsO and PsA, recruited from 2 tertiary care centers. A self-administered questionnaire was used to collect demographic and validated QoL data. QoL outcomes were measured as follow:

a. SF-12 (Physical Composite Score (PCS) and Mental Composite Score (MCS))

b. Health Assessment Questionnaire (HAQ)

c. Dermatology Life Quality Index (DLQI)

The PCS and MCS scores were expressed as Mean±SD and compared using Student's t-test. The HAQ (Disability Index DI) and DLQI scores were expressed as Median (Q1, Q3) and compared using a Wilcoxon rank-sum test. All analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC).

Results: Of the 252 (125 males, 49.6%) patients enrolled in the cohort, 107 (42.5%) had PsA. The groups were comparable with regards to gender distribution and co-morbid diseases (stroke, MI, PVD, diabetes and other cardiovascular diseases). As anticipated, PsO patients were younger compared to PsA patients (45.9±15.4 v. 50.8±12.7 yrs, p=0.02). Also, patients with PsO received biologic/DMARD treatment less frequently, compared to PsA patients (31.0% v. 75.6%).

The PCS was significantly worse in patients with PsA compared to Pso, whereas the MCS was significantly worse in patients with PsO. The Disability Index (DI) calculated by HAQ was significantly worse in patients with PsA and the DLQI was significantly worse in patients with PsO. [Table 1]

Quality of Life Outcome	Psoriatic Arthritis (N = 107)	Psoriasis (N = 145)	P-value
SF-12			
a. PCS (Mean ± SD)	41.7 ± 11.6	49.3 ± 10.3	<0.001
b. MCS (Mean ± SD)	49.6 ± 9.6	46.6 ± 12.2	0.043
HAQ (Median [Q1, Q3])	0.4 (0.0, 0.9)	0.0 (0.0, 0.1)	<0.001*
DLQI (Median [Q1, Q3])	3.0 (1.0, 9.0)	6.0 (3.0, 10.0)	0.009*

* non-parametric analysis

Conclusion: As expected PsA had worse PCS and HAQ compared to PsO. This was despite the fact that the PsA received aggressive treatment more frequently. However, PsO patients had worse MCS and DLQI compared to PsA despite a presumed lower inflammatory component of skin alone compared to skin and joint combined. This may be related to disparity in the treatments received. These results warrant aggressive treatment of the PsA patients for prevention of functional decline. The study also suggests early and more aggressive treatment of PsO patients to prevent decline in the mental health quality of life.

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Trends In Lipid Profiles In Patients with Psoriasis: A Population-Based Analysis. Bharath Manu Akkara Veetil, Eric L. Matteson, Hilal Maradit-Kremers, Marian T. McEvoy and Cynthia S. Crowson. Mayo Clinic, Rochester, MN

Background/Purpose: Psoriasis is associated with an atherogenic lipid profile but it is unknown how this profile is affected by the onset of psoriasis. We performed a population based cohort study to determine the effect of psoriasis onset on serum lipid profiles.

Methods: We compared changes in lipid profiles in a population based incident cohort of 689 patients with psoriasis diagnosed between 1988 and 2008 and 717 non-psoriasis comparator subjects. All lipid measures performed clinically during the 5 years before and 5 years after psoriasis incidence/index date were abstracted. Random-effects models adjusting for age, sex and calendar year were used to examine trends in lipid profiles, accounting for multiple measurements for each subject.

Results: There were significant declines in total cholesterol (TC) and low density lipoprotein (LDL) levels during the 5 years before and the 5 years after psoriasis incidence/index date in both the psoriasis and the non-psoriasis cohorts, with a greater decrease noted in the TC levels (p=0.022) and LDL (p=0.054) in the non psoriasis cohort. HDL levels increased significantly both before and after psoriasis incidence date in the psoriasis cohort, but there was no change in HDL during the 5 years before index date in the non-psoriasis cohort. Although the trends between the psoriasis and non psoriasis cohorts were the same, TG levels were significantly higher in psoriasis compared to non-psoriasis subjects (p<0.001), and HDL levels were significantly lower in patients with psoriasis compared to non-psoriasis subjects (−1.9 mg/dL; p=0.013). HDL levels increased significantly both before and after psoriasis incidence in the psoriasis cohort but no significant change was noted during the 5 years before index date in the non-psoriasis cohort. The proportion of psoriasis subjects with elevated lipids did not change during the 5 years before psoriasis incidence but there was a significant decrease in the proportion of subjects with abnormal TC and LDL in the non-psoriasis cohort during the corresponding time period (p<0.01). Lipid trends were otherwise similar in both cohorts during the 5 years after psoriasis incidence/index date. There were no differences in prescriptions for lipid lowering drugs between the two groups.

Conclusion: Patients with psoriasis had a significant decrease in TC and LDL levels during the 5 years before psoriasis incidence. Higher mean TG and lower mean HDL levels were noted in the 5 years before psoriasis incidence. These changes are unlikely to be caused by lipid lowering treatment alone and require further exploration, as early intervention may positively impact cardiovascular morbidity and mortality in this patient population.

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Cardiovascular Risk In Psoriasis: A Population Based Analysis with Assessment of the Framingham Risk Score. Bharath Manu Akkara Veetil, Eric L. Matteson, Hilal Maradit-Kremers, Marian T. McEvoy and Cynthia S. Crowson. Mayo Clinic, Rochester, MN

Background/Purpose: Patients with psoriasis have an increased prevalence of traditional cardiovascular risk factors and increased risk of cardiovascular (CV) mortality. Psoriasis itself may be an independent CV risk factor, perhaps related to the pro atherosclerotic effect of chronic inflammation. The utility of risk stratification tools such as the Framingham risk score (FRS) to stratify patients according to their 10-year risk for CV events, and identify those who would benefit from risk lowering measures, is unknown in these patients. We performed a population based cohort study to examine CV risk in psoriasis and examine the performance of the FRS in assessing this risk.

Methods: We compared the predicted 10 year risk of death or myocardial infarction (MI) using the FRS, based on sex, age, total cholesterol, high-density lipoprotein, blood pressure, smoking, and diabetes, to the observed coronary heart disease (CHD) risk in a population based cohort of patients with psoriasis diagnosed between 1998 and 2008. Observed follow-up was truncated at 10 years after psoriasis incidence. For patients with <10 years of follow-up, the predicted risk of CHD was adjusted proportionately. Poisson regression models were used to obtain the standardized incidence ratio (SIR), which is the ratio of the observed CHD in psoriasis to the predicted CHD obtained from the FRS.

Results: The study included 1309 patients with psoriasis aged ≥30 years without prior MI. 74% of patients had all CV data required to compute FRS. The rate of occurrence of CHD was similar in those with and without FRS (logrank p=0.07). Among patients with predicted risk scores, the median FRS was 3.8% while the actual observed 10 year risk of CHD was 5.5%. A total of 44 patients developed CHD during follow-up, and the FRS predicted 47.7 CHD events among these patients. The SIR between the observed and predicted CHD risk, was 0.90 (95% CI: 0.67, 1.22; p=0.50). The SIR was not elevated for women or for men. Among patients aged <65 years, there were no apparent differences between observed and predicted CHD risk (SIR: 0.79, 95% CI: 0.51, 1.21). The observed risk of CHD was not different from the predicted risk in patients aged ≥65 years (SIR: 1.05; 95% CI: 0.69, 1.59).There were no significant differences in the SIR based on use of systemic treatment, and no apparent differences in the CHD event rate in patients on systemic treatment compared to those without.

Conclusion: Beyond traditional risk factors, psoriasis does not appear to be an additional risk factor for CHD. The Framingham Risk Score reasonably estimates CHD risk in both men and women and all age groups in patients with psoriasis, and can be used in risk stratification and identification of those most likely to benefit from early interventions to diagnose and treat cardiovascular disease.

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Learned Helplessness Predicts 2-Year Change in Functional Disability in Patients with Inflammatory Polyarthritis. Elizabeth M. Camacho[1], Suzanne Verstappen[1], Diane K. Bunn[2] and Deborah DPM Symmons[1]. [1]University of Manchester, Manchester, United Kingdom, [2]University of East Anglia, Norwich, United Kingdom

Background/Purpose: Learned helplessness (LH) is an attributional style. In patients with inflammatory polyarthritis (IP), LH may manifest itself when an individual feels they cannot have a positive impact on their own prognosis and as a result may not take measures to help themselves, for example non-compliance with medication, potentially resulting in a poor disease outcome. It may be possible to influence disease outcome by addressing LH. We investigated the directional association between LH and subsequent functional disability, examined how LH changes over 2yrs, and identified factors associated with LH, in patients with recent-onset IP.

Methods: The Norfolk Arthritis Register (NOAR) is an inception cohort of patients with recent-onset IP.This analysis included 446 patients with baseline symptom duration of ≤2yrs, who joined NOAR during 2004–07, and had ≥2yrs of follow-up. The Health Assessment Questionnaire (HAQ) and Rheumatology Attitudes Index (RAI) were completed by all patients at baseline and 2yrs later. The RAI is a 5-item measure of learned helplessness, with possible scores as any integer between 5–25. LH was defined using total RAI score (top quartile = high, bottom quartile = low). The relationship between LH and subsequent disability (measured as 2-yr change in HAQ score from baseline), was analysed using linear regression adjusted for baseline HAQ score. The level of LH was said to have changed from baseline if total RAI score had increased or decreased by ≥5 points at 2 years. Multinomial logistic regression, adjusted for baseline RAI score was used to identify factors associated with change in RAI score (increase vs. no change; decrease vs. no change). All analyses were adjusted for age and sex.

Results: At baseline, 230 (52%) patients had normal, 97 (22%) had low, and 119 (27%) had high RAI scores. Compared to patients with normal RAI scores, those with high LH showed a significantly greater increase in HAQ score over 2yrs (mean difference (MD): 0.21; 95% CI 0.05, 0.36) and those with low LH showed a comparable change in HAQ score (MD: −0.09; 95% CI −0.24, 0.06). From baseline to year 2, LH decreased in 223 (50%) patients, increased in 165 (37%) patients, and did not change in 58 (13%) patients. Increasing age at symptom onset was significantly associated with lower baseline LH (β per decade: −0.6; 95% CI −0.9, −0.3) and an increased likelihood of a reduction in RAI score over 2yrs (relative risk ratio (RRR) per decade 1.3; 95% CI 1.0, 1.5). Compared to patients of the highest SES, those of the lowest SES had significantly higher baseline LH on average (MD: 1.8; 95% CI 0.3, 3.3). Increasing BMI was associated with increasing LH at baseline (β per unit: 0.1; 95% CI 0.04, 0.2), and a lower likelihood of a reduction in RAI score over 2yrs (RRR 0.9; 95% CI 0.8, 1.0). Patients who were autoantibody positive were significantly more likely to have worsened LH at 2yrs than autoantibody negative patients (RRR RF+ 2.5; 95% CI 1.4, 4.6; RRR ACPA+ 4.0; 95% CI 2.1, 7.6).

Conclusion: LH predicted change in disability. For the majority of people LH changed over 2 years, and hence it should be regarded as a modifiable risk factor for disease outcome in IP.

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Adverse Pregnancy Outcomes Before Symptom Onset Are Associated with a Worse Disease Outcome in Women with Recent-Onset Inflammatory Polyarthritis. Elizabeth M. Camacho[1], Suzanne Verstappen[1], Mark Lunt[1], Diane K. Bunn[2] and Deborah P.M. Symmons[3]. [1]University of Manchester, Manchester, United Kingdom, [2]University of East Anglia, Norwich, United Kingdom,[3]The University of Manchester, Manchester, United Kingdom

Background/Purpose: A number of studies have suggested that female reproductive factors, such as parity or menopause status, may impact upon a woman's likelihood of developing rheumatoid arthritis (RA), and her subsequent disease severity. For example, there is some evidence that women with a history of adverse pregnancy outcomes (APOs) may be at greater risk of developing RA. Our aim was to investigate the relationship between pre-onset APO history (spontaneous abortion or stillbirth) and disease outcome (functional disability and disease activity) over time, in women with inflammatory polyarthritis (IP), a term which includes RA.

Methods: The Norfolk Arthritis Register (NOAR) is a primary-care-based cohort of patients with recent-onset IP; 1647 gravid women joined NOAR between 1990–2004. 46 women with subsequent pregnancies during follow-up and 12 women who only had pregnancies resulting in induced abortions were excluded from this cohort; 1586 women were included in the analysis. APO history was patient-reported and those with any history of APOs before symptom onset were further categorised into overlapping groups with one or more (1+), two or more (2+), or three or more (3+) APOs. Functional disability was assessed using the Stanford Health Assessment Questionnaire (HAQ) and, for a sub-group of patients for whom the relevant data were available, disease activity scores ($DAS28_{CRP}$) were calculated. Linear random effects models were used to examine differences over time in HAQ and DAS28 score, by APO history, initially unadjusted, and then progressively adjusted for: (i) age at symptom onset and symptom duration; (ii) socio-economic status and smoking status; (iii) oral contraceptive use; (iv) comorbid conditions.

Results: 397 (25%) patients reported at least one APO before symptom onset; 125 (8%) women had 2+ APOs and 47 (3%) had 3+ APOs. The rates of APOs in NOAR were largely comparable to those in the general population of the United Kingdom. The median age at IP onset was significantly younger for women with a history of APOs than women with no APOs (52 vs. 55 years). Results from the maximally adjusted models showed that on average, women with a history of 2+ APOs had significantly higher HAQ and DAS28 scores over time than women with no APOs (mean difference: HAQ 0.13; 95% CI 0.002, 0.26; and DAS28 0.56; 95% CI 0.01, 1.11). This relationship was more pronounced, in women with 3+ APOs (mean difference: HAQ 0.23; 95% CI 0.02, 0.43; and DAS28 0.98; 95% CI 0.23, 1.74).

Conclusion: Women with APOs before IP-onset had greater functional disability and more active disease over time than women with no APOs. There was a dose response effect whereby an increasing number of APOs was associated with an increasing negative difference in HAQ and DAS28 score, when compared to women with no APOs.

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Pregnancy Outcomes In Women Exposed to Adalimumab: An Update On the Autoimmune Diseases In Pregnancy Project. Diana Johnson, Yunjun Luo, Kenneth Lyons Jones and Christina Chambers. University of California, San Diego, La Jolla, CA

Background/Purpose: The fully human, anti-tumor necrosis factor monoclonal antibody adalimumab (ADA) is approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), psoriasis, and juvenile idiopathic arthritis. The effect of ADA during pregnancy is unknown.

Methods: This report describes preliminary pregnancy outcomes from an ongoing study conducted by the Organization of Teratology Information Specialists (OTIS). In this prospective cohort, women treated with ADA for RA or CD during the first trimester of pregnancy are followed for 1-year postpartum. Outcomes are compared with a disease-matched group of women without ADA treatment during their pregnancies, and a control group of pregnant women who neither have an autoimmune disease nor have been treated with ADA. Additionally, OTIS collects information on ADA-exposed pregnancies that do not meet the cohort criteria, but are followed as a case series. These outcomes are presented separately as they have no comparison group.

Results: Between November 2004 and June 1, 2011, pregnancy outcomes have been collected on 161 women in the ADA-exposed cohort (60 RA, 101 CD); 79 women in the disease comparison group (68 RA, 11 CD), and 134 women in the healthy comparison group (Table 1). A total of 3.4% of women in the ADA-exposed RA group had a child with a major birth defect compared to 4.6% of women in the RA disease-matched group. A total of 14.1% of women in the ADA-exposed CD group had a child with a major birth defect compared to 10.0% in the CD disease-matched group. Major defects were reported in 4.1% of the healthy comparison pregnancies. The rate of spontaneous abortion in the ADA-exposed groups is 10.0% and 12.9% respectively compared to 4.4% and 9.1% in the disease comparison groups and 1.5% in the healthy comparison (Table 1).

Table 1. Pregnancy Outcomes of Women in the Cohort Study

Outcome	ADA-exposed RA (N=60)	ADA-exposed CD (N=101)	RA Disease Comparison (N=68)	CD Disease Comparison (N=11)	Healthy Comparison (N=134)
Live born–n (%)	53 (88.3)	85 (84.2)	62 (91.2)	9 (81.8)	120 (89.6)
Spontaneous Abortion - n (%)	6 (10.0)	13 (12.9)	3 (4.4)	1 (9.1)	2 (1.5)
Therapeutic Termination - n (%)	0	1 (1.0)	0	0	0
Stillbirth - n (%)	0	0	0	0	1 (0.7)
Lost to follow-up - n (%)	1 (1.7)	2 (2.0)	3 (4.4)	1 (9.1)	11 (8.2)
Preterm delivery - n (%)	7 (13.2)	17 (20.0)	11 (17.7)	1 (11.1)	6 (5.0)
Major Malformations - Live born infants - (%)	2/53 (3.8)	11/85 (12.9)	2/62 (3.2)	1/9 (11.1)	5/120 (4.2)
Major Malformations - All infants - (%)	2/59 (3.4)	14/99 (14.1)	3/65 (4.6)	1/10 (10.0)	5/123 (4.1)

Conclusion: Based on preliminary data, there is no evidence of an association between ADA exposure and major birth defects, or a specific pattern of malformation. It is difficult to draw conclusions regarding the ADA-exposed CD group without sufficient numbers in the CD disease comparison group. The proportion of pregnancies in the ADA-exposed cohort ending in spontaneous abortion is higher than the comparison groups; however, this difference may be due to earlier enrollment of ADA-exposed women, when the risk for miscarriage is highest. Formal comparisons with adjustments for confounders will be conducted when the target sample size has been achieved.

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Maternal Smoking and the Risk of Juvenile Idiopathic Arthritis. Susan Shenoi[1], Carol A. Wallace[1] and Beth A. Mueller[2]. [1]Seattle Children's Hospital, University of Washington, Seattle, WA, [2]University of Washington, Seattle, WA

Background/Purpose: Environmental factors that act as triggers in a genetically susceptible host are one of the current postulated etiologies of Juvenile Idiopathic Arthritis (JIA). To date in adult studies cigarette smoking is the only consistent environmental risk factor demonstrated to have a strong association for severe seropositive Rheumatoid arthritis. JIA is a heterogenous group of chronic childhood inflammatory arthritides specifically targeting the synovium of joints. Maternal prenatal smoking may have several effects on the fetus and child due to the placental transfer of various chemicals including nicotine in tobacco smoke.

Objectives: To determine the association between JIA and maternal prenatal smoking.

Methods: This Washington State population-based case-control study used ICD-9 codes from outpatient hospital and clinic records to identify 1518 children <20 years of age with a diagnosis of JIA from 1987–2010. Controls (n=6072) were randomly selected from birth records of children without JIA, frequency matched on year of birth. Maternal prenatal smoking exposure data was assessed from subjects' birth certificates. Stratified analysis was used to estimate odds ratios (OR) and 95% confidence intervals (CI). Parental and infant factors were considered for their possible effects on the relationship.

Results: Mothers of JIA cases (10%) were less likely to have smoked prenatally than mothers of controls (16%, OR 0.69, 95% CI: 0.56 – 0.85, adjusted for maternal age, race and Medicaid recipient status. This association appeared to be restricted to children of white women, and was most marked for those whose mothers smoked 5 or more cigarettes per day.

Conclusion: Our study demonstrates a protective association between maternal smoking and JIA and should by no means be taken as encouragement for women to smoke during pregnancy. The risks of maternal smoking on the fetus, child and mother overall far outweigh any potential benefits. This association should encourage evaluation of other environmental risk factors and may help elucidate potential biologic mechanisms of this disease. Currently the effects of maternal smoking on inflammatory diseases remains unclear and future studies with more sensitive and specific identification of JIA cases and disease categories, and improved ascertainment of smoking status, will further elucidate this association.

1876

Prevalence of Depression and Concomitant Risk Factors in Children with Rheumatic Disease. Stacey E. Tarvin[1], Nicole M. Taylor[2], Christine M. Raches[2], Lisa M. Macharoni[2], Joseph E. Hansel[2] and Susan H. Ballinger[1]. [1]Riley Hospital for Children, Indianapolis, IN, [2]University of Indianapolis, Indianapolis, IN

Background/Purpose: Rheumatic disease impacts children emotionally, socially and physically. Children who perceive that their medical condition interferes with an ability to engage in social, educational, and family activities report more depressive symptoms. The aim of this study is to examine the prevalence of depression in children with rheumatic disease and to identify concomitant risk factors for depression. It was hypothesized that, compared to healthy peers, children with rheumatic diseases may have a higher risk of developing depressive symptoms.

Methods: Children with a primary rheumatic disease, ages 8–17 years, completed the Children's Depression Inventory (CDI) and parent-child pairs completed standardized measures documenting demographics, daily functioning (Childhood Health Assessment Questionnaire), pain (VAS), health-related quality of life (PedsQL Rheumatology module), and psychosocial variables (Family Environment Scale, Child Behavior Checklist, Youth Self Report). The primary rheumatologist documented a global assessment of disease severity (VAS) and disease activity for children with the diagnosis of juvenile idiopathic arthritis (active joint count and VAS), juvenile dermatomyositis (DAS), and systemic lupus erythematosus (SLEDAI). Children with primary pain disorders were excluded. Prevalence of depression was compared with the general child and adolescent population. Appropriate parametric statistics were completed to determine statistical significance of demographic variables. Pearson product moment correlations were run to determine relationships between depression, pain, quality of life, family conflict, physical functioning and disease severity. Hierarchal multiple regression analyses were run to determine which medical and psychosocial variables were significant predictors of depression, while controlling for demographic variables.

Results: One hundred eighteen patients were screened (80% female). Four percent of the population had clinically significant symptoms of depression while another 15% of the population was found to be "at risk" for symptoms of depression. Female gender ($p<.01$), usage of medication for depression ($p<.01$), and therapy for depression ($p<.05$) were the demographic variables that correlated with increased CDI scores and thus symptoms of depression. After controlling for demographic variables, total CDI score significantly correlated (adjusted $R^2 = .508$, $p<.01$) with child report of decreased quality of life and child perception of poor rule use and poor planning within the family. Years since diagnosis, disease specific activity scores, and physician global assessment did not correlate with increased CDI scores.

Conclusion: The prevalence and risk of depression among children with rheumatic diseases is comparable to previously reported data for a healthy population of children. Risk factors for depression are related to quality of life and family characteristics. Disease specific factors did not correlate with increased depressive symptoms.

1877

Disease Modifying Anti-Rheumatic Drugs Compliance Study. Kateryna Vostretsova[1], Pam Rogers[1], Darby JS Thompson[2] and Diane Lacaille[3]. [1]Arthritis Research Centre, Vancouver, BC, [2]Simon Fraser University, Vancouver, BC, [3]Arthritis Research Centre; University of British Columbia, Vancouver, BC

Background/Purpose: The efficacy of DMARDs for Rheumatoid Arthritis (RA) is well established; however, poor compliance may limit the effectiveness of DMARDs. People often have difficulty taking medications regularly, are often reluctant to take medications, or might experience side-effects, all of which can affect compliance. Few studies have evaluated compliance with DMARDs in RA. Reported compliance ranges from 58% to 91% with wide variation in how compliance is measured and defined. The purpose of this study was to evaluate compliance with DMARDs in RA. Specific objectives were to: 1) measure the degree of compliance with DMARDs in RA; 2) understand reasons for non-compliance; and 3) identify determinants of compliance.

Methods: We performed a cross sectional survey study. Participants were recruited from a random sample of 600 RA patients who had attended the Mary Pack outpatient arthritis treatment program which provides outpatient multidisciplinary arthritis services across the province. Eligibility criteria included having an MD diagnosis of RA, having

taken a DMARD in the preceding 6 months and ability to complete a questionnaire in English. Level of compliance was assessed using the Medication Adherence Report Scale (MARS) and reasons for non-compliance using the Adherence Questionnaire of Adult AIDS Clinical Trials Group (AACTG) adapted for arthritis. Determinants of adherence were assessed, using validated instruments where available, including RA measures (pain, HAQ, disease activity (VAS and RADAI), general health, co-morbidities, medications, private insurance, self-efficacy, social support, depression and satisfaction with health care.

Results: A total of 192 completed the questionnaire (74 ineligible or deaths, 37% participation rate) with 80% female, mean (SD) age 61.9 (14) years, RA duration 13.2 (11.5) years. Many were on combination therapy (70%), 39% were on biologics and 69% on Methotrexate. The mean (SD) score for MARS was 38.00(3.97), which indicates good adherence. Most frequent non-adherent behaviours were forgetting to take their DMARDs (55%), altering the dose (33%), deciding to skip a dose (29%), taking less than instructed (27%) and stopping for a while (22%). However these behaviours were mostly reported as infrequent (rarely or sometimes). Results from the AACTG demonstrated that forgetting, life events (i.e. being busy or away) and side-effects were the most common reasons for non-adherence. People used most frequently visual reminders and pill organizers as strategies to help adherence. Regression analyses using a Generalized Linear Model with Weibull distribution of MARS scores revealed that people who were younger, had longer disease duration, higher disease activity (VAS), worse physical function (HAQ), and those who experienced side-effects were less compliant.

Conclusion: Our results suggest that the overall level of compliance with DMARDs was good in this sample. Our findings are useful to clinicians to identify people at higher risk of non-compliance (younger people with early disease who are not doing well) in whom more time could be spent evaluating compliance to therapy and discussing underlying reasons for non-compliance.

1878

Improving the Assessment of Minimal Important Change by Combining Health State Transition Questions with Patient Acceptable Symptom State and Patient Willingness to Alter Therapy. Jos Hendrikx, Jaap Fransen, Wietske Kievit and Piet LC van Riel. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: The minimal important change (MIC) is the smallest change in a health related outcome measure which is perceived as important, and in the absence of side effects and excessive cost, would mandate a change in the patient's management. Transition questions used for the assessment of MIC ask for the amount of past health change. However, transition questions do not incorporate the importance of the health status reached nor a therapeutic consequence. Therefore, this study explored if combining the concepts of patient acceptable symptom state (PASS) and patient willingness to alter therapy (PatWAT) could improve methods for the assessment of MIC.

Methods: All rheumatoid arthritis patients visiting the outpatient clinic from December 2010 to June 2011 were given a questionnaire containing questions to measure health state transition, PASS and PatWAT. Trained research nurses measured the Disease Activity Score 28 (DAS28) during each outpatient visit. MIC was ascertained in the standard way by exploring the distributions of the actual DAS28 change in three transition categories: improved, unchanged and deteriorated. This was compared with a new classification system, based on the 3 health transition categories x 2 PASS subclasses x 4 PatWAT subclasses. The resulting 24 sub-categories were used to re-classify patients as either improved, unchanged or deteriorated in a manner reflecting the definition of MIC. The standard and new method for MIC assessment were compared using the area under the Receiver Operating Curve (ROC).

Results: In total data of 257 patients with at least two DAS28 measurements were available for analysis. Mean age was 59 years, 64.6% female, 73.3% rheumatoid factor positive, mean disease duration was 11 years and mean DAS28 score was 3.16. Of these patients 23.8% reported improvement, 43% no change, and 25% deterioration in health state as compared to their prior visit. The vast overlap in DAS28 change distributions when applying standard MIC assessment methods is shown in figure 1. When applying standard methodology to assess MIC the ROC had an area under the curve (AUC) of 0.64 for improvement in health and 0.74 for deterioration. 8% of the patients were re-categorized using the new strategy of combining the transition questions with PASS and PatWAT into a new classification scheme. The AUC for this method of MIC assessment was 0.65 for improvement and 0.76 for deterioration.

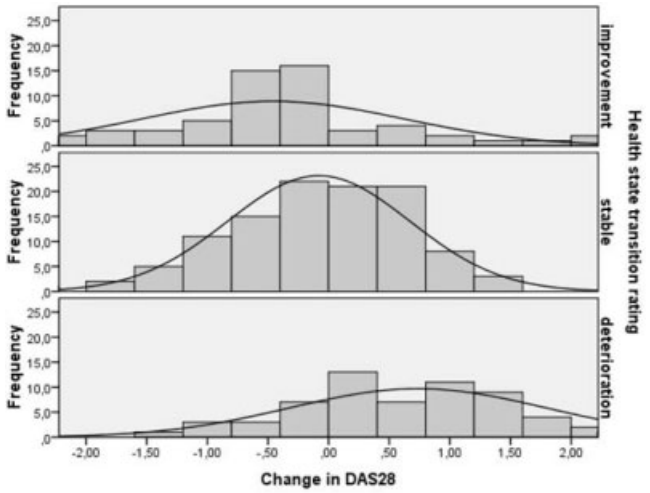


Figure 1. Distribution of DAS28 change scores according to health state transition ratings

Conclusion: The results show extensive heterogeneity in the perception of importance of change, which was minimally reduced with a new classification method that better reflected to concept of MIC. Apparently valuing health change is a highly individually determined process, expressing the need for innovative patient specific assessment methods that do more justice to each patient's unique disease course and resulting perspective on change.

1879

The Accuracy of Identifying Kidney Disease in Administrative Databases for Rheumatic Disease Research—A Systematic Review of Validation Studies. Bindee Kuriya[1], Ziv Harel[2] and Diane Lacaille[3]. [1]University of Toronto, Toronto, ON, [2]Division of Nehprology, University of Toronto, Toronto, [3]Arthritis Research Ctr Canada, Vancouver, BC

Background/Purpose: Administrative health care databases are an important resource to study the epidemiology of rheumatic diseases, their outcomes, and associated conditions. Among these, kidney disease is a frequent co-morbidity in people with rheumatic diseases and accurate classification of individuals with kidney disease is important for the control of confounding in risk models. Our objective was to assess the validity of identifying kidney disease in administrative health care data.

Methods: We conducted a systematic review of observational studies validating the accuracy of diagnostic and procedural codes for acute kidney injury (AKI), chronic kidney disease (CKD), and kidney disease requiring dialysis in administrative health care databases. Medline and Embase were searched for full length articles in English or French language from 1950 to November 2010. A hand search of eligible articles was done to identify additional relevant studies. All abstracts and articles were reviewed independently by 2 reviewers. The type of database, source population, index and reference standards used, and measures of diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) were recorded. Quality of the articles was assessed using a newly developed tool for validation studies using administrative data.

Results: 23 studies among 17 databases in 5 countries were included for review. The diagnostic performance of administrative coding for AKI was reported in 7 studies, for dialysis in 4 studies, and validation of CKD in 16 studies. The number and type of diagnostic and procedural codes, and the ascertainment periods varied widely. The reference standards used were less variable and included documentation of kidney disease in the medical record or laboratory values of serum creatinine. Sensitivity for AKI and CKD varied widely (ranging from 3% to 83%) and was highest in study samples with underlying coronary artery disease. Sensitivity for procedure codes for dialysis ranged from 33% to 100%. No validation was performed exclusively among patients with rheumatic disease. Specificity and negative predictive values were uniformly high for all 3 conditions (range 88%–100% and 72%–100%). Positive predictive values were less consistent in AKI (15%–100%) and CKD (39%–100%) but higher in the validation of kidney disease requiring dialysis (84%–100%).

Conclusion: The existing literature demonstrates variable accuracy of diagnostic and procedure-based codes to identify kidney disease using administrative data. Sensitivity was generally poor for non-dialysis requiring

AKI and CKD, which would lead to an underestimation of true AKI and CKD but may be acceptable to identify kidney disease requiring dialysis. The variable PPV of codes especially for AKI and CKD put analyses using these codes at risk of misclassification. Researchers wishing to control for kidney disease in rheumatic disease research must take these findings into consideration to avoid bias arising from poor code validity.

1880

A Systematic Review of Validation Studies of Administrative Data Used to Identify Infections. Claire Barber[1], Diane V. Lacaille[2], Joan E. Wither[3] and Paul R. Fortin[4]. [1]Mount Sinai Hospital, Toronto, ON, [2]Arthritis Research Ctr Canada, Vancouver, BC, [3]Toronto Western Research Institute, University Health Network, Toronto, ON, [4]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: To conduct the first systematic review of the literature on the validation of algorithms identifying infections in administrative data for use in studies evaluating infections as either outcomes or covariates in population-based studies of rheumatic diseases.

Methods: Medline and Embase were searched using the terms "administrative data", infection", "outcomes", and "validation" between 1950 to November 2010. All abstracts were reviewed independently by 2 reviewers (CB & PF). A hand search of all articles reviewed was done to identify any other relevant work. Inclusion criteria: validation studies of administrative data in adult populations, and serious infections resulting in hospitalization or opportunistic infections. Exclusion criteria: language other than English or French and articles on HIV/AIDS. The quality of the articles was assessed using a validated tool (Benchimol et al. 2010).

Results: 106 articles were identified after exclusion of duplicates and 52 were excluded by title or abstract, 54 articles were included for detailed review and only 2 met our criteria for entry. A hand search identified a further 6 articles for a total of 8 studies suitable for inclusion: the majority (7/8) examined bacterial infections and 2 examined opportunistic infections. The majority of the studies were from the United States (6/8) and all but one study used ICD-9 codes (1/8 used ICD-10 codes). Six of the studies were of patients who were hospitalized, one included emergency visits and one study on opportunistic infections did have some outpatient data. In 3/8 papers the population studied was that of patients with rheumatoid arthritis. Only one of the studies on opportunistic infections reported the positive-predictive values (PPV) which was 58% (0.46–0.70), and increased to 73% (0.61–0.85) if candida infections were excluded. The studies on bacterial infections in general reported a moderate to high sensitivity and PPV for the diagnosis of infections using administrative data (sensitivity range 69.8–100%, PPV range 80.0–97.2%). Only 3/8 studies compared the diagnostic accuracy of different algorithms which revealed that more comprehensive algorithms that included a wider range of ICD-9 codes had the highest sensitivity for the diagnosis of infection.

Conclusion: Validated algorithms for the identification of infections using administrative data have a moderate to high sensitivity and positive predictive value and can be applied to population studies of patients with rheumatic disease to study this important co-morbidity.

1881

Consensus Statements Concerning the Use of Administrative Data in Rheumatology Research and Surveillance. Diane Lacaille[1], Lisa Lix[2], Sasha Bernatsky[3], Siobhan O'Donnell[4], Claire Bombardier[5] and Administrative Data Rheumatology Research & Surveillance. [1]Arthritis Research Ctr; University of British Columbia, Vancouver, BC, [2]University of Saskatchewan, Saskatoon, SK, [3]McGill UHC/RVH, Montreal, QC, [4]Public Health Agency of Canada, Ottawa, ON, [5]Institute for Work & Health, Toronto, ON

Background/Purpose: Administrative health databases (for remuneration & management) exist in each province & territory in Canada. They are a great resource for rheumatic disease surveillance & research, but standards are needed to ensure comparability of findings. Our purpose was to develop consensus statements in this regard.

Methods: We convened 52 decision makers, clinicians, & researchers to a 2-day workshop. Eight months in advance, participants were organized into working groups covering 3 themes: case definitions, methods, & co-morbidity/outcomes. Each conducted systematic & scoping reviews to define themes. At the workshop, Delphi-type consensus building techniques were used to develop statements for endorsement.

Results: 13 consensus statements were endorsed. Regarding case definitions for rheumatic diseases, these should be justified based on purpose, validity assessment, & feasibility; validation studies should adhere to published guidelines on conduct & reporting; and authors should acknowledge limitations of administrative data for case ascertainment

Regarding methods, authors must address confounding by indication; use appropriate methods to address other common confounders & biases; clearly define & justify exposure risk windows: and acknowledge limitations of administrative data.

For comorbidity/outcomes, our statements note that osteoporosis diagnostic codes should not be used alone due to low sensitivity. Hospital discharge data, & physician & procedure data when available, can be used to accurately identify hip fractures. Fractures not requiring hospitalization can be identified by combining physician billing diagnoses & procedure codes. For vertebral fractures, additional research is needed.

Regarding using administrative data (exclusive of cancer registries) to define cancer outcomes, authors should use an algorithm with good sensitivity & excellent specificity in a comparable population. Implications of imperfect case definition should be discussed.

Hospitalization diagnoses can be used to ascertain serious bacterial infections. Current data is not sufficient to recommend administrative data to identify opportunistic infections.

For cardiovascular disease, hospitalization data can be used to ascertain acute myocardial infarction, but there are significant limitations for congestive heart failure.

Regarding renal disease, administrative data can be used to identify kidney disease requiring dialysis. However, current data do not support using hospitalization data for acute or chronic kidney disease as a co-morbidity or outcome.

Conclusion: Our recommendations are consistent with other recent guidelines including the ISPOR report and the EULAR Points paper to address specific needs of rheumatic disease biologics registries. Our consensus statements include other issues as well, and some Canada-specific details. Their usefulness and implications for surveillance and research extends beyond Canada's borders.

Dissemination is in progress; for background documents see our current website archive https://connect.mcgill.ca/r41824168/

1882

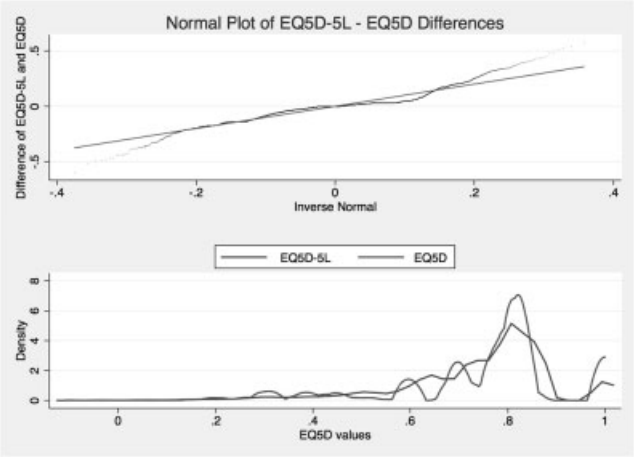
An Evaluation of the Extended Item Euroqol Compared with the Standard Euroqol. Kaleb Michaud[1] and Frederick Wolfe[2]. [1]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE, [2]National Data Bank for Rheumatic Diseases, Wichita, KS

Background/Purpose: The EuroQoL (EQ5D) is a widely used health-related quality of life utility scale that is frequently used in cost-effectiveness analyses. It is composed of 5 questions, 3 relating to function, 1 to pain, and 1 to mood. The EQ5D is limited because each question has only 3 levels: the worst possible condition, the best possible condition, and a single level in between. Since the worst level is rarely endorsed, each question effectively has two levels: perfectly normal or not perfectly normal. The limited range also results in a reduced sensitivity to change. The EuroQol Group recently developed a new scale (EQ5D-5L) in which each question contains 5 levels, thereby potentially increasing sensitivity and capturing a wider range of symptoms. A central question regarding the 2 scales is whether they yield similar results, and whether the new questionnaire has better performance characteristics.

Methods: We administered the EQ5D, EQ5D-5L and other rheumatic disease questions to 6,824 patients as part of a semi-annual long-term rheumatic disease outcome study.

Results: The Pearson correlation between the EQ5D questionnaires was 0.827, and Lin's concordance coefficient was 0.817. The average difference between questionnaires was 0.008, and the 95% limits of agreement was −0.206 to 0.190. The EQ5D-5L had a smoother and more continuous distribution, but questionnaires differed most at extreme values (Figure 1). The EQ5D-5L was more strongly correlated with all measures than the EQ5D (Table 1), and the EQ5D-5L provided a much better model fit as assessed by the Bayesian and Akaike Information coefficients. The EQ5D-5L/EQ5D mean (SD) values were: rheumatoid arthritis 0.751/0.761 (0.152/0.176), lupus 0.754/0.765 (0.172/0.189), fibromyalgia 0.666/0.666 (0.167/0.196) and osteoarthritis 0.745/0.751 (0.139/0.165). As suggested by Figure 1, the EQ5D has slightly higher scores compared to the EQ5D-5L in illnesses with better quality of life and equivalent scores in lower QOL disorders such as fibromyalgia.

Questionnaire	EQ5D-5L	EQ5D
EQ5D-L (0–1)	1.000	0.827
EQ5D (0–1)	0.827	1.000
Patient activity score (PAS) (0–10)	−0.781	−0.755
HAQ (0–3)	−0.709	−0.666
Global severity (0–10)	−0.673	−0.650
Pain (0–10)	−0.669	−0.665
Physical component score (SF–36)	0.665	0.629
Polysymptomatic distress scale	−0.648	−0.626
Fatigue (0–10)	−0.604	−0.576
Mood (0–10)	−0.525	−0.511
Sleep disturbance (0–10)	−0.494	−0.472
Mental component score (SF–36)	0.490	0.480
EuroQoL VAS (0–100)	0.484	0.456
Comorbidity Index (0–9)	−0.327	−0.309
Sex	0.067	0.050
Age (years)	0.061	0.039



Conclusion: The EuroQol scales provide similar mean scores and are well correlated. The EQ5D-5L provides a much better model fit, lower variance and greater correlation with clinical variables. The EQ5D-5L should be substituted for the older EQ5D version to provide a better assessment of health utility.

1883

Increased Ability to Meet Occupational, Home or Leisure Requirements in Patients Starting Biologic Agents. Anja Strangfeld[1], Diana Pantigoso[1], Peter Herzer[2], Hans Peter Tony[3], Elke Wilden[4], Joachim Listing[1] and Angela Zink[5]. [1]Deutsches Rheumaforschungszentrum, Berlin, Germany, [2]University of Munich, Munich, Germany, [3]Rheumatology, University of Würzburg, Würzburg, Germany, [4]Rheumatologist, Köln, Germany, [5]Deutsches Rheumaforschungszentrum and Charité University Medicine, Berlin, Germany

Background/Purpose: During the course of disease, many patients with rheumatoid arthritis (RA) become increasingly unable to fulfill their daily life tasks. For employed patients, this is reflected in the number of days of sick leave or early retirement. For patients not employed it is less clear. Our objective was to evaluate the impact of functional disability on limitations in role fulfillment in both, employed and unemployed patients. Further we were interested in the improvement with the start of a biologic or non-biologic DMARD treatment.

Methods: Data from the German biologics register RABBIT with more than 9,550 patients included until June 2011. Enrolment in the cohort is possible with a start of a biologic treatment (BIOL) or a start with a conventional DMARD (CON) after DMARD failure. Among other information, patients assess their ability to meet usual occupational, home or leisure demands during the last four weeks. The propensity score method was used to adjust for differences in the baseline status between BIOL and CON patients. The outcome after 6 months was compared between the treatment groups within propensity score strata after adjustment for further differences in the baseline status by means of multiple logistic regression.

Results: 6,160 patients had at least 6 months of follow-up and were included in the analysis. Before enrolment more than a quarter of patients starting a biologic treatment and 17% in the control group had not been able to fulfill their daily role activities on more than 14 days within the last 4 weeks (Table).

Table. Percentage of patients not able to meet their daily demands before and after inclusion in the register/start of a new treatment (CON conventional DMARDs, RTX rituximab, ABA abatacept, TOC tocilizumab)

"On how many days during the last four weeks have you been unable to meet your usual occupational, home or leisure demands due to your rheumatoid arthritis?"	CON	Anti-TNF	RTX	ABA	TOC
> 14 days					
Before start of new treatment	17.3%	26.4%	28.1%	26.5%	33.1%
After 6 months	9.0%	11.0%	15.2%	16.5%	17.4%
7 to 14 days					
Before start of new treatment	22.9%	25.8%	27.0%	27.7%	23.1%
After 6 months	15.5%	15.5%	18.9%	20.6%	16.5%
On no day					
Before start of new treatment	29.0%	20.6%	17.2%	12.4%	18.2%
After 6 months	45.5%	42.2%	31.1%	19.4%	34.7%
Sum of patients included	1934	3224	711	170	121

All treatments increased the ability to meet occupational, home or leisure demands. Significant risk factors to remain limited in fulfilling daily activities after 6 months were higher number of days with limitations in activities, fatigue, comorbidities, and previous failure of a biologic treatment. Adjusted for these factors, the improvement was significantly higher for anti-TNF treatment compared to conventional DMARD treatment (adjusted odds ratio for >=7 days of being unable to meet requirements: 0.82 or for >=1 day: 0.75). Patients treated with other biologics who had longer disease duration and more previous treatment failures (including biologics) did not show significant differences from the patients in the control group.

Conclusion: Real-world patients who start treatment with biologic agents have significant constraints in fulfilling their daily role requirements. After six months, there is considerably less limitation, especially in those patients who receive their first biologic agent.

1884

Distribution of Tumor Necrosis Factor Inhibitor Use Across Indications in Sweden: Nationwide Register-Linkage Study. Martin Neovius[1], Jonas Eriksson[1], Julia F. Simard[1], Johan Askling[1] and ARTIS Study Group[2]. [1]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Stockholm, Sweden

Background/Purpose: Despite widening use of anti-TNF drugs, most long-term safety data come from patients with rheumatoid arthritis (RA). Similarly, most assessments of the societal benefits and costs of anti-TNF drugs are based on presumed distribution across indications. Few large studies have investigated the distribution of use across indications to determine which patients are actually using these drugs today. We estimated this distribution across indications using data from national registers.

Methods: All individuals in Sweden who were dispensed etanercept and adalimumab in 2009 were identified from the nationwide Prescribed Drug Register. Infliximab was excluded as it is primarily used in hospitals, not on prescription in ambulatory care, and therefore not registered on a patient level. The dataset was linked to the National Patient Register, which holds information on all inpatient and specialist outpatient visits, including associated main and subdiagnoses. On the basis of visit diagnoses in 2001–2009, patients were identified as having RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis and/or inflammatory bowel disease (IBD).

Results: 12,142 unique patients exposed to etanercept (n=7,261) or adalimumab (n=5,402) were identified. The highest proportion of users had RA (59%), followed by PsA (17%), IBD (12%), other (10%), AS (10%), and psoriasis (7%). Rheumatic indications (RA, AS and PsA) constituted 77% of overall use. The distribution differed markedly for etanercept and adalimumab: only 2% of etanercept users had IBD compared to 24% of adalimumab users (Table).

Distribution of Etanercept and Adalimumab Use in the Swedish Population in 2009

Indication	N (%) Both (n=12,142)	Etanercept (n=7,261)	Adalimumab (n=5,402)
Rheumatology	9,375 (77%)	6,082 (84%)	3,722 (69%)
Rheumatoid Arthritis	*7,132 (59%)*	*4,763 (66%)*	*2,676 (50%)*
Ankylosing Spondylitis	*1,202 (10%)*	*625 (9%)*	*635 (12%)*
Psoriatic Arthritis	*2,039 (17%)*	*1,318 (18%)*	*852 (16%)*
Dermatology			
Psoriasis (excl PsA)	686 (7%)	473 (8%)	251 (6%)
Gastroenterology			
Inflammatory bowel disease	1,435 (12%)	179 (2%)	1,286 (24%)
Juveniles and/or Other Conditions	1,212 (10%)	819 (11%)	449 (8%)

Diagnostic categories not mutually exclusive. Therefore column percentage sums may exceed 100% due to overlap, i.e. patients having more than one diagnosis.

Conclusion: While long-term safety data are dominated by studies on patients with RA, RA accounted for only about half of anti-TNF users in Sweden in 2009. This surprisingly low proportion underscores the need for safety, cost and effectiveness studies in patients with diseases other than RA, especially as some of these patient groups display very different age-, sex-, and birth cohort-distributions, as well as dosing regimen.

1885

Cross-Sectional Validation of the Patient Reported Outcome Measurement Information System Pediatric Scales in Juvenile Idiopathic Arthritis, Childhood Systemic Lupus Erythematosus, and Juvenile Dermatomyositis. Esi Morgan DeWitt[1], Heather Gross[2], Brian D. Stucky[3], Yang Liu[3], David Thissen[3], Daniel J. Lovell[1], Carol A. Wallace[4], James F. Fries[5], Bonnie Bruce[6], Egla C. Rabinovich[7], Laura E. Schanberg[7] and Darren Dewalt[2]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina at Chapel Hill, Chapel Hill, [4]Childrens Hosp & Regional Med, Seattle, WA, [5]Stanford Univ Medical Center, Palo Alto, CA, [6]Stanford Dept of Medicine, Palo Alto, CA, [7]Duke University Medical Center, Durham, NC

Background/Purpose: The Patient Reported Outcome Measurement Information System (PROMIS) was created to develop patient-reported outcome measures using modern psychometric methods, including item response theory, to improve the assessment of self-reported health across many chronic diseases. PROMIS tools are publicly available (nihpromis.org). Our objective was to perform preliminary validation of PROMIS version 1.0 (v1.0) scales for pediatrics (8–17 years) in the more common childhood rheumatic diseases. PROMIS item banks and short forms were developed and initially validated in a sample of 4,129 children, 35% of whom had a chronic illness. This sample's overall mean HRQOL score of 74.5 on the PedsQL™ was lower than the mean of 83.8 for a healthy reference population. Pediatric PROMIS v1.0 scale scores were placed on a T-score metric such that the mean is 50, and standard deviation 10.

Methods: Participants with a physician confirmed diagnosis of juvenile idiopathic arthritis (JIA), childhood systemic lupus erythematosus (cSLE) or juvenile dermatomyositis (JDM) were recruited from rheumatology clinics. Participants were administered a combination of PROMIS short forms and/or complete item banks representing the following health domains: anger, anxiety, depressive symptoms, fatigue, pain interference, peer relationships, physical function – mobility, physical function – upper extremity. Demographics, clinical characteristics, and parental ratings of children's overall disease status and pain intensity were collected. Data were analyzed with descriptive statistics, correlations, ANOVA, and graphical display.

Results: 362 (JIA=269, SLE = 42, JDM = 23, overlap =28) participants were recruited from sites in California, North Carolina, Ohio, and Washington. Across the diagnostic categories, mean scores on parental ratings of overall well-being (0=very well, 10=very poor) were between1.28 (sd 2.43) −1.76 (sd 1.99), mean ratings of average pain over the past 7 days (0=no pain, 10=very bad pain) were between 1.04 (sd 2.12) −2.32 (sd 2.45), and the mean CHAQ score (0–3, 0=no disability) was 0.2475 (sd 0.44). Group mean scores were similar to the initial PROMIS v1.0 validation sample, or slightly better. There were no significant differences in scores across diagnostic groups, although scores of cSLE patients were numerically worse. Parental ratings had relative strong correlations with PROMIS fatigue, mobility and pain interference domains (Table). Compared to boys, girls demonstrated higher anxiety and depressive symptoms. School days missed correlated with higher fatigue and pain interference, and decreased mobility. The PROMIS mobility bank showed a modest decrease in ceiling effect compared to the CHAQ.

Table. Correlations between Child Outcomes and Parent Ratings

	Depressive Symptoms	Anxiety	Anger	Peer Relationships	Pain Interference	Fatigue	Dexterity	Mobility	CHAQ
Parent Rating of Pain	.310**	.326**	.405**	−.124	.559**	.448**	−.305**	−.463**	.325**
Parent Rating of how child is doing	.375**	.233*	.196	−.128	.519**	.435**	−.317**	−.435**	.293**

** Significant at .01, *Significant at .05; Parent Rating of Pain; 0 = No Pain; 10 = Very Bad Pain. Parent Rating of How Child is Doing: 0 = Very Well; 10 = Very Poor

Conclusion: The PROMIS v1.0 pediatric scales have undergone preliminary validation for use in JIA, cSLE and JDM and are ready for use.Longitudinal validation studies are underway.

1886

Assesment of Disease Activity in Ankylosing Spondylitis: Comparison of Rapid3, Basdai, Basfi, and Asdas Scores in Routine Care. Muhammet Cinar[1], Sedat Yilmaz[1], Suleyman Serdar Koca[2], Hakan Erdem[1], Salih Pay[1], Yusuf Yazici[3] and Ismail Simsek[1]. [1]Division of Rheumatology, Gulhane School of Medicine, Ankara, Turkey, [2]Department of Rheumatology, Faculty of Medicine, Firat University, Elazig, Turkey, [3]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Quantitative assessment of disease outcome in ankylosing spondylitis (AS), as in all other rheumatological conditions, has been a major concern in rheumatology practice. There have been different methods validated and used for monitoring AS patients including, Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis functional index (BASFI), and recently developed AS disease activity score (ASDAS). It is difficult to distribute multiple questionnaires to different patients in a reception area. A single questionnaire for all patients with rheumatic diseases may present advantages to introduce quantitative measurement into routine care. To this end, routine assessment of patient index data 3 (RAPID3) can be considered as a candidate index, which has been widely used and validated for RA and based on 3 multi-dimensional health assessment questionnaire (MDHAQ) components, patient function, pain and patient global assessment, each scored 0–10 for a total of 0–30. This study was conducted to compare the performance of RAPID3 in comparison with other validated measures in assessing patients with AS.

Methods: Patients seen consecutively at the rheumatology division of Gulhane School of Medicine, between May 1 and June 25, 2011 completed 3 questionnaires (BASDAI, BASFI, and MDHAQ) at each visit, and their physicians completed physician global assessments on VAS. CRPs were tested on the same date and used to calculate ASDAS-crp scores. Descriptive statistics and Pearson correlation coefficients were calculated for each measure.

Results: Fifty-one patients [88% male, mean (SD), age: 25.5 (8.4) years, disease duration: 2.8 (4.4) years] completed all assessments. Mean scores for BASDAI, BASFI, ASDAS-crp, and RAPID3 were 5.5 (2.1), 4.1 (2.4), 2.6 (0.9), and 14.5 (5.7) respectively. RAPID3 was strongly correlated with BASDAI, BASFI, and ASDAS-crp (r:0.84, r:072, and r:0.86, $p<0.001$ for each).

Conclusion: We found that RAPID3 on an MDHAQ, which had been in use for almost a decade in patients with rheumatoid arthritis, has a strong, positive correlation with the ASDAS-crp, a new composite index to assess disease activity in AS patients. Our results also confirmed the findings of a previous study (1) as showing very good correlation of RAPID3 with the outcome measures of BASDAI and BASFI in AS patients. An outcome measure that can be used in different patient populations may have the additional advantage of being easier to implement in a routine care setting.

References

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1887

Prevention of Latent Tuberculosis and Toxicity of Isoniazid in Patients Treated by Anti-Tumor Necrosis Factor Alpha in the Czech National Register. Katarina Hviscova[1], Liliana Sedova[1] and Karel Pavelka[2]. [1]Charles University, Prague, Czech Republic, [2]Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic

Background/Purpose: Anti-TNFα treatment has revolutionized the practice of rheumatologists all over the world, however has also raised new problems, particularly the increased risk of reactivation of latent tuberculosis (LTBI). This led to a need to screen for active and latent tuberculosis (TB) in patients before biological therapy is started. The Czech Rheumatology Society recommends performing PPD test, Quantiferon-TB Gold test and chest X-rays before the initiation of the treatment. Equally it is important to take detailed medical history focused on TB history, contact with active TB

and searching for symptoms that might point to TB infection (chronic cough, night sweats). If any of these results are abnormal before initiation or during the therapy, it is necessary to consult the pneumologist.

The Czech National Register of biological treatment in rheumatology (ATTRA) allows evaluating various parameters in patients with different diagnosis and during treatment by different drugs. In this retrospective study we have evaluated the toxicity of isoniazid (INH) in patients treated for LTBI before starting or during biological therapy.

Methods: In years 2001–2011 overall 1056 patients from Institute of Rheumatology in Prague were included in Czech National Registry of biological treatment in rheumatology ATTRA (656 RA patients, 335 AS and 65 PsA patients). In this group we have found 76 patients treated with INH and 8 of them were treated twice in this period. The aim of the study was to evaluate toxicity of INH in these cases, to evaluate the potential relationship with co-medication and to evaluate potential differences between the diagnoses.

Results: Out of 76 patients treated with INH, 44 were male and 32 female; 35 patients had AS, 26 had RA, 10 had PsA and 5 patients had undifferentiated spondylitis. Mean age in this group was 44 years (SD ± 13.3), median 40.5. More than 50% of patients had a long standing disease (duration for more than 10 years). In 34 cases the diagnosis of LTBI was made before the initiation of biological treatment and 47 cases of LTBI we have diagnosed during the biological treatment. Out of these 47 cases 3 patients have developed active TB and out of these 3 active TB cases 1 had developed TB though the patient was treated with INH before starting the biological treatment.

In a group treated with INH during biological therapy (47 cases) the mean time of treatment with biologics was 24.4 months (± 19.7), median of 16 months; most of the patients were treated with adalimumab (44 %) and infliximab (42%), only 12% with etanercept and 2% with abatacept. We had to withdraw INH in 7 cases; due to hepatotoxicity (n=4), due to allergy (n=2), due to optic neuritis (n=1).

Conclusion: In our group of 76 patients treated with INH we found increase of liver enzymes in 26. The most frequent situation was elevation of liver enzymes from 2 to 3 times more than normal range. In 8 cases we had to reduce the dose of INH or co-medication or we prescribed the hepatoprotective medication. Only in 4 cases we had to withdraw INH due to hepatotoxicity characterized by elevation more than 3 times. According to our results the risk of serious hepatotoxicity is only slightly increased.

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1888

Internet-Based Patient Registry and Biospecimen Collection: One Year Experience of the Arthritis Internet Registry. Kaleb Michaud[1], Kimberly Harp[1], Rebecca Schumacher[1], Stanley J. Naides[2], William F. Patten[2], Beth Axtell[3] and Robert M. Plenge[4]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Quest Diagnostics Nichols Inst, San Juan Capistrano, CA, [3]Arthritis Foundation, Atlanta, GA, [4]Brigham and Women's Hospital, Boston, MA

Background/Purpose: Observational cohorts that follow rheumatic disease patients longitudinally and obtain biospecimens can be extremely expensive and laborious to initiate. We sought to determine the feasibility of creating the Arthritis Internet Registry (AIR), an online-based cohort by combining the patient-study infrastructure of the National Data Bank for Rheumatic Diseases, the nation-wide availability of Quest Diagnostics Incorporated (QD) blood collection sites, and the patient outreach of the Arthritis Foundation.

Methods: Starting in July 2010, a website for AIR enrollment was created (http://www.arthritis-research.org/) and online advertising began on the Arthritis Foundation website asking visitors with arthritis to participate. After an initial consent, participants completed a questionnaire about their diagnoses and medical history to become enrolled. We obtained consent to contact their physicians about their diagnoses. Once the diagnoses were confirmed, we then requested consent to collect blood samples and mailed anonymous collection kits that they took to a nearby QD site for their blood draw. Samples were collected and analyzed by QD and stored at QD and academic sites.

Results: By June 2011, the AIR enrollment site had 3,331 unique visitors of which 923 patients from all 50 US states enrolled with 67% reporting rheumatoid arthritis (RA), 21% osteoarthritis (OA) and 12% were other rheumatic diseases (4% psoriatic arthritis, 2% lupus, 2% fibromyalgia, etc). After physician contact about diagnosis for 282 patients, 97.4% of participants reporting RA were confirmed and 1.8% had other inflammatory rheumatic diseases. There was no statistical association between RA screening questions and physician-confirmed diagnosis. Participants were primarily female (89%), younger (52 years), Caucasian (90%), married (66%), college educated (86%) and developed their condition almost 14 years prior. Overall pain, fatigue and clinical measures were moderate to high as shown in the Table. Blood specimens were collected for 163 patients, 125 were RA patients of which 51% were CCP+ and 50% RF+; of the 38 non-RA patients 5% were CCP+ and 8% RF+.

Table. Mean (SD) characteristics of 923 AIR participants at enrollment by diagnosis

	ALL (N=923)	RA (N=617)	OA (N=193)	Other (N=113)
Age (years)	51.7 (13.4)	50.1 (13.5)	57.5 (12.5)	50.3 (12.1)
Sex (% male)	10.6	9.2	11.9	15.9
Non–Hispanic White (%)	89.6	89.8	85.5	95.6
Education (years)	14.8 (2.4)	14.8 (2.3)	14.6 (2.9)	15.1 (1.8)
Married (%)	65.5	66.6	60.1	69.0
Smoker ever (%)	42.0	40.2	45.6	46.0
Disease duration (years)	13.7 (12.6)	13.5 (12.8)	14.5 (12.4)	13.2 (11.9)
HAQ–II (0–3)	1.01 (0.62)	0.99 (0.63)	1.07 (0.59)	1.07 (0.58)
Pain (0–10)	5.2 (3.0)	4.9 (3.0)	5.8 (2.8)	5.4 (2.8)
Patient global severity (0–10)	4.3 (2.6)	4.2 (2.6)	4.8 (2.7)	4.4 (2.5)
Patient activity score–II (0–10)	4.3 (2.3)	4.1 (2.3)	4.7 (2.2)	4.4 (2.1)
Fatigue (0–10)	5.8 (3.1)	5.8 (3.1)	5.6 (3.1)	6.4 (2.9)
GI severity (0–10)	2.9 (3.0)	2.9 (3.0)	2.7 (3.0)	3.4 (3.1)
Sleep disturbance (0–10)	5.2 (3.3)	5.2 (3.4)	5.3 (3.3)	5.4 (3.2)

Conclusion: Through the close cooperation of for-profit and non-profit organizations, AIR has proven that a large study of rheumatic disease patients with biospecimens can be created and conducted online. Continued recruitment, partnerships and patient-followup will be needed to determine the long-term research applications.

1889

Improving Clinical Trial Recruitment in a Real World Practice. Results From the Canadian Early Arthritis Cohort. Pooneh S.Akhavan[1], Vivian Bykerk[2], Ye Sun[3], Boulos Haraoui[4], J. Carter Thorne[5], Janet E. Pope[6], Carol A. Hitchon[7], Diane S. Ferland[8], Gilles Boire[9], Edward C. Keystone[10] and CATCH Investigators[11]. [1]University of Toronto, Toronto, ON, [2]Brigham & Women's Hospital, Boston, MA, [3]Mount Sinai Hospital, Toronto, ON, [4]Institut de Rhumatologie, Montreal, QC, [5]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [6]St. Joseph's Health Care, University of Western Ontario, London, ON, [7]University of Manitoba, Winnipeg, MB, [8]LaSalle, QC, [9]CHUS - Sherbrooke University, Sherbrooke, QC, [10]Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Mount Sinai Hospital, Toronto, ON, [11]Toronto, ON

Background/Purpose: Current clinical trials are not representative of characteristics of patients in clinical practice. A minority of patients in clinical practice meet current entry criteria for most trials. The objective was to evaluate whether using more liberal clinical trial entry criteria in a real world clinical setting will generate clinical outcomes comparable to the use of 'standard' entry criteria and will improve clinical trial recruitment.

Methods: Patients with early RA enrolled in the Canadian early Arthritis Cohort (CATCH), were evaluated. Patients were included in present study if: Age ≥ 18, met ACR 1987 criteria, initiating MTX at baseline, had ≥ 6-month follow up, did not receive biologics and had available ACR responses. Disease activity was assessed at baseline and 24 weeks.

Two "standard" enrolment criteria were defined: 1) ≥ 6 TJC68 and ≥ 6 SJC66 with either an ESR >28 or CRP >1.5 mg/dl, 2) ≥ 6 TJC28 and ≥ 6 SJC28 with either an ESR >28 or CRP >1.5 mg/dl. Five "liberal" criteria were defined as: 1) SDAI >11, 2) DAS28 >3.2, 3) ≥ 6 TJC28 and ≥ 6 SJC28 + elevated ESR or CRP (ESR >20 or CRP>1), 4)≥ 4 TJC28 and ≥ 4 SJC28 + ESR >28 or CRP >1.5 mg/dl, 5)≥ 4 TJC28 and ≥ 4 SJC28 + elevated ESR or CRP(ESR >20 or CRP>1). Proportion of patients eligible for enrolment based on each criteria were compared, their baseline characteristics, ACR and EULAR responses were compared.

Results: 312 patients were eligible for analysis. Percentages of patients who met each inclusion criteria are demonstrated in table 1. Patients in the first two liberal groups had the lowest proportion of elevated ESR/CRP(41% and 42% compared to >70% in other groups). ACR50 response rate was 56–57% in standard groups and 53–55% in liberal groups (except group 3). EULAR response rate was comparable among various groups.

Table 1. Comparison of percentage of patients who met each enrolment criteria (n=312)

	Standard 1	Standard 2	Liberal 1	Liberal 2	Liberal 3	Liberal 4	Liberal 5
Met enrolment criteria (%)	33%	28%	90%	88%	32%	33%	40%

Conclusion: Liberal trial entry criteria may improve recruitment from real world practice settings. Patients with a reduced joint count at entry (4 versus 6) and a greater than normal acute phase reactant were more likely to achieve the entry criteria with a significant proportion of patients having an elevated CRP. Entry criteria with 4 TJC28 and SJC28 with greater than normal acute phase reactant should be considered for future trials.

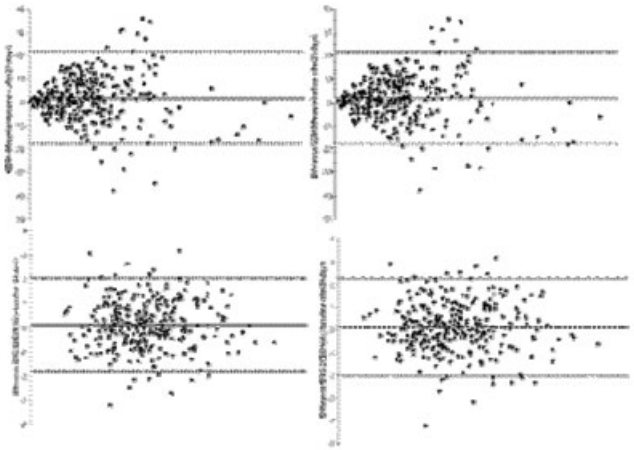
1890

Reproducibility of Composite Scores: Disease Activity 28-Joints Score, Simplified Disease Activity Score and Clinical Disease Activity Score In the Evaluation of Rheumatoid Arthritis(Ra) Disease Activity: Pursuit for A Gold Standard. Lissiane K. N. Guedes[1], Ana C. M. Ribeiro[2], Julio C. B. Moraes[2], Carla G.S. Saad[3], Nadia E. Aikawa[3], Eduardo F. Borba Neto[4], Sandra Pasotto[2], Jozelio F. Carvalho[3], Eloisa Bonfa[2] and Ieda Laurindo[5]. [1]University of Sao Paulo, Sao Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil, [5]Universidade de São Paulo, Sao Paulo, Brazil

Background/Purpose: to evaluate the reproducibility of the different composite indexes of evaluation of disease activity: DAS28 with 3 or 4 variables, SDAI and CDAI in an extreme clinical set-up designed to test the reproducibility of these tools.

Methods: 10 different physicians assessed classical parameters of disease activity in 340 adult patients with RA at baseline and after 21 days. The physicians were not uniformly familiar with the instruments; five applied these tools on regular basis and five, although experienced rheumatologists, were less familiar with these instruments. Patients were randomly allocated to each physician at baseline and after 21 days in such a way that less than 5% of the patients were assessed by the same physician at the two visits. No physician had acccess to the first evaluation. Acute-phase reactants were collected at baseline and after 21 days. All patients answered a YES/NO question regarding changes in the disease activity comparing their clinical status at baseline and after the 21 days. An affirmative answer or therapeutic changes, presence of infections, parenteral infusions or therapeutic intra-articular injection or arthrocenthesis during the 21 days of the study implied exclusion from the study.

Results: Data from 319 patients were analysed (failure to attend the second visit or incomplete laboratory data). The intraclass correlations between the different indexes were DAS28(4V)=0.681 (IC95% 0.615–0.737); DAS28(3V)=0.668 (IC95% 0.600–0.726); SDAI=0.601 (IC95% 0.524–0.668); CDAI(4V)=0.587 (IC95% 0.509–0.656) showing a similar intraclass reproducibility for all indexes with correlation coefficients between 0.5 and 0.7. Remarkably patient dependent outcomes (PGHA, pain and tender joints) did not change. After 21 days a statistically significant reduction in DAS28 was observed 3.68 (1.37) vs. 3.51(1.39, p=0.01)) but the difference 0.17 was well below clinical meaningful values. Interestingly the difference was only in the physician-dependent outcomes: number of swollen joints and global health assessment (IGHA); ESR/CRP values did not change. DAS 28 showed a slightly better performance also suggested by Bland-Altman graphics.



Conclusion: Reproducibility of the different composite scores was adequate, despite the most unfavorable artificial set-up of this study. DAS28 seems to perform slightly better.

1891

Doctor-Patient Involvement in Biologic Treatment Choice:the Benefits of a Collaborative Approach. Chris Martin and Katrina Johnson. The Research Partnership, London, United Kingdom

Background/Purpose: We recently conducted a market research study with rheumatoid arthritis (RA) patients (LWRA). Aim: to understand the link between RA patients' feelings and their history of biologic treatment.

We also collect patient chart data from a panel of rheumatologists (TKRA); using this dataset we investigated the demographic make-up of patients who are more likely to be pro-active about their RA treatment.

Methods: For LWRA, data were collected from 2,240 RA patients via online questionnaire, in March-June 2011, including disease history and experience of treatment. Of these, 739 were on biologic and were included here. Patients were asked who decided their biologic and were grouped: decided solely themselves (n=124); decided jointly with doctor (n=522); doctor decided entirely for them (n=93). Five key metrics were isolated, involving feelings about medication, relationship with doctor, dose-skipping (compliance), self-injection, and impact of disease.

For TKRA, we examined a subset featuring 5,829 RA patients reported from March-May 2011, and divided them into those who had made a request about biologic treatment vs. had not. This served as a proxy for the question about treatment decision-making.

Results: Patients who made a "**joint decision**" with the doctor about their biologic treatment felt more positive about medication, and had a stronger relationship with their doctor. When asked to agree with "My medication is making a positive difference to my life" on a 0–10 scale, co-deciders' mean was 7.8 vs. 6.9 for patients without joint ownership (i.e. either sole- or non-deciding), and for "My doctor gives me the help and support I need" co-deciders' mean was 8.2 vs. 7.4 for non-co-deciders. [All comparisons sig. at 95%+]

Patients who had **"no ownership"** over their treatment decision (i.e. doctor controlled decision) were less convinced about medication's effect on their lives, e.g. scoring 6.0 for "My medication helps me to live my life the way I want to" vs. 7.3 for patients with some ownership. This group also agreed less with the statement "my doctor provides support."

Patients with **"total ownership"** of the treatment decision disliked taking their medication more, e.g. scoring 5.7 for "I am unsure whether I want to be taking medication" vs. 3.6 for patients whose doctor had some influence, and were more likely to have skipped doses (76% vs. 47% for other patients). They skipped doses due to the belief their disease status had changed (self-diagnosis), 83% vs. 29% for doctor-influenced patients.

TKRA revealed that patients who make requests about their treatment are more severe: they have a higher DAS score (3.4 vs. 3.0) and more joints affected by RA (9.7 vs. 7.7), are further from diagnosis (9 years vs. 7.7 years) and received more DMARDs before starting biologic (2.9 vs. 2.5).

Conclusion: RA patients who felt their treatment decision was a result of "joint decision-making" between themselves and their doctor felt more positively about their RA disease and the impact the treatment was having on their lives. They were also less likely to skip doses.

In conclusion, a collaborative approach where both the doctor and RA patient make the decision, results in a more positive outcome for the patient.

1892

Older Age, Male Gender, Current Smoking and Worse Disease Activity Are Predictors of Respiratory Disease Mortality in Patients with Inflammatory Polyarthritis: Results From the Norfolk Arthritis Register. Suzanne MM Verstappen[1], Mark Lunt[1], Diane K. Bunn[2], Tarnya Marshall[3] and Deborah PM Symmons[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [2]Norfolk Arthritis Register, School of Medicine Health Policy and Practice Faculty of Health UEA, Norwich, United Kingdom, [3]Norfolk and Norwich University Hospitals Trust, Norwich, UK, Norwich, United Kingdom, Norwich, United Kingdom

Background/Purpose: Respiratory disease is one of the major causes of excess death in patients with rheumatoid arthritis (RA).Little is known about predictors of death due to respiratory disease in patients with RA. The aim of this study was to identify demographic and clinical predictors of mortality due

to respiratory disease in patients with inflammatory polyarthritis (IP) followed since 1990–1994.

Methods: Consecutive patients with early IP (≥ 2 swollen joints for ≥ 4 weeks) from a primary-care based inception cohort (NOAR), recruited between 1990–1994, were included in this study. Patients were assessed regularly since inclusion by a research nurse and flagged with the national UK death register during follow-up. All patients were followed until 31/12/2010 or death, whichever came first. Deaths with an underlying cause from ICD-10 Chapter J or lung ICD-10=C34.9 (lung carcinoma) were defined as being due to respiratory disease. Baseline clinical assessments included the DAS28 and the HAQ-score; blood was collected to determine C-reactive protein (CRP), rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA) and shared epitope (SE). The association of baseline disease and demographic characteristics, including smoking status, and death due to respiratory disease was assessed using Cox proportional hazards regression models (HR, 95% CI).

Results: 1,091 patients with IP were followed for 17194 person-years, during which a total of 69 patients died from respiratory disease (incidence rate: 4.0 per 1000 person-years, 95%CI 3.17 to 5.08). Twenty patients died with lung carcinoma as underlying cause (incidence rate: 1.16 per 1000 person-years, 95%CI 0.75 to 1.80) and 21 with chronic obstructive pulmonary disease as underlying cause (incidence rate: 1.22 per 1000 person-years, 95%CI 0.80 to 1.87). Older age, male gender and current smoking compared to never smoked were significant baseline demographic predictors of respiratory disease mortality (see Table). Satisfying the ACR criteria for RA, RF positivity, worse functional disability and high DAS28-score were baseline clinical predictors of respiratory disease mortality. There was no link between SE and respiratory disease mortality. In the multivariate regression model, age at onset and male gender were independent predictors of respiratory mortality.

Table. Predictors of mortality due to respiratory disease

	N patients with available baseline data	Univariate regression analysis HR (95%CI)	Multivariate regression analysis HR (95%CI)
Age at symptom onset	1091	1.12 (1.10 to 1.15)	1.13 (1.10 to 1.17)
Gender, *female (n)*	712/1091	0.56 (0.35 to 0.90)	0.52 (0.28 to 0.95)
HAQ-score	1079	2.02 (1.49 to 2.74)	1.48 (0.92 to 2.41)
DAS28	871	1.40 (1.15 to 1.70)	1.06 (0.82 to 1.39)
ACPA, *positive (n)*	183/810	1.66 (0.89 to 3.11)	
RF, *positive (n)*	267/952	1.98 (1.18 to 3.33)	1.74 (0.95 to 3.18)
RA, *1987 criteria (n)*	497/1091	2.30 (1.41 to 3.76)	1.48 (0.72 to 3.03)
Shared-epitope:	904		
No alleles		Ref	
One allele		1.52 (0.86 to 2.68)	
Two alleles		1.57 (0.73 to 3.37)	
Smoking status:	1090		
Never smoked		Ref	Ref
Ex-smoker		1.52 (0.81 to 2.84)	0.85 (0.41 to 1.78)
Current smoker		2.18 (1.16 to 4.12)	1.95 (0.88 to 4.29)

Conclusion: Both demographic, including current smoking but not smoking in the past, and baseline clinical variables assessed early in the disease of patients with IP are predictors of respiratory disease mortality.

1893

The Association Between Clinical and Lifestyle Factors and the Development of Inflammatory Polyarthritis and Rheumatoid Arthritis. *Results From the European Prospective Investigation of Cancer (Norfolk) Study and the Norfolk Arthritis Register.* Manjari Lahiri[1], Catharine Morgan[1], Robert N. Luben[2], Diane K. Bunn[3], Mark Lunt[1], Nick Warehan[2], Suzanne M.M. Verstappen[1], Deborah P. M. Symmons[1], Kay-Tee Khaw[2] and Ian N. Bruce[4]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, [3]University of East Anglia, Norwich, United Kingdom, [4]A, Manchester, United Kingdom

Background/Purpose: Lifestyle factors implicated in the aetiology of inflammatory polyarthritis (IP) and rheumatoid arthritis (RA) are potentially modifiable. We investigated the association of smoking and other clinical and lifestyle factors with the risk of developing IP and RA.

Methods: A prospective population-based study, the European Prospective Investigation of Cancer in Norfolk, UK (EPIC-Norfolk), recruited participants from 1994–1997. All participants provided baseline data on smoking, alcohol intake, occupational class, body mass index (BMI), diabetes mellitus (DM), and (for women) parity and duration of breastfeeding. Individuals who subsequently developed IP were identified by linkage with the Norfolk Arthritis Register (NOAR), a primary-care based disease register with an overlapping catchment area. The primary outcome was development of IP. Secondary outcomes were development of RA (1987 ACR criteria) and seropositive IP (Anti-Citrullinated Peptide Antibody [ACPA] and/or Rheumatoid Factor [RF] positive). Using Cox proportional hazards with the robust option we performed a multivariable analysis adjusted for age, gender and all other variables in the model (Table). Interaction terms were tested, and were significant only between gender and pack-years of smoking.

Results are expressed as Hazard Ratios (HR) and 95% confidence intervals.

Results: 25,455 EPIC participants aged 40–79 years were followed for a median (IQR) of 14.2 (12.9, 15.3) years (342,916 person-years of follow-up). 184 developed incident IP, of whom 138 cumulatively fulfilled 1987 ACR criteria for RA. The median (IQR) time to onset of IP was 62.7 (27.8, 104) months. The median (IQR) age of IP onset was 65.2 (57.6, 73.2) years and 69.6% were women. 107/ 177 (60.5%) were seropositive. Pack-years of smoking was associated with an increased risk of IP and RA in men but not in women, and an increased risk of seropositive IP in both genders. Self-reported DM was associated with an increased risk of IP, RA and seropositive IP in the whole cohort, while alcohol intake and higher social class (categorised as professional, non-manual/ non-professional and manual) were inversely related to risk. BMI (categorised as normal or underweight, BMI < 25; overweight, BMI 25 to <30 and obese, BMI ≥ 30) was a predictor of IP, RA and seronegative IP, but not seropositive IP. In women, higher parity (categorised as 0, 1 or ≥2 children) was a risk factor, and a longer duration of breast-feeding was protective. (Table).

Table. Demographic and Lifestyle Risk factors for Inflammatory Polyarthritis (IP), Rheumatoid Arthritis (RA) and Seropositive IP

	IP (n = 184)	RA (n = 138)	Seropositive IP (n = 107)
Risk Factor	**Fully adjusted Hazard Ratio (HR) (95% CI)**	**Fully adjusted HR (95% CI)**	**Fully adjusted HR (95% CI)**
Smoking (Every 10 pack-years)	1.21 (1.08, 1.37)[+]	1.26 (1.10, 1.44)[+]	1.24 (1.10, 1.41)
Alcohol (Every 7 units/week)	0.86 (0.74, 0.99)	0.86 (0.72, 1.04)	0.86 (0.73, 1.01)
Body Mass Index			
Underweight/normal, BMI <25	1 (ref)	1 (ref)	1 (ref)
Overweight, BMI 25 to <30	1.08 (0.76, 1.54)	1.16 (0.78, 1.74)	0.73 (0.48, 1.13)
Obese, BMI ≥ 30	1.45 (0.95, 2.21)	1.49 (0.91, 2.42)	1.05 (0.61, 1.79)
Social class			
Manual	1 (ref)	1 (ref)	1 (ref)
Non−manual, non−professional	0.71 (0.53, 0.95)	0.65 (0.45, 0.93)	0.61 (0.41, 0.92)
Professional	0.36 (0.15, 0.89)	0.37 (0.14, 1.03)	0.24 (0.06, 0.97)
Diabetes mellitus	2.54 (1.26, 5.090)	2.16 (0.92, 5.07)	1.99 (0.69, 5.74)
Parity*			
0	1 (ref)	1 (ref)	1 (ref)
1	1.34 (0.54, 3.32)	1.10 (0.40, 3.01)	1.50 (0.49, 4.56)
≥2	2.81 (1.37, 5.76)	2.55 (1.19, 5.48)	2.43 (0.99, 6.00)
Breastfeeding (every 52 weeks)*	0.66 (0.46, 0.94)	0.71 (0.49, 1.03)	0.66 (0.41, 1.05)

[+] Men only. HR for women for every 10 pack-years of smoking = 1.00 (0.82, 1.21) for IP and 0.93 (0.74, 1.17) for RA
* Women only

Conclusion: We have identified several simply ascertained clinical and lifestyle factors which are potentially amenable to modification at a population level to reduce future risk of IP.

1894

Low Levels of Formal Education Generally Are As Significant As High Age and Long Duration of Disease to Identify Poor Clinical Status in Patients with Most Rheumatic Diseases. Isabel Castrejón[1], Yusuf Yazici[2] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: To analyze whether formal education level is associated with clinical status in patients with different rheumatic diseases, and to compare possible associations of low formal education level with high age and long duration of disease to identify poor clinical status, in patients seen in usual clinical care.

Methods: A database has been maintained on all patients seen at an academic rheumatology clinical setting since 2005, which includes demographic, patient self-report questionnaire, medication and laboratory data. All new patients seen between July 2005 and April 2011 were studied: 221 with rheumatoid arthritis (RA), 166 with systemic lupus erythematosus (SLE), 238 with osteoarthritis (OA) and 958 with other rheumatic diagnoses. Each patient in this setting (with any diagnosis) completes a 2-sided, 1-page MDHAQ (multidimensional health assessment questionnaire) at every visit while waiting to see the physician in the infrastructure of clinical care. The MDHAQ includes scales for physical function, pain, patient global estimate

(PATGL), fatigue, and a self-report RADAI painful joint count. RAPID3 (routine assessment of patient index data) is an index of physical function+pain+PATGL, each scored 0–10 (total 0–30). Patients were classified into 4 groups according to years of formal education: ≤12, 13–15, 16 and >17. Differences in self-report MDHAQ scores, RAPID3 scores, and ESR (erythrocyte sedimentation rate) were analyzed. Significance of formal education level to identify clinical status was compared to age and duration of disease in multiple linear regressions.

Results: Median age for all patients was 49 years (median age by diagnosis ranged from 39 years in SLE to 62 years in OA); 72% were female and 56% Caucasian. The median formal education level was 16 years. RA patients had higher scores (poorer status) for physical function, pain, PATGL, RAPID3 and RADAI joint count, compared to patients with other diagnoses. Patients with all diseases who had 12 years or fewer of formal education had significantly higher scores for physical function, pain, PATGL, RAPID3, RADAI, fatigue, and ESR. In most regressions, years of formal education explained variation in physical function, pain, PATGL, RAPID3, RADAI and fatigue scores, at higher levels of statistical significance (greater beta coefficients and lower *p* values) than age or duration of disease. Sub-analyses were similar in patients with RA, SLE, OA, and other diagnoses.

Median values of demographics, MDHAQ scores and ESR according to 4 groups classified by years of formal education.

		YEARS OF FORMAL EDUCATION				
	All patients (n=1,583)	≤12 (n=326)	13−15 (n=310)	16 (n=329)	>17 (n=618)	P*
Age (yr)	49	53.6	50.8	43.3	48	0.0001
Disease duration (yr)	1.15	1.14	1.50	0.88	1.17	0.31
Physical function	1.3	2	1.7	1	1	0.0001
Pain	5	6	5.5	3.5	3	0.0001
PATGL	5	5	5	4	4	0.0001
RAPID3	10.7	14	11.7	10	9.3	0.0001
RADAI (0−48)	6	9	7	5	4	0.0001
Fatigue	4	5.5	5	3.5	3	0.0001
ESR	14	18.5	14	13	12	0.01

* Overall statistical significance according to Kruskall−Wallis.

Conclusion: Formal education level is as significant as age and duration of disease to explain variation in clinical status measures, and should be included in all clinical trials and clinical care databases.

1895

Higher Fruit and Fructose Consumption Is Associated with a Reduced Risk of Inflammatory Polyarthritis and Rheumatoid Arthritis in Men. *Results From the European Prospective Investigation of Cancer (Norfolk) and the Norfolk Arthritis Register.* Manjari Lahiri[1], Catharine Morgan[1], Robert N. Luben[2], Marleen Lentjes[3], Diane K. Bunn[4], Mark Lunt[1], Nick Wareham[2], Suzanne M.M. Verstappen[1], Deborah P. M. Symmons[1], Kay-Tee Khaw[2] and Ian N. Bruce[5]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, [3]Cambridge, United Kingdom, [4]University of East Anglia, Norwich, United Kingdom, [5]A, Manchester, United Kingdom

Background/Purpose: We have previously shown that higher vitamin C and fruit intake is associated with lower risk of inflammatory polyarthritis (IP) (*Pattison et al. Ann Rheum Dis 2004;63:843–7*). However, it has been suggested that the effects of fruit may be more due to fructose-mediated effects on the uric acid – allantoin antioxidant system rather than vitamin C. We examined the association between dietary fructose, fruit and vitamin C consumption and the risk of developing IP/ rheumatoid arthritis (RA).

Methods: Dietary data were obtained from a prospective population-based study, the European Prospective Investigation of Cancer in Norfolk, UK (EPIC-Norfolk) which recruited adults aged 40–79 from 1994 – 1997. Individuals who subsequently developed IP were identified by linkage with the Norfolk Arthritis Register (NOAR), a primary-care based disease register with an overlapping catchment area. Dietary intake was assessed at baseline using 7-day diet diaries and coded by computer-software (DINER) for all IP cases and a random sample of 4000 EPIC participants and analysed as a case-cohort study. The primary outcome was development of IP. Secondary outcomes were development of RA (1987 ACR criteria) and seropositive IP (Anti-Citrullinated Peptide Antibody [ACPA] and/ or Rheumatoid Factor [RF] positive). Using Cox proportional hazards with the robust option, analyses were stratified for gender and adjusted for age, total energy intake and smoking.

Results: 25,639 EPIC participants of median (IQR) age 58.9 (50.8, 66.9) years were followed. During 342,916 person-years of follow-up, 184 developed incident IP of whom 168 had dietary diaries available. Of the random sample of 4000 (including 34 cases), diaries were available for 3961 without prevalent IP. A total of 4095 participants (168 cases, 3927 unaffected cohort) were analysed for this study. The median (IQR) age of IP onset was 65.7 (57.8, 73.4) years and 67.2% were women. 127 (75.6%) cumulatively fulfilled 1987 ACR criteria for RA, and 98/161 (60.9%) were seropositive. Men, but not women, in the top tertile of fruit and total fructose consumption were at lower risk of IP, RA and seropositive IP than those in the bottom tertile (Table). Vitamin C intake showed a weaker inverse association. Fruit remained a significant predictor of IP and seropositive IP when adjusted for vitamin C, but not when adjusted for fructose intake. It remained a predictor of RA when adjusted for either vitamin C or fructose.

Table 1. Association between Fruit intake, Dietary Fructose, Vitamin C and Inflammatory Polyarthritis, Rheumatoid Arthritis and Seropositive IP.

	Males (n = 1784) Fully adjusted* Hazard Ratio (HR) (95% CI)				Females (n = 2311) Fully adjusted* HR (95% CI)			
Food/Nutrient Group	Median (IQR) intake, top vs. bottom tertile, gm	IP (n=55/1729)	RA (n=36/1729)	Seropositive IP (n=33/1751)	Median (IQR) intake, top vs. bottom tertile, gm	IP (n=113/2198)	RA (n=91/2198)	Seropositive IP (n=65/2246)
Fruit consumption (top vs. bottom tertile)	266.3 (233.0, 343.1) vs. 34.2 (0, 61.6)	0.25 (0.10, 0.66)	0.07 (0.01, 0.54)	0.26 (0.08, 0.89)	275.4 (227.0, 345.8) vs. 42.9 (14.3, 66.6)	0.87 (0.53, 1.43)	1.03 (0.62, 1.70)	0.96 (0.54, 1.73)
Fruit servings (per serving)	–	0.64 (0.50, 0.81)	0.54 (0.39, 0.74)	0.65 (0.49, 0.86)	–	0.95 (0.85, 1.06)	0.96 (0.85, 1.08)	0.94 (0.81, 1.08)
Fructose (top vs. bottom tertile)	27.0 (23.6, 31.9) vs. 8.4 (6.2, 10.8)	0.31 (0.14, 0.68)	0.39 (0.16, 0.94)	0.44 (0.17, 1.13)	26.2 (23.2, 31.2) vs. 9.8 (7.1, 11.7)	0.65 (0.39, 1.09)	0.62 (0.35, 1.11)	0.63 (0.32, 1.27)
Vitamin C (top vs. bottom tertile)	131.0 (110.0, 162.0) vs. 44.0 (35.3, 50.9)	0.50 (0.25, 1.03)	0.33 (0.12, 0.89)	0.75 (0.30, 1.88)	130.2 (111.8, 160.7) vs. (34.3, 51.6)	0.68 (0.36, 1.31)	0.70 (0.34, 1.44)	0.70 (0.38, 1.32)

IP = Inflammatory polyarthritis, RA = Rheumatoid arthritis
* Adjusted for age, total energy intake and smoking
All intakes based on 7-day diaries. 1 serving of fruit = 80gm

Conclusion: Fruit intake is inversely associated with the risk of IP, RA and seropositive IP, an effect confined to men. Fructose appears to mediate this effect rather than vitamin C.

ACR/ARHP Poster Session C
Fibromyalgia and Soft-Tissie Disorders II
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

1896

Response to Local Corticosteroid Injection In Carpal Tunnel Syndrome with Normal Electrodiagnostic Study. Domingo Ly-Pen[1], José Luis Andreu[2], Isabel Millán[3], Gema de Blas[4] and Alberto Sánchez-Olaso[4]. [1]SERMAS. CS "Gandhi" / Hospital "Ramón y Cajal", Madrid, Spain, [2]HU, Madrid, Spain, [3]HU "Puerta de Hierro Majadahonda", Madrid, Spain, [4]Hospital "Ramón y Cajal", Madrid, Spain

Background/Purpose: Electrodiagnostic testing (EMG) has usually been defined as the gold standard in carpal tunnel syndrome (CTS) diagnosis. Nevertheless, correlation between clinical symptomatology and EMG has shown to be very poor. In fact, clinical symptoms may precede EMG changes in months or years. There are very few papers about the clinical response to treatment of clinically typical CTS, but with normal EMG.

The aim of this study is to compare the clinical response to local corticosteroid injections (LCI) in clinically typical CTS, with normal and pathologic results in EMG.

Methods: We included patients older than 18 years, with typical symptoms of CTS (daily nocturnal pain, every night during at least 3 months). EMG was done on every patient. Wrists with abnormal EMG were randomised either to LCI or to surgical decompression. Wrists with normal EMG were rejected from our randomised study, and were treated with two LCI (two weeks between them). Follow-up was done at 3, 6 and 12 months. Primary outcome was visual analogue scale for pain (p-VAS), comparing wrists with abnormal EMG treated with LCI in our randomized clinical trial, with wrists with normal EMG that were all treated with LCI. Statistic signification was established by the Student′s t test, Mann-Whitney′s "U", the normal χ^2 test and with Yates′ correction. The study was approved by the ethics committees at our centers and all patients gave written informed consent.

Results: Forty four wrists were included in the group with normal EMG (NEMG) and 83 in the group with patologic EMG (PEMG).

Mean age was 49 years in the NEMG group and 54 years in the PEMG group (p = 0,063). The mean time of symptoms evolution was 26 weeks in the NEMG group and 38 weeks in the PEMG group (p = 0,33).

Mean p-VAS was 59 mm in the NEMG group and 42 mm in the PEMG group (p = 0,001). In the table we can see the percentage of wrists that reached a 20%, 50% and 70% reduction in p-VAS in the follow-up.

	Response 20%			Response 50%			Response 70%		
Months	3	6	12	3	6	12	3	6	12
NEMG	88%	85	90	81%	75	81	69%	61	62
PEMG	96%	87	87	89%	85	86	83%	79	79
p	0,199	0,706	0,910	0,186	0,205	0,551	0,076	0,03	0,07

Conclusion: Clinically relevant responses to local corticosteroid injections in CTS tend to be more frequent in wrists with pathologic EMG than in wrists with clinically typical symptoms of CTS, but with normal EMG.

1897

New Formulation to Improve Tendon Tissue Organization in Tendinopathies. Anna Torrent[1], Ramon Ruhí[1], Cristina Martínez[2], Mar Cid[2], Constanze Buhrmann[3] and Mehdi Shakibaei[3]. [1]BIOIBERICA S.A., Palafolls, Spain, [2]BIOIBERICA S.A., Barcelona, Spain, [3]LMU, Institute of Anatomy, Munich, Germany

Background/Purpose: Tendons are dense fibrous connective tissues that connect muscle to bone. The functional properties of the tendon are derived from the structure and components of the extracellular matrix (ECM). When diseased or injured, adult tendons do not heal to the same regenerative capacity of embryonic tissue, but exhibit a highly disorganized matrix that consequently affects normal tissue function. Collagen disorientation, disorganization and variations in the diameters of collagen fibrils are characteristics of a tendinopathic tendon. It is crucial to maintain the structure of the tendinous matrix for the ability of the tendon to resist mechanical forces and the repair response to injury.The aim of this study was to evaluate the potential effectiveness of a novel formulation (BIS033) including mucopolysaccharides on fibrillogenesis of collagen type I and tenomodulin (TeM) levels in the presence/absence of IL-1β in a 3-dimensional culture of human tenocytes.

Methods: Primary human tenocytes in 3-dimensional high density cultures were incubated for 0–14 days under different treatments. BIS033 is a nutraceutical formulation that contains mainly mucopolysaccharides. Tenocytes were either treated with BIS033, non-stimulated or stimulated with IL-1β or stimulated with IL-1β and BIS033.We evaluated the effect of this natural formulation on fibrillogenesis and on the tendon specific matrix glycoprotein called TeM in the presence or absence of IL-1β.The potential efficacy of BIS033 in the extracellular matrix (ECM) estructure, and especially in the orientation, organization and morphology of the collagen fibrils was investigated by Transmission Electron Microscopy (TEM).By Western Blot we evaluated whether incubation of tenocytes with the formulation could prevent IL-1β-induced upregulation of catabolic events leading to downregulation of production of matrix specific proteins such as TeM. This glycoprotein is highly expressed in normal, healthy tenocytes and is described in literature that there is a close correlation between TeM expression and the regular alignment of collagen fibers, further indicating that TeM is involved in the formation of organized tendon structures.

Results: Tenocytes treated with IL-1β underwent apoptosis and showed a completely disorganized extracellular matrix. The treatment with BIS033 was able to counteract the catabolic effects and cells looked healthy and with abundant and well organized extracellular matrix consisting of thick fibrils of collagen. Also tenocytes displayed high amount of euchromatin that indicates that cells were very active and with a high rate of protein biosynthesis. Western blot demonstrated a considerable prophylactic effect of BIS033 on human tenocytes co-treated with IL-1β on TeM synthesis. Additionally an anabolic effect of the formulation was observed: cells showed higher TeM levels compared to the untreated control cells.

Conclusion: These results indicate that the formulation BIS033 could be useful in the prevention and/or treatment of tendinopathies (tendinitis, tendinosis, etc). The administration of this product is believed to contribute to remodelling the tendon, which is crucial to return to its mature functional structure.

1898

Trochanteric Bursitis: Is there Ultrasonographic Evidence to Suggest Inflammation? P. Dundeva-Baleva[1], A. Abdel-Megid[1], A. Borham[1] and Naomi Schlesinger[2]. [1]UMDNJ/Robert Wood Johnson Medical School, New Brunswick, NJ, [2]UMDNJ-Robt Wood Johnson MS, New Brunswick, NJ

Background/Purpose: Trochanteric bursitis (Tb) is one of the most common soft tissue abnormalities in the hip region; affecting 10–25% of the population. Tb is a clinical diagnosis that includes lateral hip pain and tenderness around the greater trochanter. Power Doppler (PD) ultrasonography (US) is a sensitive method for demonstrating the presence of blood flow in small vessels. PD US enables visualization of synovial hyperemia. High frequency and PD US in combination are sensitive and reproducible tools for determining joint effusions and synovitis. The term Tb may be a misnomer given that three of the cardinal symptoms of inflammation: warmth, erythema and swelling are rarely seen in these patients. Could use of US help identify how commonly US and PD US changes suggestive of Trochanteric bursa inflammation are seen in patients with the clinical syndrome of Tb.

Methods: This study was a retrospective chart and US image review of patients seen in the Rheumatology clinic between 12/1/2006 and 2/1/2010 with a primary or secondary diagnosis of trochanteric bursitis (diagnosis codes CPT 76942 and/or 20610). Trochanteric bursa US images were reviewed for signs of inflammation (bursa swelling and capsule thickening), as well as PD US signals. Recorded were patients' past medical history and medications at the time of diagnosis and the response to intrabursal corticosteroid injections given by a Rheumatologist (AB,NS).

Results: 287 patient charts with CPT 76942 and 20610 were reviewed. Seventy five patients were found to have a diagnosis of Tb. Of these 75 patients; 52 underwent trochanteric bursa injections and had US images. 13 patients had bilateral trochanteric bursa images; 4 patients had the same bursa examined more than once. Total number of US images n=67, total number of PD US n=51.

The average age of the patients was 49 (range: 24–76) years. 50 (99%) patients were female; only two (1%) patients were male. Most patients had underlying osteoarthritis (OA) n= 23 (44%) and Fibromyalgia syndrome (FM) n= 26 (50%). Five (9.6%) patients with Tb had Sjogren's Syndome. 31(60%) patients diagnosed with Tb were on NSAIDs at the time of the diagnosis and 12(23%) on a neuropathic pain medication.

The Rt trochanteric bursa was most commonly involved (n= 44 (66%)). All (n=51 (100%)) of PD US were Grade 0 (normal: no evidence of inflammation). Only 2 of 67 (<1%) trochanteric bursa US images showed an effusion. None had bursal wall thickening. Pain relief was seen for an average of 4.5 months post-injection in 26 (50%) patients who had a follow up visit.

Conclusion: This is the first study to date examining the use of US and PD US as a means to review inflammation in patients with Tb. We found that patients with clinical Tb do not have US evidence to support a diagnosis of bursal inflammation. The right trochanteric bursa was commonly involved (dominant side in most patients). The involvement of mostly females is not surprising since females suffer more commonly from soft tissue rheumatism than men. Since we did not find signs of inflammation in the trochanteric bursa, we suggest that the most appropriate term to be used for what was previously known as trochanteric bursitis is **Trochanteric Pain Syndrome.**

1899

Stress Is a Key Modulator of Mood, Coping, Type of Control and Characteristic Symptoms in Females with Fibromyalgia. Katrina Malin[1] and Geoffrey O. Littlejohn[2]. [1]Monash Medical Centre, Clayton, Australia, [2]Monash Medical Center, Melbourne, Australia

Background/Purpose: Stress is an important feature of fibromyalgia [FM] with links to aberrant autonomic nervous system function, perturbed hypothalamic pituitary adrenal function and dysregulation of brain-related control over spinal cord sensory processing. However, it remains unclear how stress interacts with central processes such as personality, control styles, coping techniques and mood that in turn associate with the predictable phenotypic symptom characteristics of fibromyalgia, such as pain, fatigue, sleep and confusion. We aimed to identify the associations of stress with these central and "down-stream" variables in patients with FM.

Methods: We identified 98 women with fibromyalgia diagnosed according to standard ACR criteria. Applied questionnaires included Fibromyalgia Impact Questionnaire [FIQ], Perceived control of internal states scale (PCOISS), Mastery scale, the Coping Scale and Perceived Stress scale. Correlation and regression modelling were used to explore the relationships

between stress and the domains of coping, control, mood and personality as well as characteristic FM symptoms.

Results: Stress showed significant moderate to strong correlations with all the above "central' and symptom variables of FM [$p < 0.001$)]. There was a strong inverse correlation with measures of control [PCOISS and Mastery] and a strong positive correlation with mood, neuroticism, confusion and coping. When controlling for stress all variables, with the exceptions of internal control with mastery and neuroticism and confusion with mastery and coping, were not significant, indicating that stress impacts the majority of variables associated with FM. The regression model predicted ratings of stress as measured by disengagement (coping), pain, internal control, anxiety, confusion, mastery and neuroticism. Together they accounted for 75% of variance.The main significant independent elements were neuroticism (31%), mastery (29%), anxiety (23%) and disengagement (21%).

Conclusion: Stress associates with most of the central variables that have been identified as being important in fibromyalgia, as well as the phenotypic clinical characteristics. Strong predictors of stress were neuroticism, anxiety, behavioural disengagement and low mastery. Stress appears to have a pivotal role in modulating several key "up-stream" processes in fibromyalgia.

1900

Fibromyalgia and Parental Medical Histories of Depression and Alcoholism. Robert S. Katz[1], Ben J. Small[2], Sharon M. Ferbert[3], Patricia Kuenzi[1] and Susan Shott[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University Medical School, Chicago, IL, [3]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL

Background/Purpose: We investigated whether depression or alcoholism in parents is associated with an increased risk of fibromyalgia (FMS) in offspring. We had found in a previous study suggestions of an increased prevalence depression in the mothers and alcohol abuse in the fathers of fibromyalgia patients.

Methods: 115 FMS patients and 63 control patients with other rheumatic diseases answered a rheumatology office questionnaire that included questions about whether their mother or father had been diagnosed with or had symptoms of depression, alcoholism, or FMS. The chi-square test of association and Fisher's exact test were used to compare FMS and control patients with respect to percentages. The Mann-Whitney test was done to compare these groups with respect to age. A 0.05 significance level was used and all tests were two-sided.

Results: 81.7% of the FMS patients and 61.9% of the control patients were women ($p = 0.004$). The mean age was 48.1 ± 12.3 years for FMS patients and 50.7 ±13.6 for control patients ($p = 0.092$). 33.0% of FMS patients and 8.1% of control patients reported a depression diagnosis or symptoms in their mothers ($p < 0.001$). 26.3% of FMS patients reported a depression diagnosis or symptoms in their fathers, compared to 10.0% of control patients ($p = 0.013$). Although FMS patients were more likely than control patients to report an alcoholism diagnosis or symptoms in their mothers (9.6% vs. 4.8%. $p = 0.38$) and fathers (19.2% vs. 10.0%, $p = 0.18$), the differences were not statistically significant. FMS patients were significantly more likely than control patients to report a FMS diagnosis or symptoms in their mothers (26.4% vs. 3.2%. $p < 0.001$), but not in their fathers (6.2% vs. 0%, $p = 0.083$).

Conclusion: FMS patients were significantly more likely than control patients to report that their parents had a diagnosis or symptoms of depression, and significantly more likely to report that their mothers had a FMS diagnosis or symptoms. No statistically significant differences were found with respect to paternal FMS or maternal or paternal alcoholism.

1901

The Survey Diagnostic Criteria of Fibromyalgia Syndrome—Results From the German Fibromyalgia Syndrome Consumer Reports. Winfried Häuser[1], Eva Jung[1] and Frederick Wolfe[2]. [1]Technische Universität München, Munich, Germany, [2]National Data Bank for Rheumatic Diseases, Wichita, KS

Background/Purpose: A modification to the American College of Rheumatology (ACR) 2010 preliminary diagnostic criteria for the fibromyalgia syndrome (FMS) was developed for use in epidemiological and clinical studies. Patients satisfying the modified ACR 2010 diagnostic criteria meet the following 3 conditions: 1) Widespread Pain Index (WPI) ≥7 and Symptom Severity Score (SSS) ≥5 ("FMS 1") or WPI between 3–6 and SSS ≥9 ("FMS 2"); 2) Symptoms present at a similar level for at least 3 months; 3) Absence of another disorder that would otherwise sufficiently explain the pain. The feasibility and convergent validity of the survey criteria has not been tested previously. We assessed feasibility within a survey study and determined the concordance rates of FMS diagnosis according to survey, clinical and ACR 1990 criteria (convergent validity).

Methods: A questionnaire containing the WPI and SSS was included in the FMS consumer reports survey in Germany. Conducted between November 2010 and April 2011, the questionnaire was distributed by the two largest German FMS self-help organizations (German League for people with Arthritis and Rheumatism, German Fibromyalgia Association) to their members with self-reported FMS. In addition, 8 clinical institutions in different speciality areas (complementary and alternative medicine, pain medicine, psychosomatic medicine, rheumatology) and different levels of care distributed the questionnaire to consecutive patients with established or newly diagnosed FMS. The diagnosis of FMS was (re-) assessed by clinical criteria at all clinical institutions. Blinded clinicians from 4 centres performed the ACR 1990 criteria examination using the Okifuji tender point protocol (TPE).

Results: 1509 questionnaires were returned and 1291 (85.5%) to 1448 (95.9%) of the items of the survey questionnaire were answered. Data from 1446 persons were analyzed, of whom 1129 (78.1%) had been recruited by the self-help organisations. Women (n=1365) constituted 94.4% of the sample. The mean age was 54.4 (SD 9.8) years and the mean duration of chronic widespread pain was 16.8 (SD 11.0) years). The time since first diagnosis of FMS was 6.7 (SD 5.5) years. In 25 (1.7%) patients, FMS had been diagnosed for the first time. Of 1446 patients, 1182 (81.7%) met the FMS1-survey criterion and 60 (4.2%) met the FMS-2 criterion.

A TPE was performed on the 131 patients in the clinical centres with an established or initial diagnosis of FMS. Survey criteria were met by 111/(84.7%) of the patients. The 1990 classification criteria were met by 106 (80.9%)% of the patients. Survey and 1990 criteria were concordant in 100 (76.3%) of the patients.

Conclusion: The consumers reports study demonstrates the feasibility of survey diagnostic criteria in a patient survey of established or suspected FMS. The concordance rate of survey and ACR 1990 criteria was comparable to published data (75.2%) (Katz, A&R 54(1); 2006) and of defined clinical criteria and ACR 1990 criteria (86.6%) (HSuser, Clin J Pain 26(6): 2010). Survey criteria were designed to differ from the ACR 1990 classification criteria, and most disagreements were due to TP-counts <11 in patients meeting survey criteria. Feasibility and validity within a population survey needs to be determined.

1902

Prevalence of Fibromyalgia at the Medical Out Patient Clinic Kenyatta National Hospital. Sophia Dokwe and Omondi.G Oyoo. University of Nairobi, Nairobi, Kenya

Background/Purpose: Fibromyalgia syndrome is a disorder that is associated with significant morbidity. Despite its existence worldwide there is hardly any epidemiological data in Africa and none in Kenya. The prevalence of this disorder in the Kenyatta National Hospital medical out-patient and rheumatology clinics is unknown.

Objectives: To determine the prevalence of fibromyalgia, chronic regional pain and chronic widespread pain in patients attending the medical outpatient and rheumatology clinic at Kenyatta National Hospital; to investigate the frequency of fibromyalgia symptoms and to document the primary diagnosis and Cormobid conditions in the these patients.

Methods: A questionnaire that includes the 1990 American College Of Rheumatology criteria for diagnosis of widespread pain and fibromyalgia and the (FIQR) Revised fibromyalgia impact questionaire was administered on 384 patients with musculoskeletal pain.Consecutive sampling was used.

Results: The prevalence of fibromyalgia, chronic regional pain and chronic widespread pain amongst patients with chronic musculoskeletal pains (n = 384) in the medical outpatient clinic and rheumatology clinic of Kenyatta National Hospital was 13% (n = 50), 76% (n = 291) and 11% (n = 43) respectively. The overall three month prevalence of fibromyalgia in the general medical outpatient clinic was 1%,Chronic widespread pains 1.2% and Chronic regional pain 6.7%.The mean age of patients with fibromyalgia was 48.5 yrs SD 2.6 [95%CI 43.1–53.8]. Approximately forty four percent 44.2 % [95% CI 28.7–59.7] and [(34.9%) were widowed 95% CI 20.1–49.7]. More than half of fibromyalgia patients were unemployed [n =22 (51.2%) 95% CI 35.6–56.3] and 46.5 % [95% CI 30.9–62] were engaged in manual activity.There was a female predominance of 97.7% (n = 42). Mean duration of illness was 5.8 years SD 0.8 [95%CI 4.1 – 7.4]. Rheumatoid arthritis was the most frequent primary diagnosis at first consultation in the clinics [30.2% (n=13/43)]. Hypertension was the commonest Cormobid disease [53.5 %(n=23/43)] the mean total FIQR score for fibromyalgia patients was 55.94%

SD (2.85)95%CI 50.19–61.68. The most frequent symptoms were pain, fatigue, stiffness, depression, and unrefreshing sleep while balance problems, headache and increased sensitivity to the environment were the least reported symptoms.

Conclusion: Fibromyalgia is prevalent amongst patients with musculoskeletal complains in the Medical Outpatient and rheumatology clinics at the Kenyatta National Hospital. These patients present with severe fibromyalgia symptoms and frequently have other Cormobid illnesses. Primary diagnosis is often missed.

1903

Fibromyalgia in Systemic Lupus Erythematosus and Association with Fatigue and Disease Activity: Comparison of 2010 Versus 1990 Criteria. Vinicius Domingues, Hong Fang and Michelle Petri. Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Up to 90% of SLE patients complain of fatigue. Fibromyalgia (FM) occurs more frequently in SLE than in the general female population, and is highly associated with fatigue. The American College of Rheumatology (ACR) diagnostic criteria for FM were revised in 2010. We compared the 1990 and 2010 criteria for FM, in terms of association with fatigue and SLE activity.

Methods: 174 patients (90% female, 55% Caucasian, 37% African/American, mean age at entry 47.3±13) participated. FACIT-Fatigue, Fatigue Severity Scale (FSS), Fatigue Visual Analog Scale (FVAS) and Multidimensional Assessment of Fatigue (MAF) were used to quantify fatigue. Pain Score was evaluated in a scale from 0 to 10 based on patient's self report. SLE disease activity was measured by Physician's Global Assessment (PGA) and SELENA-SLEDAI. FM status was assessed by both the 1990 and 2010 criteria (Widespread Pain index ≥ 7 and Severity Scale ≥5 or Widespread Pain Index 3–6 and Severity Scale ≥9).

Results: The prevalence of FM was 39% (1990 criteria) and 41% (2010 criteria). The 2010 FM criteria were associated with disease activity by PGA, but not SLEDAI. The 1990 FM criteria were not. Both FM criteria were highly associated with fatigue, by all measures.

	Fibromyalgia 1990	Fibromyalgia 2010
	p-value	p-value
FACIT	<0.0001	<0.0001
FSS	<0.0001	<0.0001
MAF	<0.0001	<0.0001
FVAS	<0.0001	<0.0001
Pain Score	<0.0001	<0.0001
PGA	0.2658	0.009
SLEDAI	0.7614	0.5303

Conclusion: The 1990 FM criteria are not associated with SLE disease activity, but the 2010 are associated with PGA. This may limit the utility of the new FM criteria in practice. Both FM criteria are highly associated with fatigue (by any measure used). The high prevalence of fatigue in SLE is important to recognize in clinical practice and clinical trials.

1904

Return of Pain and Functional Impairment After Discontinuation of Milnacipran in Patients with Fibromyalgia. Philip J. Mease[1], Daniel J. Clauw[2], Yimin Ma[3], Arlene Baldecchi[3], Joel M. Trugman[3] and Robert H. Palmer[3]. [1]Seattle Rheumatology Associates and Swedish Medical Center, Seattle, WA, [2]University of Michigan, Ann Arbor, MI, [3]Forest Research Institute, Jersey City, NJ

Background/Purpose: Fibromyalgia (FM) is a debilitating chronic disorder characterized by widespread musculoskeletal pain and a host of symptoms that include fatigue, sleep disturbances, stiffness, and cognitive dysfunction. These multiple symptoms have a substantial negative impact on physical, mental, and social patient functioning. The objective of this analysis was to evaluate the effect of discontinuing long-term (18–54 months) milnacipran treatment on functional outcomes in FM patients.

Methods: Patients completing a long-term (up to 3.25 years) open label (OL) extension study of milnacipran 50 to 200 mg/day were eligible to participate. After completing 4-weeks of OL milnacipran treatment, patients taking milnacipran ≥100 mg/day and achieving a ≥50% reduction in visual analog scale (VAS) pain score from pre-milnacipran exposure to current status were randomized 2:1 to double-blind (DB) treatment with milnacipran (ie, milnacipran continued) or placebo (ie, milnacipran withdrawn) for 12 weeks. Functional outcomes assessed included the change from baseline (randomization visit) in Fibromyalgia Impact Questionnaire-Revised (FIQR) total score, SF-36 Physical Component Summary (PCS) score, SF-36 Mental Component Summary (MCS) score, and SF-36 individual domain scores (physical functioning, role limit-physical, bodily pain, general health perception, energy/vitality, social functioning, role limit-emotional, and mental health). Assessments were made at 2, 4, 8, and 12 weeks postbaseline. Missing patient data were imputed by using the last observation carried forward (LOCF) approach.

Results: In patients in whom milnacipran was withdrawn (n=50), there was worsening in the FIQR total score at each of the 4 postbaseline visits compared with patients in whom milnacipran was continued (n=100) (P <.001, all visits). Similarly, patients in whom milnacipran was withdrawn demonstrated a decline in physical functioning, as measured by SF-36 PCS and SF-36 physical functioning scores, compared with patients in whom milnacipran was continued (P <.05, all visits, both outcomes). Worsening in mental function (SF-36 MCS scores) was significantly greater in the placebo vs the milnacipran group at 2 out of the 4 visits (P <.05). All of the SF-36 individual domains showed greater deterioration from baseline in placebo- vs milnacipran-treated patients at every postbaseline visit; in the case of SF-36 bodily pain, these differences reached significance at each visit (P <.05). Differences in the other SF-36 individual domains (except general health perception) were significant at one or more visits (P <.05).

Conclusion: These results further support the enduring efficacy of milnacipran for improving function in patients with FM, as demonstrated by the deterioration of functional outcomes following discontinuation of long-term treatment.

1905

Safety and Tolerability of Milnacipran in a 3-Year, Open-Label, Flexible-Dosing Study of Patients with Fibromyalgia. Lesley M. Arnold[1], Yimin Ma[2], Robert H. Palmer[2], Allan Spera[2] and Arlene Baldecchi[2]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Forest Research Institute, Jersey City, NJ

Background/Purpose: Milnacipran is a dual serotonin and norepinephrine reuptake inhibitor that is approved in the United States for the management of fibromyalgia (FM). Several clinical trials have shown the efficacy of milnacipran at doses of 100 to 200 mg/day in improving the multidimensional domains of FM, including pain, global status, physical functioning, and fatigue. This open-label study enrolled patients from previous milnacipran trials, some of whom had been taking milnacipran for over 1 year, to assess further its long-term safety and tolerability.

Methods: This was a multicenter, open-label, flexible dosing study of up to 3.25 years in duration. A total of 1227 patients with FM who successfully completed a previous milnacipran study were included in this safety analysis. Patients underwent a 2-week washout period, followed by a 2-week dose-escalation period of milnacipran to 100 mg/day. After 8 weeks of dose stabilization at 100 mg/day, patients could have their dose adjusted to between 50 mg/day and 200 mg/day, depending on tolerability and/or therapeutic benefit. Safety assessments included treatment-emergent adverse events (TEAEs) (not present before study drug was taken or that increased in severity during the study period) and vital signs (including weight). In order to adjust for the extended length of time in this study, rates of TEAEs per 100 patient-years were also determined.

Results: The completion rate was 47.7%, comprising 206 patients who reached the final visit and 379 who were enrolled when the study was terminated; discontinuations due to TEAEs were 20.9%. The mean duration of treatment was 563.1 days, with 35.4% of patients completing ≥2 years; total exposure to milnacipran was 1889.1 patient-years. The mean daily dose was 133.7 mg/day. TEAEs occurred in 88.3% of patients over the 3.25 year period, with the most commonly reported TEAEs (≥10%) being nausea (25.9%), headache (13.4%), hypertension (11.2%), and sinusitis (10.4%). Expressed as incidence per 100 patient-years (nausea, 16.8%; headache, 8.7%; hypertension, 7.3%; and sinusitis, 6.8%), these rates were not inconsistent with product labeling. Serious TEAEs occurred in 8.9% of patients. Mean changes from baseline in systolic and diastolic blood pressure (supine SBP and DBP, respectively) were +4.0 and +3.3 mm Hg, respectively. Mean change from baseline in supine heart rate was +5 bpm and in body weight was −0.3 kg. Potentially clinically significant (PCS) increases in supine SBP (≥180 mm Hg and increase ≥20 mm Hg) and DBP (≥110 mm Hg and increase ≥15 mm Hg) were observed in 0.3% and 1.1% of patients, respectively; PCS increases in supine heart rate (≥120 bpm and increase ≥20) were observed in 0.4% of patients. PCS increases and decreases in

weight (≥7% change) were observed in 13.3% and 18.5% of patients, respectively.

Conclusion: Milnacipran, at doses of 50 to 200 mg/day, was generally well-tolerated and safe for periods of up to 3.25 years. No new safety concerns were identified in this long-term study.

1906

Cannabinoid Use in Fibromyalgia Is Associated with Male Gender, Opioid Use and Drug Seeking Behaviour. Peter A. Ste-Marie[1], Mary-Ann Fitzcharles[2], Ann Gamsa[2], Pantelis Panopalis[2] and Yoram Shir[2]. [1]University of Montreal, Montreal, QC, [2]McGill University, Montreal, QC

Background/Purpose: In the absence of an ideal treatment for fibromyalgia (FM), and with only three drugs having FDA approval, FM patients often seek treatments outside of mainstream medicine. Although the endocannabinoid system plays a role in pain modulatory mechanisms, little is known about the effect of administered cannabinoids in chronic pain or FM. We have had the impression that some FM patients may be using cannabinoids, either prescribed or illicit for treatment of FM symptoms. These agents, mostly subject to regulation, are also not currently recommended for treatment of FM. The prevalence of use of cannabinoids in FM patients is unknown and warrants examination.

Methods: We have examined the use of cannabinoids, both licit and illicit, in patients referred to a tertiary care pain centre clinic with a diagnosis of FM between January 2005 and December 2010 by a retrospective chart review. Demographic and clinical information, education and work activity, mental health status as assessed by a psychologist, and other medication use were documented. Univariate comparisons of continuous variables were made using Student's t-tests, and for categorical variables chi-squared tests were used.

Results: Demographic and disease related information for 457 referred patients is shown in Table 1. Three hundred and two (66%) retained the diagnosis of FM, and 155 (34%) were assigned some other primary diagnosis (140 other medical diagnosis, 65 current serious mental health disorder, 51 with both). FM patients had a mean pain VAS of 6.4 and a Fibromyalgia Impact Questionnaire score of 65.7, and were using an average of 1.9 prescription medications for treatment of symptoms. Cannabinoids were used by 59 (13%) patients, 46 (78%) used illicit marijuana, 14 (24%) used prescription cannabinoids (13 nabilone, 1 dronabinol) and 1 used both. Cannabinoid users vs. non users were more likely to be male 22% vs. 7% (p=0.0006), be taking opioids 47% vs. 29% (p=0.007) and demonstrate drug-seeking behaviours 32% vs. 4% (p=0.009). There was a tendency for cannabinoid users to suffer from more unstable current mental illness and also to be unemployed.

Table 1. Demographic and disease information for 457 patients referred with diagnosis of fibromyalgia, stratified according to cannabinoid use

	All patients n=457	Cannabinoids n=59	No cannabinoids n=398	p value cannabinoids vs no cannabinoids
Age ± SD	47±11	45±10	48±11	NS
Gender/male, no (%)	40 (9)	13 (22)	27 (7)	0.0006
Education (in 436)				
Schooling not completed, no (%)	50 (11)	9 (15)	41 (10)	NS
High school, no (%)	132 (29)	16 (27)	116 (29)	NS
College, no (%)	156 (34)	22 (37)	134 (34)	NS
University, no (%)	98 (21)	10 (17)	88 (22)	NS
Unemployed, no (%)	308 (67)	46 (78)	262 (66)	NS
Disability, no (%)	165 (36)	23 (39)	142 (36)	NS
Diagnosis				
Fibromyalgia, no (%)	302 (66)	36 (61)	266 (67)	NS
Other primary diagnosis, no (%)	155 (34)	23 (39)	132 (33)	NS
Current mental illness, no (%)	110 (24)	20 (34)	90 (23)	NS
Opioids, no (%)	144 (32)	28 (47)	116 (29)	0.007
Drug-seeking behaviour	25 (6)	8 (32)	17 (4)	0.009

Conclusion: Cannabinoids were used by 13% of all patients referred with a diagnosis of FM, and $^1/_3$ of all males. Illicit marijuana was the most cannabinoid used. The concomitant use of opioids as well as an increased rate of drug seeking behaviour raises concerns regarding the true motive for this category of mostly self medication. Although cannabinoids may possibly offer a therapeutic effect for pain relief, caution regarding any recommendation for use should be exercised until these agents are subject to rigorous evaluation in view of concerns regarding psychological health and an association with other substance abuse.

1907

3-Year Efficacy of Milnacipran in Patients with Fibromyalgia: An Open-Label, Flexible-Dosing Study. Lesley M. Arnold[1], Yimin Ma[2], Robert H. Palmer[2], Allan Spera[2] and Arlene Baldecchi[2]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Forest Research Institute, Jersey City, NJ

Background/Purpose: Milnacipran is approved for the management of fibromyalgia (FM), a chronic disorder characterized by widespread pain and other symptoms that adversely impact function and health-related quality of life. Because FM is a chronic disorder, long-term efficacy is an important treatment goal. Previous studies have demonstrated the efficacy of milnacipran in managing FM symptoms for up to 1 year. This study extends those findings by evaluating the long-term efficacy of milnacipran for a period of up to 3.25 years.

Methods: In this open-label study, the treatment effects of milnacipran were evaluated in patients with FM (N=1227) over a period of up to 3.25 years (or until the study was terminated administratively). Patients successfully completing previous milnacipran studies were eligible for enrollment. This study comprised a 2-week washout period, a 2-week dose-escalation period (to milnacipran 100 mg/day), an 8-week dose-stabilization period (at milnacipran 100 mg/day), and a flexible-dose period (milnacipran 50–200 mg/day) for the remainder of the study. Key efficacy outcomes included mean changes from study baseline (after 2 week washout) in weekly recall VAS pain (0–100 mm scale), Patient Global Impression of Change (PGIC), Patient Global Disease Status (PGDS), SF-36 Physical Component Summary (PCS), and the Brief Pain Inventory (BPI). Efficacy analyses were reported for the intent-to-treat (ITT) population at the end of study (ie, last available assessment). Additional cohort analyses for weekly recall VAS pain were performed in order to assess the long-term effects of treatment in defined groups of patients treated for varying periods of time.

Results: For the ITT population, milnacipran-treated patients showed an improvement in pain, with a mean decrease from baseline in weekly recall VAS pain score of 17.6 mm. Additionally, improvements in BPI scores, global status (PGIC, PGDS), and physical function (SF-36 PCS) were all observed with milnacipran treatment for the ITT population. Because the number of patients with available data in the ITT population varied at each visit, we used weekly recall VAS pain to assess improvements over time in specified cohorts. In the cohort of patients completing ≥3 years (n=217), the observed pain improvement was reached by Month 3 and remained relatively constant throughout the entire study; weekly recall pain VAS scores improved by 23.9 mm in these patients at the final study visit (Month 36–38). Similar improvements from baseline in weekly recall VAS pain were observed over time and remained constant in the 2-year cohort (n=461) and the 1-year cohort (n=820).

Conclusion: The findings from this open-label study provide support for sustained long-term efficacy (in some cases exceeding 3 years of continuous treatment) of milnacipran in improving pain, global status, and physical functioning in patients with FM.

1908

Improvements in Fatigue Are Incompletely Explained by Improvements in Pain in Fibromyalgia Patients Treated with Milnacipran. Philip J. Mease[1], Robert H. Palmer[2], Yong Wang[2] and R. Michael Gendreau[3]. [1]Seattle Rheumatology Associate and Swedish Medical Center, Seattle, WA, [2]Forest Research Institute, Jersey City, NJ, [3]Cypress Bioscience, Inc., San Diego, CA

Background/Purpose: In addition to chronic widespread musculoskeletal pain, patients with fibromyalgia (FM) commonly report fatigue as a major symptom. Fatigue can contribute to diminished quality of life, impaired ability to work, and a perceived worsening of disease state. Pain has previously been shown to be significantly correlated with fatigue in FM patients; however, the extent to which the clinical domain of fatigue may change independent of changes in pain has not been well characterized.

Results from several clinical trials have shown that milnacipran significantly improves pain and fatigue in patients with FM. Based on pooled data from 3 of these studies, this analysis explores the relationship between pain and fatigue, including the effects of baseline fatigue severity on pain improvements and the influence of pain improvements on fatigue improvements in milnacipran-treated patients.

Methods: Data were pooled from 3 phase III studies in FM patients randomized to placebo (n=1133), milnacipran 100 mg/day (n=1139), or milnacipran 200 mg/day (n=837). After a dose-escalation phase, patients underwent

12 weeks of stable-dose treatment. Fatigue was measured by using the Multidimensional Fatigue Inventory (MFI; 20–100 scale) and pain was measured using a VAS pain scale (0–100). In order to evaluate the impact of baseline fatigue severity on pain improvement with treatment, pain improvement was assessed in patients stratified into tertiles based on their baseline MFI total score (ie, MFI ≤63; MFI >63 and ≤74; MFI >74). Pearson correlation coefficients were determined for the relationship between improvements in MFI total score and improvements in pain VAS. Path analysis was used to describe the direct and indirect effects of milnacipran treatment on fatigue.

Results: Milnacipran-treated patients had significantly reduced pain VAS scores ($P < .05$, vs placebo) in all baseline fatigue subgroups. However, regression analysis revealed that in the milnacipran 100 mg/day group, patients who exhibited greater fatigue at baseline demonstrated a slightly reduced pain response compared with those with less fatigue at baseline ($P = .066$); this dependency was not seen in the 200 mg/day dose group ($P = .69$). Overall, improvements in MFI total score correlated only moderately well with improvements in pain (milnacipran, $r = 0.4729$; placebo, $r = 0.3898$). Path analysis suggested that 28.1% of the observed milnacipran treatment effect on fatigue could be explained by a direct effect on fatigue, not mediated by an indirect effect on pain.

Conclusion: These results suggest that milnacipran treatment improves pain in FM patients regardless of baseline levels of fatigue, although patients with higher levels of fatigue may gain additional benefit from a higher milnacipran dose. Additionally, milnacipran had a substantial direct effect on fatigue that was not attributable to improvements in pain. Taken together, these results suggest that neither of these domains can be taken as a surrogate for the other, and that both are domains that should be assessed independently.

1909

Alcohol Consumption and Symptom Severity in Patients with Fibromyalgia. Terry H. Oh, Chul H. Kim, Connie Luedtke, Jeffery Thompson and Ann Vincent. Mayo Clinic, Rochester, MN

Background/Purpose: To examine the associations between alcohol consumption and symptom severity in patients seen in a fibromyalgia treatment program.

Methods: We assessed alcohol consumption in 946 patients with fibromyalgia based on a self-reported alcohol history taken as a part of a comprehensive social history. The subjects were divided into 4 groups according to alcohol consumption by the reported number of drinks per week: none, low (≤3/week), moderate (>3–7/week) and heavy (>7/week). Multiple linear regression models were used to compare numeric rating of pain scores, number of tender points, and scores on the Fibromyalgia Impact Questionnaire (FIQ) and the Short Form-36 Health Status Questionnaire (SF-36) among the 4 groups while adjusting for potential confounder.

Results: The majority, 546 (57.7%), of the subjects reported no alcohol intake. The alcohol consumption of the remaining groups was distributed as follows: low in 338 (35.7%), moderate in 31 (3.3%) and heavy in 31 (3.3%), respectively. Employment status ($p<0.001$), education level ($p=0.009$) and BMI ($p=0.002$) differed significantly across the 4 groups with more employment among low and moderate drinkers, higher level of education in moderate drinkers, and lower BMI in moderate and heavy drinkers.

After adjusting for age, employment status, education level and BMI, we found significant group differences in number of tender points ($p=0.01$), FIQ total score ($p=0.004$), FIQ subscales of physical function ($p<.001$), work missed ($p=0.002$), job ability ($p=0.009$), and pain ($p<.001$), as well as SF-36 subscales of physical functioning ($p<.001$), pain index ($p<.001$), general health perception ($p=0.009$), social functioning ($p=0.008$) and physical component summary ($p<0.001$) with generally lower dysfunction and higher levels of quality of life for those with low and moderate alcohol consumption.

Post hoc analysis among the 4 groups showed that low and moderate drinkers had significantly better scores than none drinkers on the FIQ physical function and job ability scales and better SF-36 scores on physical functioning, pain index and physical component summary scales. Also, low drinkers had better scores on the FIQ work missed and SF-36 general health perceptions and social functioning scales. Moderate drinkers had better FIQ total scores and heavy drinkers had better scores on the SF-36 physical functioning scale than none drinkers. Furthermore, moderate drinkers had significantly lower FIQ pain subscale scores than all other groups and a lower number of tender points than low drinkers.

Conclusion: In patients with fibromyalgia, low and moderate alcohol consumption appears to be associated with lower levels of dysfunction and higher levels of quality of life when compared to none drinkers. Furthermore, moderate alcohol consumption was associated with better FIQ pain scale score when compared to none, low and heavy alcohol consumption.

1910

Six-Month Treatment Patterns and Outcomes for Patients with Fibromyalgia. Rebecca Robinson[1], Kurt Kroenke[2], David A. Williams[3], Yi Chen[4], Madelaine M. Wohlreich[5], Bill McCarberg[6] and Philip J. Mease[7]. [1]Eli Lilly and Company, Indianapolis, IN, [2]Indiana University Regenstrief Institute, Indianapolis, IN, [3]Univ of MI Hlth System-Lobby M, Ann Arbor, MI, [4]i3, Ann Arbor, MI, [5]Lilly USA, Indianapolis, IN, [6]Kaiser Permanente, Escondido, CA, [7]Seattle Rheumatology Associate, Seattle, WA

Background/Purpose: Fibromyalgia (FM) is a chronic condition in which long-term treatment and prognosis are variable. Here we describe medication use and outcomes over 6 months for patients starting a new course of medication for FM.

Methods: Data were analyzed from REFLECTIONS, a prospective, observational study of patients treated for FM in the United States and Puerto Rico, conducted between 7/2008 and 4/2011. Treatment status and outcomes were collected from patients using structured telephone interviews at baseline, and 1, 3, 6, and 12 months. Repeated measures models were used to assess changes in Brief Pain Inventory (BPI) severity (4 items) and interference (7 items) over time while adjusting for confounder variables (demographics, clinical characteristics, physician characteristics, and symptom severity) for the total sample and for select medication cohorts. Satisfaction measures (4) were compared, using chi-square tests with pairwise comparisons, to assess differences across medication cohorts.

Results: Patients (N=1700) were mostly female (94.6%) and Caucasian (82.9%), with these baseline characteristics (mean [standard deviation]): age 50.4 (11.9) years, duration of FM 5.6 (6.3) years, BPI severity 5.5 (1.8), and BPI interference 6.1 (2.2). At 6 months, 1344 (79.1%) patients were surveyed and 1233 (72.5%) completed all 4 interviews. Patients initiated 145 unique drugs and averaged 4.80 (1.8) unique medications per patient over 6 months. Most patients initiated 1 drug (87.8%) by adding it to concomitant medications (77.8%). Medication cohorts included patients initiating duloxetine (DLX, 267, 15.7%), pregabalin (218, 12.8%), milnacipran (MLC, 135, 7.9%), and tricyclic antidepressants (TCAs, 70, 4.1%). Overall, 1-, 3-, and 6-month assessments demonstrated significant least-squares mean reductions for pain severity (.18,.27, and.29, respectively) and interference (.54,.57,.65, respectively) (all $p<0.01$). Reductions in BPI severity and interference did not significantly differ between medication cohorts. At 6 months, the initiated baseline medication was discontinued in 35.5% of patients, continued in 36.6% of patients, and unavailable/unknown in 27.9% of patients. Predominant reasons for discontinuation were adverse events and lack of efficacy. At 6 months, patient satisfaction was good to excellent in 77.9% for treatment overall, 77.1% for medication(s) prescribed, 90.8% for doctor's interest in FM, and 92.4% for patient's rapport with the doctor. Patients initiating TCAs had lower rates of satisfaction across all measures compared with the other 3 medication cohorts, and significantly lower rates for overall treatment compared with DLX and MLC cohorts (all $p<0.05$). Patients initiating MLC had significantly higher rates of satisfaction for doctor's interest in FM and rapport with the doctor than patients initiating pregabalin and TCA (all $p<0.05$).

Conclusion: Over 6 months, patients experienced modest improvements in BPI severity and interference and continued to change treatments, yet measures of patient satisfaction with care were relatively high. This may underscore the importance of the doctor-patient relationship when treating FM.

1911

Subgrouping Chronic Pain Patients At a Tertiary Care Center Based on the Presence of Fibromyalgia Symptoms. Afton L. Hassett[1], Chad M. Brummett[2], Jenna Goesling[2], Kevin Rakovitis[2], Daniel J. Clauw[3] and David A. Williams[4]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Michigan Health System, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI, [4]Univ of MI Hlth System-Lobby M, Ann Arbor, MI

Background/Purpose: Most patients evaluated at tertiary care pain clinics present with chronic pain presumed to be of focal and peripheral origin; thus treatment often consists of targeted interventional strategies like epidural injections. However, there is a growing appreciation of the role for centralized pain like that observed in fibromyalgia. Pain that is more central in nature may require a different approach to treatment. The objective of this study was to identify subgroups of chronic pain patients whose pain was more like that observed in those with fibromyalgia.

Methods: 497 new patients presenting to the Back & Pain Center were included. All completed a series of self-report questionnaires, including the Brief Pain Inventory (BPI), PainDETECT and the ACR survey criteria for fibromyalgia. Exploratory and confirmatory K means cluster analyses for a 3-factor solution were conducted with 244 patients in each analysis. Variables including "fibromyalgianess" (a continuous scale of symptom severity based on the ACR survey criteria), neuropathic pain extent (total score on PainDETECT), pain severity and pain interference (BPI) were converted to Z scores for the analysis. Clinical data were entered into the APOLO Electronic Data Capture system and analyzed using PASW 18.

Results: Three subgroups characterized by severity of symptoms and pain interference were identified in the first analysis and confirmed in the second (Table 1). Analysis of variance demonstrated differences between the cluster means ($P < 0.0001$). One subgroup was characterized by high levels of fibromyalgianess, neuropathic pain, clinical pain severity and pain interference with functioning. The second group of patients had moderate levels of fibromyalgianess and neuropathic pain with less severe pain and pain interference. Lastly, the third subgroup had very low levels of fibromyalgianess and neuropathic pain with low pain severity and minimal pain interference.

Table 1.

Analysis 1	Cluster 1 (n=50)	Cluster 2 (n=115)	Cluster 3 (n=79)
Fibromyalgianess	1.386	−0.030	−0.697
PainDETECT	1.286	0.018	−0.904
BPI Pain Intensity	0.868	0.383	−1.136
BPI Pain Interference	0.947	0.308	.−1.035
Analysis 2	**Cluster 1 (n=83)**	**Cluster 2 (n=113)**	**Cluster 3 (n=48)**
Fibromyalgianess	0.841	−0.404	−0.779
PainDETECT	0.946	−0.238	−0.888
BPI Pain Intensity	0.713	−0.029	−1.159
BPI Pain Interference	0.805	0.021	−1.483

Conclusion: Our data suggest that widespread pain and concomitant symptoms associated with fibromyalgia captured in the ACR survey criteria (e.g., poor mood, cognitive problems, sleep disturbance) occur on a continuum and might help differentiate chronic pain patients in a tertiary care setting. The patients on the high end of the continuum tend to have greater pain that may be more central in nature, as well as higher levels of disability. Such patients may require a different treatment strategy than those on the low end of the continuum.

1912

Smoking and Fibromyalgia: The Need for a Multidisciplinary Approach to Treatment. Jenna Goesling[1], Chad M. Brummett[1], Kevin Rakovitis[1], Daniel J. Clauw[2] and Afton L. Hassett[3]. [1]University of Michigan Health System, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]University of Michigan Medical School, Ann Arbor, MI

Background/Purpose: Current data on smoking and fibromyalgia (FM) are limited, and thus the implications of smoking behavior for FM patients are not well understood. Therefore, a better understanding of smoking among patients with FM is important because despite nicotine's analgesic effects, most smokers typically report greater pain, worse overall functioning, and more symptoms of mood disorders compared to nonsmokers. The objective of this study was to evaluate the relation of smoking status on pain and mood in FM patients using data from a tertiary care pain clinic. We hypothesized that patients meeting FM survey criteria who smoke would be more likely to report greater pain severity and interference, as well as higher levels of anxiety and depression.

Methods: New patients seeking treatment for chronic pain at the University of Michigan's Back & Pain Center were included in this study. The American College of Rheumatology (ACR) survey criteria for FM were used to categorize patients. Current smoking status was determined based on the question "Do you smoke" (yes=current smoker, no=nonsmoker). Pain was measured using the Brief Pain Inventory and mood was assessed with the Hospital Anxiety and Depression Scale. Data were entered into the APOLO Electronic Data Capture system and analyzed using PASW 18.

Results: Among the 170 patients who met survey criteria for FM, 38.8% (66) reported being current smokers. 41% smoked a pack or more per day. In comparison, 23% (68) of patients who did not meet survey criteria for FM were smokers. Consistent with predictions, current smokers meeting survey criteria for FM reported greater pain severity ($F=9.32$, $p < 0.003$) and pain interference ($F=12.49$, $p < .001$) compared to non-smokers who met FM criteria. Further, current smokers reported higher levels of anxiety, ($F=15.04$, $p < 0.001$) and depression ($F=23.34$, $p < 0.001$) compared to non-smokers who met survey criteria for FM.

Conclusion: Smoking rates were higher among patients who met survey criteria for FM compared to patient's who did not meet FM criteria. When comparing only patients who met FM criteria, smoking was associated with greater pain, more interference, anxiety, and depression. These results suggest that smokers who met survey criteria for FM have several comorbid factors that likely interfere with functioning. In conclusion, a multidisciplinary approach to treatment of chronic pain among current smokers, especially in patients who meet FM criteria, should include both cessation advice and treatment for co-occurring mood disorders. It follows that further consideration of the complex relation between smoking, mood and pain may help inform treatment decisions and interventions among patients who meet survey criteria for FM. Future studies will focus on differences in post-treatment outcomes between smokers and non-smokers who meet FM criteria.

1913

Perspectives on Fibromyalgia From Trainees At An Academic Health Center. Jennifer Lobert[1], Xolti Morgan[1] and Lesley M. Arnold[2]. [1]University of Cincinnati, Cincinnati, OH, [2]University of Cincinnati College of Medicine, Cincinnati, OH

Background/Purpose: Fibromyalgia (FM) is a common disorder in the US with an estimated 2% prevalence in the adult population. There are no published studies on trainees' attitudes towards FM and the degree of confidence in diagnosing and managing the disorder. We hypothesized that despite recent advances in the understanding of the pathophysiology and treatment of FM, there is still uncertainty among some trainees about the legitimacy of FM as a medical disorder. We propose that this uncertainty is due to inadequate quality and quantity of education.

Methods: We conducted a survey of residents and fellows in all departments of a large academic medical center using an anonymous, secure, web-based survey that consisted of questions related to education about diagnosis and treatment of FM, experience with FM, and personal beliefs about FM. To determine which factors were significantly associated with considering FM to be a legitimate medical disorder we used the Chi-Square test and univariate odds ratios. Those variables that were significant at a p value <0.10 were included in a multivariate logistic regression model predicting which residents thought FM was a legitimate medical disorder.

Results: The survey was completed by 154 of 642 residents and fellows. Respondents were more likely than the overall group to be Caucasian, in the first 3 years of training, and in primary care. Only 36% believed that FM was a legitimate medical disorder. Respondents who believed that FM was a legitimate medical disorder were more likely to be confident in treating FM (OR 3.16, 1.4–6.9) and to believe that FM patients were not more difficult to manage than other patients (OR 2.5, 1.0–6.0). Those who were confident in treating FM were more likely to be in primary care and to have diagnosed and treated FM. They also reported satisfactory or better quantity and quality of education on diagnosis and treatment of FM. They understood the pathophysiology of FM and were comfortable discussing FM with patients and attendings.

Conclusion: Despite advances in the understanding of the pathophysiology and management of FM, a minority of residents and fellows at a large academic medical center believe that FM is a legitimate medical disorder. Those who believe in its legitimacy are more confident in diagnosing and treating the disease. Factors that contribute to increased confidence include regular exposure to patients with FM and adequate quantity and quality of the educational experience. Interventions aimed at increasing trainees' clinical experience with FM patients and improving the quantity and quality of FM education may enhance trainees' level of confidence in diagnosing and treating FM as a legitimate medical disorder. This, in turn, will increase the percentage of trainees who believe in the legitimacy of the disorder and lead to improved FM patient care.

1914

EpiFibro—A Brazilian Nationwide Databank in Fibromyalgia—Analysis of 500 Women. Roberto E. Heymann[1], Eduardo S. Paiva[2], Marcelo C. Rezende[3], Daniel Feldman[4], Milton Helfenstein Jr.[1], Jose E. Martinez[5], Jose R. Provenza[6], Aline Ranzolin[7], Luiz S. Ribeiro[8] and Eduardo J.R. Souza[9]. [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]Universidade Federal do Parana, Curitiba, Brazil, [3]Santa Casa de Campo Grande, Campo Grande, Brazil, [4]Universidade Federal de São Paulo, Sao Paulo, Brazil, [5]Pontifícia Universidade Católica de São Paulo, Sorocaba, Brazil, [6]Pontifícia Universidade Católica de Campinas, Campinas, Brazil, [7]Hospital das Clínicas - Universidade Federal de Pernambuco, Recife, Brazil, [8]Instituto de Previdência dos Servidores do Estado de Minas Gerais, Belo Horizonte, Brazil, [9]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil

Background/Purpose: Fibromyalgia Syndrome (FM) is common in Brazil, with a prevalence of 2,1%. Here we present the initial data from EpiFibro, a nationwide (9 states) databank of FM patients seen in the public and private settings, mostly in referral centers and FM experts offices.

Methods: We analyzed data from the first 500 women in the databank. All patients were seen by a rheumatologist, and all fulfilled the 1990 ACR criteria for FM. 55% of patients received the diagnosis in the moment of entering the databank, and 42.8% were follow-up patients.

Results: Patients seen in a public setting comprise 70% of this sample. They had a lower level of education, more diffuse pain at onset (77.71% vs. 55.49% in private patients), but they did not differ from private patients concerning the FIQ score (60.65 vs. 62.67).

Most patients were married (59.4%) and most of them did not complete middle level education (67%). 31% are employed, 21% are housewives and 34% are unemployed or retired. The house income for the great majority of patients (73.4%) was less than 2,000 reais/month (1,200 US dollars).

Concerning the patient's impression about what triggered FM symptoms, 39.4% blame a work injury and 51% recognized a depressive or anxiety episode as a trigger. Most of patients referred that their pain already started as diffuse pain (70.2%). The majority of patients first saw a General Practitioner or an Orthopedic Surgeon for their complaints.

Patients presented with 13.74 tender points in average. The main associated symptoms were sleep disturbances (86%), fatigue (84.6%), anxiety (77.2%), paresthesias (75%) and headache (72.6). The mean FIQ score was 60.82.

Patients that received their diagnosis as they entered the database (277 subjects) usually have had their pain for more than three years (74.37%), visited more than 3 doctors before the diagnosis was made(70%) and 44% of them saw a rheumatologist only after three years after looking for medical help. Their FIQ score was not different from the follow-up patients (65.23 vs. 62.87).

Conclusion: A preliminary analysis of the EpiFibro databank revealed that female FM patients in Brazil have a high impact of their disease measured by FIQ, high prevalence of associated symptoms, a low degree of education (this could be explained as public health care in Brazil is used mainly by the underserved) an their pain seems to be diffuse from the start.

1915

EpiFibro—A Brazilian Nationwide Databank in Fibromyalgia—2010 Fibromyalgia Criteria, "Fibromyalgianess" Score and FIQ Performances. Eduardo S. Paiva[1], Roberto E. Heymann[2], Marcelo C. Rezende[3], Daniel Feldman[4], Milton Helfenstein Jr.[5], Jose E. Martinez[6], Jose R. Provenza[7], Aline Ranzolin[8], Luiz S. Ribeiro[9] and Eduardo J.R. Souza[10]. [1]Universidade Federal do Parana, Curitiba Parana, Brazil, [2]UNIFESP - Universidade Federal de São Paulo, São Paulo, Brazil, [3]Santa Casa de Campo Grande, Campo Grande, Brazil, [4]Universidade Federal de de São Paulo, Sao Paulo, Brazil, [5]Universidade Federal de de São Paulo, São Paulo, Brazil, [6]Pontifícia Universidade Católica de São Paulo, Sorocaba, Brazil, [7]Pontifícia Universidade Católica de Campinas, Campinas, Brazil, [8]Hospital das Clínicas - Universidade Federal de Pernambuco, Recife, Brazil, [9]Instituto de Previdência dos Servidores do Estado de Minas Gerais, Belo Horizonte, Brazil, [10]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil

Background/Purpose: EpiFibro is a nationwide (9 states) databank of FM patients seen in the public and private settings, mostly in referral centers and in FM experts offices.

Methods: 500 women with FM, defined by the 1990 ACR criteria, were included in this analysis. 55% of patients received the diagnosis in the moment of entering the databank, and 42.8% were follow-up patients, and 70% of this sample was composed by patients from public hospitals.

Results: When the 2010 ACR criteria were applied in these patients, 88.5% of them fulfilled the criteria for diagnosis of FM -Widespread Pain Index(WPI) => 7 and Symptoms Severity Scale (SSS) =>5 OR WPI =>3–6 and SSS=>9. There was no difference when the group had the 1990 criteria previously or when entering the databank.

The mean WPI was 12.43 ± 4.51, the mean SSS was 9.07±2.48 and the "Fibromyalgianess Score" – WPI+SSS was 19.92±7.79. Patients that did not fulfilled the 2010 criteria had much lower scores in the WPI and in the SSS subscales:

	2010 CRITERIA NEGATIVE	2010 CRITERIA POSITIVE	P
WPI	5.98	13.29	0.001
SSS-FATIGUE	1.17	2.4	0.001
SSS-SLEEP	1.16	2.38	0.001
SSS-COGNITIVE	1.28	2.19	0.001
SSS-SOMATIC	1.63	2.63	0.001
SSS-TOTAL	5.21	9.6	0.001
FIBROMYALGIANESS	11.19	22.89	0.001

We also correlated the FIQ (Fibromyalgia Impact Questionnaire) with the 2010 criteria subscales, and found a good correlation with the SSS($r=0,53$, $p<0.001$), especially the fatigue sub-item ($r=0,48$, $p<0.001$). Interestingly, the "Fibromyalgianess" score had a lower, although positive, correlation with the FIQ ($r=0,39$, $p<0.001$).

Comparing patients seen in a public setting with those seen in private practice, we were also able to find a higher WPI: 13.25 vs. 10.52 in private patients, and as a consequence, this group had higher "Fibromyalgianess Score" and a greater proportion of patients being diagnosed as FM with the 2010 diagnostic criteria.

Conclusion: Analysis of the EpiFibro databank revealed that a high proportion of female FM patients in Brazil (88%) also fulfilled the 2010 ACR criteria for the diagnosis for FM, and we found that the FIQ score correlates well with Symptoms Severity Scale, especially with the fatigue subscale.

1916

A Randomized, Double-Blind Comparison of Duloxetine 30 Mg Once Daily (QD) and Placebo in Adult Patients with Fibromyalgia. Lesley M. Arnold[1], Shuyu Zhang[2] and Beth Pangallo[3]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Eli Lilly and Company, Indianapolis, IN, [3]ELi Lilly and Company, Indianapolis, IN

Background/Purpose: Treatment with duloxetine 60 mg QD significantly reduces pain severity in adult patients with fibromyalgia (FM) with or without major depressive disorder (MDD). In previous FM trials, 1-week treatment with duloxetine 30 mg QD resulted in statistically significant pain reduction compared with placebo before duloxetine was increased to the target dose of 60 mg QD. The present study was conducted to evaluate further the efficacy and safety of duloxetine 30 mg QD dose in adult patients with FM with or without MDD.

Methods: This study was a double-blind, randomized, placebo-controlled, fixed dose 12-week trial of duloxetine 30 mg QD. Key inclusion criteria included fibromyalgia as defined by the American College of Rheumatology (1990) with or without MDD and baseline ratings of ≥4 on the average pain severity of the Brief Pain Inventory-Modified Short Form (BPI), which was the primary measure of efficacy. Secondary measures included the Patient Global Impressions of Improvement (PGI-I), the Fibromyalgia Impact Questionnaire (FIQ) total score, and response rate (>=30% or 50% reduction in BPI average pain). Discontinuation rates and treatment-emergent adverse events were also assessed.

Results: Of the 308 patients randomized, 155 received duloxetine and 153 received placebo. The mean age was 50.80 years and 95% of the patients were female. Duloxetine- treated patients did not have statistically significant BPI average pain reduction compared with placebo-treated patients (−2.04 vs. −1.70 respectively, $P = .202$). There was a significant improvement in duloxetine-treated patients compared with placebo-treated patients assessed by PGI-I endpoint score (2.97 vs. 3.35 respectively, $P = .019$) and the change from baseline to endpoint on FIQ total score (−14.62 vs. −9.75 respectively, $P = .009$). There were no significant differences between duloxetine- and placebo-treated patients in the 30% response rate at endpoint (49.7% vs. 43.1% respectively, $P = .238$) and the 50% response rate at endpoint (36.6% vs. 35.9% respectively, $P = .902$). The number of patients who completed the study did not differ between duloxetine and placebo treatment groups (78.1% vs. 71.9% respectively, $P = .237$), and nausea was the most common (>1%) adverse event leading to discontinuation

(1.3% vs. 0.7% respectively, $P = 1.00$).Treatment-emergent adverse events experienced by ≥5% of LY2216684-treated patients and at least twice the incidence experienced by placebo-treated patients were nausea, dry mouth, somnolence and insomnia.

Conclusion: The primary result of the study did not demonstrate the analgesic effect of the duloxetine 30 mg QD in the treatment of fibromyalgia with or without MDD. Duloxetine 30 mg QD was generally well tolerated, and there were no new safety issues identified.

1917

Therapeutic Massage on Pain Relief for Fibromyalgia: A Systematic Review and Meta-Analysis. Lingjun Kong[1], Raveendhara R. Bannuru[2], Weian Yuan[1], Ying-wu Cheng[1], Min Fang[1], Timothy McAlindon[2] and Chenchen Wang[2]. [1]Shanghai University of Traditional Chinese Medicine of Yueyang Hospital, Shanghai, China, [2]Tufts Medical Center, Boston, MA

Background/Purpose: Therapeutic Massage is widely used for musculoskeletal pain relief in Asia, yet evidence of its effect for fibromyalgia (FM) is scarce. A comprehensive review of the literature is an important step for understanding the benefits of Therapeutic Massage in FM. We systematically review literature for the effect of Therapeutic Massage on pain in subjects with FM.

Methods: We performed a comprehensive search of 6 Eastern and Western databases and reference lists from published articles through June 2011. We included randomized controlled trials (RCTs) and non-randomized studies with Therapeutic Massage for FM. The FM Impact Questionnaire (FIQ) or VAS was evaluated as an endpoint. We also reviewed the treatment effect on depression, stiffness and sleep quality. Study quality was assessed with Jadad criteria assessing randomization, blinding and drop out rates for each study. The differences between treatment groups were reported as mean change (95% CI, p-value). We also performed a meta-analysis for the effects of Therapeutic Massage on FM pain of the 4 RCTs which provided sufficient quantitative data.

Results: We identified 102 potentially relevant studies. Ten studies (7 RCTs) with a total of 372 subjects (76% female) met eligibility criteria. Mean age was 47 and mean symptom duration was 10 years. Of those, 3 trials used Swedish massage, 3 used Chinese massage (Tuina) and 4 used other massage methods.

Table 1 summarizes the RCTs evaluating the effect of Therapeutic Massage on FM pain (VAS scale). Mean treatment duration was 8 weeks (range 3–24). The overall quality of RCTs was modest (mean Jadad score=1.9). All studies reported an association between the therapeutic massage and improved clinical symptom of pain. The meta-analysis results showed that 4 studies with 3 to 10 weeks of therapy had a decrease in pain versus either other therapies or no treatment controls. The pooled effect size was −0.92 (95% CI, −1.28 to −0.56) favoring therapeutic massage. In addition, 4 studies reported an improvement in stiffness measured with FIQ. 3 studies reported an improvement in depression. No adverse events were reported.

Table 1. Randomized Controlled Trials Evaluating the Effect of Therapeutic Massage on FM

Author, yr Country	Age*	N	Therapeutic massage (Dose: #times/ #sessions)	Control (Dose: #times/ #sessions)	Duration (weeks)	Pain VAS Mean difference (95% CI)*	P-value	Quality (Jadad)
#Sunshine 1996 US	50	30	Swedish massage (30 min/ 10 sessions)	1) TENS	5	1) vs. TENS ↓3.1[b]	<0.05	4
				2) Sham TENS (30 min/ 10 sessions)		2) vs. Sham TENS ↓1.6[b]	<0.05	
Blunt 1997 Canada	49	21	Chiropractic management (12–24 sessions)	Standard care	4	↓13.3	ND	3
#Brattberg 1999 Sweden	48	52	Connective tissue massage (15 sessions)	Standard care	10	↓27.7 (24.3, 31.0)	0.006	2
Alnigens 2001 US	46	37	Swedish massage (45 min/ 10 sessions)	1) Standard care	24	1) vs. Standard care ↑0.12[b]	>0.05	1
				2) Standard care and telephone		2) vs. Standard care and telephone ↑0.2[b]	>0.05	
#Field 2002, US	51	254	Swedish massage and Shiatsu (30 min/ 10 sessions)	Progressive muscle relaxation (30 min/ 10 sessions)	5	↓ 0.9 (00, 1.8)	ND	2
Tang 2009 China	ND	60	Massage in pain spots (15 min/ 9 sessions)	Chinese classical massage (Tuina) (15 min/ 9 sessions)	3	↓ 0.9 (0.5, 1.3)	<0.01	2
#Wang 2010 China	40	90	Chinese classical massage (Tuina) (1 hr/ 20 sessions)	1) Acupuncture (30 min/ 20 sessions) 2) Amitriptyline hydrochloride	3	1) vs. Acupuncture ↓18.8 (15.1, 22.5) 2) vs. Amitriptyline	ND	1

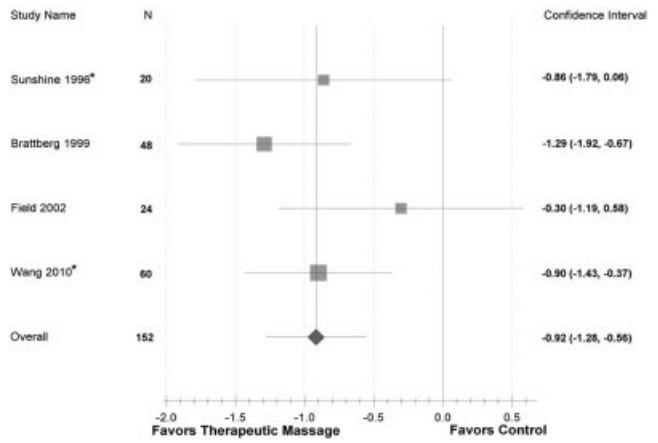


Figure 1. Meta-analysis for Effects of Therapeutic Massage on Pain of FM

Conclusion: The current body of evidence suggests that Therapeutic Massage may be helpful in the treatment of pain due to FM. The studies are very heterogeneous, and there is insufficient evidence for a definitive conclusion. Rigorous and well-controlled randomized trials are warranted.

ACR/ARHP Poster Session C
Genomics, Proteomics, and Genetics II
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

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Proteomic Profiling Following Immunoaffinity Capture of HDL Identifies Association of Acute Phase Proteins and Complement Factors with Pro-Inflammatory HDL in Rheumatoid Arthritis. Christina Charles-Schoeman[1], Yunan Miao[2], Junji Watanabe[3], Yuen Yin Lee[4], George Katselis[2], Terry D. Lee[2] and Srinivasa T. Reddy[3]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]Beckman Research Institute of the City of Hope, Duarte, CA, [3]UCLA, Los Angeles, [4]UCLA, Los Angeles, CA

Background/Purpose: To utilize proteomic analysis to identify protein biomarkers associated with pro-inflammatory HDL in patients with active rheumatoid arthritis.

Methods: Liquid chromatography-mass spectrometry (LC-MS) was used to analyze proteins associated with immunoaffinity purified HDL from plasma of two sets of RA patients carrying distinct HDL (anti- or pro-) inflammatory properties (n=4 per group). Proteins were fractionated by Offgel electrophoresis and analyzed by LC-MS/MS equipped with a high capacity high performance liquid chromatography chip (HPLC-Chip) incorporating C18 reverse phase trapping and analytical columns. iTRAQ™ 8-plex reagent kit was used to test all eight HDL samples from RA patients in a single experiment. Sandwich enzyme-linked immunosorbent assays were used to validate select HDL-associated proteins in a second RA cohort (n=31).

Results: Seventy-eight proteins were identified in the HDL complexes. Twelve proteins were significantly increased in RA patients with pro-inflammatory HDL compared to RA patients with anti-inflammatory HDL.These proteins included acute phase proteins, including apolipoprotein J, fibrinogen, haptoglobin, serum amyloid A, and complement factors (B, C3, C9). Four of the proteins associated with HDL were validated in a second RA cohort.

Conclusion: Pro-inflammatory HDL in patients with RA contains a significantly altered proteome including increased amounts of acute phase proteins and proteins involved in the complement cascade. These findings suggest that HDL is significantly altered in the setting of chronic inflammation from active RA with resultant loss of its anti-inflammatory function. Since the inflammatory nature of HDL has previously been directly linked to CVD, and is also significantly correlated with disease activity in RA, characterization of the biomarkers reported here may identify novel molecular connections that contribute to the higher risk of CVD in RA patients.

1919

Association Between Interferon Alpha Gene Expression and Disease Characteristics in Systemic Lupus Erythematosus. Michelle Petri[1], Hong Fang[1], Wenzheng Hu[1], Jadwiga Bienkowska[2], Norm Allaire[2], John Carulli[2] and Matthew D. Linnik[3]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Biogen Idec Inc., Cambridge, MA, [3]Biogen Idec Inc., Solana Beach, CA

Background/Purpose: The interferon alpha gene signature occurs in 50 to 70% of SLE patients and has been strongly associated with ENA (Ro, La, RNP). We investigated the association of the IFN gene signature in a cohort of Caucasian and African-American patients.

Methods: 272 SLE patients (92% female, 59% Caucasian, 33% African-American, mean age 46.0 years) were enrolled in a prospective observational study. At baseline, the IFN gene signature was determined in peripheral blood RNA using Affymetrix chips, and was divided into low (<8, 42.6%) and high (≥8, 57.4%) groups. Clinical associations, based on the cumulative history and the same-day visit disease activity, were then determined. The results were based on the chi-square test (SAS Institute, Cary, NC, USA). P-values were then adjusted for race. A p-value ≤0.05 was considered statistically significant.

Table 1. Association between ACR criteria and IFN signature in SLE

Variable	Low IFN (%, N=116)	High IFN (%, N=156)	P-value	Adjusted P-value for Race
Malar rash	52.3	51.9	0.91	0.82
Discoid rash	14.7	19.2	0.32	0.30
Photosensitivity	58.6	51.3	0.23	0.45
Oral Ulcers	57.8	50.6	0.24	0.45
Arthritis	75.9	73.1	0.60	0.45
Serositis	49.1	48.1	0.86	0.89
Renal disorder	36.2	49.4	0.031	0.23
Neurologic disorder	12.9	7.7	0.15	0.19
Hematologic disorder	60.3	76.3	0.0048	0.0038
Immunologic disorder	81.9	87.2	0.23	0.38
ANA positivity	95.7	98.7	0.12	0.18

Table 2. Association between cumulative history characteristics and IFN signature in SLE

Variable	Low IFN (%, N=116)	High IFN (%, N=156)	P-value	Adjusted P-value for Race
Race				
African-American	29.3	36.5	<.0001	N.A.
Caucasian	70.7	50.6		
Other	0.0	12.8		
Pericarditis	15.7	27.6	0.02	0.024
Proteinuria	36.2	49.4	0.031	0.23
Anemia	61.2	75.0	0.015	0.12
Coombs	11.2	24.5	0.0055	0.0069
Leukopenia	33.6	53.9	0.0009	0.0018
Anti-DNA	45.7	73.7	<.0001	<.0001
Anti-Sm	10.3	25.8	0.0014	0.013
Anti-Ro	14.7	45.5	<.0001	<.0001
Anti-La	6.9	19.4	0.0035	0.0035
Anti-RNP	11.2	37.4	<.0001	<.0001
Low C3	42.2	66.7	<.0001	0.0011
Low C4	32.8	58.3	<.0001	0.0002

Table 3. Association between same-day visit disease activity and IFN signature in SLE

Variable	Low IFN (%, N=116)	High IFN (%, N=156)	P-value	Adjusted P-value[§]
Physician Global Assessment (>1)	12.9	23.1	0.034	0.19
SLEDAI ('2)	46.6	66.7	0.0009	0.004
Modified SLEDAI* (>1)	34.5	46.8	0.042	0.2
Age at visit (years)				
≤ 30	7.8	15.4	0.057	0.17
> 30	92.2	84.6		
Urine Protein/Creatinine Ratio (≥0.5)	6.9	13.5	0.083	0.70
Anti-dsDNA	7.8	33.3	<.0001	<.0001
Low C3	5.2	18.0	0.0016	0.0012
Low C4	5.2	16.0	0.0053	0.0032
ESR (>20)	40.4	58.4	0.0034	0.034

* Modified SLEDAI (SLEDAI without low complement or anti-dsDNA)
§ Adjusted for race unless specified
£ Adjusted for race, prednisone dose and immunosuppressive (yes/no)

Table 4. Association between SLICC/ACR Damage Index and IFN signature in SLE

Variables	Low IFN (%, N=116)	High IFN (%, N=156)	P-value	Adjusted P-value for Race
Cataract	31.0	16.0	0.0033	0.0027
Cognitive impairment	12.9	5.1	0.022	0.02
Valvular disease	6.0	1.3	0.03	0.06
Muscle atrophy or weakness	5.2	1.3	0.076	0.068
AVN	7.8	17.4	0.02	0.018

Results: The high interferon alpha signature group was associated with non-Caucasian race, younger age, autoantibodies, and low complement. Clinical associations included leukopenia and pericarditis. The high IFN signature was not associated with clinical disease activity at the same day, once low complement and anti-dsDNA were removed from the SLEDAI.

Conclusion: IFN signature was strongly associated with Coombs positivity, leukopenia, autoantibodies, and low complement, but not with clinical disease activity. Surprisingly, SLE patients with this signature had a lower risk of developing some organ damage including cataract, cognitive impairment, valvular disease, and muscle atrophy/weakness.

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Association Between Plasma Cell Gene Signature and Disease Characteristics in Systemic Lupus Erythematosus. Michelle Petri[1], Hong Fang[1], Jie Xu[1], Wenzheng Hu[1], Ehtisham Akhter[1], Jadwiga Bienkowska[2], Norm Allaire[2], John Carulli[2], Laurence S. Magder[3] and Matthew D. Linnik[4]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Biogen Idec Inc., Cambridge, MA, [3]University of Maryland, Baltimore, MD, [4]Biogen Idec Inc., Solana Beach, CA

Background/Purpose: B cells, circulating plasma cells and tissue resident plasma cells contribute to the production of autoantibodies in SLE. The plasma cell populations have been suggested as an attractive therapeutic target. We investigated the association between clinical phenotype and circulating plasma cell signature in SLE.

Methods: 292 SLE patients (91% female, 59% Caucasian, 34% African-American, mean age 46.0 years) were enrolled in a prospective observational study. At baseline, the plasma cell gene signature (IGJ and TXNDC5) was determined in peripheral blood RNA using Affymetrix chips, and was divided into low (<7, 43.2%), medium (7 to 8, 28.4%) and high (>8, 28.4%) groups. Clinical associations, based on the cumulative history and the same-day visit disease activity, were then determined. The results were based on the chi-square test (SAS Institute, Cary, NC, USA). P-values were then adjusted for race. A p-value ≤0.05 was considered statistically significant.

Table 1. Association between cumulative history characteristics and plasma cell signature in SLE

Variable	Low PC (<7) (%, N=126)	Med PC (7–8) (%, N=83)	High PC (>8) (%, N=83)	P-value	Adjusted P-value for Race
Race					
African-American	19.1	39.8	50.6	<.0001	N.A.
Caucasian	74.6	54.2	39.8		
Other	6.4	6.0	9.6		
Malar rash	53.2	50.6	49.4	0.86	0.99
Discoid rash	16.7	16.9	21.7	0.61	0.80
Photosensitivity	57.1	56.6	48.2	0.40	0.74
Oral Ulcers	59.5	51.8	45.8	0.14	0.51
Arthritis	69.8	80.7	74.7	0.21	0.35
Serositis	49.2	50.6	43.4	0.60	0.62
Renal disorder	45.2	39.8	45.8	0.67	0.26
Neurologic disorder	10.3	8.4	12.1	0.75	0.72
Hematologic disorder	68.3	67.5	77.1	0.30	0.28
Immunologic disorder	80.2	85.5	90.4	0.13	0.28
ANA	96.0	97.6	100	0.19	0.09
Hematuria	37.3	24.1	27.7	0.099	0.027
Anemia	61.1	72.3	75.9	0.054	0.54
Leukopenia	38.1	44.6	60.2	0.0067	0.021
Anti-dsDNA	56.4	62.7	69.9	0.14	0.20
Lupus anticoagulant	27.8	44.6	36.1	0.043	0.031
Anti-Ro	22.2	26.5	48.2	0.0002	0.0004
Anti-La	11.1	9.8	20.5	0.08	0.031
Anti-RNP	19.8	23.2	33.7	0.07	0.47
Low C3	52.4	53.0	65.1	0.15	0.17
Low C4	43.7	42.2	56.6	0.11	0.11
Increased ESR	68.3	69.9	80.7	0.12	0.51

Table 2. Association between same-day visit disease activity and plasma cell signature in SLE

Variable	Low PC (<7) (%, N=126)	Med PC (7–8) (%, N=83)	High PC (>8) (%, N=83)	P-value	Adjusted P-value for Race
Physician global assessment >1	19.1	14.5	22.9	0.38	0.46
SLEDAI ≥2	53.2	55.4	66.3	0.16	0.53
Immunosuppressive use	45.2	22.9	32.5	0.0035	0.0008
Prednisone use	42.1	30.1	30.1	0.11	0.025
NSAID	27.0	31.3	15.7	0.053	0.079
Statin	31.0	15.7	16.9	0.012	0.039

Table 3. Association between SLICC/ACR Damage Index and plasma cell signature in SLE

Variable	Low PC (<7) (%, N=126)	Med PC (7–8) (%, N=83)	High PC (>8) (%, N=83)	P-value	Adjusted P-value for Race
Cranial/peripheral Neuropathy	14.3	10.8	3.6	0.045	0.045
Deforming/Erosive arthritis	5.8	11.1	0.0	0.0093	too few

Results: Elevated plasma cell gene signature was associated with leukopenia, anti-Ro, anti-La and the lupus anticoagulant, but not with the same day clinical activity by PGA or SLEDAI. It was negatively associated with neuropathy and arthritis damage but not associated with other organ damage (not shown in the table). Treatment with prednisone, immunosuppressive drugs and statins was associated with lower plasma cell gene signature.

Conclusion: Surprisingly, the plasma cell signature was not associated with a more severe clinical activity phenotype, but with leukopenia and ENA. Immunosuppressive, prednisone and statin therapy was associated with lower plasma cell gene signature. The lack of association with clinical activity calls into question whether circulating plasma cells are the optimum therapeutic target in SLE. However, our assay does not account for tissue resident plasma cells.

1921

Narrowing the *Protein Tyrosine Phospahatse-22* Locus in Mice with Cartilage Proteoglycan-Induced Arthritis Explores Disease-Promoting and Disease-Suppressive Sub-Loci Neutralizing Their *In Vivo* Arthritis Susceptibility and Severity. Timea Besenyei[1], Andras Kadar[1], Beata Tryniszewska[1], Vyacheslav A. Adarichev[2], Katalin Mikecz[1] and Tibor T. Glant[1]. [1]Rush University Medical Center, Chicago, IL, [2]Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: Genome-wide screening of cartilage proteoglycan (PG)-induced arthritis (PGIA) in six different genetic combinations explored 29 QTLs (*Pgia1-Pgia29*), of which 8 showed high correlations with other arthritis models and GWAS of RA. We have selected *Pgia 26* locus on chromosome 3 (Chr3), because this is one of the most complex traits (after the MHC) regulating arthritis susceptibility and severity both in RA (*PTPN22* locus on human Chr1) and in PGIA (*Pgia26*). (Another study targets the Traf1/C5 locus on mouse Chr2 syntenic with human Chr9.) The goal was to narrow mouse Chr3 to as small as possible for candidate gene selection. Our hypothesis was that certain genes associated with these loci in murine autoimmune arthritis (PGIA) will correspond to genes involved in RA.

Methods: To achieve these goals, we intentionally excluded MHC (intercrossing arthritis–susceptible BALB/c and arthritis-resistant DBA/2 strains, both having the same H2d MHC), and replaced the entire genome with arthritis-prone BALB/c (congenic/sub-congenic stains) except the DBA/2 region of Chr3 (*Pgia26*).

Results: Eight subcongenic strains (n=355 animals) from Chr3 congenic (DBA/2 92.7–130 Mbp) and WT (n =102) mice were immunized for PGIA, scored, and serum markers such as autoantibodies (RF, ACPA, anti mouse PG), cytokines, *in vitro* T cell responses (PG-specific proliferation and cytokine production) were tested to select regions for further narrowing using interval-specific subcongenic strains.

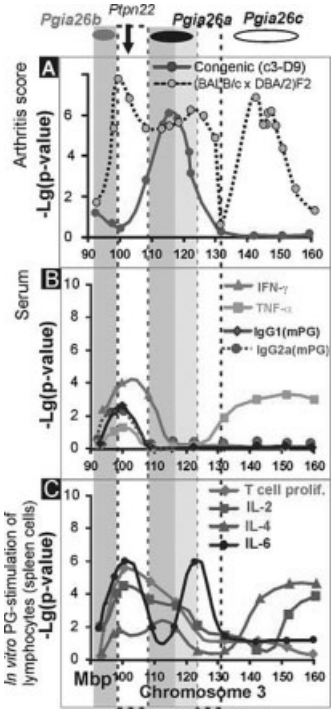


Figure 1. Linkage analysis for clinical and immune parameters in chr3 sub-congenic strains. Associations between traits and genotypes are presented as negative logarithms of p-values after Mann-Whitney U test [-Lg (p-value) on y-axis] (**Panels B and C**). Only traits (markers) that showed an association greater than $p < 0.01$ [-Lg (p-value) >2] are shown. Vertical shadowed areas indicate intervals of chr3 that were found to be associated with either arthritis promoting (*Pgia26b*) or arthritis suppressive (*Pgia26a*) effects using three independent analyses. Although we have localized the two major *Pgia26* loci, The intermediate region between the loci, however, does not seem to be "silent" either (white area throughout Fig. 1A–C).

Conclusion: We were able to distinguish between (i) a disease promoting region (both susceptibility and severity)(Pgia26b, Chr3: 92.799.5Mbp, approximately 40 genes in both human and mouse genomes), (ii) a disease suppressive locus (Pgia25a: Chr3: 109.2–115.8, ~20 genes) and (iii) regions appearing to control antigen (PG)-specific cytokine production and T cell proliferation (Fig. 1). The reduction of the sizes of these three "subloci" are in progress, and interval-specific subcongenic breeding pairs are established.

1922

Identification of microRNA-31 as a Novel Regulator Contributing to Impaired IL-2 Production in T cells From Patients With Systemic Lupus Erythematosus. Wei Fan[1], Yuanjia Tang[1], Bo Qu[1], Huijuan Cui[1], Xinfang Huang[1], Brandon W. Higgs[2], Yihong Yao[2], Bahija Jallal[2] and Nan Shen[1]. [1]Shanghai Ren Ji Hospital, Shanghai, China, [2]MedImmune, Gaithersburg, MD

Background/Purpose: MicroRNAs (miRNAs) act as fine tuner in the control of immune cells signaling. It was well-established as the abnormalities in signaling pathways related to interleukin(IL)-2 defect in lupus. miR-31 was identified as one of markedly underexpressed miRNAs in lupus patients. This study is aimed to investigate its role on IL-2 defect in lupus patients.

Methods: Quantitative analysis of miR-31 expression was done by TaqMan miRNA Assays. Transfection and stimulation of cultured cells followed by TaqMan qPCR, ELISA and reporter gene assays were conducted to determine the function of miR-31. Bioinformatics analysis, siRNA knockdown and western blotting were performed to validate miR-31 target and its function.

Results: miR-31 expression was significantly decreased and positively correlated with IL-2 expression in lupus T cells. Enforced expression of miR-31 in T cells increased, while knockdown of endogenous miR-31 reduced IL-2 production through changing the IL-2 promoter activity. RhoA as a miR-31 potential target was repressed by miR-31 in T cells. Of

note, siRNA-mediated knockdown of RhoA enhanced the IL-2 promoter activity then up-regulated IL-2 production. Consistently we also observed that RhoA expression was up-regulated and negatively correlated with miR-31 levels in lupus T cells. More importantly, manipulation of miR-31 expression in lupus T cells could restore IL-2 expression at both mRNA and protein level.

Conclusion: Our study reveals that miR-31 as a novel regulator can enhance the IL-2 production during T cell activation. Dysregulation of miR-31 and its target RhoA could be a novel molecular mechanism underlining deficiency of IL-2 in lupus patients.

1923

The Passenger Strand of MicroRNA-34a Is Epigenetically Silenced in Rheumatoid Arthritis Synovial Fibroblasts and Mediates Apoptosis Resistance Via Failure of XIAP (X-linked inhibitor of apoptosis protein) Inhibition. Fabienne Niederer[1], Caroline Ospelt[1], Joanna Stanczyk[2], Michelle Trenkmann[2], Emmanuel Karouzakis[2], Meike Dahlhaus[2], Beat A. Michel[2], Christoph Kolling[3], Renate E. Gay[2], Steffen Gay[2], Astrid Juengel[2] and Diego Kyburz[2]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Center of Exp. Rheumatology, Zurich, Switzerland, [3]Schultess Clinic, Zurich, Switzerland

Background/Purpose: Synovial fibroblasts (SF) from patients with rheumatoid arthritis (RA) are considered to be key effector cells as they are linked to synovial hyperplasia due to their apoptosis resistant phenotype. We have noted that the passenger strand of microRNA-34a (miR-34a*) is less expressed in SF from patients with RA compared to osteoarthritis (OA) and that it can modulate apoptosis. Therefore, we assessed the regulatory mechanisms accounting for the altered expression of miR-34a* and analyzed how miR-34a* influences apoptotic pathways in RASF.

Methods: Total RNA was isolated from RASF and OASF (n=8 each) using the mirVana miRNA isolation kit and human miR-34a* expression was determined using TaqMan Real-time PCR analysis. To study the regulation of miR-34a* in RASF, we treated cells with the cytokines TNF-α (10 ng/ml, n=7) and IL-1β (1 ng/ml, n=4), as well as with different ligands for Toll-like receptors (TLR) such as bLP (TLR2, 300 ng/ml, n=4), pIC (TLR3, 10 μg/ml, n=5) or LPS (TLR4, 10 ng/ml, n=4) for 2, 8 or 24 hours. For methylation studies, the inhibitor of DNA methyltransferase, 5-azacytidine (5-aza), was added to the cell culture medium at a concentration of 0.1 or 1 μM for 7 days (n=6). Synthetic precursors (pre-miRs) and inhibitors (anti-miRs) for miR-34a* were used to study the effect of miR-34a* on the expression of XIAP after 72 hours by SYBR green Real-time PCR (n=5). Furthermore, apoptosis induction was assessed by Flow Cytometry 72 hours post transfection to study the influence of miR-34a* overexpression on FasL (200 ng/ml, n=6) and TRAIL (20 ng/ml, n=4) induced apoptosis in AnnexinV/PI stained RASF. Activation of caspase 3 was assessed by a colorimetric caspase 3 activity assay (Abnova) in miR-34a* overexpressing RASF (n=3).

Results: Neither TNF-α, IL-1β nor the different TLR ligands were found to influence the expression of miR-34a*. However, demethylation of RASF by 5-aza treatment strongly modulated the expression of miR-34a*, resulting in a 70 % induction of miR-34a* compared to untreated cells ($p<0.05$). Most interestingly, we detected miR-34a* to further enhance apoptosis in FasL (from 25 to 40%, $p<0.05$) as well as in TRAIL (from 15 to 20%, $p<0.05$) stimulated RASF compared to control transfected cells. Similarly, we found that overexpression of miR-34a* resulted in a 1.9 fold induction of FasL induced caspase 3 activation. We could further show that this pro-apoptotic effect of miR-34a* was dependent on the apoptosis inhibitor XIAP, as transfection of RASF with pre-miR-34a* and anti-miR-34a* resulted in 39 $\pm$ 26% reduced and 90 $\pm$ 52% increased mRNA levels of XIAP, respectively ($p<0.05$).

Conclusion: So far, research has focused on mature miRNA strands whereas the function of passenger miRNA strands has not been analyzed in RA. Our data provide for the first time evidence that the passenger strand of miR-34a is epigenetically silenced in RASF and is involved in the modulation of apoptosis pathways. As miR-34a* was found to be down regulated in RASF, it fails to effectively inhibit the apoptosis inhibitor XIAP, thereby resulting in reduced activation of caspase 3, thus contributing to the apoptosis resistant phenotype of RASF.

1924

Adoptive Transfer of Induced-Regulatory T Cells Effectively Attenuates Murine Airway Allergic Inflammation. Qin Lan[1], Wei Xu[2], Julie Wang[1], Hui-Ming Fan[3], Bernhard Ryffel[4], Wei Shi[2] and Song G. Zheng[5]. [1]University of Southern California, Los Angeles, CA, [2]The Saban Rrsearch Institute of Children's Hospital Los Angeles, [3]Shanghai East Hospital, Tonji University, Shanghai, China, [4]University and CNRS, 3b rue de la Ferollerie, F-45071 Orleans, France, [5]USC Keck School of Medicine, Los Angeles, CA

Background/Purpose: Both nature (nTreg) and induced-regulatory T cells (iTreg) are potent regulator of autoimmune and allergic disorders. Defects in Treg cells have been reported in patients with allergic asthma, and therefore replenishment of Treg cells might attenuate asthma. Here we investigated if adoptive transfer of iTreg cells generated ex-vivo could attenuate lung and airway allergic inflammation in murine model of asthma.

Methods: Naïve CD4+ T cells purified from spleen in C57BL/6 mice, were activated with anti-CD3/CD28-coated beads (1 bead: 3 cells) and IL-2 (50U/ml), in the presence (iTregs) or absence (CD4 control) of TGF-β (2ng/ml). C57BL/6 mice were immunized with OVA mixed with aluminum hydroxide (day 0) and challenged with OVA control through an intranasal (i.n.) route for three consecutive days (days 25, 26, and 27) to generate an acute allergic asthma model. 5×10^6 of iTreg cells or control cells were intravenously injected into mice on day 22, three days before antigen challenge. Pathological changes in airway and lung were observed by H&E, Discombe's Solution and Periodic-Acid-Schiff (PAS) staining. The intracellular expression of Foxp3, IFN-γ, IL-5 and IL-17 in CD4+ cells in spleens and draining lymph nodes was examined by flow cytometry. IgE in peripheral blood serum was measured by enzyme linked immunosorbent assay.

Results: Immunized mice given iTreg cells just before antigen challenge displayed markedly reduced airway résistance, eosinophil recruitment, mucus hyper-production, airway remodeling and IgE levels. This therapeutic effect was associated with increase of Treg cells ($CD4^+FoxP3^+$) in the draining lymph nodes, and with reduction of Th1, Th2, and Th17 cell response as compared to untreated and non-Treg cell treated controls.

Conclusion: Therefore, adoptive transfer of iTreg reduces the allergic response, which might be a novel and promising therapeutic approach to treat severe asthma.

1925

Correlations Between S100 Gene Expression Levels and the Local and Systemic Inflammatory Markers (matrix metalloproteinase-3, MMP3; erythrocyte sedimentation rate, ESR) in Rheumatoid Arthritis Patients. Hooi-Ming Lee[1], Hidehiko Sugino[1], Chieko Aoki[2], Miho Murakami[2], Takaji Matsutani[2], Takahiro Ochi[3] and Norihiro Nishimoto[2]. [1]Osaka University, Suita, Japan, [2]Wakayama Medical University, Ibaraki, Japan, [3]Osaka Police Hospital, Osaka, Japan

Background/Purpose: In humans, the S100 protein family is composed of at least 24 members and is thought to be involved in cell proliferation and differentiation via calcium regulation. Overexpressions of several S100 proteins have recently been reported in rheumatoid arthritis (RA). Thus, we performed a comprehensive gene expression analysis in RA patients to investigate the S100 gene expression levels and further investigating the correlations with clinical and laboratory markers.

Methods: Gene expression profiles of the peripheral blood from 112 RA patients with active disease (DAS28, 6.2 $\pm$ 0.9; CRP, 32 $\pm$ 24 mg/l; MMP3, 308.2 $\pm$ 225.3 ng/ml; ESR, 51.9 $\pm$ 26.1 mm/h; mean $\pm$ SD) and 45 healthy individuals (HI) were obtained using DNA microarray. S100 gene expressions were compared between the two groups using unpaired Mann-Whitney test. Clinical and laboratory markers including DAS28, serum MMP3 levels, and ESR of RA patients were obtained and correlations between expression levels of differentially expressed S100 genes and each marker were investigated using Spearman's rank correlation.

Results: The expressions of fifteen S100 genes were investigated. *S100A4, S100A5, S100A6, S100A9, S100A11*, and *S100A12* are significantly overexpressed in RA patients ($P<0.0005$). *S100G* were also increased ($P<0.005$) while *S100A2, S100A13, S100A16*, and *S100B* were underexpressed ($P<0.05$). There were no correlations between the expression levels of differentially expressed S100 genes and DAS28. However, the expression levels of *S100A6* and *S100A9* were found significantly correlated to MMP3 levels (Spear r = 0.25, 0.24, respectively; $P<0.05$), which may reflect joint inflammation and it is reported to be valuable for predicting bone damage progression, especially in the

early stage of RA, and *S100A12* was correlated to ESR, an inflammatory marker (Spear r = 0.21; $P < 0.05$).

Conclusion: We confirmed the previously described up-regulation of *S100A4* and *S100A12*, and also newly found up-regulation of *S100A5, S100A6, S100A9*, and *S100A11* in RA patients' peripheral blood. Correlation of *S100A6* /*S100A9* expression levels and serum MMP3 levels; *S10012* expression levels and ESR suggested their roles in inflammatory conditions in RA.

1926

Proteomic Characterization of Plasma Microparticles in Autoimmune Diseases. Christoffer T. Nielsen[1], Ole Østergaard[1], Line V. Iversen[1], Søren Jacobsen[2] and Niels H.H. Heegaard[1]. [1]Statens Serum Institut, Copenhagen S, Denmark, [2]Rigshospitalet - 4242, Copenhagen, Denmark

Background/Purpose: Circulating cell-derived microparticles (MPs) are a heterogenous population of submicron membraneous vesicles shedded from the cell-surface involved in cell-cell communication and immune regulation. We explored differences on the proteome level between MPs isolated from well-characterized patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), and from healthy controls (HCs).

Methods: 12 SLE (6 active, 6 in remission), 6 RA (3 active, 3 in remission) and 6 SSc (3 with limited and 3 diffuse cutaneous SSc) patients were compared with 12 age- and gender-matched healthy controls. MPs from platelet-poor plasma were purified using centrifugation followed by tryptic digestion and analysis with liquid chromatography tandem mass spectrometry (LC-MS/MS) on an Orbitrap mass spectrometer. MP proteins were identified and spectral counts (SCs) were used as a semiquantitative measure of the abundance of each identified protein. Two independent statistical models, hierarchical clustering and principal component analysis (PCA) were applied to all the identified MP proteins and their associated SC values to search for disease classifiers.

Results: We identified a total of 343 unique protein entities in MPs. Of the, 143 were either membrane proteins or proteins otherwise associated with the cell membrane according to gene ontology analysis. 131 proteins represented extracellular proteins and included plasma proteins such as immunoglobulins, and other well-known opsonizing proteins including serum amyloid P component and C1q. Using both hierarchical clustering analysis and PCA, we were able to separate the different disease groups and identify several MP-associated disease classifying proteins as shown in Figure 1. Very high levels of MP-associated C1q and many forms of IgG and also galectin-3-binding protein, a protein mediating adhesion and sensing intracellular changes, were associated with MPs from the SLE group. Cytoskeletal proteins (multimerin-1 and myosin-9) and integrins (integrin-beta-3 and integrin alpha-IIb) were present in higher levels in the MPs from RA patients and HCs.

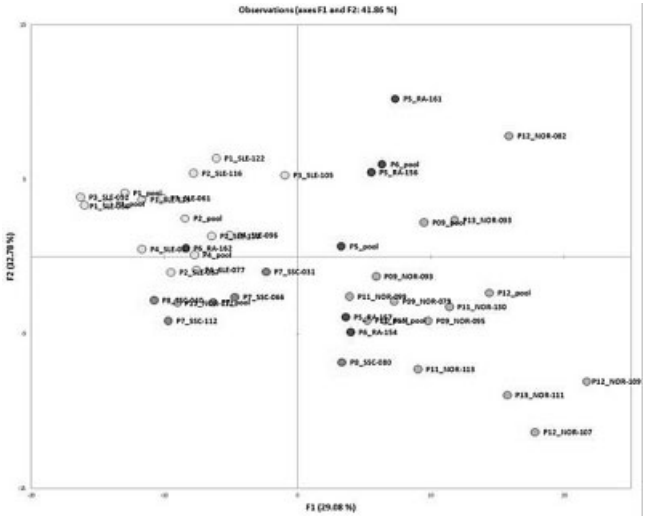


Figure 1.

Conclusion: Proteome analysis of plasma MPs in different autoimmune diseases reveals differentiating protein patterns with potential for biomarkers and supports MPs putative role in intercellular signalling and immune regulation.

1927

Feasibility of a Molecular Diagnosis of Arthritis Based on the Identification of Specific Transcriptomic Profiles in Knee Synovial Biopsies. Isabelle Focant[1], Daniel Hernandez-Lobato[2], Julie Ducreux[1], Patrick Durez[1], Adrien Nzeusseu Toukap[1], Dirk Elewaut[3], Frédéric. A. Houssiau[1], Pierre Dupont[2] and Bernard Lauwerys[1]. [1]Université catholique de Louvain, Brussels, Belgium, [2]Université catholique de Louvain, Louvain-La-Neuve, Belgium, [3]Gent University Hospital, Ghent, Belgium

Background/Purpose: Early diagnosis of arthritis is an "unmet medical need" in the field of rheumatology, as borne out by the number of publications addressing the issue. In particular, the delay in making a diagnosis of rheumatoid arthritis and initiating adequate therapy is associated with poor clinical, radiological and functional outcomes. In previous experiments, we performed transcriptomic studies on synovial biopsies from patients with arthritis using high-density oligonucleotide-spotted microarrays, and found that synovial gene expression profiles were significantly different according to the underlying disorder. Here, we wanted to explore whether these findings could translate into a useful diagnostic procedure.

Methods: Synovial biopsies were obtained from the knee of patients with a definite diagnosis of rheumatoid arthritis (1987 ACR criteria), seronegative arthritis or osteoarthritis (n=40), and from patients with undifferentiated arthritis (n=20). During each procedure, 6 to 8 biopsy fragments were stored overnight in RNALater at 4°, and next frozen at −80°. Biotinylated cDNA was synthesized and hybridized on customized low-density arrays, spotted with 100 diagnostic probes, house keeping genes and internal standards, in triplicates. Finally, the slides were scanned and the probe intensity data were collected for each sample. We performed the analyses by partitioning the microarray data into a training set and a testing set. The diagnosis of the samples in the testing set was generated using a nearest neighbor classification method, based on the Pearson correlation distance.

Results: In a first step of experiments, we looked whether the molecular diagnosis generated by the interpretation of the low-density microarray data matched the clinical diagnosis for the samples obtained from patients with a known diagnosis. We found that a right diagnosis was obtained in 73% of the samples. Because therapy can affect the gene expression profiles in the synovium and blur their diagnostic performances, we next restricted these analyses to the samples obtained from untreated patients. Doing this, we saw a slight improvement in the percentage of right molecular diagnoses, up to 75% of the cases. Next, we wondered whether addition of selected clinical symptoms could increase the accuracy of our model. Algorithms were developed that combine low-density array data and one or several relevant symptoms. Strikingly, the accuracy of the algorithm combining low-density expression data and 3 symptoms (presence of psoriasis, arthritis of the hands, presence of rheumatoid factors) was 92%. Finally, we performed the same analyses in 20 synovial samples obtained from UA patients. The combination of expression and clinical data resulted in a molecular diagnosis, which was confirmed in the 8 patients in whom a clinical diagnosis was made during the follow-up period after the biopsy.

Conclusion: Taken together, our data indicate that a diagnosis can be made in patients with UA based on the combination of gene expression data and selected clinical symptoms. As such, these results are particularly relevant from a clinical point of view, and open the perspective of valorization into a diagnostic test.

1928

Selective Inhibition of Epigenetic Factors Provide Potential New Tools for Arthritis Therapy. Timea Besenyei, Júlia Kurkó, Katalin Mikecz, Tibor T. Glant and Tibor A. Rauch. Rush University Medical Center, Chicago, IL

Background/Purpose: Rheumatoid arthritis (RA) is a degenerative inflammatory autoimmune disease that affects more than 1% of the human population. Currently, there is no ideal therapy for RA, but various types of treatments can provide alleviation of symptoms and modify disease progression. RA is considered to be a polygenic disease with strong immunogenetic components, because various immune cells (B and T lymphocytes, macrophages, dendritic cells) are involved. Besides of recently mapped genes, environmental factors can also contribute to the etiology of RA and increasing number of data proves that epigenetic factors are involved in autoimmune diseases. Therefore, enzymes that play roles in chromatin modification are plausible targets of RA therapy.

Methods: Applying specific *PCR arrays* we investigated the expression profile of 84 genes encoding key enzymes known to be specific modifiers of chromatin. Total RNA was isolated from lymphocytes from a murine model (proteoglycan-induced arthritis, **PGIA**) of RA and from mononuclear cells separated from RA patients and healthy controls.

Results: Fourteen chromatin modifying enzyme encoding genes showed arthritis-associated expression changes in arthritic mice. Six out of 14 genes showed elevated expression and eight were significantly down-regulated. Three of the up-regulated genes encode kinases involved in cell cycle regulation, while the other three are histone acetyltransferases. Application of selective kinase and acetyltransferase enzyme inhibitors was found to reduce the activity of the encoded enzymes and promote lymphocyte apoptosis both in ex vivo cell cultures and in vivo in arthritic mice. Preventive treatment of arthritis-prone mice and therapeutic treatment of established polyarthritis delayed the onset and attenuate severity of the arthritis.

Conclusion: Studies focused on human subjects revealed similar up-regulation of a set of enzymes in RA patients than in arthritic mice. Methotrexate (MTX) treatment lowered certain enzymes' expression levels in mononuclear cells of RA patients. Since MTX frequently does not provide ideal relief for RA patients, alternative treatment options including epigenetic enzyme inhibitiors can hold a great promise for next generation of RA therapies.

1929

Genome-Wide DNA Methylation Profiling Studies of Lymphocytes in Arthritic Mice. Tamas Kobezda[1], Katalin Olasz[2], Katalin Mikecz[1], Tibor T. Glant[1] and Tibor A. Rauch[1]. [1]Rush University Medical Center, Chicago, IL, [2]Pecs, Hungary

Background/Purpose: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that mainly attacks synovial joints leading to inflammatory destruction of articular cartilage and bone. Although significant progress has been made in understanding of the genetics of the disease, a global characterization involving epigenomes in polyarthritis has not been yet performed. According to some recently published genome-wide DNA methylation study there is no detectable arthritis-associated DNA methylation changes in gene promoters in white blood cells. We challenged this observation by extending our genome-wide studies beyond the previously investigated CpG Islands.

Methods: Applying specific PCR arrays we investigated the expression profile of 84 genes encoding key enzymes known to be specific modifiers of chromatin. Total RNA and genomic DNA were isolated from lymphocytes from a murine model (proteoglycan-induced arthritis, **PGIA**) of RA and from mononuclear cells of RA patients and healthy individuals. DNA methylation alterations associated with the pathogenesis of arthritis was detected by Methylated CpG Island Recovery Assay (MIRA)-on-chip technique, and the accompanying gene expression changes were monitored by quantitative RT-PCR.

Results: PCR array studies identified eight genes showed arthritis-specific down-regulation in PGIA mice. Interestingly, enzymes involved in gene silencing were among the down-regulated genes including three DNA methyltransferases (Dnmts) and two histone deacetylases (Hdacs). Decreased expression of Dnmts is followed by a global demethylation in the lymphocyte epigenomes as we detected by an anti-5-methyl-citosin-based ELISA. To identify the exact genomic location of arthritis-associated hypomethylations we investigated all annotated mouse promoters and CpG islands by MIRA-on-chip method. The identified hypomethylated events were mostly localized outside of the CpG islands, in the so called, "CpG island shores". The detected demethylation was mostly followed by increased expression one of the nearby located genes. We further investigated expression changes of DNMTs in human mononuclear cells and found similar level of down-regulation of the above-mentioned genes than in PGIA model. This observation is a good promise to identify RA-specific DNA methylation changes in the human genome.

Conclusion: Arthritis-associated DNA methylation changes do exist and promote altered expression of genes. Our data shed light onto the molecular background of the known activated state of lymphocytes in arthritis, in the sense, that the low or inefficient expression of the inhibitors (i.e., DNMTs and HDACs) can contribute to the pathogenesis of RA.

1930

The *De Novo* Revision of TCRα but Not TCRβ Is Responsible for the Generation of Autoantibody-Inducing CD4$^+$ (*ai* CD4$^+$) T Cell That Causes Systemic Autoimmunity. Kenichi Uto[1], Ken Tsumiyama[1] and Shunichi Shiozawa[2]. [1]Kobe University Graduate School of Health Science, Kobe, Japan, [2]Kobe University Graduate School of Health Science and Medicine/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Background/Purpose: We have repeatedly immunized mice normally not prone to autoimmune disease with the same antigen, and show that repeated immunization reproducibly causes systemic autoimmunity, i.e., systemic lupus erythematosus (SLE) (Tsumiyama K. *et al. PLoS ONE 4(12):e8382, 2009). Our studies show that autoantibodies are induced via de novo* T cell receptor (TCR) revision at periphery in spleen, giving rise to a novel T cell type we term an autoantibody-inducing CD4$^+$ T cell (*ai* CD4$^+$ T cell). The *ai* CD4$^+$ T cell not only stimulated B cells to generate varieties of autoantibodies but also helped final differentiation of CD8$^+$ T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to induce lupus tissue injuries. Here we investigated how *ai* CD4$^+$ T cell was generated in view of V(D)J recombination. The result showed that *ai* CD4$^+$ T cell was induced by *de novo* revision of TCRα but not TCRβ at periphery in spleen.

Methods: BALB/c mice were repeatedly immunized with staphylococcul enterotoxin B (SEB) by means of i.p. injection every 5 days. Expression of recombination-activating gene (RAG) 1/2, terminal deoxynucleotidyl transferase (TdT) and surrogate TCRα chain (pTα) in spleen were determined by using RT-PCR. GFP-positive cells in splenic Vβ8$^+$CD4$^+$ T cells of *rag1/gfp* knock-in mice were detected by using FACS. The rearranged intermediates of TCRα joining (Jα) regions from 1 to 61 and all TCRβ variable (Vβ) and diversity (Dβ) regions, which were blunt-ended DNA fragments flanked by recombination signal sequences, were detected in spleen by using ligation-mediated PCR. The histone modifications of TCR loci were examined by using ChIP assay.

Results: The V(D)J recombinase complex including RAG1/2, TdT and pTα was re-expressed in splenic T cells after immunization 8x with SEB. Expression of RAG1 gene was confirmed *in vivo* in *rag1/gfp* knock-in mice. Among varieties of Jα genes, the rearranged intermediate of TCR Jα12 gene was solely and specifically detected in splenic Vβ8$^+$CD4$^+$ T cells after immunization 8x with SEB. The studies encompassing gene regions Vβ2, 4, 16, 10, 1, 5.2, 8.3, 5.1, 8.2, 8.1, 13, 12, 11, 9, 6, 15, 20, 3, 7, 18, and 14 and Dβ1 and 2 genes, showed that rearranged intermediates of TCR Vβ and Dβ were never detectable, indicating that *de novo* revision of TCRα but not TCRβ takes place in spleen. Further, histone H3 of TCR Jα and Dβ regions but not TCR Vα and Vβ regions in splenic CD4$^+$T cells was heavily acetylated and trimethylated to the levels identical to those in thymus, indicating that the DJ region of splenic CD4$^+$T cells is constantly open to RAG1/2 and ready for TCR revision in terms of chromatin structure. The results indicate that these exists selection only for Jα chain to Jα12.

Conclusion: We show that the autoreactive (autoantibody-inducing) TCR of *ai* CD4$^+$ T cell is Jα12Vβ8 when SEB was used as a driving antigen. In view of our novel self-organized criticality theory, the structure of autoreactive TCR of *ai* CD4$^+$ T cell differs depending on driving antigen, which we investigate further. As to why TCRβ is not revised, possible explanations would be feedback inhibition of TCRβ but not TCRα revision because of locus conformation and subnuclear localization of TCRβ locus, or structural constraints of TCRβ chain against TCRα chain.

1931

The Transcriptomic Analysis From PBMC Is a Powerful Approach to Identify Specific Signatures Able to Predict Responses for Each TNFalpha Blocking Agent. Romain Normand[1], Olivier Vittecoq[2], Martine Hiron[1], Céline Derambure[1], Xavier Le Loët[2] and Thierry Lequerré[2]. [1]Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [2]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France

Background/Purpose: The number of RA biological treatments is increasing but 30 to 40% of patients do not respond to TNFαblocking agents. One way to optimize the drug prescription is to identify predictive markers of drug responsiveness for each biologic agent. We already identified a gene combination able to predict infliximab responsiveness by transcriptomic analyses. The question is to know if this approach is enough sensitive to identify specific gene expression profile for the different TNFα blocking agents.

To identify specific gene expression profiles able to predict the response of RA patients treated with methotrexate (MTX)/adalimumab (ADA) or MTX/etanercept (ETA).

Methods: Twenty-nine RA patients were randomized to receive subcutaneously either ADA (40 mg each other week) or ETA (50 mg per week). Eighteen RA patients [average age: 49 $\pm$ 16 years old (yo), MTX: 14 $\pm$ 6 mg/week (w), initial DAS28: 5 $\pm$ 0.8] received ADA while eleven RA patients (age: 55 $\pm$ 15 yo, MTX: 18 $\pm$ 2 mg/w, initial DAS28: 5 $\pm$ 1) received ETA. The drug efficacy was evaluated with the DAS28 score after 3, 6 months and after one year of treatment according to the EULAR response criteria. A blood sample was carried out in patients just before the first injection of treatment in order to isolate peripheral blood mononuclear cells (PBMC) and extract total RNA. cRNAs were synthesized, amplified, labelled and purified using the Quick AMP labelling Agilent kits. Labeled cRNAs were hybridized to Agilent 4 $\times$ 44 K array and

scanned with an Agilent Scanner. Microarray data were extracted and normalized with the Feature Extraction software. Next, a supervised analysis was performed using t-test (GeneSpring GX software) in order to identify gene expression profiles able to separate perfectly responders (R) and moderate responders (MR) to each drug. The gene expression profiles obtained for ADA and ETA were further compared to know if we have a specific signature for each drug.

Results: Demographic, clinical and biological characteristics of all the patients were comparable whatever the treatment administered. From the 18 patients treated with ADA, a combination of 46 transcripts ($p<0.01$) was able to separate perfectly R (9/18) and MR (9/18). Among the 11 patients who have been treated with ETA, 3/11 were classified as R and 8/11 as MR. A combination of 2074 transcripts ($p<0.01$) was able to separate perfectly R and MR to ETA. When we compared these two combinations of transcripts, just an overlap of 3 transcripts was found between them, leading us to consider that the signatures obtained for ADA and ETA are drug specific.

Conclusion: We identified a specific drug signature able to separate perfectly R and MR to either MTX/ADA or MTX/ETA. This study has shown for the first time that the transcriptomic approach is a sensitive, relevant and powerful tool to identify specific predictive markers for each molecule, not only through the different classes of immunotherapies but also in a same class of drug such as TNFα blocking agents.

1932

Identification of a Set of 8 Proteins Able to Predict the Response to Methotrexate/Etanercept In Rheumatoid Arthritis Patients. Antoine Obry[1], Pascal Cosette[2], Philippe Chan Tchi Tsong[3], Jéremy Siemowski[4], Paul Morel[4], Olivier Boyer[1], Patrice Fardellone[5], René-Marc Flipo[6], Christian Marcelli[7], Xavier Le Loët[8], Thierry Lequerré[8] and Olivier Vittecoq[8]. [1]Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [2]UMR 6270 CNRS, Plate-Forme d'Analyse protéomique de l'IFRMP23, Faculté des Sciences, University of Rouen, Rouen, France, [3]Inserm 982, Plate-Forme d'Analyse Protéomique de l'IFRMP23, Faculté des Sciences, University of Rouen, Rouen, France, [4]UMR 6270 CNRS, Faculté des Sciences, University of Rouen, France, [5]Rheumatology Department, Amiens University Hospital, Amiens, France, [6]Rheumatology Department, Lille University Hospital, Lille, France, [7]Rheumatology Department, Caen University Hospital, [8]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France

Background/Purpose: The number of biologic agents in RA is continuously increasing. However, clinicians observe that around 30 to 40% of treated patients fail to respond to TNFα blocking agents. One way to optimize the drug prescription is to identify predictive markers of drug responsiveness.

To identify a combination of proteins whose expression profile would predict the RA patients responses to the association of methotrexate (MTX) and etanercept (ETA).

Methods: A set of 10 patients with active RA (average age: 54 $\pm$ 16 years old, RA duration: 9 $\pm$ 9 years, MTX: 18 $\pm$ 3 mg/week, DAS28: 5.5 $\pm$ 1.0) was treated by a subcutaneous injection of ETA (50 mg/week). The clinical efficacy of these drugs was evaluated with the DAS28 score after 3, 6 and 12 months of treatment according to the EULAR response criteria. For proteomic analysis, a blood sample was carried out in patients prior to the first injection in order to extract peripheral blood mononuclear cells (PBMC). A relative quantification of protein expression from 7 samples of PBMC was performed by mass spectrometry, after labelling with stable isotopes (Isobaric Tags for Relative and Absolute Quantification: iTRAQ®). Protein identification and differential analysis between the samples from responders (R) and non-responders (NR) were made with the Spectrum Mill® software (Agilent). The statistical treatment using iQuantitator® has enabled the relative protein quantification for each patient. From 5 others samples of PBMC, a complementary approach based exclusively on mass spectrometry was implemented (the "label free approach"). "Label-free" quantification is based on extracted ion chromatograms to determine the differential expression. The differential analysis was achieved with SIEVE® (Thermofisher), a label-free dedicated software to compare LC/MS data from LTQ Orbitrap® (Thermofisher) analysis.

Results: Among the 10 patients, 6 out of 10 were classified as R.. When merging the 2 independent experimental approaches, we got consistent results for 8 overexpressed proteins and 2 underexpressed proteins among all patients responding to treatment.

Conclusion: For the first time, we identified a proteomic signature from PBMC able to predict MTX/ETA response. These proteins would thus represent valuable candidates for biomarkers of etanercept responsiveness that should be validated on a larger population. In addition, among the identified proteins, several proteins are also present in plasma, offering the possibility to explore their predictive value by ELISA tests.

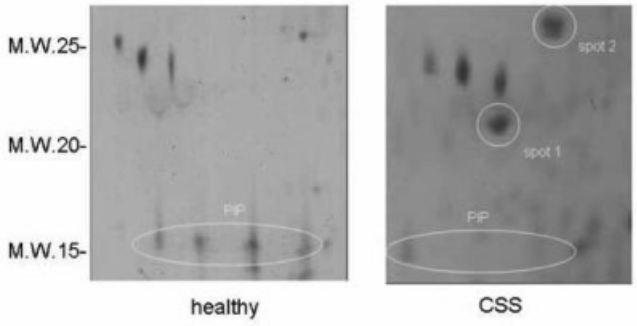
1933

Salivary Proteomics and Churg-Strauss Syndrome: A Phase IIa Case-Control Study Aimed At Identifying Novel Diagnostic Disease Biomarkers. Chiara Baldini, Daniela Martini, Sara Grossi, Nicoletta Luciano, Francesco Ferro and Stefano Bombardieri. Rheumatology Unit, Pisa, Italy

Background/Purpose: This is a IIa case-control study aimed at identifying novel proteomic biomarkers in whole saliva of patients affected by Churg-Strauss syndrome (CSS).

Methods: Consecutives subjects with a diagnosis of CSS (ACR criteria) and age- and sex- matched healthy volunteers were included in the study. Unstimulated WS samples were collected and analysed under standard conditions. Two-dimensional electrophoresis (2DE) was performed using the Immobiline-polyacrylamide system with pH 3–10L, 17 cm long IPG strips (Protean IEF Cell Biorad). The second dimension (SDS-PAGE) was performed by transferring the proteins to 15% polyacrylamide gel. The analytical gels were stained with Coomassie colloidal and images were analysed with PDQuest advanced software.

Results: Eighteen patients with a diagnosis of CSS (9 M: 9 F, mean age 62$\pm$14 yr, mean disease duration 7.8$\pm$5.3 yr) were enrolled. At the study entry, all the patients were in clinical remission (BVAS=2.5$\pm$2.9, VDI=2$\pm$1.1) with low dose steroids and weekly methotrexate ($<$ 15 mg/w). Asthma was poorly or partially controlled in 13/18 patients. Six CSS patients showed nasal polyposis and active rhinosinusitis. Two spots (Fig 1. spot n°1 e 2) with observed MW of $\sim$ 23 KDa/pI 4,3, and MW $\sim$ 30 KDa/pI 4,5 respectively, were detected in 16/18 and in 14/18 CSS cases and in none of the controls. A trend to prolactin-inducible protein precursor (PIP) decrease and fragmentation was observed in subjects with poorly controlled asthma (p-value 0.07) (Fig. 1).



Conclusion: In this preliminary study we described a different salivary proteomic profile in patients with CSS with respect to healthy controls. The identification by mass spectrometry (MALDI-TOF-MS) of the proteins differently expressed is now ongoing and will clarify the clinical and pathogenetic implications of our findings.

1934

BAFF and TACI Gene Expression Are Increased in Untreated Very Early Rheumatoid Arthritis Patients. Rita A. Moura[1], Helena Canhão[2], Joaquim Polido-Pereira[2], Ana M. Rodrigues[2], Márcio Navalho[3], Ana F. Mourão[4], Carlos M. Rosa[5], Catarina Resende[5], Raquel Campanilho-Marques[2], João Madruga Dias[2], João R. da Silva[5], Mário Bexiga[5], José A. Pereira da Silva[5], Luis Graca[6] and João E. Fonseca[7]. [1]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [2]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisbon, Portugal, [3]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Radiology Department, Hospital da Luz, Lisbon, Portugal, [4]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa and Rheumatology Department, Centro Hospitalar de Lisboa Ocidental, EPE, Hospital Egas Moniz, Lisbon, Portugal, [5]Rheumatology Department, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisbon, Portugal, [6]Cellular Immunology Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, [7]Lisbon Academic Medical Center, on behalf of Rheumatic Diseases Portuguese Register (Reuma.pt), Lisbon, Portugal

Background/Purpose: B cells play several important roles in Rheumatoid Arthritis (RA). Previous studies by our group have demonstrated that

very early RA patients have disturbances in peripheral blood memory B cells and increased circulating B-cell related cytokines. The main goal of the present work was to evaluate whether changes in the expression of genes related with B cell survival and activation were already present in untreated very early RA (VERA) patients (<6 weeks of disease duration).

Methods: The expression of a group of B-cell related activation and survival genes was quantified in peripheral blood mononuclear cells (PBMC) from VERA patients by real-time PCR and compared with untreated early RA (<1 year, ERA), established treated RA patients (RA) and other untreated early arthritis conditions (EA). Serum BAFF was quantified by ELISA.

Results: BAFF gene expression and serum levels were highest in VERA patients. The expression of BAFF-R increased with disease progression, while TACI was elevated since the first weeks of RA onset. Pax5 gene expression was also increased in all RA stages. CXCR5 was only elevated in established RA. No differences were observed in BCMA, AID, Blimp-1 and Bcl-2 expression.

Conclusion: Disturbances in the expression of B-cell related activation and survival genes, particularly BAFF and TACI, occur since the very early phase of RA and precede changes in BAFF-R. These alterations can potentiate the development of autoreactive B cells since the first weeks of RA onset.

L. Graca and J.E. Fonseca are joint senior authors.

1935

SLC2A9 Gene Expression Is Associated with a Haplotype Tagging Polymorphism. Philip L. Riches, Samuel Gray, Omar Albagha and Stuart H. Ralston. University of Edinburgh, Edinburgh, United Kingdom

Background/Purpose: SLC2A9 expresses a novel urate transporter that has been consistently identified as an important regulator of serum urate and clinical gout. Although non-synonymous coding polymorphisms of SLC2A9 have been reported these have typically shown less significant associations with serum urate than non-coding variants, suggesting that non-coding polymorphisms within regulatory elements of the gene may be more important. We have explored the effect of a haplotype tagging polymorphism on the expression of SLC2A9 in human kidney and peripheral blood. In addition we have investigated the promoter activity of putative promoters of different splice variants of the gene.

Methods: The coding polymorphism rs16890979 was selected as a haplotype tagging marker known to be in strong linkage disequilibrium with intronic SNPs identified from genome wide association studies of serum urate (Kolz *et al*, PLoS Genetics 2009). TaqMan genotyping probes recognising either allele of rs16890979 were obtained from Applied Biosystems. RNA was extracted from whole blood or surplus tissue obtained from nephrectomy or joint replacement surgery using standard techniques. For the promoter-reporter assays 2kb fragments upstream of exon 1 of both short and long splice variants of SLC2A9 were cloned as well as a 2kb region immediately upstream of exon2 which is predicted to have regulatory potential. Promotor constructs were transfected into HEK293 cells using a pGL3 basic vector with expression levels determined by measurement of firefly luciferase.

Results: In samples from patients heterozygous for the rs16890979 polymorphism consistent overexpression of SLC2A9 was observed with the minor 'A' allele relative to the major 'G' allele. Approximately 6 fold enhanced expression was observed in both peripheral blood and renal tissue. Similar levels of expression were observed in synovial tissue as were seen in renal tissue. Minimal promoter activity was observed in both putative promoter regions upstream of short and long splice variants but approximately 2 fold enhanced expression was seen within a 2kb region upstream of exon2.

Conclusion: Marked differential expression of SLC2A9 is associated with alternative alleles of the rs16890979 polymorphism suggesting that this marker is in linkage disequilibrium with a mutation influencing gene regulation. Modest promoter activity is identified in a region upstream of exon 2 of SLC2A9. Further work will be required to identify variants within this promoter region, as well as to look for further regulatory elements within SLC2A9. SLC2A9 is known to be expressed in the proximal tubule where it is expressed at both apical and basolateral membranes. Better understanding of the role of SLC2A9 in regulating serum urate and also better understanding of the regulation of urate transport in synovium may in time lead to novel strategies for the management of gout.

1936

Elevated Expression of MMP9 in Plasma of Patients with Symptomatic Knee Osteoarthritic: Correlation with Disease Severity and Progression. Mukundan Attur[1], Jeffrey D. Greenberg[2], John Todd[3], Quynh Ann Lu[3], Renita Ramirez[3], Cheongeun Oh[4], Jonathan Samuels[1], Svetlana Krasnokutsky[5] and Steven B. Abramson[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]New York University School of Medicine, New York, NY, [3]Singulex, Alameda, California, Alameda, CA, [4]New York University, New York, NY, [5]NYU Hospital for Joint Disease, New York, NY

Background/Purpose: Osteoarthritis is degenerative joint disease that leads to permanent joint damage and is a multi-factorial complex disease. It is well established that in OA cartilage and synovium that some of the metalloproteinases (MMP) are over expressed including MMP- 2, 9 and 13 and Tissue inhibitors of Matrix metalloproteinases (TIMP) are down regulated. There is currently great interest in the field of OA to identify biomarkers that provide a method for earlier diagnosis and identify patients at higher risk for disease progression. This study was designed to test the hypothesis that plasma levels of gelatinase(s) MMP-2 and 9 predict knee OA severity and progression based on radiographic findings.

Methods: 150 Symptomatic knee OA (SKOA) patients (mean age 63.09 ± 10.3, mean BMI 26.5 ± 3.6) fulfilling ACR criteria for knee OA were recruited as part of an NIH-funded 24 month prospective study. These patients were followed longitudionally for 24 months, x-ray were taken at visit 0 and 24 months. The blood samples were collected at baseline and every 6 months. Standardized semi-flexed radiographs were scored for overall Kellgren and Lawrence (KL) grade, osteophytes, joint space width (JSW) and subchondral sclerosis by the same radiologist. Plasma samples from visit 18 month of 128 OA patients (37% male) were assayed for gelatinase(s) MMP-2 and 9 using the highly sensitive Erenna Immunoassay system (Singulex, Inc). For radiographic severity, biomarker were evaluated between KL scores of 1, 2 with those with scores of 3, 4. Progression of knee OA was defined as a change between baseline and 24 month visit in narrowest joint space width (JSW) in signal knee.

Results: The mean plasma MMP2 and 9 (pro and total) levels were 83.0 ± 63.05 ng/ml, 30.7 ± 32.64 and 455.9 ± 290.09 (all ng/mL), respectively. Only total MMP-9 positively correlated with KL score both at baseline ($r=0.220$; $p<0.036$) and 24 ($r=0.249$; $p<0.015$) month. MMP-2 or proMMP9 levels did not correlate with either radiographic marker. We further analyzed association of tMMP9 level with radiographic severity and progression by JSN as defined in the methods. tMMP9 correlated with radiographic severity ($p<0.061$) at baseline, and with progressive joint space narrowing ($r= 0.228$; $p<0.015$). However, we did not observe significant association between tMMP9 and delta KL score in this 24 month study.

Conclusion: These findings indicate that elevated levels of total gelatinase −9 (tMMP9) are associated with radiographic severity of SKOA and predict an increased risk of progressive joint space narrowing (JSN). These observations, which suggest that tMMP9 is a candidate prognostic biomarker, merit further validation in larger cohort of SKOA patients.

1937

MicroRNA Expression in Vault Particles. Anne Rowzee[1], Mayank Tandon[1], Alessia Gallo[1], John Routsias[2], Athanasios G. Tzioufas[3] and Ilias Alevizos[4]. [1]NIDCR, Bethesda, MD, [2]National University of Athens, Greece, [3]School of Medicine, National University of Athens, Greece, Athens, Greece, [4]NIDCR/ NIH #10 1N110, Bethesda, MD

Background/Purpose: Vault particles are among the largest ribonucleic complexes found in the cell, however, they remain largely uncharacterized. A single protein, major vault protein (MVP), comprises nearly 70% of the 13 MDa mass of this hollow, barrel-shaped organelle. The major components of vaults have been implicated in many basic cellular processes and disease mechanisms, including viral infections, but the function and contents of vaults remain unknown. Our primary interest in vault particles is centered on their ability to bind and sequester small RNAs. A 98 bp RNA sequence named VTRNA is housed within the interior of vaults and has similar characteristics to microRNA precursors. Consequently, the objective of this study was to detect and characterize any microRNAs present in vaults.

Methods: Existing cell-fractionation protocols were optimized to isolate intact vaults from murine salivary glands. Western immunoblot analysis of MVP was then used to demonstrate that we are able to obtain a sample enriched in MVP and likely to contain intact vault particles. Total RNA extracted from isolated vaults both with and without prior RNase treatment was then evaluated by Bioanalyzer, qPCR, and microarray.

Results: Using these methods, specific microRNAs from within vaults were identified and demonstrated to be protected from RNase treatment.

Conclusion: Overall, we consider vaults to be an interesting organelle that is potentially important for regulation of microRNA processing and trafficking, or may function as a delivery vehicle for small nucleic acid sequences representing an additional mechanism of translational control.

1938

Regulation of Apoptosis and Matrix Metalloproteinase Expression by Small Ubiquitin Related Modifier-2/3 in Rheumatoid Arthritis Fibroblast-Like Synoviocytes. Svetlana Frank[1], Simon Strietholt[1], Christine Seyfert[2], Marvin A. Peters[3], Thomas Pauly[4], George Kollias[5] and Thomas Pap[6]. [1]Institute of Experimental Musculoskeletal Medicine, University of Muenster, Muenster, Germany, [2]Department of Orthopaedic Surgery, Zeisigwaldkliniken, Chemnitz, Germany, [3]Kerckhoff- Klinik GmbH, Justus-Liebig-University Gieβen, Bad Nauheim, Gieβen, Germany, [4]Department of Nephrology and Rheumatology, Heinrich-Heine University, Meerbusch, Germany, [5]Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece, [6]University Hospital Münster, Münster, Germany

Background/Purpose: Posttranslational attachment of SUMO to target proteins regulates diverse cellular functions, including transcription, nuclear translocation, stress response and protein stability. Previously, we could show that the increased expression of SUMO-1 in RA fibroblasts regulates the susceptibility to apoptosis through a SUMO-1/SENP1 dependent mechanism. As SUMO-2/3 constitutes a structurally similar but functionally distinct member of the SUMO family, we investigated the expression of SUMO-2/3 in human RA and in hTNFtg mice and studied its role in regulating both apoptosis and the expression of disease specific MMPs.

Methods: Synovial tissue samples were obtained from RA and osteoarthritis (OA) patients at joint replacement surgery and used for histological analysis as well as for the isolation of fibroblast like synoviocytes. Using specific antibodies in immunohistochemical and Western blot analyses, we studied the expression of SUMO-2/3 in fibroblasts from human RA as well as from hTNFtg and wt mice. Knockdown of SUMO-2/3 was performed using specific siRNA against both SUMO-2 and −3. The apoptotic response of the fibroblasts was measured using a Caspase-3/7 assay after induction of cell death with 100ng/ml Fas ligand over 13h. MMP-1, MMP-3 and MMP-13 production in FLS from RA and OA patients was measured by ELISAs following the stimulation with TNF-alpha and IL-1beta.

Results: Immunohistochemistry and Western blot analyses revealed a clear upregulation of SUMO-2/3 expression in all RA synovial tissue samples and in RA-FLS compared to OA control samples. In line with these data, tissue sections of hTNFtg mice, as well as FLS from these mice confirmed increased expression of SUMO-2/3. Moreover, SUMO-2/3 expression was increased after stimulation with TNF-alpha in RASF. Knockdown of SUMO-2/3 by siRNA sensitized RASF to Fas-mediated apoptosis. Interestingly, TNF-alpha and IL-1beta induced upregulation of MMP-3 and MMP-13 expression was significantly stronger after knockdown of SUMO-2/3 in RA- and OA-FLS. While the expression of MMP-1 was not affected.

Conclusion: From our data we conclude that posttranslational modification of target proteins by SUMO-2/3 and specifically increased levels of SUMO-2/3 in RA-FLS contribute to the resistance of these cells against Fas-mediated apoptosis. Moreover, they indicate that SUMO-2/3 is regulated by TNF-alpha as well as involved in the regulation and TNF-alpha stimulated production of MMP-3. Therefore, we hypothesize that SUMO-2/3 are novel players contributing to the specific activation of RASF and, thus, to the disease process of RA.

ACR/ARHP Poster Session C
Infection-Related Rheumatic Disease
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

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High Expression of GITR and OX-40 Receptors on Memory CD4+25+ T Cells in the Joint Fluid of Patients with Antibiotic-Refractory Lyme Arthritis. Nalini K. Vudattu[1], Elise E. Drouin[2] and Allen C. Steere[3]. [1]Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, [2]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, Charlestown, MA, [3]Massachusetts General Hospital and Harvard Medical School, Boston, MA

Background/Purpose: Patients with Lyme arthritis have an infection-induced synovitis, which resolves in most patients with appropriate antibiotic therapy. However, a small percentage of patients have persistent synovitis despite spirochetal killing with oral and IV antibiotics (called antibiotic-refractory arthritis), which results from a putative infection-induced autoimmune response. This human model is unique in being able to compare infection versus autoimmune activation of T cells in the same disease. In an initial study, we showed that both refractory and responsive patients have elevated numbers of IFNg+ CD4+ Teff cells in synovial fluid (SF). In addition, in refractory patients, lower numbers of CD4+CD25+ T cells (primarily FoxP3+ Treg cells) correlated with a longer duration of synovitis after antibiotic therapy. To better understand the difference between infection versus autoimmune activation of T cells, we compared herein the phenotype of these cells in patients with antibiotic-responsive or antibiotic-refractory Lyme arthritis.

Methods: PBMC and synovial fluid mononuclear cells (SFMC) were obtained in 15 patients with antibiotic-responsive arthritis (prior to antibiotic therapy) and in 16 with antibiotic-refractory arthritis (in the post-antibiotic period after spirochetal killing). The cells were assessed for expression of CD3, CD4, CD25, CD45RO, CCR7, GITR, HLA-DR, OX40, CXCR3 and a viable cell marker using 10-channel polychromatic flow cytometry. The levels of these markers were correlated with the clinical course.

Results: CD4+ T cells in SF were even more abundant and enriched in patients with antibiotic-responsive arthritis than in those with antibiotic-refractory arthritis (median value, 59% and 51%, P=0.03). In both groups, approximately 95% of these cells were CD4+CD25- Teff cells and about 5% were CD4+CD25+ cells (primarily Treg cells). However, in contrast with our previous smaller study, the lower percentage of Treg cells in SF in the refractory group did not correlate with a longer duration of arthritis after antibiotic therapy. Instead, compared with patients with antibiotic-responsive arthritis, CD4+25+ T cells in SF in patients with antibiotic-refractory arthritis had significantly higher expression of GITR (P=0.006) and OX-40 receptors (P=0.02), which are members of the TNF receptor superfamily that are known to be associated with inhibition of Treg function. Finally, almost all of both Teff and Treg cells (98%) had a memory phenotype.

Conclusion: The expression of GITR and OX-40 receptors on CD4+CD25+ Treg cells differed significantly between patients with antibiotic-responsive or antibiotic-refractory arthritis. These observations imply that Treg in patients with antibiotic-refractory arthritis are unable to effectively regulate activated Teff cells because of phenotypic differences, including receptor expression. Studies are currently underway to determine the functional differences between T cells in these patients.

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***C Trachomatis* Is Present and Metabolically Active During the Remitting Phase in Synovial Tissues From Patients with Chronic *Chlamydia*-Induced Reactive Arthritis.** John D. Carter[1], Herve C. Gerard[2] and Alan P. Hudson[2]. [1]University of South Florida, Tampa, FL, [2]Wayne State Univ Schl of Med, Detroit, MI

Background/Purpose: Patients with chronic *Chlamydia* -induced reactive arthritis (ReA) often show a remitting-relapsing disease phenotype. We have some knowledge of the genetic behavior of chlamydiae in the synovium during active disease, but we know nothing concerning the organism's metabolic or other characteristics during quiescent disease. Such information may be extremely useful in understanding the signals that trigger active disease from quiescence. Here we present the first study of chlamydial load and gene expression in synovial tissues during the quiescent disease phase of *Chlamydia* -induced inflammatory arthritis.

Methods: Synovial biopsies from 4 patients with remitting chronic ReA were procured by the Parker-Pearson method and snap frozen. All synovial tissue samples were obtained from the knee and the patients had no evidence of synovitis in the knee or any other joint or organ at the time of tissue procurement. Nucleic acids from these synovial tissue samples were prepared by the hot phenol method and analyzed by real time PCR and RT-PCR.

Results of the analyses were compared with transcript and bacterial load values averaged from the knee synovial tissue samples of 10 patients in the active disease phase of chronic *Chlamydia* -induced arthritis ReA.

Results: Quantitative real time PCR assays indicated that relative bacterial load in the remitting phase samples was about 20% of that in samples from patients with active disease. Surprisingly, transcript levels from the authentic hsp60-encoding gene were equal to those seen in active disease in 2 samples and about 5-fold higher than those of active disease samples in 2 others. Transcripts from the 2 other paralog hsp60 genes were equal to or somewhat lower than those found in active disease. mRNA from the host encoding IL-10, TNFα, and IFNγ were about 4-fold lower than those seen in

samples from patients in active disease. MCP-1 and RANTES transcript levels were equal to or higher than those in active disease samples.

Conclusion: These results show that bacterial load in the joints of patients during the remitting phase of arthritis is much lower than those during active disease. However, transcripts encoding the highly pro-inflammatory hsp60 proteins are equal to or higher than those found in active disease, and the transcriptional response of the host is attenuated in terms of several cytokines and chemokines in the remitting samples. Clearly, these initial results indicate that the sequence of genetic events characterizing quiescent disease is complex and requires more study to understand how quiescence is maintained and what triggers the transition to active disease.

1941

Interferon-γ Release Assays In Rheumatic Patients: Baseline Study and In the Course of Anti-Tumor Necrosis Factor-α Agents. Melania Martínez-Morillo[1], Sonia Mínguez[2], Lourdes Mateo-Soria[1], Irene Latorre[1], José Domínguez[1], Dolors Grados[1], Beatriz Tejera[1], Susana Holgado[1], Alejandro Olivé[1] and Xavier Tena[1]. [1]Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [2]Hospital General de Manresa, Manresa, Spain

Background/Purpose: IFN-γ release assays are useful methods for diagnosing LTBI (latent tuberculosis infection). It allow us to detect: a) false negative TST in anergic subjects, b) false positives in BCG-vaccinated patients and c) NTM (non-tuberculous mycobacterias) previously sensitized individuals. All in all, these tests contribute to detect additional cases of LTBI.

Our aim is to establish the usefulness of blood interferon-γ release assays in patients with inflammatory rheumatic diseases scheduled for anti-TNF-α treatment and at the follow up.

Methods: Prospective study including rheumatic patients starting an anti-TNF-α agent. All patients underwent TST (two step testing), a chest radiograph, QuantiFERON GOLD *in tube* (QFN-G-IT), and T-SPOT.TB. Both tests were repeated after a year of anti-TNF treatment in 21 patients. As control group, 35 adult individuals were included. Concordance between TST/T-SPOT.TB, TST/QFT and T-SPOT.TB/QFT were analyzed by Cohen's kappa test.

Results: We included 53 patients (18 male/35 female) candidates for anti-TNF-α (18 rheumatoid arthritis, 13 ankylosing spondylitis, 9 psoriatic arthritis and 13 miscellanea). Mean age was 49 ± 13 years and mean disease evolution was 8.8 ± 8 years. Twenty-four out of 53 patients (45.3%) were receiving systemic steroids, mean daily dose 9.1 ± 11.9 mg/day. BCG vaccination status was documented in 3 patients, 2 referred history suggestive of TB disease and other 3 patients had contact with a confirmed TB case in the past.

The results of our study are summarized in Table 1. The differences in the results between the IFN-γ tests were not significant ($p = 0.675$). Interestingly enough, neither T-SPOT.TB nor QFN-G-IT were significant in comparison to TST results ($p = 0.344$ and $p = 0.727$, respectively). Overall agreement between TST and T-SPOT.TB and QFN-G-IT was 77.35% (k=0.33; and k=0.40, respectively), and between both in vitro tests was 83.01% (k=0.57). Three patients with positive TST and negative T-SPOT.TB and QFN-G-IT, was positive on ELISPOT after stimulation with NTM sensitins. Positive TST, T-SPOT.TB and QFN-G-IT results were not affected by the immunosuppressive therapies. We found 4 conversions (1 patient convert T-SPOT and QFN, and 3 patients convert only T-POT) out of 21 cases evaluated after a year under anti-TNF-α agents. We also observed 2 reversions, one in a patient who had undergone prophylactic treatment for tuberculosis.

Diagnostic test	All rheumatic patients, n=53 (%)	Rheumatoid arthritis patients, n=18 (%)	All rheumatic patients 1 year after treatment with anti-TNF-α, n=21 (%)
T-SPOT.TB			
Positive	11 (20.8)	4 (22.2)	7 (33.3)
Negative	40 (75.5)	14 (77.8)	13 (61.9)
Inderteminate	2 (3.8)	0 (0)	1 (4.7)
QFN-G-IT			
Positive	9 (17)	4 (22.2)	4 (19)
Negative	40 (75.5)	13 (72.2)	17 (80)
Indeterminate	4 (7.5)	1 (5.6)	0 (0)
TST			
Positive	7 (13.2)	3 (16.7)	Not done
Negative	46 (86.8)	15 (83.3)	Not done

Conclusion: In those patients with a high risk of developing active TB, the combined use of TST and IFN-γ may be recommended to increase the overall number of LTBI diagnosis. Reversion is described in subjects who have made prophylaxis. More studies are needed to recommend prophylaxis in conversions.

1942

Xenotropic Murine Leukemia Virus-Related Virus Infection in Italian Patients with Chronic Fatigue Syndrome, Fibromyalgia or Rheumatoid Arthritis. Laura Bazzichi[1], Fabrizio Maggi[2], Francesca Sernissi[3], Pietro Scarpellini[3], Camillo Giacomelli[3], Arianna Consensi[3], Maria Linda Vatteroni[3], Mauro Pistello[3] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]University Hospital, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [3]University of Pisa, Pisa, Italy

Background/Purpose: A plethora infectious agents have been linked to Chronic Fatigue Syndrome (CFS) over the years but none stand out intense scrutiny. This long list of viruses has been recently updated with the xenotropic murine leukemia virus-related virus (XMRV). XMRV was convincingly linked to CFS in a Science manuscript authored by Lombardi and colleagues, who demonstrated the presence of the virus in 68 of 101 American patients (67%) versus 8 of 218 (3.7%) healthy controls. Unfortunately, this was followed by a number of papers claiming that XMRV was not detectable in similar cohorts of patients, creating a rift in the scientific opinion. Several explanation has been provided to support one or the other position, but the controversy is nowadays still open. This work was carried out to contribute to the scientific debate by expanding the number of CFS patients examined to the Italian population and by extending the analysis to other two chronic diseases, which are Fibromyalgia and Rheumatoid Arthritis, with basically unknown etiology and common symptoms.

Methods: Patients and controls were recruited at the division of Rheumatology, Pisa University Hospital from June 2010 to January 2011. The diagnosis of CFS was made according to the Fukuda criteria of 1994, while FM and RA patients fulfilled the American College of Rheumatology of 1990 and 1987, respectively. Samples were obtained from 145 patients (65 with CFS, 55 with FM and 25 with RA diagnosis) and 25 age-matched healthy controls. The virus was searched as viral genome and using a diagnostic algorithm including a nested polymerase chain reaction (PCR) and a single step TaqMan real-time PCR, both designed on XMRV *gag* . Amplifications were carried out with protocols set up by Lombardi and colleagues that were published in the Science paper.

Results: No sample was found XMRV RNA positive. The *gag* primers designed for the real-time PCR and the technique itself ensured sensitivity to detect XMRV RNA at least as high as the nested PCR. Yet, plasma samples that were first tested by nested PCR and then retested by real-time PCR were all consistently negative. Since these findings did not rule out that the samples might contain copy numbers of XMRV genome very low (as suggested by other reports) and below the detection threshold, most plasma samples were reanalyzed following ultracentrifugation to concentrate the XMRV virions, but again no positive signal was scored.

Conclusion: Despite having strictly followed methods and procedures described and further improved by the Science authors and used negative and positive controls as indicated, we were unable to find any XMRV sequence in plasma and PBMC. These results add to the ever-growing number of surveys reporting the absence of XMRV in CFS patients and thus further increasing skepticism on possible links between XMRV and CFS.

1943

Dexamethasone Reduces *Staphylococcus Aureus*-Induced Production of Inflammatory Cytokines and Matrix Metalloproteases in Primary Human Chondrocytes and Synovial Fibroblasts. Frank Hanses[1], Irina Fink[1], Susanne Graessel[1], Bernd Salzberger[1] and Martin Fleck[2]. [1]University Hospital Regensburg, Regensburg, Germany, [2]Asklepios Klinikum Bad Abbach, Bad Abbach, Germany

Background/Purpose: *Staphylococcus aureus* (*S. aureus*) is the most frequent pathogen involved in acute bacterial arthritis. Joint infections due to *S. aureus* are associated with a high rate of sequelae and poor functional outcome. We hypothesize that concomitant glucocorticoid therapy may reduce joint destruction during staphylococcal arthritis.

Methods: Primary human chondrocytes, synovial fibroblasts and osteoblasts were infected with viable *S. aureus* . The production of the inflammatory cytokines IL-6 and IL-8 (CXCL8), the secretion of matrix metalloproteases (MMP-1, MMP-3, MMP-13), expression of aggrecanases (ADAMTS4 and ADAMTS5), cell viability and numbers of intracellular bacteria were studied with or without co-incubation of dexamethasone for 5 days.

Results: Primary human chondrocytes produced significantly more IL-6 and IL-8 than fibroblasts and osteoblasts as well as high levels of matrix metalloproteases upon *S. aureus* infection. Co-incubation with dexamethasone led to a significant decrease in IL-6 and IL-8 production in all cell types. Additionally,

dexamethasone reduced the *S. aureus* -induced production of matrix metalloproteases MMP-1 and MMP-13 (but not MMP-3) by primary chondrocytes significantly. Similary, *S. aureus* -induced expression of the aggrecanases ADAMTS4 and ADAMTS5 was significantly reduced by dexamethasone. No differences in cell viability and intracellular numbers of *S. aureus* were observed between cells incubated with dexamethasone and controls.

Conclusion: The host immune system and tissue destructive substances contribute to permanent joint damage in *S. aureus* arthritis. Dexamethasone might modulate inflammation and tissue destruction leading to a better functional outcome following *S. aureus* arthritis.

1944

The Cellular Response to Vaccination against Pandemic 2009 Influenza A (H1N1) Virus Among Patients with Rheumatic Diseases. Ori Elkayam, Sharon Amir, Uri Arad, Jonathan Wollman, Ayelet Brill, Daphna Paran, David Levartovsky, Irena Wigler and Dan Caspi. Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Background/Purpose: Antibody and cell mediated responses are both involved in the defense against virus. We have previously shown that vaccination against pandemic H1N1 using an adjuvanted H1N1v monovalent influenza vaccine induced an appropriate humoral response response in patients with rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), Ankylosing spondylitis (AS) and Psoriatic arthritis (PsA). The purpose of this study was to assess the cellular response to vaccination against pandemic H1N1 virus in patients with rheumatic diseases compared with healthy controls.

Methods: The study population comprised 43 patients (16 RA, 12 SLE, 10 PsA, 5 AS) and 10 healthy controls, all vaccinated by Novartis MF59-adjuvanted H1N1v monovalent influenza vaccine. Peripheral blood mononuclear cells were obtained before and 4 weeks after vaccination. Cell-mediated response was evaluated by flow cytometry for IFNg and interleukin 2 (IL-2) producing CD4+ and CD8+ T-cells, following *in vitro* stimulation with virus antigen.

Results: CD4 T cell-mediated immune response to A/H1N1: Following vaccination, the percentage of IFNg producing CD4+ cells increased in the SLE, PsA and AS groups while it was decreased in RA and healthy groups. The percentage of IL-2 producing CD4+ cells increased in all groups except PsA. Among patients on TNFa blockers, RA patients had a greater response compared to PsA patients. Notably, the percentage of cytokine producing T-cells (CD4 and CD8) in either, pre- and post-vaccination was higher among the healthy group compared to the 4 patients groups.

CD8 T cell-mediated immune response to A/H1N1: After vaccination, the percentage of IL-2 producing CD8+ cells increased considerably (6-fold) in the healthy control group, the response being significantly stronger compared to the entire patient population ($P = 0.02$) and to the RA group ($P = 0.05$). In contrast, except for a slight increase among the SLE and AS groups, no increase in IFNg producing CD8+ T cells was observed.

Conclusion: The cellular response of IL-2 producing CD8+ cells following vaccination against pandemic influenza H1N1 is impaired in patients suffering from RA, SLE, PsA and AS in comparison with healthy controls. The IFNg producing CD4+ and CD8+ T-cell response was similar in patients and controls.

1945

Circulating Levels of IL6, sIL6-r, sgp130 and Gamma-IFN in Patients with Hepatitic C Virus Related Arthritis (HCVrA) and Rheumatoid Arthritis (RA). Angelo Spanò[1], Loredana Postiglione[1], Paola Sabatini[2], I. Soriente[2], M.G. Sangiolo[1], V. Bruner[1], Raffaele Scarpa[1] and Antonio Riccio[1]. [1]Federico II University Medical School, Naples, Italy, [2]Umberto I Hospital, Nocera Inferiore, Italy

Background/Purpose: To evaluate serum concentrations of IL6, sIL6r, sgp130 and gamma-IFN in HCVrA and RA patients. To verify any possible difference in circulating levels of these cytokines involved in the pathogenesis of RA and HCVrA, both conditions sharing some immunological features.

Methods: 25 HCVrA (15 with polyarticular symmetrical, 10 with oligoarticular asymmetrical involvement), 27 RA patients (fulfilling ACR criteria) and a control group of 20 healthy subjects were examinated. In the HCVrA group, 10 patients presented hepatic damage (hypertransaminasemia), 11 were virus negative HCV-RNA PCR, 17 were positive for Rheumatoid Factor (RF), 13 for Antinuclear Antibodies (ANA), 3 for Anti-Cytrullinated peptide (ACPA), 12 for cryoglobulins. None of them received steroids or immunosuppressive and viral replications inhibitors drugs. In the RA group, 22 patients were positive both for RF and ACPA, 5 only for RF and 5 for ANA, 16 received Methotrexate (15 mg/weekly), 6 Leflunomide (20 mg/day), 5 cyclosporine (3 mg/Kg bw), none steroids.ELISA Methods were used to determine serum concentrations of IL6 and sIL6r (R&D Systems – Milan –Italy), sgp130 (Bioscience International Camarillo USA) and gamma-IFN (Arcus Biologicals – Modena – Italy). Mann-Whitney test and Spearman's rho were used for statistical analysis.

Results: High IL6 serum levels were found respectively in 71% of HCVrA (60 pg/ml) and 62% of RA patients (255,6 pg/ml), sIL6r levels resulted high in 37% of HCVrA patients (36,1 ng/ml) and in 46% of RA patients (40,9 ng/ml), sgp130 levels were increased in 75% of HCVrA (37,8 ng/ml) and in 69% of RA patients (417,5 ng/ml). All these values, as in HCVrA as in RA patients, were significantly higher in comparison to the median values reported in the control group. Gamma-IFN serum levels were founded decreased in 24% (0,2 IU/ml)of HCVrA patients and 15% (0,12 IU//ml) of RA patients. No direct correlation was found between these parameters with viraemia, RF and ANA positivity in HCVrA group, while a mild correlation was found between IL6, sIL6r and sgp130 with RF levels in RA group. Furthermore, no correlation results both in HCVrA and RA group between gamma-IFN levels and IL6, sIL6r and sgp130 levels.

Conclusion: Enhanced serum levels of IL6 and its receptors both in HCVrA and in RA indicate an increased synthesis and activity of this interleukins, supporting the hypothesis of similar immune pathogenetic mechanism for both diseases. Low gamma-IFN serum levels, found in a minority of HCVrA and RA patients and above all the lack of correlations between IL6 and gamma-IFN could be explained because of gamma IFN is regulated in a composite system by many different contributing factors non yet completely evaluated.

1946

Polyarticular Septic Arthritis: A Case Series. Rajni Kalagate[1], Sherilyn T. McCollum[1], Charles H. Pritchard[2] and Lawrence H. Brent[1]. [1]Albert Einstein Medical Center, Philadelphia, PA, [2]Rheumatic Disease Associates, Willow Grove, PA

Background/Purpose: Septic arthritis (SA) is typically a monoarticular disease. Polyarticular SA has been reported, especially in patients with underlying RA and SLE. In this study we present a series of patients with polyarticular SA and compare them with monoarticular SA. Purpose: To describe the demographics, risk factors, microbial etiology, articular involvement, and outcomes of patients with polyarticular SA compared with monoarticular SA.

Methods: Medical records of all patients with a diagnosis recorded as SA admitted to Albert Einstein Medical Center and Abington Memorial Hospital from 1988 to 2010 were reviewed. Data collected included age, sex, comorbidities, joint involvement, synovial fluid analysis, and relevant culture results (synovial, others). Patients mislabeled as SA or with incomplete data were excluded. The diagnosis of SA was defined as definite (clinically inflamed joint and positive synovial fluid culture), probable (clinically inflamed joint and negative synovial fluid culture but positive culture from another source), or possible (clinically inflamed joint and all cultures negative). If data for a specific parameter was missing, percentages were calculated using the total number patients with data as the denominator. Data analysis was performed using SPSS17.0.

Results: A total of 515 patients were identified with septic arthritis. Of these patients, 39 (7.5%) had polyarticular SA. The incidence of polyarticular SA remained stable over the 22 year period. There were no significant differences between polyarticlular and monoarticular SA patiens with regards to demographics and co-morbid conditions including RA and SLE. Clinical features which were significantly different between the polyarticular and monoarticular SA were: peripheral WBC count 17,400 vs. 15,000 ($p=0.06$); positive blood cultures 64% vs. 41% ($p=0.007$); length of hospital stay 15.2 vs. 10.7 days ($p=0.01$). 74% of polyarticular SA patients had positive synovial fluid cultures vs. 62% of monoarticular SA patients ($p=0.8$). The overall bacterial etiology was not significantly different between the two groups. In polyarticular SA patients, *Staphylococcus aureus* was the most common organism identified 55 %, of which 26% were methicillin-resistant. The other organisms identified were *Streptococcus pneumoniae* (8%) and *Streptococcus* group A and B (10%). The knee was most commonly involved in both groups. Polyarticular SA had more involvement of knee (69% vs. 48%, $p=0.01$), wrist (30% vs. 5%, $p=0.000$), elbow (18% vs. 5.3%, $p=0.002$), and shoulder (36 % vs. 10%, $p=0.000$). Polyarticular SA had a worse prognosis with death occurring in 18% vs. 4.7% in monoarticular SA ($p=0.001$).

Conclusion: The incidence of polyarticular SA was less than what has been previously reported (7.5% vs. 15%). There were no specific predisposing factors identified for polyarticular SA in our study. Involvement of the knee, wrist, elbow, and shoulder joints were more common. These patients were more likely to have positive blood cultures and a prolonged hospital course. Polyarticular SA is associated with a worse prognosis including a higher mortality.

1947

Four Novel MEFV Gene Mutations in a Population Where the Prevalence of Crimean-Congo Hemorrhagic Fever and MEFV Gene Carrier Status Is Very High. Gulay Ozgon[1], Aynur Engin[2], Gulen Hatemi[3], Serdal Ugurlu[3], Elif Akyayla[1], Mehmet Bakir[2] and Huri Ozdogan[3]. [1]Nesiller Genetic Lab, Istanbul, Turkey, [2]MD, Department of of Infectious Diseases, Medical Faculty, University of Cumhuriyet, Sivas, Turkey, [3]MD, Division of Rheumatology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

Background/Purpose: Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne disease caused by an arbovirus in the family Bunyaviridae, which is associated with high mortality. CCHF is common in mid Anatolia where FMF is also very prevalent (1.2%), thus MEFV gene carrier status is very high (44%).To test our hypothesis that a selective biological advantage obtained by a carrier state for MEFV mutations may enhance the host's ability to withstand CCHF, we studied the distribution of MEFV gene mutations in patients with CCHF.

Methods: MEFV gene mutations of exon 2 and 10 were detected with polymerase chain reaction (PCR) and direct sequencing in 100 patients with CCHF with a definite diagnosis of CCHF followed in Cumhuriyet University, Sivas / Turkey, (mean age 45.6±17, 58 M: 42 F) and in 91 healthy blood donors (HC) living in the same area.All CCHF patients were classified into two groups in terms of disease severity (mild and severe), according to the predictive factors for fatal outcome reported by Swanepoel et al(1).

Results: Four new mutations were found on exon 10 of 7 CCHF patients and none of the healthy controls. A database search for these novel mutations was negative. The loci of these new MEVF gene mutations on exon 10 are as follows: Q778L, R717Q, P754A and R737K. Q778L mutation was found in four patients, one had a mild whereas the remaining 3 had severe disease. Carrier of R717Q had a severe disease and died, however the carriers of P754A and R737K had mild disease course. All of these patients except the one who died were reevaluated for co-existence of FMF but none had any personal or familial history of FMF.

Conclusion: Here we describe 4 novel MEFV gene mutations in patients with CCHF from a geographical area where MEFV gene carriership is very high. We do not yet know whether these mutations have any effect on the host's ability to withstand an infection.

References:

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1948

The Effect of CCR5-DELTA-32 Mutation On *Chlamydia*-Induced Reactive Arthritis. Jason P. Guthrie[1], Aasim Rehman[2], Herve C. Gerard[3], Jessica Stanich[4], Alan P. Hudson[3] and John D. Carter[5]. [1]Springfield, IL, [2]Tampa, FL, [3]Wayne State Univ Schl of Med, Detroit, MI, [4]Wayne State University, Detroit, MI, [5]University of South Florida, Tampa, FL

Background/Purpose: *Chlamydia trachomatis* is a known cause of reactive arthritis (ReA). Only a minority of the infected patients develop ReA, with an attack rate of about 5%. Chemokine receptor-5 (CCR5) mediates chemotaxis and is expressed with the Th1 phenotype on monocyte/macrophages. The CCR5 protein is a cell surface receptor that binds several chemokines. A 32 base pair deletion in the CCR5 (CCR5-delta-32 allele) abolishes receptor expression in homozygote, while CC5-delta-32 carriers would express less receptor than the wild type homozygote. Data suggest that the CCR5-delta-32 mutation might be important in determining disease activity in autoimmune conditions. We hypothesize that the CCR5-delta-32 allele may modulate disease susceptibility and chronicity in *Chlamydia* -induced ReA.

Methods: Patients who tested positive for *Chlamydia trachomatis* after either 1.) symptoms of an acute venereal disease or 2.) sexual contact with an individual known to be positive for the same organism were recruited from the regional communicable disease clinic and followed in a prospective fashion. At enrollment, informed consent and demographic details were obtained and two blood samples were collected. All patients were contacted at week 6 after their acute infection and queried for symptoms of arthritis, conjunctivitis, urethritis, dactylitis, or enthesitis. All patients who had new onset symptoms suggestive of *Chlamydia* -induced ReA at week 6 had follow up telephone interviews at weeks 12, 26, and 52 to follow the chronicity of the symptoms. All the collected blood samples were tested for CCR5-delta-32 mutation.

Results: 365 study participants were enrolled. Average age of the population was 25.3 years. There were 201 males (55%) and 164 females (45%). Of the enrolled patients, 231 (63%) were African Americans, 81 (22%) Hispanics, 48 (13%) Caucasians and 5 (1.3%) were others. We were able to follow up with 149 (40%) of patients at week 6. 12/149 (8 %) participants contacted at week 6 had symptoms suggestive of *Chlamydia* -induced ReA. None of these 12 patients had the CCR5-delta-32 mutation. Of the 12 patients that had symptoms at week 6, we were able to follow up with 7 at weeks 12, 26 and 52. All 7 had complete resolution of their symptoms by week 26 and remained asymptomatic at week 52. Overall 25/365 (6.8%) subjects were positive for the CCR5-delta-32 mutation. We were able to follow up with 11 (44%) of these 25 patients. None of them had symptoms suggestive of *Chlamydia* -induced ReA at week 6 follow up.

Conclusion: The CCR5-delta-32 mutation does not seem to play a role in *Chlamydia* -induced ReA disease susceptibility. Because none of the subjects with long-term follow-up developed chronic disease, the potential role this mutation might play in disease chronicity remains uncertain.

1949

Hyperuricemia, Its Prevalence and Correlation with Age, Gender, BMI, Co-Morbidities and Metabolic Syndrome in Anti- Retroviral Naive HIV Cohort. Nirupa J. Patel[1], Roy Rajan[1], Rebecca Clark[2] and Luis R. Espinoza[3]. [1]LSU Health Sciences Ctr, New Orleans, LA, [2]LSU Health Sciences Center, New Orleans, [3]LSU Medical Center, New Orleans, LA

Background/Purpose: The aim of this study was to determine the prevalence of hyperuricemia in the HIV infected population, and whether uric acid can be used as a marker of metabolic syndrome (MetS). Hyperuricemia mediates adipocyte specific pro-inflammation and increases insulin resistance as studied in the murine model of MetS. We incorporated BMI, triglyceride levels, and co-morbidities correlating with hyperuricemia to analyze the pattern of metabolic syndrome in this HIV+ cohort. Viremia induced increased cell turnover, loss of mononuclear cells, concomitant infections and increased oxidative stress can all be implicated factors for hyperuricemia in HIV patients. Anti-retroviral drugs can cause mitochondrial dysfunction, lactic acidosis, and hyperuricemia. Our study included all drugs naive patients.

Methods: We studied 283 consecutive patients seen in our HIV clinic over 18 months' duration. We selected newly diagnosed HIV+ patients who had an initial uric acid levels performed. These uric acid levels were correlated with age, gender, ethnicity, CD4 counts, HIV viral load, BMI, Triglycerides levels, and concomitant co-morbid conditions [Type II Diabetes mellitus (DM), Hypertension (HTN)]. We analyzed our data using logistic regression analysis. Significant variables at $p<0.1$ in univariate analysis were used in multivariate models. WHO criteria for MetS were used in our study. It defines as having BMI > 30kg/m2, triglycerides > 150mg/dl, Blood pressure > 140/90 mm Hg.

Results: 283 newly diagnosed HIV+ anti-retroviral naive patients were studied. Initial panels included uric acid levels. HIV+ patients in our study had mean age of 38.2 yrs (SD11.6yrs) and 68.9% were males. Ethnicities included African Americans 77.7%, Caucasians 18.4%, and unknown 3.9%. Their BMI median was 25.2 (range 13.3– 63.9). Uric acid of >7mg/dl was found in 18.4% of patients. Race, CD4 count, and viral load were not significant in univariate analysis. In the multivariate logistic model, hyperuricemia of >7mg/dl was significantly associated with increasing BMI and age, male gender and co-morbidities (HTN, DM or both) (Table 1). In our separate model of MetS, 3.2% of patients had all 3 variables of MetS and uric acid> 7 mg/dl. These 9 patients with all variables were significantly associated with OR of 12.7 and $p=0.002$.

In current study, only 1 patient had uric acid level < 2mg/dl and 1/9 patient had gout associated with MetS (having all 4 variables).

Table 1.

HYPERURICEMIA	ODDS RATIO	P VALUE	95% CONFIDENCE INTERVAL
BMI	1.09	<0.0001	1.04–1.15
AGE	1.04	0.003	1.01–1.07
GENDER	4.95	0.001	1.94–12.63
HTN/DM	2.20	0.032	1.06–4.55

Conclusion: In this study, the prevalence of hyperuricemia in HIV population was 18.4%. Our HIV+ MetS model showed a high association of hyperuricemia with MetS, increasing age and BMI along with male gender. Hyperuricemia, when present in HIV population, may be a harbinger and marker of MetS. Further trials and larger cohorts are needed to study MetS in this vulnerable HIV hyperuricemic population.

1950

Outbreak in Syphilis Presenting As Uveitis. Inés Pérez-Martín[1], David de la Hera[1], Ricardo Blanco[2], Javier Rueda[1], Carmen Bejerano[2], Orlando Pompei[1], Joaquín Cañal[1], Juan Ventosa[1], Manuel Gutiérrez-Cuadra[1], Vanesa Calvo[1], Javier Loricera[1] and Miguel Angel González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla-IFIMAV, Santander, Spain

Background/Purpose: Increased incidence of syphilis has been observed in developed countries in the last decade. In some cases indistinguishable uveitis from that related to non-infectious autoimmune uveitis may be the presenting manifestation of syphilis.

Methods: We conducted a review of the patients seen at the Uveitis Unit of the Rheumatology Service of a University Hospital that were diagnosed as having ocular syphilis as the first manifestation of this infectious disease from 2006 to 2011. The diagnosis of syphilis was established by the following tests: RPR and TPHA. The ophthalmological examination included slit lamp examination, retinography and ocular coherence tomography.

Results: Ten patients (6 men/4 women) with a mean age 50±20 (range 20–79) years were diagnosed with ocular syphilis as the first manifestation of this infection. The ocular manifestations were the following: anterior uveitis (2 cases), episcleritis (1), panuveitis (6), and posterior uveitis (1). The course before the diagnosis varied from one case to another: It was acute in 6 cases, chronic in 1, and recurrent in 3 patients. In 5 cases the inflammation was bilateral. In addition to syphilis, several concomitant infection diseases were found in some patients (hepatitis B in 3 cases and HIV infection in 1 case). Prior to the diagnosis of syphilis 3 patients were misdiagnosed as having non-infectious uveitis and were treated with high doses of prednisone. When the diagnosis of syphilis was established 9 patients received penicillin G (2 million units/4h i.v. for 2 weeks) with marked improvement and no relapses. One patient initially treated with penicillin G benzathine (2.4 million units/week for 3 weeks) suffered a relapse that was successfully treated with penicillin G. In those cases of ocular syphilis manifested by anterior uveitis the patients also received topic treatment (steroids and mydriatic drugs). Improvement of inflammatory tests/findings such as tyndall, choroiditis or vitritis was observed following antibiotic therapy. It was associated with marked improvement of visual acuity in 7 of the 10 patients. However, in the remaining 3 patients there was a impairment of visual acuity due to complications, mainly retinal detachment

Conclusion: We observed an increased incidence of syphilis presenting as uveitis in our Uveitis Unit. High level of suspicion for this infection is required to establish an early diagnosis and appropriate treatment.

1951

Anti-Cyclic Citrullinated Peptide (Anti-CCP) Antibodies with Brucellosis. Bunyamin Kisacik[1], Musa Aydinli[1], Yavuz Pehlivan[1], Muhammet sait Dag[1], Mehmet Sayarlioglu[2] and Ahmet Mesut Onat[3]. [1]Gaziantep, Turkey, [2]Kahramanmaras, Turkey, [3]Gaziantep Universitesi, Gaziantep, Turkey

Background/Purpose: Brucellosis is a zoonotic disease with a high prevalence that remains world's most commonly seen bacterial zoonosis. The clinical manifestations of brucellosis are similar with various diseases like rheumatic diseases, neurologic diseases and other infectious diseases. Anti-cyclic citrullinated peptide (Anti-CCP) is a highly specific serological marker for rheumatoid arthritis. In this study we have analyzed Anti-CCP and rheumatoid factor (RF) levels of patients with brucellosis.

Methods: The study population consist of of 113 patients with brucellosis (male/female: 37/76), 63 patients with hepatitis B (male/female: 30/33), 59 patients with hepatitis C (male/female: 11/48), 46 patients with rheumatoid arthritis (male/female: 16/30) and 49 patients with healthy controls (male/female: 20/29).

Results: Mean ages of patients with brucellosis, HCV, HBV, RA and healthy control subjects were 32.2±10.1, 34.2±8.2, 35.1±9.5, 46,6±11.1, 33.1±7.6 respectively. Artalgia was detected in 20 of 113 patients with brucellosis; arthritis was detected in 74 of 113 patients with brucellosis which was the commonest involvement. Of the 113 patients, 23 patients were mono-arthritis, 44 patients were oligo-arthritis and 7 patients were poly-arthritis. The most commonly affected joints were knee (49 patients, two patients were bilaterally), ankle (33 patients, three patients were bilaterally), hip (15 patients, three patients were bilaterally) and wrist (14 patients, three patients were bilaterally) respectively.The results of the analyses reflect that, anti-CCP was positive in 11.5% and RF was positive in 8.8% of the patients.

Conclusion: This is the first study that demonstrates potential role of anti-CCP in the diagnosis of patients with brucellosis. After a comparative evaluation, we have found out that there was not a statistical significance concerning the Anti-CCP levels between the patients with brucellosis and healthy control.

1952

Human Papillomavirus Lesion in Systemic Lupus Erythematosus. Ricardo V. Juarez. Crespo Maria Elena, Buschiazo Emilio, Sanchez Wilde Maria Cristina., Salta, Argentina

Background/Purpose: A papanicolau test and a pelvic exam are important as a part of a woman's routine health care because it can detect cancer related abnormalities. Human papillomavirus (HPV) infection is the primary risk factor for cervical cancer and is the most common sexually transmitted infection. Previous studies have demonstrated an increase prevalence of atypical cervical smears in patients with Systemic Lupus Erithematosus (SLE). These patients probably, may be predisposed to HPV infection due to SLE itself or the use of immunosuppressant or both.

The aims of this study were to compare, la prevalence of abnormal pap smears in SLE patients and to compare it with a group of healthy controls.

Methods: We studied consecutive patients fulfilling ACR criteria for SLE, recruited from one rheumatology center included between 2007 to 2010. Healthy controls were recruited from the same community and were matched by age. Each individual provided detailed medical information, medication and biochemistry. Disease activity was determined using Systemic Lupus Erithematosus Activity Index (SLEDAI) and disease damage by Systemic Lupus Erithematosus Collaborating Clinics Damage Index (SLICC). All the patients were refered to the gynecologist to take a sample of pap smear and colposcopy study.

Results: Thirty-two patients and 33 healthy controls were included. The median age of the SLE women was 35 years (IQR: 27–43.7) with a median disease duration of 6 years (IQR: 3–9.75). The prevalence of abnormal pap (Class III) smear was 12.4% (n = 4) in SLE patient compared with 6.1% (n = 2) in controls, but this difference did not reach statistical significance.

The prevalence de squamous intraepithelial lesion (SILs) was higher in patients than in controls, but was not statistically significant (7 (21.8%) vs 3 (9.09%), p = 0.139). The distribution for Low – grade SIL (LGSIL) was 3 (9.4%) vs 1 (3%), p = 0.355 and for high grade SIL (HGSIL) was 4 (12.5%) versus 2 (6.1%), p = 0.427. One of the patients had florid papillomatosis. In SLE patients there was no association between the presence of an abnormal gynecologic exam and the use of any inmunosuppressive therapy, or higher levels of SLEDAI or SLICC.

Conclusion: Abnormal Pap smear was more frequent in SLE patients than in healthy controls, though it did not reach statistical significance, perhaps due to the small number of patients.

ACR/ARHP Poster Session C
Miscellaneous Rheumatic and Inflammatory Diseases II
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

1953

A Higher Than Expected Prevalence of Autoimmune Disease in a Cohort of Patients with Recalcitrant Leg Ulcers. Victoria K. Shanmugam[1], Amber Schilling[1], Anthony Germinario[1], Mihriye Mete[2] and Christopher Attinger[3]. [1]Georgetown University Hospital, Washington, DC, [2]MedStar Health Research Institute, Hyattsville, MD, [3]Georgetown Universtiy Hosptial, Washington, DC

Background/Purpose: Wound healing is a highly regulated process progressing through hemostasis, inflammation, proliferation and maturation

regardless of the inciting etiology of the wound. Arrest of the wound in the inflammatory stage is a recognized cause of delayed healing, but the role autoimmune diseases play in this process is unknown. The purpose of this study was to determine the prevalence of autoimmune diseases in a cohort of patients presenting to a tertiary wound healing center, and to compare time to healing and graft outcomes.

Methods: Retrospective chart review was completed on consecutive patients scheduled in the Center for Wound Healing between January 1 and March 31, 2009. Subjects who did not attend and those without an open wound were excluded.

Baseline demographic and descriptive data including ulcer location, duration and size were recorded. Presence of comorbid conditions including autoimmune diseases, diabetes and vascular disease was documented. Time to healing and outcome of surgical interventions were recorded.

Data was analyzed using unpaired t-test for continuous variables, and Mann Whitney U test and Chi-square test for categorical variables using GraphPad Prism (GraphPad Software, CA).

Results: Of the 520 patients scheduled for appointments in the study period, 340 were eligible for inclusion. The remaining 180 patients either did not attend, or did not have an open ulcer.

Prevalence of diabetes, venous and arterial disease was as expected, with diabetes present in 168 patients (49%), venous disease in 120 (35%) and arterial disease in 118 (35%). However, the prevalence of autoimmune disease was much higher than expected with 78 of 340 patients (23%) having associated autoimmune disease, including rheumatoid arthritis (28%), systemic lupus erythematosus (14%), livedoid vasculopathy (14%), scleroderma (11%), vasculitis (10%), seronegative arthritis (8%), and inflammatory bowel disease (7%).

Autoimmune disease-associated wounds were significantly larger at the first visit, and were associated with higher pain scores (Table 1). While there was no significant difference in number of wounds that healed, autoimmune disease-associated wounds took significantly longer to heal (10.31 compared to 14.58 months, p=0.01).

Table 1.

	Non-Autoimmune Wounds n= 262	Autoimmune Wounds n=78	*p*
Age, years (Mean +/− SEM)	63.89+/−1.0	67.77+/−1.89	0.07
Race			
Caucasian	136 (52%)	40 (51%)	0.92
AA	106 (40%)	32 (41%)	0.92
Hispanic	6 (2.3%)	2 (2.6%)	0.88
Other	14 (5.3%)	4 (5.1%)	0.94
Sex			
Male	143 (55%)	25 (32%)	0.0005
Female	119 (45%)	53 (68%)	
Wound Size, cm^2(Mean +/− SEM)	22.5+/−3.9	33.4+/−7.8	0.02
Pain Score (Mean +/− SEM)	2.48+/−0.2	3.32+/−0.4	0.07
Wound healed over followup period	107 (41%)	31 (40%)	0.90
Time to healing, months (Mean +/− SEM)	10.31+/−0.6	14.58+/−2.27	0.01

Surgical skin graft and skin graft substitute data was available on 163 grafts from 50 subjects. Outcome was categorized into response (>50% graft take at 30 days) or no response (<50% graft take at 30 days). Only 39% of grafts to autoimmune-associated wounds demonstrated response compared to 49% of grafts to non-autoimmune associated wounds (p=0.29)

Conclusion: The 23% prevalence of autoimmune disease in this cohort is higher than in the general population, and higher than previously reported. Autoimmune-associated wounds were larger and took longer to heal than non-immune wounds, suggesting these wounds may provide important insights in to pathogenesis of delayed wound healing.

1954

Prevalence and Significance of Previously Undiagnosed Rheumatic Diseases in Pregnancy. Véronique Ramoni[1], Roberto Caporali[1], Arsenio Spinillo[2], Fausta Beneventi[2], Margherita Simonetta[2], Elena Locatelli[2], Chiara Cavagnoli[2], Claudia Alpini[3], Giulia Albonico[3], Elena Prisco[1] and Carlo M. Montecucco[1]. [1]Rheumatology, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy, [2]Obstetrics and Gynecology, IRCCS Policlinico San Matteo Foundation and University of Pavia, Pavia, Italy, [3]IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Background/Purpose: The objective of this study is to evaluate the rates of previously undiagnosed rheumatic diseases during the first trimester of pregnancy and their impact on pregnancy outcome.

Methods: Pregnant women attending the ultrasonography clinic of our Hospital for their first-trimester ultrasound scan were screened with a two-steps approach using a self administered 10 items questionnaire and subsequent testing for autoantibodies (antinuclear, anti-double-stranded DNA, anti-extractable nuclear antigen, anticardiolipin, anti-beta2-glycoprotein I antibodies and lupus anticoagulant) and evaluation by a rheumatologist. Overall, complications of pregnancy evaluated included fetal loss, preeclampsia, gestational diabetes, fetal growth restriction, delivery less than 34 weeks, neonatal resuscitation and admission to neonatal intensive care unit. Pregnancies were prospectively followed by Rheumatologists and Obstetricians to assess fetal and maternal outcomes.

Results: During a 5-year period (May 2005 to April 2010) out of the 2458 subjects screened, 291 (11.8%) patients answered positively to the questionnaire and among them 143 (49.2%) tested positive for autoantibodies. After rheumatologic evaluation we identified 62 (2.5%) women with a diagnosis of undifferentiated connective tissue disease (UCTD) and 24 (0.98%) with a major autoimmune rheumatic disease. The prevalences were 7 (0.28%) for systemic lupus erythematosus and Sjogren's syndrome, 6 (0.24 %) for rheumatoid arthritis, 3 (0.12%) for anti-phospholipid syndrome and 1 (0.04%) for systemic sclerosis respectively. Fifty-seven subjects (19.6%) had insufficient criteria for a diagnosis of inflammatory rheumatic disease despite positivity for both questionnaire and autoantibodies testing. During pregnancy, 18 patients required treatment with steroid and/or hydroxychloroquine to treat cutaneous and articular manifestations: 10 (16,1%) had UCTD e 8 (33,3%) had a major autoimmune rheumatic disease. Eleven patients received low dose aspirin and/or low molecular weight heparin as prophylaxis. Mean maternal age was higher in women with previously undiagnosed rheumatic diseases compared to healthy controls, while in this same group mean gestational age and birth weigh was lower. In multiple logistic regression, after adjustment for maternal age, the odds ratios of overall complications of pregnancy were 3.1 (95% confidence interval = 1.61 to 5.82) in subjects with UCTD and 5.74 (95% confidence interval = 2.33–14.2) in those with definite diseases, respectively, compared to asymptomatic controls.

Conclusion: In our population approximately 2.5% and 1% of first trimester pregnant women had a previously undiagnosed UCTD and definite systemic rheumatic disease, respectively. These conditions are associated with significant negative effects on the outcome of pregnancy.

1955

Eosinophilic Fasciitis (Shulman Disease): New Insights Into the Therapeutic Management From a Series of 34 Patients. David Lebeaux[1], Camille Frances[2], Stéphane Barete[2], Bertrand Wechsler[1], Odile Dubourg[1], Jérôme Renoux[1], Thierry Maisonobe[1], Olivier Benveniste[1], Marc Gatfossé[3], Pierre Bourgeois[1], Zahir Amoura[1], Jean-Charles Piette[4], Patrice Cacoub[4] and Damien Sène[1]. [1]Pitie-Salpetriere Hospital, Paris, France, [2]Tenon Hospital, Paris, France, [3]Centre Hospitalier Coulommiers, Coulommiers, France, [4]CHU Pitié-Salpêtrière, Paris, France

Background/Purpose: Eosinophilic fasciitis (EF) is a rare connective tissue disease characterized by a symmetrical and painful swelling with a progressive induration the skin and soft tissues. The therapeutic management of EF is one of the most significant challenges, as there is consensus on the use of steroids (dose and duration) and the interest of immunosuppressive drugs (ISD). The aim of this study was to analyze and report the results of the therapeutic management of 34 patients with a biopsy-proven EF.

Methods: We reviewed 34 adult-patients with a biopsy-proven EF. The analyses focused on the clinical, biological and histological features and the therapeutic management, which included the treatment modalities, responses and associated prognostic factors.

Results: 1) Clinical, biological and histological features: Thirty-four patients were included with a diagnosis age of 53±15.4 years. They were featured by cutaneous manifestations (88%) including morphea (41%), myalgia (86%) and hypereosinophilia (85%). The inflammatory infiltrates included lymphocytes in all patients (100%) and eosinophils in 26 patients (76.5%). A fascia fibrosis was present in 14 patients (41.2%) and an interstitial myositis in 23 patients (67.6%). A dermal fibrosis (histological morphea) was present in 11/30 patients (36.7%).

2) Therapeutic management and results: Thirty-two patients (94%) were eligible for treatment evaluation and all received corticosteroids as a first line therapy with a prednisone mean daily dose at initiation of 0.77±0.29 mg/kg. Fifteen patients (47%) received methylprednisolone pulses prior to prednisone treatment. At the end of follow-up: (A) 18 patients (56.25%) received steroids alone with a 45±31 month-treatment mean duration; (B) due to the lack of a complete remission, 14 patients (43.75%) required an ISD as a second line therapy in association with the steroid treatment in a 16.9±20.3

month-mean time interval (median=6.5): methotrexate for 12 patients (85.7%) with a 24.7±23.3 month-treatment mean duration and azathioprine for two patients (14.3%).

A complete remission was achieved for 69% of patients, a remission with disability (non progressive sequelae) for 19% and failure for 12%. The lack of complete remission was associated with a diagnosis time delay above 6 months (OR=14.7) and the lack of methylprednisolone pulses (OR=12.9). The relative risk of requiring an ISD was 4.7 times and 4.4 times higher in presence of a morphea and in patients who did not receive methylprednisolone pulses, respectively. EF-associated morphea was associated with a more frequent ISD requirement, mostly methotrexate (OR=64.4)

Conclusion: Our study reports new insights into the therapeutic management of EF: 1) corticosteroids treatment remains the standard therapy for EF, taken alone or in association with an ISD; 2) methylprednisolone pulses at treatment initiation are associated with a better outcome and a lower need of ISD use; 3) an ISD, mostly methotrexate, might useful as a second line therapy, mainly in patients with morphea-like lesions. Naturally, these practical conclusions should be confirmed by a prospective and multicentre study.

1956

Some of Subgroups in Rheumatoid Arthritis Are Difficult to Differentiate with Polymyalgia Rheumatica by a Genome-Wide Gene Expression Analysis. Yoshinobu Koyama[1], Chinami Era[1], Motohiko Tanino[2], Daisuke Hidaka[1], Toshiyuki Ota[1] and Ayumi Uchino[1]. [1]Iizuka Hospital, Iizuka, Japan, [2]DNA Chip Research Inc., Yokohama, Japan

Background/Purpose: There are many similarities between polymyalgia rheumatica (PMR) and rheumatoid arthritis (RA), especially late-onset RA, which in some cases, may lead to significant diagnostic difficulties. Microarrays for gene expression analysis are the most powerful technologies developed in recent years. It has been applied in the search for diagnostic patterns by comparing gene expression with other diseases to reveal markers for diagnostic and prognostic classification. So far, the differences of transcription profiles between PMR and RA have not been elucidated. The objectives of this study was to: (i) investigate whether the cluster analysis for genome-wide gene expression profiles of peripheral blood was able to distinguish RA from PMR; (ii) identify the gene expression signature that may distinguish RA from PMR.

Methods: The study included 44 RA patients (age 62.8±12.1) and 10 patients of Polymyalgia rheumatica (PMR: age 67.4±10.3). The final diagnosis of RA or PMR was confirmed after at least one year following up. In order to clarify the signature of gene expression, peripheral blood was drawn from the patients who were newly diagnosed and exposed neither steroids nor anti-rheumatic drugs. The samples were prepared and subjected to RNA extraction using PAXgene system (QIAGEN). Messenger RNA levels were then measured using Agilent whole human genome 60K (single-color procedure) and the log-transformed raw intensity data were normalized with a quantile algorithm. Based on the difference in gene expression between RA and PMR ($P<001$ by t-test), 4076 probes were selected and subjected to an unsupervised hierarchical clustering with assessment of the statistical robustness using a software, clusterStab (Bioconductor).

Results: The hierarchical clustering showed that the optimal number of clusters was 5. The statistical robustness was calculated for each cluster as 90%, 95%, 100%, 100% and 100%, respectively. Although the 4th and 5th cluster consisted of RA only, PMR was nested and distributed in the 1st to 3rd clusters. The percentage of PMR was 60%, 29% and 18% in these clusters, respectively. The average age of RA patients in the 1st cluster was statistically higher as compare with that of RA patients in the 4th and 5th clusters ($P<0.05$, 68.3±3.2 vs. 60.0±16.0). Application of pathway analysis reveals that B cell receptor (BCR) pathway was up-regulated in the 4th and 5th clusters.

Conclusion: PMR is an inflammatory rheumatic condition, which is sometimes difficult to distinguish from RA especially in elderly onset. Although the required treatments or features of pathophysiology are basically different between RA and PMR, these diseases occasionally seems to be overlapped. Although we defined 5 subgroups for RA and PMR by genome-wide transcription profiles, RA and PMR could not be distinguished clearly. It may support a hypothesis that some of RA or PMR cases may consider as an "overlap syndrome". The finding that BCL pathway was up-regulated in the "only-RA" clusters may explain that some of RA subgroups are susceptibility to B cell targeting treatments.

1957

Biologics In Relapsing Polychondritis: a Literature Review. Fernando Kemta Lekpa[1], Virginia Byers Kraus[2] and Xavier Chevalier[1]. [1]Hopital Henri-Mondor, Creteil, France, [2]Duke University Medical Center, Durham, NC

Background/Purpose: Emergence of biologics holds much hope in the management of patient with connective tissue disease, especially relapsing polychondritis (RP), a rare and severe disease which may lead to destruction of elastic cartilages. Until now, there is no standardized therapeutic protocol for RP. Objectives**:** To evaluate the efficacy and safety of biologics in patients with active RP.

Methods: A PubMed search up to December 2010 was performed without language restriction. MeSH terms and keywords were used relating to RP and biologics and various synonyms. All papers reporting the efficacy and/or safety of biologics in RP were selected. Reference lists of included papers were also search.

Results: All publications relate to case series or isolated case reports. No randomized controlled trial has been performed. Thirty papers including 61 patients were published. These patients were treated with TNFα blockers (n= 42), rituximab (n= 11), ankinra (n= 5), tocilizumab (n= 2) and abatacept (n= 1). Efficacy of these biologics is summarized in table 1. Safety appears to be good. However, four deaths were recorded (2 sepsis, 1 postoperatively after aortic aneurysm surgery and 1 after accidental dislocation of the tracheostomy device).

Table 1. Efficacy of biologics in relapsing polychondritis

Biologic Agent	Efficacy (Number of Patients) Yes	Partial	No	Total (Number of Patients)
Anti-TNFα				
Infliximab	14	3	14	31
Etanercept	4	0	3	7
Adalimumab	2	0	2	4
Rituximab	0	2	9	11
Anakinra	4	0	1	5
Tocilizumab	2	0	0	2
Abatacept	1	0	0	1

Conclusion: The experience with biologics in RP is very limited, and their real efficacy and indications need to be better defined. Randomized controlled trials, although difficult to realize because of the rarity of RP, are needed to determine the real role of biologics in the treatment strategy of this orphan disease.

1958

HM-018, An Oral Small Molecule JAK Inhibitor, Ameliorates Experimental Autoimmune Encephalomyelitis (EAE) in Mice. Yu Cai[1], Wuzhong Shen[1], Qianqian Dong[1], Zhipeng Wu[1], Xiaoning Yang[1], Ping Ren[1], Youjun Yu[1], Hongxia Shen[1], Jia Li[1], Jian Wang[1], Yang Sai[1], James Yan[1], Wei Deng[1], Jianguo Ji[2], Weiguo Su[1] and Haoran Zhao[1]. [1]Hutchison Medipharma Limited, Shanghai, China, [2]Abott, Shanghai, China

Background/Purpose: Multiple small molecule kinase inhibitors have been developed and advanced into clinical trials for the treatment of rheumatoid arthritis (RA) and represent a new class of oral DMARD therapies with immense potential. Janus family of non-receptor tyrosine kinases (JAKs), INCB018424, INCB028050, and CP690550 have demonstrated rapid and dramatic improvement in clinical measures of autoimmune diseases —consistent with their respective preclinical experiments. However, the effect of JAK inhibition has not been examined in animals with EAE, the experimental animal disease model for multiple sclerosis—a life-long, potentially debilitating autoimmune condition of the central nervous system in man.

Methods: Using both in vitro and in vivo assays for establishing structure-activity relationships, compounds were synthesized and screened to identify the ones with excellent potency, selectivity, and drug-like properties. PLP or MOG-induced EAE in mice was used to assess compound's effect in vivo. Clinical evaluation was carried out daily while histopathological analysis of the spinal cord was performed at the end of compound treatment. Inflammatory cytokine mRNA levels in spinal cords were quantified using real-time PCR.

Results: HM-018 was identified as a structurally unique, orally bioavailable, pan-JAK inhibitor with nanomolar potency against JAK1 (9.5 nM), JAK2 (14.8 nM), JAK 3 and TYK2 (less than 50 nM). It demonstrated superb selectivity to a panel of >63 additional kinases. HM-018 potently inhibited

signaling of multiple cytokines including IL-6 and IL-2 in vitro or in vivo. Prophylactic or therapeutic administration of HM-018 at 1 to 10 mg/kg significantly inhibited the progression of EAE and EAE-associated histological change in the spinal cords of SJL/J mice induced by immunization with $PLP_{139–151}$ peptide. Consistent with data from SJL/J mice, significant efficacy, as assessed by improvements in clinical score and histological signs of disease, was also achieved in the therapeutic setting of the more aggressive $MOG_{35–55}$-induced EAE model in C57BL/6 mice at total daily doses of 3~30 mg/kg. Disease development was nearly prevented completely at 30mg/kg. Histopathological examination of spinal cords showed that disease scores for inflammation and the area of demyelination were both significantly decreased in HM-018 treated animals versus vehicle control group. In the mean time, a rapid and sustained inhibition of the expression of mRNAs encoding multiple inflammatory mediators was detected. Moreover, HM-018 did not inhibit cytochrome P450s and demonstrated excellent oral PK properties in rodents and dogs. HM-018 also exhibited a favorable safety profile including a negative AMES test and no adverse effect level (NOAEL) in rats.

Conclusion: We demonstrated for the first time that HM-018, a potent and selective JAK inhibitor with attractive oral drug-like properties, exhibited strong beneficial effects under both prophylactic and therapeutic conditions in EAE models. These results support further development of JAK inhibitors for the treatment of MS patients.

1959

Safety and Efficacy of Mizoribine in Patients with Connective Tissue Diseases Other Than Rheumatoid Arthritis. Ryo Rokutanda[1], Mitsumasa Kishimoto[1], Hisanori Shimizu[1], Atsushi Nomura[2], Yasuhiro Suyama[1], Yuri Ohara[1], Akira Takeda[1], Ken-ichi Yamaguchi[3] and Masato Okada[1]. [1]St. Luke's International Hosptal, Tokyo, Japan, [2]Chubu-Rosai hospital, Nagoya, Japan, [3]St. Luke's International Hospital, Tokyo, Japan

Background/Purpose: Mizoribine (MZR) is an immunosuppressive agent which inhibits lymphocyte proliferation via inhibitory effect on the synthesis of inosine monophosphate dehydrogenase. Although MZR has the similar mechanism of action with Mycophenolate Mophetil, its anti-viral activity, such as against Cytomegalovirus, makes it more preferable as add-on therapy on high dose corticosteroids. While its efficacy for rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune nephritis and suppression of rejection in renal transplantation is well established, few studies have examined the use of MZR for various other connective tissue diseases (CTDs). The primary objective of this study was to evaluate the safety and tolerability of using MZR in a heterogeneous sample of patients with various CTDs other than RA. A secondary objective was to examine the impact of MZR on treating CTDs.

Methods: We identified all patients who had ever been treated with MZR for CTDs at our institution during the period from January 2001 to May 2011. After excluding patients with RA, a retrospective review of medical records was performed. Collected data included age, sex, race, type of CTD, time since diagnosis of CTD, previous treatment, and the reason for starting MZR. For the safety evaluation, information about adverse events, duration of therapy, and reasons for stopping MZR were also recorded. To categorize the purposes of adding MZR to corticosteroids therapy, patients who received high doses of PSL (prednisolone, 0.5 mg/kg/day or more) were defined as the induction therapy group, while those who received relatively low doses of PSL (less than 0.5 mg/kg/day) were defined as the maintenance therapy group. Longitudinal changes in the PSL doses were analyzed in each patient group.

Results: A total of 64 patients (14 receiving induction and 50 maintenance therapy with MZR) were included. The patient population comprised 34 with SLE, 6 with Sjögren syndrome, 6 with ANCA-associated vasculitis. Mean patient age at the time of starting MZR was 49.8 ± 16.5 years and the follow-up period was 400 ± 417 days. During 70.2 patient-years of follow-up, only two adverse events were identified: one was stomatitis which resulted in stopping MZR, and the other was leukocytopenia which improved with an MZR dose reduction. During the observational period, 17 patients discontinued MZR for various reasons. The reasons for discontinuation of treatment were lack of improvement/worsening of CTDs in 47.1% (8/17 patients), withdrawal after achieving remission in 11.8% (2/17 patients), and loss to follow-up in 11.8% (2/17 patients). In terms of efficacy, doses of PSL were significantly decreased at last follow-up in both the induction (44.1 ± 16.2 vs 10.7 ± 10.2 mg/day, $p<0.01$) and the maintenance group (12.4 ± 7.6 vs 9.3 ± 6.4 mg/day, $p<0.01$).

Conclusion: MZR appears to be safe and well tolerated in patients with CTDs other than RA. In addition, MZR seemed to be a effective steroid-sparing agent when combined with corticosteroids.

1960

Idiopathic Hindfoot Problems As An Early Rheumatological Manifestation of Hereditary Hemochromatosis Type I. Elena Becerra-Fernandez[1], Pantelis Panopalis[2] and Henri A. Menard[3]. [1]University College London, London, United Kingdom, [2]McGill University Health Center, Montreal, QC, [3]Montreal General Hospital, Montreal, QC

Background/Purpose: Ankle involvement in the arthropathy of Hereditary Hemochromatosis type I (HH) has been considered rare, but the number of reports describing this condition has increased over the past few years, highlighting the importance of further investigations for degenerative arthritis in unusual sites. Furthermore, two phenotypes of polyarticular osteoarthritis (OA) have been recently described, one of which, Type II OA, affects joints typically involved in HH and has been linked to mutations in the HFE genes in patients that do not suffer iron overload. Recent reports show that ferritin concentrations in synovial fluid are higher in those patients, suggesting that osteochondral damage in both arthropathy of HH and Type II POA may have the similar etiology. Currently, HFE genotyping is not done if the clinical or biochemical phenotypes are absent. Since frank idiopathic hindfoot OA can be a clue to undiagnosed HH, we hypothesized that unexplained idiopathic hindfoot arthralgia and/or joint swelling could be the presenting symptom of pre-clinical HH.

Methods: We report a pilot case series of 10 patients who presented to our clinic with idiopathic hindfoot problems and had a positive result for a major (C282Y) or minor (H63D) mutation in the HFE gene.

Results: All patients presented hindfoot symptoms, consisting of unilateral or bilateral arthralgia or joint swelling. Only one of the patients had been previously diagnosed with HH, and our studies revealed a bilateral marked subtalar joint osteoarthritis. In four of the patients, HH was diagnosed thanks to the hindfoot symptoms in otherwise asymptomatic patients, since bloods revealed data consistent with iron overload, and gene typing confirmed the diagnosis, with homozygosity for the major mutation in patients 2–4, and heterozygosity for the major mutation in patient 5. Patients 6–10 did not show the biochemical phenotype and were all heterozygote for the minor mutation. Patients 6 and 7 were initially diagnosed as chondrocalcinosis, but had persistent symptoms in the MCPs 2 and 3 bilaterally and ankles. Patient 8 presented with bilateral ankle pain and subtalar OA on X-Rays. Patient 9 presented as a polyarthralgia with involvement of his left hindfoot. Patient 10 had been diagnosed and treated for seropositive rheumatoid arthritis but had persistent non inflammatory swelling and bilateral mechanical pain in ankles and MCPs 2–3 (Pseudo-RA vs coexistent HH + RA?).

Conclusion: Hindfoot rheumatic symptoms can be the first manifestation of HH, long before occurrence of organ failure. This highlights the importance of including HH in the differential diagnosis of arthritis of unknown origin or degenerative arthropathy of unusual sites, especially the hindfoot which may have been overlooked in the past. In patients without iron overload, the HFE mutation would seem to operate via a different mechanism. For the rheumatologist, HFE genotyping of patients with hindfoot problems of unknown origin is useful. Our observations and other publications suggest that patients with the so-called "silent" H63D HFE mutation have early rheumatic symptoms. It follows that given their high frequency, those mutations may be a still insufficiently recognized major genetic risk factor for OA.

1961

Tumor Necrosis Factor Receptor Associated Periodic Fever Syndrome: A Case Series with Characteristic Features. Qingping Yao. Cleveland Clinic, Cleveland, OH

Background/Purpose: Autoinflammatory diseases (AIDs) are characterized by seemingly unprovoked episodes of inflammation, without high titer autoantibodies or antigen specific T cells, and derive from genetic variants of the innate immune system. Tumor necrosis factor receptor associated periodic fever syndrome (TRAPS) is an autosomal dominant AID. This study aimed to analyze a small case series of TRAPS with characteristic phenotypic and genotypic features.

Methods: Three adult patients with autoinflammatory clinical phenotypes were seen by the author in the Rheumatology Clinic at the Cleveland

Clinic between January, 2009 and October, 2010. A retrospective and prospective study of these cases was performed.

Results: These patients presented with autoinflammatory phenotypes compatible with TRAPS by genetic testing. Patient 1 was a 58-year-old Jewish woman with photographic evidence of various skin disease, including previously unreported severe alopecia, self limiting episodes of fever, abdominal pain/diarrhea, oligoarthralgia and myalgia. Complaints of urinating foreign bodies prompted a diagnosis of ureteral strictures with atypical cells, indicating a sequela of long-term autoinflammation. Patient 2 was a 32-year-old Caucasian woman with recurrent erythematous macules and papules (Photo), polyarthralgia and oral lesions. She was also found to have Ehlers-Danlos syndrome type III (Photo) which may complicate the arthralgia. Both TRAPS and Ehlers-Danlos syndrome could share common gene mutations. Patient 3 was a 56-year-old Caucasian man who presented with 4 years of periodic episodes of the right upper quadrant pain with nausea and vomiting. Both patients 1 and 2 had TNF receptor superfamily 1A (TNFRSF1A) gene mutation, R92Q and the patient 3 had TNFRSF1A missense mutation, V20A. Therapeutically, the patient 1 responded well to a short course of high dose prednisone, the patient 2 was treated with nonsteroidal anti-inflammatory agents, and the patient 3 had minimal response to high dose prednisone and failed a trial of etanercept.

Conclusion: Our small case series study suggests that patients with TRAPS may present with unusual phenotypes. TRAPS generally has oligoarthralgia which should be differentiated from concurrent joint disease. TNFRSF1A VA20 mutation has been linked to the clinical phenotypes of this disease.

1962

Atypical Persistent Plaquelike Skin Rash of Adult Onset Still's Disease. Case Report and Review of Literature. Asha Muthalaly[1], Dennis C. Ang[2], Steven T. Hugenberg[3], Roy Sampson[1] and Agith Muthalaly[4]. [1]Indiana University School of Medicine, Indianapolis, IN, [2]Indiana University, Indianapolis, IN, [3]Indiana Univ Schl of Medicine, Indianapolis, IN, [4]St. James School of Medicine, Chicago

Background/Purpose: 25 y/o Malaysian woman with no past medical history presented to the hospital with a 2 month history of fevers, chills, night sweats, diffuse myalgia, lethargy and sore throat. She also had a diffuse pruritic persistent hyper pigmented rash on back, chest, distal extremities. The patient was diagnosed with adult-onset Still's disease (AOSD) based on Yamaguchi criteria and skin biopsy revealed spongiotic psoriasiform dermatitis with scattered necrotic keratinocytes and confluent hyperkeratosis. Our patient met criteria for diagnosis of prurigo pigmentosa based on clinical and histopathologic findings. There have only been two other reported cases. However, when a review of literature was performed of all known cases of persistent plaques associated with AOSD, it was found that prurigo pigmentosa may be associated more commonly with AOSD than previously thought.

Methods: Meta analysis of 10 articles reviewed (total of 21 patients with AOSD) with persistent papules and plaques

Results: The histopathologic findings reported are commonly found in different stages of prurigo pigmentosa. See attached table for details.

Diagnosis	Laboratory Data	Gross findings	Pruritic	Description of Histology	Pathologic Diagnosis	Response to treatment	Duration of disease
AOSD (Case 1 presentation)	Ana negative, RF factor negative, elevated ferritin, normocytic anemia, and leukocytosis	Diffuse persistent hyperpigmented rash on back, chest, distal extremities	Yes	Spongiotic psoriasiform dermatitis with scattered necrotic keratinocytes and confluent hyperkarotosis	Meets criteria for prurigo pigmentosa based on histopathologic findings	Complete resolution of rash and systemic symptoms with prednisone 20mg and started on methotrexate for maintenance	2 months
Case 2 AOSD	Leukocytosis,elevated LFTS, elevated ferritin	Persistent skin rash on upper chest and back and evanescent skin eruption on lower extremities	N/A	Mild acanthosis, slight spongiosis, exocytosis and dyskaratotic cells	Prurigo pigmentosa	Complete resolution of rash with prednisone 40mg.	3 weeks
Case 3 AOSD	Leukocytosis, elevated LFTS, elevated ferritin, normocytic anemia, RF, ANA negative	Popular eruption arranged in reticulate pattern and distributed on face, neck, trunk and legs	Yes	Mild hyperkaratosis, acanthosis and mild spongiosis of epidermis. Lymphocytic infiltrate	Prurigo pigmentosa	Responded to prednisolone 1mg/kd/d and then prednisone therapy	10 days
Case 4 AOSD	Elevated sed rate, negative ANA and RF, elevated ferritin	Popular eruption which then became hyperpigmented papules over thighs,prethial areas and upper back, forearms	Yes	Hyperorthokeratosis, with dyskaratotic keratinocytes, mild perivascular infiltrate composed of lymphocytes and occasional eosinophils	Dyskaratosis w/ no specific diagnosis	Initial prednisone therapy with no response then methotrexate and etanercept and switched to interleukin 1 receptor antagonist (anakinra)	unknown
Case 5 AOSD	Normocytic anaemia,elevated liver function tests, negative ANA, RF	Migratory plaquelike rash on lower legs then became fixed and spread symmetrically on arms, dorsal hands,upper chest and back	Yes	Foci of eosinophilic spongiosis, epidermis with scattered necrotic keratinocytes with dermal lymphocytic perivascular infiltrate	No specific skin diagnosis	Methylprednisilone for 3 days with resolution of rash and then prednisone oral daily with methotrexate	8 months
Case 6 AOSD	Anemia, leukocytosis, thrombocytosis, elevated ESR and CRP. Elevated ferritin. Negative	Generalized edematous pink, maculopapular and urticarial lesions in arms and chest	N/A	Parakeratosis, acanthosis, and scattered intraepidermal	No specific skin diagnosis	Rapid resolution of all systemic symptoms with the skin lesions	5 weeks

Conclusion: The typical salmon colored evanescent rash is observed in 87% of patients in AOSD with histopathology showing relatively sparse perivascular mixed inflammatory infiltrate containing some neutrophils. Prurigo pigmentosa is a distinctive inflammatory disease first described in Japan. Clues to diagnosis include impression of trunk centered "scratched urticaria" Usually involves back, chest and neck and may also involve proximal extremities and upper extremities. It is rarely diagnosed outside of Japan because of its unfamiliarity. Various mechanisms proposed have been friction, contact allergy, sensitivity to sunlight, endocrine disorders such as diabetes, and metabolic disorders such as ketosis. Early lesions have superficial infiltrate of neutrophils and spongiosis with a few necrotic keratinocytes. Fully developed lesions have lymphocytic predominate infiltrate. In late lesions the epidermis is slightly hyperplastic and parakaratotic. Pruritis of early lesions is severe, however resolving lesions are devoid of symptoms. The pathologic skin diagnosis of the cases reviewed was unclear in the majority of cases. Prurigo pigmentosa may be an unusual yet more common, but under recognized skin manifestation of AOSD of which rheumatologists need to be aware in clinical practice.

1963

Clinical and Genetic Features of Autoinflammatory Syndromes in Hispanic Patients: The Chilean Experience. Cristian Vergara[1], Arturo Borzutzky[1], Miguel A. Gutierrez[1], Sergio Iacobelli[1], Eduardo Talesnik[1], Maria Eugenia Martinez[1], Lilith Stange[1], Javier Basualdo[2], Viviana Maluje[3], Renato Jimenez[4], Elena Jarpa[5], Roberto Wiener[6], Javier Tinoco[6], Juan I. Arostegui[7], Jordi Yague[7] and Manuel Alvarez-Lobos[1]. [1]Pontificia Universidad Catolica de Chile, Santiago, Chile, [2]Universidad de Chile, Santiago, Chile, [3]Hospital FACH, Santiago, Chile, [4]Hospital Gustavo Fricke, Valparaiso, Chile, [5]Hospital Naval Almirante Nef, Vina Del Mar, Chile, [6]Hospital Militar, Santiago, Chile, [7]Hospital Clínic/IDIBAPS, Barcelona, Spain

Background/Purpose: Hereditary autoinflammatory syndromes (AIS) are rare genetic diseases characterized by recurrent episodes of inflammation. Little information is available concerning AIS in Latin American Hispanic population. The purpose of this study was to determine the clinical and genetic characteristics of AIS in Chilean population.

Methods: A multicenter retrospective study of Hispanic patients from Chile with genetically-confirmed AIS was performed. Inclusion criteria for Familial Mediterranean Fever (FMF) were the presence of the characteristic clinical features associated with at least one mutated *MEFV* allele, whereas the TNF receptor-associated periodic syndrome (TRAPS) inclusion criteria were the presence of long inflammatory episodes associated with *TNFRSF1A* mutations. We included 13 patients, eight with FMF and five with TRAPS, evaluated at rheumatology or pediatric rheumatology clinics between January of 2007 and December of 2010. No patients with other AIS were seen in the study period.

Results: All 13 patients were Chilean and had Hispanic Latin American ethnicity with no other known genetic backgrounds. Median age of onset of clinical symptoms was 8 years (range: 1–35) and 8 years (range: 0.3–21) for FMF and TRAPS, respectively. Median duration of fever was 3 days (range: 2.5–15) for FMF and 21 days (range: 9.5–30) for TRAPS. In FMF patients, fever was associated with abdominal pain (6/8), myalgias (5/8), arthritis (4/8), and rash (3/8). All FMF patients had at least partial response to colchicine therapy, with two patients fully resolving episodes of recurrent fevers. Reactive AA-type amyloidosis was not observed among this group of FMF patients. In TRAPS patients, febrile episodes were preceded by malaise and periorbital edema in two patients. During episodes symptoms accompanying fever were migratory myalgias (4/5), rash (3/5), arthralgias/arthritis (3/5), and abdominal pain (3/5). Two patients with TRAPS underwent surgery for acute abdomen. Fever episodes were responsive to high-dose corticosteroids in 4/5 patients with TRAPS. Genotyping of the *MEFV* gene in FMF patients revealed one patient with a homozygous M694V missense mutation, and heterozygous missense mutations in seven patients: M694V (n=3), E148Q, R717H, A744S, and A511V. Sequencing of the *TNFRSF1A* gene in TRAPS patients revealed heterozygous missense mutations in four patients: T50M, C30R, R92Q, and IVS3+30:G>A, and a 2-base pair deletion (IVS2–17_18del2bpCT) in one patient. Mutation in *MEFV* R717H and mutations in *TNFRSF1A* IVS2–17_18del2bpCT and IVS3+30:G>A are novel and have not been reported previously.

Conclusion: This study reports the largest series of genetically-confirmed AIS in Latin America, and adds evidence regarding the clinical and genetic characteristics of patients with FMF and TRAPS in Hispanic population. In this series, mutations identified in *MEFV* and *TNFRSF1A* genes include defects reported in other ethnicities and novel mutations.

1964

Use of Canakinumab in the Routinary Clinical Practice in Severe Cryopyrin-Associated Periodic Syndrome: One Year of Follow-up.

Roberta Caorsi[1], Loredana Lepore[2], Francesco Zulian[3], Maria Alessio[4], Achille Stabile[5], Martina Finetti[6], Alberto Martini[6] and Marco Gattorno[1]. [1]G. Gaslini Institute, Genova, Italy, [2]Ospedale-Infantile Trieste, Trieste, Italy, [3]University of Padua, Padova, Italy, [4]University of Naples Federico II, Napoli, Italy, [5]DipartimentoPediatria, Policlinico Gemelli, Roma, Italy, [6]IRCCS G Gaslini, Pediatria II, Reumatologia, Genova, Italy

Background/Purpose: Preliminary studies have shown the efficacy of Canakinumab (Ilaris™) in patients with Cryopyrin associated periodic syndromes (CAPS). So far, few information is available about the optimal dosage and frequency of administration of Canakinumab, especially in children presenting a more severe phenotype. Aim of the study was to analyse the efficacy and optimal dose regimen of Canakinumab in CAPS patients in 12 months of routinely clinical practice.

Methods: 12 patients (F:M = 7:5, 9 children and 3 adults) with a clinical diagnosis of CINCA (6 patients), Muckle-Wells (MWS) overlapping with CINCA syndrome (3 patients) and MWS (3 patients) were analyzed. Nine out of them carried mutations of NLRP3 gene. All patients were previously enrolled in the CACZ885D2306 trial and followed in an open fashion for 12 months after the end of the study. Modifications of dose and/or frequency were performed according to the judgment of the physician in charge. Complete remission was considered as the absence of clinical manifestations and normal acute phase reactants. Patients with no clinical remission and elevation of acute phase reactants were considered in partial remission. Patients with clinical manifestations and elevation of acute phase reactants were considered in relapse or active.

Results: At the end of CACZ885D2306 trial (baseline) 7 patients (3 CINCA patients, 1 MWS/CINCA and 3 MWS) were treated with the initial dosage of 2 mg/kg (or 150 mg if weight was higher than 40 Kg) every 8 weeks. Five were in complete remission, 2 CINCA in partial remission. In 5 patients (3 CINCA patients and 2 MWS/CINCA) the dosage was increased to 4 mg/kg (or 300 mg) every 8 weeks. All of them were in partial remission. During observational study, modifications of dosage or frequency were performed in 7/12 patients. The 5 patients who required a higher dosage during the CACZ885D2306 displayed a persistent elevation of acute phase reactants associated, in 2 patients, with a mild clinical disease activity (mild rash, headache, arthralgia). In these patients the frequency of the administration of Canakinumab was gradually increased to 7 weeks (1 CINCA, 1 MWS/CINCA), to 6 weeks in 2 CINCA patients and every 4 weeks in 1 MWS/CINCA patient. At the end of the 12 months of observation 1 patient was in complete remission and 3 in partial remission. In one CINCA patient the treatment was discontinued due to persistence of disease activity and poor compliance. During the 12 month of follow-up other two patients (1 CINCA, 1 MWS) displayed a mild relapse of their diseases that required to increase the frequency of administration (6 and 7 weeks, respectively) without a modification of the dosage (2 mg/kg). In 5 patients (2 MWS, 1 MWS/CINCA and 2 CINCA patients) the treatment was not modified being effective in the control of the disease.

Conclusion: This study confirms the efficacy of Canakinumab in the control of disease activity in CAPS. However, paediatric patients and those with a more severe phenotype require higher and more frequent dosage than previously described

1965

Classification of Two Subtypes in Adult-Onset Still's Disease.

Hisae Ichida, Yasushi Kawaguchi, Tomoko Sugiura, Takahisa Gono, Kae Takagi, Yuko Ota, Ikuko Masuda and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Adult-onset Still's disease (AOSD) may be a clinical entity including heterogenous etiology and pathogenesis. Clinical characteristics are systemic inflammations of unknown origin with hyperferritinemia in the absence of any autoantibodies. We encountered patients with AOSD having severe polyarthritis corresponding with the classification criteria of rheumatoid arthritis (RA), although most of patients with AOSD showed mild arthritis in general. In the present study, we propose two clinical subsets in AOSD and investigate clinically significant characteristics of the two subtypes.

Methods: We retrospectively observed consecutive 73 patients with AOSD in our outpatient clinic from 1995 to 2008. We observed the medical records of all patients for more than 2 years. We classified all patients with AOSD into 2 subsets: RA-subtype who finally met the revised criteria of American College of Rheumatology clinical diagnostic criteria for RA; and nonRA-subtype who didn't met it at all.

Results: The levels of both serum ferritin and IL-18 were significantly higher in nonRA-subtype than those in RA-subtype. To define the optimal cut-off point with the highest diagnostic accuracy, we performed receiver operating characteristic analyses for distinct serum ferritin and IL-18 concentrations. In both less than 1500 ng/dl of serum ferritin and less than 44000 pg/ml of serum IL-18, the sensitivity of RA-subtype was 82% and the specificity was 82% (Table 1). The frequency of patients whose family had autoimmune diseases showed a tendency to be high in nonRA-type. NonRA-subtype was accompanied with some severe inflammatory complications (i.e.; pleuritis, DIC, HPS). Interestingly, in patients with RA-subtype only a patient had anti-CCP antibody and no patients had rheumatoid factor, which is completely different from patients with true RA. The treatments with methotrexate and/or salazosulfapyridine were more frequent in RA-subtype than those in nonRA-subtype. All patients treated with biologics belonged to RA-type. Tocilizumab were applied to two patients, resulting in attenuating inflammation in the two patients.

Table 1. Predictive values of serum ferritin and serum IL-18

	RA-subtype n, (%)	NonRA-subtype n, (%)	P-value OR (95% CI)
Ferritin < 1500 ng/dl	12/15 (80)	15/52 (29)	0.0005 10 (2.4–40)
IL-18 < 44000 pg/ml	10/11 (91)	14/34 (41)	0.0043 14 (1.6–125)
Ferritin < 1500 and IL-18 < 44000	9/11 (82)	6/34 (18)	0.0002 21 (3.6–123)

The P-value was estimated by Fisher's exact test. n: number

Conclusion: We concluded the existence of two subsets in patients with AOSD. Patients with high levels of IL-18 or ferritin were complicated with severe systemic inflammatory disorders (nonRA-subtype), and patients with low levels of them developed to severe arthritis (RA-subtype).

1966

Free Interleukin 18 As a Predictor of Remission and Flare up in Adult-Onset Still's Disease Patients.

Kyong-Hee Jung[1], Joo Hyun Lee[2], JinJu Kim[2], Jin Sook Lee[2], Won Park[1], Tae-Hwan Kim[2] and Dae-Hyun Yoo[2]. [1]Center for Rheumatism, Inha University Hospital, Incheon, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

Background/Purpose: Recent investigations have shown that the serum level of interleukint-18 (IL-18) is extremely high in adult-onset Still's disease (AOSD) patients. However, IL-18 binding protein (IL-18BP), a natural antagonist of IL-18, and free IL-18 in AOSD have not been studied yet. The aim of this study was to investigate the usefulness of free IL-18 in AOSD patients.

Methods: The levels of free IL-18 were compared between 66 AOSD patients and 90 controls (30 unaffected controls, 30 rheumatoid arthritis patients, and 30 ankylosing spondylitis patients). The AOSD patients were divided into active and inactive groups according to disease activity based on clinical and laboratory findings. The inactive patients were further subdivided into remission group (the absence of clinical symptoms and laboratory evidence of disease activity for at least 12 months) and maintenance group. We compared ESR, CRP, ferritin and free IL-18 in AOSD patients. We measured serum IL-18, IL-18BP using enzyme-linked immunosorbent assay and calculated free IL-18 by applying the law of mass action.

Results: AOSD patients showed significantly higher levels of free IL-18 than controls (mean±SD, AOSD 14762±30586 pg/ml, RA 402±449 pg/ml, AS 192±98 pg/ml, healthy controls 175±74 pg/ml, $p<0.001$). Like conventional activity marker such as ESR, CRP and ferritin, free IL-18 was significantly higher in active group than inactive group (active 20913±27691 pg/ml, inactive 4523±8993 pg/ml, p-value <0.001). Within the inactive group with normal ESR, CRP and ferritin, free IL-18 levels in the remission group were significantly lower than in the maintenance group (remission 710±714 pg/ml, maintenance 6884±10856 pg/ml, p-value=0.047). During follow up, 4 out of 14 inactive AOSD patients with higher levels of free IL-18 despite of normal ESR, CRP and ferritin had a disease flare up within 3 months.

Conclusion: Free IL-18 level was significantly high in AOSD patients despite compensation of IL-18BP. Free IL-18 could be useful in the assessment of disease activity especially in clinically inactive AOSD patients, a useful predictor of remission and flare up.

1967

Study Design of the β-Confident-Registry Aiming to Evaluate the Largest Cohort of Cryopyrin-Associated Periodic Syndromes Patients. Hal M. Hoffman[1], Ulrich A. Walker[2], Hugh Tilson[3], Jasmin B. Kuemmerle-Deschner[4] and Philip Hawkins[5]. [1]Division of Rheumatology and Allergy/Immunology, La Jolla, CA, [2]Dept. of Rheumatology at Basel University, Felix-Platter Spital, Basel, Switzerland, [3]University of North Carolina, North Carolina, [4]University Hospital Tuebingen, Tuebingen, Germany, [5]Department of Medicine, University College London Medical School, London, United Kingdom

Background/Purpose: Cryopyrin-associated periodic syndromes (CAPS) is an extremely rare inflammatory disorder with limited available clinical and especially long-term follow-up data. Canakinumab (Ilaris®) has recently been approved for the treatment of CAPS, however, data on longer-term follow-up in larger patient cohorts is warranted. We report here the design of a global observational registry for canakinumab. The registry is monitored by an external steering committee with expertise in auto-inflammatory disease and registry design. The primary objective is to monitor overall safety of routine care with canakinumab in a large cohort (N≥400) of CAPS patients. Secondary objectives include exploring growth and development patterns in children and to measure the long-term impact of canakinumab on disease progression.

Methods: CAPS patients receiving canakinumab as part of their routine care are included in this study for a minimum of 5-years follow-up. Data from routine clinic assessments is supplied at 6-monthly intervals via a web-based application. Selected safety events potentially associated with anti-IL-1 therapy such as serious infections, malignancies, hypersensitivity and disease activity/progression is analyzed. Signs and symptoms of systemic inflammation, neurologic and ophthalmologic status and the potential for canakinumab therapy to prevent amyloidosis and to ameliorate sensorineural deafness are assessed. Patterns of growth/development, pregnancies, outcomes of vaccination, dosing pattern and tolerability are ascertained. All patients are followed until the registry ends.

Results: Baseline data from the first 58 CAPS patients, including 15 pediatric patients (age <18 years), enrolled to date, are presented (Table). Updated data will be provided during the presentation at the congress.

Table. Baseline characteristics of CAPS patients enrolled in B-Confident-Registry study till date

	FCAS (n=10)	MWS (n=37)	NOMID (n=6)	Other (n=5)
Age <4 years, n	0	2	0	1
Age 4-<18 years, n	2	6	3	1
Age ≥18 years, n	8	29	3	3
Male, n (%)	3 (30.0)	20 (54.1)	3 (50.0)	2 (40.0)
NLRP3 mutation, n (%)	10 (100.0)	35 (94.6)	5 (83.3)	2 (86.7)
Disease duration (months, mean)	550	370	172	64
Prior IL-1 inhibitor treatment, n (%)	0	14 (37.8)	1 (16.1)	2 (40)
Rash/arthralgia/headache/ conjunctivitis (%)	100/100/ 50/80	97.3/97.3/ 78.4/75.7	100/100/ 83.4/66.6	80/100/ 20/40
History of anaemia (%)	10	8.1	50	0
Prior SAA value (mg/L, mean)	37	26	47	3

FCAS=familial cold auto-inflammatory syndrome; IL-1=interleukin-1; MWS=Muckle-Wells syndrome;
n=number of patients; NOMID=neonatal-onset multisystem inflammatory disease;
SAA=serum amyloid A

Conclusion: Baseline characteristics validate an expected disease background in all patients enrolled to date. Upon availability of larger data-sets, subanalyses will yield valuable insights into disease characteristics and modification properties and safety profile of canakinumab in this rare disease.

1968

Anti-TNFα Therapy in 15 Patients with Severe and Refractory Sarcoidosis. Inés Pérez-Martín[1], Ricardo Blanco[2], Javier Rueda[1], Carmen Bejerano[2], Orlando Pompei[1], M. Carmen González-Vela[1], Marcos A. González-López[1], Héctor Fernández-Llaca[1], Agustín Oterino[1], María J. Sedano[1], Mario Agudo[1], Víctor M. Martínez-Taboada[1] and Miguel Angel González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla-IFIMAV, Santander, Spain

Background/Purpose: Sarcoidosis is a systemic granulomatous autoimmune disease. Clinically it may range from a mild to a severe life-threatening disease.

Methods: We reviewed the medical records of patients seen at the Rheumatology Service of a University hospital that were diagnosed with sarcoidosis and treated with anti-TNFα therapy because of disease severity.

Results: We assessed 15 patients (8 women/7 men); mean age at disease diagnosis: 49±15 years (range: 28–69); mean duration of sarcoidosis before the onset of anti-TNFα therapy 74±95 months (range 12–360) **(TABLE).**

patient	age/sex	main clinical complication	immunosuppressive agents prior to anti-TNFα	prednisone dose at anti-TNFα onset	1st anti-TNFα/2nd anti-TNFα	immunosuppressive drug with anti-TNFα
1	64/F	lupus pernio	HQ/AZA/MTX	–	infliximab	MTX
2	46/M	general syndrome and myopathy	HQ/MTX	40mg/d	infliximab	MTX
3	48/F	uveítis	MTX	45mg/d	infliximab	MTX
4	33/F	uveítis	SZP/MTX	30mg/d	infliximab/ adalimumab	MTX
5	28/M	uveítis	AZA	40mg/d	adalimumab	AZA
6	30/M	uveítis	HQ/MTX	30mg/d	infliximab	AZA
7	69/M	bone marrow-pancytopenia	MTX	30mg/d	infliximab/ adalimumab	MTX
8	67/F	neurosarcoidosis	MTX	40mg/d	infliximab	MTX
9	65/F	neurosarcoidosis	MTX	40mg/d	infliximab/ adalimumab	MTX
10	54/M	uveitis	CyA	45mg/d	adalimumab	–
11	58/M	neurosarcoidosis	–	60mg/d	infliximab	MTX
12	54/F	neurosarcoidosis	MTX/AZA	45mg/d	infliximab/ adalimumab	MTX
13	29/M	neurosarcoidosis	–	60mg/d	infliximab	MTX
14	56/M	aortitis	MTX	30mg/d	adalimumab	MTX
15	62/F	neurosarcoidosis	–	30mg/d	infliximab	MTX

Abbreviations: HQ: hydroxichloroquine, MTX: methotrexate, AZA: azathioprine, CyA: cyclosporine A SZP: sulfasalazine, M: male, F: female

The main clinical complications that made necessary the use of anti-TNFα agents were: uveitis (5 cases), neurosarcoidosis (6), bone marrow involvement-pancitopenia (1), skin-lupus pernio (1), systemic-myopathy (1), and aortitis (1).

Most patients had been refractory to corticosteroids and at least one immunosuppressive drug. However, in 3 patients with neurosarcoidosis anti-TNFα agents were prescribed along with corticosteroids as the initial therapy. Besides high-dose prednisone, patients had received the following drugs: i.v. methylprednisolone (500–1000 mg for 3 consecutive days) (4 cases) methotrexate (10 cases), cyclosporine (1 case), azathioprine (3 cases), sulfasalazine (2 cases), and hydroxychloroquine (3 cases).

Anti-TNFα drugs were associated to an immunosuppressive agent (methotrexate, or azathioprine). Infliximab was the most commonly anti-TNFα drug used in this series- in 12 cases (3–5 mg/kg/i.v. at 0, 2, 6 and then every 4–8 weeks). Adalimumab was administered in the other 3 patients (40 mg/sc EOW or EW if necessary). Infliximab was discontinued in 2 cases because of inefficacy and in another 2 due to adverse events (severe rash and gastrointestinal intolerance, respectively). In these 4 cases, infliximab was switched to adalimumab. Adalimumab was discontinued in 1 of 7 cases because of development of a lupus-like syndrome. After a mean time of anti-TNFα therapy of 25 ± 20 months (range 1–72), complete clinical remission was achieved in 9 cases and partial improvement in the remaining 6 patients. Of major importance, in most patients anti-TNFα treatment allowed withdrawal or significant reduction of corticosteroid therapy.

The most common adverse events were infections. Three of them were severe: pneumonia by *P. jirovecii*, septic shock by *P. aeruginosa* and VV Zoster infection.

Conclusion: Infliximab and adalimumab appear to be effective and safe drugs in the management of severe and refractory sarcoidosis.

1969

Sonographic Detection of a Bifid Median Nerve and Persistent Median Artery Among Patients with Clinical Diagnosis of Carpal Tunnel Syndrome in Rheumatology Office. Francis Luk, Carolyn R. O'Connor, Humaira Hussain, Vincent Zarro and Angel E. Checa. Drexel University College of Medicine, Philadelphia, PA

Background/Purpose: Patients with carpal tunnel syndrome (CTS) are often managed in rheumatology by corticoid injections with or without ultrasound guidance. Although, there is an increasing use of new imaging techniques which permit the identification of the bifid median nerve (bmn) and persistent median artery (pma), the prevalence of these variants continue to be unclear. The pma is a potential source of complication by laceration during interventional procedures.

Methods: To determine the prevalence and sonographic characteristics of bmn and pma in patients with CTS, a total of 129 wrists of 77 consecutive patients (9 males, 68 females) with clinical diagnosis of CTS assessed by ultrasound in rheumatology office were studied. A longitudinal and transverse

scan of the volar aspect of the wrist was performed with a GE LOGIQ e machine equipped with a broadband linear transducer from 8 to 13 MHz. The cross sectional area of the median nerve was calculated with the ellipse at the scaphoid-pisiform level. In those cases with bmn both branches were measured separately. The functional status of the median artery was evaluated by the presence or absence of a Doppler signal.

Results: Out of 77 patients (129 wrists), 13 (14 wrists) showed bmn or pma. The mean age of those with bmn or pma was 52.5 (31–81) years, with a prevalence of 8.5% and 4.6% respectively. The bmn was more common in the left hand, and a greater lateral branch was the most characteristic sonographic pattern, observed in 70%. The average cross sectional area for bmn was 11.4 (range 6–18) square millimeters. The pma was associated with a bmn in three wrists, and it appeared as an isolated variant in 3 other wrists. The average diameter of pma was 1.4 (range 0.8–3.1) millimeters. In three of them, Doppler signal showed a functional artery.Doppler signal was absent in two pma's and in one artery, the Doppler was not explored. In those patients with pma but no Doppler signal, a non-functional cord-like remnant may be present.

Conclusion: Although studies of large populations are needed, the increased observation of bmn and pma by ultrasound in patients with CTS should be considered more than a medical curiosity. Because corticoid injection and surgery are common therapeutic modalities in patients with CTS, an ultrasound should be part of the initial work-up to detect their presence and avoid the potential complication of laceration, bleeding, and nerve damage.

1970

The Role of Sufficient Starting Dose of Steroids in Adult-Onset Still's Disease. You Jae Kim[1], Bon San Koo[1], Min Wook So[1], Wook Jang Seo[2], Ji Seon Oh[3], Yong-Gil Kim[1], Chang-Keun Lee[1] and Bin Yoo[1]. [1]University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Seoul Veterans Hospital, Seoul, South Korea, [3]University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, South Korea

Background/Purpose: To evaluate the clinical features, laboratory findings, response to therapy in patients with adult-onset Still's disease (AOSD) and to determine the prognostic factors related with unfavorable outcomes.

Methods: The medical records of 82 patients, diagnosed with AOSD from January 1992 through December 2009 at a single tertiary hospital, were retrospectively reviewed. The patients were divided into two groups according to the disease course, i.e. favorable (monocyclic course, n=33) and unfavorable (chronic or polycyclic and death, n=49). The clinical parameters were compared and the odds ratio (OR) for an unfavorable course was assessed.

Results: The mean age at onset was 36.7±14.9 years, and women accounted for 60 of the total 82 patients (73.2%). Thirty-three (40.2%) patients had monocyclic disease, 33 (40.2%) experienced disease relapse at least once, and 14 (17.1%) had chronic articular disease. The major clinical features were high spiking fever (96.3%), polyarthralgia (85.4%), skin rash (80.5%), myalgia (70.7%), and sore throat (68.3%). Polyarthralgia ($p = 0.01$), leukocytosis ($p = 0.08$), anemia ($p = 0.05$), the serum erythrocyte sedimentation rate (ESR, $p = 0.03$), lactate dehydrogenase (LDH, $p = 0.04$), and the ferritin levels ($p = 0.04$) showed a significant correlation with the unfavorable disease course. Interestingly, an insufficient starting dosage of prednisolone or its equivalent (less than 30 mg/day) was a significant predictive factor (OR 9.2, $p = 0.007$). Response rate is decreased with insufficient dose of steroids, patients within unfavorable group subsequently exhibited a longer mean time from the initiation of treatment to disease remission, i.e. 4.6±2.9 months and 9.0±9.1 months ($p = 0.04$). They also had a longer duration of steroid use ($p < 0.001$) and received more disease-modifying anti-rheumatic drugs ($p = 0.002$).

Conclusion: Analyzing the risk factors for a poor prognosis, an insufficient starting dosage of steroids, i.e. less than 30mg/day of prednisolone, was seen to be significantly related to chronic or relapsing disease course and longer steroid use. Patients may require early treatment with sufficient steroids to control the disease activity and achieve quicker remission.

1971

Off-Label Use of Biological Therapies in Systemic Autoimmune Diseases. Ana Carolina Araújo, Carla Noronha, Ana Grilo, Maria Francisca Moraes-Fontes, Nuno Riso and Manuel Vaz Riscado. Hospital de Curry Cabral, Lisbon, Portugal

Background/Purpose: Patients with systemic autoimmune diseases (AID) may not respond to first line immunosupressants or relapse after initial clinical remission. The emergence of biological therapies has increased therapeutic options despite the lack of controlled trials.

Methods: Retrospective study of data from our Autoimmune Disease Clinic's database on the use of biological agents in patients with systemic autoimmune diseases (AID). The analysis included a total of 14 AID and by June 2011, the Database included 133 patients who had been treated with biological agents (16 received infliximab, 29 rituximab, 73 etanercept, 1 golimumab, 6 tocilizumab and 37 adalimumab).

Results: Off-label use of biological agents in 21 patients with AID included systemic lupus erythematosus (eight cases with nephritis and neuropsychiatric manifestations), autoimmune thrombocytopenia (five cases), Behçet disease (two cases) and one patient in each of the following diseases (overlap syndrome consisting of Sjögren's Syndrome with rheumatoid arthritis, Wegener granulomatosis, adult-onset Still′s disease, Churg Strauss vasculitis, ulcerative colitis and SAPHO syndrome). Patients calling for off-label use of biological drugs were also refractory to conventional therapies obtaining partial or no response to high dose conventional immunosupressants (namely steroids, full-dose cyclophosphamide and highest tolerated methotrexate dose). Regarding SLE, most patients had already been on cyclophosphamide for at least six months without adequate disease control. Both ANCA-vasculitis patients experienced only a partial response to the traditional treatment with cyclophosphamide and steroids.

The favorable response to Rituximab is highlighted. Five patients required re-treatment once and of these, one patient required a further re-treatment. Three were SLE patients and two had immune thrombocytopenic purpura. Of note, the Behçet's disease patients showed none or very small improvement with anti-TNF blockade.

Conclusion: Current evidence on the use of biological therapies in patients with refractory AID is mainly based on uncontrolled, observational data. In our experience, the best results have been observed in the use of rituximab for refractory SLE nephritis and ITP. Lack of efficacy was demonstrated for infliximab in Behçet's disease. Until future controlled trials confirm the potential use of biological therapies in patients with refractory AID, it is hoped that we can gather national data in a registry for refractory AID, from which further evidence can be drawn to support their use.

1972

Subacromial Steroid Injection Do Not Seems to Increase the Rate of Full-Thickness Rotator Cuff Tear. Julio Ramirez[1], Isaac Pomés[2], Jaume Pomés[2] and Juan D. Cañete[3]. [1]Hospital Clinic, Barcelona, Spain, [2]Hospital Clínic, Barcelona, Spain, [3]Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain

Background/Purpose: Up to 35% of patients with shoulder pain have a full-thickness rotator cuff tear. Although it has been demonstrated a deleterious effect of corticosteroid on collagen, the impact of corticosteroid injection on rotator cuff tears remains unclear. The aim of this study was to evaluate whether corticosteroid injection increase the incidence of full-thickness rotator cuff tear. Secondary objectives were to determine the percentage of partial-thickness rotator cuff tears which become full-thickness rotator cuff tear along the study, as well as to evaluate changes in shoulder pain and function between two groups of local treatment.

Methods: This is a prospective, open-label, controlled study designed to include a total of 100 patients along two years. Patients with unilateral painful shoulder without previous local steroid injection were enrolled. Clinical and ultrasound assessment in the first (day 0) and the last visit (day 120) were performed, excluding patients with full-thickness rotator cuff tear at day 0.Patients were randomized to receive either a standard subacromial infiltration of 1 ml of triamcinolone acetate or 1ml of mepivacaine.A radiologist and a rheumatologist with expertise in musculoskeletal ultrasound performed the ultrasound scans and clinical examination, respectively, of the painful shoulder.

Results: 43 patients with shoulder pain were evaluated. 23 (53%) had full-thickness rotator cuff tear in the first visit and were excluded. 20 patients completed the study (15 women and 5 men, mean age 60 years): 14 received one injection of triamcinolone acetate and 6 patients one of mepivacaine.

After 4 months of follow-up, 4 full-thickness rotator cuff tears were found: 2/14 (14%) in the triamcinolone group, and 2/6 (33%) in the mepivacaine group. Among 8 patients who had a partial-thickness rotator cuff tear in the first visit, 3 developed a complete tear after 4 month: 1/4 (25%) in the triamcinolone group and 2/4 (50%) in the mepivacaine group.

5/6 patients (83%) in the mepivacaine group and 8 /14 (57%) in the triamcinolone group experimented a great improvement in shoulder pain. All patients recovered the normal range of movement after 4 months.

Conclusion: These very preliminary results suggest that around 50% of patients with chronic shoulder pain have full-thickness rotator cuff tear, and that subacromial steroid injection did not increase the expected rate of

full-thickness rotator cuff tear in a population with shoulder pain. Furthermore, subacromial injection with mepivacaine or triamcinolona seems to produce similar clinical results a 4 months of follow-up. These findings should be confirmed in a greater sample of patients.

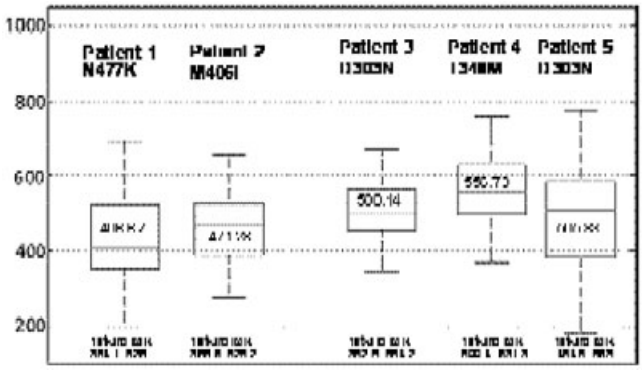
1973

Magnetic Resonance Imaging Cartilage Composition As a Potential Early Marker for Degenerative Joint Disease in Patients with Cryopyrinopathies. Clara Malattia[1], Martina Finetti[1], Maria Beatrice Damasio[2], Chiara Mattiuz[2], Gabriele Chiusano[3], Curzio Basso[3], Aldo Naselli[1], Alberto Martini[1] and Marco Gattorno[1]. [1]IRCCS G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [2]IRCCS G Gaslini, U.O. Radiologia, Genova, Italy, [3]Dipartimento di Informatica e Scienze dell'Informazione, Università di Genova, Genova, Italy

Background/Purpose: Cryopyrinopathies (FCAS, MWS and CINCA) are autosomal-dominant disorders characterized by different mutations in a gene, NLRP3, encoding a protein called cryopyrin. Cryopyrin is expressed in granulocytes, dendritic cells, monocytes, B and T lymphocites; interestingly, high-level expression was also detected in chondrocytes. The most characteristic skeletal features observed in the most severe phenotype (CINCA) are represented by bone overgrowth that predominantly involves the knees and the distal extremities of hands and feet. These and other skeletal anomalies suggest a cartilage target. In these patients the cartilage burst causes deformity that leads to an early degenerative arthropathy. MRI has been established as the standard cartilage imaging modality, and techniques have been developed to visualize cartilage morphology and to analyze its biochemical composition. Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) is a non-invasive molecular imaging technique that provides *in vivo* quantitative information about the fixed charged density of the articular cartilage, with is closely related to the glycosaminoglycane (GAG) concentration of the extracellular matrix. The purpose of the study was to investigate morphologic changes of the articular cartilage and to analyze its biochemical composition in patients with CAPS by using MRI.

Methods: 5 patients with CAPS (F:M = 3:2, mean age 11,4 years, range 6 – 16 years) with a clinical diagnosis of CINCA (N=2) or Muckle-Wells syndrome (N=3) were enrolled. The following *NLRP3* mutations were found: N477K, M406I, T348M, D303N (2 unrelated patients). All CAPS patients were receiving anti-IL-1 treatment with complete control of clinical and laboratory manifestations. MRI of the dominant knee was performed with a 1.5 Tesla MR scanner. The study included a morphologic and the ultrastructural assessment of the articular cartilage. The T1 maps were analyzed by using region of interest measurements. dGEMRIC values [in milliseconds] were determined after administration of contrast agent.

Results: The CINCA patients showed an evident frontal bossing with saddle back nose and late closure of the fontanel. No evident joint or skeletal abnormalities were observed in MWS patients. Clinical examination of the imaged knee was normal in all patients. No morphologic cartilage changes or inflammatory signs were detected by MRI. dGEMRIC values in the CINCA patients were lower than in MWS patients, suggesting a reduced GAG content in CINCA (figure).



Conclusion: dGEMRIC provides information beyond morphological changes in articular cartilage. Imaging of cartilage quality with dGEMRIC may provide pathophysiologic information relevant to disease progression and may be a promising tool for monitoring the effect of anti-IL-1 treatment on cartilage integrity. Evaluation of age-matched healthy controls is in progress.

1974

E148Q Is Not a Disease Causing Allele in Familial Mediterranean Fever in Populations Where FMF Is Prevalent. Servet Akar[1], Dilek Solmaz[2], Fatos Onen[1], Vedat Gerdan[2], Ozgul Soysal[2] and Nurullah Akkoc[1]. [1]Professor, Izmir, Turkey, [2]MD, Izmir, Turkey

Background/Purpose: About 200 sequence variations of the Mediterranean fever (*MEFV) gene* have been described. Even though the role of the three most frequent mutations located in exon 10 of the *MEFV* gene (M694V, V726A, M680I) in development of FMF has been widely recognized, the role of E148Q which was initially described as disease causing allele is yet controversial. Therefore the aim of this study is to assess the frequency of E148Q among FMF patients and healthy controls (HCs) based on the data from the published case control studies.

Methods: We conducted a systematic literature search using PubMed, Embase and The Cochrane Library. Search terms were "MEFV" and "MEFV gene". Hand searching of the reference lists of key articles and, hand/electronic searching of abstract books of the relevant conferences were performed. Statistical analysis was carried out using the Comprehensive Meta-Analysis statistical software (Biosta, Englewood, NJ, USA). Random-effects model was used.

Results: A total of 536 studies were identified of which 29 were retrieved for full review. Three of them assessed the frequency of MEFV variations in 11 ethnically different populations. A total of 13946 alleles of FMF patients and 9556 of HCs were included in the meta-analysis which yielded an overall odds ratio (OR) of 1.8 (95% CI 1.3–2.6) for E148Q in susceptibility to FMF. As the target populations in these studies show wide variation with regard to *FMF prevalence, a* subgroup-based meta-analysis was performed which revealed an OR of 1.3 (95% CI 0.9–1.8) and 6.1 (95% CI 3.3–11.3) in populations with high (Jews, Turks, Arabs and Armenians) and low prevalence (Greek, Japanese, Spanish and others), respectively (Figure 1). Homozygosity for E148Q was identified in 15/1875 FMF patients and 8/1878 healthy subjects in 17 studies which appropriate information was provided (p=0.144). On the other hand a clear association of M694V, M680I and V726A with FMF were observed in the pooled analysis.

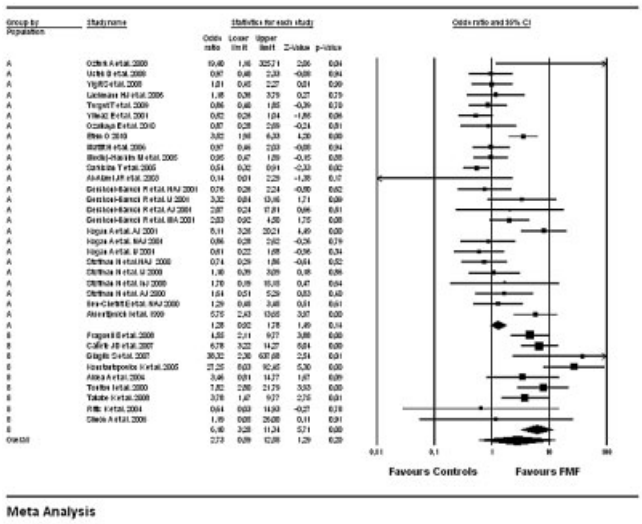


Figure 1. Odds ratios and corresponding 95% CI, for the association of the E148Q with familial Mediterranean fever in populations with high (group A) and low disease prevalence (group B).

Conclusion: Our results indicate that the presence of E148Q does not appear to be associated with an increased risk of FMF in populations with high disease prevalence whereas it may be associated with an increased risk in populations with low disease prevalence. However, in these latter populations further research is required to eliminate the role of over-emphasis on genetic testing which may lead to an over diagnosis of FMF.

1975

Long Term Follow-up of Infliximab Efficacy in Pulmonary and Extrapulmonary Sarcoidosis Refractory to Conventional Therapy. Eric Russell, Carolyn R. O'Connor and Humaira Hussain. Drexel University College of Medicine, Philadelphia, PA

Background/Purpose: Sarcoidosis is a multi-organ disorder histologically characterized by non-caseating granuloma formation. An etiology remains unclear, but TNF- a is known to play a crucial role and TNF- a blockade is a potential approach in the therapy of sarcoidosis. Infliximab, a chimeric monoclonal human mouse antibody against TNF- a has been shown to reduce the pulmonary and extrapulmonary manifestations of sarcoid, however, long term follow-up of sarcoidosis patients treated with infliximab has not been evaluated.

Methods: Subjects (18–85 years of age) with multi-organ sarcoidosis were identified retrospectively from the sarcoidosis clinic center of our outpatient office, in which infliximab had been prescribed due to failure of conventional therapy, between January 2000 to August 2010. Both symptomatic and clinical extra-pulmonary findings (constitutional, ocular, cutaneous, musculoskeletal, cardiac, neurologic, and renal) were evaluated pre-infliximab and post or concurrent infliximab therapy. When available, pulmonary assessment was evaluated using pulmonary function testing results also comparing pre-infliximab and post or concurrent infliximab therapy. Any adverse events of infliximab therapy were noted.

Results: All patients had biopsy-proven sarcoidosis and a clinical and/or radiographic presentation consistent with the diagnosis. Of the forty-five patients identified with sarcoidosis who received treatment with infliximab, cutaneous, lymphatic, neurologic, pulmonary and musculoskeletal sarcoidosis was recognized. Our data demonstrates that patients on long-term infliximab therapy had either sustained maintenance of disease improvement or cessation of disease progression as measured by patient description in addition to objective laboratory and/or imaging studies. Infliximab side effects or adverse events were rare.

Conclusion: Infliximab is effective and well tolerated in long-term control of pulmonary and extrapulmonary symptoms in patients with sarcoidosis refractory to other agents or in whom other agents were poorly tolerated due to side effects.

1976

Early Recognition of Hearing Loss in Muckle-Wells Syndrome. Jasmin B. Kuemmerle-Deschner[1], Assen Koitschev[2], Pascal N. Tyrrell[3], Katharina Ummenhofer[1], Peter Lohse[4], Sandra Hansmann[1], Stefan Plontke[5], Christiane Koitschev[6] and Susanne M. Benseler[3]. [1]University Hospital Tuebingen, Tuebingen, Germany, [2]Department of Otorhinolaryngology, Klinikum Stuttgart, Stuttgart, Germany, [3]The Hospital for Sick Children, Toronto, ON, [4]Department of Clinical Chemistry Groβhadern, University Munich, Munich, Germany, [5]Department of Otorhinolaryngology, University Hospital Halle (Saale), Halle (Saale), Germany, [6]Department of Otorhinolaryngology, University Hospital Tuebingen, Tuebingen, Germany

Background/Purpose: Hearing loss is the most common, debilitating long-term deficit in patients with Muckle-Wells syndrome (MWS). Standard audiology assessment includes the four pure tone average (4PTA) determining hearing thresholds at the four frequencies most relevant for speech discrimination (0.5, 1, 2, and 4 kHz). Inflammation in MWS results in early high-tone hearing loss at frequencies above 4Hz frequently undetected by standard hearing tests. Interleukin-1 (IL-1) inhibition can reverse hearing loss in MWS patients at an early stage. The aims of this study were to determine hearing thresholds of MWS patients at all frequencies, propose a MWS-specific audiology composite score (MWS-PTA) and compare the MWS-PTA with the standard 4PTA testing in MWS patients at baseline and following IL-1 inhibition.

Methods: A single center cohort study between 4/2008 and 8/2008 determined hearing thresholds in decibel (dB) at 0.5, 1, 2, 4, 6, 8 and 10 kHz by age-specific pure-tone audiometry in consecutive patients with clinically active and genetically confirmed MWS before and during treatment with the IL-1 receptor antagonist Anakinra and the fully human anti-IL-1β monoclonal antibody Canakinumab. The MWS-PTA was constructed including 0.5, 1, 2, 4, 6 and 8 kHz in all patients. The established parameter 4PTA was compared to the new parameter MWS-PTA regarding ability to discriminate hearing threshold differences before and with IL-1 inhibition.Change in summary score between baseline and follow-up was determined for mean right and left ear audiometry measures. Descriptive statistics and comparisons were performed using parametric and non-parametric methods when appropriate. The Shapiro-Wilk test for normality was used when testing observed distributions.

Results: A total of 23 MWS patients were included. These were 15 females and 8 males, median age at diagnosis 18.0 years (range 3–72). Mean audiometry scores at baseline were: PTA 40.7 ±27.8; MWS-PTA 49.2 ±30.7 and at follow-up: PTA 38.0 ±26.8; MWS-PTA 46.3 ±30.4. The difference in scores between timepoints were found to be significantly different from 0: PTA −2.7 ±6.1 p=0.01; MWS-PTA −2.9 ±5.0 p=0.01. Scores were found to be normally distributed at baseline and follow-up (Shapiro-Wilk all p>0.05). No statistically significant difference was observed for the change in scores between the two IL-1 blockers used in this study.

This was in accordance to the significant improvement of the clinical MWS-DAS (p=0,0005) and the inflammatory markers CRP, ESR and SAA.

Typical audiometry changes in MWS-patients appear as hearing loss in high frequencies which is in contrast to patients with hearing loss from other causes who usually have reduced hearing in frequencies relevant for speech discrimination, which detected by the 4PTA. The challenge is to establish a tool to detect early changes in MWS patients.

Conclusion: The MWS-PTA is a simple modification of the standard audiology assessment. It allows for early detection of hearing loss in patients with MWS. Early recognition and treatment of sensory neural hearing loss in MWS patient may enable physicians to prevent the debilitating long-term deficit in patients with Muckle-Wells syndrome.

ACR/ARHP Poster Session C
Osteoarthritis - Clinical Aspects II
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

1977

Association Between Sports Participation and the Risk of Knee Osteoarthritis: A Systematic Review. Jeffrey B. Driban[1], Jennifer M. Hootman[2], Michael R. Sitler[3], Kyle P. Harris[4] and Nicole M. Cattano[5]. [1]Tufts Medical Center, Boston, MA, [2]Centers for Disease Control and Prevention, Kennesaw, GA, [3]Temple University, Philadelphia, PA, [4]Bucks County Community College, Newtown, PA, [5]West Chester University, West Chester, PA

Background/Purpose: Information regarding the relative risks of developing knee osteoarthritis (KOA) as a result of sports participation is critical for shaping public health communication messages and for informing KOA prevention strategies. The purpose of this systematic review was to investigate the association between specific sports participation and the risk of KOA. A secondary purpose was to attempt to separate out the effects of joint injury versus sport participation on the risk of KOA.

Methods: A systematic literature search was completed in March 2011 using 6 bibliographic databases (e.g., PubMed, OVID), by manual searches (4 journals), and reference lists (56 articles). Studies were included if they met 4 criteria: 1) a study aim was to investigate an association between sport participation and KOA; 2) the outcome measure was radiographic KOA, clinical KOA, total knee replacement (TKR), or placement on a waiting list for a TKR; 3) cohort study design; and 4) written in English. Study quality was assessed with the New-Castle Ottawa Scale (range 0–9; low < 4, high >4). One investigator extracted data (e.g., group descriptions, KOA prevalence, source of unexposed [NE] controls). Level of play was categorized as elite (national team/Olympic/professional) and non-elite (scholastic/recreational). Significant relative risks (RR) were defined as 95% confidence intervals (CI) that excluded 1.00. Sensitivity analyses were used to assess the influence of injury status among studies that excluded patients with a history of knee injury or stratified by history of joint injury and by source of NE controls.

Results: The overall prevalence of KOA in sports participants (n = 3192) was 8.4%; 9.1% among NE (referent group; n = 3485; RR [CI] = 0.9 [0.8 to 1.1]). NOS scores ranged from 3 to 6. Risk of KOA was similar for low and high quality studies. Specific sports with significantly higher risk of KOA were soccer (RR 4.4); as well as elite-level long-distance running (RR 3.2), competitive weight lifting (RR 6.4), and wrestling (RR 3.7). Sport participants were at an elevated risk of KOA compared to NE participants from local communities, hospital/medical practices, and sports (shooters), but at decreased risk compared to NE participants selected from national military service. Elite-sport participants (soccer or orienteering) without a history of knee injury were at greater risk for KOA than NE participants (studies excluding injuries: RR = 1.8; studies stratifying by history of injury: RR =

8.6). Nonelite-sport participants (soccer or American football) with no history of knee injury were at greater risk for KOA than NE participants (RR 3.6).

Conclusion: The risk of KOA is sport specific. Participants in soccer (elite and nonelite); as well as elite long distance running, weight lifting, and wrestling have increased risk of KOA and should be targeted for risk reduction strategies. Soccer, even in the absence of an injury is associated with increased risk of KOA; especially among elite participants. There are considerable gaps in the literature, including a lack of data on female sport participants, history of injury, and nonelite sport exposure.

1978

Physical Activity Levels and the Risk of Incident Radiographic Knee Osteoarthritis: The Johnston County Osteoarthritis Project. Kamil E. Barbour[1], Jennifer M. Hootman[1], Charles G. Helmick[2], Louise Murphy[1], Yiling Cheng[2], Kristina A. Theis[1], Barbara Do[2] and Joanne M. Jordan[3]. [1]CDC, Atlanta, GA, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]UNC Thurston ARC, Chapel Hill, NC

Background/Purpose: Physical activity has been shown to reduce risk of cardiovascular disease, diabetes and hypertension; however the impact of physical activity on incident radiographic knee osteoarthritis (rKOA) remains unclear.

Methods: Using data from visits 2 (1999–2003) and 3 (2005–2010) Johnston County Osteoarthritis Project; we tested the association of physical activity with incident rKOA (mean follow-up 6.5 ± 1.9 years) among adults (n=641 without rKOA at visit 2) aged 45 years and older. Incident rKOA was defined as the development of a Kellgren-Lawrence (K-L) grade of ≥2 in either knee. Minutes per week of moderate-to-vigorous intensity physical activity (MVPA) were calculated at visit 2 using the Minnesota Leisure Time Physical Activity questionnaire. MVPA was categorized as meeting 2008 U.S. physical activity recommendations (>150 min/week) or not (<150 min/week). Weibull parametric regression estimated hazard ratios (HR) for interval censored data. Sampling weights at visit 3 and the Jackknife resampling method were used to account for the complex sampling design.

Results: Participants who reported ≥150 min/week MVPA had a non-significant 48% higher risk of incident rKOA (HR: 1.48; 95% CI: 0.99–2.22) compared with those with <150 min/week of MVPA after adjusting for age, race, sex, body mass index, education, diabetes status, and history of knee injury.

Conclusion: Results suggest that physical activity was modestly, but not significantly associated with incident rKOA. Further investigation is required to better understand the contribution of health-enhancing levels of MVPA with rKOA.

1979

Recent Heavy Physical Activities Trigger Knee Pain Exacerbation in Persons with Symptomatic Knee Osteoarthritis. Yuqing Zhang[1], Diane Wheaton[2], Jingbo Niu[1], Barton Wise[3], William Havey[4], Joyce Goggins[1] and David J. Hunter[5]. [1]Boston University School of Medicine, Boston, MA, [2]New England Baptist Hospital, Boston, MA, Boston, MA, [3]University of California, Davis School of Medicine, Sacramento, CA, [4]New England Baptist Hospital, Boston, MA, [5]Royal North Shore Hospital, Sydney, Australia

Background/Purpose: Subjects with symptomatic knee osteoarthritis (SxKOA) often experience recurrent pain exacerbation, with episodes lasting for days or weeks. Identifying the triggers for pain exacerbation and quantifying their effects are challenging because traditional study designs are ill-suited to answer this type of research question. We conducted an online case-crossover study to examine the relation of physical activity to pain exacerbation among subjects with SxKOA.

Methods: Subjects with a diagnosis of SxKOA (i.e., K/L> 2 and knee pain on most days on the past month) were recruited from the database of persons with SxKOA and followed for 3 months at 10 day intervals (control periods). Subjects were instructed to log on to the study website if they experienced a knee pain exacerbation during the follow-up period (hazard periods). Via the internet we collected data on triggers occurring during "***control periods*** " (i.e., periods without pain exacerbation) and "***hazard period"*** (i.e., period immediately preceding the pain exacerbation). *Pain exacerbation was defined as an increase of* ***100 units*** in a subject's WOMAC knee pain score (VAS 0–500) over the follow-up from his/her mildest pain score reported at the baseline visit. We collected data on potential triggers, including participation of various levels of physical activities (i.e., moderate, heavy and extremely heavy), on 1 day prior, 2 days prior, and 3–7 days prior to the index dates (i.e., date of pain exacerbation for hazard period, and date of data assessment for control periods). We examined the relation of heavy physical activities to the risk of pain exacerbation using the conditional logistic regression model.

Results: Of 52 subjects (women: 57.6%, mean age: 63 years, mean BMI: 29.3 kg/m^2) recruited in the study, 33 subjects (33 index knees) experienced at least one episode of knee pain exacerbation. Compared with no heavy/extremely physical activity, odds ratios of knee pain exacerbation was 2.7 10.8, and 0.03 for participation in heavy/extremely heavy physical activities on 1 day prior, 2 days prior, and 3–7 days prior to index date, respectively (Table).

Participation of Heavy/extremely Heavy Physical Activities prior to Index Date	Control periods	Case Periods	0.03 (0.01–0.14)
1 day			
No	122	51	1.0
Yes	48	31	2.7 (0.9–8.2)
2 days			
No	119	50	1.0
Yes	51	32	10.8 (1.9–61.4)
3–7 days			
No	105	65	1.0
Yes	65	17	0.03 (0.01–0.14)

Conclusion: Heavy physical activity occurred within 2 days was associated with an increased risk of knee pain exacerbation among patients with SxKOA. This finding suggests that individuals with SxKOA should avoid participation of heavy physical activity.

1980

Sedentary Behavior and Functional Performance Among Participants in the Osteoarthritis Initiative (OAI). Jungwha Lee[1], Rowland W. Chang[1], Larry Manheim[2], Pamela A. Semanik[3], Jing Song[2] and Dorothy D. Dunlop[2]. [1]Northwestern University, Chicago, IL, [2]Northwestern Univ Med School, Chicago, IL, [3]Rehabilitation Institute Chicago, Oak Park, IL

Background/Purpose: Physical activity offers important health benefits to adults, including those with lower limb osteoarthritis (OA). This study examined whether there is a graded relationship between objectively measured physical activity and functional performance among people with or at risk of knee OA.

Methods: Functional performance was assessed by gait speed measured in feet/speed based on the average speed over two 20-meter walk tests. Physical activity was objectively measured using accelerometers at the 48-month clinic visit in 1876 OAI participants (1076 with radiographic knee osteoarthritis (RKOA) in at least one knee and 800 participants without RKOA in both knees and at risk of RKOA at baseline). Accelerometer output is an activity count monitored for 7 consecutive days. Accelerometer data included at least 4 or more valid days for each participant. A valid day was defined as 10 or more wear hours in a day. Sedentary behavior, defined by activity counts/minute< 100, was used to calculate the percentage of daily wear hours spent in sedentary behavior. The association between gait speed and sedentary behavior percentage quartiles was examined by multiple regression models adjusting for socio-demographic factors (age, gender, income, education) and health factors (comorbidity, depressive symptoms, overweight/obesity, presence and severity of knee pain).

Results: Mean of average daily sedentary behavior percentage for participants was 40% (SD=5.5%). Functional performance measured by gait speed had mean ± SD of 4.36 ± 0.68 feet/second. Mean functional performance increased going from the highest sedentary quartile to the lowest (unadjusted mean gait speed 4.1, 4.2, 4.4, and 4.5 feet/second, respectively, P for trend <0.001). These trends remained significant in multivariate analyses after adjusting for socio-demographic factors and health factors (Table), and among subgroups with and without RKOA at baseline.

Adjusted Gait speed (feet/second)* by sedentary behavior quartiles** of adults with and without baseline radiographic knee OA after adjustment for age, gender, education, income***

	Sample Size (n)	Quartile 1**** (most sedentary)	Quartile 2	Quartile 3	Quartile 4 (least sedentary)	P for trend
Overall	1876	4.11 ± 0.03	4.38 ± 0.03	4.42 ± 0.03	4.47 ± 0.03	<.0001
Participants with Baseline RKOA	1076	4.04 ± 0.04	4.34 ± 0.04	4.37 ± 0.04	4.38 ± 0.04	<.0001
Participants without Baseline RKOA	800	4.22 ± 0.05	4.42 ± 0.05	4.56 ± 0.05	4.57 ± 0.04	<.0001

* Values are the mean ± SEM in average gait speed for sedentary behavior quartiles.
** Sedentary behavior quartiles are based on percentage of average sedentary minutes/day over wear hour (sedentary minutes: minutes of counts <100).
*** 4+ valid days of accelerometer monitoring; reference group are men aged 49–64 with 13+ education years and >$50k income.
**** Quartile 1 is the group with most sedentary behavior.

Conclusion: Despite the known benefits of physical activity to decrease disability, adults with or at risk for knee OA are largely sedentary. The OAI data indicate a strong relationship between greater levels of sedentary behavior and worse functional performance in adults with knee OA. These findings support guidelines that encourage adults with knee OA to decrease sedentary behavior regardless of current sedentary status.

1981

Differences in Patient Acceptable Symptomatic State (PASS) Thresholds and Minimal Clinically Important Improvement (MCII) for Pain At Rest and on Movement in Patients with Lower Limb Osteoarthritis. Serge Perrot[1], Philippe Bertin[2] and Philippe Ravaud[3]. [1]Hopital Hotel Dieu, Paris, France, [2]Chu Dupuytren, Limoges, France, [3]Hopital Hotel Dieu, Paris Descartes University, Paris, France

Background/Purpose: Two concepts have been developed to make patient assessment more clinically relevant: the patient acceptable symptomatic state (PASS)1, and the minimal clinically important improvement (MCII). Osteoarthritis (OA) is a painful disease in which pain intensity varies with activity. We compared PASS and MCII for pain at rest and on movement, in patients with painful lower limb OA.

Methods: A national multicentrer cohort study, in outpatients over the age of 50 years with painful knee or hip OA (pain VAS >3/10), visiting a GP and requiring treatment for more than seven days. During the visit, demographic characteristics were noted and PASS and pain were assessed at rest and on movement. This was a naturalistic study, with no specific recommendations made to the physicians, who were free to prescribe any type of analgesic or other drug. Seven days after the initial visit, patients were asked to complete a self-reported questionnaire, for the assessment of changes in pain and MCII.

Results: In total, 2414 patients (50.2% men, 67.3 ± 8.8 years old, BMI 27.9 ± 4.3, 33.5% with hip OA) were enrolled by 1116 GPs. Pain intensities were: 5.1 ± 1.9 at rest and 7.0 ± 1.4 on movement. The frequency of acceptability did not differ between knee (70.1%) and hip (68.3%) OA and was not affected by OA duration. PASS was estimated at 4 at rest and 5 on movement, with no difference between the hip and knee. After seven days of treatment, the perceived improvement in hip and knee OA was significantly correlated with initial acceptability ($p<0.001$). MCII was estimated at 1, both at rest and on movement, with no significant difference between hip and knee OA.

In knee OA, acceptability was more frequent in men under the age of 75 years, without synovial effusion, with pain (VAS< 6/10) on movement, in several professional categories (farmers vs others), and in patients specifically seeking an improvement in sporting activities.

In hip OA, pain acceptability was influenced only by pain at rest and on movement (more acceptable when below 6/10), and by BMI (more acceptable in non obese patients).

Conclusion: PASS thresholds are similar for hip and knee OA, but different at rest and in movement. MCII is similar in hip and knee OA, and at rest and in movement. In all situations, pain improvement is significantly associated with initial acceptability, whatever the treatment prescribed. The factors determining pain acceptability differ between hip and knee OA, demonstrating that these two conditions are distinct clinical entities. In both conditions, the determining factors should be assessed precisely, for the identification of additional factors and to improve personalized patient management.

1982

Relationship Between Aspects of the Pain Experience in Knee Osteoarthritis and Function and Disability. September Cahue, Joan Chmiel, Karen W. Hayes, Orit Almagor, Kirsten Moisio, Carmelita J. Colbert, Clifton Saurel, Yunhui Zhang and Leena Sharma. Northwestern University, Chicago, IL

Background/Purpose: It is widely accepted that knee pain influences physical functioning in knee osteoarthritis (OA), but how specific aspects of the pain experience relate to function impairment and disability is unclear. Our goal was to analyze separate aspects of the pain experience to determine which is most closely associated with measures of function and disability in persons with knee OA.

Methods: All participants had knee OA (osteophyte presence in at least one knee). Four aspects of the pain experience were evaluated: pain intensity (0–10 numeric rating scale); how much pain affected sleep (ICOAP item); pain after 20 m walk (0–10 rating scale); pain catastrophizing (Pain Catastrophizing Scale). Function was evaluated by: WOMAC function scale; Late Life Function Instrument (LL-FI), basic and advanced lower extremity function scales; 20 m walk time; time to complete 5 chair stands. Disability was evaluated by: Late Life Disability Instrument (LL-DI), activity frequency and activity limitation scales. Lower LL-FI and LL-DI scores are worse; higher WOMAC function, 20 m walk time, and chair stand time are worse. We used linear regression with function or disability as dependent variable, including each pain measure and age, gender, and BMI in each model, after screening for problematic multicollinearity. We calculated standardized regression coefficients [i.e., estimate of the expected change in standard deviation (SD) units in average value of dependent variable per SD change in predictor, after considering all other variables in the model] to compare the strength of association of different predictors with the outcome variable within the same model.

Results: The sample was 250 persons (mean age 64.8 yrs, BMI 28.6, 76% women). The table shows standardized coefficients for each model (bold and italicized when significant). Row variables and gender were included in each model. Pain intensity was associated with WOMAC function but no other measure, pain affecting sleep with almost all function measures but no disability measure, and pain after 20 m walk with self-report function measures. Pain catastrophizing was the only aspect to be associated with disability measures.

Standardized Coefficients from Multipredictor Regression Models

	WOMAC function	LL-FI, basic LE function	LL-FI, advanced LE function	20 m walk time	Chair stand time	LL-DI, activity frequency	LL-DI, activity limitation
Pain intensity	***0.10***	−0.05	−0.05	0.11	0.06	−0.05	−0.05
Pain affecting sleep	***0.36***	***−0.19***	***−0.14***	0.12	***0.18***	−0.05	−0.12
Pain after 20 m walk	***0.26***	***−0.20***	***−0.29***	0.11	−0.06	−0.06	−0.13
Pain catastrophizing	***0.25***	***−0.29***	***−0.18***	0.11	***0.22***	***−0.23***	***−0.30***
Age	0.04	***−0.17***	***−0.32***	***0.35***	***0.17***	0.05	0.11
BMI	***0.19***	***−0.21***	***−0.30***	***0.36***	0.03	−0.04	−0.08

Conclusion: When the four aspects of the pain experience were considered concurrently, pain catastrophizing was most consistently associated with measures of function and disability. Most closely associated with function measures were: pain affecting sleep, for WOMAC function; pain catastrophizing, for LL-basic function, chair stand time, and disability; and pain after 20 m walk, for LL-advanced function. These findings suggest that different aspects of the pain experience in knee OA may have unique relationships with function and disability. Ultimately, specific multidisciplinary attention to these aspects of pain may yield a more meaningful approach for the person with painful knee OA, and potentially have greater impact on function and disability over time.

1983

Relationship of Specific Pain Patterns in Knee Osteoarthritis with Severity of Pain and Functional Disability. Nehal Shah[1], Michael J. Hannon[2], WANG Zhijie[3] and C. Kent Kwoh[4]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Pittsburgh school of medicine, Pittsburgh, PA, [4]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, PA

Background/Purpose: Osteoarthritis is one of the most common causes of disability. Knee pain is the main reason for patients to seek care for knee osteoarthritis (OA), but the cause for knee pain is unclear. This study examines differences in pain and disability among specific knee pain patterns in knee OA.

Methods: This is an ancillary analysis of data from 4796 participants in the Osteoarthritis Initiative (OAI), a population-based cohort study designed to identify biomarkers of the development and/or progression of knee OA. Pain patterns in knee OA were characterized into localized, regional or diffuse using the Knee Pain Map, an interviewer-administered assessment of knee pain patterns based on pain in the past 30 days. Data on severity of pain and disability was obtained using Western Ontario and McMaster Universities (WOMAC) knee pain scale, including the scale scores(scaled from zero to 100, with 100 representing the most knee pain), and individual WOMAC items, from the OAI dataset at the 24 -month visit (Release 3.2.1). Data was analyzed using pain patterns as the dependent variable in multinomial logistic regression models, controlled for demographic characteristics, risk factors for knee OA and for clustering by knee.

Results: Of the 9383 knees studied, 19% had localized pain, 14.3% had regional pain, 8.8% had diffuse pain, and 58% had no pain. Controlling for demographic factors and participant characteristics, WOMAC knee pain, disability, and total scores were significantly different among knees with no

pain vs local, local vs. diffuse and regional vs. diffuse pain patterns ($p<.001$). For local vs. regional pain, only WOMAC disability ($p=0.013$) and the total WOMAC scores ($p=0.02$) were different. In multivariate analysis, the WOMAC knee pain score was different among those with no pain vs. those with only local pain ($p<.001$); and regional pain vs. diffuse pain ($p=0.02$). The WOMAC disability score was different among those with no pain vs. those with only local pain ($p<.001$); and those with local vs. diffuse pain ($p=0.03$). Individual items in the WOMAC differed among the various pain patterns in bivariate analysis, but none of the individual items remained significant in the multivariate analyses.

Conclusion: WOMAC pain and disability scores varied among the different knee pain patterns. Higher scores were associated with the diffuse pain pattern followed by regional and then the localized pain patterns, suggesting a gradient of disease severity across the pain patterns

1984

Relation of Knee Cartilage Loss to Pain and Functional Limitation: The Multicenter Osteoarthritis Study. Barton Wise[1], Jingbo Niu[2], Nancy E. Lane[3], Michael C. Nevitt[4], Daniel K. White[2], James Torner[5], Cora E. Lewis[6] and Yuqing Zhang[2]. [1]University of California, Davis School of Medicine, Sacramento, CA, [2]Boston University School of Medicine, Boston, MA, [3]UC Davis School of Medicine, Sacramento, CA, [4]University of California-San Francisco, San Francisco, CA, [5]University of Iowa, Iowa City, Iowa City, IA, [6]University of Alabama, Birmingham City, Birmingham, AL

Background/Purpose: Worsening radiographic knee osteoarthritis (OA) is associated with increased risk of incident severe functional limitation. While MRI is a more sensitive measure of changes in specific structures of the knee than radiographs, it is unclear if such improved sensitivity is significant when evaluating its association with worsening of pain and function.

Methods: The NIH-funded Multicenter Osteoarthritis Study (MOST) is an observational study of persons age 50 to 79 years with either symptomatic knee OA or at high risk of disease. Participants were evaluated at baseline and 60 months. A subset of MRIs acquired at baseline and 60 months from participants with unilateral whole knee OA at baseline or at 30 months but without endstage knee OA at either of those timepoints were assessed using the semi-quantitative Whole-Organ Magnetic Resonance Imaging Score (WORMS). Cartilage scores (range 0–6) were obtained for 14 subregions of the index knee for each subject. Cartilage loss at each subregion was defined as cartilage morphology score increase of $\geq$2 over 60 months. For each knee we summarized the number of subregions with cartilage loss. Knee pain worsening was defined as Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score (range 0–20) increased by $\geq$18% and an absolute increase of $\geq$2 over 60 months. Functional limitation worsening was defined as either an increase of WOMAC physical function (range 0–68) by $\geq$26% and an absolute increase $\geq$6.1, or objectively by a decrease in walking speed by $\geq$0.1 meter/second over 60 months. We used multiple logistic regression to examine the association between cartilage loss and worsening of pain and function adjusting for age, sex, BMI, race, clinic site, CES-D score, number of co-morbidities, K/L grade, and for function analyses WOMAC pain in contralateral knee.

Results: Of 210 subjects included in the analysis 60.5% were women, 26.7% had frequent knee pain (FKP) in the index knee, and 11.9% had FKP in the contralateral knee at baseline. Over a 60 month follow-up period, 109 (52.9%) knees had cartilage loss in at least one subregion, 28.1% had worsening WOMAC knee pain, 21.4% had self-reported worsening functional limitation, and 20.5% had functional limitation worsening by walking speed. As shown in the table, compared with those with no cartilage loss, increased number of subregions with cartilage loss was associated with higher odds of pain worsening (P for trend $<$ 0.01) and worsened functional limitation measured by WOMAC (P for trend = 0.04). However, no such relation was observed for worsening of walking speed.

# of subregions with cartilage worsening ≥2	WOMAC Pain Worsening		WOMAC Function Worsening		Walking Speed Worsening	
	Adj OR	95% CI	Adj OR	95% CI	Adj OR	95% CI
0	1.0		1.0		1.0	
1	1.64	0.70–3.65	1.06	0.41–2.75	0.65	0.24–1.81
2	2.28	0.89–5.87	1.09	0.37–3.17	1.62	0.59–4.45
3	2.76	1.01–7.59	1.50	0.49–4.59	1.36	0.42–4.43
4+	6.85	2.00–23.46	4.24	1.21–14.83	1.26	0.33–4.82
P for trend	< 0.01	0.04	0.45			

Conclusion: In this sample of subjects with unilateral radiographic OA, cartilage loss on MRI over 60 months is associated with worsening of pain and subjective physical function.

1985

Muscle Parameters and Function Self-Efficacy in Knee Osteoarthritis. Carmelita J. Colbert, Karen W. Hayes, Orit Almagor, Joan S. Chmiel, Alison H. Chang, Kirsten Moisio, September Cahue, Yunhui Zhang, Clifton Saurel and Leena Sharma. Northwestern University, Chicago, IL

Background/Purpose: Self-efficacy has been associated with physical function outcome in persons with knee osteoarthritis (OA). Efforts to understand factors contributing to self-efficacy may identify targets to improve self-efficacy. Little is known about how hip and knee motor activity relate to self-efficacy in knee OA. Quantitative gait analysis provides insight into dynamic muscle unit function during gait. We hypothesized that knee extensor, hip abductor, and hip external rotator strength and the knee extensor and hip abductor moments during gait are each associated with function self-efficacy.

Methods: 250 persons with knee OA were evaluated. Isokinetic knee extensor and isometric hip abductor and external rotator average peak torques were determined using a Biodex dynamometer. Quantitative gait analysis at self-selected walking speed was performed using external passive reflective markers and an 8-camera motion analysis system to calculate knee and hip joint moments (internal moments normalized to %BW*Ht). Self-efficacy was assessed using the Arthritis Self-Efficacy Scale function subscale. Data were also collected using: questionnaire adaptation of the Charlson index, Geriatric Depression Scale, WOMAC pain scale, Pain Catastrophizing Scale, and Physical Activity Scale for the Elderly. Multiple linear regression analysis was used to evaluate the association of self-efficacy (dependent variable) with each muscle factor. We used the worse (of the two limbs) value for the factor to derive the unadjusted regression coefficients and associated 95% CI, and the coefficient (95% CI) adjusting for age, gender, BMI, comorbidity, depressive symptoms, knee pain severity, pain catastrophizing, and physical activity.

Results: 250 participants had a mean age of 64.8 (SD 10.2), BMI 28.6 (5.6), and 189 (76%) were women. Mean self-efficacy score was 25.2 (5.4), hip abductor strength 57.5 Nm (17.7), hip external rotator strength 27.0 Nm (11.0), knee extensor strength 63.3 Nm (24.6), hip abductor moment during gait 4.1 (0.8), knee extensor moment during gait 1.25 (0.4). The table shows the coefficients (95% CI), with significant results bolded. In an additional model including knee extensor strength, hip abductor moment, and hip external rotator strength and the covariates noted above, knee extensor strength, hip abductor moment during gait, BMI, knee pain severity, and depressive symptoms were each significantly associated with self-efficacy (R^2 of this model 0.48).

Factors Associated with Function Self–Efficacy

	Unadjusted Coefficient (95% CI)	Adjusted Coefficient (95% CI)
Knee extensor strength (per 10 Nm)	**0.73 (0.47, 0.99)**	**0.80 (0.50, 1.09)**
Knee extensor moment during gait (per 1%BWxHT)	**2.73 (1.25, 4.21)**	**1.39 (0.03, 2.74)**
Hip abductor strength (per 10 Nm)	**0.69 (0.32, 1.06)**	0.25 (−0.16, 0.65)
Hip abductor moment during gait (per 1%BWxHT)	**0.86 (0.01, 1.70)**	**1.14 (0.41, 1.87)**
Hip external rotator strength (per 10 Nm)	**1.12 (0.52, 1.72)**	**1.25 (0.55, 1.95)**

Conclusion: Knee extensor strength and hip abductor moment during gait (as well as BMI, knee pain severity, and depressive symptoms) were independently associated with function self-efficacy in analyses adjusting for potential confounders. Longitudinal analyses will help to elucidate the direction of these relationships towards the goal of enhancing intervention to improve function self-efficacy in knee OA and lessen its deleterious consequences.

1986

Functional Impairment As a Predictor of Knee Replacement in the Multicenter Osteoarthritis Study. Barton Wise[1], Jingbo Niu[2], Nancy E. Lane[3], Michael C. Nevitt[4], David T. Felson[2], Jean Hietpas[5], Alesia Sadosky[6], James Torner[7], Cora E. Lewis[8] and Yuqing Zhang[2]. [1]University of California, Davis School of Medicine, Sacramento, CA, [2]Boston University School of Medicine, Boston, MA, [3]UC Davis School of Medicine, Sacramento, CA, [4]University of California-San Francisco, San Francisco, CA, [5]UCSF, San Francisco, CA, [6]Pfizer, Inc., New York, NY, [7]University of Iowa, Iowa City, Iowa City, IA, [8]University of Alabama, Birmingham City, Birmingham, AL

Background/Purpose: Functional impairment may influence an individual to receive a knee replacement (KR), but few studies have explored this assumption. We conducted a cohort study to evaluate the association between functional impairment and risk of KR over 30 months.

Methods: The NIH-funded Multicenter Osteoarthritis Study (MOST)

is an observational study of persons age 50 to 79 years with either symptomatic knee OA or at high risk of disease. We performed a repeated measures analysis using baseline Western Ontario McMaster (WOMAC) physical function score to predict the risk of KR from baseline to 30 months, and WOMAC score at 30 months to predict risk of incident KR from 30 months to 60 months. We examined the association between function and risk of KR using generalized estimating equations to account for the correlation between two knees within one subject and across the two periods of the repeated analysis. We calculated relative risk of KR over 30 months for groupings of WOMAC function using 0–5 group as referent. In the multiple binomial regression with log link we adjusted for clinic site, age, BMI, sex, race, education, depressive symptoms as measured by CES-D, comorbidity, ipsilateral K/L grade. We performed analyses with and without adjustment for ipsilateral visual analog scale (VAS) knee pain to assess whether an association between physical function or functional impairment and KR is independent from pain.

Results: Our sample consisted of 2,890 subjects with 5,780 native knees; 1,738 (60%) were women. 1,631 (57%) of subjects had a baseline WOMAC function score ≥10 (range 0–68).Over 60 months there were 445 incident KRs in 10506 knee-periods (4.3%). 311 (69.8%) were in women and 192 (43%) occurred in the first 30 month period. As shown in the Table, those with the highest function scores (greatest functional impairment; 40–68) had 18 times the risk of total knee replacement over 30 months compared with those with baseline function scores of 0–5 after adjustment for covariates other than pain (95% CI 8.4–38.3). Further adjustment for ipsilateral knee pain attenuated but did not eliminate the effect of function score on the risk of KR among those with the highest function scores (RR 7.2, 95% CI 3.3–15.9; P for linear trend <.0001).

WOMAC Function (0–68)	Knee-Periods (#)	TKR (#)	Adj RR (95% CI) (Basic Covariates)			Adj RR (95% CI)(Basic Covariates plus ipsilateral VAS pain score)		
			RR	95% CI		RR	95% CI	
0–5	3581	11	**1.0**			**1.0**		
6–9	1164	20	**3.9**	1.7	9.1	**3.5**	1.5	8.1
10–19	2405	97	**6.3**	3.0	13.0	**5.0**	2.4	10.3
20–29	1841	137	**9.4**	4.6	19.3	**6.1**	2.9	12.5
30–39	1056	117	**12.8**	6.2	26.5	**6.7**	3.2	14.2
40–68	459	63	**18.0**	8.4	38.3	**7.2**	3.3	15.9
P for linear trend				<0.001			<0.001	

Conclusion: Baseline physical function strongly predicts KR over a 30 month period. This relation is independent of concurrent knee pain severity.

1987

Clinical Characteristics and Medication Use of Patients with Knee Osteoarthritis Selected for Total Joint Replacement Surgery. T.N. de Boer[1], M.J.P.M. Stukstette[2], P.M.J. Welsing[1], A.M. Huisman[3], A.A. Polak[3], J.W.J. Bijlsma[1], Simon C. Mastbergen[1] and F.P.J.G. Lafeber[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Sint Maartenskliniek, Nijmegen, Netherlands, [3]Sint Franciscus Gasthuis, Rotterdam, Netherlands

Background/Purpose: Costs related to total knee replacement (TKR) surgery, are tremendous and will increase further due to increasing prevalence of obesity and aging in developed countries. TKR is clearly effective in reducing pain and improving function in progressive knee osteoarthritis (OA). The outcome of revision surgery is less and even more costly. Postponing a first prosthesis and maintaining quality of life is at present the major goal in treatment of end-stage OA. Specific indications for TKR surgery are not clearly defined or evidence based. Generally accepted indications are pain and limitations in function in spite of the use of (non-)pharmacological interventions. However, substantial variations in referral behaviour between health professionals exist. Experts in the field believe that in many patients with severe OA conservative treatment options are not optimally prescribed. It seems plausible that TKR surgery can be postponed or even prevented. The aim of this explorative study is to obtain insight in characteristics and previous pharmacological management of end-stage knee OA patients submitted to TKR surgery, and to explore if patients without adequate pain medication still benefit from pain medication.

Methods: 172 successive patients referred for TKR were evaluated. Patients not using adequate analgesics, defined by no or occasional paracetamol (PCM), were randomized to an adequate dose of a NSAID (celecoxib; 2dd200mg daily or naproxen; 3dd250mg) or no medication for 6 weeks prior to surgery. Patient characteristics, severity of symptoms (WOMAC pain, stiffness and physical function), medication use in past year and radiological features (K&L and Altman) were collected. To calculate the percentage responders, modified OMERACT/OARSI responder criteria were used. A responder was defined by an improvement of ≥50% in function or pain, or an improvement of ≥20% in pain and function. The study was conducted according to the declaration of Helsinki and received ethics approval of the hospital.

Results: The year prior to TKR referral 26% (n= 44) of patients used daily NSAIDs, 27% (n=47) used daily PCM, or occasional NSAID, and nearly half (47%; n=81) used an occasional PCM or no medication at all. No differences in baseline characteristics or radiographic features were found between these three groups. Of the 81 patients not using adequate analgesics, 46 patients were randomized to NSAID treatment and 35 were randomized to no treatment. Patients without prior adequate pain medication treated for 6 weeks with an NSAID improved on average statistically significant in pain and stiffness (−5.7 [−10.9; −0.5] and −9.6 [−16.4; −2.8], resp. both $p<0.05$). 27% of patients could be classified as an actual responder.

Conclusion: In this explorative study most patients awaiting TKR experienced significant pain levels and limitations in activities, but surprisingly the majority did not use NSAIDs daily. Patients with inadequate medication, starting NSAID use daily, improved clinically significantly. Properly designed RCTs are warranted to study potential effects of adequate pain medication to delay the need for TKR surgery in case of severe OA, an area where rheumatologists can support orthopaedics.

1988

Psychological Predictors of Failure to Improve After Lower Extremity Joint Arthroplasty. Chad M. Brummett[1], Brian Hallstrom[1], Andrew Urquhart[1], Michelle Morris[1], Daniel J. Clauw[2] and David A. Williams[3]. [1]University of Michigan Health System, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]Univ of MI Hlth System-Lobby M, Ann Arbor, MI

Background/Purpose: The lifetime risk for symptomatic knee osteoarthritis has been estimated at 45%, and the number of lower extremity arthroplasties conducted each year is anticipated to rise exponentially. The rate of failure to improve following arthroplasty is estimated to be between 20–40% for knees and 10% for hips. We present preliminary results of an ongoing study investigating the phenotypic predictors of failure to improve after lower extremity joint arthroplasty.

Methods: Patients scheduled for total hip and knee arthroplasty (THA and TKA) were recruited in the immediate preoperative area. The anticipated recruitment for the study is 2000 lower extremity total joint arthroplasty patients over a 5-year period. Patients completed a preoperative phenotyping battery of validated self-report questionnaires, including the Brief Pain Inventory and Hospital Anxiety and Depression Scale. Patients were then contacted at 1- and 3-months after surgery by phone and at 6-months postoperatively by mail with the same measures, as appropriate. At each follow up, patients were asked to rate the success of their surgery using the Patient Global Impression of Change (PGIC). Data were analyzed using PASW Version 18. THA and TKA patients were grouped for analysis of predictors of outcome. For comparisons of outcomes at 6-months, patients were categorized using the PGIC as treatment "Success" (+2 or +3) or "Failure" ([-3] – [+1]) for comparisons of baseline characteristics. Between-group comparisons were made using the Mann-Whitney test. A Bonferroni correction for multiple comparisons was conducted ($\alpha = 0.0125$).

Results: To date, 337 arthroplasty patients have been recruited with a recruitment rate of 83%. Retention rates are 96%, 91%, and 77% at 1-, 3-, and 6-months respectively. At 6-months (n = 211), 16% of patients were classified as failed therapy using the PGIC (TKA = 24.3% vs THA = 9.3%, p = 0.011). There were no significant differences in baseline pain score between patients classified as failed versus success (median 4.75 [IQR 3, 6.75] vs 4.75 [3.25, 6.0], p = 0.555) Patients classified as failed therapy reported higher baseline scores for depression (median 6.5 [IQR 5, 8] vs. 4 [2, 6], p = 0.012) and anxiety (7 [5, 8] vs. 5 [3, 7], p = 0.091). Patients in the Success group showed a trend towards a more positive affect on the positive subscale of the HADS (3 [1, 5] vs. 4.5 [3, 7], p = 0.052).

Conclusion: Preliminary data indicate that higher levels of depression are associated with poor outcomes in lower extremity joint arthroplasty. Anxiety and low positive affect show trends towards poor outcome. Recruitment is ongoing, and future analyses of predictors of success and failure will be conducted.

1989

Is the Impact of Knee Osteoarthritis Diminishing Because of Knee Replacements? the Multi-Center Osteoarthritis Study. Jingbo Niu[1], Michael C. Nevitt[2], Charles E. McCulloch[3], James Torner[4], Cora E. Lewis[5] and David T. Felson[1]. [1]Boston University School of Medicine, Boston, MA, [2]University of California-San Francisco, San Francisco, CA, [3]Department of Epidemiology and, San Francisco, CA, [4]University of Iowa, Iowa City, Iowa City, IA, [5]University of Alabama, Birmingham City, Birmingham, AL

Background/Purpose: Rates of knee replacement (KR) have increased so much that they may have an effect on the overall impact of symptomatic knee osteoarthritis (SxOA). Specifically, as more persons with severe knee SxOA get KR and get it at an earlier disease stage, only a limited number of persons with severely disabling SxOA are left in the population. Thus, there might be a secular trend of improvement in functional score among persons with SxOA. We described the secular trend of function among subjects with SxOA in the Muliticenter Osteoarthritis (MOST) Study in which > 300 subjects had KR over 5 years.

Methods: The MOST Study is a cohort study of 3026 persons with or at high risk of knee OA drawn from the community. Subjects had knee radiographs, filled out WOMAC surveys, and reported knee surgery every 30 months. Self reported KR was confirmed on radiographs or medical records. At each visit, a subject was defined as having SxOA if ≥1 knee had frequent knee pain plus K/L grade ≥2 at that time or had any KR prior to the visit. The WOMAC function score at 0M, 30M and 60M *among subjects who currently had SxOA at the visit* were compared by ANCOVA, adjusting for age, sex, BMI, clinical site, CES-D, comorbidity, number of painful joints in lower limbs other than knees, and number of SxOA knees. Analyses were done among Whites and Blacks separately, with age limited to 55–79 at all visits. GEE was used to adjust correlation between repeated measures within subjects. We repeated analyses excluding subjects (a) with bilateral KR and (b) with any KR. To mimic the function in a hypothetical sample in which no new KRs were done during follow-up, we set the post-KR WOMAC function scores to missing and imputed them based on the covariates above as well as race, baseline function score and K/L grade *among subjects with SxOA at 0M*.

Results: Subjects with SxOA (673 at 0M, 656 at 30M, and 616 at 60M) had similar characteristics (mean age 66–67 years, mean BMI 33 kg/m^2, 65–70% women, 82% Whites). Among them, the proportion of any KR (bilateral KR) were 12(0)%, 26(4)%, 44 (17)% in Whites, 8(0)%, 20(5)%, 33(14)% in Blacks at 0M, 30M, and 60M, respectively. The mean WOMAC function score was highest (worst) at 0M, not different at 30M, and significantly lower (better) at 60M compared to 0M in both Whites and Blacks (change from 0M = −5.8 and −3.9 respectively). After excluding subjects with bilateral KR or any KR, the improvement between 0M and 60M disappeared among Blacks (−0.7 to −1.6, p=0.22 to 0.63), but remained among Whites (−3.2 to −3.8, p<.0001). Post-KR function score was imputed among 469 subjects. Their observed mean WOMAC function decreased during follow-up, 24.2, 22.1, and 19.1, which became 24.2, 24.0, and 24.2 after imputation, suggesting no change in function without KR.

Table 1. WOMAC function score among subjects with knee symptomatic osteoarthritis (higher score is worse function)

	Whites			Blacks		
	0M	30M	60M	0M	30M	60M
Subjects with SxOA						
N	555	541	520	118	115	96
Crude	24.4 (23.5, 25.4)	22.9 (21.9, 23.9)*	18.2 (17.2, 19.2)*	30.6 (28.6, 32.6)	29.2 (26.7, 31.7)	27.1 (24.3, 30.0)*
Adjusted**	26.0 (25.1, 26.9)	25.8 (24.7, 26.9)	20.2 (19.1 21.3)*	32.1 (29.9, 34.2)	31.1 (28.9, 33.2)	28.2 (25.8, 30.6)*
Subjects with SxOA, excluding those with bilateral KR						
N	555	518	433	118	109	83
Crude	24.4 (23.5, 25.4)	23.5 (22.5, 24.6)	20.0 (18.9, 21.1)*	30.6 (28.6, 32.6)	29.8 (27.2, 32.3)	29.5 (26.7, 32.3)
Adjusted**	26.5 (25.6, 27.4)	26.5 (25.4, 27.6)	22.7 (21.5, 23.8)*	31.8 (29.7, 33.9)	31.3 (29.1, 33.4)	30.2 (28.0, 32.4)
Subjects with SxOA, excluding those with any KR						
N	489	398	290	108	92	64
Crude	25.2 (24.2, 26.1)	25.3 (24.2, 26.4)	22.0 (20.7, 23.2)*	31.7 (29.7, 33.7)	31.6 (29.0,34.2)	31.6 (28.6, 34.5)
Adjusted**	26.8 (25.8, 27.7)	27.5 (26.3, 28.6)	23.6 (22.3, 24.8)*	31.8 (29.6, 34.0)	32.5 (30.3,34.7)	31.1 (28.7, 33.4)

* P-value <0.05 compared to baseline.
** Adjusting age, sex, BMI, clinical site, CES-D, comorbidity, number of painful joints in the lower limbs, number of knees with SxOA.

Conclusion: A trend for better WOMAC function over time among subjects with SxOA suggests that KR has decreased the overall impact of SxOA on function. This decreased impact was less in Blacks probably due to their lower rate of KR.

1990

Gait Biomechanics As Predictors of Hip Osteoarthritis Progression. Kharma C. Foucher[1], Bryan R. Schlink[2], Najia Shakoor[1] and Markus A. Wimmer[1]. [1]Rush University Medical Center, Chicago, IL, [2]University of Illinois at Chicago, Chicago, IL

Background/Purpose: While it is generally believed that osteoarthritis (OA) progression may be exacerbated by abnormal loading patterns during daily activities, the underlying processes have not been fully characterized for hip OA. While reduced hip range of motion and peak external moments during walking are associated with OA severity[1], it is not known how gait may relate to disease progression. This study was a preliminary investigation of the relationship of baseline gait characteristics and radiographic hip OA progression.

Methods: We evaluated 11 subjects with hip OA (60±7 y; 1.7±0.1 m; 87±18 kg; 7 male). Speed, stride length, cadence, %gait cycle spent in stance, dynamic range of motion, and 3D peak external moments were averaged from 3 trials collected at subjects' self-selected normal walking speeds. A single observer assessed OA severity using the modified Kellgren-Lawrence (KL) grade from baseline and 1–2 year f/u hip radiographs. Disease progression (P group) was defined as increased KL grade or THR during the study period. All other subjects were assigned to the 'stable' (S). To assess between-group differences we calculated effect sizes (ES) from the means and standard deviations of the WOMAC scores, demographic and gait variables. We focused on variables with medium (≥0.5) and large (≥0.8) effect sizes[2].

Results: 6 of 11 subjects showed OA progression (Table). Baseline KL grade and WOMAC scores were unrelated to progression. P group subjects walked with longer steps and spent less time in stance, and had higher peak flexion and external rotation moments, but lower peak adduction moments.

Table. Baseline characteristics (N or mean ± standard deviations) and group comparisons for subjects who did and did not show radiographic OA progression. Bold text indicates variables for which group differences had medium or large effect sizes.

	Progression group	Stable group	Group comparisons KL grade and Gender: Chi-square p value Other variables: Effect size with 95% confidence interval
KL Grade	KL 1: N=1 KL 2: N=2 KL 3: N=3 KL 4: N=0	KL 1: N=0 KL 2: N=1 KL 3: N=2 KL 4: N=2	0.387
# Men/# Women	3/3	4/1	0.383
WOMAC	550±303	561±561	−0.03 (−1.21, 0.58)
Age (years)	60±8	61±6	−0.14 (−1.32, 0.47)
Height (m)	1.71±0.13	1.75±0.11	−0.33 (−0.94, 0.28)
Mass (kg)	83.3±22	91.6±11	−0.46 (−1.08, 0.15)
Speed (m/s)	1.22±0.19	1.16±0.10	0.48 (−0.23, 0.99)
Stride length (m)	**1.33±0.14**	**1.26±0.14**	**0.50 (−0.11, 1.11)**
Cadence (steps/min)	110±10	111±12	−0.09 (−0.70, 0.52)
Percent time in stance	**58.7±1.4**	**59.6±1.1**	**−0.71 (−1.33, −0.08)**
Dynamic range of motion (degrees)	22.5±4.3	23±8.5	−0.08 (−0.68, 0.53)
Peak flexion moment (%Body weight × Height)	**5.9±1.4**	**4.8±1.4**	**0.79 (0.16, 1.41)**
Peak extension moment (%Body weight × Height)	2.25±0.79	2.12±0.91	0.15 (−0.45, 0.76)
Peak abduction moment (%Body weight × Height)	1.95±1.1	1.65±0.56	0.33 (−0.28, 0.94)
Peak adduction moment (%Body weight × Height)	**2.97±0.99**	**3.61±0.89**	**−0.68 (−1.3, −0.05)**
Peak external rotation moment (%Body weight × Height)	**0.443±0.13**	**0.227±0.17**	**1.15 (0.5, 1.81)**
Peak internal rotation moment (%Body weight × Height)	0.43±0.23	0.523±0.13	−0.48 (−1.10, 0.13)

Conclusion: Several variables distinguished subjects with OA progression. These subjects adopted a gait pattern in which they spent less time bearing weight on their diseased hip; however this adaptation was seen along

with increased peak flexion moments (a large impulsive load that may be detrimental to cartilage). The reduced external adduction moment seen in the P group suggests more substantial overall abductor dysfunction compared to those with stable disease, however the higher external rotation moment indicates a relative overactivity of the anterior portions. Larger longitudinal studies are needed to confirm these findings and elucidate the underlying mechanisms. However, this preliminary work suggests that gait analysis may be used to help predict disease progression, and may provide specific biomechanical targets for intervention, such as those currently being evaluated for knee OA.

[1]Shakoor et al., Osteoarthritis Cartilage 18(Supp 2): S67, 2010.
[2]Cohen, Psychological Bulletin, 112(1): 155–159, 1992.

1991

The Relationship of Toe-Out Walking to Clinical Characteristics of 1st Metatarsophalangeal Joint Osteoarthritis in Older Adults: The MOST Study. K. Douglas Gross[1], Howard J. Hillstrom[2], Jingbo Niu[3], Michael C. Nevitt[4], Cora E. Lewis[5], James Torner[6] and David T. Felson[3]. [1]MGH Institute of Health Professions, Boston, MA, [2]Hospital Special Surgery (HSS), New York, NY, [3]Boston University School of Medicine, Boston, MA, [4]University of California-San Francisco, San Francisco, CA, [5]University of Alabama, Birmingham City, Birmingham, AL, [6]University of Iowa, Iowa City, Iowa City, IA

Background/Purpose: The 1st metatarsophalangeal joint (MTPJ) is the most common site of OA in the foot. While clinical diagnostic criteria have not been defined, characteristics of 1st MTPJ OA include frequent joint pain, hallux valgus malalignment, and limited joint dorsiflexion during gait (functional hallux limitus). The degree to which a person toes-out when walking is of interest to OA investigators because of the desirable effects that toe-out has in reducing load on the medial knee. However, evidence suggests that toe-out may also increase load on the 1st MTPJ, possibly putting this joint at greater risk of OA. This study determined the cross-sectional relationship of toe-out with clinical characteristics of 1st MTPJ OA, including joint pain, alignment, and dorsiflexion in a population of older adults at risk of OA.

Methods: The Multicenter Osteoarthritis Study (MOST) includes older adults who have or are at risk of knee OA. At the 60-month exam, we inquired about frequent 1st MTPJ pain, measured hallux valgus alignment from foot photos, and measured peak 1st MTPJ dorsiflexion and mean toe-out angle using a 4.9 meter instrumented GAITRite walkway and 60 Hz videos during 3–4 self-paced walking trials. Using the quintile distribution among pain cases to form cutpoints, we applied logistic regression to determine the relative odds of 1st MTPJ pain within categories of increasing toe-out while adjusting for age, sex, BMI, and walking velocity. Generalized estimating equations (GEE) accounted for inclusion of two feet from a subject. Using linear regression with GEE, we compared mean hallux valgus alignment and mean 1st MTPJ dorsiflexion within these categories while making similar adjustments.

Results: 2027, 534, and 626 participants with available 60-month exam data contributed 4054, 1066, and 1247 feet to assess the relation of toe-out to 1st MTPJ pain, alignment, and dorsiflexion, respectively. Mean toe-out was 6.8 +/− 5.6 degrees, mean hallux valgus alignment was 20.6 +/− 10.2 degrees, and mean 1st MTPJ dorsiflexion was 39.6 +/−10.8 degrees. After adjustments, the odds of 1st MTPJ pain and the means of hallux valgus alignment were similar across categories of increasing toe-out (p for trend = 0.36 and 0.22, respectively). Mean 1st MTPJ dorsiflexion decreased (p for trend = 0.04), but only slightly (≤ 2 degrees) (see table).

Table. Relative odds of 1st MTPJ pain, mean hallux valgus alignment, and mean 1st MTPJ dorsiflexion within categories of increasing toe-out during walking.

	1st MTPJ Pain N=4054 feet, 2027 ppts			Hallux Valgus N=1066 feet, 534 ppts		1st MTPJ Dorsiflex N=1247 feet, 626 ppts	
Toe-Out Categories	N of feet	N (%) painful	Adj. OR* (95% CI)	N of feet	Adj. Mean* (95% CI)	N of feet	Adj. Mean* (95% CI)
Lowest −10.3°, 2.3°	825	109 (13.2)	1.0 (ref)	198	21.0° (19.6, 22.4	225	40.7° (39.5, 41.9)
2nd 2.4°, 5.8°	904	111 (12.3)	1.0 (0.8, 1.3)	256	21.4° (20.2, 22.6)	301	39.4° (38.4, 40.5)
3rd 5.9°, 8.5°	810	114 (14.1)	1.1 (0.8, 1.4)	244	21.0° (19.9, 22.2)	268	40.2° (39.1, 41.3)
4th 8.6°, 11.7°	744	107 (14.4)	1.2 (0.9, 1.5)	194	20.9° (19.7, 22.1)	240	39.8° (38.6, 40.9)
Highest 11.8°, 32.6°	771	110 (14.3)	1.1 (0.8, 1.4)	174	19.7° (18.3, 22.1)	213	38.7° (37.4, 40.0)
p for trend			p=0.36		p=0.22		p=0.04

* Adjusted for age, sex, BMI, and walking velocity.

Conclusion: Increased toe-out during walking was not associated with increased prevalence of 1st MTPJ pain or increased hallux valgus malalignment. While greater toe-out was associated with slightly reduced 1st MTPJ dorsiflexion, the magnitude of this association was small and its relevance to OA etiology remains equivocal. Based on these findings, gait training to increase toe-out among adults with medial knee OA could be considered without substantial concern for OA characteristics at the 1st MTPJ.

1992

Relationships Between the Peak Adduction Moment and Symptoms During Walking in Knee Osteoarthritis Patients with Valgus Knee Brace: A Cross-Sectional Study. Paul Ornetti, Clementine Fortunet, Davy Laroche, Claire Morisset, jean-Marie Casillas and jean-Francis Maillefert. Dijon University Hospital, Dijon, France

Background/Purpose: The use of valgus knee brace has been recently recommended in the OARSI guidelines to decrease pain and functional impairment. Symptomatic effects are thought to be mediated by distracting the medial compartment via external valgus forces applied to the knee, which could be evaluated by the peak knee adduction moment.However, there is limited evidence regarding the symptomatic benefits of valgus knee brace in knee OA patients and their correlations with the peak adduction moment. Objective: To evaluate the clinical efficacy and biomechanical effectiveness of a new valgus knee brace (developed and provided by PROTEOR) with a rotating shift axis

Methods: *Design*: 5-week prospective open-labeled therapeutic trial in outpatients with symptomatic painful medial knee OA. *Inclusion and exclusion criteria*: age between 40 et 80, pain of at least 40 (100 visual analog scale (VAS)) on a daily basis for at least one month during the last three months, evidence of medial femoro-tibial OA on plain antero-posterior X-rays (Kellgren and Lawrence stage ^{3} 2), predominance of pain and radiographic OA in the medial part of the knee. *Outcome measures.* Three-dimensional (3D) Vicon gait analyses were performed at weeks 0 and 5 for all patients. Primary outcome measure was pain severity as measured on VAS. Secondary outcome measures were patient global assessment (PGA) on VAS (0–100), KOOS function activity of daily life (0–100, worst to best), gait parameters (gait speed, step length and walking frequency) and peak adduction moment. *Statistical analysis:* comparison of pre and post-treatment clinical and 3D gait data was performed using the Wilcoxon paired test and calculation of effect size (ES). Correlations between change in symptoms and peak adduction moment were calculated using Spearman correlation coefficient.

Results: Twenty patients (16 women and 4 men, mean age 64.2±10.2 years, mean body mass index 27.2±5.4 kg/m^2) were included. The mean VAS pain (63.0 to 29.8, $p < 0.001$, ES=2.34), VAS PGA (64.3 to 34.0, $p < 0.001$, ES=1.85) scores improved significantly from baseline to week 6, as well as KOOS function activity of daily life (ADL): 44.5 to 67.8, $p < 0.001$, ES=1.83; 85% of patients (17/20) considered their state as improved or very improved at week 6. NSAIDs and analgesic drug intake decreased significantly at week 6 ($p=0.018$ and $p=0.004$, respectively). No serious side-effects were observed. The gait speed and step length were significantly increased at the end of the study ($p<0.05$). The reduction of peak adduction moment was correlated with the improvement in pain ($r = 0.67$, $p<0.002$) and physical function ($r = 0.57$ for KOOS ADL, $p<0.01$).

Conclusion: The preliminary results demonstrate a good clinical efficacy of a new valgus knee brace in medial compartment knee OA patients. This efficacy is statistically correlated with the reduction of the peak adduction moment on the knee medial compartment.

1993

Consequences of Knee Buckling: The Multicenter Osteoarthritis Study. Uyen Sa D. Nguyen[1], David T. Felson[1], Jingbo Niu[1], Yanyan Zhu[1], Daniel K. White[1], Neil Segal[2], C.E. Lewis[3], Margaret Rasmussen[4] and Michael C. Nevitt[4]. [1]Boston University School of Medicine, Boston, MA, [2]University of Iowa, Iowa City, [3]University of Alabama, Birmingham City, AL, [4]University of California-San Francisco, San Francisco, CA

Background/Purpose: Recent studies suggest that knee buckling, a feeling of sudden "giving way" of the knee, is a common symptom in people with knee pain and knee osteoarthritis (OA). People may avoid physical activity out of fear of falling if their knee buckled, possibly leading to decreased physical function. Little is known about the psycho-social or physical consequences of knee buckling. We examined the association of buckling with fear of falling, decreased balance confidence, and decreased physical function. We further explored whether people whose knees buckled

repeatedly were at a greater risk for these outcomes than people whose knees did not buckle.

Methods: We used data from the 60-month visit of the Multicenter Osteoarthritis Study (MOST), an NIH funded longitudinal study of persons with or at high risk of knee OA. During clinic visits, participants were asked if their knees buckled or gave way in the past 12 months and if so, whether they buckled in the past 3 months and the frequency of such buckling. Repeated bucklers were defined as people who had 2 or more buckling episodes in the past 3 months. Participants were also asked about fear of falling, and balance confidence (ABC Balance Scale, range: 0–100, with poor confidence defined as ≤ 67). Low physical function was defined as WOMAC function score ≥ 28.0[1], and impaired walking speed as <1.22 m/s.[2] Poisson regression was used to estimate the prevalence ratio (PR) and 95% confidence interval (CI) for the cross-sectional association between buckling and each of the outcomes of interest, adjusting for age, sex, BMI, number of co-morbidities, severity of WOMAC knee pain score, radiographic OA (ROA) and quadriceps strength.

Results: Of 2,299 persons with buckling frequency and outcome data (60% female, 39% ≥ 65 years, mean BMI: 31), 24% had knee buckling in the previous year, 34% had a fear of falling, 14% had low confidence in their balance, 14% had low WOMAC physical function, and 50% had impaired walking speed. Overall, knee buckling was significantly associated with fear of falling, poor balance confidence, and poor WOMAC physical function, independent of knee pain and other confounders (Table). The associations were greatly attenuated after adjustment of covariates, particularly knee pain. Additionally adjusting for ROA and quadriceps strength did not further alter the estimates of association. Moreover, the magnitude of the association was slightly higher for repeated bucklers than non-repeated bucklers, especially for poor physical function. There was no association between buckling and impaired gait speed once confounders were adjusted.

Table. Association between Knee Buckling and Outcome of Interest All subjects and by Repeat or Non-Repeat Bucklers

	Knee Buckling			
Outcome of interest	**Any Buckling**	**Repeated Buckling**	**Non-Repeated Buckling**	**No Buckling**
Fear of Falling	N=552	N=310	N=240	N=1742
% with Fear of Falling	49.6	55.8	41.7	29.2
Unadjusted PR (95% CI)	17 (1.5, 1.9)	1.9 (1.7, 2.2)	1.4 (1.2, 1.7)	REF
Adjusted PR (95% CI)	1.3 (1.2, 1.5)	1.4 (1.3, 1.6)	1.2 (1.0, 1.4)	REF
Low Balance Confidence	N=552	N=310	N=242	N=1742
% with Balance Score ≤ 67	30.1	35.5	23.1	8.8
Unadjusted PR (95% CI)	3.4 (2.8, 4.2)	4.0 (3.3, 5.0)	2.6 (2.0, 3.5)	REF
Adjusted PR (95% CI)	2.0 (1.6, 2.5)	2.2 (1.7, 2.7)	1.8 (1.4, 2.3)	REF
Poor Physical Function	N=533	N=295	N=238	N=1727
% with WOMAC function ≥28.0	31.0	37.3	23.1	8.6
Unadjusted PR (95% CI)	3.6 (2.9, 4.4)	4.3 (3.5, 5.3)	2.7 (2.0, 3.5)	REF
Adjusted PR (95% CI)	1.3 (1.0, 1.6)	1.3 (1.1, 1.7)	1.2 (0.9, 1.6)	REF
Impaired Gait Speed	N=536	N=299	N=237	N=1704
% with Gait Speed < 1.22m/s	60.6	67.6	51.9	46.7
Unadjusted PR (95% CI)	1.3 (1.2, 1.4)	1.4 (1.3, 1.6)	1.1 (1.0, 1.3)	REF
Adjusted PR (95% CI)	1.0 (0.95, 1.1)	1.1 (1.0, 1.2)	0.9 (0.8, 1.1)	REF

Adjusted for Sex, Age (<65 vs. ≥), BMI, Comorbidity, WOMAC Knee pain severity. Additionally adjusting for ROA and quadriceps strength did not further alter the estimates of association.

[1] Ayis S et al. J Rheum 2007:34:1905–12
[2] White et al. AC&R 2010;62:938–43

Conclusion: Independent of knee pain and other confounders, knee buckling was significantly associated with fear of falling, poor balance confidence, and poor physical function. Future studies should examine the longitudinal effect of buckling on psycho-social and physical outcomes.

1994

Is Medial Knee Osteoarthritis Associated with Adverse Effects At the Ankles? Berna Goker[1], Abdurrahman Tufan[1], Roy H. Lidtke[2] and Joel A. Block[2]. [1]Gazi University Medical School, Ankara, Turkey, [2]Rush University Medical Center, Chicago, IL

Background/Purpose: Primary ankle osteoarthritis (OA) is considered to be uncommon, however, an association of radiographic ankle OA with symptomatic knee OA has recently been reported (McDaniel G, PMID 21310252), and lateral ankle pain is common in patients with knee OA. We hypothesized that the the tibio-femoral malalignment and lateral shift observed in medial knee OA would be associated with radiographic OA of the ankle.

Methods: 90 subjects with symptomatic medial knee OA (K-L grade 2–3, ambulatory pain >30 mm on a 100 mm VAS) were included. Full limb mechanical axis and AP X-rays of the ankles were obtained. Joint space width (JSW) of the medial and lateral tibiotalar joints were measured using a validated method (Goker B, PMID 19381746). Also, in addition to the knee alignment angle, the tibial lateral shift, defined as the distance between the center of the intercondylar notch of the femur and midpoint of the tibial plateau, was measured, using Image J software (US NIH, Bethesda, MD, http://rsbweb.nih.gov/ij/). Pearson's correlations were calculated to analyze the relationship between the ankle JSW and the other radiographic parameters. $p < 0.05$ was considered significant.

Results: The mean±SD tibial lateral shift was 5.18±2.45 mm, and was inversely related to the lateral ankle JSW (r=-0.27, p=0.01). In contrast, there was no relationship with the medial ankle JSW (r=-0.16, p=0.12). Also, the knee alignment angle (mechanical axis) was not associated either with medial or lateral ankle JSW (r=0.11, p=0.23 and r=0.16, p=0.12, respectively).

Conclusion: Radiographic JSW is a measure of cartilage loss, and is directly related to strucutral OA progression. These findings of an association between the magnitude of lateral tibio-femoral shift in knee OA and narrowing of ankle JSW suggest that the aberrant loading of the knee in OA has structural implications at the ankle, and may explain the previously described association between medial knee OA and radiographic ankle OA.. The clinical significance of this finding, and its relationship to lateral ankle pain in patients with knee OA, needs further study

1995

The Association of Vibratory Perception with Foot Plantar Pressures: The MOST Study. Najia Shakoor[1], Howard J. Hillstrom[2], K. Douglas Gross[3], Ke Wang[4], David T. Felson[5], Neil Segal[6], Cora E. Lewis[7] and Michael C. Nevitt[8]. [1]Rush University Medical Center, Chicago, IL, [2]Hospital Special Surgery (HSS), New York, NY, [3]MGH Institute of Health Professions, Boston, MA, [4]Boston University, Boston, MA, [5]Boston University School of Medicine, Boston, MA, [6]University of Iowa, Iowa City, [7]University of Alabama, Birmingham City, Birmingham, AL, [8]University of California-San Francisco, San Francisco, CA

Background/Purpose: Somatosensory alterations at the lower extremities have previously been recognized in osteoarthritis (OA), including deficits in vibratory perception. It is hypothesized that these sensory deficits may increase mechanical loading of tissues and joints in individuals with knee OA and that the mediator of this may be increased plantar pressures at the foot.Here, we evaluated the association between vibratory perception and plantar pressures in a large cohort study of knee OA.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH-funded longitudinal study of persons with or at increased risk of knee OA. Those with total knee replacement or diabetes, defined by the use of medication, were excluded in this analysis. At the 60-month visit, participants underwent bilateral evaluation of vibratory perception threshold (VPT), using a biothesiometer. The applicator tip was placed at the dorsum of the 1st MTP joint. Voltage was initially set at "0" and then increased by 1 volt/second until the participant acknowledged sensation. This was defined as the VPT.Plantar pressures were captured using a high resolution digital pedobarograph (EmedX) during 5 self-paced walking trials for each foot. Peak pressures (N/cm2) and pressure-time integrals (Ns/cm^2) were evaluated in each anatomical region of the plantar foot using a masking algorithm. The hallux and medial and lateral heel were chosen as anatomic areas of interest that may be susceptible to increased pressures during the push off and weight acceptance phase of stance, respectively. Categories of "low", "normal", and "high" VPT, in order of better to worse vibratory sense, were formed at < or > 1 standard deviations from the mean. Mean plantar pressures were compared between these three VPT groups while adjusting for age, sex, race, body mass index, clinical site, and walking speed. Generalized Estimating Equations (GEE) accounted for the inclusion of two feet from a single subject.

Results: 1560 participants (2926 knees) were included in this analysis (59.3% female with a mean age (±SD) of 67±8 years). Results are summarized in Table 1 and demonstrate a "dose-response" trend, such that with worsening vibratory perception, increased hallucial peak pressures were observed as well as increased pressure-time integrals at the hallux and lateral and medial heel.

Table.

	Hallucial peak pressure (N/cm^2)	**Hallucial pressure-time integral (Ns/cm^2)**	**Medial heel pressure (N/cm^2)**	**Medial heel pressure–time integral (Ns/cm^2)**	**Lateral heel pressure (N/cm^2)**	**Lateral heel pressure-time integral (Ns/cm^2)**
"Low" VPT	63.3 (59.8, 66.9)	17.8 (16.6, 18.9)	33.6 (31.6, 35.5)	9.4 (9.0, 9.9)	30.2 (29.0, 31.4)	8.6 (8.3, 9.0)
"Normal" VPT	64.7 (63.1, 66.3)	18.2 (17.7, 18.8)	36.4 (35.4, 37.4	10.4 (10.0, 10.7)	32.1 (31.5, 32.7)	9.3 (9.1, 9.5)
"High" VPT	71.4 (68.4, 74.4)	20.5 (19.4, 21.6)	37.4 (35.3, 39.5)	10.8 (10.1, 11.4)	32.8 (31.3, 34.2)	9.6 (9.2, 10.1)
P for linear trend	**<0.001**	**<0.001**	0.132	**0.049**	0.153	**0.034**

Conclusion: Vibratory sense deficits have previously been observed in OA compared to age-matched controls. The role of these alterations in the OA disease process and OA mechanics is not clear. These results suggest that those with lower vibratory perception have increased plantar loading, indicating that sensory deficits may have mechanical associations in persons with or at risk of knee OA.

1996

Associations Between Pain on Movement, Range of Movement and Radiographic Change in Osteoarthritis of the Knee. Roger Hilfiker[1], Peter Juni[2], Eveline Nüesch[2], Paul A. Dieppe[3] and Stephan Reichenbach[1]. [1]Universtiy of Bern, Bern, Switzerland, [2]University of Bern, Bern, Switzerland, [3]University of Exeter, Plymouth, United Kingdom

Background/Purpose: Patients with osteoarthritis are at higher risk of death compared with the general population, and the presence of a walking disability is one major risk factor. Based on gait analyses, full extension of the knee is important for walking. We determined whether limitations in the range of motion (ROM) of the knee joint were associated with the presence of pain independently of structural damage as detected on radiographs.

Methods: Data from the follow-up study of the Somerset and Avon Survey of Health (SASH), a community-based prospective cohort study, were used. Passive knee flexion and extension were measured using a goniometer, and patients were asked whether the passive movements were painful [no/yes]. Knee radiographs were read for K&L grades [0–4], osteophytes [0–3] and joint space narrowing [0–3]. After adjustments for sex, body mass index (BMI), and radiographic characteristics, we evaluated whether extension and flexion deficits were associated with pain. Data were analysed at joint level using linear regression models with robust standard errors to account for clustering of knees within patients. We then explored potential interactions between the presence or absence of pain and the association of radiographic changes with limitations in ROM.

Results: 820 patients (1639 knees) had complete information for knee range of motion, radiographs and pain. 41.2% of the knees had a K/L grade of 0 or 1. The median range of knee extension was 0° (range −15° (hyperextension) to 50° (extension deficit)) with a mean extension deficit of 1.4° (sd 4.9). Passive extension caused pain in 322 knees (20%). The median knee flexion was 125° (range 40° to 158°) and mean flexion was 125° (sd 13.5). Passive flexion caused pain in 486 (30%) knees.

Extension deficits were more pronounced in individuals with pain on passive extension (difference after initial adjustment: 2.8°, 95% CI 1.9° to 3.8°). This difference was similar after adjustment for K/L (2.5°, 95% CI 1.5° to 3.5°). The association between K/L and extension was more pronounced in patients with pain on passive extension (extension deficit per K/L grade: 1.4°, 95% CI 0.6° to 2.1°) than in those without such pain (0.4°, 95% CI 0.2° to 0.7°), with a positive test for interaction (p=0.024).

Flexion was more restricted in individuals with pain on passive flexion (difference after initial adjustment: −5.9°, 95% CI −7.6° to −4.3°). This difference was slightly lower after adjustment for K/L (−4.4°, 95% CI −6.1° to −2.7°). The association between K/L and flexion was also more pronounced in patients with pain on passive flexion (reduced flexion per K/L grade: −2.4°, 95% CI −3.5° to −1.3°) than in those without such pain (−1.5°, 95% CI −2.2° to −0.8°), with a non-significant test for interaction (p=0.174).

Conclusion: Pain on extension and flexion were both associated with ROM, even after adjustment for radiographic severity. The presence or absence of pain on passive extension modified the association of ROM with K/L grade, with a more pronounced association in the presence of knee pain. For flexion, pain did not modify the association between radiographic severity and ROM. Pain and extension deficits may both be possible targets for preventing or ameliorating walking disability.

1997

Radiographic Joint Damage and Not Clinical Characteristics Are Related to the Actual Cartilage Damage in Severe Knee Osteoarthritis Patients. T.N. de Boer[1], Simon C. Mastbergen[1], A.M. Huisman[2], J.W.J. Bijlsma[1] and F.P.J.G. Lafeber[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Sint Franciscus Gasthuis, Rotterdam, Netherlands

Background/Purpose: Clinically, osteoarthritis (OA) is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and local inflammation. Pain, joint deformation, and stiffness of the joint capsule may lead to severe restriction of function, and in the long term to disability. In end-stage disease specific indications for total knee replacement (TKR) surgery are not clearly defined. The decision to proceed to TKR is based upon the clinical parameters like pain and limitation of movement accompanied by radiographic characteristics. Because there are no clearly defined indications for TKR surgery, patients with little radiographic damage (K&L grade 1 or 2) frequently undergo TKR surgery. The aim of this study is to evaluate whether pre-operative radiographic characteristics, better than clinical characteristics, relates to actual cartilage damage of patients with end-stage knee osteoarthritis.

Methods: 172 successive patients with severe knee OA selected for TKR seen at a peripheral hospital in the Netherlands were evaluated (age 67.4; female/male ratio 119/53). Patient characteristics, radiographic features of OA (K&L score, Altman joint space narrowing and osteophytes) and severity of symptoms (WOMAC pain, stiffness and physical function) were assessed shortly before surgery. During joint replacement surgery, cartilage and synovial tissue were obtained and evaluated by macroscopy, histology, and biochemistry, blinded to the clinical and radiographic characteristics. The study was conducted according to the declaration of Helsinki and received ethics approval of the hospital.

Results: The average K&L score of this population was 3.1 (range 1–4). The average Altman scores for this population were 2.5 (range 0–3) for the joint space narrowing and 3.2 (range 0.8–6) for the osteophyte score. Both the K&L score and the Altman osteophyte score were statistically significant associated with the actual macroscopic cartilage damage [R=0.865, p=0.006/ R=0.801, p=0.005, respectively]. The Altman joint space narrowing showed also an association with the macroscopic cartilage damage [R=0.482, p=0.067]. The cartilage histology and the PG content showed no evident correlation with either of the radiographic parameters. The Altman osteophyte score was also significantly associated with the macroscopical synovial inflammation [R=0.466, p=0.029] and histological synovial inflammation [R=0.374, p=0.039]. None of the clinical parameters did relate to any of the actual structural cartilage damage of synovial inflammation.

Conclusion: The present study demonstrates that there is a good correlation between K&L score and actual cartilage damage in end-stage knee OA considered for replacement surgery. This indicates that radiographs give a good indication of the actual severity of joint damage. Osteophytes, dominating the overall K&L score, also on their own (Altman score) correlate with actual cartilage damage as well as actual synovial inflammation. Because no relations between clinical parameters and actual joint damage were found it might be concluded that radiographic joint damage is underestimated in the selection of patients considered for prosthesis surgery.

1998

Peri-Articular Apparent Bone Volume Fraction Is Associated with Numerous Patient Characteristics in Knees with Osteoarthritis: Data From the Osteoarthritis Initiative. Jeffrey B. Driban[1], Lori Lyn Price[1], Anna M. Tassinari[1], Grace H. Lo[2] and Timothy E. McAlindon[1]. [1]Tufts Medical Center, Boston, MA, [2]Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Boston, MA

Background/Purpose: Recent evidence suggests that peri-articular bone changes are integral to knee osteoarthritis (OA) pathophysiology. Peri-articular trabecular morphology changes have been associated with radiographic knee OA severity and may identify individuals at risk for knee OA progression. However, it is unclear how patient characteristics are associated with peri-articular trabecular morphology in knees with OA. The purpose of this study was to evaluate the association between patient characteristics and apparent bone volume fraction (aBVF), one measure of trabecular morphology, in knees with OA.

Methods: The sample comprised 421 participants in the Osteoarthritis Initiative (OAI) progression cohort who at the 30- or 36-month OAI visit had 3-tesla magnetic resonance imaging (MRI) that included a coronal 3D Fast Imaging with Steady State Precession (FISP) trabecular morphometry sequences of one knee (right knee unless contraindicated). We used a trabecular morphometry program (calcDCN, University of California-San Francisco) to measure aBVF in the medial tibial plateau. aBVF was calculated in 20 consecutive central slices within a 15 mm × 3.75 mm region of interest placed in the peri-articular medial tibia and then averaged. Intra-tester reproducibility was high (ICC = 0.99). We used three multiple linear regression models to evaluate patient characteristics associated to aBVF: 1) individual-level model (sex, race, age at time of MRI, body mass index at time of MRI, college, income, and history of smoking), 2) individual-level model with history of knee injury/surgery model, and 3) model 2 with knee-specific variables of radiographic severity (joint space narrowing [JSN] and joint space width [JSW] at 300 mm).

Results: Participant and knee-specific characteristics are reported in the table. Average (± s.d.) peri-articular aBVF was 0.10 ± 0.07. All three regression models were statistically significant ($p < 0.001$). Individual-level variables accounted for 12.0% of the variance in aBVF. The combination of individual-level and knee-specific variables accounted for 22.2% of the variance in aBVF. Females were characterized by lower aBVF in all three models. In contrast, Caucasians and patients with a higher body mass index had higher aBVF in all three models. History of knee injury/surgery and greater radiographic severity in the medial compartment (higher JSN score, lower JSW) were associated with higher aBVF. Age at the time of the MRI was only related to aBVF when radiographic severity was included in the model.

Conclusion: Among individuals with knee OA, peri-articular morphology is influenced by multiple individual-level (sex, race, body mass index) and knee-specific variables (knee injury/surgery, OA severity). Increases in aBVF were associated with individuals with higher body mass index and history of knee injury/surgery, Caucasians, and markers of local knee OA severity.

Table. Characteristics Associated with Peri-articular Apparent Bone Volume Fraction

Variable	Descriptives Mean ± SD or % (n)	Individual-Level Model (R^2 = 0.120)	Individual-Level + Injury/Surgery Model (R^2 = 0.134)	Individual + Knee Specific Model (R^2 = 0.222)
Female	46.3 % (195)	**−0.037 (0.007)***	**−0.036 (0.007)***	**−0.038 (0.007)***
White/Caucasian	73.9 % (311)	**0.023 (0.008)***	**0.021 (0.008)***	**0.025 (0.008)***
Age (years)	64.6 ± 9.2	0.000 (0.000)	0.000 (0.000)	**−0.001 (0.000)***
Body mass index (kg/m^2)	29.4 ± 4.6	**0.002 (0.001)***	**0.002 (0.001)***	**0.001 (0.001)***
College Graduate	60.6 % (255)	0.004 (0.008)	0.004 (0.007)	0.003 (0.007)
Income (< $50,000/yr)	38.2 % (161)	0.002 (0.008)	0.002 (0.008)	0.001 (0.007)
History of Smoking	46.1 % (194)	−0.003 (0.006)	−0.004 (0.006)	0.001 (0.006)
History of Knee Injury/Surgery	38.5 % (162)	n/a	**0.017 (0.007)***	**0.015 (0.006)***
Presence of Medial JSN	55.1 % (232)	n/a	n/a	**0.025 (0.007)***
Presence of Lateral JSN	14.7 % (62)	n/a	n/a	−0.006 (0.009)
Medial JSW	6.6 ± 1.7	n/a	n/a	**−0.007 (0.002)***

* $p<0.05$; SD = standard deviation, MRI = magnetic resonance imaging, JSN = joint space narrowing, JSW = joint space width

1999

Safety of Diclofenac Sodium Topical Solution Compared with Oral Diclofenac for Osteoarthritis of the Knee in Patients Aged ≥65 Years: Pooled Analysis From 2 Controlled Trials. Sanford H. Roth[1] and Philip Fuller[2]. [1]Arizona Research & Education, Paradise Valley, AZ, [2]Covidien, Hazelwood, MO

Background/Purpose: Despite proven efficacy of oral nonsteroidal anti-inflammatory drugs (NSAIDs) for the management of osteoarthritis (OA), chronic systemic exposure to oral NSAIDs in patients aged ≥65 years is of concern due to documented increased risk of gastrointestinal (GI) and cardiovascular adverse events (AEs). Compared with oral NSAIDs, topical NSAIDs produce significantly less systemic exposure and may result in fewer and less severe systemic AEs. Clinical trials have shown that diclofenac sodium topical solution (TDiclo) with the penetration enhancer dimethyl sulfoxide (DMSO) is effective and well tolerated in the management of OA of the knee. This pooled analysis was conducted to characterize the safety profile of TDiclo vs oral diclofenac (ODiclo) in patients aged ≥65 years with radiologically confirmed symptomatic OA of the knee.

Methods: Data were pooled from two 12-week randomized, double-blind, multicenter trials of TDiclo that included an ODiclo comparator, in patients with primary OA of the knee. Safety assessments included AE monitoring, recording of vital signs, dermatologic examination of the study knee, and clinical laboratory evaluation. AEs were evaluated for statistical significance by system organ class (SOC); specific AEs were evaluated in the SOCs showing significant difference in AEs between treatment groups.

Results: A total of 927 patients were included; 427 (46%) were aged ≥65 years (223 TDiclo; 204 ODiclo). In this age group, significantly fewer GI-related AEs occurred with TDiclo (24.7%) vs ODiclo (42.6%; $P<0.0001$); the most common were dyspepsia (9.4% vs 24.0%; $P<0.0001$), diarrhea (6.7% vs 14.2%; $P=0.011$), and upper abdominal pain (5.8% vs 17.2%; $P=0.0002$). Application-site AEs were significantly more common with TDiclo (28.3%) vs ODiclo (3.4%; $P<0.0001$); the most common application-site AE was dry skin (TDiclo 21.5%; ODiclo 1.5%; $P<0.0001$). Overall incidence of cardiovascular AEs was low but was not statistically significantly different between groups (TDiclo 1.8%; ODiclo 4.4%; $P=0.159$).

Conclusion: The results of this analysis demonstrate that TDiclo was associated with a significantly lower incidence of GI-related AEs compared with ODiclo and may therefore represent a viable therapeutic option for older patients.

2000

Prevention of Celecoxib Induced Gastrointestinal Events by Concomitant Therapy with Rebamipide, Gastro-Protective Drug. Masahiro Hasegawa[1], Kyosuke Tanaka[1], Noriyuki Horiki[1], Hiroki Wakabayashi[1], Yoshiyuki Takei[1], Atsumasa Uchida[1], Akihiro Sudo[1] and GLORIA study group[2]. [1]Mie University Graduate School of Medicine, Tsu City, Mie, Japan, [2]Tsu City, Mie, Japan

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) can induce ulcer complications such as bleeding and perforation. Substitution of NSAIDs with a selective cyclo-oxygenase-2 (COX 2) inhibitor reduces the risk of gastroduodenal ulcer complications. However, gastroduodenal ulcer induced by COX 2 inhibitor was reported. In Japan, no randomized prospective gastrointestinal outcome trials have been designed to examine the benefit of combined treatment with a COX 2 selective inhibitor (celecoxib) and any kinds of anti-ulcer drug yet. Rebamipide, increases gastric mucous and stimulates the production of endogenous prostaglandins, has been frequently prescribed as gastroprotective agent in Japan. We aimed to confirm the hypothesis that combined treatment with celecoxib and rebamipide would be more effective than celecoxib alone for prevention of gastrointestinal endoscopic events.

Methods: This prospective, randomized, open-label blinded end point study was conducted from August 2008 to July 2011 in Japan. Patients with rheumatoid arthritis, osteoarthritis, and low back pain enrolled to this study. Gastroduodenal mucosal damage was evaluated using endoscopy before treatment and at the end of the study. The patients presented peptic ulcers before treatment were excluded. Patients were randomized to two groups: mono-therapy group (100 mg celecoxib twice daily) and combination group (100 mg celecoxib twice daily and 100 mg of rebamipide three times a day). These patients were tested for the presence of *Helicobacter pylori*. The primary endpoint was designed to endoscopic gastrointestinal events as occurring peptic ulcer within three months. Statistical analyses were performed using chi-squared test, Fisher's exact test, or Mann-Whitney U-test.

Results: Seventy-three patients were eligible. Seven patients were withdrawn. Thirty-five patients were assigned to the mono-therapy group, and 31 were in the combination group. No differences were found between the groups in terms of the demographics; age, gender, diagnosis, concomitant of aspirin, and past history of peptic ulcer. The prevalence of gastrointestinal events was 7/35 (20%) in the mono-therapy group, and 0/31(0%) in the combination group ($p=0.012$). Gastroduodenal ulcers were detected in six patients. No correlations were observed between the presence of *Helicobacter pylori* or past history of peptic ulcer and gastrointestinal events.

Conclusion: Use of celecoxib during three months induced gastrointestinal events in 20% in the present study and preventive strategy for gastrointestinal ulcer should be investigated. Combination treatment was more effective than celecoxib alone for prevention of gastrointestinal events in the present study, and our hypothesis was verified. Rebamipide could be candidate option for the prevention of COX 2 inhibitor induced gastrointestinal events.

2001

GI-REASONS: A Novel 6-Month, Prospective, Randomized, Open-Label, Blinded End Point (PROBE) Trial. Byron Cryer[1], Chunming Li[2], Lee S. Simon[3], Gurkirpal Singh[4], Martin Stillman[5] and Manuela Berger[2]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Pfizer Inc, New York, NY, [3]SDG LLC Consulting, West Newton, MA, [4]Stanford University School of Medicine, Palo Alto, CA, [5]Hennepin County Medical Center, Minneapolis, MN

Background/Purpose: The GI Randomized Event and Safety Open-Label NSAID Study (GI-REASONS) was a novel prospective, randomized, open-label, blinded end point (PROBE) study that measured adju-

dicated clinical outcomes throughout the GI tract. It was designed to assess if celecoxib use in patients with osteoarthritis (OA) at moderate GI risk (≥55 y) is associated with a lower incidence of clinically significant upper and lower GI events compared to nonselective (ns)NSAIDs, with/without proton-pump inhibitors (PPIs), in standard US clinical practice.

Methods: Patients were randomized 1:1 for 6 months to receive celecoxib or any nsNSAID, stratified by *H pylori* status. The primary end point was a composite of adjudicated clinically significant upper and lower GI events. Aspirin use was not permitted. Treatment doses could be adjusted per US prescribing information. Patients randomized to the nsNSAID arm could switch between nsNSAIDs; however, crossover between treatment arms was not allowed. PPIs and histamine-2 receptor antagonists (H_2RAs) were prescribed at the providers' discretion.

Results: 4035 celecoxib and 4032 nsNSAID patients with OA were randomized and included in the ITT analyses. Baseline demographics were similar. Overall, significantly more nsNSAID users met the primary end point at 6 months (OR, 1.82; 95% CI 1.31–2.55; $p=0.0003$; Table 1). The most commonly used nsNSAIDs were meloxicam (42%), naproxen (21%), diclofenac (20%) and nabumetone (14%). 2596 celecoxib (64.3%) and 2611 (64.8%) nsNSAID users completed the study. 189 patients were lost to follow-up (LTFU; 2.1% celecoxib and 2.6% nsNSAID). Attributing the primary end point to all LTFU patients (worst-case sensitivity analysis), celecoxib remained superior (OR 1.46; 95% CI 1.18–1.82; $P=0.0006$). AEs, SAEs and discontinuations were similar in both treatment groups. 23% of celecoxib and 24% of nsNSAID patients used a PPI (P=NS). Moderate to severe abdominal symptoms were experienced by 94 (2.3%) celecoxib and 138 (3.4%) nsNSAID patients ($P=0.0035$).

Table 1. Clinically Significant Upper and Lower GI Events: Primary Analysis

		Celecoxib		nsNSAID	
		N	Patients With Event n (%)	N	Patients With Event n (%)
All patients		4035	54 (1.3)	4032	98 (2.4)
***H pylori* status**	**Positive**	1401	25 (1.8)	1386	34 (2.5)
	Negative	2634	29 (1.1)	2646	64 (2.4)
OR (95% CI); P value		1.82 (1.31–2.55); $p=0.0003$			

Conclusion: Celecoxib use had a lower risk of clinically significant upper and lower GI events than nsNSAIDs. A major strength of this study is its PROBE design. Simple inclusion and exclusion criteria allowed for a broad patient population of moderate GI risk. Switching among nsNSAIDs and allowing for dose adjustments, along with use of PPIs and H_2RAs as needed, more closely reflects daily clinical practice. GI-REASONS demonstrates the superiority of the GI safety profile of celecoxib throughout the GI tract in patients treated in a "real-world" setting.

2002

COX-1 Affinity Determines NSAID - Aspirin Interactions. Inger L. Meek[1], Jeannine Kasemier[1], Harald E. Vonkeman[1], Kris Movig[1] and Mart AF van de Laar[2]. [1]Rheumatology Center Twente, Medisch Spectrum Twente & Twente University, Enschede, Netherlands, [2]Medisch Spectrum Twente & Twente University, Enschede, Netherlands.

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) are often prescribed concurrently in patients with osteoarthritis. Both drugs inhibit the same COX-enzymes, and thus may interact. Preceding pharmacodynamic studies confirm significant inhibition of ASA's antiplatelet effect by concurrent use of ibuprofen or indomethacin, but show conflicting results for naproxen. ASA's cardioprotective antiplatelet effect is entirely COX-1 dependent, which may explain the limited interaction between ASA and COX-2 selective NSAIDs. The aim of this study was to examine the interaction between ASA and different selective and non-selective NSAIDs on thrombocyte function.

Methods: Single blind, prospective, placebo controlled, ex-vivo, serial crossover trial of three-day cycles separated by washout periods of at least 12 days in healthy volunteers, evaluating interaction on ASA's antiplatelet effect by naproxen, ibuprofen, meloxicam, or etoricoxib taken two hours before ASA. Ex vivo platelet function, expressed as closure time (CT) in seconds, was measured using the Platelet Function Analyzer 100 (PFA-100). CT-prolongation during a cycle reflects the platelet inhibitory effect. ASA nonresponse was defined as CT-prolongation <40% in the placebo cycle, ASA nonresponders were excluded from the study. The effect of different NSAIDs on CT-prolongation was evaluated by Wilcoxon signed-rank test.

Results: Ibuprofen and naproxen show inhibition of ASA's antiplatelet effect below the nonresponse threshold. Etoricoxib and meloxicam show no relevant change in ASA thrombocyte inhibition.

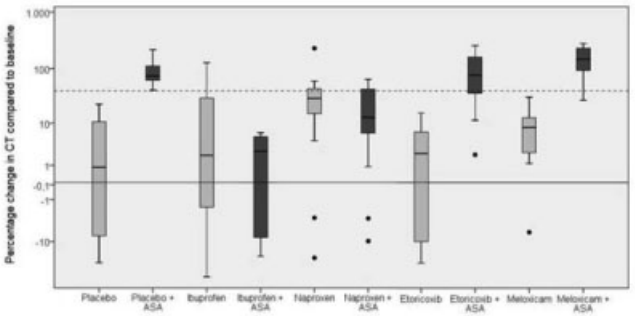


Figure 1. The y-axis shows percentage CT change after use of NSAID or placebo alone (grey boxes) and in combination with ASA (dark boxes) on a loglinear scale. ASA nonresponse threshold (<40% CT-prolongation from baseline) is indicated by the dotted line. The continuous line represents baseline reference.

Conclusion: COX-1 affinity determines the interaction between NSAIDs and ASA on thrombocyte function: aggregation and clotting. Ibuprofen and naproxen, but not etoricoxib or meloxicam, taken two hours before ASA significantly inhibit ASA's antiplatelet effect.

2003

Effects of Opioid and Neurotoxin Analgesics on Pain Behaviors and Function Over Time in Mice with Collagenase-Induced Osteoarthritis. Hollis E. Krug[1], Christopher W. Dorman[2], Sandra Frizelle[2] and Maren L. Mahowald[3]. [1]Minneapolis VA Health Care System and University of Minnesota Medical School, Minneapolis, MN, [2]Minneapolis VA Health Care System, Minneapolis, MN, [3]University of Minnesota Medical School and Minneapolis VA Health Care System, Minneapolis, MN.

Background/Purpose: Osteoarthritis pain remains a significant health problem due to a growing elderly population, increasing longevity, and lack of safe and effective therapies. Understanding the origins of chronic arthritis pain is important for developing effective therapies. Osteoarthritis pain does not correlate well with radiographic severity, and loss of function in patients with osteoarthritis may result from pain, from altered biomechanics or from toxicity of analgesics. In order to better understand the relationship between osteoarthritis, pain and function, we measured different types of pain behaviors in mice with osteoarthritis as a function of age, duration of arthritis and in response to different analgesic treatments.

Methods: Osteoarthritis was produced by intra-articular (IA) injection of 10 μl collagenase (10 IU) into the left knee of 4-week-old C57Bl6 male mice. Arthritic mice were compared to uninjected naïve mice of the same age at 4 weeks and 6 weeks after collagenase injection and to arthritic mice treated with IA analgesics. Analgesics tested were IA morphine sulfate (0.7 mg/kg in 5 μl) or IA Botulinum toxin type A (BoNT/A) (0.02 IU 3 d before testing). Pain behavior measures included evoked pain response to firm palpation of the knee for 1 minute, spontaneous nocturnal wheel-running, mechanical withdrawal thresholds by Von Frey filament testing and digitized video gait analysis using DigiGait™ (Mouse Specifics, Inc, Quincy, MA). The nonarthritic knee was the internal nonpainful control.

Results: Evoked pain responses in arthritic knees were increased at both 4 and 6 weeks after collagenase injection, but this response was 65% greater at 4 weeks than at 6 weeks. Arthritis caused an increased swing/stride ratio measured by gait analysis and increased mechanical allodynia in the arthritic limb by Von Frey filament testing at both 4 and 6 weeks. Spontaneous nocturnal wheelrunning was reduced in both the 4 and 6 week arthritic groups, as well as in 6 week naïve mice. Both BoNT/A and Morphine were effective analgesics at 4 and 6 weeks as measured by evoked pain but did not normalize gait function at either time point. Only morphine normalized the threshold for mechanical allodynia to Von Frey filament testing at 4 weeks, but IA BoNT/A was more effective at 6 weeks.

Conclusion: Arthritis pain produced by IA injection of collagenase in mouse knees produces pain that can be measured at 4 weeks and persists to 6 weeks. Both opioids and BoNT/A given IA are effective analgesics when pain is measured by evoked pain behavior. Changes in functional measures such as gait analysis do reflect the development of arthritis pain but are not clearly normalized by analgesia and may be due not only to pain but to biomechanical changes in the joints. Chronic osteoarthritis

pain produces mechanical allodynia, one indication of peripheral sensitization. Mechanical allodynia may be decreased by opioids if arthritis pain is not longstanding but IA BoNT/A may be more effective for sensitization due to arthritis that is more chronic. More work needs to be done to determine which pain behaviors best measure chronic pain in murine arthritis and are sensitive for detecting analgesia in order to use preclinical models for testing potential new analgesics.

2004

Validation of the Longitudinal Reproducibility of Medial Joint Space Width Quantification in Knee Osteoarthritis. Berna Goker[1], Tayfun Akalin[1] and Joel A. Block[2]. [1]Gazi University Medical School, Ankara, Turkey, [2]Rush University Medical Center, Chicago, IL.

Background/Purpose: Quantification of the radiographic tibio-femoral joint space width (JSW) is a widely used method to evaluate progression of osteoarthritis (OA) and remains the only structural outcome accepted by the US FDA to demonstrate OA disease modification. The aim of this study was to validate the short and long term reproducibility of measurements using Image J (US NIH, Bethesda, MD, http://rsbweb.nih.gov/ij/) in medial knee OA. In addition to being a freely available public access software, it provides a flexible platform for optimizing measurement views for JSW quantification that can be readily learned in only a few minutes.

Methods: 42 patients with symptomatic medial knee OA (Kellgren-Lawrence grade 2–3, pain on ambulation >30 mm on a 100 mm visual analog scale) were assessed. Semi-flexed fluoroscopy-guided PA knee radiographs (Schuss view) were obtained. Medial knee JSWs, defined as the narrowest interbone distance, were measured independently by two observers, one of which was an experienced observer and the other was a first time Image J user. Inter-observer variability (before and after one hour training) and intra-observer variability, at short term (3 weeks) and long term (4 years) were calculated by using coefficient of variation (CV), as well as intraclass correlation coefficient (ICC).

Results: The index knees (most painful) of 37 patients were analyzed. Patients with lateral compartment OA and medial JSW less than 1 mm were excluded (5 patients). Intra-observer variability at 3 weeks was similar to that at 4 years (Table). One hour training resulted in significant improvement in inter-observer variability.

	CV (%)	ICC
Inter-observer variability		
Before training	6.6	0.89
After training	4.4	0.98
Intra-observer variability		
Experienced observer		
Short term (3 weeks)	3.5	0.98
Long term (4 years)	3.8	0.97
First-time user after training		
Short term (3 weeks)	3.8	0.98

Conclusion: Quantification of the medial JSW of the knee in patients with OA using Image J is reproducible. This method is convenient to apply and requires only brief training to obtain high reproducibility. Moreover, these data confrim that quantitative JSW measurements provide meaningful information, as the method yields results that are stable over a several year period.

2005

Validity of within-Grade Scoring of Longitudinal Changes of MRI-Based Cartilage Morphology and Bone Marrow Lesion Assessment—the MOST Study. Frank Roemer[1], Michael C. Nevitt[2], David T. Felson[3], Jingbo Niu[1], John Lynch[4], Michel Crema[1], Cora E. Lewis[5], James Torner[6] and Ali Guermazi[7]. [1]Boston University, Boston, MA, [2]University of California-San Francisco, San Francisco, CA, [3]Department of Clinical Epidemiology, Boston University School of Public Health, Boston, MA, USA, Boston, MA, [4]San Francisco, CA, [5]University of Alabama, Birmingham City, Birmingham, AL, [6]University of Iowa, Iowa City, Iowa City, IA, [7]Boston Medical Center, Boston, MA.

Background/Purpose: Semiquantitative MRI scoring systems for knee osteoarthritis (OA) typically define longitudinal change in cartilage morphology and bone marrow lesions (BMLs) within a subregion in terms of at least one full-grade change between time points. In order to increase the sensitivity to detect change, we introduced the practice of scoring within- (or "partial-") grade changes for WORMS cartilage and BML assessment. The aim of this study was to examine the validity provided by within-grade scoring of cartilage and BMLs in comparison to full-grade assessment using baseline and 30 months follow-up MRIs from the MOST study.

Methods: The Multicenter Osteoarthritis (MOST) Study is a longitudinal study of subjects with knee OA or at risk of OA. The present analysis included all knees with available baseline and 30 months MRI and radiographic readings. MRIs were read according to the modified WORMS scoring system including scoring of within-grade and full-grade or greater changes for cartilage and BMLs. The sensitivity and specificity of MRI-defined cartilage loss to detect increase in X-ray defined joint space narrowing was assessed using cartilage scores applying within-grades plus full grades vs. full grades only. The ability of baseline knee malalignment and meniscal damage to predict compartment-specific structural progression was assessed using ordinal logistic regression adjusting for age, sex and body mass index. Progression was defined as cartilage loss and BML worsening considering half grade scoring only vs. full grade scoring only.

Results: 1867 knees were analyzed. Sensitivity and specificity to detect progression of joint space narrowing by ≥ full grade cartilage worsening were 0.55 and 0.86, respectively, and by ≥ partial grade worsening were 0.66 and 0.81, respectively. Severe meniscal damage predicted both partial grade and ≥ full grade worsening of cartilage loss and worsening of BMLs in a comparable fashion (Table 1). Any varus malalignment predicted both within-grade and full grade worsening of BMLs in the medial compartment. Malalignment similarly predicted half (and full) grade WORMS medial cartilage loss. Results were comparable for valgus malalignment. Severe meniscal damage predicted within-grade and full grade worsening of cartilage and BMLs in a comparable fashion.

Table 1. Medical[1] mensical damage and its relation to cartilage loss and BML worsening in the medial tibio-femoral compartment

Meniscal damage (predictor) (max. score in medial compartment)	Cartilage loss in medical compartment (outcome)				[2]Adjusted OR (95% CI)	
	Total number of knees	Knees with no change (%)	Knees with half grade worsening only (%)	Knees with ≥ full grade worsening (%)	Outcome: half grade worsening vs. No change	Outcome: ≥ full grade worsening vs. No change
0	1224	1002 (81.9)	43 (3.5)	179 (14.6)	1.0	1.0
1	78	48 (61.6)	6 (7.7)	24 (30.8)	1.0 (0.3, 3.7)	1.8 (0.8, 3.9)
2	243	139 (57.2)	26 (10.7)	78 (32.1)	2.1 (0.9, 4.6)	2.1 (1.3, 3.5)
3 and 4	320	185 (57.8)	51 (15.9)	84 (26.3)	4.4 (2.2, 8.7)	1.3 (0.8, 2.2)
Meniscal damage (predictor) (max. score in medial compartment)	**BML worsening in medial compartment (outcome)**				**[2]Adjusted OR (95% CI)**	
	Total number of knees	Knees with no change (%)	Knees with half grade worsening only (%)	Knees with ≥ full grade worsening (%)	Outcome: half grade worsening vs. No change	Outcome: ≥ full grade worsening vs. No change
0	1225	1039 (84.8)	28 (2.3)	158 (12.9)	1.0	1.0
1	78	57 (73.1)	2 (2.6)	19 (24.4)	0.3 (0.03, 2.5)	0.9 (0.4, 2.0)
2	243	164 (67.5)	14 (5.8)	65 (26.8)	1.5 (0.5, 4.7)	1.2 (0.7, 2.0)
3 and 4	320	157 (49.1)	34 (10.6)	129 (40.3)	9.6 (3.6, 25.1)	5.1 (3.2, 8.2)

[1] Results for lateral compartment comparable and not shown
[2] Adjusting for age, sex, BMI

Conclusion: Recording of within-grade subregional changes between time points for WORMS cartilage scores increases sensitivity for the detection of X-ray defined wosening of joint space narrowing by only slightly decreasing specificity. Both, within-grade and full-grade or more cartilage and BML changes are predicted by baseline malalignment and meniscal damage. Scoring of partial grade changes increases number of compartments and subregions showing change and the association of partial grade changes with risk factors and outcomes suggests that they are clinically relevant.

2006

Similar Reliability of DESS and TSE Magnetic Resonance Imaging Sequences in the Assessment of Bone Marrow Lesions in Knee Osteoarthritis Patients: Data From the Osteoarthritis Initiative Cohort. Jean-Pierre Raynauld[1], Lukas M. Wildi[1], François Abram[2], Thomas Moser[3], Manon Girard[2], Johanne Martel-Pelletier[1] and Jean Pierre Pelletier[1]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [2]ArthroVision Inc., Montreal, QC, [3]Department of Radiology, University of Montreal Hospital Centre (CHUM), Notre-Dame Hospital, Montreal, QC

Background/Purpose: To assess bone marrow lesions (BML) in a head to head comparative study using a T2/T1-weighted steady-state gradient echo (DESS) and a fluid-sensitive intermediate-weighted turbo spin echo (TSE) sequence and the sensitivity to change over time of these sequences. Using a subset of the Osteoarthritis Initiative (OAI) cohort (public MR image sets), we assessed the BML prevalence, lesion size, and change over time comparing data from a TSE to a DESS magnetic resonance imaging (MRI) sequence.

Methods: A subgroup of 144 patients (mean age 61.3 ± 9.8, mean BMI 30.0 ± 4.3, 51.4% were female) was selected from the OAI cohort of progressors who all had DESS and TSE MRI acquisitions at baseline and 24 months. BML were assessed blindly using a semi-quantitative score (scale, 0–3) for the global knee, as well as the medial and lateral compartments. Intra-reader reliability was assessed on a subset of 51 patients. Statistical analysis used a Spearman rho for intra-reader correlation, and a Fisher exact test or Wilcoxon signed rank test for comparison between DESS and TSE where appropriate.

Results: Intra-reader reliability was very good: Spearman rho for DESS sequence were 0.89 for the global knee, 0.91 for the medial compartment, and 0.78 for the lateral compartment; for the TSE sequence, 0.85, 0.86, and 0.77 were found respectively. The prevalence (presence or absence) of BML at baseline was only slightly greater for TSE compared to DESS sequences and this difference did not reach statistical significance (global knee, 80.6% vs. 79.2%; medial compartment, 70.1% vs. 68.1%; lateral compartment, 53.5% vs. 48.6%, respectively; p=ns). As expected, the mean BML score at baseline was lower for DESS than TSE sequences (2.7 ± 2.4 vs. 3.4 ± 3.0 for the global knee respectively, 1.7 ± 1.9 vs. 2.2 ± 2.3 for the medial compartment, and 0.9 ± 1.2 vs. 1.2 ± 1.6 for the lateral compartment, all p≤0.006). However, change at 24 months was similar for DESS and TSE sequences for the global knee (increment of 1.1 ± 1.7 vs. 1.0 ± 2.2 respectively, p=0.18) and for the lateral compartment (0.5 ± 1.0 vs. 0.6 ± 1.5, p=0.33), but superior for DESS in the medial compartment (0.6 ± 1.5 vs. 0.4 ± 1.6, p=0.03).

Conclusion: This is the first report of a direct comparison between DESS and TSE MRI sequences in the assessment of BML and their changes over time. Contrary to common belief, these results demonstrate a similar sensitivity to assess BML prevalence as well as their changes over time in the global knee and lateral compartment, and a slightly superior evaluation of changes over time for the DESS in the medial compartment. These data show that the use of the DESS sequence may have an advantage in clinical trials since, in contrast to the TSE sequence, it could be used for both BML and cartilage volume assessments.

ACR/ARHP Poster Session C
Pediatric Rheumatology - Clinical and Therapeutic Aspects II: Pediatric Rheumatology Systemic Lupus Erythematosus, Juvenile Dermatomyositis, Vasculitis and Other
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

2007

The Childhood Myositis Assessment Scale (CMAS) Total Score in Healthy Children, Age 4–5 Years, is 46, Not 52. Rebecca Quinones[1], Gabrielle Morgan[1], Maria Amoruso[1], Deli Wang[2] and Lauren M. Pachman[3]. [1]Children's Memorial Hospital, Chicago, IL, [2]Northwestern University's Feinberg School of Medicine, Chicago, IL, [3]Northwestern University Feinberg School of Medicine, Chicago, IL

Background/Purpose: JDM is a systemic vasculopathy primarily affecting the neck flexors and proximal muscles of both the upper and lower extremities, as well as the child's core strength. Previous national epidemiology studies have documented that the mean age diagnosis is 6.7 years (boys, girls) but 25% are age 4 or less at the time of their first visit to the physician. We had observed that treated children with JDM who had achieved a disease activity score for muscle weakness of "0", still had an average CMAS score of 46, raising the question: "Could healthy children, age 4–5, ever achieve a CMAS score of 52?" Hypothesis: The "normal" total value for CMAS of 52 is not attainable by healthy children who are 4–5 years of age.

Methods: To evaluate healthy boy and girls, age 4.0–4.9 years of age, the validated CMAS 14 point scale was used. The CMAS was administered by the same evaluator, who had been trained in the CMAS administration. The study is descriptive and Spearman rank correlation coefficient was used for age comparisons and Mann-Whitney for comparisons of items by gender.

Results: The test population of 28 healthy children was recruited after obtaining IRB approved consent (IRB#2010–14188). The group was composed of 14 boys and 14 girls, age 4.0–4.9 years. Their mean age was 4.4 years +/−0.3 years. The racial composition was: 68% White/Hispanic, 32% non-White, non-Hispanic. As a group, they achieved a total mean CMAS score of 46.6 ± 2.3 SD. There were no significant differences between boys and girls, and their scores were unaffected by their height or weight. The greatest variation in the scores involved those that were effort dependent. Item 1, neck raise score yielded a mean of 28.12 seconds ± 19.17 SD, CMAS score=2.5 ± 0.9/5. For item 3, the leg lift score =55.27± 36.94 SD seconds; CMAS score=3.1, ± 1.1/5. Finally, item 8, arm raise score=57.73 ± 6.53 seconds, CMAS score3.8 ±0.4/4. The remainder of the CMAS items were very consistent between the boys and the girls.

Conclusion: Healthy children age 4–5 are not able to achieve a total CMAS of 52, expected of older children. In fact, children of this age, both boys and girls were remarkable consistent, both performing at a CMAS mean level of 46. These data suggest that young children with JDM, who are between 4–5 years of age and who reach a score of 46, are in fact performing in a normal fashion, and should not be considered to be impaired.

Supported solely by CureJM.

2008

The Pediatric Automated Neuropsychological Assessment Metrics Has Reproducibility and Criterion Validity in Childhood-Onset Lupus. Hermine Brunner[1], Aimee Baker[1], Adlin Cedeno[2], Jennifer L. Huggins[1], Anna Carmela P. Sagcal-Gironella[3], Jun Ying[4], Marisa Klein-Gitelman[2] and Tresa Roebuck-Spencer[5]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Children's Memorial Hospital, Chicago, IL, [3]Cincinnati Children's Hospital, Cincinnati, OH, [4]University of Cincinnati, Cincinnati, OH, [5]University of Oklahoma, Norman, OK

Background/Purpose: The Childhood-onset Systemic Lupus Erythematosus (cSLE) *Neuropsychological Battery* (AC&R 2010; 62: 1029–33) was introduced to standardize neuropsychological testing (NPT), specifically probing the domains *Attention, Working Memory, Psychomotor Speed, Visuoconstructural Ability (VCA)*. The Pediatric Automated Neuropsychological Assessment Metrics (Ped-ANAM) software was developed to measure cognition in children ≥ 10 years. Performance on the Ped-ANAM subtests is assessed by accuracy (AC = % of correct answers), mean reaction time for correct responses (MNc), & throughput (TP), the number of correct responses per minute. The *purpose of this study* was to (1) assess the reproducibility & (2) investigate the criterion validity of the Ped-ANAM, using the *cSLE Neuropsychological Battery* as external standard.

Methods: cSLE patients and best-friend controls underwent NPT and completed the Ped-ANAM twice in one day. Neurocognitive dysfunction (NCD) was graded as per the performance on standardized tests that are part of the NPT [no-NCD: all z-scores > −1; mild/moderate NCD: at most two z-scores < −1 but > −2 or one z-score < −2; severe: at least three z-scores < −1 or two z-scores < −2].

Results: Among 37 cSLE & 37 controls (87% females), 23 (39%) had NCD. Most subtests had good reproducibility especially for tests of higher cognitive complexity (Table 1). Deficits in *Working Memory* resulted in lower AC on the subtests CS, PRT, & Spatial (all $p < 0.05$). Deficits in *Psychomotor Speed* resulted in worse performance on CS-Delayed, CS, Logical, MG & Spatial (all $p < 0.03$). Deficits in *Attention* resulted in worse performance on all subtests but MG & PRT (all $p < 0.04$), and deficits in *VCA* resulted in worse performance on Logical, MS & Spatial (all $p < 0.02$). Compared to others, the severe NCD group showed lower AC on several subtests (Table 2) with corresponding faster reaction times indicative of inefficient responding. In contrast, the severe NCD group was significantly slower on tests of simple reaction time (SRT1, SRT2) that did not require cognitive demands.

Table 1. Test-Retest reliability of the Ped-ANAM using TP as an example*

Ped-ANAM subtests	Cognitive Domain/ Function	All (n = 74)	Control (n = 37)	SLE (n = 37)	SLE without NCD (n = 28)	SLE with NCD (n = 9)
Code substitution delayed (CS delayed)	Delayed Memory	0.39 (0.22, 0.56)	0.40 (0.16, 0.65)	0.40 (0.17, 0.64)	0.59 (0.37, 0.81)	0.00 (0.00, 0.00)
Running Memory Continuous Performance Test (CPT)	Working Memory	0.82 (0.75, 0.89)	0.83 (0.72, 0.93)	0.82 (0.71, 0.92)	0.84 (0.74, 0.95)	0.66 (0.29, 1.00)
Mathematical Processing (Math)	Working Memory	0.83 (0.77, 0.90)	0.85 (0.76, 0.94)	0.82 (0.72, 0.92)	0.84 (0.73, 0.94)	0.76 (0.49, 1.00)
Memory Search (Memory)	Working Memory	0.65 (0.53, 0.78)	0.73 (0.59, 0.88)	0.62 (0.44, 0.81)	0.65 (0.45, 0.85)	0.50 (0.03, 0.97)
Matching to Sample (MS)	Spatial Working Memory	0.60 (0.47, 0.74)	0.67 (0.50, 0.84)	0.55 (0.34, 0.76)	0.51 (0.26, 0.76)	0.75 (0.43, 1.00)
Matching Grids (MG)	Spatial Processing	0.64 (0.51, 0.77)	0.81 (0.70, 0.92)	0.54 (0.33, 0.75)	0.52 (0.27, 0.76)	0.69 (0.33, 1.00)
Spatial Processing (Spatial)	Spatial Processing)	0.71 (0.60, 0.82)	0.58 (0.38, 0.78)	0.85 (0.75, 0.94)	0.84 (0.74, 0.95)	0.85 (0.65, 1.00)
Code substitution (CS)	Associative Learning	0.82 (0.75, 0.89)	0.75 (0.61, 0.89)	0.88 (0.81, 0.95)	0.92 (0.86, 0.98)	0.71 (0.38, 1.00)
Logical Relations (Logical)	Reasoning and verbal syntax	0.86 (0.80, 0.92)	0.82 (0.71, 0.92)	0.89 (0.82, 0.96)	0.93 (0.89, 0.98)	0.60 (0.19, 1.00)
Procedural Reaction Time (PRT)	Processing Speed (choice RT/rule adherence)	0.64 (0.52, 0.77)	0.50 (0.28, 0.72)	0.76 (0.62, 0.89)	0.77 (0.63, 0.91)	0.68 (0.30, 1.00)
Simple reaction time, 1st trial (SRT1)	Basic neural processing (speed/ efficiency)	0.48 (0.32, 0.65)	0.48 (0.25, 0.72)	0.52 (0.30, 0.73)	0.52 (0.28, 0.76)	0.45 (0.00, 1.00)

Table 2. Relationship between Ped-ANAM performance & level of NCD*

Ped-ANAM Parameter	Ped-ANAM Subtest	(A) No NCD	(B) Mild/ Moderate NCD	(C) Severe NCD	P-value (A) vs (C)	(B) vs (C)
	Number of subjects	45	16	7	–	–
Accuracy (AC) [i.e., % of correct answers]	Code substitution delayed (CS delayed)	80.23 ± 1.81	78.04 ± 2.53	68.64 ± 5.44	0.047	0.122
	Code substitution (CS)	96.05 ± 0.48	96.31 ± 0.68	92.28 ± 1.45	0.016	0.014
	Running Memory Continuous Perfor. Test (CPT)	54.29 ± 2.89	77.76 ± 4.13	60.33 ± 8.66	0.011	0.074
	Logical Relations (Logical)	95.44 ± 0.82	95.84 ± 1.14	39.74 ± 2.45	0.031	0.027
	Matching to Sample (MS)	85.50 ± 2.35	81.00 ± 3.29	62.66 ± 7.06	0.003	0.021
	Matching Grids (MG)	92.50 ± 1.27	93.04 ± 1.78	91.00 ± 3.82	0.711	0.629
	Mathematical Processing (Math)	90.00 ± 0.85	90.00 ± 1.19	89.00 ± 2.55	0.711	0.724
	Procedural Reaction Time (PRT)	95.89 ± 0.77	94.18 ± 1.08	95.00 ± 2.32	0.717	0.748
	Spatial Processing (Spatial)	91.50 ± 0.91	90.76 ± 1.28	83.11 ± 2.74	0.005	0.014
	Memory Search (Memory)	92.00 ± 1.24	91.07 ± 1.73	87.33 ± 3.72	0.237	0.364
	Simple reaction time, 1st trial (SRT1)	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	–	–
	Simple reaction time, 2nd (SRT2)	99.94 ± 0.07	99.89 ± 0.09	100.00 ± 0.20	0.772	0.608
Mnc [i.e., mean reaction time for correct response]	Code substitution delayed (CS delayed)	1.20 ± 0.06	1.27 ± 0.08	0.77 ± 0.17	0.015	0.008
	Code substitution (CS)	1.13 ± 0.05	1.22 ± 0.06	1.01 ± 0.14	0.415	0.155
	Running Memory Continuous Perfor. Test (CPT)	0.59 ± 0.02	0.63 ± 0.03	0.54 ± 0.06	0.478	0.193
	Logical Relations (Logical)	1.54 ± 0.08	1.72 ± 0.11	1.48 ± 0.24	0.813	0.356
	Matching to Sample (MS)	2.06 ± 0.09	2.51 ± 0.12	1.85 ± 0.26	0.440	0.024
	Matching Grids (MG)	1.71 ± 0.08	2.10 ± 0.11	1.83 ± 0.24	0.615	0.310
	Mathematical Processing (Math)	1.55 ± 0.10	1.70 ± 0.14	1.88 ± 0.30	0.307	0.594
	Procedural Reaction Time (PRT)	0.59 ± 0.02	0.61 ± 0.02	0.56 ± 0.05	0.501	0.347

Conclusion: The Ped-ANAM has good reproducibility and criterion validity. Severe NCD is associated with significant differences in the performance of several Ped-ANAM subtests with a propensity for lower accuracy as tests increased in cognitive complexity. These results are in line with our earlier research.

2009

Therapeutic Approaches for the Treatment of New Onset and Flared Juvenile Systemic Lupus Erythematosus with Active Renal Disease: An International Multicenter PRINTO Study. Paivi Miettunen, Angela Pistorio, Angelo Ravelli, Sheila Oliveira, Maria Alessio, Ruben Cuttica, Dimitrina Mihaylova, Graciela Espada, Srdjan Pasic, Elisabetta Cortis, Seza Ozen, Oscar Porras, Flavio Sztajnbok, Alberto Martini and Nicolino Ruperto. IRCCS G. Gaslini, Pediatria II, PRINTO, Paediatric Rheumatology, Genova, Italy

Background/Purpose: To evaluate in a prospective international cohort of juvenile systemic lupus erythematosus (JSLE) with active renal disease (ARD) response to therapy over a 24-month period.

Methods: ARD was present in 240 (78.3% female) out of 557 patients with JSLE, age < 18 years (yr): 134 new onset JSLE (N-JSLE) and 106 flared JSLE (F-JSLE). Disease activity parameters and therapeutic approaches were analyzed at baseline, 6, 12 and 24 months, in 4 geographic areas. Response was assessed according to the PRINTO/ACR JSLE criteria, serum creatinine and glomerular filtration rate (GFR). Logistic regression was used to identify potential prognostic indicators at baseline for poor renal outcome at 24 months, defined as end stage renal disease (ESRD) or urinary protein >=3.5 grams/24 hours.

Results: The mean age at disease onset was 13.1 (SD 2.8) yr for N-JSLE and 10.2 (SD 2.9) yr for F-JSLE, with mean disease duration of 0.3 (SD 0.2) yr for N-JSLE and 4.2 (SD 2.9) yr for F-JSLE. A total of 143/240 (59.6%) patients had all 4 time point assessments available. At baseline, new and flared patients had similar renal activity, but N-JSLE had higher SLE activity overall, with more serositis, hematological, mucocutaneous and musculoskeletal manifestations. Corticosteroids were initiated at similar median doses: 1.0 mg/kg/day in N-JSLE and 0.8 mg/kg/day in F-JSLE. Pulse steroids were initiated in 33.6% of N-JSLE and 40.6% of F-JSLE. Cyclophosphamide was the most common (41.2%; 99/240) immunosuppressive medication, followed by azathioprine (25%; 60/240).Mycophenolate mofetil and azathioprine were used more commonly in F-JSLE. Latin American patients received more pulses and higher doses of oral steroids when compared to Western Europe. Use of cyclophosphamide was similar in all 4 regions. Seventy eight % (103/132) of N-JSLE compared to 57.4% (58/101) of F-JSLE (p=0.0007) reached at least PRINTO/ACR 70 level of response at 6 months, which increased to 87.1% in N-JSLE and 77.2% in F-JSLE at 24 months (p=0.12). The median serum creatinine and GFR were within normal range at all time points; all other measures showed statistically significant improvement over time in both groups (p <=0.0002). ESRD developed in 6 patients. Urinary protein >=3.5grams/24 hours was present in 50/240 patients at baseline and in 7/143 patients at 24 months. No predictors for poor renal outcome were identified. Twelve patients (5%) died, 10/12 before 12 months, and 7/12 of sepsis. Corticosteroids were discontinued in 20/143 by 24 months.

Conclusion: Despite higher overall lupus activity at baseline, N-JSLE and F-JLSE improved similarly over 24 months. ESRD was rare. Some differences in therapeutic approaches exist worldwide.

2010

Race, Ethnicity and Gender Affect the Severity of Renal Outcomes in Patients with Pediatric Systemic Lupus Erythematosus: An Analysis of the CARRAnet Data At Baseline Visit. Ornella J. Rullo[1], Deborah K. McCurdy[1], Ora Yadin[1], Alice DC Hoftman[1], Jennifer M.P. Woo[1], Emily von Scheven[2] and CARRAnet Investigators[3]. [1]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [2]UC San Francisco, San Francisco, CA, [3]Durham

Background/Purpose: The onset of SLE in adolescence has been associated with increased organ damage compared with adult-onset SLE. However, differences between ethnic and racial groups in young SLE patients have not been fully described. We hypothesize that U.S. pediatric SLE (pSLE; diagnosis < 18 years) patients of not uniquely European descent have more severe renal outomes compared to patients of European descent, independent of socio-economic factors.

Methods: CARRAnet registry data of pSLE patients including demographic, socio-economic status and renal biopsy data were correlated with each other and with renal outcome: chronic kidney disease (CKD stages I-V; Kendall correlation). The stages of CKD reflect functional chronic kidney damage with assessment of glomerular filtration rate [GFR; determined by MDRD or Schwartz (for age < 12 years) formulas]. The independent effect of each relevant factor on renal outcome in pSLE with biopsy-proven lupus nephritis (LN) was calculated with use of multiple regression models.

Results: Of 368 pSLE patients enrolled in CARRAnet with baseline demographic and clinical data, 159 patients have undergone renal biopsy (Table 1). In combined non-white and Hispanic pSLE LN, there is an enrichment of CKD (p = 0.003; Table 1) and a trend towards end-stage renal disease (ESRD, 5% vs 0%, p = 0.06; Table 1). Non-white/Hispanic and male gender were independently associated with CKD (OR 1.21 and 1.26, respectively, p < 0.05; Table 2) by multivariate logistic regression of subjects with biopsy-proven LN. Although non-white/Hispanic and white (excluding white Hispanics) pSLE differed in multiple socio-economic parameters including median household income and percentage of families below poverty line at diagnosis (both based on 1999 U.S. Census data using 3-digit zip code at diagnosis), and current reported income (p < 0.01), there was no correlation between these parameters and GFR (p > 0.1). Furthermore, there may be a negative correlation between renal biopsy and time to rheumatologic care in both white and non-white pSLE (Spearman r = −0.1; p = 0.07).

Table 1. Clinical and demographic features of the CARRAnet SLE registry

	White	Non-white†	p-value*
Female:Male	301:67		
White:Non-white†	97:269		
Disease duration at baseline visit, mean (years)**	3.2	3.6	0.5
SLE renal involvement, total number‡	33	126	
Prevalence of renal involvement, %	34	47	0.08
SLEDAI at baseline visit, median	2	4	0.02
SLEDAI-renal component scored at baseline visit, %	12	21	0.047
Prevalence of moderate/severe chronic kidney disease, %††	0	9	0.003
Prevalence of end-stage renal disease‡‡	0	5	

† Non-white is defined as people who self-identified as not uniquely of white race, including: Americans of Asian, native American, African and/or Hawaiian/Pacific Islander descent; and/or of Hispanic ethnicity
** Increased disease duration is correlated with increased rates of CKD (r = 0.2; p = 0.002); however there is no difference among these comparator groups in disease duration
‡ Chronic Kidney Disease Stages I–V, and with biopsy-proven renal disease
†† GFR < 60 ml/min/1.73 m2; CKD Stage II–V
‡‡ Dialysis or renal transplant endorsed in registry; CKD Stage V
* Calculated using Fisher's exact test, except disease duration (t-test) and median SLEDAI at baseline (Mann-Whitney test)

Table 2. Factors independently associated with CKD by multivariable logistic regression in patients with SLE renal disease from the CARRAnet registry

	OR	(95% CI)	p value
Age at baseline CARRAnet visit	0.99	(0.97, 1.03)	0.9
Male gender	1.26	(1.04, 1.53)	0.019*
Time since diagnosis	1.09	(0.98, 1.2)	0.105
Community poverty rate at diagnosis†	0.99	(0.99, 1.01)	0.3
Non-white race/Hispanic ethnicity‡	1.21	(1.02, 1.43)	0.023*
Time to first pediatric rheumatology visit††	0.97	(0.94, 1.01)	0.074
Current family income	0.99	(0.95, 1.04)	0.6

† Percentage of families below poverty level in the subject's zip code area at the time of diagnosis, based on 1999 U. S. Census data
‡ Subjects self-identifying as non-white and/or not uniquely of white race plus subjects of Hispanic ethnicity
†† From the onset of symptoms
* denotes p value < 0.05

Conclusion: The risk of CKD or ESRD in patients with pediatric-onset SLE renal disease is increased based on non-white race and/or Hispanic ethnicity (OR 1.21) and male gender (OR 1.26), independent of demographic and socio-economic factors. The trend towards shorter time to pediatric rheumatology care in patients of all groups requiring renal biopsy suggests adequate access to health care. Long-term follow-up data will be required to fully assess the impact of specific race/ethnicity and socio-economic factors on renal outcome.

2011

Behavior, Executive and Perceived Neuropsychological Functioning with Childhood-Onset Systemic Lupus Erythematosus—Results of a Best-Friend Controlled Study. Adlin Cedeno[1], Aimee Baker[2], Marisa Klein-Gitelman[1], Anna Carmela P. Sagcal-Gironella[2], April German[2], Cynthia Scharf[2], Jun Ying[3], Hermine Brunner[2], Dean Beebe[2] and Frank Zelko[1]. [1]Children's Memorial Hospital, Chicago, IL, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]University of Cincinnati, Cincinnati, OH

Background/Purpose: Childhood-onset Systemic Lupus Erythematosus (cSLE) is a phenotypically diverse disease with the potential for adverse neuropsychological (NP) effects due to chronic disease or central nervous system involvement. Best-friend controlled studies are one effective approach to delineate the impact of disease upon cognition. The BRIEF (Behavior Rating Inventory of Executive Function), CBCL (Child Behavior Checklist-Parent Report), CDI (Child Depression Inventory), and SAND-C (Subjective Awareness of Neuropsychological Deficits Questionnaire for Children) are validated questionnaires which assess various aspects of NP and behavioral functioning.

Methods: For cSLE patients & same-sex, similar-aged best-friend controls completed the CDI, SAND-C, BRIEF & CBCL. To diagnose neurocognitive dysfunction (NCD), neuropsychological testing (NPT) was performed, using a standardized cSLE NP Battery as previously published by our group (Arthritis Care Res. 2010; 62:1029–33).

Results: This interim analysis included 37 cSLE patients and 37 controls (87% females). Mild, moderate or severe NCD was present in 14%, 14% or 11% of cSLE patients and in 30%, 5% or 5% of controls. As summarized in Table 1, ratings of executive functioning (BRIEF) in the cSLE and control groups were comparable but school functioning (CBCL) was rated more poorly with cSLE. Table 2 provides a comparison among cSLE patients with consideration of their NCD-status. The presence of NCD had little impact on the NP and behavioral functioning of children and adolescents with SLE, with the exception of self-esteem which was rated as more problematic in the NCD cSLE group. Perceived neurocognitive functioning (SAND-C) was similar in the cSLE and control groups, irrespective of NCD-status.

Table 1. cSLE versus Best-Friend Controls adjusted for race, ethnicity and income

Features/Questionnaires		A. All cSLE*	B. Best-friend Controls	P-values (A vs. B)
Demographics	White: Non-White/% Hispanics	30%/14%	32%/18%	–
	Age in years	14.92 ± 0.37	14.71 ± 0.44	–
	Family income in USD	57,932 ± 6,806	56,929 ± 6,213	–
BRIEF–Executive Functioning†	1. Behavioral Regulation Index	46.1 ± 1.22	47.8 ± 1.24	0.312
	2. Metacognition Index	49.0 ± 1.48	48.3 ± 1.50	0.869
	3. Global Executive Composite Scale	47.7 ± 1.32	47.8 ± 1.34	0.854
	Total Clinical Scale Score (1–3)	***47.6 ± 1.34***	***48.0 ± 1.36***	***0.735***
CBCL–Behavior‡	a. Total Activities Score	44.1 ± 1.83	45.2 ± 1.88	0.651
	b. Total Social Scale Score	49.4 ± 1.54	49.1 ± 1.56	0.990
	c. Total School Scale Score	**48.2 ± 1.26**	**51.8 ± 1.29**	**0.008**
	Total Competency Score (a –c)	***45.6 ± 1.99***	***47.9 ± 2.05***	***0.214***
	1. Externalizing Problems	***46.7 ± 1.32***	***47.8 ± 1.34***	***0.536***
	2. Internalizing Problems	***53.6 ± 1.49***	***49.3 ± 1.51***	***0.024***
	Total Problem Score	***49.1 ± 1.49***	***47.3 ± 1.51***	***0.271***
CDI–Depressionμ	A. Negative Mood	47.0 ± 1.29	47.0 ± 1.29	0.627
	B. Interpersonal Problems	47.3 ± 1.25	47.3 ± 1.25	0.765
	C. Anhedonia	46.9 ± 1.48	47.5 ± 1.48	0.964
	D. Ineffectiveness	44.6 ± 1.31	47.1 ± 1.31	0.248
	E. Negative Self-esteem	42.8 ± 0.78	41.5 ± 0.78	0.172
	Total Depression Score (A–E)	44.3 ± 1.31	44.7 ± 1.31	0.915
SAND-C- Perceived Cognitive Function*		2.89 ± 0.06	2.97 ± 0.06	0.152

* Values are (mean ± SEM, unless indicate differently
† Higher scores signify better functioning, T-Scores with a mean of 50 and SD of 10 (here: SEM of 1.64)
‡ Higher scores signify better/ worse performance; T-Scores with a mean of 50 and SD of 10 (here: SEM of 1.64)
μ Higher scores signify higher depressive features
** Higher scores signify better cognitive function; healthy children mean ±SEM: 2.91 ± 0.08

Table 2. cSLE without versus with Neurocognitive Dysfunction (NCD) adjusted for race/ethnicity and income

Features/Questionnaires		A. cSLE without NCD	B. cSLE with NCD	P-values (A vs. B)
	N	28	9	–
Disease features	Disease activity	3.82 ± 0.78	8.33 ± 1.38	0.0001
	Disease damage*	0.39 ± 0.16	0.43 ± 0.14	0.972
	1. Behavioral Regulation Index	46.3 ± 1.39	45.4 ± 2.64	0.440
	2. Metacognition Index	48.8 ± 1.68	50.0 ± 3.19	0.780
BRIEF–Executive Functioning†	3. Global Executive Composite Scale	47.6 ± 1.50	48.0 ± 2.86	0.934
	Total Clinical Scale Score (1–3)	47.6 ± 1.41	47.8 ± 2.69	0.862
	a. Total Activities Score	43.0 ± 2.06	48.4 ± 3.92	0.089
	b. Total Social Scale Score	50.6 ± 1.72	44.8 ± 3.28	0.364
	c. Total School Scale Score	49.2 ± 1.41	44.5 ± 2.69	0.290
CBCL–Behavior‡	***Total Competency Score (a–c)***	46.2 ± 2.25	43.4 ± 4.29	0.838
	Externalizing Problems	53.7 ± 1.72	53.3 ± 3.03	0.921
	Internalizing Problems	46.8 ± 1.53	46.4 ± 2.70	0.904
	Total Problem Score	49.3 ± 1.69	48.3 ± 3.22	0.347
	A. Negative Mood	46.28 ± 1.46	49.75 ± 2.77	0.626
	B. Interpersonal Problems	47.28 ± 1.42	47.50 ± 2.71	0.714
CDI–Depressionμ	C. Anhedonia	46.10 ± 1.67	49.88 ± 3.17	0.642
	D. Ineffectiveness	43.66 ± 1.47	48.00 ± 2.81	0.298
	E. Negative Self-esteem	**41.86 ± 0.85**	**46.13 ± 1.62**	**0.028**
	Total Depression Score (A–E)	43.31 ± 1.46	48.00 ± 2.78	0.358
SAND-C - Perceived Cognitive Function*		2.95 ± 0.065	2.71 ± 0.12	0.169

* None of the patients had neuropsychiatric damage
† Higher scores signify better functioning, T-Scores with a mean of 50 and SD of 10 (here: SEM of 1.64)
‡ Higher scores signify better/ worse performance; T-Scores with a mean of 50 and SD of 10 (here: SEM of 1.64)
μ Higher scores signify higher depressive features
** Higher scores signify better cognitive function; healthy children mean ±SEM: 2.91 ± 0.08

Conclusion: Compared to controls, school functioning seems to be worse with cSLE but the disease has comparatively little systematic effect on reported executive or behavioral functioning. If NCD is present, cSLE patients may have more negative self-esteem. Confirmation of these results in a larger cohort is necessary to substantiate these preliminary observations.

2012

The PRINTO Provisional Definition of REMISSION In Juvenile Dermatomyositis. Dragana Lazarevic[1], Angela Pistorio[1], Paivi Miettunen[1], Angelo Ravelli[1], Clara Malattia[1], Clarissa Pilkington[1], Nico Wulffraat[1], Stella Maris Garay[1], Michael Hofer[1], Pierre Quartier[1], Pavla Dolezalova[1], Inmaculada Calvo Penades[1], Virginia P.L. Ferriani[1], Gerd Ganser[2], Ozgur Kasapcopur[1], Jose Antonio Melo-Gomes[1], Malgorzata Wierzbowska[1], Alberto Martini[1] and Nicolino Ruperto[1]. [1]IRCCS G. Gaslini, Pediatria II, PRINTO, Paediatric Rheumatology, Genova, Italy, [2]Sankt Josef Stift, Sendenhorst, Germany

Background/Purpose: To define a definition of remission in juvenile dermatomyositis (JDM) that is stringent but achievable and could be applied uniformly as an outcome measure in clinical trials.

Methods: 275 patients in active phase of JDM <18 years, median disease duration 7.7 months, were evaluated at baseline and 24 months. Out of 275 patients, all patients (38/275) who were off treatment at 24 months were defined as being "inactive" and were included as the "gold standard" group. A random sample of 76 patients who were in an active phase of JDM at baseline and on medications at 24 months, were selected as the "comparison group". Literature was reviewed for definitions of remission and then other definitions were tested which included PRINTO core set variables, muscle enzymes, and other JDM activity measures. Accuracy measurements were calculated: sensitivity (Se), specificity (Sp), Cohen's kappa (k≥0.8 almost perfect).

Results: Seven best single variables with kappa≥0.8 were Manual Muscle Testing (MMT)=80 (se:0.89, sp:1.00, k:0.92), followed by MMT≥78 (se:0.94, sp:0.97, k:0.92), Physician Global Assessment of Muscle Activity (PhyMAVAS)=0 and Physician Myositis Activity Assessment (MYOACT)≤0.2, Physician Global Visual Analogue Scale (PhyGloVAS)≤0.2, Childhood Myositis Assessment Scale (CMAS)≥48, and Disease Activity Score (DAS)≤3. The most accurate combination of variables included 4 variables with 3 out of 4 required to be present: creatine phosphokinase≤150, CMAS≥48, MMT≥78, PhyGloVAS≤0.2 (se:0.97, sp:1.00, k:0.98).

Conclusion: The combination definition performed the best overall in defining inactive disease/remission in JDM and could be used for the evaluation of global response to therapy in future clinical trials.

2013

Determination of Pediatric Doses of Colchicine for Familial Mediterranean Fever on the Basis of Population Pharmacokinetics. Yackov Berkun[1], Eldad Ben-Chetrit[1], Suman Wason[2], Robert Faulkner[2] and Stephen Levenstein[3]. [1]Hadassah Hebrew University Medical Center, Jerusalem, Israel, [2]URL Pharma, Philadelphia, PA, [3]GCP Clinical Studies Ltd., Rosh Ha'Ayin, Israel

Background/Purpose: Define appropriate dose of colchicine (COL) in children age 2–4 yrs with familial Mediterranean fever (FMF), this study sought to determine steady-state pharmacokinetics of multiple doses of oral COL in pediatric FMF patients ages 2 to <16 yrs compared to adult FMF patients 16 to 65 yrs. Optimal starting doses of COL in pediatric FMF patients were determined.

Methods: Outpatients were given a new oral pediatric formulation of Colchicine, USP (Pediatric Granules, 0.3 mg) in 3 phases: 7-day up-titration phase (if required), fixed-dose 14-day phase culminating in pharmacokinetic (PK) blood sample on Days 14 and 15 (PK period); and flexible-dose phase for safety assessment (90-day total treatment duration, exclusive of up-titration). Approximately 10 male and female FMF patients in each age group were targeted for enrollment. Sample size was determined from population PK analysis of COL plasma data obtained from Phase 1 studies in healthy adults administered multiple oral doses of COL.

Colchicine Pediatric Granules Dosing

Age Group	Daily Dose	% of Referenced Daily Dose
≥2 – <4 years old	0.6 mg	50%
≥4 – <6 years old	0.9 mg	75%
≥6 – <12 years old	0.9 mg	75%
≥12 – <16 years old	1.2 mg	100%
Adults ≥16 to ≤65 years	1.2 mg	Reference

COL-naïve patients were to have a 1-wk dose up-titration period prior to attaining full target dose. After the PK period, the daily dose could be adjusted as needed for the balance of the study.

Blood was collected on Days 14 and 15 with plasma analyzed for COL. Sampling time windows for collection of PK samples were 0.25–0.5 hrs, 1.5–2.5 hrs, 3–5 hrs, 7–9 hrs, and 24 hrs post-Day 14 dose. Population PK modeling to a 3-compartment model with zero-order absorption was performed on COL plasma data to derive individual patient PK parameters.

Descriptive Statistics of C_{max} and AUC by Age Group

ONCE-DAILY DOSING

		Age Group				
		2–<4 yrs	4–<6 yrs	6–<12 yrs	12–<16 yrs	≥ 16 yrs
N		5	4	11	8	6
C_{max} (ng/mL)	Mean (SD)	8.6 (2.24)	11.2 (3.17)	7.9 (2.46)	6.9 (2.39)	7.2 (2.10)
	Range	6.7–12.5	8.4–15.6	5.2–12.1	3.8–11.0	4.9–9.6
AUC_{0-24} (ng·h/mL)	Mean(SD)	38.6 (7.40)	57.3 (21.3)	41.1 (12.38)	41.3 (8.68)	50.7 (18.55)
	Range	27.1–46.0	38.4–87.9	28.4–62.1	31.4–55.3	35.5–78.3

TWICE-DAILY DOSING

		Age Group				
		2–<4 yrs	4–<6 yrs	6–<12 yrs	12–<16 yrs	≥ 16 yrs
N		2	1	4	0	2
C_{max} (ng/mL)	Mean(SD)	–	–	9.6 (4.1)	–	3.1 (0.9)
	Range	6.1, 7.6	8.1	6.4–15.6	–	2.2–4.7
AUC_{0-24} (ng·h/mL)	Mean(SD)	–	–	55.2 (33.71)	–	42.7 (12.2)
	Range	33.1, 42.2	63.7	30.1–104.8	–	31.4–73.3

Results: The most common adverse event (AE) was breakthrough attacks of FMF (n=17) with no apparent trend by age. Consistent with the known COL safety profile, the most common AEs were GI disorders (abdominal pain, diarrhea, vomiting) which were mild and resolved with the majority untreated.

Conclusion: COL was safe when given as an age-appropriate dosage form in recommended doses and the safety profile in children 2 yrs of age is comparable to that seen in older children and adults. Results showed similar C_{max} (rate of absorption) and AUC (exposure) seen across the 2-<4, 6-<12, 12-<16 yr and adult age groups indicating that administration of half of the adult daily dose in children aged 2-<4 yrs, three-quarters of the adult daily dose in children aged 6-<12 yrs, and full adult dose in those aged 12-<16 yrs are most appropriate starting daily doses.

In the 4-<6 yr old group, the administered dose, which was three-quarters of the adult daily dose, provided exposures 30% higher than adults. The starting dose of COL in this age group should be reduced to half the adult dose (0.6 mg/day).

2014

Performance of the Systemic Lupus Erythematosus Responder Index in Juvenile Systemic Lupus Erythematosus. Rina Mina[1], Marisa Klein-Gitelman[2], Shannen L. Nelson[3], B. Anne Eberhard[4], Gloria C. Higgins[5], Nora G. Singer[6], Deborah M. Levy[7], Karen Onel[8], Judyann C. Olson[9], Joshua D. Pendl[10], Aimee Baker[10], Lisa F. Imundo[11], Lori B. Tucker[12], Laura E. Schanberg[13], Marilynn G. Punaro[14], Kathleen M. O'Neil[15], Nicolino Ruperto[16], Daniel J. Lovell[10] and Hermine Brunner[10]. [1]Cincinnati Children's Med Ctr, Cincinnati, OH, [2]Children's Memorial Hospital, Chicago, IL, [3]Cincinnati Children's Hospital, Cincinnati, OH, [4]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [5]Nationwide Childrens Hosp, Columbus, OH, [6]MetroHealth Medical Center, Cleveland, OH, [7]The Hospital for Sick Children, Toronto, ON, [8]University of Chicago, Chicago, IL, [9]Medical College of Wisconsin, Milwaukee, WI, [10]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [11]Childrens Hospital of New York, New York, NY, [12]BC Childrens Hospital, Vancouver, BC, [13]Duke University Medical Center, Durham, NC, [14]Texas Scottish Rite Hospital, Dallas, TX, [15]Okla Univ Health Science Ctr, Oklahoma City, OK, [16]PRINTO-IRCCS, Genova, Italy

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a heterogeneous disease where changes in many organ systems must be concomitantly considered when assessing the overall disease course. In a recent RCT, the SLE Responder Index (SRI) proved to be a robust measure of improvement in adults with SLE; the SRI has yet to be evaluated in juvenile SLE (jSLE). The purpose of this study is to determine the concurrent validity of the SRI in assessing improvement in jSLE.

Methods: The SRI defines response (improvement) in SLE as the presence of all of the following: 1) ≥ 4-point reduction in SLEDAI score; 2) no new BILAG A or no more than 1 new BILAG B domain score; and 3) no worsening in the physician assessment of global disease activity (PGA) by ≥ 0.3 points in the 3-point PGA. Using prospectively collected data from 1443 unique visits of 331 jSLE patients, concurrent validation of the SRI was done by comparison with three external standards [i.e. physician assessment of overall disease activity (MD Likert scale: major improvement vs. not), patient/parent assessment of overall well-being (Parent Likert scale: much improved vs. not), and change in systemic steroid dose (decreased vs. not). Modified versions of the SRI using worsening of 1 cm and 2 cm in the 10 cm-PGA visual analog score, and ≥ 2-point reduction in the SLEDAI were evaluated as well. Agreement of the SRI with the ACR/PRINTO Provisional Criteria for Improvement of jSLE (PCI_{SLE}) was examined using Kappa statistic.

Results: Using chi-square statistics, the SRI has a sensitivity of 51% and specificity of 95% in determining the presence of major improvement using the MD Likert scale as external standard. The sensitivity of the SRI was lower when considering the Parent Likert scale or the change in systemic steroids as external standards. The modified versions of the SRI and the PCI_{SLE} had similar sensitivities and specificities as the SRI *(see Table 1)*. Agreement between the SRI and PCI_{SLE} was fair *(see Table 2)*.

Table 1. Performance of the SLE Responder Index (SRI) in assessing improvement in jSLE

Response Criteria	Physician Assessment of Overall Disease Activity Major Improvement vs. No Major Improvement	Patient Assessment of Overall Well-being Much Improved vs. Not Much Improved	Change in Systemic Steroids¶¶ Decreased vs. Not Decreased
SRI: Responder vs. Non-Responder	p-value < 0.0001¶	p-value = 0.0001	p-value = 0.05
Total number of Responders	110	110	111
Total number of Events±	72	266	826
Sensitivity	51%	12%	9%
Specificity	95%	93%	94%
Positive Predictive Value	34%	29%	66%
Negative Predictive Value	97%	82%	44%
Modified SRI_{PGA1}‡: Responder vs. Non-Responder	p-value < 0.0001	p-value < 0.0001	p-value = 0.64
Total Number of Responders	124	123	125
Total Number of Events	71	265	822
Sensitivity	52%	14%	9%
Specificity	94%	92%	92%
Positive Predictive Value	30%	29%	59%
Negative Predictive Value	97%	82%	43%
Modified SRI_{PGA2}∫: Responder vs. Non-Responder	p-value < 0.0001	p-value < 0.0001	p-value = 0.13
Total Number of Responders	85	85	86
Total Number of Events	71	265	822
Sensitivity	48%	11%	7%
Specificity	96%	95%	95%
Positive Predictive Value	40%	35%	65%
Negative Predictive Value	97%	82%	43%
Modified SRI_{MCID}∫∫: Responder vs. Non-Responder	p-value < 0.0001	p-value = 0.01	p-value = 0.64
Total Number of Responders	331	328	332
Total Number of Events	71	265	822
Sensitivity	66%	29%	23%
Specificity	79%	78%	78%
Positive Predictive Value	14%	23%	58%
Negative Predictive Value	98%	82%	43%
$PCI_{SLE}\mu$: Responder vs. Non-Responder	p-value < 0.0001	p-value < 0.0001	p-value = 0.76
Total Number of Responders	82	83	83
Total Number of Events	46	225	744
Sensitivity	37%	14%	7%
Specificity	95%	95%	94%
Positive Predictive Value	21%	37%	59%
Negative Predictive Value	98%	84%	43%

¶ p-values are for association of responder/non-responder vs. major improvement (improved)/not major improved (not improved) under consideration of the external standards and definitions of SRI used
¶¶ Change in systemic steroids—Improved is defined as any decrease in oral steroids and cessation of intravenous pulse steroids
‡ Event defined as major improvement in MD Likert scale, much improved in Parent Likert scale, and decreased systemic steroids
± SRI_{PGA1}—Modified SRI where PGA-10 cm VAS (i.e. no worsening by 1 cm) instead of the PGA-3 point VAS is used as a part of the response criteria
∫ SRI_{PGA2}—Modified SRI where PGA-10 cm VAS (i.e. no worsening by 2 cm) instead of the PGA-3 point VAS is used as a part of the response criteria
∫∫ SRI_{MCID}—Modified SRI where Responder is defined by improvement of the SLEDAI by 2 points, no worsening of the PGA-10 cm VAS by 1 cm, and no new BILAG A or no more than 1 new BILAG B
μ PCI—Responder is defined as improvement of at least 2 of the core response variables (CRV) by ≥ 50%, with worsening by >30% in no more than 1 one of the remaining CRV (CRV: PGA-10 cm VAS, parent-global, validated disease activity score, proteinuria, Child Health Questionnaire-Physical Summary Score)

Table 2. Agreement of SLE Responder Index (SRI) with modified versions SRI and PRINTO/ACR provisional criteria for improvement in jSLE¶

Responder Tool	Kappa coefficient (95% Confidence Interval)			
	SRI	SRI_{PGA1}	SRI_{PGA2}	SRI_{MCID}
SRI	–	0.66 (0.58–0.73)	0.66 (0.59–0.74)	0.39 (0.33–0.45)
SRI_{PGA1}	0.66 (0.58–0.73)	–	0.80 (0.74–0.86)	0.49 (0.43–0.54)
SRI_{PGA2}	0.66 (0.59–0.74)	0.80 (0.74–0.86)	–	0.34 (0.29–0.41)
SRI_{MCID}	0.39 (0.33–0.45)	0.49 (0.43–0.54)	0.34 (0.29–0.41)	–
PCI	0.30 (0.20–0.40)	0.45 (0.34–0.55)	0.40 (0.29–0.51)	0.32 (0.25–0.39)

¶ For LEGEND, please see Table 1

Conclusion: The SRI has excellent specificity, but only fair sensitivity in identifying overall major improvement in children with jSLE. Thus, if used in clinical trials, the SRI tool may require larger sample sizes to detect important differences between treatment groups.

ACR/ARHP Poster Session C
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Pediatric Rheumatology Systemic Lupus Erythematosus, Juvenile Dermatomyositis, Vasculitis and Other
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

2015

A Secondary Analysis of the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) Study Shows That Atorvastatin Therapy Reduces Progression of Carotid Intima Medial Thickening in Pubertal SLE Patients with Higher C Reactive Protein. Stacy P. Ardoin[1], Laura E. Schanberg[2], Christy I. Sandborg[3], Huiman Barnhart[4], Eric Yow[4], Greg Evans[5], Kelly Mieszkalski[2], Norman T. Ilowite[6], Emily von Scheven[7], B. Anne Eberhard[8], Lisa F. Imundo[9], Deborah M. Levy[10], Yuki Kimura[11], Earl D. Silverman[12], Suzanne L. Bowyer[13], Marilynn G. Punaro[14], Nora G. Singer[15], David D. Sherry[16], Deborah K. McCurdy[17], Marisa Klein-Gitelman[18], Carol A. Wallace[19], Richard M. Silver[20], Linda Wagner-Weiner[21], Gloria Higgins[22] and Hermine Brunner[23]. [1]Ohio State University, Columbus, OH, [2]Duke University Medical Center, Durham, NC, [3]Stanford University, Palo Alto, CA, [4]Duke Clinical Research Institute, Durham, NC, [5]Winston-Salem, NC, [6]Children's Hospital Montefiore, Bronx, NY, [7]UC San Francisco, San Francisco, CA, [8]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [9]Childrens Hospital of New York, Columbia University Medical Center, New York, NY, [10]The Hospital for Sick Children, Toronto, ON, [11]Pediatrics, Hackensack, NJ, [12]Hospital for Sick Children, Toronto, ON, [13]James Whitcomb Riley Hospital, Indianapolis, IN, [14]Texas Scottish Rite Hospital, Dallas, TX, [15]Director, Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, [16]Children's Hospital of Philadelphia, Philadelphia, PA, [17]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [18]Children's Memorial Hospital, Chicago, IL, [19]Childrens Hosp & Regional Med, Seattle, WA, [20]MUSC, Charleston, SC, [21]University of Chicago Hospital, Chicago, IL, [22]NATIONWIDE CHILDRENS HOSPITAL, Columbus, OH, [23]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: APPLE assessed atorvastatin's efficacy in reducing carotid intimal medial thickening (CIMT) progression in pediatric SLE (pSLE). While the primary endpoint of reduced mean-mean common CIMT progression was not met, observed trends of near significance in several CIMT segments suggested atorvastatin may reduce CIMT progression. Secondary analyses were performed to determine whether treatment effect was consistent across subgroups defined by LDL, high-sensitivity c-reactive protein (hscrp), age, pubertal status, SLE duration and medication adherence.

Methods: APPLE is a randomized, placebo-controlled, multicenter trial randomizing 221 subjects with pSLE (age 10–21 years) to 36 months of atorvastatin or placebo. CIMT was measured by standard protocol at 0, 12, 24 and 36 months. Fasting lipids and hscrp were measured centrally. Subgroups were defined as LDL < or >/= 110 mg/dL, hscrp < or >/= 1.5 mg/dL, age < or >/= 15.5 yrs, SLE duration < or ^{3} 24 months, adherence < or >/= 75%. Prepubertal status was defined by self-reported Tanner stage < 4. An additional combined subgroup of post-pubertal subjects with hscrp ^{3} 1.5 mg/dL vs. others was defined.

The statistical approach replicated primary APPLE efficacy analysis comparing CIMT progression rates between treatment groups based on

test of interaction between treatment group and time in a longitudinal linear mixed effects model. Similar models were used to assess non-CIMT outcomes. Indicator variables were included for subgroup level as well as two- and three-way interactions between subgroup, treatment group and time between subgroup level, treatment group and time. All statistical analyses were 2-sided, and the level of significance for all analyses was 0.05.

Results: Differences in treatment effects between hscrp subgroups were identified for mean-mean common (p=0.029) and mean-mean near wall (p=0.014). In both cases, the reduction in CIMT progression associated with atorvastatin assignment was more pronounced in the elevated hscrp subgroup. Similar differences were identified by pubertal status for mean-mean bifurcation (p=0.019) mean-max near wall (p=0.027) and mean-mean near wall (p=0.021), and by adherence for mean-mean far wall (p=0.035) and mean-mean near wall (p=0.028), where reduction in CIMT progression with atorvastatin assignment was more pronounced among post-pubertal or more adherent participants. No significant differences in treatment effects were observed between subgroups defined by LDL, age or SLE duration. The combined pubertal and high hscrp subgroup atorvastatin group had lower CIMT progression rates in five of 12 CIMT segments: mean-mean common (p=0.005), mean-mean (p=0.008), mean-mean bifurcation (p=0.023), mean-max near wall (p=0.029), and mean-mean near wall (p=0.002).

Conclusion: These exploratory results need to be confirmed and interpreted cautiously as multiple comparisons were performed. APPLE secondary analyses showed a trend of lower CIMT progression rates in the atorvastatin-treated pubertal and elevated hscrp subgroups, particularly in the combined pubertal subjects with high hscrp, suggesting that this subgroup may benefit from statin therapy.

2016

Ovarian Reserve in Juvenile Systemic Lupus Erythematosus Patients without Amenorrhea. Nadia E. Aikawa[1], Adriana M. Sallum[2], Rosa M.R. Pereira[3], Eloisa Bonfa[4], Lisa Suzuki[5], Vilma S.T. Viana[1] and Clovis A. Silva[6]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo-SP, Brazil, [3]Disciplina de Reumatologia da FMUSP, Sao Paulo, Brazil, [4]University of Sao Paulo, Sao Paulo, Brazil, [5]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [6]Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: Intravenous cyclophosphamide (IVCYC) use is a cause of premature ovarian failure in juvenile systemic lupus erythematous (JSLE). Assessment of markers of ovarian reserve is therefore of great interest in these patients and may allow a more accurate prediction of immunosuppressor-related risk to future fertility. Therefore, the objective of this study was to assess ovarian reserve using a combination of tests in JSLE patients without amenorrhea.

Methods: Twenty-seven consecutive JSLE female patients and 13 healthy subjects without amenorrhea (cessation of menstruation for more than 4 months after menarche) were evaluated prospectively for at least 6 months. Ovarian reserve was concomitantly assessed by serum levels of the following hormones (third to fifth day of the menstrual cycle): follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol by fluoroimmunoassay, and inhibin A, inhibin-B and anti-mullerian hormone (AMH) by enzyme-linked immunosorbent assay in duplicated samples. Ovarian size was measured by abdominal ultrasonography. Demographic data, disease activity score (SLEDAI), disease cumulative damage (SLICC/ACR-DI) and treatment of JSLE patients were also analyzed.

Results: The median of current age and body mass index were similar in JSLE patients and controls (16.5 vs. 15years, p=0.31; 23 vs. 22.4kg/m^2, p=0.48). The age at menarche was significantly higher in JSLE patients that presented their first menstruation after disease onset *versus* controls (12.9 vs. 12years, p=0.044), whereas the frequencies of Tanner pattern 4 or 5 was similar in JSLE and controls (63% vs. 92%, p=0.07). The median levels of serum FSH (5.1 vs. 5.6IU/L, p=0.57), LH (2.7 vs. 3IU/L, p=0.8), estradiol (44.5 vs. 34pg/mL, p=0.37), inhibin A (0.3 vs. 0.1pg/mL, p=0.94), inhibin B (23.5 vs. 29.3pg/mL, p=0.58) and AMH (1.4 vs. 1.4ng/mL, p=0.7) were comparable in patients and controls. The median of ovarian volumes was also similar in JSLE versus controls (4.5 vs. 4.7cm^3, p=0.1416). Eleven patients were under IVCYC with median duration time between the last dose and study entry of 2.5 years (range 0–7.7). Further evaluation of ovarian reserve revealed that the median levels of serum FSH was significantly higher in JSLE patients under IVCYC (n=11) compared to those without this treatment (n=16) (6.4 vs. 4.6IU/L, p=0.023), however the lower inhibin B and AMH levels, and ovarian volume in the former group did not reach statistical significance (10.8 vs. 27.6pg/mL, p=0.17; 0.6 vs. 1.5ng/mL, p=0.28; 3.5 vs. 4.6cm^3, p=0.231; respectively). LH (2.7 vs. 2.9IU/L, p=0.43), estradiol (50 vs. 38pg/mL, p=0.34) and inhibin A (1.1 vs. 0pg/mL, p=0.49) levels were comparable in both groups. No correlation was found between FSH levels and duration of IVCYC use, inhibin A, inhibin B, AMH, SLEDAI and SLICC/ACR-DI in JSLE patients (p>0.05).

Conclusion: Our study suggest that ovarian reserve after cyclophosphamide treatment may be hampered in spite of menstrual cycles reinforcing the importance of gonadal function protection during the use of this alkylating agent. Further studies are necessary to determine the relevance of this subclinical condition for lupus fertility.

2017

Maternal Autoimmunity and Neonatal Brain Abnormalities: Cerebral Dysmaturation, Diencephalon Abnormalities, and Lenticulostriate Vasculopathy. Jennifer D. Frankovich[1], Patrick D. Barnes[1], Christy I. Sandborg[1] and Eliza F. Chakravarty[2]. [1]Stanford University, Palo Alto, CA, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Case reports have suggested that neurologic disease may be part of the spectrum of neonatal lupus (NLE) in infants presenting with classical features of NLE, including diffuse cerebral hypomyelination, hydrocephalus, and vasculopathy. We report a similar spectrum of neurological findings in 9 infants born to mothers with lupus and associated autoimmune diseases in the absence of classical features of NLE (heart block, rash).

Methods: We report 9 infants born to mothers with lupus and associated autoimmune conditions, with evidence of idiopathic cerebral dysmaturity on brain MRI followed at a single center from birth through 3 years.

Results: Maternal autoimmune diseases include lupus (6), lupus nephritis (4), autoimmune thyroiditis (5), antiphospholipid antibody syndrome (3), Sjogren's or Ro/La antibodies (4), and ulcerative colitis (1). Only 2 of the 9 mothers received immunosuppression during pregnancy: cyclosporine (1) and low dose prednisone (2). Three mothers were diagnosed with autoimmune disease shortly after their infant was born. Median gestational age was 35 weeks (range 28–38 weeks). Median birth weight was 2350 grams (range 890–3260). ***Cerebral dysmaturity*** was seen in all 9 infants, which was primarily manifested as diffuse hypomyelination relative to adjusted gestational age at the time of MRI. Cortical dysmaturity was seen in 5 infants: polymicrogyria (1), coarse gyral pattern (1), wide sylvian fissures (1), and prominent Virchow-Robin Spaces (2). Ventriculomegaly was appreciated on 6 of the infant MRIs. ***Diencephalon abnormalities*** include optic tract hypoplasia (3), basal ganglia abnormalities (3), colossal or septum pellucidum abnormalities (5). ***Vasculopathy:*** Four head ultrasounds were available for review, and all 4 indicated lenticulostriate vasculopathy. Four infants also had brain calcifications consistent with prior hemorrhage and or vasculitis. ***Clinical neurological manifestations through 3 years*** include: static encephalopathy and death (2), persistent muscle tone abnormalities (6), seizures (3), persistent feeding abnormalities (4), delayed cognitive and language development (2), behavior abnormalities (2), macrocephaly (1), microcephaly (1), persistent congenital nystagmus and strabismus (1), opsiclonus and myoclonus (1), hyperekplexia (1).

Conclusion: A spectrum of cerebral and diencephalon abnormalities were present in infants born to mothers with lupus and associated autoimmune conditions. Lenticulostriate vasculopathy, previously reported in this setting, is of particular interest as these blood vessels supply the diencephalon and the germinal matrix (which gives rise to neurons and cells that myelinate the brain). While a causal connection between maternal autoantibodies or autoimmunity and these abnormalities cannot be firmly established, these neonatal neurologic abnormalities may be the result of passive autoimmunity. Clinicians should consider evaluation for maternal autoimmunity in cases of idiopathic cerebral dysmaturation, hypomyelination, or lenticulostriate vasculopathy.

2018

Long-Term Methotrexate Efficacy in Juvenile Localized Scleroderma. Francesco Zulian[1], Cristina Vallongo[1], Fabio Vittadello[1], Annalisa Patrizi[2], Maria Alessio[3], Anna Belloni Fortina[1], Silvana Martino[4] and Giorgia Martini[1]. [1]University of Padua, Padova, Italy, [2]University of Bologna, Bologna, Italy, [3]University of Naples Federico II, Napoli, Italy, [4]University of Turin, Italy

Background/Purpose: Recent studies reported that methotrexate (MTX), appears beneficial in juvenile localized scleroderma (JLS) but little is known about its long-term efficacy. We assessed the long-term efficacy of MTX in a cohort of patients with JLS.

Methods: We prospectively followed a cohort of patients with JLS who were enrolled in a double-blind, randomized controlled trial[1]. Oral MTX was used at a dose of 15 mg/m^2 once a week (max 20 mg) for at least 24 months; prednisone (1 mg/Kg/day, max 50 mg), as bridging therapy for 3 months was added. A target lesion was evaluated clinically, with infrared thermography and using a computerized scoring system with skin score rate (SSR) evaluation[2]. Response to treatment was defined as: no new lesions; SSR$<$1; decrease lesion temperature by at least 10% compared to baseline. Treatment failure was defined by appearance of new lesions, SSR$>$1, or increased lesion temperature. As far as outcome, partial remission (PR) was defined when the state of responder was maintained ON treatment for at least 6 months, complete remission (CR) when the state of responder was maintained OFF treatment for at least 6 months.

Results: 65 patients have been treated with MTX during the open-label phase of the study. Seven patients were lost to follow-up. Of the remaining 58 patients, after a mean follow-up of 43 months (median 36; range 6–72 months), 48 (82.8%) were responders, 10 (17.2%) relapsed by 24 months since MTX start. Among the responders, 35 (60.4%), after a 27.5 months of MTX treatment for (median 24, range 18–30) maintained CR for 25 months after stopping treatment (median 24, range 6–48), none relapsed. 13 patients (22.4%), after a mean follow-up of 20.5 months (median 15.5, range 6–45), were in PR. Among the ten MTX-refractory patients, 4 had linear subtype (2 limb, 2 ECDS), 4 had mixed subtype (2 linear-circumscribed, 2 linear-pansclerotic) and 2 generalized morphea. MTX-related side-effects were seen in 28 patients (48.3%), were generally mild and rarely required treatment discontinuation.

Conclusion: Long-term methotrexate therapy is a safe and effective treatment for JLS. Three months of combined MTX and glucocorticoid bridging therapy and MTX duration of treatment longer than 24 months ensure prolonged disease remission.

References:

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2019

Diagnostic Evaluation and Medication Usage in a Cohort of Subjects with Juvenile Dermatomyositis Recruited within the First 11 Months of the Children's Arthritis and Rheumatology Research Alliance Registry. Angela B. Robinson[1], Mark F. Hoeltzel[2], ML Becker[2], Dawn M. Wahezi[3], Adam M. Huber[4], Brian M. Feldman[5], Ann M. Reed[6] and Juvenile Myositis CARRA Subgroup for CARRAnet Investigators[7]. [1]Rainbow Babies and Childrens Hospital, Cleveland, OH, [2]Children's Mercy Hospital, Kansas City, MO, [3]Children's Hospital Montefiore, Bronx, NY, [4]Dalhousie University, Halifax, NS, [5]The Hospital for Sick Children, Toronto, ON, [6]Mayo Clinic, Rochester, MN, [7]Varies by Investigator

Background/Purpose: Juvenile dermatomyositis (JDM) has been difficult to study due to the low incidence of disease. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) initiated a multi-center observational registry to create a clinical database for the major rheumatic diseases of childhood, including JDM. Initial data from the JDM cohort (prevalent and incident cases) enrolled in the first 11 months of this ongoing study are described here.

Methods: Children under 21 years of age with onset of JDM prior to 16 years were included. Subjects or their guardians gave consent for the study. IRB approval was obtained at each enrolling site. JDM was diagnosed by modified Bohan and Peter criteria. Clinical data were collected from the subjects, guardians, and providers using both general and JDM-specific case report forms at the time of enrollment. Data regarding demographics, diagnostic assessment, and medication exposure were collected. Data were pooled and stored in a secure centralized database and de-identified prior to analysis.

Results: Between May 28, 2010 and May 3, 2011, 198 subjects meeting modified criteria for JDM were enrolled from 40 sites in the US. Diagnostic studies commonly used include muscle biopsy, electromyography (EMG), and magnetic resonance imaging (MRI). All subjects had evidence of inflammatory myopathy by at least one of these modalities, with MRI being more sensitive than EMG or muscle biopsy (Table 1). Two or more studies were performed in 103 subjects, with 50.5% of the subjects exhibiting at least one non-diagnostic study. When evaluating medication use, 100% of subjects were treated with corticosteroids and 97% of subjects received methotrexate, suggesting that these medications are almost universally prescribed for JDM. Medication usage in order of frequency is presented in Table 2.

Table 1. Evaluation of diagnostic modalities in JDM

	N (%)
Muscle biopsy (n = 194)	
Performed	102 (52.6)
Consistent with JDM	78 (76.5)
Non-diagnostic	24 (23.5)
EMG (n = 192)	
Performed	62 (32.3)
Consistent with JDM	33 (53.2)
Non-diagnostic	29 (46.8)
MRI (n = 191)	
Performed	172 (90.1)
Consistent with JDM	152 (88.4)
Non-diagnostic	20 (11.6)
Combination of ≥2 studies (n = 194)	
Performed	103 (53.1)
3 studies consistent with JDM	1 (1.0)
2 studies consistent with JDM	66 (64.1)
1 study consistent with JDM	36 (35.0)

Table 2. Medication usage within the CARRAnet JDM cohort (N=198)

	Current use	Previous use	Ever used	Missing
All corticosteroids	94 (48.5%)	100 (51.5%)	194 (100.0%)	4
Daily corticosteroids	91 (47.2%)	98 (50.8%)	189 (97.9%)	5
Methotrexate	125 (65.1%)	62 (32.3%)	187 (97.4%)	6
Pulse corticosteroids	23 (12.0%)	104 (54.5%)	127 (66.5%)	7
Hydroxychloroquine	71 (37.4%)	38 (20.0%)	109 (57.4%)	8
Intravenous gammaglobulin	38 (19.3%)	50 (25.4%)	88 (44.7%)	1
Mycophenolate mofetil	27 (13.8%)	11 (5.6%)	38 (19.4%)	2
Cyclosporine A	8 (4.1%)	16 (8.2%)	24 (12.2%)	2
Rituximab	3 (1.5%)	15 (7.6%)	18 (9.1%)	1
Cyclophosphamide	0 (0.0%)	4 (2.0%)	4 (2.0%)	2

Conclusion: MRI was the most common diagnostic modality used and demonstrated the highest diagnostic sensitivity for JDM. Overall, the false negative rates of muscle biopsy, EMG and MRI were higher than expected. This may raise concerns about the underlying diagnosis or adequacy of these investigations, but may also be a more accurate representation of true false negative rates. Corticosteroids and methotrexate appear to be standard first line medications used by US pediatric rheumatologists for JDM. Pulse corticosteroids, intravenous gammaglobulin, and hydroxychloroquine were prescribed in about half of the enrolled subjects and further investigation of these subject characteristics is warranted.

2020

Influenza A H1N1/2009 Vaccine in Juvenile Dermatomyositis: Reduced Response in Patients Under Immunosuppressive Agents. Vanessa R. Guissa[1], Nadia E. Aikawa[2], Adriana M. Sallum[1], Lucia M.A. Campos[3], Rosa M.R. Pereira[4], Eloisa Bonfa[5] and Clovis A. Silva[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo-SP, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil, [4]Disciplina de Reumatologia da FMUSP, Sao Paulo, Brazil, [5]University of Sao Paulo, São Paulo, Brazil

Background/Purpose: We recently evaluated in adults the immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine

in a large cohort of autoimmune rheumatic diseases, including those with dermatomyositis (Ann Rheum Dis 2011;70:1068–73). However, there are no data regarding immunogenicity and the safety of this immunization in juvenile dermatomyositis (JDM). We therefore, evaluated in these patients vaccine immunogenicity and adverse events, as well as, disease safety and the possible influence therapy in antibody response.

Methods: 30 JDM patients and 81 healthy controls were vaccinated with non-adjuvanted influenza A/California/7/2009 (H1N1) virus-like vaccine. All participants were evaluated pre- and 21 days post-vaccination and serology for anti-H1N1 was performed by hemagglutination inhibition (HI) assay. Seroprotection (percentage of subjects with HI antibody titer ≥ 1:40), seroconversion (percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer) rates, geometric mean titres (GMTs) and factor increase (FI) in GMT (ratio of the GMT after vaccination to the GMT before vaccination) were analyzed. Muscle enzymes levels and JDM scores [disease activity score (DAS), Manual Muscle Test (MMT-8) and Childhood Myositis Assessment Scale (CMAS)] were evaluated before and after vaccination. Adverse events were also reported.

Results: JDM patients and healthy controls were comparable regarding median current age and female gender [15.5 (9–21) vs. 15 (9–21) years, p=0.511; 63 vs. 51%, p=0.286]. After immunization, seroconversion rates were significantly lower in JDM patients compared to controls (86.7 vs. 97.5%, p=0.045), whereas seroprotection (p=0.121), GMT (p=0.992) and FI in GMT (p=0.827) were similar in both groups. Clinical and laboratorial evaluations revealed that DAS [0 (0–11) vs. 0 (0–14), p=0.993)], CMAS [52 (45–52) vs. 52 (41–52), p=0.804], MMT [80 (74–80) vs. 80 (79–80), p=0.986], CPK [124 (49–533) vs. 102.5 (33–481), p=0.339], AST [20 (10–45) vs. 23 (11–36)UI/L, p=0.246], ALT [32.5 (12–72) vs. 31 (11–63)UI/L, p=0.826] and LDH [187 (93–469) vs. 179 (83–446)UI/L, p=0.907] remained stable throughout the study. Regarding therapy, seroconversion rates among JDM patients under current prednisone (p=0.005), methotrexate (MTX) (p=0.004), MTX and cyclosporine (p=0.005) and immunosuppressants other than MTX (p=0.039) were significantly lower compared to healthy controls. Local and systemic vaccine adverse events were uniformly mild and with similar frequency in patients and controls (p>0.05).

Conclusion: This first study of non-adjuvanted influenza A/H1N1 2009 virus immunization in JDM patients revealed a reduced immunoresponse particularly associated with immunosuppressive agents. The observed overall vaccine and disease safety supports its recommendation and suggest that a booster may be appropriate to improve antibody response. (ClinicalTrials.gov, #NCT01151644)

2021

Creation of a Cohort of French Patients with Chronic Recurrent Multifocal Osteitis: Preliminary Results. Julien Wipff[1], M.-A. Dumitrescu[2], Mathie Lorrot[3], Albert Faye[2], S. lacassagne-Compeyrot[4], B. Bader Meunier[4], R. Mouy[4], Carine H. Wouters[5], Marine Desjonqueres[6], S. Jean[7], V. Despert[7], A. Duquesne[6], I. Lemelle[8], P. Pillet[9], M. Grall-Lerosey[10], Pierre Quartier[11] and Chantal Job-Deslandre[12]. [1]Paris descartes Universityn Rheumatology A, Cochin Hospital, Paris, France, [2]Paris, France, [3]Paediatry, Robert Debré hospital, Paris, France, [4]University Paris Descartes, Paediatry, Necker hospital, Paris, France, [5]University Hosp Gasthuisberg, Leuven, Belgium, [6]Hopital Femme Mere Enfant, Groupement Hospitalier Est, Lyon, France, [7]Paediatry, CHU, Rennes, France, [8]Paediatry, CHU, Nancy, France, [9]Paediatry, CHU, Bordeaux, France, [10]Paediatry, CHU, Rouen, France, [11]Hôpital Necker-Enfants Malades, Paris, France, [12]Hopital Cochin, Paris Cedex 14, France

Background/Purpose: Chronic recurrent multifocal osteomyelitis (CRMO), also known as chronic nonbacterial osteomyelitis, is an orphan disease that manifests by recurrent flares of inflammatory bone pain with or without fever. Its frequency seems to be underestimated and it often leads to consequential residual impairments. The aim of this study is to collect the French cases of CRMO in order to precise clinical, biological, radiological and histological features.

Methods: Creation of a French national database of cases of CRMO. In the absence of validated international diagnostic criteria, our inclusion criteria were: patient with at least one lesion of aseptic osteitis highlighted by imaging techniques (MRI or isotopic bone scan) and beginning before 18 years. Exclusion criteria were: onset after 18 years, other diagnosis (malignancy, infection, enthesitis related arthritis).

Results: 70 patients were included (46 females and 24 males) mean aged 15.71±4.61 years. Mean age at diagnosis was 10.9±3.90 years. The mean time between first symptom and diagnosis was 22.63±34.14 months. 19/70 (27%) patients had unifocal symptom, mainly located on lower limbs (n=7) [leg (n=3), thigh (n=2) and ankle (n=3)]. For the other patients, the mean number of clinical locations was 2.33±1.3 mainly in lower limbs. 30/70 patients had inflammatory skin appearance opposite the osteitis, 14/70 had fever and 37/70 had biological inflammatory syndrome.

Imagery plain radiographs and/or bone scan and/or MRI) showed 2.67±1.67 lesions per patients and confirm multifocal involvement in 8/19 cases with clinical unifocal symptom.

Bone biopsy was performed in 45/70 and was followed by antibiotherapy in 15 cases, including 10 without bacteriological proof NSAIDs were given as first line therapy to 68/70 patients. In case of failure second line treatment were bisphosphonates for 4 patients and anti-TNFalpha for 3.

Only 23 patients were considered in remission at the last visit after a mean follow-up of 50.66 ± 44.2 months. 16/70 patients had sequellae including localized deformations (n=8), growth retardation (n=6) or vertebral fractures (n=2).

Conclusion: Our first results confirm that the use of imagery (bone scan, MRI) can demonstrate the multifocal pattern of osteitis in patients with clinical monofocal lesion. This confirmation may avoid a bone biopsy which is invasive in these young patients. NSAIDs remained first line treatments with remarkable efficiency. Bisphosphonates and anti-TNFalpha are second line treatment options only if NSAIDs failed to improve symptoms.

2022

Recurrent Arthritis As the Sole Presenting Manifestation of Hereditary Autoinflammatory Syndromes. Giulia Vigo[1], Giorgia Martini[1], Fabio Vittadello[1], Isabella Ceccherini[2], Laura Obici[3] and Francesco Zulian[1]. [1]University of Padua, Padova, Italy, [2]G. Gaslini Institute, Genova, Italy, [3]IRCCS Policlinico S. Matteo, Pavia, Italy

Background/Purpose: Hereditary autoinflammatory syndromes (HAS) are a group of rare monogenic inherited conditions characterized by recurrence of symptoms of whom fever is the most frequent. We analyze the prevalence of recurrent arthritis in a cohort of patients with HAS.

Methods: We performed a retrospective study on 302 patients with periodic and recurrent fevers referred to a single tertiary center in 17 yrs of activity. Patients with recurrent arthritis were identified and fully investigated. On the basis of the clinical features and genetic tests, patients were divided into two groups: 275 PFAPA syndrome and 27 HAS (11 FMF, 3 TRAPS, 3 HIDS, 3 CAPS, 7 Undefined).

Results: Patients with monogenic HAS showed a later disease onset (63.4 months vs 27.9) and a higher frequency of abdominal pain (60% vs 16.4%), headache (32% vs 7.3%) than PFAPA. Recurrent arthritis, defined as episodes lasting less than 7 days, was found in 11 patients with HAS (40.7%): 4 had FMF, 2 TRAPS, 3 HIDS, 2 CAPS. No patient with arthritis was found in the PFAPA group. Interestingly, five out of 11 patients (3 FMF, 2 HIDS) had unexplained recurrent arthritis as unique manifestation of the disease for a long time. Arthritis consisted in episodes of joint swelling, pain and limitation of movement involving, asymmetrically, large joints. In three patients most episodes occurred after infections. During the disease-free intervals, acute-phase reactants (CRP and SAA) persisted elevated. Genetic analysis showed heterozygous missense changes of the MEFV gene in three patients (A289V father and daughter, P369S) and of MVK gene (V250I/G336S, I268T) in the other two. Before genetic confirmation, attacks resolved spontaneously or under NSAIDs treatment in few days. After genetic confirmation, four patients have been treated with colchicine and all responded.

Conclusion: Unexplained recurrent arthritis may be the unique manifestation of a monogenic HAS and should be added to the list of possible differential diagnosis of the so called "palindromic arthritis". Elevation of acute-phase reactants, during the arthritis-free intervals, might be a suspicion finding to address a genetic test for HAS. Colchicine may represent the drug of choice in this condition.

2023

Description of the Localized Scleroderma Subgroup of the CARRA *net* Registry. Eveline Y. Wu[1], Egla C. Rabinovich[2], Kathryn S. Torok[3], Suzanne C. Li[4], Robert C. Fuhlbrigge[5] and CARRANet Investigators[6]. [1]Duke Univ Med Ctr, Durham, NC, [2]Duke University Medical Center, Durham, NC, [3]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [4]Hackensack Univ Med Ctr, Hackensack, NJ, [5]Childrens Hospital, Boston, MA, [6]Stanford

Background/Purpose: Localized scleroderma (LS) is a chronic inflammatory and fibrosing skin disease. We present baseline data on the juvenile LS (jLS) cohort from the Childhood Arthritis and Rheumatology Research Alliance (CARRA*net*) registry, a United States observational longitudinal study of pediatric rheumatologic disorders.

Methods: We performed a cross-sectional baseline analysis of registry data for jLS.

Results: Data were available on 119 children. 80% were female and 90% were Caucasian, of which 11% were Latino. Mean age at onset was 7.8 years (± 4.1), yet first evaluation by a pediatric rheumatologist was 9.9 years (± 4.1). Mean disease duration at time of data collection was 4.8 years (±3.8). Reported subtypes were 67 (56%) with linear scleroderma (LiS: 44 trunk/limbs, 23 face/scalp), 22 (18%) with circumscribed morphea (13 deep, 11 superficial), 6 with generalized morphea, 4 with eosinophilic fasciitis, and 1 with pansclerotic morphea. There were 19 (16%) cases of mixed morphea. Features of activity included erythematous/violacious color (37), lesion extension (30), induration at lesion perimeter (29), and warmth (22). Damage included subcutaneous atrophy (88), hyperpigmentation (87), dermal atrophy (82), hypopigmentation (60), induration at lesion center (58), and hair loss (43). Musculoskeletal features of damage included muscle atrophy (27), joint contracture (25), hemifacial atrophy (10), and limb shortening (9). Eight children (7%) had arthritis. ANA positivity was found in 50% of tested patients, otherwise there were no consistent laboratory or imaging abnormalities.

	Antinuclear Antibody	Elevated IgG	Eosinophilia	Abnormal Aldolase	Abnormal Creatine Kinase	Abnormal CNS Imaging	Abnormal GI Study
Positive	46 (50.5%)	8 (12%)	18 (17.2%)	8 (13.6%)	4 (5.6%)	2 (4.5%)	3 (12%)
Negative	45 (49.5%)	59 (88%)	85 (82.5%)	85 (86.4%)	67 (94.4%)	42 (95.5%)	22 (88%)
Unknown	27	51	15	59	47	75	93
Total	**118**	**118**	**118**	**118**	**118**	**119**	**118**

Mean visual analog scale (VAS) physician global assessment of activity was 1.71 and mean CHAQ score was 0.17. By VAS (0–10), mean parent/subject score of overall well-being was 1.92 (±1.94) and pain was 1.30 (±1.91). Health related quality of life was reported as excellent in 30, very good in 54, good in 30, and poor in 3 subjects. A worst ever and current ACR functional class > I was reported in 24.2% and 11.2%, respectively. Medications used are listed below.

	Oral methotrexate (MTX)	Subcutaneous methotrexate (MTX)	Mycophenolate mofetil (MMF)	Intraveneous corticosteroids (CS)	Longterm daily corticosteroids (CS)
Subjects (%)	66/113 (58%)	91/113 (81%)	23/113 (20%)	58/93 (62%)	57/91 (63%)
Current Use	33	47	17	16	20
Past Use	33	44	6	42	37

Conclusion: jLS is reported more frequently in females and Caucasians in the CARRA*net* registry. LiS is the most common lesion subtype, representing 56% of all patients. 50% of the jLS cohort is ANA positive. Subcutaneous and oral MTX and pulse and long term daily CS are the most commonly used medications for treatment, followed by MMF. There is over a 2 year delay from symptom onset and referral to pediatric rheumatology. There is significant morbidity with 25% reporting limitation in functional capacity and only 25% reporting an excellent health related quality of life.

2024

Parents' Attitudes towards Research and Research Study Participation in Pediatric Rheumatology (PR). America Uribe[1], Lori B. Tucker[2], Louise Masse[1], Jaime Guzman[1] and David A. Cabral[3]. [1]BC Children's Hospital, Vancouver, BC, [2]BC Childrens Hospital, Vancouver, BC, [3]University of British Columbia, Vancouver, BC

Background/Purpose: To improve the outcome for children with rare PR diseases, it would be optimal for all patients to be treated in the context of a clinical study or clinical trial. In our clinic, we have fostered a milieu of integrated clinical care and research, in part through regular distribution of a Research newsletter for families. For our patients, we aimed to describe their parent's attitudes towards research in general, and to determine factors associated with their decisions to allow their child to participate in research studies

Methods: Parents of children attending the BC Children's Hospital tertiary PR clinics for at least 6 months, who were able to read English, were surveyed (April-June 2011) using a questionnaire. The questionnaire was developed using a three-stage process; a)13 family interviews to develop themes and itemized questions; b) items refined by members of the PR clinic team (4 MD, 2 RN, 1 PT, 1 OT, 1 SW) and a second group of 17 parents; c) the questionnaire was piloted (including re-test reliability) on a subset of 25 parents. Descriptive statistics were used.

Results: 124 of 163 eligible parents completed the survey (75.8% mothers). Patients' diagnoses were 78 (62.9%) JIA, 12 (9.7%) SLE, 7 (5.6%) vasculitis, 4 (3.2%) scleroderma, 20 (16.1%) other; median (range) age 14 (1–17) years. For 86 families (69.4%), English was the primary language at home. A majority of parents (N=110; 88.7%) reported to have looked for information related to the treatment/diagnosis of their child; 39 (35.5%) of these sought information specifically about research into their child's condition. 100 (80.6%) parents were open to participating in a research project; 107 (86.3%) considered it was important to carry out that research related to their child's disease, and a majority (85.0%) indicated their preference for this research to be done at our clinic. Sixty-two (50.0%) surveyed families had been invited to join a research study in the past (93.5% of these joined/6.5% declined). Factors influencing parent's decision of allowing their child to participate in a research study are shown in Table.

Table.

Factors influencing participation in a research study, n (%)	Study participation		
	More Likely	Less Likely	No difference
Child is doing well	20 (16.1)	26 (21.0)	**78 (62.9)**
Child is not doing well	57 (46.3)	18 (14.6)	48 (39.0)
My child is young	20 (16.4)	12 (9.8)	**90 (73.8)**
Study adds time to clinic visit	8 (6.6)	44 (36.4)	69 (57.0)
Study visits/procedures can be coordinated with regular clinic appointments	**91 (74.6)**	6 (4.9)	25 (20.5)
Involves additional visit to the hospital	2 (1.7%)	**88 (73.3)**	30 (25.0)
Study involves additional work at home	9 (7.3)	41 (33.3)	73 (59.3)
Study collects personal data	26 (21.1)	7 (5.7)	**90 (73.2)**
Study involves a blood draw	5 (4.2)	48 (40.0)	67 (55.8)
Study requires testing of a new medication/treatment	7 (5.7)	**82 (66.7)**	34 (27.6)
Side effects of new medication are unknown	2 (1.7)	**111 (91.7)**	8 (6.6)
Study includes the possibility of receiving placebo	6 (5.0)	59 (48.8)	56 (46.3)
Study drug/intervention is randomly assigned	5 (4.1)	**77 (62.6)**	41 (33.3)
Double-/single-blinded study	6 (4.9)	**68 (55.7)**	48 (39.3)
Study benefits child directly	**99 (79.8)**	1 (0.8)	23 (18.5)
In-person invitation instead of phone or paper invitation	50 (41.0)	12 (9.8)	60 (49.2)
Study will provide compensation (coupons/out-of-pocket expenses)	49 (40.0)	2 (1.6)	72 (58.5)
Family knows the investigators	57 (47.5)	2 (1.7)	61 (50.8)
Family feels satisfied with information given about study goals and procedures	**84 (68.9)**	1 (0.8)	37 (30.3)
Study results will be available quickly	**92 (74.8)**	6 (4.9)	25 (20.3)
Child is willing to join the study	51 (41.5)	3 (2.4)	**69 (56.1)**
Child is not willing to join the study	6 (4.9)	**85 (69.7)**	31 (25.4)

Conclusion: The majority of our patient's parents were interested in joining research studies and believed it was important to carry out research related to their child's condition. Parents in this study identified that studies involving additional visits to the hospital, testing of a new medication (with potential unknown side effects), randomized assignment of study intervention and blinding procedures were deterrents for study participation. Perceived direct benefit to child, study visits/procedures coordinated to regular clinical appointments, and feeling well informed about the study were facilitators of participation in research. Addressing these factors may increase enrolment to research studies in PR.

2025

Long-Term Mental Health Outcomes in Pediatric-Onset Systemic Lupus Erythematosus. Erica F. Lawson[1], Aimee O. Hersh[2], Laura J. Julian[1], Laura Trupin[3], Emily von Scheven[3], Patricia P. Katz[4] and Edward Yelin[1]. [1]University of California San Francisco, San Francisco, CA, [2]University of Utah, Salt Lake City, UT, [3]UC San Francisco, San Francisco, CA, [4]Univercity of California San Francisco, San Francisco, CA

Background/Purpose: Neuropsychiatric syndromes are prevalent in pediatric-onset systemic lupus erythematosus (pSLE), but the long-term risk of mood disorders in adults with pSLE is unknown. We aim to describe the prevalence of depression among adults with pSLE, and to compare subjects with pSLE to subjects with adult-onset SLE (aSLE) using the UCSF Lupus Outcomes Study (LOS).

Methods: Data derive from the 2009 cycle of the LOS, an annual longitudinal telephone survey of diverse English-speaking subjects with confirmed SLE. Subjects age 18–60 years (N=625) were included. Subjects were classified as pediatric-onset if age at diagnosis was < 18 years (N=86). Mental health was assessed with the Center for Epidemiological Studies Depression Scale (CESD), the ACR Committee on Neuropsychiatric Lupus' suggested measure of depression in SLE, using validated cutoff values. Outcome variables included CESD > 23 (indicative of major depression) and CESD > 19 (indicative of a mood disorder). We used logistic regression

analysis to compare pSLE and aSLE with and without adjustment for other characteristics that could affect depression risk. Age, gender, ethnicity, marital status, poverty, the presence of renal disease, self-reported disease activity according to the Systemic Lupus Activity Questionnaire (SLAQ) score, and physical disability according to the SF-36 Scale of Physical Function (SF36-PF) were included as predictors.

Results: Mean age of subjects was 45±10 years, and 93% were female. Ethnicities included Caucasian (60%), Hispanic (10%), African American (10%), Asian (12%) and other (8%). Subjects with pSLE were more likely to be ethnic minorities (p=0.003). Mean age at diagnosis was 14±2.9 years for subjects with pSLE and 32±8.8 years for subjects with aSLE. Mean disease duration was 19±9.3 years for subjects with pSLE and 16±7.5 years for subjects with aSLE. Mean SLAQ score at the time of the survey was 11.4±8.0 for all subjects. The prevalence of mood disorders was similar among subjects with pSLE and aSLE (22% vs. 20% for major depression and 30% vs 36% for all mood disorders, respectively, p=NS). Subjects with aSLE were more likely to report a diagnosis of depression (35% vs. 25%, p = 0.08). In multivariate logistic regression analysis, there was no statistically significant difference in the odds of any mood disorder between the two groups. However, the odds of major depression among subjects with pSLE was more than double the odds of major depression for subjects with aSLE after adjustment for covariates (Table 1).

Table 1. Regression-adjusted ORs for the presence of any mood disorder or the presence of major depression among subjects age 18–60 with SLE*

Variable	OR for any mood disorder (95% CI)†	OR for major depression (95% CI)†
Pediatric-onset SLE	1.42 (0.73–2.74)	2.34 (1.06–5.17)
Age	1.01 (0.99–1.03)	0.99 (0.96–1.02)
Female	1.03 (0.46–2.28)	0.67 (0.25–1.77)
Ethnicity		
Caucasian	referent	referent
Latino	1.37 (0.73–2.56)	1.62 (0.77–3.42)
African American	1.11 (0.58–2.13)	1.68 (0.80–3.49)
Asian	1.08 (0.58–2.04)	1.40 (0.63–3.10)
Other	1.00 (0.47–2.14)	2.07 (0.88–4.85)
Married or Partnered	0.88 (0.45–1.03)	1.03 (0.82–1.72)
Poverty¶	1.75 (1.01–3.02)	1.10 (0.60–2.01)
Renal disorder	0.81 (0.51–1.27)	0.84 (0.47–1.48)
SLAQ	1.09 (1.05–1.13)	1.10 (1.06–1.14)
SF36-PF	0.97 (0.95–0.99)	0.95 (0.92–0.97)

* OR = odds ratio; 95% CI = 95% confidence interval; SLAQ = Systemic Lupus Activity Questionnaire (0–47); SF36-PF = SF-36 Scale of Physical Functioning (0–100).
† OR from logistic regression, adjusted for variables shown.
¶ Income below 125% of the Federal poverty level.

Conclusion: While subjects with pSLE are not at increased risk for all mood disorders, including mild depression, as compared to subjects with aSLE, onset of lupus in childhood may significantly increase the risk of major depression in adulthood. Appropriate screening and treatment for depression is important to maximize long-term quality of life and functional outcomes in patients with pSLE.

2026

Quality of Life and Psychosocial Aspects Among School Adolescents with Diffuse Chronic Musculoskeletal Pain in Brazil. AK Nascif[1], V. Valim[1], M. Dorio[2], JR Gomes[1], AFA Pereira[1], E. Zandonade[1] and Claudio Len[3]. [1]Universidade Federal do Espírito Santo, Vitória, Brazil, [2]Vitória, Brazil, [3]Universidade Federal de São Paulo / UNIFESP, Sao Paulo, Brazil

Background/Purpose: Diffuse chronic musculoskeletal pain (DCMP) is part of the pain amplification syndromes and is defined by the presence of pain in three or more body sites for at least three months, excluding other diseases that could explain the symptoms. Its prevalence on the pediatric age varies significantly among studies due to the diversity of populations, definitions and methods used, ranging from 1 to 15%. It is closely related to psychosocial disorders (behavioral and sleep disturbances, depression, anxiety, catastrophization and impaired self-perception). The aim of this study is to evaluate the prevalence, quality of life and psychosocial aspects of adolescents with DCMP.

Methods: All 175 adolescents from 16 to 17 years old from a public school in Vitoria, Brazil, were evaluated. The diagnosis of DCMP was based on medical interview and physical examination by a pediatric rheumatologist. For each case of DCMP, four healthy controls were selected, matched by gender and age. Self-applicable questionnaires were used for comparison: Children's Depression Inventory (CDI), Child Behavior Checklist (CBCL), Harter Self Perception Scale for Adolescents (HSPS-A) and the Pediatric Quality of Life Inventory™ Version 4.0 (PedsQL™ 4.0).

Results: Five adolescents were diagnosed with DCMP (prevalence 2.86%) and compared with 20 matched controls. The results of psychosocial aspects and quality of life are in table 1.

Table 1. Analysis of CDI, CBCL, HSPS-A and PedsQLTM 4.0 questionnaires from cases and controls.

Questionnaire		Results			
		Group	Mean	SD e	p-value
CDI a	Score	Case	7.20	5.40	**0.0411**
		Control	3.28	3.12	
CBCL b	Score	Case	72.60	18.06	0.1051
		Control	57.50	17.86	
HSPS-A c	Total Score	Case	2.72	0.43	0.1704
		Control	2.96	0.32	
	Scholastic competence	Case	2.76	0.43	0.8202
		Control	2.82	0.54	
	Athletic competence	Case	1.88	0.54	0.0756
		Control	2.54	0.74	
	Social acceptance	Case	2.76	0.70	0.5527
		Control	2.95	0.63	
	Close friendship	Case	2.52	0.97	**0.0214**
		Control	3.28	0.51	
	Romantic appeal	Case	2.64	0.43	**0.0318**
		Control	3.15	0.45	
	Physical appearance	Case	2.48	0.69	0.1979
		Control	2.95	0.71	
	Behavioral conduct	Case	3.28	0.52	0.2159
		Control	2.98	0.47	
	Job competence	Case	3.20	0.35	0.2692
		Control	2.92	0.53	
	Global self-worth	Case	3.00	0.62	0.8494
		Control	3.06	0.59	
PedsQL™ 4.0 d	Total	Case	68.47	3.99	**0.0094**
		Control	81.62	10.04	
	Physical Health	Case	71.88	6.25	**0.0192**
		Control	85.89	11.90	
	Emotional Functioning	Case	60.00	11.73	0.1138
		Control	74.25	18.30	
	Social Functioning	Case	73.00	2.74	**0.0001**
		Control	87.75	12.30	
	School Functioning	Case	66.00	8.22	0.2967
		Control	74.73	17.59	

[a]Children's Depression Inventory; [b]Child Behavior Checklist; [c]Harter Self Perception Scale for Adolescents; e Pediatric Quality of Life Inventory™ Version 4.0; [e]Standard-Deviation

Conclusion: The prevalence and greater incidence of depressive symptoms in adolescents with DCMP are similar to the data available in the literature. The lack of difference in self-perception and self-evaluation of behavior possibly suggests a greater focus on their own pain and physical limitations instead of their mental health, since other studies show detriment of psychosocial aspects when reported by parents. Besides, DCMP patients have impaired quality of life, difficulty in interpersonal relationship and loss of functional capacity for daily life activities. Therefore, it is important to value DCMP as an entity that causes a negative impact on the patient's life and has to be tackled in a multidisciplinary and effective manner.

2027

Race Is a Risk Factor for Calcinosis in Patients with Juvenile Dermatomyositis: Early Observations From the Childhood Arthritis and Rheumatology Research Alliance Registry (CARRAnet). Mark F. Hoeltzel[1], ML Becker[1], Angela B. Robinson[2], Adam M. Huber[3], Brian M. Feldman[4], Ann M. Reed[5] and Juvenile Myositis CARRA Subgroup for CARRAnet Investigators[6]. [1]Children's Mercy Hospital, Kansas City, MO, [2]Rainbow Babies and Childrens Hospital, Cleveland, OH, [3]Dalhousie University, Halifax, NS, [4]The Hospital for Sick Children, Toronto, ON, [5]Mayo Clinic, Rochester, MN, [6]Various

Background/Purpose: Previously established risk factors for calcinosis include duration of disease and the length of time to treatment, suggesting early aggressive treatment may be important in preventing calcinosis. Race has also been suggested to be a risk factor, but this observation was thought to be

secondary to delays in treatment and longer disease duration. We utilized the CARRAnet registry to investigate potential risk factors for calcinosis.

Methods: Children with juvenile dermatomyositis (JDM) in the CARRAnet registry were included in this analysis. Race and ethnicity were self-reported. Subjects with current or past calcinosis were identified. Potential predictors of calcinosis identified *a priori* included race, ethnicity, sex, ANA status, age, age of onset, duration of disease, and time to rheumatologic care. Bi-variable associations between clinical variables and calcinosis were evaluated by Chi-square test, Fisher exact test, two-sample t-test, or Wilcoxon Rank Sum test as appropriate. A multivariable logistic regression model was run with variables significantly associated in bi-variable analyses ($P<0.1$). All statistical analyses were conducted using JMP Stats version 8.0 (SAS Institute, Cary, NC).

Results: 198 subjects meeting modified Bohan and Peter criteria for JDM were enrolled from 40 U.S. sites. Four subjects were excluded due to lack of data regarding calcinosis or race. Twenty-three (12%) of the remaining 194 patients had a history of calcinosis. Seven of 26 (27%) subjects reporting African American (AA) ancestry and 16 of 168 (10%) subjects without AA ancestry had a history of calcinosis.

Bi-variable analyses revealed a significant association between calcinosis and AA ancestry [OR 3.5 95% CI (1.3, 9.6) $P=0.019$], disease duration in years [median (quartiles), 5.6 (4.0, 9.1) vs. 3.1 (1.7, 5.3) $P=0.0002$], and age at study visit in years [mean (± SD), 13.1 (± 3.5) vs. 10.8 (± 4.4) $P=0.015$]. Analyzing these three variables in a multiple logistic regression model revealed that AA ancestry [Adjusted OR 5.2, 95% CI (1.6 16.3) $P=0.005$], and disease duration [Adjusted OR 3.7, 95% CI (1.6, 9.0) $P=0.003$], were independent predictors of calcinosis.

When demographic variables and outcome assessments were compared between AA patients and non-AA patients, both CHAQ scores (mean (±SD), 0.58 (±0.68) vs. 0.3 (±0.54) [$P=0.002$]) and pain scores (mean (±SD), 2.4 (±0.4) vs. 1.5 (±0.2) [$P=0.045$]) were statistically significantly higher in AA patients, but there was no difference in age of onset, disease duration, or time to rheumatologic care.

Conclusion: Children of AA ancestry with JDM have increased odds of developing calcinosis. While longer disease duration remains a significant risk factor for calcinosis in the cohort as a whole, there was no difference in the disease duration of patients with AA ancestry and those without in the CARRAnet cohort, and AA ancestry remained a significant predictor after controlling for age and disease duration in multiple logistic regression modeling. These findings warrant further investigation to determine if the increased risk of calcinosis can be attributed to differences in genotype, disease phenotype, or treatment practices in the AA population.

2028

Anakinra for the Treatment of Hyper-IgD with Periodic Fever Syndrome in Children. Donald P. Goldsmith[1], Karyl S. Barron[2], Amanda K. Ombrello[3], Robert Lembo[3], Deborah Stone[3], Anne Jones[4], Dawn C. Chapelle Neal[5] and Daniel L. Kastner[6]. [1]Drexel University College of Medicine/St Christophers Hosp for Child, Philadelphia, PA, [2]NIAID-NIH, Bethesda, MD, [3]National Institutes of Health, Bethesda, MD, [4]NIH-NIAMS, Bethesda, MD, [5]NIAMS, Bethesda, MD, [6]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

Background/Purpose: Hyper-IgD with Periodic Fever Syndrome (HIDS) is an autosomal recessive autoinflammatory disorder thought to result from increased inflammasome activation. Various therapeutic agents have been proposed but there is no established treatment. Recent in vitro data indicates increased caspase-1 activity leading to active IL-I beta release (*Kuijk LM et al.Blood 2008;112:3653*). In earlier case reports and small series (*Rigante d et al. Rheumatol Int 2006;27:97* and *van der Hilst JC et al. Medicine 2008; 87:301*) clinical benefit has been noted using the Il-1 blocker, anakinra. To further explore its efficacy we assessed the therapeutic response of a cohort of pediatric HIDS patients to anakinra.

Methods: This study is a retrospective chart review of 11 children with HIDS. Eleven of 25 patients followed in the NIH Periodic Fever Clinic with known MVK mutations and symptoms compatible with HIDS, ages 4–17, were treated with anakinra. Five children had only one mutation in the MVK gene. Seven were started on intermittent administration at the onset of a febrile episode and 4 were treated with daily administration. Dosage most often was initiated at 1mg/kg with further increases when needed up to 3–5mg/kg/day. Clinical response was assessed at each outpatient visit by interview and clinical examination with determination of a clinical score based on changes in fever (frequency, duration, and apex), G-I symptoms, arthralgias/arthritis, and rash.

Results: Intermittent Rx (7patients): In 3 children there was a sustained reduction in the severity and frequency of febrile episodes (complete response). In 3 there was a reduction of in the severity but an increased frequency of episodes (partial response). In 1 there was no response (this child later developed JIA associated with dyserythropoietic anemia).

Daily Rx (4 patients): In 1 child there was reduced episode severity and no change in episode frequency (positive response). In 1 child there was reduced severity but increased episode frequency (partial response). In 2 there was no response.

Side effects were confined to localized cutaneous reactions. Those treated with daily therapy were assessed initially as having more severe clinical manifestations. Of 3 total patients with no clinical response 2 had previously been treated unsuccessfully with etanercept. With this small number of patients we were unable to correlate a specific mutation pattern with therapeutic results.Of note, however was that all 3 children who experienced an increased frequency of episodes had single MVK mutations.

Conclusion: The majority (8 [72%]) of 11 children with HIDS demonstrated a beneficial response to anakinra therapy, 4 complete and 4 incomplete. However, an increased frequency of episodes was an unexpected finding associated with benefit. These data emphasize that predictable, complete and enduring response to treatment with currently available biologic agents remains elusive. In this regard our results are similar to the analysis of 13 patients (adults and children) with HIDS treated with anakinra as reported by van der Hilst JC et al *(Medicine 2008;87:301).*

2029

Mycophenolate Mofetil in Children with Lupus: Clinical Findings in Favour of Therapeutic Drug Monitoring. Brigitte Bader-Meunier[1], Camille Jurado[2], Bruno Ranchin[3], Stéphane Decramer[4], Michel Fischbach[5], Etienne Berard[6] and Franck Saint Marcoux[2]. [1]Hôpital Necker, Paris, France, [2]INSERM UMR –S850, Limoges, France, [3]Hôpital Femme-Mère-Enfant, Lyon, France, [4]hôpital Purpan, Toulouse, France, [5]Hôpital Hautepierre, Strasbourg, France, [6]Hôpital Lenval, Nice, France

Background/Purpose: The use of mycophenolate mofetil (MMF) in children with Systemic Lupus Erythematosus (SLE) is increasing. However, the clinical benefit of its monitoring has been scarcely studied, and little is known about its pharmacokinetics in this context. We have launched a non interventional study with analysis of clinical, biological and pharmacokinetic (PK) information obtained from paediatric inpatients with SLE already treated with a maintenance immunosuppressive therapy including MMF. The main purpose of the study was (i) to model mycophenolic acid (MPA; the active moiety of MMF) PK profiles; (ii) to explore the relationships between exposure indices to MPA and the clinical status.

Methods: Full-PK profiles of MPA were collected and the observed concentration-time curves were fitted using a one compartment open PK model where a potential secondary peak of absorption is taken into account. Clinical data were summarized using the consensually recommended Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the disease was considered active for a score ≥ 6. The relationships between MPA through concentrations (C_0), Area Under the Curve (AUC) or AUC/dose values, and the activity of the disease were then explored using Receiver Operating Curve (ROC) and logistic regression analysis.

Results: According to the design of the study, indications of performing MPA PK profiles with the aim of calculating AUC values were based on clinical decisions made by the patients' physicians. Full-PK profiles of MPA were obtained at steady state from twenty six children aged from 10 to 17 years with SLEDAI score ranging from 0 to 20 (median: 4) and followed-up in five different French centres. The PK model fitted accurately the data and reported a high interpatient variability: $AUC_{0-12h} = 40.51 \pm 20.49$ mg.h/L. Trough concentrations were poorly correlated to the global exposure to MPA (AUC). Multivariate analysis found: (i) no relationship between C_0 and SLEDAI; (ii) that patients with an AUC_{0-12h} / dose < 0.058 mg.h/L/mg were more likely to have an active disease (OR= 4.8; 95CI: 0.9–25.0; $p = 0.067$).

Conclusion: A PK model enabling the description of MPA PKs in children given MMF for lupus treatment was developed. Preliminary results obtained in this small population showed a tendency to a relationship between the activity of the disease and a too low exposure to MPA at the time of PK sampling. Further data are needed (i) to develop PK tools that could estimate the AUC using a limited sampling strategy (i.e. Bayesian estimators) and (ii) to lead prospective trials testing the potential impact of the therapeutic drug monitoring of MMF based on the AUC.

1. Saint-Marcoux F et al. Pharmacol Res 2011.

2030

Autoantibody Testing for Children on Biologic Therapies for Rheumatological Conditions: Results of Audit. Julie Duncan, Jill Heath, Eileen M. Baildam, Gavin Cleary, Michael W. Beresford and Liza J. McCann. Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom

Background/Purpose: Biologic agents may cause auto-antibody formation and drug induced lupus but no paediatric guidelines exist regarding monitoring of auto-antibodies. The UK Royal College of Nursing Guidance advises checking ANA and anti-dsDNA before starting biologic treatment and repeating anti-dsDNA if concerned. A large tertiary paediatric rheumatology centre in the UK, Alder Hey, tended to test an autoantibody profile (see table) 3–6 monthly for data entry for the British Paediatric and Adolescent Rheumatology (BSPAR) Biologics and New Drugs Registry (BDNR). Children receiving IV biologic administration often had automatic antibodies testing more frequently, sometimes 4–6 weekly.

Methods: A retrospective audit of a 2 year period, August 2008 to July 2010 was carried out to determine frequency of abnormal autoantibody results in children on biologic therapies at a large tertiary paediatric rheumatology centre. All patients on biologics were included with data on auto-antibodies collated using the hospital computer system. Data were analysed including frequency of abnormal results and a cost analysis of tests done. The results were used to devise a rational protocol for frequency of testing.

Results: 111 children were receiving biologic therapy and 2511 auto-antibodies were tested at a cost of over £26,000.

Diagnosis of patients receiving biologic therapies	No. of Patients
JIA	102
SLE	1
JDM	2
Scleroderma	2
Uveitis (without arthritis)	2
Systemic sclerosis	1
Sarcoid vasculitis	1

Antibody	No. of children with positive results/ No. children with antibodies checked [%]	No. of positive antibodies/ No. antibodies checked [%]	Comments
ANA	80/111 [72%]	431/540 [79%]	36 children [32%] ANA always +ve; 44 children ANA sometimes +ve but not always.
Anti ENA	4/109 [<4%]	18/501 [<4%]	Always non-specific. Negative on subsequent testing.
Anti dsDNA	1/111 [<1%]	2/510 [<1%]	Negative on subsequent testing.
ANCA	14/41 [34%]	25/66 [38%]	Always non-specific (non PR3/ MPO).
Anticardiolipin	6/98 [6%]	8/894 [<1%]	Negative on subsequent testing.

Conclusion: With the exception of ANA antibody, all other antibody tests were usually negative. Those that were positive tended to be non specific (ie. ANCA non-PR3/MPO; ENA no specific specificity) and/or were negative on subsequent testing. The results did not alter patient care yet costs are significant. This audit would suggest that antibody tests are checked too frequently at Alder Hey Hospital. A new protocol as a result of this audit recommends testing auto-antibodies annually in the absence of clinical signs / symptoms of lupus.

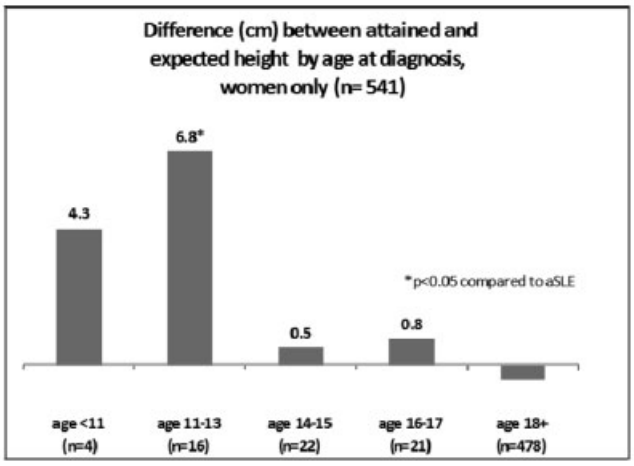
2031

Effects of Pediatric-Onset Systemic Lupus Erythematosus on Final Linear Height: Evidence From a Large Observational Cohort. Laura Trupin[1], Aimee O. Hersh[2], Jinoos Yazdany[3], Erica F. Lawson[1] and Emily von Scheven[1]. [1]UC San Francisco, San Francisco, CA, [2]University of Utah, Salt Lake City, UT, [3]University of California San Francisco, San Francisco, CA

Background/Purpose: Children with systemic lupus erythematosus (SLE) are at risk for decreased and delayed growth due to the effects of glucocorticoid exposure and the disease itself on skeletal bone development. However, due to lack of follow-up data, little is known about the final height attainment of patients with pediatric SLE. Using a large cohort of adults with SLE, we compared expected and actual heights for those diagnosed in childhood and adulthood.

Methods: Data derive from the 2007 cycle of the Lupus Outcomes Study (LOS), an annual telephone survey of diverse English-speaking adults with confirmed SLE. Subjects reported their current height and both parents' heights. Subjects aged 18–60 years with complete height data (N=580) were included. We defined pediatric-onset SLE (pSLE) as age at diagnosis < 18 years (N=72). Expected height was estimated by the Tanner formula, a validated measure for calculating midparental height. We used linear regression to compare the difference in expected and final linear height for pSLE and adult-onset SLE (aSLE) subjects, before and after adjustment for current age, gender, ethnicity, and end stage renal disease (ESRD). We examined expected vs. final height by age at diagnosis for pSLE women only, as there were too few men for a stratified analysis.

Results: Mean age of subjects was 43±10 years; 93% were female; 32% were ethnic minorities (9% Hispanic, 7% African American, 11% Asian, 5% other). PSLE subjects were younger ($p<0.01$), more likely to be nonwhite ($p<0.01$), and to report ESRD ($p=0.01$). Mean age at diagnosis was 14±3 years for pSLE and 34±10 years for aSLE subjects. Mean disease duration was 15±10 years for subjects with pSLE and 11±7 years for subjects with aSLE. Among pSLE subjects, the average difference between expected and final height was 2.4cm (95% CI 0.7–4.1), significantly greater than for aSLE subjects (−0.5cm; 95%CI −1.0–0.6; $p<0.01$). Thirty-one percent of pSLE subjects were ≥5cm below expected heights as compared to 14% of aSLE subjects, a difference seen in both men and women. Controlling for age, gender, ethnicity, and ESRD slightly increased the effect of pediatric onset disease on final height (adjusted mean: 2.8cm, 95% CI 1.1–4.4). No other variable in the model was associated with final height. Among women with pSLE, most of the effect on difference between expected and final height was seen in those diagnosed between age 11–13 years (see figure).



Conclusion: In this observational cohort of adults with SLE, we find a significant association between pediatric onset disease and shorter than expected adult stature. Patients who are peri-pubescent at disease onset may be at particular risk for growth delay. A larger, prospective cohort would allow for examination of the effects of disease activity and glucocorticoid use on final height attainment and better define which pediatric SLE patients are at highest risk for delayed or decreased growth.

2032

"Living Well" Chronic Disease Self-Management Program for Adolescents with Rheumatic Disease. Sheetal Vora[1] and Elizabeth L. Roth-Wojcicki[2]. [1]Medical College of Wisconsin, Milwaukee, WI, [2]Medical College of WI, Wauwatosa, WI

Background/Purpose: Chronic health conditions (CHC) in adolescents is a critical issue with estimates of 12–18% affected and with 6.5% experiencing disability. Childhood rheumatic disease contributes to increasing morbidity and costs of medical care and decreased health related quality of life (HQRL). Studies in CHC have demonstrated that self-management interventions that augment medical treatments improve health outcomes and HRQL. Evidence of the effectiveness of self-management therapies in adolescents has been sparse. The purpose of this research is to evaluate an adult self-management program (SMP) for its effectiveness in adolescents with rheumatic disease.

Methods: 15 adolescents, ages 13–20, together with their parents, followed in the rheumatology clinic at the Children's Hospital of Wisconsin (CHW) for greater than 3 months with a documented rheumatic disease were asked to participate. All were English speaking, and with no known cognitive delays. The program consists of 6 weekly sessions lasting 2 hours. To evaluate effectiveness of CDSMP, adolescents completed qualitative instruments including demographics, visual analog score of general health of adolescent by both parent and adolescent, general health symptoms (discouraged, worry, frustrated), self-management efficacy (SME), quantifying health service utilization, Peds QL Rheumatology and Peds QL Inventory teen reports. Data was collected at baseline, program completion and 3 months post program. Repeated measures analysis of variance with multiple comparisons corrections was used to identify changes from baseline.

Results: Demographics revealed that 60% were white, all were attending school, 60% came from a 2 parent household and 60% had the diagnosis of juvenile idiopathic arthritis, with the remainder either systemic lupus erythematosus or other defined rheumatic disease. Statistically significant variables found an increase in hospital and emergency visits ($p=0.029$) at each measurement; and increase in SME ($p=0.011$) and communication, a subscale of SME ($p=0.037$) from baseline to 3 months post program. Urgent care doctor visits, hospitalizations and missed doctor visits showed no significant (NS) difference. General health symptoms, discouraged and frustrated, showed improvement (NS) from baseline to 3 months post program only; worried improved successively (NS). Peds QL Inventory subscales; physical health showed no difference; emotional social and school functioning, and psychosocial health all showed improvement from baseline to 3 months post program (NS). Peds QL Rheumatology subscales pain and hurt, daily activities, treatment, worry and communication had no improvement.

Conclusion: CDSMP effectiveness in adolescents with rheumatic disease showed significant improvement in self-management efficacy and communication related to SME. General health symptoms and Peds QL Inventory subscales documented improvement despite an apparent increase in doctor hospital and emergency visits. Future plans include development of an adolescent SMP to improve self-management skills and allow for evaluation of health care utilization, health behaviors and status, and HRQL.

2033

Ethnic Differences of Early Disease Severity in Pediatric Systemic Lupus Erythematosus At An Urban Tertiary Care Center. Jennifer M.P. Woo[1], Peony Liu[2], Miriam F. Parsa[1], Gil Amarilyo[1], Alice DC Hoftman[2], Deborah K. McCurdy[2] and Ornella J. Rullo[2]. [1]University of California, Los Angeles, Los Angeles, CA, [2]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA

Background/Purpose: Systemic lupus erythematosus (SLE) can be characterized by increased incidence and disease severity in individuals of non-European descent. However, there exists a paucity of information describing disease manifestation at presentation and during the early stages of the disease process in pediatric SLE patients of different racial and ethnic backgrounds. We hypothesize that non-Caucasian pediatric SLE patients (pSLE) have an earlier, more severe disease course compared to Caucasian patients.

Methods: We retrospectively reviewed the medical records of 152 patients with pSLE (diagnosis $<$ 18 years) treated at an urban tertiary-care center between 2000 and 2010. Demographic and socioeconomic data were collected for each subject. ACR SLE criteria and SLE Disease Activity Index (SLEDAI) were evaluated at diagnosis, and any renal biopsy results were recorded. All subjects were assessed for cumulative steroid use, use of additional immunosuppressive agents, and urine protein-creatinine ratios at 12 months. Comparison of these data between Hispanic- (HA), Asian- (A), African- (AA), and Caucasian-(CA) American pSLE for was conducted using computed means, 95% confidence intervals, Student's one-tailed t-test, and Fisher's exact test.

Results: HA, AA, and A pSLE patients were diagnosed at a younger age than CA pSLE ($p < 0.05$; Table 1). Although the number of ACR criteria at diagnosis did not differ among the groups compared to CA, AA and HA were more likely to have arthritis at diagnosis than CA (44% and 37% vs 25%; $p = 0.007$ and 0.09, respectively). Furthermore, A and HA were more likely to present with proteinuria than CA (42% and 44% vs. 25%, $p = 0.02$ and 0.007, respectively) although prevalence of renal involvement by ACR criteria at SLE diagnosis only reached statistical significance in A vs CA (53% vs 38%; $p = 0.047$). Interestingly, increased rates of abnormal urine protein-creatinine ratios were observed at 12 months after SLE diagnosis in the HA and AA groups (64% and 40% vs. 25% in CA; $p < 0.0001$ and 0.03, respectively), but not in A (33%; $p = 0.3$ vs. CA). Over the first 12 months, significantly more HA, AA, and A required $>$150mg/kg of cumulative steroids compared to CA subjects ($p \leq 0.03$ for all) with additional immunosuppressive agents required for HA, AA, and A (Table 1). Of note, non-CA groups were significantly more likely to have government-assisted insurance and HA and AA tended to live in areas of significantly lower median family income compared to CA (Table 1).

Table 1. Clinical and socio-economic characteristics of CA, HA, AA and A rSLE patients.

	CA (n = 21)	HA (n = 68)	*p**	AA (n = 27)	*p**	A (n = 33)	*p**
Female:male	18.3	57.11		22:5		27.6	
Age at diagnosis, years	14	12.1	0.02	12	0.04	12.2	0.04
Clinical							
ACR SLE criteria, median (range)	5 (4.8)	4 (4.7)	0.5	4 (4.8)	0.8	4 (4–6)	0.3
SLEDAI at diagnosis, median (range)	8 (0–21)	10 (0–27)	0.3	12 (3–18)	0.4	12 (2–26)	0.19
Cumulative steroid use, %[1]	31	46	0.03	56	0.0004	47	0.03
Immunosuppression mean	1	16	0.04	1.8	0.04	17	0.06
Abnormal urine Pr/CR, %†	25	64	<0.0001	40	0.03	33	0.3
Sociodemographic							
Median household income, $‡‡	59,437	39,484	<0.0001	49,739	0.01	57,047	0.4
Insurance status, %			<0.0001		<0.0001		0.01
Uninsured	5	2		4		0	
Government	9	62		39		23	
Private	86	36		57		77	

CA-Caucasian; HA-Hispanic American; AA-African American, A-Asian American
* *p*-values taken in comparison to CA values and considered significant at $p < 0.05$
† % of patients requiring cumulative prednisone >150mg/kg in 1st year after diagnosis
†† Number of immunosuppressive agents required in addition to steroids and/or hydroxychloroquine in 1st year after diagnosis
‡ Urine PL/Cr >0.2 at 1 year after SLE diagnosis
‡‡ Based on 1999 US census figures for zip codes of patients at diagnosis

Conclusion: Pediatric patients of non-Caucasian background were diagnosed with SLE at a younger age, seemed to differ from Caucasian-American groups in SLE presentation, and had a potentially more severe early disease course, including increased immunosuppressive requirements. Prospective studies will help to clarify differences between these groups and to determine impact of socioeconomic factors.

2034

Clinical Characteristics of Children with Juvenile Dermatomyositis Recruited within the First 11 Months of the Children's Arthritis and Rheumatology Research Alliance Registry (CARRAnet). Mark F. Hoeltzel[1], ML Becker[1], Angela B. Robinson[2], Adam M. Huber[3], Brian M. Feldman[4], Ann M. Reed[5] and Juvenile Myositis CARRA Subgroup for CARRAnet Investigators[6]. [1]Children's Mercy Hospital, Kansas City, MO, [2]Rainbow Babies and Childrens Hospital, Cleveland, OH, [3]Dalhousie University, Halifax, NS, [4]The Hospital for Sick Children, Toronto, ON, [5]Mayo Clinic, Rochester, MN, [6]Various

Background/Purpose: Performing quality research in juvenile dermatomyositis (JDM) is difficult due to the rarity of the disease. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) initiated a multicenter observational cohort study to create a foundational clinical database for the major rheumatic diseases of childhood, including JDM. Initial data from the JDM cohort (prevalent and incident cases) enrolled in the first 11 months are described here.

Methods: Patients under the age of 21 yrs with onset of JDM prior to 16 yrs of age were included. JDM was established using modified Bohan and Peter criteria. IRB approval was obtained at each enrolling site. Subjects or their guardians gave consent, and clinical data were collected from the patients/guardians and medical providers using both general and

JDM-specific case report forms at the time of enrollment. Data regarding demographics, disease characteristics, diagnostic assessments, and medication exposure were collected. Measures of muscle strength, physical functioning, and quality of life were performed, including the Childhood Myositis Assessment Scale (CMAS), Childhood Health Assessment Questionnaire (CHAQ), Health Related Quality of Life measure (HRQOL), ACR Functional Class rating, global disease assessments, and pain scores.

Results: Over an 11 month period, 198 subjects with JDM were enrolled from 40 sites in the U.S. A summary of subject demographics and disease characteristics is provided in Table 1. At enrollment, the median (quartiles) CMAS score was 51 (46, 52), range from 0–52, the median CHAQ score was 0 (0, 0.5), range from 0–3, and the median physician and subject global assessment scores were 1 (0, 2), range from 0–8, and 1 (0, 3), range from 0–9, respectively. HRQOL rating, ACR functional class, and pain scores are represented in Figure 1.

Table 1. Demographics and Disease Characteristics

Characteristic	Number (%) of Subjects	Range, yrs	Characteristic	Number (%) with characteristic *ever*	Number (%) with characteristic *at enrollment*
Sex			Elevated muscle enzymes	190/196 (97%)	21/196 (11%)
Female	147 (74%)		Arthritis	74/190 (39%)	7/190 (4%)
Male	51 (26%)		Calcinosis	23/194 (12%)	19/194 (10%)
Race			Dysphagia/Dysphonia	51/189 (27%)	2/189 (1%)
White	154 (78%)		ILD	5/186 (3%)	1/186 (1%)
African American	21 (11%)		GI Ulceration	6/187 (3%)	1/187 (1%)
American Indian	2 (1%)		Cardiac involvement	2/187 (1%)	1/187 (1%)
Asian	4 (2%)		Weakness		
Pacific Islander	1 (1%)		None	–	139/197 (71%)
Multi-racial	8 (4%)				
Unknown	8 (4%)		Mild	–	44/197 (22%)
Ethnicity			Moderate	–	12/197 (6%)
Non-Hispanic	169 (60%)		Severe	–	2/197 (1%)
Hispanic	29 (15%)		Periungual telangiectasia	–	79/190 (42%)
1° Family hx of autoimmunity	35/179 (20%)		Malar or facial erythema	–	59/197 (30%)
Positive ANA	100/163 (61%)		Contractures	–	16/198 (8%)
Chronology	Median, yrs (quartiles)	Range, yrs	V or shawl sign	–	10/198 (5%)
Age	10.8 (7.7, 14.5)	2.4–21.0	Lipodystrophy	–	9/198 (5%)
Age of onset	6.2 (3.5, 9.3)	0.2–15.9	Skin ulcer	–	6/197 (3%)
Disease duration	3.7 (1.9, 5.9)	0.2–14.0	Gottron sign, papules, or heliotrope	–	89/198 (45%)
Time to rheumatologist	0.38 (0.16, 0.90)	0–5.1			

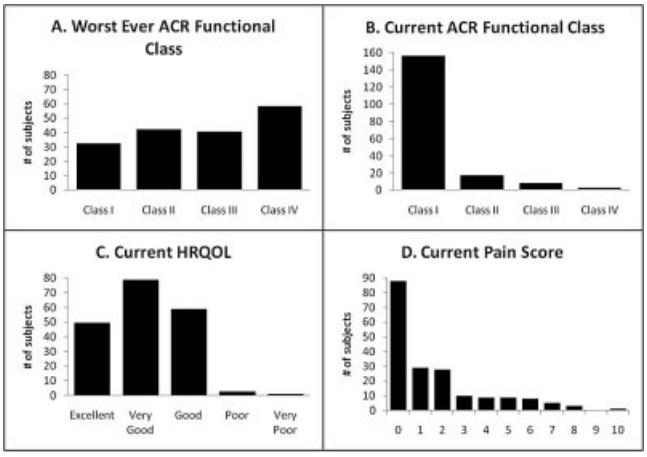


Figure 1.

Conclusion: The ongoing CARRAnet registry has collected clinical data on 198 children with JDM and has the potential to become one of the largest JDM cohorts in the world. Subject demographics are similar to other reported JDM cohorts from the U.S. and elsewhere. This is the first U.S. study to report prevalence of disease manifestations and functional and quality of life outcomes in a cross-sectional manner. The relatively mild disease severity observed at enrollment likely reflects the disproportionate number of prevalent cases collected to date, and is similar to other international cross-sectional JDM cohorts. This registry provides the infrastructure needed to advance clinical and translational research and represents a major step towards improving outcomes of children with JDM.

2035

Outcome of Babies Born to Mothers with Systemic Auto-Immune Diseases. Noemie Abisror[1], Arsene Mekinian[1], Eric Lachassinne[2], Pascale nicaise-Roland[3], Jerome Stirnemann[4], Loic de Pontual*[2], Lionel Carbillon[5] and Olivier Fain[4]. [1]Jean Verdier Hospital, Bondy, France, [2]Service de néonatologie et pédiatrie, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France, Bondy, France, [3]Unité Fonctionnelles d'Immunologie «Autoimmunité et Hypersensibilités», AP-HP, Hôpital Bichat-Claude Bernard, Paris, Paris, France, [4]Service de médecine interne, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France, Bondy, France, [5]Service de gynécologie-obstétrique, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France, Bondy, France

Background/Purpose: To evaluate the neonatal complications, the long-term outcome and the immunological profile of babies born to mothers with primary antiphospholipid syndrome and lupus erythematosus.

Methods: Retrospective study from 2003 to 2010, assessing the clinical characteristics and psychomotor development, as well as biological data of children born to mothers with antiphospholipid syndrome (APS) (Group 1) and systemic lupus erythematosus (Group 2).

Results: Group 1 consisted of 45 children born to mothers (n=35) with a primary APS (median age 33 years [27–44]). The treatments during pregnancy were aspirin 100 mg (n = 31) and low-molecular weight heparin (LMWH) (n=35). Premature term < 37 weeks was present in 6 cases (13%). The median weight at birth was 3000 grams [920–4100], and 8 children had a weight < 2500 grams (18%) (table). The median follow-up was 11 months [1–72]. Since no thrombosis, or lupus were noted, an abnormal psychomotor development occurred in 5 cases [motor distal disorders (n=2) and autism (n =3)], associated with a language delay in 5 cases (11%). Three children with autism had persistent antibéta2GP1 IgG antibodies.

	APS group children (n=45)	Lupus group children (n=13)
Term	38 [32–41]	38 [37–41]
Term <37 weeks	6 (13%)	0
Birth weight (g)	3000 [920–4110]	3000 [2500–4000]
Birth height (cm)	49 [37–58]	49 [44–52]
Birth cranial perimeter (cm)	34 [30–39]	34 [32–50]
Apgar 1/5 minutes	10 [9–10]/10 [5–10]	10 [9–10]/10 [10]
Birth weight<2500 g	7 (18%)	0
Psychomotor development trouble	5 (13%)	0
Neonatal lupus	0	3 (23%)*
Follow-up (months)	11 [1–72]	9 [3–48]
Antinuclear antibodies	0 [0–80]	320 [0–1280]*
Anti-SSA antibodies	0	4 (31%)

*p<0.05

Group 2 consisted of 13 children born to mothers with systemic lupus (n=10) (median age 37 ([31–42]).) During pregnancy, treatments were aspirin 100 mg in association with low-molecular weight heparin (n = 6), hydroxychloroquine (n=8) and corticosteroids (n=8). Median birth weight was 3000 grams [2500–4000], and no preterm birth or weight<2500 g were noted (table). During follow-up of 9 months [3–48], three children experienced cutaneous neonatal lupus, but there were no thrombosis, or psychomotor development abnormalities. Antinuclear antibodies were present in 8 children (320 UI [0–1280]), and anti-SSA antibodies in 4 cases. Significant correlation was noted between antinuclear antibodies in mothers and children of group 2 (r =0.9; p = 0.01).

Comparing the characteristics of group 1 and 2, no significant difference was found with regard to the parameters at birth, during the follow-up or the presence of antiphospholipid antibodies. The children in Group 2 had more frequently antinuclear antibodies (p < 0.05), with median titers 320 UI [0–1280] in group 2 versus 0 [0–80] in group 1 (p = 0.0002).

Conclusion: Despite a significant rate of premature birth in babies born to mothers with APS, it does not seem to be increase of psychomotor development abnormalities. Nevertheless the presence of 3 cases of autism and of disorders in language acquisition should be analysed in a

study with a control group. The presence of anti-nuclear antibodies and neonatal lupus is more common in children born to mothers with lupus, inversely of children from APS mothers, in concern to antiphospholipid antibodies and thrombosis.

2036

Accrual Damage Assessment In Juvenile-Onset Systemic Lupus Erythematosus. Juan G. Ovalles, Julia Martínez-Barrio, Francisco J. López-Longo, Inmaculada de la Torre, Lina Martínez-Estupiñán, Juan C. Nieto and Luis Carreño. Gregorio Marañón Hospital, Madrid, Spain

Background/Purpose: Several studies have shown that patients with juvenile-onset systemic lupus erythematosus (JOSLE) develop more organ involvement and accrue irreversible damage at faster rates than adult SLE patients[1–4]. To investigate the frequency of cumulative organ damage in JOSLE and its association with demographic, clinical and immunological variables.

Methods: Data was obtained from a single-center inception cohort of 92 cases diagnosed at 18 years old or less between 1986 and 2006. Demographic, clinical and laboratory features were collected at disease onset and every 12 months with a minimum follow-up time of 1 year (median 12, 1–20). Damage was scored at the end of the study using SLICC/ACR Damage Index. Sera samples were tested for autoantibodies, complement and immunoglobulins. Student′s T, Chi-square or Fisher′s exact test was applied for bivariate analysis and multiple logistic regression for multivariate analysis.

Results: Overall, 68% patients had organ damage (SLICC/ACR≥1) with a mean score of 1.8. At disease onset renal involvement was associated with the presence of damage (p<0.002). Developing irreversible system damage was related to anaemia (p=0.006), thrombocytopenia (p=0.001), arthritis (p=0.01), neurologic (p<0.001), renal (p=0.002), hypertension (p=0.001) and musculoskeletal (p=0.02) manifestations during the follow-up. Also the accrual damage has shown relation with evolution time (p=0.009). The genre and mortality was no related to SLICC/ACR score (p>0.05). In logistic regression models, the occurrence of anaemia, arthritis, renal manifestations during follow-up and longer disease duration showed the strongest association with the presence of damage.

CHARACTERISTICS n=92	SLICC/ACR = 0 (n=29)	SLICC/ACR ≥ 1 (n=63)	p
At Disease Onset			
DEMOGRAPHIC FEATURES			
Sex Ratio (Female/Male)	8.6 (26/3)	5.2 (53/10)	NS
Age, Mean±SD	12.1±4.5	13.3±3.1	NS
CLINICAL MANIFESTATIONS (%)			
Renal	0 (0)	16 (25.4)	0.002
During Follow-Up			
Arthritis	20 (69)	57 (92)	0.01
Neuropsychiatric	2 (6.9)	35 (55.6)	<0.001
Renal	12 (41.4)	46 (73)	0.002
Hypertension	4 (13.8)	31 (49.2)	0.001
Musculoskeletal	3 (10.3)	21 (33.3)	0.02
Anaemia	12 (41.4)	45 (71.4)	0.006
Thrombocytopenia	1 (3.4)	21 (33.3%)	0.001
Disease Duration, Mean±SD	9.7 ± 5.6	14.8 ± 9.6	0.009
Exitus Letalis	0 (0)	7 (11.3)	NS

Best Predictor Logistic Regression Model for JOSLE patients with cumulative organ damage vs. patients without damage

	Odds Ratio	95% CI	p
Renal manifestations during follow-up	6.4	1.9–21.5	0.003
Anaemia	3.2	1.1–9.5	0.036
Arthritits	8	1.7–37.5	0.008
Evolution time	1.1	1.1–1.2	0.005

Conclusion: We found evidence of cumulative organ damage in 68% of the JOSLE cases. Damage was significantly more likely in patients who had experienced renal manifestations at diagnosis, had longer disease duration, anaemia, arthritis and renal manifestations during follow-up. Autoantibodies, in spite of being helpful for the diagnosis and prediction of SLE's activity, are not useful to predict damage.

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2037

Low Vitamin D in Juvenile Onset Systemic Lupus Erythematosus: Association with Disease Activity and Low Bone Mineral Density. Luciana P.C. Seguro[1], Caio B. Casella[1], Liliam Takayama[2], Eloisa Bonfa[3] and Rosa M.R. Pereira[4]. [1]University of Sao Paulo, Sao Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]University of Sao Paulo, São Paulo, Brazil, [4]Disciplina de Reumatologia da FMUSP, Sao Paulo, Brazil

Background/Purpose: Vitamin D plays an essential role in calcium homeostasis and bone health. There is also growing evidence that vitamin D may be involved in immunoregulation but there are few data regarding Juvenile onset SLE (JoSLE). This is the first study that evaluates vitamin D, bone mass and lupus activity concomitantly in this group of patients. The aim of this study was, therefore, to evaluate 25 hydroxyvitamin D (25OHD) levels in JoSLE patients and its possible association with disease activity, treatment, bone mineral density (BMD), body composition (BC).

Methods: Fifty-seven JoSLE patients were compared to 37 healthy controls. Disease activity was evaluated by SLEDAI. The serum concentration of 25OHD was used to measure the vitamin D reserves using a radioimmunoassay technique (DiaSorin, Stillwater, MN, USA). The intra and inter-assay variation coefficients were 16.6% and 22.6%. BMD and BC were measured using dual-energy X-ray absorptiometry (DXA).

Results: 25OHD levels were similar in patients and controls (21.44±7.91 vs. 22.54±8.25 ng/mL, $p=0.519$), despite vitamin D supplementation in 65% of patients and none in controls. The mean vitamin D supplementation was 429 UI/day. Patients with low levels of vitamin D (≤ 20 ng/mL) presented higher SLEDAI (3.10 ± 3.90 vs. 1.08 ± 2.50, $p=0.033$), lower C4 levels (12.79 ± 6.78 vs. 18.38 ± 12.24 mg/dL, $p=0.038$), lower lumbar spine BMD (0.798 ± 0.148 vs. 0.880 ± 0.127 g/cm^2, $p=0.037$) and whole body BMD (0.962 ± 0.109 vs. 1.027 ± 0.098 g/cm^2, $p=0.024$) compared with patients with vitamin D level >20ng/mL. BC was similar in both groups of patients (lean mass: 37.03 ± 7.79 vs. 38.40 ± 8.98 kg, $p=0.549$, fat mass: 18.17 ± 7.80 vs. 17.57 ± 6.67 kg, $p=0.764$) likewise the frequency of previous ($P=1.0$) and current use of glucocorticoids (GC) ($P=1.0$) and immunosuppressors (71 vs. 77%, $P=0.765$), and mean current daily dose of GC (14.19 ± 13.62 vs. 10.48 ± 15.78 mg/day, $P=0.345$).

Conclusion: Vitamin D insufficiency was associated with JoSLE flares and low bone mass independent of current CG dose, fat percentage and conventional vitamin D supplementation. This finding suggests that higher doses of vitamin D supplementation may be recommended not only for JoSLE with reduced BMD but also for those with active disease.

2038

Use of Urinary Metabolites to Distinguish Proliferative From Membranous Lupus Nephritis. Shannen L. Nelson[1], Rina Mina[2], Lindsey Romick-Rosendale[3], Hermine Brunner[4], Michael Bennett[2], Joshua D. Pendl[4], Michelle Petri[5], Adnan Kiani[5], Prasad Devarajan[2] and Michael Kennedy[6]. [1]Cincinnati Children's Hospital, Cincinnati, OH, [2]Cincinnati Children's Med Ctr, Cincinnati, OH, [3]Miami University, Ohio, Oxford, OH, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Johns Hopkins University School of Medicine, Baltimore, MD, [6]Miami University, Oxford, Oxford, OH

Background/Purpose: Lupus Nephritis (LN) is a severe complication of many patients with childhood-onset Systemic Lupus Erythematosus. Kidney biopsy is currently the standard for assessing LN, but due to their invasive nature is not done on a routine basis. The identification of specific and sensitive biomarkers may allow for more timely diagnosis of LN allowing for more prompt treatment. Objective: To identify urinary metabolites that discriminate between proliferative and pure membranous lupus nephritis (LN) as defined by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification using nuclear magnetic resonance (NMR) spectroscopy.

Methods: Metabolic profiling was conducted using urine samples of patients with proliferative LN but without membranous features (Class III/IV; n=7) or pure membranous LN (Class V; n= 7). Patients with primary focal segmental glomerulosclerosis (FSGS; n=10) and proteinuria served as disease controls. For each patient, information about demographic and clinical data was obtained a random urine sample collected to measure NMR spectra. Data and sample collection for patients with LN occurred around the time of kidney biopsy. Metabolic profiling analysis was done by visual inspection and principal component analysis.

Results: Urinary concentrations of the metabolite taurine were significantly higher with Class V LN as compared to Class III/IV LN ($p < 0.01$) (see Figure 1). There was also a trend towards lower urinary concentrations of the metabolite citrate with Class V LN as compared to Class III/IV LN ($p < 0.1$). Urinary concentrations of the metabolite hippurate were significantly higher with Class V LN as compared to FSGS but not different from Class III/IV LN ($p < 0.001$).

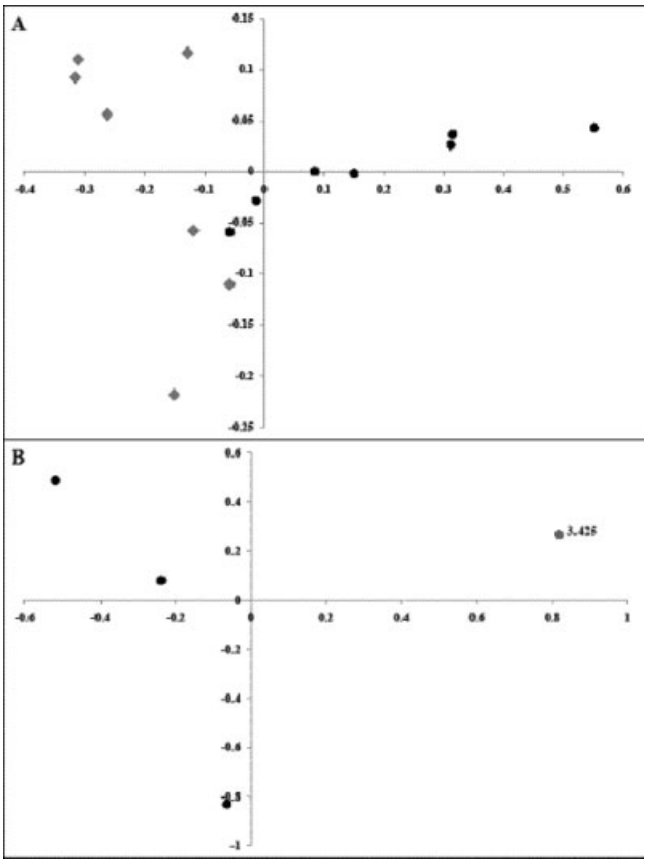

Figure 1. Principal Component Scores Plots of NMR-Spectra of Urine Samples with Proliferative and Pure Membranous Lupus Nephritis

Conclusion: This pilot study supports that there are differences in the urinary metabolite profiles of proliferative as compared to pure membranous LN. If confirmed in larger studies, these urine metabolites may serve as biomarkers to help discriminate between different classes of LN.

2039

Effectiveness of Anti-Tumor Necrosis Factor-α Agents in the Treatment of Refractory Juvenile Dermatomyositis. E.L. Boulter[1], L. Beard[2], Clive Ryder[3], Clarissa Pilkington[1] and Juvenile Dermatomyositis Research Group[4]. [1]Great Ormond Street Hospital, London, United Kingdom, [2]UCL Institute of Child Health, London, United Kingdom, [3]Birmingham Children's Hospital NHS Foundation Trust, Birmingham, United Kingdom, [4]London, United Kingdom

Background/Purpose: Juvenile dermatomyositis (JDM) is a rare, chronic inflammatory disease. Anti-TNF-α agents are increasingly being used to treat disease that is refractory to other treatments. There is a lack of literature regarding the effectiveness of anti-TNF-α agents in JDM. The aim of the study was to describe the response of refractory JDM patients to anti-TNF-α agents.

Methods: The Juvenile Dermatomyositis National (UK and Ireland) Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopathies database was searched for patients treated with anti-TNF-α agents.

Results: INFLIXIMAB: 28/30(93%) patients had data available. Indicators for starting infliximab were: muscle weakness (70%), non-ulcerative skin disease (57%), calcinosis (33%), and nail fold changes (30%). All patients with a low CMAS (n=18) improved. Physician VAS improved in 20/26(77%), CHAQ score in 11/16(69%), skin disease in 19/23(83%), calcinosis in 6/13(46%) and muscle enzymes in 6/10(60%). Prednisolone dose decreased in 17/21(81%).

ADALIMUMAB: 10/11(91%) had previously been treated with infliximab. 6/10(60%) were changed to improve disease control: 4 had persistent skin disease, 2 improved; 3 had progressive calcinosis, 1 improved, 2 remained stable. 8/9(89%) maintained previous gains or made further improvement in other parameters other than skin and calcinosis.

ETANERCEPT: 4/7(57%) patients had data available. 2 improved, 2 were switched to infliximab, one for increasing calcinosis, one for compliance issues.

Conclusion: Infliximab provides clinical benefit to patients with JDM refractory to other treatments; particularly muscle weakness. Switching to adalimumab benefited some patients; gains made on infliximab were maintained in most cases.

2040

Treatment Delay in Kawasaki Disease—the Role of Non-Traditional Risk Factors. Nadia Luca[1], Joyce C. Y. Ching[1], Cedric Manlhiot[2], Brian W. McCrindle[2] and Rae SM Yeung[1]. [1]Hospital for Sick Children, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON

Background/Purpose: Duration of fever is the most important predictor of coronary outcome in children with Kawasaki Disease (KD). The aim of this study is to define a specific and comprehensive profile for patients at risk for a delayed diagnosis of KD, including non-traditional factors such as physician experience with KD and health service utilization.

Patients and Methods: All hospitals and pediatric cardiologists in Ontario were contacted for identification of patients diagnosed with KD over a 12 year period (1995–2006). The only tertiary hospital, with KD experts on-site, was the Hospital for Sick Children in Toronto. Data on demographic information, day of the week admitted, symptoms, clinical features, treatment, and coronary outcome were collected. Hospital caseload was defined as low (<20 cases of KD per year) or high (>20 cases per year). The primary outcome was the number of days of fever prior to treatment with intravenous immunoglobulin (IVIg). Secondary outcomes were the number of days between admission and treatment, and coronary outcome. Data analysis was performed using multivariable linear and logistic regression models. Estimates (est), with associated standard error, are reported, which represent the change in outcome associated with each increment of 1 unit (continuous) or the presence (binary) of the independent variable.

Results: 2378 children were included, 13% of which were treated after the tenth day of fever. Clinical features associated with a greater delay in treatment were consistent with previously reported traditional risk factors and included older age and fewer KD features. Patients at the extremes of age had a greater risk of coronary artery aneurysm (CAA) development.

Earlier year of diagnosis was associated with delay of 0.04 days in IVIg administration ($p<0.001$) and an increased incidence of CAA (est 0.07; $p=0.03$). Patients prescribed antibiotics had 0.67 days more fever at time of treatment ($p<0.001$). Children admitted to hospitals with lower KD caseloads had fewer days of fever at admission (est 0.0031; $p=0.005$), but had a greater delay between admission and IVIg treatment (est 0.002; $p=0.01$).

Children admitted on Sunday had 0.80 more days of fever at time of treatment with IVIg (est 0.80; $p=0.04$). In addition, admission on Sunday was associated with a delay of 0.30 days between the time of admission and treatment with IVIg (est 0.30; $p=0.04$). When the tertiary care centre was excluded both of these delays were more significant. When the tertiary care centre was analyzed separately, no pattern for day of the week was identified.

Conclusion: We have identified critical non-traditional risk factors including health care centre characteristics and caregiver factors as important contributors to delay in diagnosis and treatment of KD.

2041

Health Care Transition Improvement Utilizing Learning Collaborative and the New Six Core Transition Elements. Patience H. White[1], Peggy McManus[2], Jeanne McAllister[3] and Carl Cooley[3]. [1]Arthritis Foundation, Washington, DC, [2]National Alliance to Advance Adolescent Health, Washington, DC, [3]Center for Medical Home Improvement, Concord, NH

Background/Purpose: Transition for youth with special health care needs from pediatric to adult health care remains a challenge. Needs assessments of youth, families and pediatric and adult providers reveal the requirements for successful transition. Practice improvement processes have been successful in medical home initiatives and the timing is right for their application to assist practices to improve their health care transition processes in partnership with youth and families.

Methods: Got Transition?, the new federally funded National Health Care Transition Center, has brought together the collective knowledge, tools and supports to facilitate the use of quality improvement and collaborative learning methods in 3 US regions (Washington DC, Denver, Colo, Boston, Mass) to help practices improve health care transition for youth and their families. The learning collaboratives are using a new clinical report that provides explicit practice-level guidance that is jointly endorsed by the American Academy of Pediatrics, American College of Physicians and American Academy of Family Physicians. The six core elements for health care transition and the Health Care Transition Indices for both pediatric and adult practices have been created to bring the clinical report to life and make it operational. To date two of the three national learning collaboratives have been created in Washington DC and Denver, Colo. The learning collaboratives include pediatric, family medicine and internal medicine teams with physicians, residents, nurses, social workers and youth and family partners.

Results: The combined baseline results from the self rated transition indices for the 10 practices in Washington DC and Denver, Colo participating in the learning collaboratives showed the need for the learning collaborative process and practice level health care transition support. Each practice rated their ability on a scale of 0–8 on the transition indices for each of the 6 core transition elements. The rating scale uses 8 as being most prepared and 0 being the least prepared in a particular element on the transition indices. The average rating of the 10 practices in the 6 core elements for health care transition were as follows: policy/privacy development 2, knowledge and skills 2.25, identification population 2.1, transition preparation 2, transition plan 2.5, transfer 2.6. The clinical report, six core elements of transition, and the transition indices with the baseline results for each of the Washington DC and Denver practices and the lessons learned from the Washington DC learning collaborative in will be presented.

Conclusion: The learning collaborative process is a new approach for supporting practices to improve the quality of the care for their patients moving from pediatric to adult models of health care and can be utilized in both primary and subspecialty health care transition initiatives.

2042

Mycophenolate Mofetil (MMF) Versus Azathioprine As Maintenance Therapy Combined with Monthly Intravenous Cyclophsophamide (IVCY) in Juvenile Lupus Nephritis. Toshitaka Kizawa, Tomoyuki Imagawa, Tomo Nozawa, Masako Kikuchi, Tomonori Harada, Takako Miyamae and Shumpei Yokota. Yokohama City University, Yokohama, Japan

Background/Purpose: The treatment failure to IVCY (as induction therapy) with azathioprine (as maintenance therapy) still remains to be a big problem in juvenile lupus nephritis patients. There is a growing body of evidence for the use of Mycophenolate mofetil (MMF) for maintenance treatment of lupus nephritis intractable to IVCY plus azathioprine.

Methods: Accompanying with monthly IVCY (500 mg/BSA) as induction therapy for 12 months, MMF (initial dose 1,000 mg/day, increased to 1,500 mg/day) as maintenance therapy was initiated in 10 patients with juvenile lupus nephritis for the same period, and compared to IVCY plus azathioprine (2 mg/kg/day) in 14 patients. Small doses of prednisolone (PSL) were administered in both groups. The primary endpoint was the improvement of renal histology by ISN/RPS classification, serum C3, C4 and CH50 titers, and other serum markers of disease activity, SLEDAI and reduced PSL doses.

Results: Ten patients who treated with IVCY + MMF (2 males and 8 femailes) revealed a significant improvement of renal histology (5/7, 71.4%) compared to 14 patients (2 males and 12 females) treated with IVCY + azathioprine (4/10, 40.0%) after 12 months treatment (Figure). Oral PSL doses were less in IVCY + MMF group (8.7 mg/day) than IVCY + azathioprine group (11.1 mg/day). At 12 months later, both the titers of serum activity markers (C3, C4, CH50, creatinine, and albumin) and SLEDAI were found no differences between the two groups. Adverse events, cytopenia, abnormal liver function tests, and abdominal abnormalities were found in IVCY + azathiprine group but not in IVCY + MMF group.

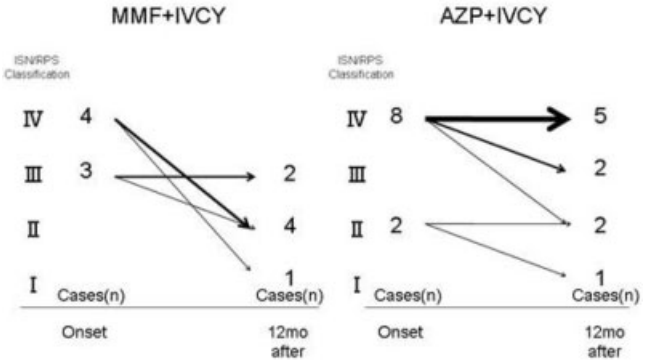

Figure.

Conclusion: MMF was well-tolerated, and efficacious as an induction therapy with monthly IVCY in patients with juvenile lupus nephritis.

2043

Inpatient Treatment Variation of Children Hospitalized with Complex Regional Pain Syndrome. Cara Hoffart[1], Pamela Weiss[2], Andrew J. Klink[3], David D. Sherry[3] and Chris Feudtner[4]. [1]The Childrens Hospital of Philadelphia, Philadelphia, PA, [2]The Children's Hospital of Philadelphia, Philadelphia, PA, [3]Children's Hospital of Philadelphia, Philadelphia, PA, [4]Division of General Pediatrics, Children's Hospital of Philadelphia; University of Pennsylvania Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA

Background/Purpose: Treatment for complex regional pain syndrome (CRPS) is comprised of intensive physical therapy, pain management, and psychological therapy. The pharmacologic and non-pharmacologic regimens used for CRPS treatment in children are incompletely characterized and optimal treatment is debated. The objective of this study is to characterize use of medications, physical therapy, and practice variation in CRPS treatment at U.S. children's hospitals.

Methods: We conducted a retrospective cohort study of children hospitalized between January 2004 and December 2009 with a discharge ICD-9-CM code for CRPS. We examined variation among 31 children's hospitals in the use of opioids and physical therapy services using multivariate mixed effects logistic regression models.

Results: During this 6-year study, we identified 644 individuals with 848 CRPS admissions. Physical therapy was prescribed for 583 patients (77.5%) during hospitalization. Pharmacologic drug therapy during admission included opioids (652 patients, 80.0%), non-steroidal anti-inflammatory drugs (493 patients, 60.5%), psychotherapeutics (511 patients, 62.7%), sedative hypnotics (206 patients, 25.3%), and anesthetics such as ketamine (245 patients, 30.1%). After adjustment for patient characteristics, hospitals varied significantly in their use of physical therapy, NSAIDs, anesthetics, psychotherapeutics, and sedative hypnotics ($p<0.001$). In contrast, hospitals did not differ significantly regarding administration of opioids.

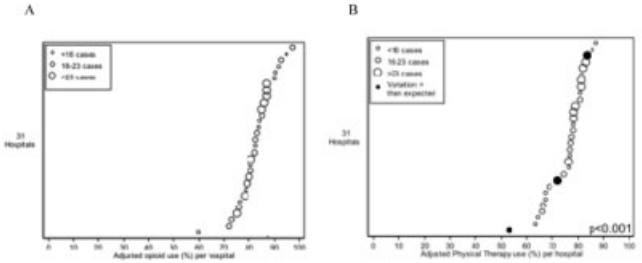

Figure 1. Use of Opioids (A) and PT/OT (B) among children's hospitals. There is no significant variation in opioid use across hospitals; however, the use of PT/OT is not uniform.

Conclusion: Significant variation in the inpatient treatment of CRPS exists across U.S. children's hospitals. Opioids are used consistently across hospitals in the majority of patients but the use of other drugs (psychotherapeutics, sedative hyponotics, anesthetics, NSAIDs) and PT/OT is not uniform. Future studies are warranted to evaluate whether these differences in treatment impact clinical outcomes such as duration and costs of hospitalization, readmission frequency, and further outpatient interventions.

2044

Children with Ehlers-Danlos Syndrome and Airway Dysfunction. Sanjay J. Khiani[1], Sara Lowe[1], Michael Zacharisen[1] and Sheetal Vora[2]. [1]Medical College of Wisconsin and the Children's Research Institute, Wauwatosa, WI, [2]Medical College of Wisconsin, Milwaukee, WI

Background/Purpose: Adults with hypermobility-type syndromes such as Ehlers-Danlos (EDS) have multiple issues including joint hyperextensibility, skin laxity/scarring, hearing, voice, speech, and swallowing disorders. Recent reports suggest a predominance of atopy and respiratory symptoms. Such information is not available in children. We report respiratory symptoms in children with EDS that complicates asthma or was erroneously diagnosed as asthma.

Methods: A series of 5 children with hypermobility-type EDS (1 and 3) presented to allergy/asthma clinic for evaluation of shortness of breath, chest tightness/pain, recurrent croup or chronic cough. At the discretion of their providers, evaluations included radiographic procedures, spirometry, videostroboscopy, rhinoscopy, largyngoscopy, methacholine challenge, airway fluoroscopy, and allergy testing.

Results: 5 children ages 9–14 years, 3 females, 2 siblings, all had recurrent respiratory symptoms and previously diagnosed as asthma. All had normal lung function with FEV1 96–124% of predicted. Only 2 had asthma confirmed with either reversible airway obstruction with albuterol or exercise pulmonary function test. One of these had 50% tracheal collapse and compression by aorta presenting as stridor. Two patients had environmental allergies confirmed by specific *in vitro* IgE or skin testing. Three patients had paradoxical vocal cord fold motion abnormalities on direct visualization with or without videostroboscopy. One had obstructive sleep apnea with 100% choanal obstruction by adenoid hypertrophy. Four of 5 had been diagnosed with GE reflux and 3 of these patients had g-tube placement and surgical intervention. Two patients had psychological issues such as anxiety and conversion disorder.

Conclusion: Children with EDS can have recurrent respiratory symptoms due to many etiologies including paradoxical vocal cord dysfunction, airway compression which may be erroneously attributed to asthma and possibly related to the underlying connective tissue abnormality.

2045

Cytomegalovirus in Pediatric Systemic Lupus Erythematosus: Screening and Therapeutic Implications. Evelyn V. Rozenblyum, Deborah M. Levy, Elizabeth Harvey, Diane Hebert and Earl D. Silverman. Hospital for Sick Children, Toronto, ON

Background/Purpose: Cytomegalovirus (CMV) is a beta-herpes virus. Its prevalence increases with age and infections may be severe or fatal in an immunocompromised host. Although there have been case reports of CMV in SLE patients, the relationship of CMV to SLE remains unclear as to which is the initial triggering disease. Determining the prevalence and outcome of CMV infection in pSLE would help establish the need for routine CMV testing prior to initiation of immunosuppressive therapy when indicated for pSLE. Currently, CMV is not routinely tested at the time of diagnosis of pSLE.

Objectives:

(1) Determine the incidence and prevalence of CMV infection at the time of diagnosis and during the course of pSLE.

(2) Determine if there are specific clinical and laboratory findings predictive of an active CMV infection.

Methods: Database review of all 540 patients seen in pSLE Clinic over a 20 year period identified 7 patients with SLE and concomitant CMV infection. Clinical manifestations, laboratory findings, virology studies and treatments were reviewed.

Results: CMV infection was detected in 7 adolescent patients; 6 (86%) at the time of diagnosis and one 5 years after diagnosis. Five were female and the mean age of the cohort was 14 years (10–17 years). All patients presented with fever, 6 had rash, 6 joint pain, 4 were nephrotic with peripheral edema and/or ascites, 3 respiratory symptoms, and 2 hepatomegaly. Six patients had nephritis and 2 required dialysis pre CMV detection. None of the patients were Caucasian- 4 patients were Asian (53%), 2 South East Asian (29%), and one Afro-Canadian (14%) ($p<0.01$ as compared to the total SLE cohort). Notable laboratory findings included: anemia in 6 (mean 101 g/L), lymphopenia in 5 with 3 patients having an absolute lymphocyte count of <500 cells (mean 1250 cells), hypoalbuminemia in 5 (mean 31 g/L) and mildly elevated liver function tests (LFTs) in 4. CMV was diagnosed by culture in 5 (urine in 3 and BAL in 2) and blood PCR in 2. All patients were on prednisone, 2 were on azathioprine and 1 was on cyclophosphamide prior to diagnosis of CMV infection. Six patients received gancyclovir and 5 Cytogam for CMV infection (1 patient received no therapy). All patients were maintained on prednisone throughout the treatment period. Six of 7 fully recovered without sequelae but one treated patient died during active CMV infection.

Conclusion: CMV infection was found in 6/540 (1.1%) patients at the time of diagnosis of pSLE. Non-Caucasian ethnicity, persistent fevers on prednisone, significant lymphopenia, abnormal LFTs and nephrotic syndrome were associated with CMV infection. We suggest routine testing for CMV at initial presentation of pSLE prior to immunosuppression.

2046

Alveolar Hemorrhage: Distinct Clinical Profile in Adult and Juvenile Systemic Lupus Erythematosus Patients. Daniel B. Araujo[1], Eduardo F. Borba Neto[1], Clovis A. Silva[1], Lucia M.A. Campos[1], Rosa M.R. Pereira[2], Eloisa Bonfa[1] and Samuel K. Shinjo[1]. [1]Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil, [2]Disciplina de Reumatologia da FMUSP, Sao Paulo, Brazil

Background/Purpose: Alveolar hemorrhage (AH) is a rare and severe manifestation of systemic lupus erythematosus (SLE). Therefore, the aim of this study was to compare characteristics of AH in juvenile (JSLE) and adult SLE (ASLE) patients.

Methods: from January 1990 to January 2010, 28 out of 1785 SLE patients (13 JSLE and 15 ASLE) had AH in our tertiary hospital.

Results: JSLE and ASLE had comparable disease duration (2.6 ± 3.0 *vs.* 5.6 ± 7.0 years, $p=0.151$) with the mean age at AH diagnosis of 15.3 ± 2.7 and 28.7 ± 10.3 yrs for JSLE and ASLE, respectively. The frequency of AH events was significantly higher in JSLE [4.94% (13/263)] compared to ASLE patients [0.99% (15/1522)], $p<0.001$ and it was diagnosed at SLE onset in two (15.4%) JSLE and six (40.0%) ASLE patients $p=0.221$). Before AH event, the JSLE patients were using a higher mean dose of prednisone (>0.5mg/kg/day) when compared to ASLE 54% *vs.* 15%, $p=0.042$). Macrophage activation syndrome with macrophage hemophagocytosis was only observed in JSLE compared to ASLE patients with AH diagnosis (23% *vs.* 0%, $p=0.087$). Regarding outcomes, frequencies of death were significantly higher in JSLE than ASLE patients (69% *vs.* 13%, $p=0.006$), with a trend of higher frequency of mechanical ventilation use (85% *vs.* 47%, $p=0.055$). In spite of that, the mean drop of hemoglobin was significantly lower in JSLE patients (2.9 ± 0.9 *vs.* 5.5 ± 2.9 g/dL, $p=0.006$). All other demographical, clinical and laboratory features were alike in both groups ($p>0.050$).

Conclusion: This study revealed that AH is more prevalent in juvenile lupus with a worse outcome compared to adult SLE patients.

2047

CD146+ Endothelial Progenitor Cell Number Increases Following 36 Months of Atorvastatin Therapy in Children and Adolescents with SLE: The Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) Cohort. Stacy P. Ardoin[1], Thomas Povsic[2], Laura E. Schanberg[3], Christy I. Sandborg[4], Huiman Barnhart[5], Eric Yow[5], Greg Evans[6], Kelly L. Mieszkalski[3], Norman T. Ilowite[7], Emily von Scheven[8], B. Anne Eberhard[9], Lisa F. Imundo[10], Yuki Kimura[11], Earl D. Silverman[12], Suzanne L. Bowyer[13], Marilynn G. Punaro[14], Nora G. Singer[15], David D. Sherry[16], Deborah K. McCurdy[17], Marisa Klein-Gitelman[18], Carol Wallace[19], Richard M. Silver[20], Linda Wagner-Weiner[21], Gloria C. Higgins[22] and Hermine Brunner[23]. [1]Ohio State University, Columbus, OH, [2]Duke University, Durham, NC, [3]Duke University Medical Center, Durham, NC, [4]Stanford University, Palo Alto, CA, [5]Duke Clinical Research Institute, Durham, NC, [6]Winston-Salem, NC, [7]Children's Hospital Montefiore, Bronx, NY, [8]UC San Francisco, San Francisco, CA, [9]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [10]Childrens Hospital of New York, Columbia University Medical Center, New York, NY, [11]Pediatrics, Hackensack, NJ, [12]Hospital for Sick Children, Toronto, ON, [13]James Whitcomb Riley Hospital, Indianapolis, IN, [14]Texas Scottish Rite Hospital, Dallas, TX, [15]Director, Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, [16]Children's Hospital of Philadelphia, Philadelphia, PA, [17]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, [18]Children's Memorial Hospital, Chicago, IL, [19]Childrens Hosp & Regional Med, Seattle, WA, [20]MUSC, Charleston, SC, [21]University of Chicago Hospital, Chicago, IL, [22]Nationwide Childrens Hosp, Columbus, OH, [23]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: Endothelial progenitor cells (EPCs) promote endothelial repair, and their number and function are reduced in adult SLE.

In the general population, statins decrease cardiovascular (CV) mortality, reduce EPC apoptosis and increase circulating EPCs. The impact of statins on EPCs has not been studied in SLE. We hypothesized that 36 months of statin therapy increase circulating EPC number in pediatric SLE (pSLE).

Methods: In the APPLE trial, 221 pSLE patients were randomized to receive atorvastatin or placebo. Carotid intima medial thickening (CIMT) was measured by b-mode ultrasonography using standard protocol. Lipids, high sensitivity c-reactive protein were measured after a 12 hour fast in a central laboratory. Samples were selected from subjects with CIMT and stored cell samples at 0, 12, 36 months (n=107).

Peripheral blood mononuclear cells (MNCs) were assayed using fluorescent antibodies against CD34, CD 133 and CD 146. Samples containing < 20,000 MNCs were excluded from analysis (n=35). EPC number was calculated as % of total MNC number.

Baseline characteristics were summarized using descriptive statistics. Differences between treatment groups were assessed with chi-square test, Fisher's exact test, or the nonparametric Wilcoxon test. Univariable relationships between CD 146+ cell subset and clinical variables were assessed, followed by multivariable linear regression modeling. All statistical analyses were 2-sided, and the level of significance was 0.05.

Results: At baseline, atorvastatin- (n=35) and placebo- (n=37) treated subjects had similar proportions of CD133+ CD34+, CD133+/34+ and CD146+ cells and did not differ according to age, gender, sociodemographics, BMI, renal status, disease duration or activity, or medications. In the placebo group, the proportion of CD133+, CD34+, CD133+/34+, and CD146+ cells did not change significantly over time. In the atorvastatin group, there were no significant changes from baseline in the CD133+, CD34+, CD133/34+ groups. The mean increase in proportion of CD146+ cells from baseline to 36 months was +1.48% (SD 1.0) in the atorvastatin group and +0.06% (SD 0.9) in the placebo group (p 0.011). In multivariable analysis, after covariate adjustment for age, gender, LDL, hscrp, prednisone dose, mean-mean CIMT, disease activity and damage, atorvastatin remained significantly associated with increase in CD 146+ cells (p 0.025; 95% CI 0.07, 1.04).

Conclusion: After 36 months of atorvastatin therapy, the proportion of CD146+ MNCs increased in the atorvastatin group but not in the placebo group. CD34+, 133+, 133+/34+ MNCs did not change significantly from baseline in either treatment group. Atorvastatin was independently associated with CD 146+ MNC increase in multivariable analysis. The CD146 marker is specific for EPCs but limitations include the following: EPC measurement is not widely standardized, normal values for adults and children are not defined, and clinically relevant magnitude of change in EPCs remains unknown. Despite these limitations, these exploratory analyses suggest that statin therapy may increase circulating EPCs, potentially enhancing capacity for CV repair in pSLE.

ACR/ARHP Poster Session C
Quality Measures and Innovations in Practice Management and Care Delivery II
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

2048

Serum Uric Acid Testing Patterns In Gout Patients: A Need for Improved Monitoring. Michael A. Becker[1], Bhavik J. Pandya[2], Jason R. Young[3], Xiangyang Ye[3], Sudhir Unni[3], Shawn Yu[2] and Carl V. Asche[3]. [1]University of Chicago Medical Center, Chicago, IL, [2]Takeda Pharmaceuticals International, Inc., Deerfield, IL, [3]University of Utah College of Pharmacy, Salt Lake City, UT

Background/Purpose: Hyperuricemia (serum urate level [sUA] >6.8 mg/dL) is the major pathogenetic factor in gout. Reducing sUA to subsaturating levels (usually recommended as <6.0 mg/dL) is an important goal for therapy. When goal range sUA is maintained long-term, urate crystal deposition ceases and even reverses, with eventual clinical benefits including reduction in gout flares, resolution of tophi, reduced pain, and improved physical function and quality of life. Monitoring of sUA is important for optimal long-term gout management, because it allows detection of the need for medication adjustment or confirms that chronic therapy is appropriate. Since stable levels of sUA are established within 2 to 4 weeks after initiation or escalation of oral urate-lowering therapy (ULT) with agents such as allopurinol and febuxostat, sUA measurement at biweekly to monthly intervals is an effective means to monitor ULT dose titration. Once goal range sUA is established, less monitoring is appropriate, but annual assessment of sUA in gout patients (pts) on ULT is frequently recommended. The purpose of this study was to evaluate current sUA testing patterns in gout pts in a real-world setting.

Methods: This retrospective study used an ambulatory care-based electronic medical record database with health records of primary care pts. Pts ≥18 years with diagnosis of gout (ICD-9 code 274.xx) and a prescription for allopurinol (ALLO) or febuxostat (FEB) from April 1, 2009 to Dec 31, 2009 and with 13+ months of database activity prior to and ≥6 months of activity after index date (first Rx of ALLO or FEB) were included. Pts with a diagnosis of neoplasm or with an Rx ≥2 ULTs on index date were excluded.

Results: The study included 17,542 ALLO-treated pts (mean age 65±12 years, 76% male) and 394 FEB-treated pts (mean age 62±13 years, 75% male). Of the 17,936 total pts included in the study, 7,998 (44.6%) had at least 1 sUA measurement in the year prior to index date. Only 4,721 (26.3%) pts had both a pre-index (within 1 year) and follow-up (anytime after index) sUA measurement. Of 564 ALLO-treated pts whose dose was adjusted at index date, 165 (29.3%) had a follow-up sUA measure reported. For those pts receiving a dosage escalation (378 patients), 95 (25.1%) had a subsequent sUA measurement compared with 70 of 186 pts (37.6%) who had the ALLO dose reduced. Median time to the first follow-up sUA was 56 days (mean: 67 days) for pts with a dose escalation and 73 days (mean: 71 days) for pts with a dose decrease. For the 394 FEB-treated pts, 216 (54.8%) had a follow-up sUA measure at a median time of 44 days (mean: 59 days).

Conclusion: Based on real-world data, sUA monitoring is not adequate for the majority of gout pts. As sUA measurement is the only immediate means to determine the effectiveness of therapy (clinical benefit is usually not apparent for many months to several years), improved sUA testing patterns could favorably influence the quality of care for gout pts by identifying those not at goal and allowing appropriate adjustments to ULT. The establishment of sUA testing pattern guidelines may improve testing patterns.

2049

Patient Reported Outcomes In a Single Community Based Rheumatology Practice—Outcomes Not As Good As We Think? Melinda K. Pemberton[1], Gary Runde[2] and Wendell D. Bronson[3]. [1]Heartland Clinic, St Joseph, MO, [2]Heartland Regional Medical Center, Saint Joseph, MO, [3]Heartland Clinic, St. Joseph, MO

Background/Purpose: Patient reported outcomes and benchmarking provide an opportunity for quality improvement initiatives. Collecting data in a community based clinical practice can be challenging. The Electronic Medical Record (EMR) makes patient reported outcomes readily recordable and queryable. We report RAPID 3 (routine assessment of patient index data) scores of all patients seen with RA who received care in 2010 in a single community based Rheumatology practice and identify opportunities for quality improvement and benchmarking.

Methods: A query of the EMR database identified 386 patients diagnosed with RA were seen between January 1, 2010 and December 31, 2010. The RAPID 3 was calculated at the time of each visit from patient reported questionnaires entered into the EMR. The EMR query identified the lowest and average reported RAPID 3 scores. RAPID 3 scores were reported in four groups (total range 0–30): 0–3 = remission, 3.01–6.0 = low disease activity, 6.01–12.0 = moderate disease activity, >12.01 high disease activity.

Results:

Total Patients = 386
68.9% Female (n=266)
31.1% Male (n=120)
Average Age = 63.3
Total Visits = 1202
Average # of visits/patient = 3.3

Average Reported RAPID3 RAPID3 Score	**#Patients**	**%Patients**
0–3	29	7.5%
3.01–6.0	42	10.9%
6.01–12.0	128	33.2%
>12	187	48.5%
TOTALS	386	100%

Lowest Reported RAPID3 RAPID3 Score	**#Patients**	**%Patients**
0–3	62	16.1%
3.01–6.0	63	16.3%
6.01–12.0	131	33.9%
>12	130	33.7%
TOTALS	386	100%

Conclusion: 31% of these patients were exposed to biologics agents for RA in 2010. The rate of remission using average and lowest RAPID 3 would be between 7.5–16%. High disease activity was reported 33–48% of the time. Our data suggests a low level of remission and a high level of moderate to severe symptomatology. Results of patient reported outcomes analysis in a community based Rheumatology practice differs from randomized controlled drug trial results. A snapshot of RA patient reported outcomes define sub groups receiving optimal therapy (RAPID 3 <3) and groups that might benefit from intensification of therapy or other interventions to reduce symptomatology (RAPID 3 >12). This or similar patient reported data may be useful in benchmarking between practices in the care of patients with Rheumatoid arthritis.

2050

Less-Experienced Rheumatologists Can Improve Agreement in the Detection of Clinical Synovitis Through Consensus in Rheumatoid Arthritis (RA). Peter Cheung[1], Vincent Andre[2], Natalie Balandraud[3], Gerard H. Chales[4], Isabelle Chary-Valckaneare[5], Emmanuel Chatelus[6], Emmanuelle Dernis[2], Ghislaine Gill[5], Melanie Gilson[7], Sandrine Guis[3], Thierry Marhadour[8], Gael Mouterde[9], Stephan Pavy[10], Francois Pouyol[11], Pascal Richette[12], Adeline Ruyssen-Witrand[13], Martin Soubrier[14], Maxime Dougados[15] and Laure Gossec[16]. [1]Hospital Cochin, Paris, France, [2]Centre Hospitalier, Le Mans, France, [3]Hopital de la Conception, Marseilles, France, [4]CHR—Hopital Sud, Rennes, France, [5]Hopital de Brabois, Nancy, France, [6]Hopital Hautepierre, Strasbourg, France, [7]CH Grenoble Hopital Sud, Grenoble, France, [8]CHU La Cavale Blanche, Brest, France, [9]Hopital Lapeyronie, Montpellier, France, [10]Hopital Bicetre, Paris, France, [11]Hopital de Roger Salengro, Lille, France, [12]Lariboisière Hospital, Paris, France, [13]Hopitaux de Toulouse, Toulouse, France, [14]CHU Clermont-Ferrand, Clermont-Ferrand, France, [15]Paris-Descartes University, Cochin Hospital, Paris, France, [16]Cochin Hospital, Paris, France

Background/Purpose: Synovitis assessment through evaluation of swollen joints (SJ) is integral in steering treatment decisions in RA, and in determining clinical remission. Studies indicate agreement in the assessment of SJ is low; there is limited data on practical methods of achieving consensus at the "joint level" among rheumatologists. The aim was to assess if a short collegiate consensus, would improve SJ agreement between rheumatologists, and whether this improvement was affected by experience.

Methods: 18 rheumatologists from French rheumatology University units participated in a half day national initiative. Clinicians were divided into groups of 4–5 and underwent two 30-minute rounds evaluating SJ in 9 RA patients with moderate disease activity, followed by short consensus discussions. Rheumatologists then assessed one additional patient as measurement of their final SJ agreement. Agreement was evaluated at the joint level, and according to level of experience of the rheumatologist; newly-qualified (<5 years), experienced (5–10 years) and very experienced (>10 years), expressed as kappa (k), proportion of positive agreement (synovitis) and negative agreement (no synovitis).

Results: In all, 9 male and 9 female rheumatologists participated, with median 9.5 years (Q1:Q3, 2.8:14.3) of experience. As seen in Table 1, there was only moderate agreement globally, with initial k=0.50 (95%CI 0.41–0.59) and no improvement over the 3 rounds. Rheumatologists agreed on the presence of synovitis 60% of the time and on the absence of synovitis 90% of the time, also with no improvement over the 3 rounds. When agreement was analyzed according to level of experience, SJ agreement of the "recently qualified" rheumatologists improved with k=0.28 (95%CI 0.05–0.51) going up to k=0.54 (95%CI 0.38–0.70) when compared to "very experienced" rheumatologists; and k=0.33 (95%CI 0.15–0.51) to k=0.47 (95%CI 0.31–0.64) when compared with "experienced" rheumatologists. The proportion of positive agreement (synovitis) between "recently qualified" and "very experienced" rheumatologists also increased from 40% to 64%. On the other hand, agreement between an "experienced" versus a "very experienced" rheumatologist was good initially, with k=0.74 (95%CI 0.61–0.87), but decreased over the subsequent 2 rounds.

Table 1. Agreement of swollen joints among the 18 rheumatologists and categorized according to level of experience

	Global	Recently qualified vs Experienced	Recently qualified vs Very Experienced	Experienced vs Very Experienced
Round 1				
Kappa (95%CI)	0.50 (0.41, 0.59)	0.33 (0.15, 0.51)	0.28 (0.05, 0.51)	0.74 (0.61,0.87)
Positive Agreement	60%	44%	40%	81%
Negative Agreement	90%	88%	87%	93%
Disagreement	31%	19%	21%	10%
Round 2				
Kappa (95%CI)	0.53 (0.46, 0.60)	0.49 (0.36, 0.63)	0.53 (0.37, 0.68)	0.42 (0.24,0.59)
Positive Agreement	61%	63%	63%	54%
Negative Agreement	87%	87%	88%	86%
Disagreement	33%	20%	17%	21%
Round 3				
Kappa (95%CI)	0.52 (0.44, 0.60)	0.47 (0.31, 0.64)	0.54 (0.38, 0.70)	0.42 (0.24,0.61)
Positive Agreement	58%	56%	64%	53%
Negative Agreement	90%	91%	90%	88%
Disagreement	33%	15%	15%	18%

Conclusion: "Recently trained" rheumatologists appeared to have improved their level of SJ agreement with a more senior rheumatologist although global SJ agreement for the study group did not change.

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A Clinical Microsystem Analysis of An Academic Rheumatology Practice Is High-Yield for Identifying Improvement Opportunities. Natalie B. Riblet, Alicia J. Zbehlik, Yvonne Y. Cheung and Daniel A. Albert. Dartmouth-Hitchcock Med Ctr, Lebanon, NH

Background/Purpose: The objective of this project was to complete a microsystem analysis of the Division of Rheumatology at Dartmouth-Hitchcock Medical Center (DHMC) as a basis for continual quality improvement work. We focused primarily on access and sufficiency of staffing as these problems are shared by many Rheumatology practices.

Methods: The Division of Rheumatology at DHMC is a referral-based, academic medical practice located in a tertiary care center in rural New Hampshire. In April and May 2011, we performed a detailed analysis of the Division of Rheumatology using a clinical microsystems approach. Data was obtained from the computerized Hitchcock Database Reporting System, a review of medical records, staff surveys and directly observations of routine clinic processes. Qualitative analysis included patient and staff interviews and a round-table discussion.

Results: Our findings indicate that access to the Division of Rheumatology is poor, with third next available new appointment being 107 days on May 1, 2011. Access acutely worsened with the introduction of a new electronic health record (EHR) in April 2011 from a baseline of 81 days on March 27, 2011. Stratified analysis of third next available appointment by staff provider clinical full time equivalent showed no statistically significant variation from the mean. Of approximately 12,500 patients seen annually, almost 3500 appointments were cancelled during 2010. Of these cancellations, 63% were due to inconvenient time or date. The initiation of an exit secretary to include patients in the scheduling process in January 2011 decreased the cancellations due to inconvenient day or time to 58%. Practice patterns included a lower than benchmark new patient to established patient ratio (17% DHMC vs. 38% benchmark), and fewer nurses per provider than Medical Group Management Association (MGMA) benchmarks (0.03 DHMC vs. 0.49 benchmark). Only one fifth of providers who responded to a survey during this time frame felt they had adequate nursing support. Clinic efficiency was negatively impacted by insufficient communication, providers leaving exam rooms to obtain paperwork and prescriptions, and lack of "huddles" to anticipate bottlenecks in flow. Formal data collection, analysis and display are not currently integrated into the daily work of the practice.

Conclusion: This analysis identifies multiple opportunities for improving access and work flows within the Division of Rheumatology at DHMC. Contextual factors such as adopting a new EHR may adversely impact patient access, at least temporarily. Interventions that include patients in the workflow such as an exit secretary may decrease redundant work. Incorporating meaningful use measures into the EHR's daily workflows may facilitate continual improvement and enhance patient care and outcomes. Access may be improved by adopting open access and patient initiated scheduling models. Microsystem analysis may benefit other Rheumatology practices by identifying high-yield targets for improvement and engaging stakeholders in improvement efforts.

2052

Scores for Sleep, Anxiety, and Depression on the Multidimensional Health Assessment Questionnaire (MDHAQ) in the Patient-Friendly HAQ Format Are Higher Than for Any of the 8 Traditional HAQ Queries to Identify Problems in Patients with Rheumatic Diseases. Isabel Castrejón[1], Yusuf Yazici[2] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: To compare scores for psychological queries concerning anxiety, depression and sleep in the patient-friendly HAQ format on a multidimensional health questionnaire (MDHAQ), compared to scores for the 8 MDHAQ activities from the traditional HAQ and 2 unique MDHAQ complex activities, "walk 2 miles" and "participate in sports and recreation", in 1,583 patients with rheumatic diseases, and subsets with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), osteoarthritis (OA), fibromyalgia, and other rheumatic diseases.

Methods: All patients seen at an academic rheumatology practice complete a 2-sided, 1-page MDHAQ at each visit while waiting to see the physician in the infrastructure of clinical care. Scores are available prior to the patient encounter, and are maintained in a longitudinal database. The MDHAQ includes 13 queries in the patient-friendly HAQ format on a 0–3 scale, concerning "Are you able to. . .?", with 4 response options: "without and difficulty" (=0), "with some difficulty" (=1), "with much difficulty" (=2), "unable to do" (=3). The 13 queries include 8 from the traditional HAQ—dress, arise, lift a cup, walk outdoors, hygiene, reach, grip, household chores; 2 complex activities unique to the MDHAQ–"walk 2 miles (3 kilometers)" and "participate in recreation"; and 3 psychological queries—"get a good night's sleep," "deal with feelings of anxiety or being nervous" and "deal with feelings of depression or feeling blue." Mean and standard deviation were calculated for responses to each of the 13 queries at baseline for all 1,583 new patients seen between 2005 and 2011, and subsets of 221 patients with RA, 166 with SLE, 238 with OA, 41 with fibromyalgia, and 917 with other diagnosis, using analysis of variance (ANOVA).

Results: In all patients, mean scores (on a 0–3 scale) for the 3 psychological queries concerning sleep (1.00), anxiety (0.64) and depression (0.54) were higher than, or in the range of highest scores for, all 8 traditional HAQ activities (Table). The only scores higher than seen for anxiety and depression in all patients were for unique MDHAQ items concerning ability to "walk 2 miles/3 kilometers" (1.00) and "participate in sports and recreation" (1.44). Similar trends were seen for all diagnoses, including "other rheumatic diseases" which does not include fibromyalgia, although scores for the 3 psychological queries were highest in patients with fibromyalgia.

Table. Mean MDHAQ scores for physical function, sleep, anxiety and depression in all 1,583 patients with rheumatic diseases, and according to diagnosis category (*p* determined by analysis of variance among all patient categories).

		All Patients (n = 1,583)	RA (n = 221)	SLE (n = 166)	OA (n = 238)	Fibromyalgia (n = 41)	Other (n = 917)	*p*
MDHAQ physical function items (0–3 scale)	Physical function items on traditional HAQ (0–3 scale)							
	Dress yourself	0.42	0.71	0.33	0.47	0.24	0.35	<0.001
	Get in/out of bed	0.48	0.76	0.40	0.50	0.51	0.42	<0.001
	Lift full glass to month	0.15	0.36	0.11	0.10	0.17	0.12	<0.001
	Walking	0.46	0.69	0.36	0.49	0.31	0.42	0.005
	Wash/dry yourself	0.34	0.60	0.26	0.32	0.15	0.30	<0.001
	Bend down	0.55	0.75	0.48	0.61	0.53	0.49	<0.001
	Turn faucets	0.22	0.56	0.15	0.18	0.12	0.17	<0.001
	Get in/out of a car	0.53	0.83	0.40	0.69	0.36	0.44	<0.001
	Walk two miles (3 km)	1.00	1.28	0.86	1.19	1.00	0.94	0.79
	Participate in sports/ recreation	1.44	1.70	1.17	1.62	1.25	1.39	0.96
MDHAQ function (0–10 scale)		1.85	2.74	1.51	2.03	1.54	1.68	<0.001
Get a good night's sleep (0–3 scale)		1.00	1.15	1.19	1.01	1.29	0.93	0.37
Cope with anxiety (0–3 scale)		0.64	0.70	0.84	0.59	1.12	0.60	0.49
Cope with depression (0–3 scale)		0.54	0.64	0.72	0.52	0.85	0.49	0.42

Conclusion: Three psychological queries as well as two complex activity queries on the MDHAQ that are not found on the HAQ appear to identify problems in patients with rheumatic diseases – including specifically in RA, SLE and OA – at higher levels than for most traditional activity queries from the HAQ. The MDHAQ is an informative screening tool for usual clinical care to assess and monitor patients with all rheumatic diseases.

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A Self-Report RADAI (Rheumatoid Arthritis Disease Activity Index) Count of Painful Joints Can Be Informative in Patients with Rheumatic Diseases Other Than Rheumatoid Arthritis. Isabel Castrejón[1], Yusuf Yazici[2] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: To analyze a self-report painful joint count based on the rheumatoid arthritis disease activity index (RADAI) [Stucki G, et al. Arthritis Rheum 1995;38:795–8], in patients with rheumatic diseases other than rheumatoid arthritis (RA), including systemic lupus erythematosus (SLE), gout, psoriatic arthritis (PsA) and osteoarthritis (OA), in comparison with RA patients, and with other measures of clinical status, in a usual care setting.

Methods: A database has been maintained on all patients seen at an academic rheumatology clinical setting since 2005, which includes demographic, patient self-report MDHAQ (multidimensional health assessment questionnaire), medication, and laboratory data. Each patient completes a 2-sided, 1-page multidimensional health assessment questionnaire (MDHAQ) at each visit while waiting to see the rheumatologist in the infrastructure of clinical care. RAPID3, an index of the 3 patient self-report RA Core Data Set measures – physical function, pain, and patient global estimate (each scored 0–10; total 0–30) – is scored on the MDHAQ by the rheumatologist prior to seeing the patient. The MDHAQ also includes a self-report joint count based on the RADAI, with scores for pain ranging from 0 ("no pain") to 3 ("severe pain") bilaterally for 8 specific joint groups, for a total of 0–48. A physician global estimate of status (DOCGL) also was scored by the rheumatologist, and erythrocyte sedimentation rate (ESR) was obtained. A random visit of 465 patients was analyzed including 174 with RA, 75 with SLE, 50 with gout, 53 with PsA and 113 with OA. RADAI self-report painful joint counts were compared to other MDHAQ measures, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), in patients with RA, SLE, gout, PsA and OA according to Spearman rank-order correlations.

Results: RADAI scores were correlated significantly with MDHAQ scores for function, pain, patient global estimate and RAPID3 in patients with each of the 5 different diagnoses (rho = 0.44–0.81, p <0.001; Table). RADAI was correlated significantly with DOCGL in patients with all diagnoses except SLE. RADAI was correlated with DOCGL at higher levels than with ESR and CRP in all diseases studied, including RA.

Table. Spearman correlations of RADAI self-report joint count with other MDHAQ scores and laboratory tests

	RADAI self-report painful joint score (range 0–48)					
	Total (n=465)	RA (n=174)	SLE (n=75)	Gout (n=50)	PsA (n=53)	OA (n=113)
DOCGL (0–10)	0.48*	0.54*	0.25	0.54	0.48	0.40*
PATGL (0–10)	0.67*	0.75*	0.50*	0.60	0.71*	0.50
Function (HAQ) (0–10)	0.67*	0.69*	0.60*	0.66	0.70*	0.50*
Pain (0–10)	0.74*	0.77*	0.64*	0.77*	0.80*	0.48*
RAPID3 (0–30)	0.77*	0.81*	0.63*	0.72*	0.80*	0.56*
ESR	0.15	0.25*	0.13	0.46*	0.28	0.15
CRP	0.18	0.22	0.06	−0.07	0.22	0.014

* p<0.0001

Conclusion: A self-report joint count derived from the RADAI can be informative in patients with many rheumatic diagnoses, including SLE, gout, psoriatic arthritis and OA, in addition to RA.

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Teens' Perception of Reproductive Health Counseling in Pediatric Rheumatology. Tova Ronis[1], Jennifer D. Frankovich[1], Christy I. Sandborg[1] and Peter Chira[2]. [1]Stanford University, Palo Alto, CA, [2]Indiana University School of Medicine, Indianapolis, IN

Background/Purpose: Psychosocial development during adolescence can be challenging for teens with rheumatic conditions. Unprotected sexual behavior is hazardous, especially for females on high risk teratogenic medications. Yearly screening of sexual health is recommended by the AAP and AMA and is

a proposed quality measure in JIA. Data from pediatric rheumatology patients regarding reproductive health counseling impact are lacking.

Methods: Females ages 13–20 seen at Stanford pediatric rheumatology clinic ≥2 visits for rheumatic conditions were prospectively enrolled during routine visits. Prior to study start, providers were instructed in the following: 1) HEADSS (home, education, activities, drugs, sexual activity, and suicide/depression) assessment; 2) reproductive health counseling; and 3) medical record documentation. Patients were invited to participate if providers indicated that the patient received the HEADSS assessment and the reproductive health counseling tool. At enrollment, patients completed a survey to assess perceptions of reproductive health counseling. Chart review assessed discussion documentation. Stanford IRB approved the project. Descriptive statistics are used.

Results: 90 females (aged 17 ± 2) participated (Table 1). 85 (94%) had a documented HEADSS. 23 (26%) were sexually active and 3 (3%) were considering sexual activity. 11 (12%) were followed by another provider for reproductive health care.

Table 1. Patient demographics and baseline information

Patient Characteristics	n	%
Total	90	100
Age (SD) (yrs)	17 ± 2	
Diagnosis		
JIA	41	45.6
SLE/MCTD/Sjogren's	36	40
Vasculitis	4	4.4
Juvenile Dermatomyositis	3	3.3
Scleroderma	2	2.2
Other	4	4.4
+ Pain syndrome	15	16.7
Disease duration (SD) (yrs)	5 ± 4	
Race		
Non-Hispanic white	45	50
Hispanic	22	24.4
Asian	17	18.9
Non-Hispanic black	3	3.3
Pacific Islander	1	1.1
Unanswered	2	2.2
Insurance status		
Private	70	77.8
Public	20	22.2
Medication use		
Remission off medications	5	5.6
History of high risk medication use	74	82.2
Current high-risk medications		
biologics	21	23.3
mycophenolate	17	18.9
methotrexate	16	17.8
azathioprine	11	12.2
leflunomide	2	2.2
cyclophosphamide	1	1.1
tacrolimus	1	1.1
none	13	14.4
Development		
Post-menarchal	88	97.8

Within the survey, 89 patients (99%) agreed reproductive health was discussed and 88 (98%) felt confidentiality was assured. 64 (71%) reported that pregnancy risks of medications were discussed. All patients agreed they felt comfortable enough with the provider to ask questions. 88 (98%) understood the need to take medications for disease control. 38 (42%) had recent concerns about reproductive health. 30 (33%) reported their provider recommended that they seek further reproductive health care and 9 (10%) were unsure. Of these 30 teens, 10 were already followed for reproductive health care, 2 said they would definitely go, 12 planned to go in the future, 5 were noncommittal, and 1 did not answer.

Conclusion: This first study investigating patient perception of reproductive health counseling in pediatric rheumatology shows that a significant number of teens (42%) had recent reproductive health concerns, indicating the importance of routine discussion and counseling, especially given the risks associated with unplanned pregnancy. Despite these discussions, teens reported feeling hesitant about pursuing further reproductive health care, highlighting the potential need for a formal referral process that providers can follow. Understanding patient motivation for seeking this type of care will improve the screening and counseling process and inform the development of provider guidelines.

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Placing Serious Infection Risk in Perspective: A Randomized Trial Evaluating a Patient Decision Aid to Reduce Focusing Illusion. Richard W. Martin[1], Newsha Lajevardi[1], Shruti Sevak[1], Andrew J. Head[1], Aaron T. Eggebeen[1] and Donald J. Tellinghuisen[2]. [1]Michigan State University College of Human Medicine, Grand Rapids, MI, [2]Calvin College, Grand Rapids, MI

Background/Purpose: Disease modifying anti-rheumatic drugs (DMARDs) increase the risk of serious infectious events (SIE). In rheumatoid arthritis (RA) the incidence varies by individual agent, but ranges from around 1–7/100 pt-year. A clinician counseling a patient who is choosing a new DMARD faces the dilemma of how to frame the discussion to avoid unfairly minimizing medication risks. Focusing illusion is an error in cognition where patients exaggerate the importance of a single factor on their health.[1] This study evaluates the hypothesis that presenting safety monitoring procedures simultaneously with SIE risk will reduce patient perception of drug riskiness and increase their likelihood to be willing to switch to a new DMARD.

Methods: We conducted a randomized controlled trial of 1438 RA patients seen in the past year in a community rheumatology practice. In a mail survey, patients were randomly assigned to read 1 of 4 variations of a hypothetical decision scenario where they were asked to consider switching DMARDs. The format of risk and safety information was derived from an existing DMARD patient decision aid.[2] The scenarios varied by the risk of DMARD related of SIE (1% vs. 8%), and if safety monitoring procedures to reduce risk of SIE were presented simultaneously (yes or no). After reading the scenario, each subject completed a 10 point Likert scale rating the riskiness and likelihood they would take the new DMARD.

Results: The response rate was 70%. Data was analyzed on 1002 respondents. Patient characteristics: female 75%, minority 6.5%, education less than high school graduation 12.6%, Medicaid 18.8%. Means: age was 61.6 years (range 18–93), duration of RA 13.1 years (range 0.5–68), CDAI 11.8 (range 0–54) and HAQ2 0.765 (0–3.0). 51% had started a new DMARD in the preceding 3 years. Multivariate analysis was conducted using 2-way ANOVA. There was a significant main effect of the presence of safety monitoring information but not level of risk on the perceived riskiness of the DMARD [($P< 0.007$) and ($P< 0.084$) respectively]. There were significant main effects of level of risk and presence of safety monitoring information on the likelihood that the patient would take would take the new DMARD [($P< 0.009$) and ($P< 0.005$) respectively]. A consistent pattern was seen where including monitoring procedures in the SIE risk presentation increased RA patient perception of riskiness and reduced the likelihood they would take a proposed DMARD. No significant interaction effect was present between risk level and contextual information on patient rating of either dependent variable.

Conclusion: Even when presented with SIE risk information reinforced with a natural frequency pictogram[3], RA patients differentiated poorly between the riskiness of a low vs. high risk DMARD. Presenting safety monitoring procedures simultaneously with SIE risk information, does not bias patients by reducing risk perception. Rather by presenting DMARD SIE risk in the context of proposed monitoring procedures may intensify patient deliberation of risk and lead to more conservative patient medication decisions.

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Measurement of the Quality of the Patient-Physician Interaction in An Outpatient Rheumatology Clinic. Shawnta R. Pittman-Hobbs[1] and Andreas M. Reimold[2]. [1]UT Southwestern Medical Center, Dallas, TX, [2]Dallas VA and University of Texas Southwestern, Dallas, TX

Background/Purpose: Strengthening of the patient-doctor interaction is the basis of quality improvement efforts. Balancing a full schedule for the provider can come at the cost of longer wait times for the patient. The use of electronic medical records has added to potential distractions during a visit. Patients and providers can have different perspectives on the impact of computer use. Here we examine the impact on the perceived quality of the patient-doctor interaction with respect to time perception, communication, and use of electronic medical records.

Methods: This was a prospective observational study to measure quality of care in a VA rheumatology outpatient clinic. After verbal consent, written anonymous questionnaires were given to 144 patients who came for follow-up appointments over a 3 month interval. New patients were excluded. In addition, 20 surveys were administered to faculty, residents, and fellows involved in the patients' care.

Patients were asked 13 questions to rate the perceived wait time, the amount of time spent with the doctor, how well the doctor explained the plan of care, and how well the doctor listened while typing data into the EMR. Physicians were asked similar questions to rate the perceived patient wait time, their perception of how well they explained the plan of care, and if they felt distracted by entering data in the computer during the visit. The responses were rated on a scale of 1–5. Student's *t*-test was used to compare the averages of the two groups.

Results: The main outcome measures were the effects of the perceived wait time and of electronic medical record use on the reported quality of the physician-patient encounter. Perceived wait time was estimated at 30 to 60 minutes by 65.5% of the patients and 60% of physicians. Patients with longer wait times did not report a perceived lower quality of the encounter. Over 90% of both patients and physicians rated the amount of time spent discussing the plan of care as 4 (good) or 5 (very good). Half of physicians felt that entering information into the computer via electronic medical record was a distraction. However, 45% of physicians felt that they listened about the same to patients while entering data or not, while 40% felt that they listened less. This was in contrast to 58.1% of patients who felt that physicians listened about the same, 23.4% of patients felt that their physician listened more and 16.9% much more while entering data, whereas 1.6% felt the physician listened less. Differences were not statistically significant.

Conclusion: Physicians and patients agreed on the length of the wait time at the start of an appointment. Longer wait times did not correlate negatively with the patients' impression of their physician encounter quality. Use of the electronic medical record caused 40% of physicians to feel that they listen less to their patients while working at the computer, while only 1.6% of patients had this perception. These findings indicate that follow-up patients in rheumatology clinic perceive undiminished quality of care despite longer wait times or provider use of the computer during an encounter.

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Are United States Rheumatologists Interested in Using Electronic Mail in Patient Care? Concerns From a National Survey. Gregory Wilson[1], Chokkalingam Siva[2], Celso Velazquez[1], Karen L. Smarr[3], John Fresen[1] and Marius Petruc[1]. [1]University of Missouri, Columbia, MO, [2]Univ of Missouri Sch of Med, Columbia, MO, [3]Harry S Truman Mem VA Hospital, Columbia, MO

Background/Purpose: Numerous surveys have found patients expressing strong interest in email communication with their providers. However, no literature is available on the level of interest among rheumatologists.

Methods: 4895 U.S. clinical members of the American College of Rheumatology (ACR) with listed email addresses were surveyed. A SurveyMonkey link was provided by email. The survey contained questions on frequency of use, practice policies, and concerns surrounding the use of patient-provider email. Provider demographics and practice characteristics data were also collected. A total of 630 ACR members responded (13%). A small number of respondents skipped questions or answered questions inappropriately. Statistical analyses were performed using the R version 2.12.1 statistical package. Chi-square tests were performed to assess the relationships between several categorical variables and were assessed at 95% significance level (i.e. $p<0.05$).

Results: The majority of respondents do not use email at all to communicate with patients (n=334, 54%) and 34% do not plan to use it in the future. The most important concerns among all respondents were inappropriate use of email by patients, liability, and confidentiality (Table 1). Analysis of these three concerns revealed differences between users and non-users that were significant ($p<0.05$). Non-users (n=334), when compared to users (n=284), were extremely concerned about inappropriate use (61% vs. 38%), liability (56% vs. 36%) and confidentiality (50% vs. 35%). Regarding compensation, 32% of respondents indicated the insurance company and patient should pay for email consultations and 41% were unsure. A majority (83%) of respondents believed $30 or less would be an appropriate fee for a simple, clinical question taking ≤ 5 minutes. For clinical questions taking ≥ 10 minutes of time, 28% of respondents believed the reimbursement should be over $50. Rheumatologists from single specialty practices favored higher reimbursements compared to those from other practice types. Of all respondents, 92% do not distribute any written policy guidelines on email use to patients. Age, gender, and clinical experience did not impact the likelihood of use ($p > 0.05$), but there was a trend towards academic rheumatologists comprising the largest group of users (63%).

Table 1. Reasons for not using e-mail communication (n=590[a])

Concerns about:	1	2	3	4	5
Confidentiality	54 (9.2%)	58 (9.9%)	91 (15.5%)	129 (21.9%)	256 (43.5%)
Liability	48 (8.1%)	50 (8.5%)	71 (12.1%)	141 (23.9%)	279 (47.4%)
Reimbursement	133 (22.5%)	102 (17.3%)	112 (19%)	107 (18.1%)	136 (23.1%)
↓ Quality of care	117 (19.9%)	100 (17.0%)	130 (22.1%)	119 (20.2%)	123 (20.9%)
Inappropriate use	23 (3.9%)	50 (8.6%)	75 (12.8%)	134 (22.9%)	302 (51.7%)

1 = not important, 5 = extremely important, a = question skipped by 31 respondents

Conclusion: There appear to be significant concerns about email use among U.S. rheumatologists. This is likely an underestimation of the level of reluctance, since we surveyed only those with a listed email address. This survey identifies several concerns that are important to practitioners which may impede their use of email in patient care. Addressing these concerns may allow email to expand into the clinical setting as an effective method of patient-provider communication.

2058

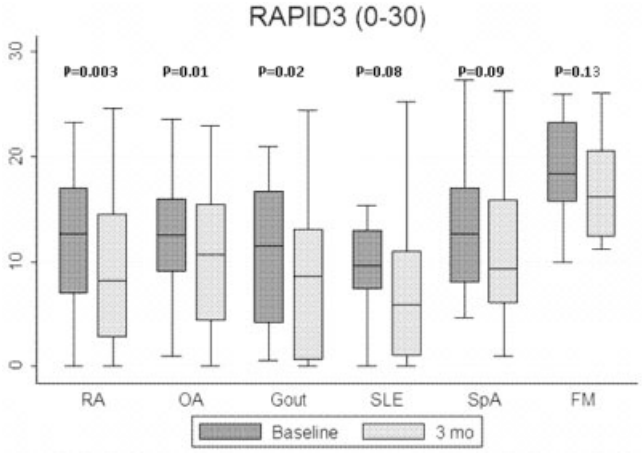
Routine Assessment of Patient Index Data-3 (RAPID3) Is Informative in Patients with All Rheumatic Diseases to Depict Patient-Reported Information As Quantitative Data, Rather Than As Narrative Descriptions. Isabel Castrejón[1], Martin J. Bergman[2], Yusuf Yazici[3] and Theodore Pincus[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Taylor Hospital, Ridley Park, PA, [3]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Patient history information is more prominent in clinical decisions in rheumatic diseases than in most chronic diseases, such as diabetes and hypertension, in which medical history information is considerably less important. Recording patient history information as quantitative, standardized, "scientific" data, rather than as narrative descriptions, may enhance clinical decisions and documentation of clinical changes in usual care of patients with rheumatic diseases. We analyzed scores for physical function, pain, and patient global estimate, and RAPID3 (routine assessment of patient index data) on an MDHAQ (multidimensional health assessment questionnaire) in patients seen in usual care with 6 diagnoses: rheumatoid arthritis (RA), osteoarthritis (OA), gout, systemic lupus erythematosus (SLE), spondyloarthropathy (SpA), and fibromyalgia (FM).

Methods: In one solo rheumatologist private practice setting, every patient (with any diagnosis) completes a 2-sided, 1-page MDHAQ at every visit while waiting to see the physician. RAPID3, an index of the 3 patient self-report Core Data Set measures – physical function, pain, and patient global estimate, each scored 0–10 (total 0–30)—is reviewed by the rheumatologist prior to seeing the patient. RAPID3 severity categories are >12=high, 6.1–12=moderate, 3.1–6=low, ≤3=remission. RAPID3 median and interquartile ranges, and the proportion of patients in each of the 4 categories of clinical status, were computed at first visit and 3 months later for 156 new patients in 6 groups according to diagnosis: RA (n=39), OA (n=41), gout (n=24), SLE (n=14), SpA (n=23), and FM (n=15). Statistical significance was assessed by analysis of variance (ANOVA) of all diagnoses, and *t* test to compare first visit to 3 month later.

Results: A decrease in median RAPID3 scores over 3 months was seen in patients with all 6 diagnoses studied: from 12.7 to 8.2 in RA, 12.5 to 10.7 in OA, 11.5 to 8.6 in gout, 9.7 to 5.9 in SLE, 12.7 to 9.3 in SpA, and 18.3 to 16.2 in FM (Figure). A higher proportion of patients improved from RAPID3 high/moderate severity to low severity/remission over 3 months in 5 of the 6 conditions (all but FM, in which all patients had high/moderate severity at both time points): from 15% at first visit to 49% at 3 months in RA, 19% to 34% in OA, 29% to 46% in gout, 14% to 50% in SLE, and 22% to 26% in

SpA. Changes over 3 months in median scores and in the proportion of patients in low severity/remission were statistically significant ($p<0.05$) for RA, OA and gout, but not for the other diseases.



Conclusion: RAPID3 appears useful in patients with all rheumatic diseases in usual clinical care to document clinical improvement according to a patient history, as quantitative scores rather than as traditional narrative descriptions.

2059

Ethical Issues in Rheumatology: A Survey of the American College of Rheumatology Membership. C. Ronald MacKenzie[1], Michele Meltzer[2] and Elizabeth A. Kitsis[3]. [1]Hosp for Special Surgery, New York, NY, [2]Jefferson Universtiy, Philadelphia, PA, [3]Albert Einstein College of Med, Bronx, NY

Background/Purpose: Despite the chronicity and complexity of rheumatologic disease, the literature pertaining to ethical considerations arising in the practice of rheumatology is negligible. In order to more fully understand the scope of ethical problems arising in the field, the Committee on Ethics and Conflict of Interest of the ACR polled the membership for their opinion. The goals of the survey were to learn: 1) the perceived frequency of ethical issues arising in rheumatology; 2) the identification of activities that pose ethical problems in rheumatolgic practice; 3) the extent of education that members have received in bioethics; and 4) member interest in additional learning activities related to bioethics.

Methods: A survey consisting of 14 closed-end and 4 open-ended questions was developed, pilot tested, and sent electronically to 5,500 US members of the ACR. A second offer for participation was sent to increase the response rate.

Results: Seven-hundred and seventy one (14%) members responded to the questionnaire. While there was general agreement that ethical issues arise in all areas of rheumatology, respondents believed that they arise more frequently in clinical research (61%) and clinical practice (44%) as opposed to basic research (26%). The 3 most common issues reported were the high costs of treatment to society (51%) or to patients (48%) and the practice of defensive medicine (45%). When asked to list the three most relevant ethical issues pertaining to rheumatologic practice, 10% of respondents reported conflict of interest in profiting from the over-utilization of infusions; 9% reported physician-pharmaceutical relationships; and 8% cited providing care for those with limited or no insurance. Industry-related activities identified as posing ethical problems include serving on boards of directors (76%) and serving on an industry-sponsored speakers bureaus (66%). Fifty-eight percent of respondents had received formal training in bioethics; 89% indicated an interest in additional education.

Conclusion: This survey suggests that ethical problems in rheumatology are of concern to the ACR membership. Further there is a perceived need for educational resources directed at helping members deal with such professional challenges. These results suggest that an active discourse and more formal education in bioethics should be a professional priority.

2060

Assessment of Cardiovascular Risk in Rheumatoid Arthritis: Comparison of Two Indices and Related Variables. José L. Rosales-Alexander, César Magro-Checa, Juan Salvatierra, Jesús Cantero-Hinojosa and Enrique Raya-Alvarez. University Hospital San Cecilio, Granada, Spain

Background/Purpose: Last year the European League Against Rheumatism (EULAR) developed a modified systematic coronary risk evaluation (mSCORE) index to guide in the cardiovascular (CV) risk management in patients with rheumatoid arthritis (RA) and other forms of inflammatory arthritis. In RA patients, the mSCORE is calculated according to the SCORE by the application of a multiplier factor 1,5 in those who meet some clinical criteria. EULAR recommends the use of the mSCORE when no local guidelines are available. In our country the SCORE table has been calibrated by our national Cardiology Society, although it is not systematically applied to our RA patients. For that reason we decide to compare the assessment of the CV risk in RA patients using the SCORE table calibrated for our population and the mSCORE following the EULAR recommendations as well as to analyze the correlation of several clinical and serological variables with these SCORE indices.

Methods: We included 161 consecutive patients diagnosed of RA according to the 1987 classification criteria of American College of Rheumatology (ACR) and followed in our outpatient clinics. We recorded demographic data, classic CV risk factors, previous ischemic events, clinical and laboratory parameters of disease activity like ESR, CRP, tender and swollen joint counts, DAS28, patient global assessment by visual analogue scale (VAS global), lipid profile and RA characteristics. We calculated the CV risk using the SCORE table calibrated for our population and the mSCORE following the EULAR recommendations. Data were collected in Excel 2007 and analyzed with the statistical software SPSS 15. Descriptive data were shown as percentages and mean ± standard deviation (SD). Differences between qualitative variables were assessed using Chi-squared test or McNemar's test and for comparing means we used the ANOVA Bonferroni adjustment. The limit of statistical significance was located in the α error of 0,05.

Results: Using the SCORE table calibrated for our population the mean ± SD score was 2,4 ± 2,9% and after the application of the mSCORE was 3 ± 4,2%. A change in the score occurred in 19 (55,8%) patients with intermediate risk being reclassified into high risk 18 (52,9%) and very high risk 1 (2,9%). Likewise 3 (17,6%) patients with high risk were reclassified into very high risk after applying the EULAR recommendations. It was observed that 58,8% of men had high and very high CV risk and that 61,9% of women had low CV risk. Of interest, in our study the levels of CRP and the values of the VAS global seemed to have a direct association with the final SCORE CV risk indices ($p<0,03$ and $p<0,02$ respectively) which suggest the influence of disease activity on the high CV risk associated to RA.

Conclusion: The use of the mSCORE index in RA patients involves an overestimation of the CV risk in comparison with the application of local guidelines, what could have implications in management of these patients. Of the analyzed variables, CRP and VAS global seem to affect the final CV risk scores, supporting the importance of a good control of the inflammation in RA.

2061

Measuring Quality of Care in Juvenile Idiopathic Arthritis: The Pediatric Rheumatology Care and Outcomes Improvement Network. Esi Morgan DeWitt[1], Timothy Beukelman[2], Beth S. Gottlieb[3], Nancy Griffin[4], Yukiko Kimura[5], Itara Barnes[6] and Murray H. Passo[7]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]Schneider Children's Hospital, New Hyde Park, NY, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, [5]Hackensack Univ Medical Ctr, Hackensack, NJ, [6]Atlanta, GA, [7]MUSC, Charleston, SC

Background/Purpose: Representatives from the ACR, ARHP, American Academy of Pediatrics, and American Board of Pediatrics (ABP) recently proposed 12 Quality Measures (QM) as a suitable baseline of data for the development of quality improvement projects. Implementation of the proposed QM set may improve the process of care, facilitate continuous quality improvement (QI), and eventuate in improved health outcomes of children with JIA.

Methods: The Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) is a multi-site QI learning collaborative formed to improve the outcomes of care of children with JIA and to accelerate adoption of evidence into medical practice. Our collaborative approach is based on the

Institute of Healthcare Improvement (IHI) Breakthrough Series Collaborative Model and utilizes the Model for Improvement to guide performance improvement activities. Using the ACR's Rheumatology Clinical Registry (RCR), PR-COIN is designed to aggregate data from participating pediatric rheumatology practices to study performance of sites on both process measures of care delivery and measures of patient outcomes to better understand which disease management approaches are optimal. Change strategies based on a chronic illness care model include pre-visit planning, population management, auditing, treatment protocols and preparing patients/parents in self-management techniques. Initial activities include collection of pre-intervention baseline data and training teams in performance improvement methodology, prior to testing change strategies at individual team sites. Teams will convene during three Improvement Learning Sessions over a 12 month period (June 2011, September 2011, April 2012) where they receive intensive training and coaching from QI experts. Between Learning Sessions, teams conduct tests of change using "Plan-Do-Study-Act" cycles, and submit data regarding their performance. Site specific and aggregate feedback reports are provided monthly to enable teams to assess progress on quality measures.

Results: 11 sites in the US and one in Canada are enrolled in the network which leverages a public website (pr-coin.org) with members only section for transparent sharing of data reports. The web-based JIA data entry system was created within the RCR. After completing an IRB approval process, subject data is entered into the RCR to populate run charts documenting performance on quality measures. QI measures have been embedded into some participating sites' electronic health records (EHRs) for more reliable data collection and with special programming, data may be uploaded from EHRs into the registry forms.

Conclusion: PR-COIN, by putting measurement of quality of care into practice, provides an opportunity for validation of recently published quality measures for process of care of JIA. QI learning networks organized in the IHI Breakthrough Series approach and utilizing the Model for Improvement to guide improvement activities may improve the quality of care of patients with chronic illness. The PR-COIN QI collaborative, which follows the IHI approach, offers an option to rheumatologists to meet part 4 QI project requirements for maintenance of certification by the ABP.

2062

Detection of Adverse Events in Routine Rheumatology Practice by a New Computer Application. Zulema Rosales[1], Ana B. Rodríguez-Cambrón[1], Lydia Abásolo[1], Leticia León[1], Oscar Fontsere[1], Cristina Vadillo[1], J.L. Fernández Rueda[1] and Juan A. Jover[2]. [1]Hospital Clínico San Carlos, Madrid, Spain, [2]Hospital Clinico San Carlos, Madrid, Spain

Background/Purpose: There is a high risk of developing adverse events (AEs) in rheumatology practice due, mainly, to the immunosuppressive drugs used. Also, we must take into account the high workload and the difficulty of register AEs in daily clinical practice.

Our purpose was to describe the AEs collected in a routine practice of Rheumatology, by implementing a software system Reporting and Analysis for Incident Learning and Adverse Events (SNAIEA).

Methods: We performed an observational prospective study from October 1st 2010 to May 31st 2011. All patients seen, at least once, in the Rheumatology Service at the Hospital Clínico in Madrid since the introduction of SNAIEA were included. Primary endpoint: AEs collected by SNAIEA from patients attended during the study period. We also collected a) the severity (mild, moderate, severe, fatal), b) relationship to medication (Unlikely, Possible, Probable, Certain), c) causes of AE, d) the diagnosis of patients with some type of AE in that period, e) and drugs associated with these events. We collected demographic data (age and sex) of all patients. Statistical analyses: to estimate the incidence of adverse events we used survival techniques, expressing the incidence per 100 inhabitants per year (95% CI). A description of the sociodemographic, clinical, of the patients by frequency distribution and the mean and standard deviation or median and percentiles was completed. Analyses were performed using Stata statistical package 10.0.

Results: 7539 patients were attended during follow-up. Of these, 75% were female with a mean age of 61.92 ± 16 years. There were 241 AE (table 1) (84.6% female, mean age of 62.3 ± 15.3 years) during follow-up with an incidence of 8.5 % (95% CI: 7.5–9.7). The incidence of AE by sex was 9.5% (95% CI: 8.2–10.8) in females and 5.4% (95% CI: 3.9–7.5) in males. Of the AE, 5 were severe with an incidence of 0.2% (95% CI: 00.7–00.4). In 61% of the patients the relationship of the AE to medication was certain. The main diagnose in the patients with AE was Rheumatoid Arthritis (37%) followed by osteoarthritis (13%). The most frequent drugs causing AE were classical DMARDs (46.44%) followed by opioids (10.5%) and NSAIDs (9.6%).

AE	Number	Percentage (%)
Gastrointestinal	78	35.14
General Syndrome	27	12.16
Mucocutaneous	23	10.36
Laboratory Abnormalities	20	9.01
Neurological	18	8.11
Eye	16	7.21
Infections	14	6.31
Cardiological	10	4.50
Muscular	7	3.15
Fractures	6	2.70
Genitourinary	3	1.35

Conclusion: AEs in routine rheumatology practice are common; however the vast majority is mild. The most common adverse events were gastrointestinal. DMARDs are the drugs most associated with adverse events. Using SNAIEA has been a transition from the traditional manual model to the electronic analysis of AE, identifying those events, their severity and relationship to the medication, thus contributing to improving the quality of care.

2063

A Quality Indicator for Osteoporosis in a Japanese Hospital. Yasuhiro Suyama[1], Mitsumasa Kishimoto[1], Yuri Ohara[1], Ryo Rokutanda[1], Atsushi Nomura[2], Hisanori Shimizu[1], Ken-ichi Yamaguchi[1], Yukio Matsui[1] and Masato Okada[1]. [1]St. Luke's International Hospital, Tokyo, Japan, [2]Chubu-Rosai hospital, Nagoya, Japan

Background/Purpose: Bone fractures are the third most common reason why patients become bedridden in Japan and prevention is often more important than treatment, especially in patients with known risk factors. Quality indicators (QI) have received increasing attention in rheumatology and the ACR QIs for systemic lupus erythematosus include an indicator for glucocorticoid-induced osteoporosis. Furthermore, according to 2010 ACR recommendations for prevention and treatment of glucocorticoid-induced osteoporosis, patients on prednisolone as low as 7.5 mg daily or equivalent for more than 3 months should take anti-osteoporosis drugs. However, few studies have reported the effectiveness of the implementation of this QI measure for glucocorticoid-induced osteoporosis in the clinical setting.

Methods: We performed a retrospective review of medical records in our hospital, examining the number of patients with prescription for the equivalent of prednisolone 7.5 mg daily or more for at least 3 months each year from 1994 to 2010. The number of patients with prescriptions for a bisphosphonate (alendronate, risedronate, or zoledronic acid) and vitamin D analogue(Alfacalcidol)was also analyzed. The sample was categorized into 3 groups by gender and age. Group A comprised female patients over 50 years old who were recommended to take a bisphosphonate with vitamin D analogue; Group B was comprised of female patients less than 50 year-old taking the defined dose of steroid and who were recommended to take vitamin D analogue; Group C was male patients who were recommended to take a bisphosphonate with vitamin D analogue.Then we assessed the rate of following these recommendations in each group in each year.

Results: A total 2479 patients were included in this study. 1448 (58.4%) patients were female and the mean age of patients was 53.6±18.4 years. 528 (19.2%) patients underwent dual-energy x-ray absorptiometry scan during the study period. An average of 354 patients received the defined dose of steroid each year (316 – 381 patients/year). Analysis of data revealed that the rate of following the ACR recommendations were 40.1% in Group A (32.0% – 52.9% in each year), 41.8 % in Group B (26.1% – 58.4% in each year), and 11.4% in Group C (8.2% – 14.5% in each year)..

Conclusion: In our study, targeted anti-osteoporosis drug prescriptions per QI standards was found to be inadequate and the situation was worse in male patients. It is imperative to inform clinicians of the existence of evidence-based recommendations to combat steroid-induced osteoperosis and urge them to follow QI standards. Sequential analysis of QI would be an effective way to implement the recommendation in clinical practice, with the end goal of reducing the burden of preventable osteoporotic fracture.

2064

A Randomized Clinical Trial of a Comprehensive Behavioral Intervention in Systemic Lupus Erythematosus Demonstrates Improvement in Mental Health but Not in Physical Health, Cardiovascular Risk or Endothelial Function At One Year. Paul R. Fortin[1], Ellie Aghdassi[2], Anne Cymet[2], Stacey Morrison[3], Jiandong Su[3], Willy Wynant[4], Janet E. Pope[5], Sara Hewitt[5], Christian A. Pineau[6], Carolyn Neville[7], Paula Harvey[8], Jean-Claude Tardif[9], Michal Abrahamowicz[10] and Deborah DaCosta[11]. [1]Toronto Western Hospital, Toronto, ON, [2]University Health Network, Toronto, ON, [3]The Toronto Western Hospital, Toronto, ON, [4]McGill University, Quebec, QC, [5]St. Joseph's Health Care, University of Western Ontario, London, ON, [6]McGill Univ Health Center, Montreal, QC, [7]Royal Victoria Hospital, Montreal, QC, [8]Toronto General Hospital, Toronto, ON, [9]Universite de Montreal endowed research chair in atherosclerosis, Quebec, QC, [10]McGill UHC/RVH, Montreal, QC, [11]Montreal General Hospital, Montreal

Background/Purpose: The Health Improvement and Prevention Program (HIPP) in systemic lupus erythematosus (SLE) is the first randomized intervention aimed at the improvement of health status and coping while reducing risky behaviours for cardiovascular disease (CVD).

Methods: An unblinded RCT of the HIPP intervention (HIPP NOW) compared to usual care (HIPP LATER) assessed physical (PCS) and mental (MCS) component summary scores of SF-36, the CVD risk derived from the Framingham risk score (CVD risk) and the flow mediated dilatation (FMD) of the brachial artery. Patients with no CVD were recruited from three academic centres. After providing consent, SF-36, SLEDAI, SDI as well as FMD were collected. Those randomized to HIPP NOW were administered a personalized risk modification program by a nurse (disease education, CVD risk reduction {including smoking cessation}, exercise, psychological intervention). Repeated clinical assessments and FMD were performed at one year. A cross-over of the LATER group occurred at one year and all patients will be re-assessed at 2 years. We report here the one year results. Power calculations showed that 260 patients ensured 80% power to detect ≥10% improvement in the SF-36 MCS and PCS and 20% in CVD risk. Between groups differences (1year - baseline) were tested, separately for each primary outcome, using t-tests and multivariable linear regressions (MLR) adjusting for baseline values and for patients' characteristics associated with the outcome.

Results: We randomized 288 patients. There were no differences between groups for mean age (44 yrs), race (70% Caucasian), marital status (53% married), education (91% high school graduates), mean disease duration (11.3 yrs) and mean SLEDAI (4.04). The NOW group had a higher mean SDI (1.37 vs 1.00, p=0.03). Table 1 shows the results of the HIPP intervention at one year on the outcomes of PCS, MCS, CVD risk and the post-occlusive FMD change in brachial artery diameter.

	Unadjusted analyses			Adjusted analyses	
Outcome	Δ HIPP NOW (1 year-baseline)	Δ HIPP LATER (1 year-baseline)	p-value	$\beta_{study\text{-}group}$ in MLR (95%CI)	p-value study-group in MLR
SF36-physical	0.026	0.695	0.471	−0.10 (−1.80; 1.60)	0.909
SF-36 mental	1.837	−1.441	0.008	−2.67 (−4.84; −0.50)	0.017
CVD risk (logit)	−0.023	0.056	0.087	+0.08 (−0.01; 0.17)	0.067
FMD (% change)	−0.290	−0.205	0.922	+0.18 (−1.43; 1.79)	0.828

The MCS score increased during the first year of follow-up in the HIPP NOW group by 1.84 units but decreased in the LATER group by 1.44. The resulting un-adjusted difference (p=0.008 for the 2-tailed t-test) and the adjusted difference from MLR (2.67, 95% CI: 0.50 to 4.84, p=0.017) were both statistically significant. There was a trend toward improvement in CVD risk (p= 0.087 for t-test and p=0.067 for MLR). The differences in the other primary outcomes were not significant.

Conclusion: The HIPP intervention significantly improved the mental health but not the physical health in SLE as measured by the SF-36; other primary outcomes were not significant. Since SF-36 mental health improvement may precede changes towards healthier behaviour, this study will re-examine outcomes at two years.

2065

Cardiovascular Risk Assessment and Management in a Nationally Representative Sample of Routine Ambulatory Visits for Patients with Rheumatoid Arthritis and Systemic Lupus Erythematosus. Laura Tarter[1], Laura Trupin[1], Gabriela Schmajuk[2], Mary Margaretten[1], Edward Yelin[1] and Jinoos Yazdany[1]. [1]University of California San Francisco, San Francisco, CA, [2]Stanford University, Palo Alto, CA

Background/Purpose: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). We examined patient and physician factors associated with CVD risk factor screening in a nationally representative sample of routine ambulatory medical visits in the United States. Additionally, we analyzed management strategies among those with known CVD risk factors.

Methods: We studied the National Ambulatory Medical Care Survey (2005–2007), including all visits for patients > 17 years of age with SLE or RA presenting for routine (not acute) care. Data were recorded in standardized templates by the primary medical provider. We used logistic regression to examine the association between assessment of traditional CVD risk factors (hypertension, hyperlipidemia, diabetes, smoking and obesity) and patient sociodemographics, insurance status, and physician specialty (primary care provider, rheumatologist or other). We also examined the frequency with which physicians recorded addressing known CVD risk factors during routine visits (via lifestyle modification counseling (LMC) or pharmacotherapy).

Results: A total of 298 visits were included in the analysis (RA 72%, SLE 28%). Patients were 57.1 years old (SD 15.5), 78% female, 84% White, and 92% insured. Prevalence of CVD risk factors varied (hypertension 30%, hyperlipidemia 15%, diabetes 9%, smoking 8%, obesity 9%). Rates per visit of risk factor evaluation also varied (blood pressure measurement 88%, cholesterol measurement 12%, diabetes screening 11%, tobacco use assessment 58%, body mass index calculation 40%). In multivariate models adjusting for the number of visits to the reporting physician over the previous year, sociodemographic characteristics (age, sex, race/ethnicity) were not associated with receipt of CVD screening. Screening for hyperlipidemia and diabetes were more likely to be recorded for primary care visits than rheumatology visits (OR 5.04: 1.57–16.17; OR 4.54: 1.54–13.39). Patients with hypertension (n=60) were the most likely to have a management strategy recorded (60% received pharmacotherapy and 30% received LMC). In visits in which hyperlipidemia was recorded (n=30), 47% received pharmacotherapy and 40% received LMC. Cessation counseling was associated with only 6% of visits in which smoking was recorded (n=18).

Conclusion: In this nationally representative sample of ambulatory visits, screening for CVD risk factors in patients with RA and SLE occurred both during rheumatology and primary care visits; however, screening for hyperlipidemia and diabetes were more likely to occur during primary care visits. In patients with known CVD risk factors, a minority of visits were associated with relevant LMC or pharmacotherapy, suggesting opportunities for quality improvement.

2066

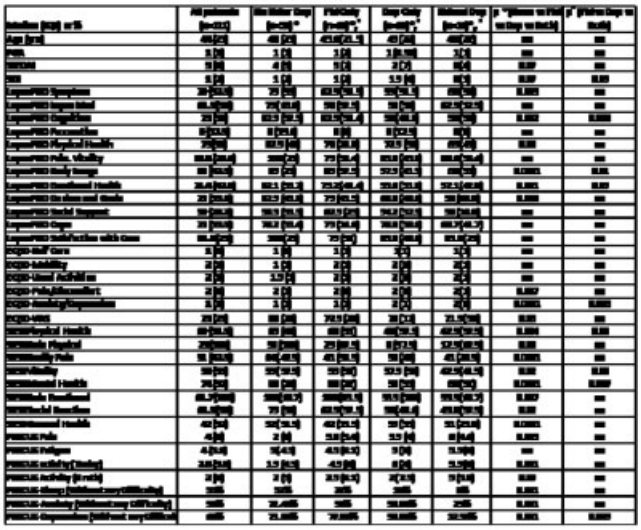
Is Having Fibromyalgia Worse Than Having Depression or Both in Lupus: Impact on Health Outcomes? Meenakshi Jolly[1], Jessica Cornejo[2], Rachel A. Mikoliatis[2] and Joel A. Block[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University, Chicago, IL

Background/Purpose: Adverse effects of Fibromyalgia and Depression on health outcomes in Systemic Lupus Erythematosus (SLE) have been noted previously. Herein we present physician and patient reported health outcomes in SLE using wide variety of patient reported health outcome tools in rheumatology practice, and compare them (a) against a group without fibromyalgia and Depression, and (b) stratified by the presence of Fibromyalgia, Depression or both.

Methods: 111 SLE patients were administered patient reported health outcome tools prior to their routine clinic visit. The tools included LupusPRO, EuroQoL, MDHAQ (PINCUS) and SF36. Disease activity and damage were assessed using Physician Global Assessment (PGA), SELENA-SLEDAI, and damage Index (SLICC-ACR/SDI). In addition, patients provided their demographic, self reported history of fibromyalgia and Depression (Yes/No). These diagnoses were confirmed in all cases by medical chart review. Statistical methods include descriptive, non-parametric t tests and Chi square analyses. All p values noted are two sided.

Results: Age, PGA and SLEDAI were similar in all groups. Summary scores for the entire group and stratified by underlying co morbidity are shown in the table. Comparisons between SLE patients without fibromyalgia and depression with the other three groups showed significant differences on most tools. Differences in sleep, pain, fatigue, psychological and social health were noted on most tools. In addition, LupusPRO domains scores of symptoms, Cognition, Body Image and Desires and Goals showed significant differences in these four groups.

When we compared SLE groups with fibromyalgia, depression and both, we found fibromyalgia group to have better health outcomes than the other two groups. Notable differences were in the LupusPRO domains (Cognition, Body Image, Emotional Health), EuroQoL Anxiety/Depression, SF36 domains (Physical Function, Vitality and Mental Health) and MDHAQ (Depression item).



Conclusion: SLE Patients with depression have the worst patient reported health outcomes as compared to SLE patients with and without Fibromyalgia. Aggressive screening, counseling and appropriate intervention/s for such patients are indicated.

2067

Hydroxychloroquine Retinopathy in Inflammatory Arthritis: A Retrospective Analysis in Canadian Patients. Mohammed Osman[1], Heather Burnett[1], Alison Kydd[2], Paul Davis[1], Christopher Rudnisky[1], Matthew Tennant[1] and Elaine Yacyshyn[1]. [1]University of Alberta, Edmonton, AB, [2]University of British Columbia, Vancouver, BC

Background/Purpose: Antimalarial agents, hydroxychloroquine (HCQ, Plaquenil®) and chloroquine (CQ, Aralen®) have been linked to toxic ocular changes after prolonged use. The incidence of toxic changes is unclear for patients with inflammatory conditions, although prior studies show a low incidence (0.8–3.4%). In this study, we examined the frequency of true HCQ retinopathy in patients treated for various inflammatory conditions, with an abnormal mfERG.

Methods: Sixty-eight patients (age range 26 – 90 years) treated with HCQ between 2004 and 2010 were identified in this qualitative retrospective study. Patients with potential retinopathy were identified after having an abnormal multifocal electroretinogram (mfERG). Follow-up serial mfERG and complete ophthalmic assessments (visual acuity, dilated fundoscopy, automated Humphrey visual field (HVF)) were conducted to distinguish patients with HCQ retinopathy, as opposed to other conditions contributing to an abnormal mfERG. Repeated measures were completed 6 months to one year apart.

Results: Of the total number of patients identified with an abnormal mfERG, four female patients (age range 59–72 years) were identified with probable retinal toxicity (approximately 5.88 %) after 2.2, 4, 6 and 8 years of treatment with HCQ (mean dose 400 mg/d). None of these patients had ocular symptoms, although one of them had cataracts. Both patients using HCQ for more than 5 years developed Bull's eye maculopathy and had an abnormal HVF, while the other two were identified with serial mfERG and ophthalmic assessments. In addition, twenty-nine patients (age range 36–90 years) were found to have a persistently abnormal mfERG with no evidence of toxicity (approximately 42.6 %). Twenty-two patients had other ocular diseases (glaucoma, macular degeneration, diabetic retinopathy, cataracts, retinal pigment epithelial changes), and diabetes or hypertension (17 patients). Seventeen patients (age range 29–75 years) initially thought to have potential retinopathy were shown to have no evidence of antimalarial retinopathy after subsequent clinical and mfERG assessments.

Conclusion: We report a much higher rate of true postive abnormal mfERG than previously described in this select population of patients treated with HCQ. Of the sixty-eight patients, none of the patients with ocular toxicity were symptomatic and one of them developed ocular disease after only 2.2 years of treatment. Patients who have risk factors for potential toxicity, including duration of HCQ use, age, and other ocular diseases may benefit from mfERG screening, even in the absence of ocular symptoms. Our study highlights the important role mfERG may play in the early detection of patients at risk for developing antimalarial toxicity.

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Real-Time, Cohort-Based Clinical Decision Support Using a Novel Bioinformatics Platform to Assess Thrombotic Risk in a Critically Ill Pediatric Patient with Systemic Lupus Erythematosus. Jennifer D. Frankovich, Chris Longhurst, Scott Sutherland and Christy I. Sandborg. Stanford University, Palo Alto, CA

Background/Purpose: We often find ourselves in clinical situations where the medical literature is sparse or not applicable to our patients' unique medical milieu, particularly in pediatric medicine. Although previous groups have highlighted the secondary use of Electronic Health Record (EHR) data for clinical research, the following case highlights how this same approach can be used to guide real-time clinical decisions. We report the case of a 13 year old patient with SLE who presents with a 2 month history of heavy proteinuria complicated by mild pancreatitis and antiphospholipid (APL) antibodies. We feared that our patient had a high risk for thrombosis—but it is not commonplace to anticoagulate critically ill pediatric patients with these risk factors. Since the published literature was insufficient to guide us in the care of this complex patient, we used historical patient data to guide our decision to use anticoagulation.

Methods: We used an online tool to conduct a rapid automated review of EHR data from 98 historical SLE patients treated at our institution. The pediatric SLE cohort used for this chart review and the IRB approval were previously established. We predefined a list of 10 keywords that allowed us to rapidly identify risk factors and outcomes which were relevant to our patient's clinical situation. In all cases, the sentences surrounding the keywords were manually reviewed.

Results: 36/98 patients had heavy proteinuria (protein to creatinine ratio >2.5 g/dL) and 23 had heavy proteinuria which persisted >60 days. 9 patients had pancreatic dysfunction: 5 with clinical pancreatitis and 4 with subclinical pancreatitis. 53 patients had APL antibodies and were eventually started on aspirin. Among the 36 patients with heavy proteinuria, 9 (25%) developed thrombosis while acutely ill. Among the 9 patients with clinical or sub-clinical pancreatitis, 6 (67%) developed thrombosis while acutely ill. Only 11% of the patients with APL antibodies developed thrombosis. As compared to our lupus patients without these risk factors, the risk of thrombosis among patients with heavy proteinuria was high (RR 7.8, 95% CI 1.9–5.5) and even higher for those patients with heavy proteinuria lasting $>$ 2 months (RR 14.7, 95% CI 3.3–96). Risk of thrombosis among patients with pancreatic dysfunction was also high (RR 15.8, 95% CI 5–49). APL antibodies did not appear to be a risk factor for thrombosis in this cohort (RR 1.0, 95% CI 0.3–3.7). This chart review study was completed in 4 hours. Based on the high rate of thrombosis in patients with heavy proteinuria and pancreatic dysfunction, we decided to anticoagulate our patient within 24 hours of admission and prior to the administration of pulse methylprednisolone.

Conclusion: Real-time availability of data to guide decision making has already transformed other industries. The growing prevalence of EHRs, along with the development of sophisticated tools for real-time analysis of deidentified data sets, will further catalyze this data-driven approach to healthcare delivery. We look forward to the future of medicine in which our systems learn from every patient, at every visit, and help close the clinical decision-making feedback loop in real-time.

2069

The Juvenile Systemic Sclerosis Clinic: An Interdisciplinary Approach. Marìa M. Katsicas, Erica Hammermuller, Betina Cervini and Ricardo A. Russo. MD, Caba, Argentina

Background/Purpose: Juvenile Systemic Sclerosis (JSS) is a rare, complex disease. Usually, patients with JSS receive specialized care from a multidisciplinary team in tertiary hospitals. In order to deliver high standard care, systematic clinical practice strategies should be designed. Based on these premises, we developed a JSS Clinic in the year 2008. We describe the structure and process of a JSS interdisciplinary Clinic, as well as outcomes observed

Methods: During the period 2008–2010, patients with a diagnosis of JSS entered a structured follow-up in a dedicated clinic. Clinic analysis was based on A) structure (teamwork members, databases, guidelines); B) process (tasks and activities related to patient care and evaluation of the JSS clinic); and C) clinical outcomes (skin thickness by Modified Rodnan Score, functional capacity by CHAQ and CMAS; quality of life (QoL) by PedsQL). The quality of the JSS clinic is assessed using a Quality Measure score (QM). This QM is a set of 20 items related to the timely assessment of lung-heart impact, outcome measures, drug adverse effects, cardiovascular risk factors, growth, autoimmunity, treatment appropriateness.

Results: The JSS clinic is the setting where patients diagnosed with JSS are regularly followed. A) Structure. The clinic team gathers monthly in the Day Hospital facility of a tertiary pediatric hospital. This interdisciplinary team includes: pediatricians (2), pediatric rheumatologists (2), pediatric dermatologists (2), pulmonologist (1), cardiologists (1), social workers (2), nutritionists (1), kinesiologists (1), psychiatrists (1) and nurses (1). Databases comprising clinical, epidemiological, and psychosocial variables, as well as electronic records of the clinic personnel and activities, were developed for this clinic and are regularly updated. Clinical guidelines including assessment of general, vascular, musculoskeletal, gastrointestinal, cardiopulmonary, renal and neurologic aspects of patients, as well as therapeutic recommendations. B) Process. Short reviews of the patients′ charts are distributed electronically to the team members 3 days prior to the clinic day. During the clinic, all patients are assessed according to guidelines. Outcome measures (Rodnan score, CMAS, CHAQ) are assessed at each visit; PedsQL is administered a once year. After the evaluation phase, team members discuss tailored work-up and therapeutic strategies for each individual patient. A final report is elaborated and sent both to our records and to the patients′ primary physician. C) Outcomes. Twelve patients (F:11, M:1) are currently included in the JSS clinic program, and they attend it every 3 months. Their age at onset is 96 (9–180) months; delay in diagnosis 21 (4–48) months. Medians at baseline: Rodnan score 21, CMAS 29 and CHAQ > 5: 5 patients. PedsQL Child Self-Report score: 68,45 and Parent Proxy-Report score: 71,71.

Conclusion: The JSS clinic is an interdisciplinary approach that allows a better quality of care, based on the interaction of participating members and the development and use of disease-specific guidelines. A systematic follow-up of patients with JSS is probably best accomplished in this setting.

2070

Lipid Testing Gaps in Patients with Rheumatoid Arthritis and Key Cardiovascular-Related Comorbidities. Christie M. Bartels[1], Amy J. Kind[2], Carolyn Thorpe[1], Christine Everett[3] and Maureen Smith[1]. [1]Univ of Wisconsin School of Medicine and Public Health, Madison, WI, [2]Univ of Wisconsin and William S. Middleton VA, Madison, WI, [3]University of Wisconsin School of Medicine and Public Health, Madison, WI

Background/Purpose: For patients with rheumatoid arthritis (RA) and comorbid cardiovascular disease (CVD), diabetes or hyperlipidemia, secondary prevention through annual lipid testing is recommended to reduce morbidity and mortality from comorbidities. Given trends encouraging complex patients to receive care in "medical homes" we examined associations between regularly seeing a primary care provider (PCP) and secondary lipid testing in eligible RA patients.

Methods: We performed a retrospective cohort study examining a 5% random US Medicare sample (2004–2006) of beneficiaries over 65 years old with RA and concomitant CVD, diabetes, or hyperlipidemia (N=16,893). We examined the relationship between receiving secondary lipid testing in 2006, and having at least one PCP visit per year, 2004, 2005, and 2006, using multivariate regression.

Results: 90% of patients had prevalent CVD, 46% had diabetes, and 64% had hyperlipidemia, however, annual lipid testing was only performed in 63% of these RA patients. Thirty percent of patients saw a PCP less than once per year, despite frequent visits (mean >9) with other providers. Patients without at least one annual PCP visit were 16% less likely to have lipid testing. Increased age, complexity scores, and hospitalization predicted decreased lipid testing, while diabetes and hyperlipdemia increased lipid testing.

Conclusion: Despite comorbid CVD, diabetes, or hyperlipidemia, 30% of Medicare RA patients saw a PCP less than once per year, and one in three lacked annual lipid testing. Findings support advocating primary care visits at least once per year. Remaining gaps in lipid testing suggest the need for additional strategies to improve secondary lipid testing in at-risk RA patients.

2071

Safety, Tolerability, and Immunogenicity of Zoster Vaccine in Patients on Chronic/Maintenance Corticosteroids. Janie Parrino[1], Farid Marquez[2], Chester L. Fisher Jr.[3], Wolfgang Spieler[4], Tadeusz Tomala[5], Jon E. Stek[1], Amy F. Russell[1], Kathleen E. Coll[1], Shu-Chih Su[1], Jin Xu[1], Xiaoming Li[1], Katia Schlienger[1] and Jaffrey L. Silber[1]. [1]Merck Sharp & Dohme Corp., Whitehouse Station, NJ, [2]Palm Springs Research Institute, Hialeah, FL, [3]Health Research of Hampton Roads, Newport News, VA, [4]Rheumatology Specialty Practice, Zerbst, Germany, [5]Svelvik Medical, Svelvik, Norway

Background/Purpose: This study evaluated safety, tolerability, and immunogenicity of zoster vaccine (ZV) in individuals receiving chronic/maintenance systemic corticosteroid therapy (daily dose equivalent of 5 to 20 mg prednisone) for ≥2 weeks prior to enrollment, and ≥6 weeks postvaccination.

Methods: Three-hundred-nine varicella-zoster virus (VZV)-experienced adults ≥60 years old were randomized 2:1 to receive either ZV or placebo (P), stratified by prevaccination corticosteroid dose (5 to 10 mg; >10 to 20 mg) and age (60 to 69 yrs; 70 to 79 yrs; ≥80 yrs). Patients were vaccinated on Day 1 and followed for adverse experiences (AEs), exposure to varicella or herpes zoster (HZ), or development of varicella/varicella-like or HZ/HZ-like rashes for 42 days (primary safety follow-up period). Patients were followed for all serious AEs (SAEs) through Day 182 postvaccination (secondary follow-up period). Blood samples obtained immediately prior to vaccination and at Week 6 postvaccination were assessed for VZV antibody titer by glycoprotein enzyme-linked immunosorbent assay (gpELISA).

Results: During the primary safety follow-up period, 40.2% of patients in the ZV group and 30.3% of patients in the P group reported one or more AEs, with the difference due primarily to the different rates of injection-site AEs following administration of ZV (21.6%) and P (12.1%). The overall proportion of patients reporting systemic clinical AEs was similar between ZV (27.9%) and P (24.2%).

SAEs within 42 days postvaccination were similar for ZV (5.4%) and P (6.1%). One vaccine-related SAE (ophthalmic HZ, Day 16 postvaccination) was reported in the ZV group, and PCR testing confirmed the presence of wild-type (not vaccine strain) VZV. The percentage of patients who reported SAEs within 182 days postvaccination were similar for ZV (10.3%) and P (11.1%), with no vaccine-related SAEs reported between Day 43 and 182.

Geometric mean titer (GMT) at 6 weeks postvaccination was higher for ZV (531.1; 95% CI: 453.3, 622.1) than for P (224.3; 95% CI: 169.8, 296.2). Estimated geometric mean fold rise (GMFR) was 2.3 (95% CI: 2.0 to 2.7) for ZV and 1.1 (95% CI: 1.0 to 1.2) for P.

Conclusion: In adults ≥60 years old on chronic/maintenance corticosteroids: (1) ZV was generally well tolerated; (2) VZV-specific gpELISA antibody GMT at 6 weeks postvaccination was higher in ZV than in P; and (3) VZV gpELISA antibody GMFR from prevaccination to 6 weeks postvaccination was higher in ZV than in P.

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Factors Involved in the Decision to Take Medications to Prevent Rheumatoid Arthritis in First Degree Relatives of Patients with Rheumatoid Arthritis. A Discrete Choice Experiment. Axel Finckh[1], Monica Escher[2], Matthew H. Liang[3] and Nick Bansback[4]. [1]University Hospital of Geneva, Geneva, Switzerland, [2]University Hospital of Geneva, Geneva 14, Switzerland, [3]Brigham & Womens Hospital, Boston, MA, [4]University of British Columbia, Vancouver

Background/Purpose: The identification of biomarkers for RA and recent therapeutic advances suggest that it may be possible to identify persons at high risk, treat RA in its pre-clinical phase, and thereby prevent its occurrence. However to take a medication with potential side effects, for an unspecified period of time, possibly to prevent symptoms or disease, is extremely complex. No formative research has been conducted in presymptomatic individuals at high risk of developing RA to understand what factors

they might consider or what preventive treatment would be most acceptable to them.

Methods: We recruited individuals at increased risk of developing RA, namely first degree relatives of patients with RA, to participate in a screening study of preclinical RA. Before the results of biomarker tests were known, participants were invited to consider a scenario in which they were at high risk of developing RA and were offered preventive treatment. They were presented nine treatment profiles, each describing 4 attributes of possible treatments: reduction in risk of developing RA (80%, 20% risk reduction or only delay in RA development), risk of mild side effect (10%, 20%, or 40%), risk of serious side effect (<1%, 5% or 10%) and mode of administration (oral daily tablet, biweekly injections, or a single infusion cycle). The subjects were asked to choose the best and worst feature of each profile. The levels of each attribute were chosen using an orthogonal design. Conditional logit analysis was used to determine the relative preferences for each attribute level.

Results: Only 17 out of 48 subjects completed the questionnaire consistently. Most participants were female (83%), Caucasian (94%), and had one first degree relatives with RA (mean 1.2). Mean age was 49 years. The most important treatment attribute was preventive efficacy (reducing the risk of developing RA by 80%: B=1.99, p<0.01), which was given twice the weight of treatment safety (10% risk of a serious side effect: B=-0.72, p<0.01). A biweekly self-injection was valued worse (B=−0.44, p=0.06) than a 5% risk of serious adverse events (B=−0.09, p=0.06). A single infusion was the preferred mode of administration (B=0.01, p=0.003).

		Est	p
Reduction in risk of developing RA	0% but reduce for 1 year	−1.3582	0.00004
	20% reduction	−0.5888	0.06
	80% reduction	1.9986	0.023
Risk of mild side effect	40%	−0.1066	0.55
	20%	−0.5653	0.24
	10%	−0.0593	0.67
Risk of serious side effect	10%	−0.721	0.0034
	5%	−0.0872	0.056
	0%	1.0472	0.003
Mode of administration	Oral	−0.0499	0.33
	Injection	−0.4461	0.067
	Single Infusion cycle	0.0098	0.003

Conclusion: Our results suggest that efficacy of a preventive therapeutic intervention is the most important factor for individuals at risk of developing RA, followed by the risk of serious adverse events and the convenience and mode of administration of a particular therapy. In this pilot study, participants found it difficult to ponder the various treatment attributes. We suspect the lack of consistency reflects a real difficultly with the competing trade-offs inherent to therapeutic interventions in a primary prevention setting. The development of communication strategies are needed to help FDRs make these value judgments.

2073

Effect of Health Insurance Coverage on Quality of Care in SLE. Edward Yelin[1], Jinoos Yazdany[2], Laura Trupin[3], Chris Tonner[1], Patricia P. Katz[4], Gabriela Schmajuk[5], Joann Zell[6], Pantelis Panopalis[7], Lindsey A. Criswell[2] and Laura J. Julian[2]. [1]UCSF, San Francisco, CA, [2]University of California San Francisco, San Francisco, CA, [3]UC San Francisco, San Francisco, CA, [4]Univercity of California San Francisco, San Francisco, CA, [5]Stanford University, Palo Alto, CA, [6]National Jewish Health, Denver, CO, [7]McGill University, Montreal, QC

Background/Purpose: Quality indicators (QIs) for SLE care have recently been developed.[1] However, the extent to which the quality of SLE care varies between those with and without health insurance coverage and by the kind and source of insurance is unknown.

Methods: Cross-sectional analysis of data derived from the UCSF Lupus Outcomes Study, a prospective, longitudinal cohort study of 814 persons with SLE. Principal data collection was through annual structured telephone surveys between 2009–2010. Data on 13 SLE QIs covering diagnosis, monitoring, treatment, and preventive services were collected. Insurance status was categorized by presence of any insurance, source (public vs. private), and type (managed care [MC] vs. fee-for-service [FFS]); these variables were then combined into 5 mutually exclusive categories. We examined performance on each QI, and also performance on all indicators for which participants were eligible (pass rate). Logistic regression was used to estimate the impact of insurance status, with and without adjustment for demographic and socioeconomic characteristics, SLE and overall health status, specialty of main SLE physician, and total number of SLE physician visits.

Results: Participants were eligible for a mean of 5 QIs (range 2–12). Performance on individual QIs varied from 29% (assessment of cardiovascular risk factors) to 90% (sun avoidance counseling). The overall pass rate was 65% (95% CI 64%, 65%). In unadjusted and adjusted analyses, lack of health insurance was associated with lower pass rates and receiving care in public sector managed care organizations was associated with higher pass rates (see table). Poverty and being a member of a racial or ethnic minority were associated with lower overall pass rates in unadjusted but not adjusted analyses (data not in table).

	Insurance Status				
	None	Public-FFS	Public-MC	Private-FFS	Private-MC
	Cells are Pass Rates (95% CI)				
Unadjusted	.51 (.42, .60)	.66 (.64, .69)	.75 (.70, .80)	.64 (.61, .67)	.63 (.59, .67)
Adjusted*	.57 (.47, .66)	.66 (.63, .69)	.74 (.68, .79)	.64 (.61, .67)	.64 (.60, .67)

FFS= fee-for-service, MC=managed care
* Adjusted for age, gender, race/ethnicity, education, poverty status, disease activity, duration, number of physician visits, and specialty of main SLE physician

Conclusion: Lacking insurance was associated with lower quality of SLE care while having coverage in a public sector managed care organization was associated with higher quality. Health insurance status accounted for part of the effect of poverty and race/ethnicity on quality of care in SLE.

1. Yazdany, et al. Arthritis Rheum 2009; 61: 370–377.

2074

Adherence to Gout Guidelines in a Rheumatology Clinic. Richard Conway, Robert J. Coughlan and John J. Carey. Galway University Hospitals, Galway, Ireland

Background/Purpose: Gout is a common cause of severe acute and chronic debilitating arthopathy. Current drug treatments can reduce the frequency and severity of acute attacks, and eliminate or reverse long term sequelae of gout. Unfortunately many gout patients are poorly managed. Recently published guidelines have set treatment goals for gout management based on serum uric acid levels. A treat to target strategy in a subspeciality gout clinic has the potential to improve patient management.

The aim of this study was to evaluate adherence to recommended serum uric acid levels in the rheumatology outpatients department of a university teaching hospital.

Methods: We performed a retrospective study of all patients with a definitive diagnosis of gout attending our subspeciality gout clinic between 1st January 2010 and 31st December 2010. We evaluated adherence with two recently suggested uric acid thresholds, <5mg/dL and <6mg/dL. Patient management was judged to adhere to the guidelines if either 1) The latest serum uric acid level was less than the specified guideline targets, or 2) Uric acid lowering therapy was titrated upwards or the agent changed if the serum uric acid was above the guideline targets.

Results: 102 patients with a definitive diagnosis of gout attended the outpatients department between 1st January 2010 and 31st December 2010 and were included in the study. Median serum uric acid level was 5.57mg/dL (IQR 4.64mg/dL – 7.67mg/dL). With respect to uric acid lowering therapy, 86 patients (84%) were treated with allopurinol, 6 patients (6%) were treated with febuxostat (one of whom also received probenecid) and 1 with rasburicase. 9 patients (9%) were receiving no uric acid lowering therapy. In 80 patients (78%) the management adhered to a target guideline of <6mg/dL. In 66 patients (65%) the management adhered to a target guideline of <5mg/dL.

Conclusion: A treat to target approach has the potential to improve patient outcomes in the management of gouty arthritis. Our study shows encouraging results with the majority of patients on appropriate therapy, and reaching recommended targets, but there is room for improvement.

2075

Rheumatoid Arthritis: Patient Insights, Strategies and Expectations—Dual Survey Offers Physicians Unique Insight Into Patient Experience. Gerd R. Burmester[1], Theresa Lupton[2], JM Alvaro-Gracia[3] and Boulos Haraoui[4]. [1]Charité—Universitätsmedizin Berlin, Berlin, Germany, [2]Univ of Calgary Medical Clinics, Calgary, AB, [3]Hospital Universitario de la Princesa, IIS Princesa,, Madrid, Spain, [4]Institut de Rhumatologie, Montreal, QC

Background/Purpose: The 2009 Rheumatoid Arthritis: Patient Insights, Strategies + Expectations (RAISE) "Patient Needs Survey" identified gaps in patient-physician communications. The 2011 RAISE "Patient Experience Survey" allowed physicians to identify patients in their practice who could share their daily life with RA and user knowledge of TNF inhibitors (TNFi). Objectives: further define the best patient experience; identify + bridge gaps between actual patient experience and physician perceptions of patient experience; develop the foundation for an information-based program that opens a dialogue between patients and physicians about RA quality-of-life (QoL).

Methods: 47 rheumatologists from Spain, Canada, and Germany identified patients who met entry criteria: ≥18 years old + receiving a subcutaneous biologic for treatment of moderate-to-severe RA for ≥2 months. Patients completed a 30-minute survey via computer-assisted telephone interview. Survey topics: impact of RA on work and social interaction, optimism about QoL, experience with injection site reactions (ISRs), training and education on use of subcutaneous TNFi. All physicians saw aggregate country-level patient data, and those with participation of ≥5 patients also saw practice-level data. Physicians completed a survey that assessed their perceptions of patient needs—both before and after seeing patient data.

Results: 239 patients (78% female, mean age 52 yrs, mean 11 yrs since diagnosis) currently receiving etanercept (51%) or adalimumab (49%) completed the survey. 47 physicians reviewed country-level data (16/47 reviewed practice-level data) and completed a survey. *Patient Data:* 80% of patients felt their RA was moderately/very well controlled in the week pre-survey; 37% reported it significantly affected their daily activities. Two-thirds stated their physician was very aware of these difficulties, while 28% wished he/she asked about it more. Most patients (94%) experienced a degree of discomfort when injecting. The most common patient-reported ISRs were needlestick pain and burning, and 23% (55/239) have these sensations every time. 34% said the burning sensation is moderately or very bothersome and lasts 1.4 hours (mean). 13% have considered skipping injections because of ISRs. 60% reported discussing ISRs with their physician, with 36% of these conversations initiated by the physician. *Physician Data:* Before reviewing patient data, 64% of physicians said they initiated discussions about ISRs and believed that only 18% of their patients experience any ISR. Physicians believed needlestick pain was most common and burning was rarer (<10%) and probably not bothersome. Responding to patient data, 50% felt the incidence and bothersomeness of ISRs were somewhat worse than expected; 30% were motivated to change their approach to managing ISRs; and 75% were more likely to discuss ISRs with patients. 85% agreed that patient data provided new insights.

Conclusion: The RAISE Patient Experience Survey reveals gaps between patient reality and physician perceptions about TNFi treatment and living with RA. Education and dialogue will enable both physician and patient to benefit from improved management of RA.

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Implementation of An Electronic Interface for Medical Record Documentation in An Academic Pediatric Rheumatology Outpatient Clinic: An 18-Month Update. Jennifer M.P. Woo[1], Miriam F. Parsa[1], Gil Amarilyo[1], Nasim Afsar-manesh[1], Ornella J. Rullo[2] and Deborah K. McCurdy[2]. [1]University of California, Los Angeles, Los Angeles, CA, [2]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA

Background/Purpose: The transition to electronic medical records (EMR) from traditional paper clinic notes (PCN) reflects a nationwide effort to improve clinic efficiency, to standardize best practices, and to ensure that critical disease processes are documented. Commercial EMR platforms are designed to universalize medical records within a healthcare network; however, they may take years to be fully implemented at large sites and are not always designed to fully capture the specific elements that characterize subspecialty clinic exams. Our healthcare center currently utilizes a transitional EMR that requires physicians to document patient visits with PCN, which are then uploaded to the center-wide EMR by a central department. This process generates a lag period of up to 3 weeks, during which PCN are inaccessible electronically. In response, we created an EMR interface (EMRI) or electronic note. Its implementation in our outpatient pediatric rheumatology clinics began in June 2010 and allows physicians to document and upload their findings directly to the patient's center-wide EMR via laptop or computer in the exam room. Objective: To evaluate clinic workflow and to assess patient perceptions as we transition from PCN to a complete EMR system.

Methods: Our EMRI is a Microsoft Excel form with VBA macros, enabling physicians to compile an accurate measure of the patient's present health. Clinic efficiency is evaluated by monitoring the length of: 1) patient-physician interactions, 2) patient wait time, 3) time dedicated to follow-up charting, and 4) time required for clinic notes to be uploaded to the EMR. Patients or their parents are asked, via paper and/or internet survey, to anonymously assess the quality of care in clinic and their perception of EMRI use throughout the transition process. Data is collected and assessed in 6 month blocks (Block 1: months 1–6; Block 2: months 7–12; and Block 3: months 13–18) and will continue until our EMRI is fully integrated into clinical practice.

Results: One year has elapsed since the implementation of our EMRI, and approximately 56% of our weekly clinic notes are documented electronically. On average, EMRI notes become available within 12 hours of the clinic visit, whereas PCN notes require approximately 7 days ($p < 0.0001$). Compared to early PCN data, EMRI-use during block 2 significantly lessened patient wait time (48 vs. 23 min.; $p = 0.001$) and clinic visit length (85 vs. 51 min.; $p < 0.0001$). Patient-physician interaction time has continued to comprise approximately 50% of clinic visit duration. Of patients and parents surveyed during block 1 or 2 ($n = 31$; $n = 43$), 93% of both groups were receptive to the use of a clinical EMRI. In addition, 81% of patients/parents surveyed during block 2 believed that an EMRI would benefit the patient's quality of care compared to 67% of patients/parents surveyed during block 1 ($p = 0.1$).

Conclusion: The transition from PCN to EMRI notes can be tenuous, albeit necessary. Our preliminary data suggests EMRIs specific for targeted assessments (e.g. rheumatological evaluation) can improve medical documentation while increasing clinic efficiency, patient-physician interactions, and patient perception of quality of care.

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The Use of Hydroxychloroquine in Patients with Rheumatoid Arthritis and Systemic Lupus Erythematosus: To Check or Not to Check Glucose-6-Phosphate Dehydrogenase Levels Prior to Its Initiation in Everyday Rheumatology Practice. Mercedes Quinones[1], Sharon Dowell[1], Archana Sharma[2], Raymond Flores[1], Marc Hochberg[1], Jamal Mikdashi[1] and Violeta Rus[1]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]Maryland General Hospital, Baltimore, MD

Background/Purpose: Recent recommendations support the use of Hydroxychloroquine (HCQ) in Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). There are no recommendations, however, regarding the utility of routinely checking serum Glucose-6-Phosphate-Dehydrogenase (G6PD) levels prior to the initiation of HCQ therapy. G6PD deficiency is the most common enzymatic disorder of red blood cells in humans and affects primarily those of African or Mediterranean descent. HCQ has been implicated as a potential inducer of hemolytic anemia in individuals with G6PD deficiency. Our aim was to identify the frequency with which serum G6PD levels are checked prior to the initiation of HCQ therapy and whether individuals with low G6PD levels suffered any adverse clinical events.

Methods: We conducted a retrospective chart review of our cohort of RA and SLE patients. A total of 170 patient charts were reviewed and we identified patients who were currently taking HCQ, taking it in the past, or had never taken it before. We identified the frequency with which serum G6PD levels were checked prior to starting HCQ. We identified those patients who had low G6PD levels and whether or not they had suffered any adverse clinical events, mainly hemolytic anemia. Descriptive statistics were used for data analysis.

Results: Of the 170 total patients, serum G6PD levels were checked in only 24 patients [14%] of the total study population. A total of 56 patients had a diagnosis of RA, 110 patients had a diagnosis of SLE, and 4 patients had a diagnosis of both RA and SLE. G6PD levels were checked in a total of 7 out of 60 patients with RA [11.6%] and 17 out of 114 patients with SLE [14.9%]. Of those patients in whom G6PD levels were checked, only 1 was found to have a low level [4.2%] without any adverse clinical events despite the long-term use of HCQ. With regards to ethnicity, 137 out of 170 patients were African-American [80.5%] and 29 out of 170 patients were Caucasian [17%]. Of those 24 patients in whom serum G6PD levels were checked, 21 out of 24

[87.5%] were African-American and 3 out of 24 [12.5%] were Caucasian. The 1 patient identified with low serum G6PD levels was African-American.

Conclusion: In our inner city outpatient population of patients with RA, SLE, or both, routine screening for G6PD deficiency prior to the initiation of HCQ therapy was done in only 14% of patients. One patient with RA was noted to have G6PD deficiency and was treated with HCQ with no adverse clinical events. This preliminary data supports the lack of any existing ACR recommendations for checking G6PD levels prior to the initiation of HCQ therapy in RA and SLE patients. Further data collection at our institution is currently in progress.

2078

A Pilot Cardiovascular Risk Reduction Clinic for Inflammatory Rheumatic Diseases. Kevin Martell, Michael Sean McMurtry, Finlay McAlister, Gabor Gyenes and Stephanie O. Keeling. University of Alberta, Edmonton, AB

Background/Purpose: A recent practice audit of 9 rheumatologists at a tertiary care site demonstrated poor cardiovascular (CV) risk management of inflammatory rheumatic disease (IRD) patients. Therefore the utility of a CV risk reduction clinic for these patients warrants investigation. This study established a new model-of-care independent of the standard rheumatology clinic and describes the original inception cohort.

Methods: Patients with moderate to severe inflammatory arthritis (IA) were invited to attend the "CV Risk Reduction Clinic for IRD" as part of a biologics surveillance program in northern Alberta. After initial postal screening of traditional CV risk factors & fasting labs (lipid panel, glucose), clinic attendees were evaluated with pre-specified case report forms including IA activity and traditional CV risk factors. Framingham & Reynold's risk scores were calculated & the European League Against Rheumatism (EULAR) CV risk multiplicative factor of 1.5 applied when criteria were met. Carotid intima media thickness (CIMT) measurements were measured on a separate visit for all consenting patients. Patients were offered dietician counseling, smoking cessation therapies, physiotherapy referrals, lipid lowering (according to 2009 Canadian Cardiovascular Society guidelines) & antihypertensive treatments. RA disease management was left for the attending rheumatologist. Descriptive statistics were calculated with Microsoft excel & the study approved by the University of Alberta ethics.

Results: Twenty-five patients (M:F 7:18) attended the clinic to date, mean age 55.8 (±13.5) years, with the following diagnoses: 19 (76%) RA; 2 (8%) juvenile idiopathic arthritis; 4 (16%) psoriatic arthritis. Fifteen (60%) patients were RF positive, 17 (68%) anti-CCP positive and 9 (36%) had rheumatoid nodules. Mean disease duration was 18±14 years, ESR 15 ± 12 mm/hr, CRP 5 ±4 mg/l & DAS28 2.5 ± 2.2. Radiographic erosions were noted in the hand and feet x-rays of 14 (58%) and 8 (38%) patients respectively. Traditional cardiovascular risk assessment confirmed four (16%) patients as active smokers, 10 (40%) with high cholesterol (LDL > 3.5 mmol/L), 2 (8%) with diabetes, 7 (28%) treated for systolic hypertension, 11 (44%) with family history of premature heart disease & 5 (20%) with personal history of CVD. The mean Framingham and Reynolds risk score of a CV event in the next 10-years was 10% and 2.2% & the mean Framingham applying the EULAR multiplicative factor (8 patients) was 8.0%. Mean CIMT measurement for any observed carotid artery was 0.70 mm (± 0.21; n=74 arteries), & number of arteries with significant thickness (>0.75 mm) was 27 with mean thickness of 0.96 ± 0.15 mm. Plaques were noted in 6 patients.

Conclusion: The CRRC-IRD provides a new model-of-care to evaluate and manage CV risk in a high-risk patient population. Future evaluations from this clinic model include (1) reviewing prospective CV outcomes from the clinic compared to standard-of-care, (2) applicability of different risk scores in IA (given the discrepancy of mean Framingham & Reynold's scores in this study) & (3) contributions of treat-to-target RA disease approach & (4) CIMT to CV risk assessment.

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A Screening Tool for Knee Osteoarthritis. C. Kent Kwoh[1], Michael J. Hannon[2], Stephanie M. Green[3], Ali Guermazi[4] and Robert M. Boudreau[3]. [1]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA, [4]Boston Medical Center, Boston, MA

Background/Purpose: This study was conducted to develop and validate a screening tool for knee osteoarthritis that could be administered on paper or thru a web-based interface.

Methods: Potential questions were identified through a literature review of risk factors for the development of radiographic knee osteoarthritis (ROA), examples from other OA screening questionnaires and an Expert Panel. A 42-item set of questions was created that included questions (yes/no) about participant characteristics, knee pain under varying conditions, and related symptoms.

The set of 42 questions was mailed to participants from 2/5 OAI Clinical Centers based on KL grade=0 in both knees (no ROA) or definite ROA (KL≥2 in at least one knee) at their enrollment visit. For the 951/1119 (85%) that responded, ROA status was updated (i.e., their most recent x-ray was read). Those that had a TKR were excluded. The final sample was 777 with 694 (89.32%) having ROA.

Classification and Regression Tree (CART) analysis was used to develop a screening tool using a test set and then validated on the remainder of the sample.

Results: The most predictive model yielded an ROC of.80 but translation of this model into an online screening tool would be relatively complex. Nodes with the least predictive power were pruned yielding a tree of seven variables with an ROC of 0.79, a specificity of 77.1% and sensitivity of 77.8%. The positive predictive value was 96.6%. The negative predictive value was low (29.4%), likely due to the low number of people without any ROA.

The most discriminating items were age, race (African-American (AA) or white), gender, BMI (obese or not), whether they had a history of knee surgery or talked to a doctor about having knee surgery, knee pain when squatting in the past year, stiffness in the knees lasting more than 20 minutes in the past year, swelling of the knees in the past year, and grinding or other noises in the past year.

ROA was very common (N = 268, 98.2%) in participants who had knee surgery or talked to their doctor about it. Among those participants who had not talked to their doctor, ROA was found in all of the participants in three nodes: AA participants ≥age 65 with no pain when squatting; white participants < 65 who were obese and had grinding in their knees; and white participants from 60 to 65 who were not obese but who had grinding in their knees. There was also a very elevated risk of ROA for the following: Anyone > 65 who reported pain while squatting (97.85%); Anyone over 65 who did not have pain when squatting but who was white and had stiffness (96.6%), and anybody under 65 who was AA (92.9%).

Risk of OA was more moderate only for white participants 65 and over who reported no stiffness and no pain when squatting (76.6%); white participants under age 60 who had grinding in their knee but were not obese (67.6%); and white participants under 65 with no grinding in their knee (58.2%).

Conclusion: We have developed and validated a knee OA screening tool. ROA risk was highest among those who were AA, older, heavier, and reported more knee pain symptoms.

ACR/ARHP Poster Session C
Rheumatoid Arthritis - Animal Models II
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

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Importance of E3 Ubiquitin Ligase Synoviolin In Fibrogenesis. Naoko Yagishita[1], Daisuke Hasegawa[1], Satoko Aratani[2], Yoshihisa Yamano[1] and Toshihiro Nakajima[2]. [1]St.Marianna University School of Medicine, Kawasaki, Kanagawa, Japan, [2]Tokyo Medical University, Tokyo, Japan

Background/Purpose: The symptoms of rheumatoid arthritis (RA) are based on the many processes; chronic inflammation, overgrowth of synovial cells, bone and joint destruction and fibrosis. To clarify the mechanism of outgrowth of synovial cells, we carried out immunoscreening using anti-rheumatoid synovial cell antibody, and cloned 'Synoviolin'. Synoviolin was highly expressed in the rheumatoid synovium, and confirmed that this molecule is one of the causative factors of arthropathy. Further analysis using

gene targeting approaches showed that in addition to its role in RA, Synoviolin is essential for embryogenesis. Synoviolin deficient ($syno^{-/-}$) mice exhibited severe anemia caused by enhancement of apoptosis in fetal liver, and the results suggested that the liver is sensitive organ for Synoviolin. Thus, this study aimed to explore the involvement of the Synoviolin in fibrosis process of RA using mice model of liver fibrosis.

Methods: The expression and localization of synoviolin in the liver were analyzed in CCl_4-induced hepatic injury models and human cirrhosis tissues. The degree of liver fibrosis and the number of activated hepatic stellate cells (HSCs) was compared between wild type (WT) and synoviolin heterozygote ($syno^{+/-}$) mice in the chronic hepatic injury model. We also analyzed the effect of synoviolin on collagen synthesis in the cell line from HSCs using siRNA-synoviolin and a mutant synoviolin in which E3 ligase activity was abolished. Furthermore, we compared collagen synthesis between WT and $syno^{-/-}$ mice embryonic fibroblasts (MEFs) using quantitative RT-PCR, western blotting, and collagen assay; then, we immunohistochemically analyzed the localization of collagen in $syno^{-/-}$ MEFs.

Results: In CCl_4-induced hepatic injury model, $syno^{+/-}$ mice are resistant to onset of liver fibrosis. The number of activated HSCs was decreased in $syno^{+/-}$ mice, and some of these cells showed apoptosis. Furthermore, collagen expression in HSCs was upregulated by synoviolin overexpression, while synoviolin knockdown led to reduced collagen expression. Moreover, in $syno^{-/-}$ MEFs, the amounts of intracellular and secreted mature collagen were significantly decreased, and procollagen was abnormally accumulated in the endoplasmic reticulum.

Conclusion: In conclusion, Synoviolin is involved in not only overgrowth process of synovial cells but also fibrosis process.

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Pemetrexed Ameliorates Experimental Arthritis in Rats. Metin Ozgen[1], Suleyman Serdar Koca[1], Ahmet Karatas[1], Adile Ferda Dagli[2], Fazilet Erman[3], Nuran Sahin[4], Kazim Sahin[4] and Ahmet Isik[1]. [1]Department of Rheumatology, Faculty of Medicine, Firat University, Elazig, Turkey, [2]Department of Pathology, Faculty of Medicine, Firat University, Elazig, Turkey, [3]School of Health Sciences, Firat University, Elazig, Turkey, [4]Department of Animal Nutrition, Faculty of Veterinary Science, Firat University, Elazig, Turkey

Background/Purpose: Methotrexate (MTX) is considered as the 'anchor drug' and internationally accepted as the first choice in the treatment of rheumatoid arthritis (RA). Pemetrexed (PMTX) is an antifolate drug, as MTX. However, PMTX inhibits several folate-requiring enzymes, apart from MTX, and thus is termed a multitargeted antifolate.

The purpose of this study was to assess the efficacy of PMTX on collagen-induced arthritis (CIA) in rats.

Methods: Forty Wistar albino female rats were randomized to four groups (n=10 in each group): Group-I as the control group, Group-II as the arthritis group, Group-III as the low dose PMTX group, and Group-IV as the high dose PMTX group were assigned. Arthritis was induced by intradermal injection of chicken type II collagen combined with incomplete Freund's adjuvant in Group-II, III, and IV rats. The doses of 0.2 and 1 mg/kg/week PMTX were intraperitoneally administered in Group-III and IV, respectively after the onset of arthritis.

Animals were sacrificed at the 15th day after the onset of arthritis. The trunk bloods and paws of the rats were obtained for further analysis. Tumor necrosis factor (TNF)-α, interleukin (IL)-17, malondialdehyde (MDA) levels and superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) activities in serum and articular tissue nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxgenase-1 (HO-1) expressions, perisynovial inflammation and cartilage-bone destruction were determined in the paws.

Results: When compared with Group-I, TNF-α, IL-17, and MDA levels were increased, and SOD, CAT, GPx activities and the expressions of Nrf2 and HO-1 were decreased in Group-II (Table). Histopathological analysis demonstrated the extensive perisynovial inflammation and marked cartilage-bone destruction in Group-II rats. PMTX treatment decreased the levels of TNF-α, IL-17 and MDA, and increased the activities of SOD, CAT, GPx and the expressions of Nrf2 and HO-1, and decreased the perisynovial inflammation and cartilage-bone destruction in the paws.

Table. Clinical and laboratory data in the study groups

	Group-I (Control) (n=10)	Group-II (Arthritis) (n=10)	Group-III (PMTX 0.2 mg/kg) (n=10)	Group-IV (PMTX 1 mg/kg) (n=10)
14th day arthritis score	–	1.4±0.7	1.9±1.3	1.4±0.5
29th day arthritis score	–	2.4±0.5	1.0±0.6[d]	0.4±0.5[e,f]
Inflammation score	–	4.0±0.0	3.2±0.9[c]	2.4±0.9[e]
Cartilage-bone destruction score	–	3.9±0.3	3.3±0.7[d]	2.0±0.0[e,g]
TNF-α (pg/mL)	25.6±5.0	62.7±12.9[b]	31.7±7.1[d]	30.7±10.4[d]
IL-17 (pg/mL)	29.5±8.3	65.7±8.9[b]	42.3±4.8[b,d]	47.0±5.6[b,d]
MDA (μmol/L)	0.58±0.23	1.60±0.20[b]	0.69±0.14[d]	0.70±0.16[d]
SOD (U/mL)	12.0±7.3	3.4±1.6[b]	6.5±2.7[b,d]	6.5±1.8[b,d]
CAT (nmol/min/mL)	0.33±0.07	0.12±0.08[b]	0.23±0.08[a,c]	0.13±0.1[b]
GPx (nmol/min/mL)	335±179	179±45[b]	292±126[c]	322±198[d]

Data were presented as mean±standard deviation. PMTX: Pemetrexed, TNF: Tumor necrosis factor, IL: Interleukin, MDA: Malondialdehyde, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase.
vs Group-I: [a]p<0.05, [b]p<0.0; vs Group-II: [c]p<0.05, [d]p<0.01,[e]p<0.001; vs Group-III: [f]p<0.05, [g]p<0.01

Conclusion: This study is the first to show that PMTX prevents the development of cartilage-bone destruction in the CIA model. These results suggest that PMTX may be candidate of a novel disease modifying antirheumatic drug for the treatment of RA.

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Increased Density of Sympathetic Nerve Fibers in Metabolically Activated Fat Tissue Surrounding Human Synovium and Mouse Lymph Nodes in Arthritis. Christine Wolff[1], Luise Rauch[1], Torsten Lowin[1], Susanne Klatt[2] and Rainer H. Straub[1]. [1]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, Department of Internal Medicine I, University Hospital, Regensburg, Germany, [2]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital, Regensburg, Germany

Background/Purpose: The loss of sympathetic nerve fibers in inflamed tissue and secondary lymphoid organs has been detected during chronic inflammatory diseases such as rheumatoid arthritis (RA). However, it is unclear whether nerve fibers appear in higher density in surrounding non-participating normal tissue. Since fat tissue is often found in the proximity of inflammatory lesions, this study aimed to investigate density of sympathetic nerve fibers in and metabolic activation of fat tissue surrounding human synovium in rheumatoid arthritis/osteoarthritis (OA) and draining lymph nodes in arthritic and normal mice.

Methods: Synovial tissue samples were obtained from 10 OA and 10 RA patients, that underwent knee joint replacement surgery. DBA/1 mice were immunized with collagen type II (CII) in Freund's adjuvant (FA) on day 0 and boosted with CII in incomplete FA on day 21. When a score of 3 points was reached animals were killed and tissue subjected to further analysis. Stainings of sympathetic nerve fibers were performed by immunofluorescence. Presence of nerve repellent factors and beta-3adrenergic receptors was investigated using immunohistochemistry. Metabolic activation of fat tissue was estimated by occurrence of small-vacuoled adipocytes (Sudan-III staining), expression of beta3-adrenoceptors, and adipose tissue weight.

Results: Density of sympathetic nerve fibers was markedly increased in fat tissue surrounding RA compared to OA synovium. In adipose tissue adjacent to draining lymph nodes, density of sympathetic nerve fibers was higher in arthritic compared to normal animals. In human synovium and mouse draining lymph nodes, the two sympathetic nerve repellent factors semaphorin 3C and 3F were highly expressed. In arthritic compared to normal mice, fat tissue around lymph nodes was markedly lighter, adipocytes had more fragmented lipid droplets, and fat tissue demonstrated a high expression of beta3-adrenoceptors.

Conclusion: This study demonstrated an increased density of sympathetic nerve fibers in metabolically activated fat tissue surrounding human RA synovium and draining lymph nodes of arthritic mice. Since sympathetic neurotransmitters stimulate lipolysis, the repulsion of sympathetic nerve fibers from inflamed regions and their increased occurrence in fat tissue is probably an adaptive program to support the proinflammatory process by releasing energy-rich substrates.

2083

Gemcitabine Ameliorates Experimental Arthritis in Rats. Metin Ozgen[1], Suleyman Serdar Koca[1], Adile Ferda Dagli[2], Ahmet Karatas[1], Cemal Orhan[3], Mehmet Tuzcu[4], Nuran Sahin[3], Kazim Sahin[3] and Ahmet Isik[1]. [1]Department of Rheumatology, Faculty of Medicine, Firat University, Elazig, Turkey, [2]Department of Pathology, Faculty of Medicine, Firat University, Elazig, Turkey, [3]Department of Animal Nutrition, Faculty of Veterinary Science, Elazig, Turkey, [4]Department of Biology, Faculty of Science, Firat University, Elazig, Turkey

Background/Purpose: T and B lymphocytes are known to have important roles in initiating and/or perpetuating synovial inflammation in rheumatoid arthritis (RA). Gemcitabine (2',2'-difluorodeoxycytidine, GEM), an antimetabolite drug, has anti-proliferative and apoptotic effects on T and B lymphocytes.

This study investigated the therapeutic potential of the GEM on collagen-induced arthritis (CIA) in rats

Methods: Forty Wistar albino female rats were randomized to four groups (n=10 in each group): Group-I as the control group, Group-II as the arthritis group, Group-III as the low dose GEM group, and Group-IV as the high dose GEM group were assigned. Arthritis was induced by intradermal injection of chicken type II collagen combined with incomplete Freund's adjuvant in Group-II, III, and IV rats. The doses of 5 and 20 mg/kg GEM were intraperitoneally administered in Group-III and IV, respectively twice a week after the onset of arthritis.

Animals were sacrificed at the 15th day after the onset of arthritis. The trunk bloods and paws of the rats were obtained for further analysis. Tumor necrosis factor (TNF)-α, interleukin (IL)-17, malondialdehyde (MDA) levels and superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) activities in serum and articular tissue nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxgenase-1 (HO-1) expressions, perisynovial inflammation and cartilage-bone destruction were determined in the paws.

Results: When compared with Group-I, TNF-α, IL-17, and MDA levels were increased, and SOD, CAT, GPx activities and the expressions of Nrf2 and HO-1 were decreased in Group-II (Table). Histopathological analysis demonstrated the extensive perisynovial inflammation and marked cartilage-bone destruction in Group-II rats. GEM treatment decreased the levels of TNF-α, IL-17, MDA, and increased the activities of SOD, CAT, GPx and the expressions of Nrf2 and HO-1, and decreased the perisynovial inflammation and cartilage-bone destruction in the paws.

Table. Clinical and laboratory data in the study groups

	Group-I (Control)	Group-II (Arthritis)	Group-III (GEM 5 mg/kg)	Group-IV (GEM 20 mg/kg)
14th day arthritis score	–	1.4±0.7	1.4±0.5	1.7±0.4
29th day arthritis score	–	2.4±0.5	0.0±0.0[e]	0.0±0.0[e]
Inflammation score	–	4.0±0.0	1.8±0.6[e]	1.3±0.6[e]
Cartilage-bone destruction score	–	3.9±0.3	1.1±0.6[e]	0.5±0.5[e,f]
TNF-α (pg/mL)	25.6±5.0	62.7±12.9[b]	25.8±4.9[d]	30.8±5.5[d]
IL-17 (pg/mL)	29.5±8.3	65.7±8.9[b]	47.4±4.6[b,d]	44.7±5.6[b, d]
MDA (μmol/L)	0.58±0.23	1.6±0.2[b]	0.91±0.28[a,d]	0.76±0.32[d]
SOD (U/mL)	12.0±7.3	3.4±1.6[b]	4.9±1.3[b,c]	4.8±1.4[b]
CAT (nmol/min/mL)	0.33±0.07	0.12±0.08[b]	0.26±0.05[d]	0.30±0.07[e]
GPx (nmol/min/mL)	335±179	179±45[b]	362±208[c]	351±243[c]

Data were presented as mean±standard deviation. GEM: Gemcitabine, TNF: Tumor necrosis factor, IL: Interleukin, MDA: Malondialdehyde, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase.
vs Group-I: [a]p<0.05, [b]p<0.01; vs Group-II: [c]p<0.05, [d]p<0.01,[e]p<0.001; vs Group-III: [f]p<0.05

Conclusion: GEM treatment suppresses inflammatory pathways and oxidative stress and ameliorates clinical symptoms and reduces histological scores in the experimental CIA model. These results suggest that GEM may be a potential therapeutic agent in inhibiting joint destruction in RA.

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A Novel, Highly Selective Syk Kinase Inhibitor Significantly Ameliorates the Severity of Arthritis in Rodents. Zhong Cui Sun[1], Yu Cai[1], Yan Qiu[1], Lei Fang[1], Xiaoming Dai[1], Zhipeng Wu[1], Ping Ren[1], Jianlin He[1], Changwu Lu[1], Yongjuan Yu[1], Jian Wang[1], Yang Sai[1], James Yan[1], Jia Li[1], Wei Deng[1], Weihan Zhang[1], Jianguo Ji[2], Weiguo Su[1] and Haoran Zhao[1]. [1]Hutchison Medipharma Limited, Shanghai, China, [2]Abott, Shanghai, China

Background/Purpose: SYK non receptor tyrosine kinase is a key mediator of signaling events downstream of a wide array of receptors important for immune function, including the B cell antigen receptor, immunoglobulin receptors bearing the Fcgamma chain, and other ITAM-containing C-type lectin and integrin receptors. In this study we seek to discover a highly potent and selective, orally available small molecule inhibitor for Syk kinase and evaluate its effects in rodent models of arthritis.

Methods: Using both in vitro enzymatic and cell-based assays and in vivo pharmacological assays for establishing structure-activity relationships, compounds were synthesized and screened to identify the ones with excellent potency, selectivity, and drug-like properties. Mouse collagen induced arthritis (CIA) was induced in DBA/1 mice by intradermal administration of chicken collagen type II (CCII) with complete Freund's adjuvant (CFA) on days 0 and 21. Paws were scored using a 0–4 scale with a maximum score of 16 for each animal. Rat adjuvant arthritis (AA) was induced in Lewis rats by intradermal administration of CFA on day 0. Paw volumes were measured daily after arthritis onset. In both models, HM-029 was administered by daily oral gavage.

Results: HM-029 was discovered as a potent and highly selective inhibitor of Syk. It has been tested against a panel of 24 representative tyrosine and serine-threonine kinases and exhibited good general selectivity against other kinases, including KDR, JAK, and Src kinases. In bone marrow-derived mast cells (BMMCs), HM-029 potently inhibited IgE receptor cross-linking stimulated phosphorylation of LAT, ERK, p38 and Akt. The secretion of IL-6, TNFa and IL-13 was blocked by HM-029 as well. In mice with collagen-induced arthritis, treatment with HM-029 after disease onset significantly reduced disease severity in a dose dependent manner. Consistent with its efficacy in mice, HM-029 administered to rats with established AA also ameliorated disease severity compared to vehicle group.

Conclusion: This study showed that HM-029, acting through selective inhibition of Syk activation, exhibited strong beneficial effect in rodent arthritis models. These results support the development of HM-029 as a promising new agent for the treatment of rheumatoid arthritis.

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A Novel Role of h2-Calponin in the Development of Anti-GPI Serum-Induced Arthritis. M. Moazzem Hossain[1], Qi Quan Huang[2], Linda D. Hazlet[3], Sharon A. McClellan[3], Richard M. Pope[2] and J.-P. Jin[1]. [1]Departments of Physiology, Wayne State University School of Medicine, Detroit, MI, [2]Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, MI

Background/Purpose: Calponin is an actin cytoskeleton-associated regulatory protein. Three homologous isoforms (h1, h2 and h3) have been identified. H2-calponin is found in smooth muscle and several types of non-muscle cells, including monocytes and macrophages. H2-calponin inhibits proliferation and migration of various types of cells. Our previous study (Huang et al., *JBC*. 283:25887–99, 2008) demonstrated that h2-calponin KO mice showed reduced numbers of peripheral blood neutrophils and monocytes. In addition, the lack of h2- calponin significantly increased migration and phagocytotic activity of macrophages. In the present study, we investigated the role of h2-calponin in the development of anti-GPI serum-induced arthritis.

Methods: H2-calponin knockout (KO) and age- and genetic background-matched C57BL/6 wild type (WT) mice were intraperitoneally injected with 300 ml of anti-GPI mouse serum. Delta-ankle circumference and arthritis clinical score were determined at days 0, 2, 4, 7 and 9 after injection. The ankles harvested at day 9 post-arthritis induction were analyzed for histology by H&E staining. IL-1b concentration in ankle homogenates and serum collected from day 9 post-arthritis induction mice were determined by ELISA. Brewer's thioglycollate-elicited peritoneal macrophages from h2-calponin KO and WT mice were also examined for their cytokine production in response to LPS stimulation in culture using quantitative PCR.

Results: Injection of anti-GPI serum resulted significantly ($P<0.05$) lower Delta-ankle circumference and clinical arthritis score in h2-calponin KO mice in comparison to WT mice. H&E stained sections of ankle joints showed significantly ($P<0.05$) lower inflammation and bone erosion in h2-calponin KO group than that of controls. In contrast, there was no difference in IL-1b in joint tissues of H2-calponin KO and WT mice. Further, compared with the WT controls, h2-calponin-null macrophages demonstrated increased *in vitro* synthesis of IL-1b, IL-6, IL-10, IL-12, TNFa, MIP-2, IFNg, HIF-1a, and INOS both at baseline and upon LPS stimulation. The levels of TLR2 and VEGF-A in h2-calponin-null cells were also higher than WT cells at baseline but were not different after LPS stimulation. TLR4, TGF-b, VEGF-R1 and VEGF-R2 were unchanged in the KO macrophages.

Conclusion: The results demonstrated that h2-calponin plays a novel role in the development of anti-GPI serum-induced arthritis. The function of h2-calponin in regulating macrophage activity may form a basis for its role in inflammation and autoimmune responses. Since there was no reduction of IL-1b in joint tissue, a critical cytokine in this model of passive arthritis, the results may suggest that the mechanisms down stream of the induction of cytokines contributed to the reduction of arthritis development despite the elevation of IL-1b and TNFa. The increased phagocytotic activity of h2-calponin-null macrophages may facilitate the clearance of autoimmune complexes to reduce the severity of arthritis. Further studies are underway to investigate the underlying mechanisms and explore the value of inhibiting h2-caloponin expression for the treatment of arthritis.

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An Endogenous TLR2 Ligand Promotes Chronicity of Arthritis Which Is Modulated by Fas Signaling. Qi Quan Huang[1], Alexander Misharin[1], Robert Birtett[1], Carla M. Cuda[1], Christopher V. Nicchitta[2], Harris R. Perlman[1] and Richard M. Pope[1]. [1]Northwestern University, Chicago, IL, [2]Duke university Medical Center, Durham, NC

Background/Purpose: To define the role of non-apoptotic Fas-FasL signaling in the anti-GPI serum induced arthritis model and identify its association with TLR2 or TLR4-mediated macrophage activation.

Methods: Genetically modified mice were generated by crossing floxed Fas ($Fas^{f/f}$) mice with $LyzM^{cre}$ mice to obtain a mouse line deficient in Fas in myeloid lineage ($Fas^{f/f}$, $LyzM^{cre}$). Cell types in peripheral blood were determined by complete cell count and in peritoneal cavity by immunophenotyping. Expression of Fas, TLR2 and TLR4 on the surface of macrophages was determined by flow cytometry. Arthritis was induced by transfer of anti-GPI serum (300ml or 150ml/mouse) from K/BxN mice. The ankles harvested on day10 post-induction were analyzed for histology, cytokines, and gp96 expression, an endogenous TLR2 ligand. Cytokines and gp96 concentration in ankle homogenates were determined by ELISA. Resident peritoneal macrophages were cultured for 3–4 days, and activation following incubation with TLR4 (LPS) or TLR2 (Pam3) ligation was assessed by IL-6 and TNFa ELISA.

Results: When arthritis was induced by a low dose of anti-GPI serum (150 ml), arthritis was significantly reduced in both males and females, while at the higher dose (300 ml), and the reduction of arthritis was greater in the male $Fas^{f/f}$, $LyzM^{cre}$ mice, compared to littermate controls. The ankle homogenates from mice at day10 (300ml anti-GPI) demonstrated reduced IL-1b in both male and female $Fas^{f/f}$, $LyzM^{cre}$ mice compared with same gender littermate controls ($p< 0.05$), however, IL-1b was significantly ($p< 0.05$) lower in the ankles of male compared with female $Fas^{f/f}$, $LyzM^{cre}$ mice. We have demonstrated earlier that the 96 kD heat shock protein (gp96) is an endogenousTLR2 ligand which is increased in the joints of patients with rheumatoid arthritis. We observed that the expression of gp96 is strongly correlated with the course of anti-GPI serum induced arthritis in both $Fas^{f/f}$, $LyzM^{cre}$ ($r= 0.81$, $p<0.001$) and littermate controls ($r= 0.63$, $p<0.01$). gp96 concentration is greatly reduced in the ankles of male $Fas^{f/f}$, $LyzM^{cre}$ mice compared with the same gender littermate controls ($p< 0.01$) or female $Fas^{f/f}$, $LyzM^{cre}$ mice at day10. Resident peritoneal macrophages from the male mice demonstrated reduced IL-6 ($p<0.05$) and TNFa ($p<0.05$) production in response to Pam3, but not to LPS. The expression of TLR2 and TLR4 was not reduced in any myeloid cell in the $Fas^{f/f}$, $LyzM^{cre}$ mice. Supporting the role of gp96, treatment of wild type mice with a neutralizing antibody to gp96, ameliorated the chronicity of the arthritis in male but not female mice.

Conclusion: These observations demonstrate that Fas deficiency on myeloid cells results in reduced arthritis, which is more apparent in males. The local expression of the endogenous TLR2 ligand gp96 correlated with disease activity, and TLR2-mediated activation of macrophages from $Fas^{f/f}$, $LyzM^{cre}$ was reduced. Further, a neutralizing antibody to gp96 suppressed arthritis in male mice. These observations suggest that the local release of endogenous TLR2 ligands may contribute to the chronicity of anti-GPI induced arthritis and that this progression is enhanced by intact Fas signaling.

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Suppression of Established Rat Collagen-Induced Arthritis and Inhibition of TNF-α with Small Molecule Aminopyridizines. Soo I. Choi[1], Lori D. Klaman[2], Weiling Chen[1] and Ernest Brahn[1]. [1]UCLA School of Medicine, Los Angeles, CA, [2]Transition Therapeutics, Toronto, ON

Background/Purpose: In rheumatoid arthritis (RA), activated macrophages and synoviocytes produce many key cytokines and mediators that contribute to the inflammation and joint destruction. Blocking proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 has led to clinical and radiographic benefits in RA patients. TT301 and TT302 are unique, orally available, small molecules that can suppress proinflammatory cytokines and reduce inflammation in rodent models of multiple sclerosis and Alzheimer's disease. We report the effects of these compounds on inflammatory pathways *in vitro*, and in established rat collagen-induced arthritis (CIA) *in vivo*.

Methods: The in vitro effects of TT301 and TT302 on cytokine production were examined in stimulated primary synovial fibroblasts and RAW264.7 macrophages. Cells were preincubated with compound or vehicle in serum-free media and stimulated with LPS (5 mg/mL), IL-1β (5 mg/mL) or TNF-α (30ng/mL). Supernatants were analyzed by cytokine ELISA. *In vivo* studies used Lewis rats immunized with porcine type II collagen on day 0 to induce CIA. A total of 84 rats were immunized and 71 rats with arthritis by day 14 were randomized to vehicle controls or 5 treatment arms: TT301 (1 and 7 mg/kg) or TT302 (at 1, 7, or 15mg/kg). Based on the degree of joint involvement and soft tissue swelling, each limb was scored from 0–4, with a maximum total score of 16. At the end of study (day 28), plasma was harvested for multiplex cytokine profiles, the left hind limbs were fixed for immunohistochemistry, and the right hind limbs were microdissected/snap frozen to obtain pure synovium for gene expression profiles, gene hub, module, and network analysis. All 142 hind limbs were also evaluated with high resolution digital radiographs using a 0–3 scale (0=normal, 1=soft tissue swelling only, 2=minor erosions, and 3=marked erosions).

Results: In stimulated RAW264.7 macrophages and synovial fibroblasts, TT301 and TT302 dose-dependently inhibited the induction of key cytokines relevant to RA pathology including TNF-α, IL-6, and MCP-1. By protocol design, all Lewis rats that developed CIA between days 11–14 entered the study and were then randomized. The clinical severity was significantly lower than vehicle controls for both agents with a dose-response benefit (TT302 $p< 4 \times 10^{-6}$, $p< 8 \times 10^{-7}$, and $p< 4 \times 10^{-9}$ for 1mg/kg, 7mg/kg or 15mg/kg, respectively) (TT301 $p< 1 \times 10^{-6}$, $p< 2 \times 10^{-8}$ for 1mg/kg or 7mg/kg, respectively). Statistical differences, compared to controls, were typically noted within 48–72 hours after initiation of therapy and this was sustained. By the end of the study on day 28, TT302 and TT301 suppressed radiographic damage (TT302 $p< 1 \times 10^{-2}$, $p< 5 \times 10^{-4}$, and $p< 3 \times 10^{-8}$ for 1mg/kg, 7mg/kg or 15mg/kg, respectively) (TT301 $p< 7 \times 10^{-2}$, $p< 2 \times 10^{-8}$ for 1mg/kg or 7mg/kg, respectively). Cytokine profiles post-treatment demonstrated that TT301 and TT302 tended to lower circulating TNF-α levels. The analysis of joint immunohistochemistry and synovial gene expression profiles is ongoing.

Conclusion: TT301 and TT302 suppressed established CIA and inhibited TNF-α. The studies indicate that these novel small molecules might have therapeutic benefits in RA.

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Treatments with Glycogen Synthase Kinase-3β Inhibitor Mitigate the Severity of Arthritis in Mice with Collagen-Induced Arthritis. Yong-Jin Kwon, Tae-Yeon Kim, Sang-Won Lee, Yong-Beom Park, Soo Kon Lee and Min-Chan Park. Yonse University College of Medicine, Seoul, South Korea

Background/Purpose: Glycogen synthase kinase (GSK)-3β is a multifunctional serine-threonine kinase, which was originally identified as a rate-limiting enzyme involved in the control of glycogen metabolism. Recently, it has been shown that GSK-3β performs a critical function in the regulation of various signaling pathways involving inflammatory responses, and the mechanisms for these anti-inflammatory effects are thought to be primarily mediated via antagonizing the transcriptional activities of NF-κB. This study was performed to investigate the therapeutic effects of selective GSK-3β inhibitors; lithium chloride, 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione (TDZD-8) and 6-bromoindirubin-3'-oxime (BIO) on the severity of arthritis and inflammatory response in collagen-induced arthritis (CIA) mice.

Methods: DBA/1J mice were immunized with CII in Freund's complete adjuvant and administered with booster injection 3 weeks later to induce CIA. Mice were subsequently injected intraperitoneally with 0.1 mM and 10 mM of lithium chloride, TDZD-8, or BIO once daily between day 24 and day 45 postimmunization. Clinical assessment for arthritis scores and histopathological assessment of joint sections were performed. The infiltration of T cells and macrophages were determined by immunohistochemical staining for CD3 and F4/80 and the activity of osteoclast

was assessed by tartrate resistant acid phosphatase (TRAP) staining in joint sections from CIA mice. Serum levels of IL-1β, IL-6, TNF-α and IFN-γ were evaluated using ELISA.

Results: Histologic analysis of joints from vehicle-treated CIA mice showed severe synovial proliferation, significant infiltration of inflammatory cells, and bone erosion. Treatments of each GSK-3β inhibitors significantly attenuated the clinical and histological severity of CIA, compared with vehicle-treated mice, and these effects were shown in dose-dependent manners. The infiltration of T cells and macrophages were decreased in immunohistochemical analysis of joint sections and TRAP-positive cells were also down-regulated by treatments with GSK-3β inhibitors. The serum levels of IL-1β, IL-6, TNF-α and IFN-γ were significantly decreased by treatments with GSK-3β inhibitors in dose-dependent manners.

Conclusion: GSK-3β inhibitors treatment reduces inflammation and joint destruction in CIA, and suppressed the productions of various pro-inflammatory cytokines. These findings suggest that inhibition of GSK-3β can be an effective therapeutic agent in rheumatoid arthritis.

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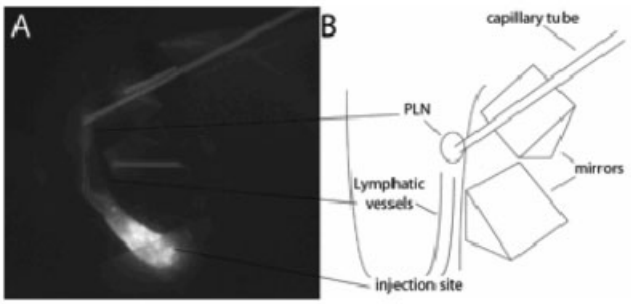
Pressure and Viscosity Measurements in Efferent Lymphatics to Better Understand the Mechanisms of Arthritic Flare and Response to Therapy. Echoe M. Bouta, Ronald Wood, Christopher T. Ritchlin and Edward M. Schwarzy. University of Rochester School of Medicine and Dentistry, Rochester, NY

Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease distinguished by episodic flares in affected joints. Recently, we showed that altered lymph node volume and lymph drainage from the affected joint precede arthritic flare while novel therapies that target lymphatics are being developed. Unfortunately, methods to directly measure the lymphatic pressure and viscosity changes during and after arthritic flare and responses to therapy are not available for the established animal models of RA. Thus, the goal of this study was to develop quantification methods suitable for studying the lower limbs of mice during arthritic flare and in response to therapy.

Methods: Pressure measurements were performed by the insertion of a glass micropipette connected to a pressure transducer into the popliteal lymph node (PLN) of WT mice. Placement was confirmed by examining the temporal association of pressure changes with optical pulsations detected by near infrared-indocyanine green (NIR-ICG) imaging, and by an increase of signal intensity in the lymphatic vessels that occurred after injecting ICG into the PLN through the glass micropipette. Viscosity was measured by multi-photon fluorescence recovery after photobleaching (MP-FRAP) of FITC-dextran in lymphatic vessels afferent to PLN, after introducing the dye by footpad injection. The recovery time was measured to determine the diffusion coefficient of lymph, which was then used to calculate the viscosity of the lymph with the Stokes-Einstein equation.

Results: Correct placement of the glass micropipette into the node was achieved and verified by no evidence of leaking, increase of intensity in the surrounding lymphatic vessels and a detected pulse in the pressure measurement. Lymphatic pressure was determined to be ~14cm water. In vivo viscosity measurements could be verified by finding the diffusion coefficient of a solution of a known viscosity, and the viscosity of the lymph was determined to be ~2mPa s.

Conclusion: Here we describe novel methods to quantify lymphatic pressure and viscosity in lymphatic vessels and PLN of mice. Additional preliminary results with these methods to quantify lymphatic function during the acute and chronic phases of arthritis in TNF-Tg mice will be discussed together with translational modification that may facilitate elucidation of the mechanisms of arthritic flare in RA.



2090

IL-6 Blockade Augments the Therapeutic Effect of MTX in Mice with Glucose-6-Phosphate Isomerase-Induced Arthritis. Hiroto Yoshida[1], Misato Hashizume[1], Keisuke Tanaka[1], Miho Suzuki[1], Takayuki Sumida[2], Isao Matsumoto[2] and Masahiko Mihara[1]. [1]Chugai Pharmaceutical Co., Ltd., Gotemba, Shizuoka, Japan, [2]Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan

Background/Purpose: Methotrexate (MTX) is a front-line drug for rheumatoid arthritis (RA), but progressive loss of efficacy is a major problem. Transporters are determinants of the pharmacological effect of drugs. MTX enters cells through the reduced folate carrier (SLC19A1). Here, we elucidated the relevance of SLC19A1 expression for MTX therapeutic effects using glucose-6-phosphate isomerase (GPI)-induced arthritis.

Methods: GPI-induced arthritis in DBA/1J mice was triggered by intradermal injection of recombinant GPI and pertussis toxin. MTX was given orally thrice weekly from the first day of immunization. Mice were injected once with 4 mg of rat anti-mouse IL-6R monoclonal antibody (MR16-1) intraperitoneally 10 days after immunization. Clinical symptoms of arthritis were evaluated visually on a scale of 0 – 3 for each limb. SLC19A1 mRNA in hind limbs was quantified by real-time PCR. Serum anti-GPI antibody, antigen-specific IL-17 production from splenocytes and serum cytokines were measured by ELISA. Synovial cells from arthritic mice were cultured with MTX, TNF-α and IL-6 for 3 days, and cell proliferation assessed by BrdU incorporation. To analyze gene expression, synovial cells were cultured with MTX, TNF-α and IL-6 for 24 h, after which SLC19A1 mRNA was quantified by real-time PCR.

Results: First, we examined the effect of MTX on GPI-induced arthritis. Whereas MTX reduced arthritis up to day 20 after immunization, its efficacy gradually decreased between day 20 and 30. Arthritic mice expressed less hind limb SLC19A1 than controls, and MTX decreased this further. Because TNF-α and IL-6 levels were elevated in the affected paws of mice with GPI-induced arthritis, we next examined the effects of MTX, TNF-α and IL-6 *in vitro*. Culture of synovial cells with MTX or IL-6, but not TNF-α, decreased the expression of SLC19A1. In the presence of IL-6, MTX further reduced SLC19A1 expression. Additionally, the inhibitory effect of MTX on synovial cell proliferation was reduced in the presence of IL-6. Although MR16-1 did not improve arthritis when injected at day 10, MTX and MR16-1 together reduced symptoms better than MTX alone. Injection of MR16-1 resulted in the return of SLC19A1 mRNA to normal levels. Combining MTX and MR16-1 increased SLC19A1 mRNA more than MTX alone. Antigen-specific IL-17 production by splenocytes from arthritic mice was higher than in controls. Unexpectedly, MTX treatment increased IL-17 production and a combination of MTX + MR16-1 did not reduce it. Anti-GPI antibody was present in the serum of arthritic but not control mice, and this was more strongly suppressed by MTX and MR16-1 than by MTX alone.

Conclusion: We demonstrated that MTX-treated arthritic mice was resistant to MTX along with continuous administration and reduced SLC19A1 expression in mice with GPI-induced arthritis. IL-6 blockade augments the therapeutic effect of MTX via up-regulation of SLC19A1 expression.

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Laquinimod Inhibits Disease Severity in Murine Collagen Induced Arthritis. Joel F. Kaye and Eran Blaugrund. Teva Pharmaceuticals Ltd, Netanya, Israel

Background/Purpose: Laquinimod (TV-5600; LAQ) is a synthetic compound being developed by Teva for the treatment of multiple sclerosis (MS). Laquinimod has demonstrated therapeutic effect in various experimental autoimmune models, including animal models of Guillain-Barré Syndrome, Inflammatory Bowel Disease, and Type I Diabetes. The mechanism of action of laquinimod in these models includes the reduction of leukocyte infiltration and modulation of the cytokine milieu. Furthermore, in a spontaneous model of SLE in MRL/lpr mice, laquinimod treatment inhibited many aspects of systemic lupus including arthritic joint swelling. These promising findings prompted the present study to evaluate whether laquinimod can inhibit disease severity in a mouse model of arthritis.

Methods: Male DBA/1OlaHsd mice were immunized with type II collagen in CFA on days 1 and 21. From day 18 (semi-established arthritis) mice were dosed orally (PO) daily (QD) with vehicle, LAQ (0.2, 1, or 5 mg/kg), methotrexate (0.5 mg/kg, MTX), or LAQ (0.2 or 1 mg/kg) in combination with MTX (0.5 mg/kg) until day 33. Efficacy evaluations were

based on animal body weights, daily clinical arthritis scores, arthritis scores expressed as area under the curve (AUC) and histopathology on fore paws, hind paws, and knees from all mice. Evaluation of serum anti-type II collagen antibody levels was also performed

Results: Clinical arthritis scores expressed as AUC were significantly reduced for mice treated with MTX (50% reduction), 0.2 mg/kg LAQ (32%), 1mg/kg LAQ (52%) or 5 mg/kg LAQ (69%). When treatment with MTX and LAQ was combined, clinical arthritis scores were reduced to 82% (0.2mg/kg LAQ) or 95% (1mg/kg LAQ), as compared to vehicle controls.

All paw histopathology parameters were significantly reduced toward normal, for mice treated with 1 mg/kg LAQ (61% reduction of summed scores), 1 mg/kg LAQ+MTX (96%), or MTX (46%) as compared to vehicle controls. Treatment with 1 mg/kg LAQ significantly reduced knee inflammation (51% reduction), pannus (59%), cartilage damage (62%), and summed knee scores (57%) as compared to vehicle controls. All knee histopathology parameters were significantly reduced toward normal for mice treated with 1 mg/kg LAQ+MTX (97% reduction of summed scores) as compared to vehicle controls.

Conclusion: Results of this study indicate that daily oral treatment with laquinimod (0.2, 1, or 5 mg/kg) had significant and dose dependent effect on the clinical and histopathalogical parameters associated with semi-established type II collagen arthritis in mice. In addition, combining laquinimod and methotrexate treatment resulted in an additive effect on all tested parameters.

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Blocking the Granulocyte Macrophage Colony Stimulating Factor Receptor Alpha Chain Prevents Mechanical Hypersensitivity in a Mouse Model of Inflammatory Pain. John P. Hatcher, Justine Whitworth, Ian K. Anderson, Iain P. Chessell and Matthew A. Sleeman. MedImmune Ltd, Cambridge, United Kingdom

Background/Purpose: Over the last decade the GM-CSF pathway has been proposed as playing a pivotal role in the pathology of rheumatoid arthritis (RA) by promoting macrophage and neutrophil activation, survival and differentiation. Consequently a number of clinical studies are underway in RA targeting either GM-CSFR or GM-CSF. Recently it has also been shown that GM-CSF may have a role in peripheral pain sensation in models of cancer pain. As refractory pain remains a significant problem in many individuals with RA, we have investigated the role of GM-CSFR blockade in a mouse model of inflammatory pain. Objective: In these studies we aimed to characterize the role of GM-CSFR alpha in inflammatory pain by blocking GM-CSF signalling using a neutralising antibody to the GM-CSF receptor.

Methods: Mechanical hypersensitivity was determined using a mouse incapacitance tester. Mice were placed into the apparatus such as each hind paw was located on one of two weight bearing sensors. Weight bearing was calculated by measurement of ipsilateral and contralateral weights in grams over a period of 4s. Following the establishment of baseline readings mice received a single intra-plantar administration of Complete Freunds Adjuvant (FCA) (30μl of 1mg/ml). 24 hrs later mice underwent pre-dose testing for changes in mechanical hypersensitivity as described above. Mice were then randomly allocated into treatment groups of 9/10 with approximately equal ipsilateral/contralateral ratios and were administered one of the following treatments; PBS vehicle (10ml/kg), CAT-004, the isotype control (30mg/kg) or CAM-3003, a GM-CSFR antibody (3, 10 or 30mg/kg). All doses were administered intra-peritoneally. Mice were re-tested for changes in mechanical hypersensitivity at 4hr, 1, 2, 3 and 7 days post dose as described above.

Results: FCA caused a mechanical hypersensitivity which manifested as a reduction in the ipsilateral/contralateral ratio when compared to naive readings. The administration of CAT-004 did not produce any significant reversal of the FCA induced hypersensitivity at any time point when compared to PBS vehicle control. CAM-3003 (3, 10 and 30mg/kg) caused a reversal of the FCA induced hypersensitivity (vs CAT 004 control) which reached significance 1 day post dose for all treatment groups. Significance was maintained out till 2 days post dose for the 30mg/kg group. No significant inhibition of mechanical hypersensitivity was observed following administration of 3mg/kg or 10mg/kg CAM-3003 when compared with isotype control (CAT-004).

Conclusion: This study demonstrates that inhibiting GM-CSF signalling is effective in a mouse inflammatory pain mouse model, supporting continued development of agents targeting GM-CSFR for this therapeutic area.

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Prophylactic Injection of Non-Citrullinated Alpha-Enolase Has Immunomodulatory Effects in Collagen-Induced Arthritis Mice. Clément Guillou[1], Gilles Avenel[1], Céline Derambure[1], Mathieu Verdet[1], Martine Hiron[1], Maude Maho[1], Xavier Le Loët[2], Sahil Adriouch[1], Olivier Boyer[1], Thierry Lequerré[2] and Olivier Vittecoq[2]. [1]Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [2]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France

Background/Purpose: Identification of autoantibodies associated with rheumatoid arthritis (RA) has been of major interest. In this context, we have previously identified for the first time α-enolase as a new auto-antigen in early RA*. Moreover, subsequent studies have shown that citrullination of α-enolase is crucial for its autoantigenicity. α-enolase is an evolutionary conserved protein implicated both in glycolysis pathway and as a plasminogen receptor. Here, we have evaluated, in the well-known collagen induced arthritis (CIA) model, the clinical and immunological effects of both recombinant non-citrullinated α-enolase and immunodominant peptides from human and bacterial species.

Methods: Different doses of α-enolase (10 and 100 μg) or immunodominant enolase peptide 1 from human [hEP1] or P*orphyromonas gingivalis* [pEP1] (1, 10 or 100μg) were intraperitoneally injected to 6 week-old DBA/1 mice one day prior to collagen II arthritis induction. Both clinical (weight, arthritis score, tarsal thickness) and biological (anti-collagen II and anti-α-enolase antibodies) were assessed during the 90 days follow-up period.

Results: Prophylactic injection of recombinant α-enolase was able to significantly prevent weight loss and to decrease the severity of arthritis evaluated by the arthritis score as well as the tarsal thickness. There was a dose-effect since 100 μg led to better results. Levels of anti-collagen II antibodies were significantly lower whereas titers of anti-α-enolase antibodies were significantly higher in mice treated with 100 μg of a-enolase compared to control mice. As regards to hEP1 and pEP1, we etablished a dose-dependant protective effect in CIA which is significant for pEP1. This protective effect is not due to once again a decrease of anti-collagen II antibodies titer.

Conclusion: Prophylactic treatment with recombinant α-enolase as well as immunodominant peptides has immunomodulatory effects in collagen-induced arthritis mice. The regulatory mechanisms induced by this protein seem to be partially due to a control of the production of anti-collagen II antibodies. Those results suggest that non-citrullinated α-enolase could constitute a potential new therapeutic approach in RA.

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Preventive and Therapeutic Effects of Epigallocatechin-3-Gallate (EGCG) on Collagen-Induced Arthritis in Rats. Metin Ozgen[1], Suleyman Serdar Koca[1], Adile Ferda Dagli[2], Ahmet Karatas[1], Cemal Orhan[3], Hasan Gencoglu[4], Nurhan Sahin[3], Kazim Sahin[3] and Ahmet Isik[1]. [1]Department of Rheumatology, Faculty of Medicine, Firat University, Elazig, Turkey, [2]Department of Pathology, Faculty of Medicine, Firat University, Elazig, Turkey, [3]Department of Animal Nutrition, Faculty of Veterinary Science, Elazig, Turkey, [4]Department of Biology, Faculty of Science, Firat University, Elazig

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by cellular infiltration and proliferation of synovium, leading to progressive destruction of the joints through the interaction between infiltrating cells and mediators they produce. A number of factors including inflammation and oxidative stress are believed to play a role in the development of chronic joint diseases. Epigallocatechin-3-gallate (EGCG) is a potent antioxidant, antiinflammatory, antiangiogenic, and antioncogenic compound derived from green tea.

The purpose of this study was to assess the preventive and therapeutic effects of EGCG on collagen-induced arthritis (CIA) in rats.

Methods: Forty Wistar albino female rats were randomized to four groups (n=10 in each group): Group-I as the control group, Group-II as the arthritis group, Group-III as the prenventive EGCG group, and Group-IV as the therapeutic EGCG group were assigned. Arthritis was induced by intradermal injection of chicken type II collagen combined with incomplete Freund's adjuvant in Group-II, III, and IV rats. In Group-III, the EGCG treatment was started one day before the induction of arthritis, while in Group-IV, EGCG treatment was started after the onset of arthritis at day 14.

Animals were sacrificed at the 15th day after the onset of arthritis. The trunk bloods and paws of the rats were obtained for further analysis. Tumor necrosis factor (TNF)-α, interleukin (IL)-17, malondialdehyde (MDA) levels and superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) activities in serum and articular tissue nuclear factor erythroid 2-

related factor 2 (Nrf2) and heme oxgenase-1 (HO-1) expressions, perisynovial inflammation and cartilage-bone destruction were determined in the paws.

Results: When compared with Group-I, TNF-α, IL-17, and MDA levels were increased, and SOD, CAT, GPx activities and the expressions of Nrf2 and HO-1 were decreased in Group-II (Table). Histopathological analysis demonstrated the extensive perisynovial inflammation and marked cartilage-bone destruction in Group-II rats. The decreased levels of TNF-α, IL-17, MDA, and the increased activities of SOD, CAT, GPx and the expressions of Nrf2 and HO-1, and the reductions in perisynovial inflammation and cartilage-bone destruction in the paws were determined in Group-III and IV. Compared with Group-IV, the decreased 14th day arthritis score was significant while the 29th day arthritis score was relatively lower in Group-III.

Table. Clinical and laboratory data in the study groups

	Group I (Control) (n=10)	Group II (Arthritis) (n=10)	Group III (EGCG1) (n=10)	Group IV (EGCG2) (n=10)
14th day arthritis score	–	1.4±0.7	1.0±0.6	1.6±0.5[f]
29th day arthritis score	–	2.4±0.5	0.6±0.5[e]	0.9±0.3[e]
Inflammation score	–	4.0±0.0	3.0±0.5[e]	3.1±0.7[d]
Destruction score	–	3.9±0.3	2.4±0.5[e]	3.0±0.8[d]
TNF-α (pg/mL)	25.6±5.0	62.7±12.9[b]	44.6±18.8[b,c]	31.6±8.4[d]
IL-17 (pg/mL)	29.5±8.3	65.7±8.9[b]	44.8±4.5[b,d]	47.0±4.6[b,d]
MDA (μmol/L)	0.58±0.23	1.60±0.20[b]	0.96±0.43[d]	0.77±0.14[d]
SOD (U/mL)	12.0±7.3	3.4±1.6[b]	8.5±5.2[d]	10.6±5.0[e]
CAT (nmol/min/mL)	0.33±0.07	0.12±0.08[b]	0.27±0.04[e]	0.28±0.04[e]
GPx (nmol/min /mL)	335±179	179±45[b]	403±88[e]	461±99[a,e]

Data were presented as mean±standard deviation. EGCG: Epigallocatechin-3-gallate, TNF: Tumor necrosis factor, IL: Interleukin, MDA: Malondialdehyde, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase.
EGCG1: The administrations of EGCG were started one day before the induction of arthritis.
EGCG2: The administrations of EGCG were started after the onset of arthritis.
vs.Group-I: [a]p<0.05, [b]p<0.01; vs. Group-II: [c]p<0.05, [d]p<0.01,[e]p<0.001; vs. Group-III: [f]p<0.05

Conclusion: These results suggest that EGCG may be of potential preventive and therapeutic value in inhibiting joint destruction in RA.

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Trichostatin A Induces CD8á Positive Tolerogenic Dendritic Cells, Regulatory T Cells in SKG Mice, and Ameliorates the Severe Arthritis. Kenta Misaki, Akio Morinobu, Jun Saegusa, Shimpei Kasagi, Masaaki Fujita, Yoshiaki Miyamoto, Fumichika Matsuki and Shunichi Kumagai. Kobe university graduate school of medicine, Kobe, Japan

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disorder, characterized by cellular infiltration of and proliferation in the synovium, leading to the progressive destruction of the joints. Dendritic cells (DC) play a pivotal role by triggering the immune responses in RA pathogenesis. Trichostatin A (TSA) plays a significant role of controlling gene transcription as a histone deacetylase inhibitor, and has been reported to regulate immune responses. Here we examined to elucidate the effects of TSA on the phenotype and function of DC and on arthritis in SKG mice.

Methods: Arthritis was induced in SKG mice by Zymosan A (ZyA) injection. TSA was administered and its effects on arthritis were evaluated by joint swelling and histological evaluation. IL-17A production in lymph node cells was determined by ELISA. Foxp3 expression in lymph node cells and the phenotypes of splenic conventional DC (cDC) were examined by flow cytometry. Bone marrow-derived DC (BM-DC) were generated with granulocyte macrophage colony-stimulating factor. The effects of TSA on cytokine production, cell surface molecules, indoleamine 2,3-dioxygenase (IDO) expression and T cell stimulatory capacity of BM-DC were examined by flow cytometry, ELISA, quantitative real-time polymerase chain reaction and Western blot, and the allo-mixed lymphocyte reaction, respectively.

Results: TSA, when administered before the onset of arthritis, prevented SKG mice from arthritis. TSA treatment also showed therapeutic effects on arthritis in SKG mice, when administered after the onset of arthritis. TSA treatment reduced IL-17A production and increased in the ratio of CD4+CD25+Foxp3+ cells among CD4+ cells in lymph node, suggesting that regulatory T cells are involved in the prevention of arthritis in SKG mice with TSA. In the CD8α+ splenic cDC subset, the expressions of CD86, CD80, and CD40 were significantly decreased in the TSA-treated group compared to the control group. In contrast, there were no significant differences in the expression of these molecules in the CD8α− cDC subset. Thus, TSA predominantly affects CD8α+ cDC *in vivo*. *In vitro*, TSA markedly suppressed ZyA-induced IL-12 and IL-6 productions, cell surface molecules by BM-DC and up-regulated IDO expression at mRNA and protein levels. TSA-treated BM-DC also showed less T cell stimulatory capacity.

Conclusion: TSA changes DC to a tolerogenic phenotype, induces regulatory T cells and ameliorates arthritis in SKG mice.

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Brucellosis-Induced Murine Arthritis and Spondylolisthesis. Elizabeth T. Lyons[1], Diogo Magnani[2], Toni S. Forde[1], Gary Splitter[2] and Vyacheslav A. Adarichev[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]University of Wisconsin, Madison, WI

Background/Purpose: Approximately 500,000 people world-wide are infected with Brucella each year and most develop spondyloarthropathy by mechanisms which are poorly understood. Brucellosis is a zoonotic disease that remains endemic to many parts of the world and therefore presents a problem for public health due to possible transmission to domestic animals and humans. The goal of the study was to establish a murine model for human Brucellosis to better understand mechanisms of association between Brucella infection and spondylitis of lumbar and sacral spine in human patients.

Methods: BALB/c females were infected via i.p. injection with 100M *B.abortus S19* or *B.melitensis GR023*, then sacrificed 3 and 26 weeks post-infection. Bacterial dissemination was monitored using bioluminescence and histopathology. Axial skeleton from thoracic to tail, front and hinds paws, spleen, and liver were included in the evaluation. Histopathology slides were stained with hematoxylin & eosin, alcian blue, tartrate-resistant acid phosphatase. Immunohistochemistry was performed for IBA-1 marker and Brucella cell wall.

Results: *B.abortus* and *B.melitensis* demonstrated similar peaks of bacterial infection at day seven, but bacteria remained detectable in the intraperitoneal cavity, spleen, and skeletal tissues for several weeks post-infection. *In vivo* bioluminescence showed accumulation of luminescent *B.melitensis* in tarsal parts of front and hind paws and in knees, but the strongest signal was detected in the tail following the distribution of vertebrae. Upon immunohistochemical staining, intracellular bacteria were found in the spleen, liver, epiphysis and metaphysis of peripheral joints, as well as in the subchondral region of vertebrae. Three weeks post-infection, bacteria-infected cells were not found in the peridiscal space or in the joint cavity, but were located in the subchondral bone. Though bacteria could be seen in association with cartilaginous structures, infiltration by inflammatory cells was undetectable. At 26 weeks post-infection with Brucella spp, infected cells were not found in spleen and subchondral bone, but were visible only as a weak and very rare staining of granulomas in liver. Despite the general absence of infection at this time point, mice developed arthritis in ankle joints, spondylolisthesis, and torsion/rotation misalignment in caudal spine.

Conclusion: Acute infection with *B.melitensis* or *B.abortus* is not associated with arthritis or spondyloartyhropathy in this murine model. Inflammation in joints and changes in skeleton were found at later time weeks after the bacteria were already cleared from subchondral bone marrow. Therefore, Brucella-induced osteomyelitis demonstrated features which are typical to reactive arthritis.

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IL-23 Upregulates IRF5 and Polarizes Inflammatory M1 Macrophages to Promote Inflammation in a Mouse Model of Arthritis. Hao Li[1], Hui-Chen Hsu[1], Jun Li[1], Qi Wu[1], PingAr Yang[1], Daniel Cua[2] and John D. Mountz[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Merck Research Laboratory, Palo Alto, CA, [3]University of Alabama at Birmingham and Birmingham VAMC, Birmingham, AL

Background/Purpose: The pathogenic mechanism of IL-23 is often associated with expansion and maturation of IL-17 producing CD4 cells, but expression of IL-23 receptor (IL-23R) is not limited to T cells. Increased numbers of macrophages is an early hallmark of active arthritis. Expression of IL-23R has been identified on myeloid cells. The present study determines if IL-23 can regulate the pathogenesis of collagen II-induced arthritis (CIA) via its effects on inflammatory macrophages.

Methods: Chicken CII (cCII) was administered to IL-23 $p19^{+/+}$, p19 deficient ($p19^{-/-}$), $Il23p19^{+/+}$ *GFP-Foxp3,* and $Il23p19^{-/-}$ *GFP-Foxp3* mice on day 0 and was boosted on day 21. AdIL-17 was administered on day 10 to ensure equivalent circulating levels of IL-17. FACS analysis was carried out to determine the percentages of $Foxp3^{+}$ regulatory (Tregs) and IL-$23R^{+}$ macrophages in the draining lymph nodes (LN) of mice with CIA. ELISA and real-time PCR was carried out to determine the effects of IL-23 on cytokine

profiles of GM-CSF-induced inflammatory M1 macrophages or M-CSF-induced suppressor M2 macrophages both *in vivo* and *in vitro.*

Results: CIA was developed by IL-23 $p19^{+/+}$ mice whereas $p19^{-/-}$ mice stayed resistant to CIA despite no deficiency of IL-17. Accumulated $Foxp3^+$ Tregs were only observed in $Il23p19^{-/-}$ *GFP-Foxp3* (from 8% to 18%) but not $Il23p19^{+/+}$ *GFP-Foxp3* mice on day 45 of CIA. Dramatic expansion of macrophages (from 5% to 19% of total) especially IL-$23R^+$ macrophages (from 7% to 23% of macrophages) occurred only in $Il23p19^{+/+}$ mice on day 45 post cCII injection. Macrophages are the major producers of inflammatory cytokines including IL-6 and TNFα in the draining LN of $Il23p19^{+/+}$ mice that developed CIA. IL-23 suppressed the expression of anti-inflammatory cytokine by M2 macrophages including TGFb and IL-10 and promoted the expression of inflammatory cytokines including IL-6, TNFα and IL-17 by M1 macrophages *in vitro*. Interestingly, IL-23 promoted M-CSF polarized M2 macrophages into M1 macrophages by inducing the expression of *Irf5*, an M1 specific transcription factor. Coculture of IL-23 stimulated macrophages with naïve CD4 T cells prevented the development and function of Treg cells.

Conclusion: Our results suggest a novel function of IL-23 in promoting inflammatory responses that can perpetuate the development of CIA via its effects to promote the differentiation of inflammatory M1 macrophages. Upregulation of IRF5 can be a potential factor promoted by IL-23 to turn off the differentiation of M2 macrophages. One important function of IL-23-activated macrophages was to prevent the development of Treg cell by inhibiting the conversion from conventional T cells.

2098

Metformin Attenuated An Autoimmune Arthritis in Animal Models of Rheumatoid Arthritis Via AMP-Activated Protein Kinase Activation. Kwi Young Kang[1], Inje Kim[2] and Ji Hyeon Ju[3]. [1]Division of Rheumatology, Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, South Korea, [2]Hallym University Kangdong Sacred Heart hospital, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul, South Korea

Background/Purpose: Metformin is one of the most widely used drugs for diabetes. However, metformin takes a growing interests for its anti-inflammatory property. This study was undertaken to evaluate the anti-inflammatory effect of metformin in collagen induced arthritis (CIA) mice.

Methods: CIA mice in which inflammatory arthritis was developing were treated with metformin. The effect of treatment on clinical disease activity and histological joint destruction were studied. Naïve T ells were differentiated to Th17 or regulatory T cell by various cytokine stimulation and metformin was treated at each culture conditions. FACS analysis and ELISA were used for delineating the effect of metformin on T cell differentiation. The expression of proinflammatory cytokines such as TNF-α, IL-1β and IL-6 was also evaluated in splenic macrophage of DBA1 mice after metformin treatment. We transfected adenoviral vectors which overexpressing or inhibiting AMP-activated protein kinase (AMPK) into macrophages before stimulation. By adenoviral transfection, we evaluated the association between inflammation and AMPK which is well known major mediator of metformin.

Results: Metformin-treated mice revealed milder arthritis score than CIA mice ($p=0.014$), in which less inflammatory cells and bone destruction were observed. Metformin inhibited the expression of proinflammatory cytokines, such as TNF-α, IL-1β and IL-6, from splenic macrophage in a dose-dependent manner. The inhibition of AMPK by adenoviruses expressing dominant-negative-AMPKα attenuated the production of proinflammatory cytokines from macrophages. Metformin suppressed Th17differentiation and enhanced Treg portion, further supporting its anti-inflammatory property.

Conclusion: These results suggest that metformin has the anti-inflammatory effect via AMPK activation, even if it was developed for diabetes drug. Therefore, metformin may have therapeutic application for the optimal treatment of patients who suffer from rheumatoid arthritis and diabetes together.

2099

SH3BP2 "Cherubism" Gain-of-Function Mutation Exacerbates Inflammation and Bone Erosion in Collagen Induced Arthritis. Tomoyuki Mukai[1], Teruhito Yoshitaka[1], Keiichiro Nishida[2] and Yasuyoshi Ueki[1]. [1]University of Missouri-Kansas City, Kansas City, MO, [2]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama city, Japan

Background/Purpose: SH3BP2 is a signaling adapter protein in which gain-of-function mutations result in cherubism due to enhance TNF-α production in macrophages and RANKL-induced osteoclastogenesis. In addition to its important roles in myeloid cell functions, SH3BP2 has been reported to be required for optimal B-cell activation. Cherubism is an autosomal dominant craniofacial disorder in children characterized by the extensive growth of fibrous lesions containing TRAP-positive multinucleated cells, resulting in facial swelling and jaw bone destruction. However, it remains unclear whether SH3BP2 is involved in the pathogenesis of other forms of inflammatory bone diseases other than cherubism. In this study, we examined the role of SH3BP2 in the development of arthritis using collagen induced arthritis (CIA) model.

Methods: Wild type (WT) and SH3BP2 "cherubism" mutation knock-in heterozygous (KI/+) mice on the C57BL/6 background were immunized with chicken type II collagen in complete Freund's adjuvant. Clinical arthritis scores (max score=16) were determined by visual inspection of the paws up to 56 days. Synovial inflammation and bone erosion were evaluated by histological analysis. Bone volume of the talus and trabecular bone properties of the proximal tibia were quantified by micro-CT to evaluate bone erosion and systemic bone loss, respectively. Serum levels of anti-type II collagen antibody were measured by ELISA.

Results: The incidence of arthritis was increased in KI/+ mice compared to WT mice (50.0% vs 27.3%, n=10–11). The arthritis score in KI/+ mice was higher than WT mice (7.20 $\pm$ 4.09 vs 4.33 $\pm$ 0.58 at day 28). KI/+ mice exhibited persistent inflammation compared to WT mice (8.00 $\pm$ 4.00 vs 1.00 $\pm$ 1.73 at day 56). Histological analysis showed that synovial inflammation and bone erosion in KI/+ mice were more severe than WT mice. Micro-CT analysis revealed that bone volume of the talus in KI/+ mice was reduced compared to WT mice (6.84% and 1.71% reduced from control mice of each genotype, respectively). And bone volume/tissue volume of the tibia in KI/+ mice was also reduced compared to WT mice (58.4% and 23.6% reduced from control mice of each genotype, respectively). Serum levels of anti-type II collagen antibody in KI/+ mice (108,884 $\pm$ 73,927units/ml) were 2.5 fold higher than WT mice (43,181 $\pm$ 45,590 units/ml).

Conclusion: A gain-of-function mutation in SH3BP2 increased the incidence and severity of arthritis accompanied by more severe bone destruction in the CIA model. These data suggest that adaptor protein SH3BP2 plays a role in the induction and development of arthritis by controlling the production of autoantibody by B cells.

2100

Skin Fibroblasts Are Potent Suppressors of Inflammation in Experimental Arthritis. C. Bouffi[1], C. Bony[2], Christian Jorgensen[3] and Daniele Noel[1]. [1]UM1, Montpellier, France, [2]INSERM U844, Montpellier, France, [3]CHU Lapeyronie, Montpellier, France

Background/Purpose: Fibroblasts possess *in vitro* immunomodulatory properties that are similar to those of multipotent mesenchymal stromal cells (MSC) but their role has been poorly investigated *in vivo*. Here, we compared the effect of MSC or skin fibroblast injection on the host immune response in the collagen-induced arthritis model.

Methods: Fibroblasts were isolated from the skin of DBA1 mice and immunophenotyped by flow cytometry. Their capacity to differentiate into chondrocytes, adipocytes and osteoblasts was evaluated after culture in specific inducing conditions. Immunosuppresssion was evaluated in concanavalin A-induced proliferative assay. In the CIA model, 10^6 fibroblasts were intraveinously injected at day 18 and 24 after collagen II immunization. Arthritis was evaluated by the measure of clinical signs (paw swelling and inflammation) and immunological parameters (dosage of collagen II-specific immunoglobulins, inflammatory cytokines and proliferation of T lymphocytes).

Results: We first confirm that skin fibroblasts isolated from DBA1 mice lack the capacity to differentiate into osteoblasts or chondrocytes but possess the capacity to differentiate into adipocytes. We also report that fibroblasts inhibit the proliferation of T lymphocytes in a concanavalin A-induced proliferative assay and secrete modulatory molecules, in particular PGE2 and NO. To assess their role *in vivo*, 10^6 fibroblasts were intravenously injected at day 18 and 24 after collagen II immunization of DBA1 mice. We show that similar to MSCs, the intravenous injection of fibroblasts efficiently suppress the clinical signs of arthritis and delay the disease onset. This effect is associated with a reduced inflammation and notably, increased levels of IL-5, IL-10 and IL-13 in the spleens of treated mice. To further characterize the mechanism of immunosuppression, we performed phenotypic analyses and could not detect any induction of $CD4^+CD25^+Foxp3^+$ Treg cells whereas a

population of $CD4^+IL\text{-}10^+$ T cells is slightly increased after fibroblast injection and significantly up-regulated after MSC administration.

Conclusion: Our study shows the therapeutic efficacy of systemic injection of syngeneic fibroblasts to reduce the clinical signs of arthritis and strongly suggests that fibroblasts induce a Th2 immune profile although we cannot exclude that IL-10 secreting Treg cells may be generated.

2101

Treatment of Collagen Induced Arthritis with Human Adipose-Derived, Bone Marrow-Derived and Cord Blood-Derived Mesenchymal Stem Cells. Kyu-Hyung Park, Ji-Hye Kim, Sang-Won Lee, Soo Kon Lee and Yong-Beom Park. Yonse University College of Medicine, Seoul, South Korea

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic joint inflammation. Mesenchymal stem cells (MSC) have a capacity to differentiate into mesenchymal tissues and also have an immunomodulatory property. We investigated optimizing treatment condition for collagen induced arthritis (CIA) model using human adipose (AD)-derived, bone marrow (BM)-derived and cord blood (CB)-derived MSC. And, we explored the mechanism of immune modulation by MSC in CIA.

Methods: We obtained clinically available human AD, BM and CB-derived MSC, and evaluated the therapeutic effect of MSC on RA inflammation using DBA/1 mice with CIA. CIA mice were injected intraperitoneally with 1×10^6 of three types of MSC for 5 days, or 2.5×10^6 twice times. Control group were injected with 35mg/kg of methotraxate (MTX) twice a week. Clinical activity of CIA mice with total joint score and paw thickness, the degree of inflammation, joint destruction and cytokine expression in the joint tissue, and serum levels of cytokines were evaluated. Micro-CT for joint was also performed. Treg (CD4+CD25+FoxP3+) cell were evaluated from lymph node and spleen of CIA mice by FACS.

Results: Both 5 times ($1\times10^6\times5$) and 2 times ($2.5\times10^6\times2$) injections of human AD-MSC, BM-MSC and CB-MSC showed significant improvement of clinical joint score and paw thickness, comparable to MTX. H & E slides from mice injected with three types of MSC or MTX showed much less joint inflammation and damage than untreated mice. MSC treated mice had decreased TNF-α, IL-1β, IL-6, COX-2 expression and increased TGF-β expression in the joint tissue. AD-MSC, BM-MSC and CB-MSC injection significantly decreased serum pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, INF-γ) and increased the anti-inflammatory cytokine (IL-10). Micro-CT showed little joint damage in MSC or MTX treated groups. Treg cells (CD4+CD25+FoxP3+) were increased in the lymph node and spleen of mice treated with AD-MSC, BM-MSC and CB-MSC compared with untreated mice or MTX-treated mice.

Conclusion: In this study, human AD-MSC, BM-MSC and CB-MSC significantly suppressed joint inflammation of CIA mice. They upregulated anti-inflammatory cytokines and Treg cells. Our study suggests human AD-MSC, BM-MSC and CB-MSC could be an effective therapeutic approach for arthritis.

2102

A Novel Mouse Model of Atherosclerosis in Inflammatory Arthritis. Shawn M. Rose and Harris R. Perlman. Northwestern University, Chicago, IL

Background/Purpose: Inflammatory arthritides, such as rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA), are associated with significant morbidity and increased mortality. Patients with RA are at increased risk for cardiovascular (CV) events, which contributes greatly to their higher mortality. This elevated CV risk is independent of traditional CV risk factors and may be related to increased systemic inflammation. Alarmingly, premature atherosclerosis is already evident in teenage children with JIA. Progress in understanding the relationship between inflammatory arthritis and atherosclerosis has been hampered by the lack of a suitable animal model. For the first time, we introduce an animal model that faithfully recapitulates both human diseases.

Materials & Methods: 12 week-old K/BxA^{g7} and C57BL/6 control animals were maintained on an atherogenic diet for 9 weeks. Arthritis severity was assessed weekly, beginning at 4 weeks of age. Serial measurements of joint width (mm), clinical inflammation score (0–3 scale, 4 paws), and a novel clinical joint destruction index (0–40 scale, paw joints, wrists, ankles) were obtained. Sudan IV staining of aortas from 21 week-old mice was performed to assess atherosclerosis. Atherosclerotic lesions were quantitated using Image-Pro morphometric analysis, with lesion area normalized to total aortic area (aortic sinus to iliac bifurcation).

Results: All three measures of arthritis were significantly greater in K/BxA^{g7} animals compared to controls ($p<0.001$). The mean percentage area of total aortic atherosclerosis was significantly ($p<0.001$) higher in K/BxA^{g7} mice (21.1 +/− 7.6) compared to controls (0.7 +/− 0.4).

Conclusion: K/BxA^{g7} mice develop spontaneous arthritis beginning at 4–5 weeks of age followed by severe aortic atherosclerosis when receiving an atherogenic diet. This exciting discovery will spur novel mechanistic studies linking arthritis and atherosclerosis. Our model will also be highly informative for developing new biomarkers and therapeutic agents for both diseases.

2103

Arthritic ApoE-Deficient Mice Are Protected From the Development of Atherosclerosis. Shawn M. Rose and Harris R. Perlman. Northwestern University, Chicago, IL

Background/Purpose: Rheumatoid arthritis (RA) is a chronic debilitating disorder characterized by reduced life expectancy. The shortened lifespan in RA is largely due to cardiovascular (CV) disease. This elevated CV risk is independent of traditional CV risk factors and may be related to increased systemic inflammation in patients with RA. Dyslipidemia is also likely to contribute to increased CV mortality, as altered lipid profiles have been described in patients with RA. Progress in understanding the relationships among inflammation, dyslipidemia, and atherosclerosis in RA has been hampered by the lack of a suitable animal model. We have generated a novel model, ApoE$^{-/-}$.K/BxA^{g7} mice, to address this question.

Materials & Methods: Arthritis severity was assessed weekly in ApoE$^{-/-}$.K/BxA^{g7}, K/BxA^{g7}, and ApoE$^{-/-}$ control animals, beginning at 4 weeks of age. Serial measurements of joint width (mm), clinical inflammation score (0–3 scale, 4 paws), and a novel clinical joint destruction index (0–40 scale, paw joints, wrists, ankles) were obtained. Atherosclerosis was assessed in aortic specimens from 21–23 week-old mice via Sudan IV staining. Atherosclerotic lesions were quantitated using Image-Pro morphometric analysis, with lesion area normalized to total aortic area (aortic sinus to iliac bifurcation).

Results: All three measures of arthritis were significantly greater in ApoE$^{-/-}$.K/BxA^{g7} and K/BxA^{g7} animals compared to ApoE$^{-/-}$ controls ($p<0.001$). The onset and severity of arthritis was similar in ApoE$^{-/-}$.K/BxA^{g7} and K/BxA^{g7} controls. Serum lipid levels were also comparable in ApoE$^{-/-}$.K/BxA^{g7} and ApoE$^{-/-}$ mice. Aortic atherosclerosis was significantly lower ($p<0.05$) in ApoE$^{-/-}$.K/BxA^{g7} animals compared to ApoE$^{-/-}$ mice whether the mice were maintained on standard chow or an atherogenic diet.

Conclusion: Our findings suggest that ApoE-deficiency does not affect the onset or severity of arthritis in the K/BxA^{g7} model of spontaneous arthritis. Strikingly, despite severe dyslipidemia, arthritis is protective for the development of atherosclerosis in these animals. Understanding the mechanisms behind this phenomenon will be imperative for developing novel therapies for cardiovascular disease in RA.

ACR/ARHP Poster Session C

Rheumatoid Arthritis Clinical Aspects III: Clinical Features of Rheumatoid Arthritis; Disease Severity; Outcomes Research and Metrology

Tuesday, November 8, 2011, 9:00 AM–6:00 PM

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Chronic Kidney Disease in Rheumatoid Arthritis. Cynthia S. Crowson, LaTonya Hickson, Sherine E. Gabriel, James T. McCarthy and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Rheumatoid arthritis (RA) is associated with a variety of comorbidities including cardiovascular disease (CVD). Chronic kidney disease (CKD) is associated with CVD in the general population. It is unclear whether patients with RA are more likely to develop CKD than persons in the general population, or whether CKD plays a role in the increased risk of CVD in RA. We sought to elucidate the occurrence of CKD in a well characterized population of patients with RA.

Methods: A retrospective medical record review was performed on all incident cases of adult onset RA from a defined geographic population base that fulfilled criteria for RA in 1980–2007. A comparison cohort of patients without RA from the same population base of similar age and sex was also

examined. Patients in both cohorts were followed until 12/31/2008 and all available creatinine values were collected. Estimated glomerular filtration rate (eGFR) was obtained using the Modification of Diet in Renal Disease (MDRD) formula. CKD was defined as eGFR <60 ml/min/1.73m^2 and moderate CKD was defined as eGFR <45 ml/min/1.73m^2. The cumulative incidence of CKD was estimated adjusting for the competing risk of death.

Results: 813 patients with RA and a comparison cohort of 813 patients without RA were assembled (mean age 55.9 years; 68% female in both cohorts). There was no significant difference in the presence of CKD at time of RA incidence, $p=0.84$. Among patients with RA, 38% had an eGFR<60 and 11% had eGFR<45, similar to non-RA patients (38% and 9%, respectively) observed at the RA incidence/reference date. However, the 10 year cumulative incidence of CKD was significantly higher in patients with RA compared to non-RA (43% vs 32%, $p=0.008$). This difference occurred primarily in the first year after RA incidence. The 10 year cumulative incidence of moderate CKD was also higher in patients with RA compared to non-RA (18% vs 14%, $p=0.037$). This difference became apparent three years after incident RA. The development of CKD was associated with erythrocyte sedimentation rate (HR 1.1 per 10 mm/hr, CI 1.03–1.20, $p=0.008$) and CVD (HR 2.1, CI 1.4–3.2, $p<0.001$).

Conclusion: Patients with RA are more likely to develop CKD than patients without RA. Inflammation and CVD appear to play a role in the development of CKD in RA. Further studies are needed to improve understanding of these relationships.

2105

Increased Activity of the platelet glycoprotein (GP) VI pathway in Patients with Rheumatoid Arthritis. Paul A. MacMullan[1], Eimear Dunne[2], Anne M. Madigan[1], Michael C. Berndt[2], Robert K. Andrews[3], Elizabeth E. Gardiner[3], Dermot Kenny[2] and G M. McCarthy[1]. [1]Mater Misericordiae University Hospital, Dublin 7, Ireland, [2]RCSI, Dublin 2, Ireland, [3]Monash University, Melbourne, Australia

Background/Purpose: Recent experimental evidence using an animal model of rheumatoid arthritis (RA) has shown that platelet-derived microparticles exacerbate joint inflammation following engagement of the platelet-specific glycoprotein (GP) VI receptor by collagen (1). We have previously shown that GPVI engagement by collagen causes shedding of the soluble extracellular domain of GPVI (sGPVI) (2). Therefore we set out to evaluate 1) platelet aggregation in response to collagen and 2) plasma sGPVI levels in patients with RA.

Methods: Patients with an established diagnosis of RA were recuited consecutively. Those with a history of cardiovascular disease or who were receiving anti-platelet therapy or thromboembolic prophylaxis were excluded. Disease activity was assessed using standard inflammatory biomarkers and the internationally validated DAS-28 score. Platelet aggregation in response to increasing doses of collagen was tested in RA($n=62$) patients and healthy controls ($n=80$). We also measured sGPVI levels by ELISA in double-spun plasma from a subset of these RA patients ($n=10$) and controls ($n=20$).

Results: Patients with RA ($n=62$) had a significantly decreased platelet response to submaximal doses of collagen compared to healthy controls ($n=80$)(logEC50 1.99 ± 0.09 vs 1.6 ± 0.04, $p<0.0001$). Plasma sGPVI levels were several fold higher in RA patients ($n=10$) compared to controls ($n=20$) (mean$\pm$s.d; 49 ± 14 *vs* 19 ± 8 ng/mL, $p<0.0001$). There was no gross correlation between disease activity indices, platelet count, demographic data or cardiovascular risk factors and either platelet collagen aggregation response or sGPVI levels.

Conclusion: Patients with RA have decreased platelet response to GPVI stimulation by collagen compared to controls. Furthermore, levels of sGPVI are dramatically elevated in RA. This implies enhanced activity of the platelet GPVI pathway in RA, a phenomenon that could contribute to the underlying thrombotic risk in this patient population.

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2. Al-Tamimi M, Mu FT, Moroi M, Gardiner EE, Berndt MC, Andrews RK. Measuring soluble platelet glycoprotein VI in human plasma by ELISA. Platelets 2009;20(3):143–9.

2106

Comparison of Respiratory Function in Patients with Inflammatory Polyarthritis and the General Population in the United Kingdom. Suzanne MM Verstappen[1], Mark Lunt[1], Robert N. Luben[2], Jackie Chipping[3], Nick Wareham[2], Kay-Tee Khaw[2], Ian N. Bruce[1] and Deborah PM Symmons[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [2]University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, [3]Norfolk Arthritis Register, School of Medicine Health Policy and Practice Faculty of Health UEA, Norwich, United Kingdom

Background/Purpose: Pulmonary complications are common in patients with inflammatory polyarthritis (IP) and its subset rheumatoid arthritis (RA). Limited data are available on spirometry measures in these patients and whether the results differ from the general population. The objective of this study was to compare lung function in patients with IP with that in a matched general population.

Methods: Patients with early IP ($\geq$ 2 swollen joints for $\geq$4 wks) from a primary-care based inception cohort (the Norfolk Arthritis Register), recruited between 1990–1994, underwent spirometry at 15 years follow-up. FEV1 and FVC were recorded. Spirometry measurements were compared with those obtained during the second health check (1998 and 2000) from participants of the European Prospective Investigation of Cancer (EPIC-Norfolk) cohort, representing the general population in Norfolk, UK. People with IP, RA or using DMARDs in the EPIC-Norfolk cohort were excluded from analysis. 379 patients with IP aged 32–82 years were matched with people from the general population (1:2) by gender, age and season when spirometry was performed. First, a random effect model was applied to test the difference in FEV1 and FVC between patients with IP and the general population univariately. Secondly, possible confounders were included in the model (smoking status and BMI).

Results: Of the 379 patients with IP, 79% fulfilled the 1987 ACR criteria for RA in NOAR. In both cohorts, mean age was 62 (SD 11) years and 68% were women. More people of the IP-cohort were ex-smokers (53.6% vs 42.7%) or current smokers (12.7% vs 7.6%) (Chi2, $p<0.001$) and they had a higher BMI (median 27.2 vs 26.2, $p<0.001$) than people from the general population. In addition, more patients with IP used drugs for COPD/asthma compared to people from the general population (12.4% vs 2.2%, Chi2 $p<0.001$). In univariate regression analysis, compared to the general population, patients with IP had significantly lower FEV1 (β=-0.0797, 95%CI -0.141 to -0.019). However, when adjusting for confounders, no difference in FEV1 between the IP population and the general population was observed ($\beta=-0.0417$, 95%CI 0.104 to 0.021). In univariate analysis, FVC was similar between the IP population and the general population ($\beta=0.0467$, 95%CI -0.031 to 0.124). After adjustment for confounders, IP patients had higher FVC compared to people from the general population ($\beta=0.0826$, 95%CI 0.027 to 0.163).

Conclusion: Obstructive lung disease is the prominent spirometric abnormality in patients with IP. Patients with IP had a higher prevalence of COPD and asthma and lower FEV1 than the general population. This difference appears to be due to confounders, predominately smoking status and high BMI, rather than the disease itself.

2107

C-Reactive Protein Associated with Depression in Patients with Rheumatoid Arthritis. Mary E. Margaretten, Laura J. Julian, Vladimir Chernitskiy, Jonathan D. Graf, Patricia P. Katz, John B. Imboden and Edward H. Yelin. University of California San Francisco, San Francisco, CA

Background/Purpose: Depression is common in patients with rheumatoid arthritis (RA) and leads to worse health outcomes. Systemic inflammation may contribute to depression in patients with chronic inflammatory diseases, and there is conflicting evidence regarding the association of the acute phase reactant, high-sensitivity C-reactive protein (CRP) with depression in patients with RA. Our objective is to determine if CRP is correlated with depression scores in a large, diverse sample of patients with RA.

Methods: This is a cross-sectional study from an observational, clinical cohort. Patients fulfill the ACR criteria for RA and are enrolled into the cohort from two rheumatology clinics, a county, public-hospital and a university medical center. Once enrolled, data are collected for patients at each clinic visit. The outcome variable is a score on Patient Health Questionnaire-9 (PHQ-9), a self-report questionnaire validated to correlate with a diagnosis of major depression. A PHQ-9 score of 5–9 is consistent with mild depressive symptoms, 10–14 moderate, 15–19 moderate-severe, and > 20 severe depressive symptoms. The primary independent variable is CRP; covariates included gender, age, clinic site, disease activity (DAS 28) score, disability (HAQ) score, prednisone, and disease-modifying anti-rheumatic drug (DMARD) use, defined as one or more of the following: methotrexate, hydroxychloroquine, sulfasalazine, azathioprine, leflunomide, anti-TNFa medications, or other biologic medications. The DAS 28 includes scores of tender and swollen joint counts, patient global disease activity rating scale, and erythrocyte sedimentation rate (ESR). For the analyses, we use generalized estimating equations with robust standard errors to take into account the repeated measures from an individual's multiple clinical encounters.

Results: There are 1,042 clinical visits for 495 patients included in the analysis. The average number of rheumatology clinic visits per patient was 2.0 (range 1–8). 37% of patients reported depression of at least moderate severity during at least one clinic visit. CRP, care at a public hospital rheumatology clinic, disease activity, and disability are associated with depression in this cohort of patients with RA. In the full multivariate model, CRP, younger age, care at a public hospital rheumatology clinic, and higher disability scores were associated with higher depression scores. For every 10-unit increase in a subject's CRP, there was a 2-point increase in depression score.

Predictors of Depression among 495 Patients with Rheumatoid Arthritis

	Univariate		MV* Adjusted	
	GEE Coefficient (95% CI)	p-value	GEE Coefficient (95% CI)	p-value
C-Reactive Protein	0.1 (.06, 1.6)	<.0001	0.2 (.01, .4)	0.05
Female Gender	−.54 (−1.6, 5.4)	.33	0.9 (−.06, 2.1)	.066
Age (years)	−.02 (−.05, .004)	.09	−.06 (−.09, −.03)	<.0001
Public Hospital	1.4 (.59, 2.2)	.001	0.4 (0.1, 0.9)	.02
DAS 28-ESR	1.4 (1.1, 1.6)	<0.01	0.50 (−0.2, 0.8)	0.11
HAQ Score	3.6 (3.1, 3.9)	<.0001	3.6 (3.1, 4.1)	<.0001
Prednisone Use	.05 (−.63, .74)	.88	−0.4 (−1.1, 0.3)	0.25
DMARD Use	−0.4 (−1.1, .18)	.17	−0.3 (−0.9, 0.7)	0.42

Multivariate model adjusts for all variables shown.

Conclusion: Among patients with RA, the acute phase reactant, CRP, correlates with depression scores beyond the contribution from RA disease activity and disability. It will be important for longitudinal studies to identify whether systemic inflammation is a modifiable risk factor for depression in patients with RA, and if so, more tailored treatment approaches for depression in RA would be possible.

2108

Using Genome-wide Single Nucleotide Polymorphism Analysis to Investigate the Possibility of the CYB5R Gene Promoting Interstitial Pneumonia in Rheumatoid Arthritis Patients. Takeshi Nakamura[1], Satoru Koyano[2], Keiko Funahashi[2], Takafumi Hagiwara[1], Takako Miura[1], Kosuke Okuda[3], Akira Sagawa[4], Takeo Sakurai[5], Hiroaki Matsuno[6], Tomomaro Izumihara[7], Eisuke Shono[8] and Tsukasa Matsubara[9]. [1]Matsubara mayflower hospital, Kato, Japan, [2]Research Institute of Joint Diseases, Kobe, Japan, [3]Matsubara Mayflower Hospital, Kato, Japan, [4]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [5]Inoue Hospital, Takasaki, Japan, [6]Matsuno Clinic for Rheumatic Diseases, Toyama, Japan, [7]Izumihara Rheumatic and Medical Clinic, Kagoshima, Japan, [8]Shono Rheumatology Clinic, Fukuoka, Japan, [9]Matsubara Mayflower Hospital, Kato-shi HYOGO-KEN, Japan

Background/Purpose: Interstitial pneumonia (IP) is a serious complication for collagen diseases such as RA. However, the pathogenesis of IP remains to be elucidated.We investigated SNPs which seem to be closely correlated with the pathogenesis of IP using genome-wide SNP analysis of IP in RA patients.

Methods: A total of 330 RA patients from 6 hospitals in different regions of Japan were enrolled in the study. The diagnosis of IP was performed by three doctors, one physician and two radiologists, according to IP criteria. As a result, it was determined there were 67 IP patients and 263 non-IP patients. Genome-wide SNP genotyping was performed by HumanHap300K chip. Case-control analyses between 285,548 SNPs and the association with IP were examined by Fisher's exact tests and Bonferoni's correction.

Results: We detected one SNP which is strongly associated with IP and located adjacent to the cytochrome-b5 reductase (CYB5R) gene (p value: 0.0000000117, $p < 0.05$, after Bonferoni's correction). It is reported that CYB5R plays an important role in the resolution of superoxide. In this present analysis, we propose a hypothesis of the functional and/or quantitative reduction of the CYB5R gene which promotes the resolution of superoxide-,according to the SNP detected in this study, and the increase of superoxide may lead to the high susceptibility of IP in RA patients, even though further investigation is required to confirm this.

Conclusion: The pathway of superoxide generation may associate to advancement of IP observed in RA patients.

2109

Contraception Use in Women with Rheumatoid Arthritis. Megan E. B. Clowse[1], Eliza F. Chakravarty[2], Karen H. Costenbader[3], Christina Chambers[4], Frederick Wolfe[5] and Kaleb Michaud[6]. [1]Duke University Medical Center, Durham, NC, [2]Stanford University, Palo Alto, CA, [3]Brigham and Women's Hospital, Boston, MA, [4]University of California, San Diego, La Jolla, CA, [5]National Data Bank for Rheumatic Diseases, Wichita, KS, [6]National Data Bank for Rheumatic Diseases, University of Nebraska, Omaha, NE

Background/Purpose: Women of reproductive age are frequently prescribed potentially teratogenic medications making the use of effective contraception of utmost importance. Pregnancies conceived while taking these medications have a higher rate of miscarriage and the decision whether to continue the pregnancy can be difficult. The frequency of contraceptive use in women with RA is little studied and whether this rate if different for women taking potentially teratogenic medications is unknown.

Methods: A one-time reproductive health questionnaire was sent to women in a large prospective cohort. Premenopausal women who were not trying to conceive were asked to report the methods they had used to avoid pregnancy in the prior year. Forms of contraception were divided into three categories: ineffective (no method, abstinence, withdrawal, rhythm, and barrier methods); effective (hormonal contraceptives or an intrauterine device (IUD)); and sterilization (either the woman or her partner had surgically sterilization). Women could report multiple forms of contraception; they were classified according to the most effective method reported. The current medications from the most recent biannual cohort questionnaire were merged with the reproductive health questionnaire results. Medications were analyzed according to the FDA pregnancy classification indicating the degree of potential risk to a fetus from *in utero* drug exposure.

Results: 108 premenopausal women with RA completed this questionnaire. Ineffective contraception was used by 33% of women; including 16 who reported that they used no contraception, 11 who used abstinence, 4 withdrawal, 3 the rhythm method, and 9 who used barrier methods. Effective contraception was used by 22% of women; including 21 using hormonal contraception and 4 with an IUD. The remaining 45% were sterilized; including 22 with a tubal ligation and 26 with a partner with a vasectomy.

FDA class X medications (methotrexate and/or leflunamide) were taken by 56% of women. Of these, 28% used ineffective contraception, 23% used effective contraception, and 48% were sterile.

Hydroxychloroquine (FDA class C) was used by 19% of women, 30% of whom used ineffective contraception, 35% used effective contraception, and 35% were sterile. Sulfasalazine (FDA class B) was only used by 6 women, 1 using ineffective contraception, 2 using effective, and 3 sterile.

TNF-inhibitors (FDA class B) were used by 53% of the women. Of these, 40% used ineffective contraception, 25% used effective contraception, and 35% were sterile. Other biologics, which included abatacept and rituximab, (both FDA class C) were used by 13 women, of whom 23% used ineffective contraception and 77% were sterile.

Conclusion: Almost half of women with RA in this cohort took FDA class X medications and 29% of these women were using ineffective contraception, leaving them at high risk for pregnancy. This study highlights the importance of contraceptive education and prescription by rheumatologists to ensure that patients taking potentially teratogenic medications do not become pregnant.

2110

Ethnic Minority Rheumatoid Arthritis Consortium: A Clinical Registry of Minority Patients with Rheumatoid Arthritis. Gail S. Kerr[1], Yvonne R. S. Sherrer[2], Raj G. Nair[3], Edward L. Treadwell[4], Angelia D. Mosley-Williams[5], Asia M. Mubashir[6], Luis R. Espinoza[7], Jeffrey Huang[6], Christopher Swearingen[8] and Yusuf Yazici[9]. [1]Washington DC VAMC and Georgetown University and Howard University Hospital, Washington, DC, [2]Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, [3]Washington Hospital Center, Washington, DC, [4]E Carolina Univ Sch of Med, Greenville, NC, [5]John Dingell VAMC, Detroit, MI, [6]Howard University Hospital, Washington, DC, [7]LSU Medical Center, New Orleans, LA, [8]University of Arkansas for Medical Sciences, Little Rock, AR, [9]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Minority ethnic groups with rheumatoid arthritis (RA) are under-represented in clinical trials and chronic disease registries. Hence potential differences in clinical presentations, response to therapies, quality of life and outcomes are unknown. We describe a clinical registry and database, Ethnic Minority Rheumatoid Arthritis Consortium (EMRAC) that evaluates disease characteristics, comorbidities, treatments, and outcomes in "real-world" rheumatology settings serving ethnic minority patients.

Methods: RA patients satisfying ACR diagnostic criteria, of self-reported ethnicity, and seen at 8 US sites are enrolled. Collected data include patient demographics, comorbidities, disease related characteristics (MDHAQ, ESR, CRP, swollen and tender joint counts, composite disease activity indices). Analyses of overall differences in clinical variables between racial groups was performed using Kruskal-Wallis for continuous variables and Chi-square test for qualitative variables; post-hoc pairwise comparisons between groups were adjusted using Bonferonni correction ($p<0.008$ for significance).

Results: Since 9/2010, 338 RA patients have been enrolled (Table). Significant differences amongst ethnic groups were observed in age, duration of disease and education, RAPID3, biologic use and comorbidites.

Table 1. Demographic and Clinical Characteristics of Patients enrolled in EMRAC[#]

	Total	African-American	Caucasian	Hispanic	Other	p-value
n	338	102	105	82	49	
Age (years)	54.5 (15.7)	58.3 (15.5)	52.1 (16.1)	55.5 (14.3)	50.3 (15.6)	0.001
Duration (years)	7.5 (9.2)	8.2 (9.3)	7.4 (10.0)	8.8 (9.4)	4.2 (5.1)	0.004
Education (years)	14.1 (4.1)	13.7 (3.6)	15.5 (3.8)	11.9 (4.1)	16.2 (3.6)	<0.001
Female (N, %)	274 (83%)	91 (89%)	86 (82%)	61 (74%)	36 (84%)	0.072
RAPID3 [0–30] (N=310)	10.8 (7.1)	11.2 (6.9)	9.5 (6.9)	13.1 (7.1)	8.9 (7.2)	0.002
DAS28 [0–10] (N=56)	3.1 (1.4)	3.1 (1.1)	3.4 (1.9)	3.0 (2.0)	2.9 (0.8)	0.848
CDAI [0–76] (N=87)	10.4 (1.7)	10.4 (11.0)	13.0 (13.2)	10.9 (9.7)	6.0 (5.6)	0.559
Prednisone (N, %)	117 (35%)	41 (40%)	34 (32%)	28 (34%)	14 (29%)	0.487
DMARD (N, %)	266 (79%)	85 (83%)	78 (74%)	62 (76%)	41 (84%)	0.294
Biologic (N, %)	119 (35%)	22 (22%)	43 (41%)	40 (49%)	14 (29%)	0.001
Comorbidities (N, %)						
Hypertension	69 (20%)	37 (36%)*	12 (11%)	14 (17%)	6 (12%)	<0.001
Asthma	24 (7%)	5 (5%)	6 (6%)	10 (12%)	3 (6%)	0.226
Diabetes	30 (9%)	17 (17%)**	4 (4%)	8 (10%)	1 (2%)	0.003
Cigarette Use (Ever)	63 (19%)	22 (22%)	20 (19%)	14 (17%)	7 (14%)	0.721

Mean (SD) presented unless otherwise specified.
p-values reflect the overall test between all groups. Pairwise tests were done after the global tests were performed.
* Unadjusted OR = 4.4 (95% CI: 2.1, 9.4), p <.01, reference group = Caucasian
** Unadjusted OR = 5.1 (95% CI: 1.6, 16.0), p =.01, reference group = Caucasian

African Americans were older and received less education compared to Caucasians. African Americans also had longer disease duration, received less biologic agents, and more frequently had hypertension. Hispanics received less education compared to Caucasians and were the only ethnic group to demonstrate high disease activity via the RAPID3 assessment.

Conclusion: EMRAC provides data that can address important gaps in knowledge regarding patient characteristics, treatments, and outcomes in a diverse ethnic cohort. By so doing, EMRAC can inform efforts to improve the quality of care and treatment outcomes in this historically understudied population.

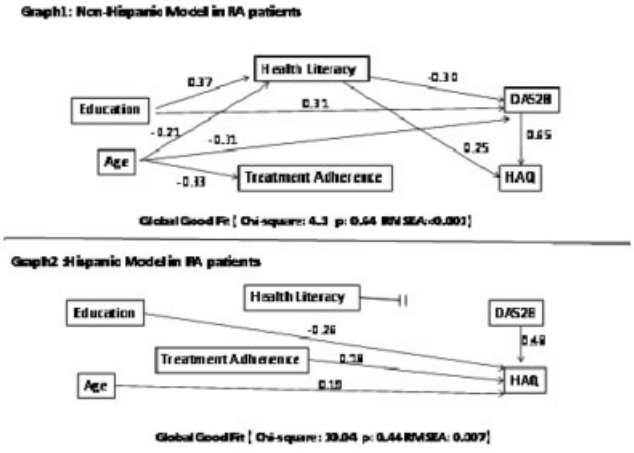
2111

Impact of Health Literacy on Treatment Adherence and Clinical Outcomes in Patients with Rheumatoid Arthritis. Maria F. Marengo[1], Michael A. Kallen[1], Sofia De Achaval[2], Vanessa Cox[1], Araceli Garcia[3], Marsha Richardson[4] and Maria E. Suarez-Almazor[5]. [1]UT MD Anderson Cancer Center, Houston, TX, [2]U.T. MD Anderson Cancer Center, Houston, TX, [3]UT MD Anderson, Houston, [4]UT MD Anderson, Houston, TX, [5]University of Texas. M.D Anderson Cancer Center, Houston, TX

Background/Purpose: Limited Health Literacy (HL) is associated with poorer health outcomes. Little is known about the effects of low HL among patients with Rheumatoid Arthritis (RA). The objective of our study was to measure the level of HL among patients with RA and determine its impact on disease activity and functional status.

Methods: This study was part of a 2– year prospective cohort study of 201 patients with RA; 170 RA patients completed the HL assessment. HL was measured using the numeracy score (0–50) from the Test of Functional Health Literacy (TOFHLA) and the reading comprehension score (0–50) from the TOFHLA-Short. A total score (total TOFHLA) was obtained (0–100, 0 worst HL). Patients were categorized as having low or adequate HL using the traditional cutoff (≥60). Patient information was assessed at BL, 12, and 24 months, including functional status (mHAQ), Disease Activity Index 28 (DAS28), and treatment adherence (AACTG). A conceptual model was developed, with demographic variables predicting HL and adherence, all of which predicted disease activity and functional status. Path analysis was conducted to test the model. Statistical analyses were carried out using STATA 11.1 and LISREL 8.8.

Results: 74.6% of patients were female, 52.7% Hispanic, 25% White and 21.4% African-American; mean age was 51y (±11.4), disease duration 7.5y (±5), DAS28 4.5(±1.6), MHAQ 0.87(±0.6) and AACTG 0.57 (±0.42). Mean total TOFHLA was 81.1(±19.2). Of 170 patients, 42 (24.7%) had low HL; these patients were more frequently female ($p=0.04$), Hispanic ($p<0.01$), with lower education ($p<0.01$) and higher DAS28 ($p=0.03$). In the path analysis, we found significant differences by ethnicity. For non-Hispanics, the model (Graph1) showed age had negative direct effects on HL, adherence, and DAS28, while education had positive direct effects on HL and DAS28. HL had a negative direct effect on DAS28. A dual effect was observed with HL on functional status: HL had a positive direct effect on HAQ, and a positive total effect via disease activity. For Hispanic, the model (Graph2) showed age and adherence had positive direct effects on HAQ, while education had a negative direct effect on HAQ, which itself was affected by a positive direct effect from DAS28. In the Hispanic subpopulation, age and education had no effect on HL, which had no effect on treatment adherence or clinical outcomes. Both overall path analytic models displayed good fit to the data (non-Hispanic chi-2= 4.3, p= 0.63, RMSEA<0.001 and chi-2= 10.04, p= 0.44, RMSEA=0.007).



Tuesday, November 8

Conclusion: Low HL was observed among 1 in 4 RA patients. The impact of HL on clinical outcomes differs by ethnicity. For non-Hispanic, limited HL is associated with worse functional status via disease activity. For Hispanics, worse functional status was associated with higher age and lower education, with no apparent impact of HL on treatment adherence or clinical outcomes.

2112

Rheumatoid Arthritis (RA) is Associated with Increased Mortality in Patients Undergoing Total Joint Arthroplasty. Kaleb D. Michaud[1], Edward Fehringer[2], Kevin Garvin[2], James R. O'Dell[3] and Ted R. Mikuls[3]. [1]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Omaha VA and University of Nebraska Medical Center, Omaha, NE

Background/Purpose: Although total joint arthroplasty (TJA) is a commonly used procedure in rheumatoid arthritis (RA), risks and benefits of TJA in this specific population have not been well defined. The purpose of this study was to examine the association of RA with post-operative mortality following total hip, knee, shoulder and elbow arthroplasty.

Methods: Study subjects were enrolled in the Veterans Affairs (VA) Surgical Quality Improvement Program (VASQIP) undergoing TJA from fiscal years 1999 through 2006. Dispensed medications and ICD9 codes were indentified using links to the VA Pharmacy Benefits Management (PBM) database. Patients were classified as having RA if they had ICD9 code 714.0 plus use of a DMARD within 1 year before TJA; the osteoarthritis (OA) control group had ICD9 code 715. The association of RA with overall mortality through 2006 was examined using multivariate Cox proportional hazards regression, adjusting for age, gender, TJA type, calendar year, race, select baseline comorbidity / health behaviors (diabetes, COPD, dyspnea, congestive heart failure, cerebrovascular disease, renal insufficiency, anemia, alcohol use and current smoking), preoperative functional status, and ASA class. The effects of specific RA medications were examined using sequential models.

Results: There were 37,103 patients (n = 888 with RA) undergoing TJA, with total knee arthroplasty being most common (64%), followed by hip (33%), shoulder (2%), and elbow (0.2%). Patients were predominantly men (96%) and had a mean (SD) age of 64.4 (10.7) years. Glucocorticoid use was much more common in RA cases vs. OA (41% vs. 2%). There were a total of 4,093 deaths over a mean follow-up of 3.7 (2.3) years. After multivariate adjustment, RA was associated with a significantly higher mortality (HR = 1.48; 95% CI 1.24 to 1.76). This risk was attenuated after further adjustment for glucocorticoid use (HR = 1.23; 95% CI 1.02 to 1.49). Factors significantly associated with mortality in patients with only RA are shown in the Table. There was no association of other biologic or non-biologic DMARDs with mortality in RA-only sub-analyses.

Patient factor	Hazards Ratio (95% CI)
Glucocorticoid use	1.81 (1.28 to 2.53)
Age (year)	1.06 (1.04 to 1.08)
Chronic obstructive pulm disease	2.10 (1.39 to 3.19)
Congestive heart failure	4.05 (1.62 to 10.12)
Anemia, Hematocrit < 38%	1.57 (1.10 to 2.24)
Current smoking	2.03 (1.39 to 2.96)

Conclusion: RA patients have a higher long-term mortality risk than OA patients following TJA, a risk that is most pronounced among glucocorticoid users in addition to current smokers and those with select comorbid conditions. Perioperative interventions that target high risk patients with RA need to be evaluated and implemented with a goal of reducing postoperative mortality following TJA.

2113

Sex Differences in Cytokine Response of Patients with Rheumatoid Arthritis. Melissa A. Wells, John M. Davis III, Keith L. Knutson, Michael A. Strausbauch, Cynthia S. Crowson, Terry M. Therneau and Sherine E. Gabriel. Mayo Clinic, Rochester, MN

Background/Purpose: Sex differences have been observed in the incidences of autoimmune disorders as well as in the cytokine response to immune stimulation. However, very little is understood regarding sex differences in cytokine response in the setting of autoimmune disorders. We sought to explore the sex differences in cytokine response in patients with rheumatoid arthritis (RA).

Methods: We performed a cross-sectional analysis of data from a population-based cohort study of patients with RA. Patient information collected included age, RA duration, BMI, CRP, HAQ disability index, current smoking status, rheumatoid factor positivity, anti-CCP antibody positivity, and RA medication use. Peripheral blood mononuclear cells (PBMC) from subjects were stimulated with a variety of stimulants to determine their cytokine response. Stimulants included anti-CD3/anti-CD28, CpG oligonucleotides (CpG), combined cytomegalovirus and Epstein Barr virus lysates (CMV/EBV), phorbol myristate acetate with ionomycin (PMA/ionomycin), phytohemagglutinin, and combined Staphylococcal enterotoxins A and B (SEA/SEB). Collected supernatants were analyzed for 17 cytokines using multiplexed immunoassays. The data were normalized using mixed models with random effects for subject and plate, to adjust for assay effects. Males and females were compared using linear regression models on the ranks of the cytokine values (due to skewed distributions) with adjustment for the patient factors listed above.

Results: Our study included 234 females (mean age 59.6 years) and 83 males (mean age 63.3 years). Significant differences (p-value <0.05) were found between males and females after adjustment for disease activity, severity and treatment status for six of the cytokines using PMA/ionomycin and SEA/SEB as stimulants. Using PMA/ionomycin, the cytokine responses for granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-10 (IL-10), and IL-17 were increased in females compared to males. Using SEA/SEB, cytokine response in females was decreased compared to males for IL-12, IL-5, and interferon gamma (IFN-γ). Similar trends were noted for several other cytokines in response to PMA/ionomycin and SEA/SEB, but these comparisons did not reach statistical significance.

Conclusion: The involvement of T cells has been an important component to the pathophysiology and management of RA. Our understanding of subsets of T cells is still under development. In relation to sex, there are differences in the cytokine response for Th1 cells (IL-2, IL-12 and IFN-γ), Th2 (IL-5 and IL-13) and Th17 (IL-17). These results may shed light on sex differences in the incidence and characteristics of auto-immune disorders; and on sex differences in treatment response, especially as cytokine-targeted therapy continues to evolve.

2114

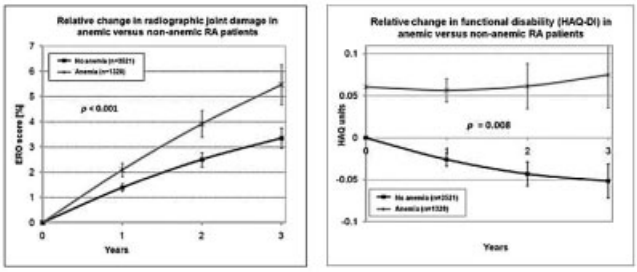
Anemia Is An Independent Indicator of Disease Progression In Rheumatoid Arthritis. Burkhard Moller[1], Doris Wisler[1], Frauke Foerger[1], Peter M. Villiger[1] and Axel Finckh[2]. [1]Inselspital-University Hospital, Bern, Switzerland, [2]University of Geneva, Geneva, Switzerland

Background/Purpose: To study the impact of anemia on disease specific outcomes and health related quality of life in rheumatoid arthritis (RA) patients.

Methods: In this longitudinal cohort study, we examined all patients with available consecutive hemoglobin assessments. Anemia was defined by hemoglobin <13 g/dl in men or <12 g/dl in women. We examined the impact of anemia on the evolution of the RA disease activity score (DAS28), erosive progression, functional disability (HAQ-DI), and health related quality of life (physical functioning and vitality scales SF-36) in longitudinal regression analyses, adjusting for potential confounders.

Results: 4377 patients (77% female, baseline median age 54 years) were followed over 2.8 years with a mean of 4.4 hemoglobin assessments. Median hemoglobin concentrations were 12.9 g/dl (interquartile range 12.0–13.7) in women and 14.2 g/dl (13.1–15.0) in men. At inclusion, anemia was present in 24% of patients and persisted in 63% of cases after one year. The incidence rate of new anemia was 7.6% per year. Anemia was significantly associated with high levels of DAS28 and the use of non-selective NSAIDs. Furthermore, anemia was independently associated with more progression of radiographic damage, functional disability, and lower health related quality of life, which persisted after adjustment for RA disease activity and severity. Figures represent the long-term evolution of radiographic damage and functional disability in RA patients with and without anemia. The lines represent the mean change over time

of radiographic damage (ERO) and functional disability (HAQ-DI). Vertical lines represent the 95% confidence intervals of the means. Analyses were adjusted for age, gender, rheumatoid factor, disease duration, baseline data of the erosion score, DAS28, HAQ-DI (only for ERO), SF36V and SF-36PF, and for co-morbidities, use of analgesics, conventional non-selective and cyclooxygenase-II selective (coxibs) nonsteroidal anti-rheumatc drugs (NSAIDs), corticosteroids, MTX, other synthetic disease modifying anti-rheumatic drugs, and TNF-α inhibitors.



Conclusion: Anemia in RA indicates an unfavorable course of the disease, which is not fully accounted for by DAS28 or other measures of disease severity. Anemia in RA requires a careful differential diagnosis and should prompt a more detailed disease activity assessment.

2115

Assesment of Physical Activity by Accelerometry: Relationship Between Physical Function and Disease Activity in Rheumatoid Arthritis Patients. Vanesa Hernandez-Hernandez[1], Esmeralda Delgado-Frías[1], Ivan Ferraz-Amaro[1], Jose A. Garcia-Dopico[2], Lilian Medina[2], Inmaculada Alonso[1], M. Teresa Arce-Franco[1], M. Jesus Dominguez-Luis[3] and Federico Diaz-Gonzalez[1]. [1]Rheumatology Service, La Laguna, Spain, [2]Central Laboratory, La Laguna, Spain, [3]Hospital Universitario de Canarias, La Laguna, Spain

Background/Purpose: In patients with rheumatoid arthritis (RA) the ability to perform activities of daily life may be deteriorated. However, the relationship between disease activity and global movement capability remains to be fully clarified in theese patients. The aim of this study was to determine to which extent RA features affect physical activity in these patients

Methods: 66 RA patients, without significant involvement of lower limbs, (56/10 female/male, age 53.6±9.6 years, disease duration 7.5±4.8 years) underwent physical activity monitoring through two methods: triaxial accelerometry output measured in vector magnitude (counts·min-1) and International Physical Activity Questionnaire (IPAQ) (MET-min/week). Patients were retested 6 months later to assess pre and post-test reliability. Demographic data, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Health Assessment Questionnaire Disability index (HAQ), Disease Activity Score (DAS 28), and quality of life through Functional Assessment of Chronic Illness Therapy (FACIT), and SF-36v2 Health Survey were performed at baseline and after 6 months of follow up.

Results: Univariate analysis showed that patients with higher DAS28 score express lower physical activity (coefficient beta 24.5 counts·min-1, (−46.7)–(−1.57)IC95%, p=0.03). These data remain statistically significant when adjusted for age, disease duration and body mass index. Similarly results were obtained for physical function (HAQ), showing a non-significant trend (coefficient,-35.2 counts·min-1,(−90.6)-(20.1) IC95%, p=0.07). Regard IPAQ questionnaire, the physical activity was also associated with HAQ (r^2=−0.41, p=0.00) and FACIT (r^2=−0.31, p=0.03) but not with DAS28 score. In fact, IPAQ and accelerometry did not correlate in RA patients (intraclass correlation index 0.01, (−0.29)-(0.32)IC95%, p=0.47). SF-36, both physical and mental component, did not showed relationship with physical activity by neither IPAQ nor accelerometry. Six months later reliability study showed that HAQ (coefficient beta −45.4 counts·min-1, (−70.9)–(−19.9)IC95%, p=0.00) and DAS28 (coefficient beta −15.9 counts·min-1, (−34.3)-(−3.35) IC95%, p=0.04) were still correlated with physical activity measured by accelerometry. This data suggest an optimal test-retest reliability. Multivariate analysis to construct the best explaining model for physical activity, assessed by accelerometry, in RA patients showed that disease duration, HAQ, DAS28 and ESR explain 29% of physical activity variation (r^2 adj=0.29).

Conclusion: Physical activity is related overtime to both disease activity and physical function in RA patients. Objective assesment of physical activity by accelerometry may be a valuable aspect to take into account in the evaluation of RA patients in clinical practice.

2116

Gender Differences in Disease Characteristics in Rheumatoid Arthritis, Inflammatory Bowel Disease and Psoriasis: Evidence for a Greater Symptomatic Burden in Females. N. Lesuis[1], R. Befrits[2], Filippa Nyberg[3] and R. F. van Vollenhoven[2]. [1]Radboud University, Nijmegen, Netherlands, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Previous studies in rheumatoid arthritis (RA) have shown a gender difference in disease characteristics, with women generally having worse scores than men.[1] Similarly, in inflammatory bowel disease (IBD) health related quality of life is worse in females.[2] In RA, we previously suggested that biologics use differs subtly between men and women. For a third auto-immune disease, psoriasis (PSO), less is known on this subject. In our study we have compared gender differences in characteristics among RA, IBD and PSO.

Methods: Data on RA and IBD patients were obtained from two different registries at the Karolinska University Hospital, and data on patients with PSO were obtained from the published report by the Swedish psoriasis register [3]. For RA and IBD, demographic data and disease activity measures prior to biologic treatment start were compared for female vs male patients; for patients with PSO, data at inclusion in the register were used which corresponded roughly with the use of systemic (but not necessarily biologic) therapies for these patients. To compare differences between men and women, the Mann-Whitney U test or the students t-test was used for continuous variables, and the X^2 test for proportions.

Results: In total 4493 patients were included in the study (RA 1912; IBD 131; PSO 2450); in RA, the majority were women and in IBD and PSO the majority were men. In RA significant differences were seen in ESR, patients' global assessment, Tender Joint Count (TJC), Health Assessment Questionnaire (HAQ), Disease Activity Score (DAS28) and DAS28-CRP; all values were higher in women (table); in contrast, Swollen Joint Count (SJC) and CRP were nominally higher in the male patients. In the IBD patient group no statistically significant differences were seen in disease activity as measured with the Harvey Bradshaw index, but there was a trend towards higher scores on the Short Health Scale (SHS, disease-specific symptom survey) in women compared to men. For PSO, a high score on the Psoriasis Area and Severity Index (PASI) was noted in a significantly greater proportion of men, whereas a high Dermatology Life Quality Index (DLQI), ie, a worse quality of life, occurred more often in women. Overall, a greater proportion of men with IBD or PSO received biologic/systemic treatment, but for the biological treatment of RA this was not seen.

		Men	Women	p-value
RA	Swollen Joint Count	9.1	8.8	0.36
	Tender Joint Count	7.8	8.7	0.01
IBD	ESR	29.5	23.8	0.52
	SHS-Influence daily life	55.6	71.1	0.12
	Harvey Bradshaw	9.8	10.5	0.71
Psoriasis	PASI ≥10 (% pts)	35.3	27.0	0.00
	DLQI ≥10 (% pts)	27.7	37.7	0.00

Conclusion: Women with RA scored significantly higher on subjective disease activity measures than men, while SJC was comparable. A similar trend towards worse subjective disease symptoms despite similar measured disease activity is also seen in IBD and PSO, providing a framework for studies of gender differences in autoimmune diseases.

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2117

Early Rheumatoid Arthritis in Latin America. Low Socioeconomic Status Relates to High Disease Activity At Baseline. Loreto Massardo[1], Bernardo A. Pons-Estel[2], Mario H. Cardiel[3], Claudio Galarza-Maldonado[4], Mónica P. Sacnun[5], Enrique R. Soriano[6], Ieda Laurindo[7], Eduardo M. Acevedo-Vásquez[8], Carlo V. Caballero-Uribe[9], Oslando Padilla[10], Marlene Guibert-Toledano[11], Rubén A. Montufar Guardado[12], Sergio H. Jacobelli[13] and Daniel E. Furst[14]. [1]Catholic University of Chile, Santiago 114-D, Chile, [2]Hospital Provincial, Rosario, Argentina, [3]Hospital General "Dr. Miguel Silva", Morelia, Mexico, [4]Hospital Monte Sinai, Cuenca, Ecuador, [5]Hosp. Provincial, Rosario, Argentina, [6]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [7]Universidade de São Paulo, Sao Paulo, Brazil, [8]Hospital Nacional "Guillermo Almenara Irigoyen", Lima, Peru, [9]Continential Med Ctr, Barranquilla, Colombia, [10]Pontificia Universidad Catolica de Chile, Santiago, Chile, [11]Centro de Investigaciones Médico Quirúrgicas, Habana, Ciudad Habana, Cuba, [12]Instituto Salvadoreño del Seguro Social, San Salvador, El Salvador, [13]Universidad Catolica de Chile, Santiago, Chile, [14]UCLA Medical School, Los Angeles, CA

Background/Purpose: To determine the influence of social factors on disease activity at baseline in a large multinational inception cohort of Latin American (LA) patients with early rheumatoid arthritis (RA).

Patients and Methods: Patients with early RA (<1 year disease duration from first symptoms, ≥18 years old) were examined between 2004/05 and followed for 3 years. Patients attended 46 rheumatology centers in 14 LA countries. Clinical evaluation, ethnicity, socioeconomic status (SES) (Graffar's method), DAS28-ESR, HAQ-DI, and hand and feet radiographs were performed and recorded on an agreed data base (ARTHROS 6.1). Chi-square, Kruskal Wallis or Mann Whitney U tests (p value<0.01) were used for comparisons. Multivariate analyses were applied to evaluate the influence of all the above factors.

Results: Among the 1,093 patients who had been enrolled in July 2005, 85.3% were females. Mestizo (mixed European and Amerindians): 43%, Caucasians: 31%, African-LA (ALA): 19%, Amerindians: 4%, Others: 3%. 58% were in the lower or middle-lower SES; 41.7% had < 8 yrs of education; 44% had no or only some medical insurance coverage. Separated/divorced/widowed: 14%, and married/single: 86%. Age at onset: 46 (SD: 14) years; duration of disease at baseline 6.7 (SD: 3.2) months. Women and Mestizo, ALA, and Amerindian had earlier onset (5 years) than men or Caucasians ($p < 0.01$). Disease was clinically quite active- DAS28 score 6.0 (SD: 1.7) and moderately functionally disabling: HAQ-DI 1.29 (SD: 0.87). Surprisingly, joint erosions were present in only 25% (no stat. differences among ethnic groups).

ANCOVA multivariate analysis showed low/low middle SES, female sex and partial insurance are associated with both worse HAQ-DI and higher DAS28. Marital status was only associated with HAQ-DI, while older age was only associated with DAS28. Logistic regression analysis showed that older age, lack of insurance, and ethnic groups Amerindian and Other associated with the presence of erosions. When models included country of origin, differences between countries were found. (Cuba had highest HAQ-DI and DAS28 scores while Venezuela had lowest HAQ-DI and DAS28).

Conclusion: This report compares early RA patients from the four LA main ethnic groups. Women and LA ethnicities (Amerindian, ALA, Mestizo) had significantly younger RA onset. Higher HAQ-DI and DAS28 scores related to poor SES status, femaleness and partial insurance suggesting that poverty/low/ middle low SES influence are important factors in determining disease activity. A more genetic related background for erosions is possible.

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Forefoot Plantar Pressure and Gait Characteristic of Patients with Early Rheumatoid Arthritis: A Case-Control Study. Sze Man Lau[1], Chi Chiu Mok[2], Chi Hung To[2] and Wing Yuk Ip[3]. [1]Pok Oi Hospital, Hong Kong, Hong Kong, [2]Tuen Mun Hospital, Hong Kong, Hong Kong, [3]University of Hong Kong, Hong Kong, Hong Kong

Background/Purpose: Foot and ankle symptoms are common in patients with established rheumatoid arthritis (RA). These are caused directly or indirectly by synovitis, subluxation and deformities of the foot joints. There is little information regarding the biomechanical features of the feet and gait of patients with early RA. We aimed to study the plantar pressure and gait characteristics of RA with early disease and their relationship with disease characteristics.

Methods: Patients who fulfilled the 1987 ACR criteria for RA and had disease duration of less than 4 years were recruited. Subjects without arthritis matched for sex and body mass index (BMI) were also invited as controls for comparison with patients. Barefoot plantar pressure (9 forefoot areas) and gait parameters including pressure time integral (total plantar pressure in a period of time) and the anterior progression of the centre of force over the plantar area from heel to mid-foot were measured by the Matscan ® pressure mapping system (TekScan, Inc, Massachusetts, United State) and processed by F-scan research STAM ver. 5.83 software. The Foot Function Index (FFI; 0–100 points; with subscales of pain, disability and activity limitation), Health Assessment Questionnaire Disability Index (HAQ), disease activity scores (DAS28) were obtained in patients with RA. Correlation analyses were performed between plantar pressures and various clinical and disease-related parameters.

Results: 47 consecutive RA patients (77% women; mean age 49.3 ± 11.1 years; mean BMI 23.3 ±3.6; disease duration 2.3 ± 1.1 years; DAS 28 score 3.29 ± 1.52) and 36 matched controls were studied. The median HAQ score of RA patients was 0.25 (IQR 0.63). Compared to control subjects, patients with RA had significantly lower forefoot peak plantar pressures (RA 249.9±44.1 vs controls 281.4±32.1 kPa; $p<0.001$) and pressure time integrals (RA 34.5±7.4 vs control 42.9±8.0 kPa·sec; $p<0.001$). The anterior progression of the centre of force from heel to midfoot was delayed (increase in time of walking on heel) in RA subjects but the difference was not statistically significant (RA 50% vs control 48% of stance). Correlation studies revealed that the peak pressure at the medial forefoot (hallux) was significantly and inversely associated with disease activity (DAS 28 score) ($r= 0.30$; $p= 0.04$), HAQ score ($r= -0.40$; $p= 0.005$), FFI score ($r= -0.32$; $p= 0.03$) and disability subscale of FFI ($r= -0.37$; $p= 0.01$). Overall, 40% of RA patient had abnormal pressure parameters (<2 standard deviations from the control group mean) of the forefeet.

Conclusion: In a substantial proportion of RA patients with relatively early disease, the centre of force of the plantar area of the feet is shifted to the heel during walking, which is likely contributed by pain and active synovitis of the feet and ankle joints. The altered loading of the feet and shifting to a heel-walking gait activates toe extensors which may further aggravate pain and deformities. Early identification of this gait drift and orthotic intervention to modify forefoot loading pattern may retard functional deterioration and deformity development in patients with early RA.

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The Effect of Patient Reported Pain on Disability Is Partially Mediated Through Depression in Vulnerable United States Hispanics with Rheumatoid Arthritis. Soha Dolatabadi[1], Rosalinda C. Moran[2], Galen Cook-Wiens[1], Ning Li[1], Michael H. Weisman[3], Perry M. Nicassio[4] and George A. Karpouzas[5]. [1]Cedars Sinai Medical Center, Los Angeles, CA, [2]Harbor UCLA Medical Center, Carson, CA, [3]Cedars Sinai Med Ctr, Los Angeles, CA, [4]UCLA, Los Angeles, CA, [5]Harbor-UCLA, Torrance, CA

Background/Purpose: US Hispanics with Rheumatoid Arthritis (RA) experience worse functional disability and quality of life compared to Caucasians. In a cross-sectional design, we previously characterized the predictors of such disability, assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI); patient-reported pain was the most significant, followed by irreversible articular damage (IAD- defined as subluxation, arthrodesis, fusion, or prosthesis), disease activity (DAS28-3v-ESR), depression (evaluated by the physician Health Questionnaire- PHQ-9), joint replacement surgeries, and age. In the present report we examined the interactions and effects of pain, disease activity, depression and age longitudinally on disability. We additionally explored whether the effects of pain and disease activity on disability would be mediated through depression.

Methods: One hundred patients evaluated over 3 time points 6 months apart, in a single institution were studied. Regression models were constructed using pain and disease activity from time point 1 to predict depression at point 2; a subsequent model examined the ability of time 1 pain and disease activity to predict disability at time 3, with or without the addition of depression from time 2. Sobel test was used to address mediation of effects of pain and disease activity from time 1 on time 3 disability by time 2 depression. Additional modeling investigated the independent contribution of pain on disability, as well as the proportion of the effect of pain on disability that would be mediated by depression.

Results: Both pain and disease activity from time 1 were associated with depression at time 2 in decreasing order of significance (table 1). Pain from time 1 predicted disability at time 3 ($p=0.00002$);

Depression predicted disability at Time 3 after pain, but the effect of pain remained significant (p=0.0006); this suggested that depression partially mediated the effects of pain on disabililty. The Sobel test confirmed this mediation, and depression accounted for 35% of the effect of pain on disability. Disease activity at time 1 was not predictive of time 3 disability.

Regression 1	**Outcome: Depression (PHQ-9) at time 2**		
(time 1)	***b***	***95% CI***	***p*-value**
Pain-VAS	2.52	(0.9, 4.13)	0.0026
DAS28-3v-ESR	1.44	(0.16, 2.71)	0.0275
Regression 2	**Outcome: Disability (HAQ-DI) at time 3**		
(time 1)			
age	0.02	(0.003, 0.027)	0.016
Pain-VAS	0.44	(0.25, 0.64	0.00002
DAS28-3v-ESR	0.04	(−0.11, 0.2)	0.593
Regression 3	**Outcome: Disability (HAQ-DI) at time 3**		
(time 1)			
age	0.02	(0.006, 0.03)	0.0038
Pain-VAS	0.35	(0.15, 0.54)	0.0006
DAS28-3v-ESR	−0.01	(−0.17, 0.14)	0.858
PHQ-9	0.04	(0.01, 0.06)	0.0019
Sobel Test	***b* (SE) from Regression 1**	***b* (SE) of PHQ-9 from Regression 2**	***p*-value for Sobel test**
Pain-VAS	2.47 (0.81)	0.038 (0.012)	0.0273

Conclusion: Baseline self-reported pain is the most robust longitudinal predictor of disability in vulnerable US Hispanics with RA. Its effects are both direct (65%) and indirect, mediated through depression (35%). Therefore, future interventions addressing prevention of long-term disability in this group should target both depression and pain.

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The Public Health Impact of Risk Factors for Physical Inactivity in Adults with Rheumatoid Arthritis. Jungwha Lee[1], Dorothy D. Dunlop[2], Linda S. Ehrlich-Jones[3], Pamela A. Semanik[4], Jing Song[2], Larry Manheim[2] and Rowland W. Chang[1]. [1]Northwestern University, Chicago, IL, [2]Northwestern Univ Med School, Chicago, IL, [3]Rehabilitation Institute Chicago, Chicago, IL, [4]Rehabilitation Institute Chicago, Oak Park, IL

Background/Purpose: Physical activity offers important health benefits to adults, including those with rheumatoid arthritis (RA). This study investigated the potential public health impact of modifiable risk factors related to physical inactivity in adults with RA.

Methods: Physical activity was measured using accelerometers at the baseline visit of a clinical trial in 176 RA participants. Time spent in moderate-to-vigorous (MV) intensity activities was calculated to assess if participants were inactive (no MV minutes/week in bouts lasting 10 or more minutes). The cross-sectional relationships between modifiable risk factors (motivation for physical activity (strong vs. not strong), beliefs related to physical activity's benefits (strong vs. not strong), weight status (obese vs. not obese), pain (any vs. none), mental health (poor vs. not poor based on Mental Component Summary Score[MCS])) with inactivity were assessed by estimating odds ratios (OR) and attributable fractions (AF), controlling for potential confounding factors (age, gender, race, education, disease duration, and co-morbidity).

Results: Over two in five adults (42%) with RA were inactive. Modifiable factors most strongly related to inactivity were lack of strong motivation for physical activity (adjusted OR=2.85, 95% confidence interval [CI]=[1.31, 6.20]; adjusted AF=53.1%, 95% CI=[21.7, 74.6]) and lack of strong beliefs related to physical activity's benefits (OR=2.47, 95% CI=[1.10, 5.56]; AAF=49.2%, 95% CI=[7.0, 76.4]), controlling for age, gender, race, education, disease duration, and co-morbidity mobility limiting. Together, these two factors are related to almost 65% excess inactivity in this sample.

Conclusion: Despite known benefits from physical activity, adults with RA were substantially inactive (42%). Being inactive was strongly related to a lack of strong motivation for physical activity and a lack of strong beliefs in benefits from physical activity. These results support development of interventions that increase motivation for physical activity and that lead to stronger beliefs related to physical activity's benefits in order to reduce the prevalence of physical inactivity and improve health status in adults with rheumatoid arthritis.

Modifiable risk factor frequency, odds ratio, and attributable fraction for physical inactivity in adults with rheumatoid arthritis (n=176)

Modifiable Risk Factor	**Risk category on top**	**Frequency (%)**	**Adjusted Odds Ratio* [95% CI]**	**Adjusted Attributable Fraction* [95% CI]**
Motivation	Lack of strong motivation	60	2.85 [1.31, 6.20]	53.1 [21.7, 74.6]
	Strong motivation	40	Reference	
Belief	Lack of strong belief	67	2.47 [1.10, 5.56]	49.2 [7.0, 76.4]
	Strong belief	33	Reference	
HAQ pain	Some pain	90	1.40 [0.45, 4.38]	26.5 [−51.1, 80.3]
	No pain	10	Reference	
Weight	Obese	31	1.80 [0.85, 3.81]	23.6 [−3.6, 47.5]
	Overweight/Normal weight	69	Reference	
Mental health status	Poor mental health	11	1.38 [0.47, 4.04]	2.9 [−8.0, 13.8]
	Not poor mental health	89	Reference	

* Adjusted for age, gender, race, disease duration, college graduate, mobility limiting comorbidity

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Aldosterone Is Not Increased in Patients with Rheumatoid Arthritis. Michelle J. Ormseth, Margaret Randels, Annette M. Oeser, Joseph F. Solus and C. Michael Stein. Vanderbilt Medical Center, Nashville, TN

Background/Purpose: Activation of the renin-angiotensin system and consequent increased aldosterone production is associated with adverse cardiovascular outcomes as a result of inflammation, fibrosis, and increased insulin resistance. There is no information about aldosterone in patients with rheumatoid arthritis (RA), a population with accelerated cardiovascular disease and increased prevalence of insulin resistance. We tested the hypothesis that aldosterone concentrations are increased in RA and associated with inflammation, insulin resistance, and markers of myocardial dysfunction in patients with RA.

Methods: We measured concentrations of serum aldosterone, high sensitivity troponin, brain natriuretic peptide (BNP), inflammatory cytokines, fasting insulin, glucose, and lipids, along with clinical variables in 35 patients with RA and 34 control subjects not taking any antihypertensive medications. We assessed the relationship between aldosterone and high sensitivity troponin and NT-proBNP, inflammatory cytokines, disease activity, and measures of insulin resistance using Spearman correlation analysis in patients with RA.

Results: Aldosterone concentrations were lower in patients with RA than controls (48.54 pg/ml [38.88–61.86] vs. 58.24 [50.75–76.49], p=0.01). Concentrations of markers of myocardial stress, high sensitivity troponin (p= 0.31) and NT-proBNP (p= 0.32), were not significantly correlated with serum aldosterone levels in RA. Similarly, interleukin 6 (IL-6) (p= 0.10), tumor necrosis factor alpha (TNFα) (p= 0.38), and RA disease activity (DAS28) (p= 0.57) were not associated with aldosterone. Finally, aldosterone was not correlated with markers of insulin resistance including fasting insulin (p= 0.33) and glucose (p= 0.77) and HOMA (p= 0.29).

Conclusion: Activation of the renin-angiotensin system does not appear to contribute to accelerated myocardial disease or insulin resistance in patients with RA.

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Clinical Characterization of Extensive Interstitial Lung Disease in Rheumatoid Arthritis Patients. Masaomi Yamasaki, Yoshiteru Haga, Makoto Inoue, Kumiko Tonooka and Naooki Katsuyama. St Marianna University, Yokohama City Seibu Hospital, Yokohama, Japan

Background/Purpose: To investigate clinical characteristics of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients, and to analyze whether high resolutional CT (HRCT) can predict the outcome of ILD in RA.

Methods: 340 patients with RA were treated at our hospital and followed up at least one year. All patients were performed chest radiological examinations at the initial presentation. The HRCT findings which include (1) ground glass opacity, (2) air-space consolidation, linear opacity including (3) septal line and (4) non-septal line, (5) honeycomb lung, (6) traction bronchiectasis, (7) pleural irregularity, and (8) pleural effusion were scored as the CT scoring system. The extent of involvement of each abnormality was assessed independently for each of the three

zones of each lung. The HRCT extent score was represented the sum of the score of each lung. HRCT parameters which include the extension score and the clinical features at the initial presentation were retrospectively analyzed.

Results: 162 out of 340 patients had abnormal chest radiological findings which included bronchiectasis, bronchitis and ILD (47.6%). 76 (26 male (39.3%), 50 female (18.2%)) out of 340 patients showed ILD at initial presentation (22.4%). 5 out of 76 patients had shortness of breath and showed a rapidly progressive ILD (6.6%). In HRCT findings, ILD in these 5 cases were widely spread at the initial presentation. The rest of 71 patients showed no progression of ILD and asymptomatic. However there were no difference in the HRCT findings which include nonseptal linear attenuation, ground-glass attenuation and air space consolidation between rapidly progressive ILD group and asymptomatic group, rapidly progressive ILD group showed more higher degree in honeycombing ($p=0.0003$) and extensive ILD ($p=0.0061$). Prognosis of the rapidly progressive ILD was variable. The rapidly progressive ILD are treated with immunosuppressive agent which include high dose steroid, cyclophosphamide, azathioprine, cyclosporineA (CsA) and Mycophenolate Mofetil(MMF) for IP. 2 patients treated with CsA and one patient treated with MMF shows improving of ILD on HRCT. But in other 2 patients were resistant to these immunosuppressive agents.

Table 1. HRCT findings at the initial presentation in RA-ILD

	asymptomatic ILD (n = 71)	rapidly progressive ILD (n = 5)	p value
nonseptal linear attenuation	91.5% (65)	100% (5)	0.4982
ground-glass attenuation	25.4% (18)	60.0% (3)	0.1258
honeycombing	16.9% (12)	100% (5)	0.0003*
air space consolidation	1.4% (1)	0.0% (0)	0.7894
extensive ILD (more than 4 areas of ILD)	16.9% (12)	80.0% (4)	0.0061*

Conclusion: HRCT findings focused on the extension score at the initial presentation is a useful predictor of the outcome of ILD in RA.

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Lobular Panniculitis: A Characteristic Skin Manifestation in Rheumatoid Arthritis. Takehiko Ogawa, Takehisa Ogura, Kana Ogawa, Ayako Hirata and Norihide Hayashi. Toho University Ohashi Medical Center, Tokyo, Japan

Background/Purpose: Although panniculitis has been described in various systemic inflammatory disorders such as systemic lupus erythematosus, sarcoidosis and Weber-Christian disease, but it has seldom been reported in RA. We encountered 8 RA patients with skin manifestations of which histologic findings revealed the lobular panniculitis. Those serial cases led us to investigate the incidence and clinical characteristics of lobular panniculitis occurring in RA.

Methods: We retrospectively reviewed the medical records of 8 patients with RA who developed lobular panniculitis. To investigate whether lobular panniculitis is characteristic of RA, we non-selectively recruited 100 RA patients without episode of panniculitis, and reviewed the patients' medical records for clinical manifestations and laboratory data. Patients were excluded if they had a rheumatic autoimmune disease other than RA or significant systemic involvement secondary to RA.

Results: Among the 8 patients with panniculitis studied (women/men: 6/2), those ages ranged from 30 to 78 years (58.1 ± 16.9 years) and duration of illness ranged from 2 to 15 years (8.9 ± 3.9 years). The cutaneous manifestations were edematous and tender erythematous indurations with partially hirsute, which were quite similar among those 8 patients and characteristic. Histologic studies revealed lobular panniculitis without vasculitis. In all 8 patients, the eruptions arose over the periarticular extensor surfaces of the forearms or the distal legs, which had the most active synovitis at the time. Compared with 100 RA patients without panniculitis, large joints including shoulder, elbow, wrist, knee and foot joints were more frequently affected in patients with panniculitis ($p=0.007$). Mean number of tender joints and swollen joints were significantly smaller ($P=0.002$), whereas patient's global assessment of disease activity, patient's global assessment of pain, mean values of CRP and the Disease Activity Score in 28 joints (DAS28) were significantly higher in RA patients with panniculitis ($p=0.007$, $p<0.0005$, $p=0.001$, respectively). The activities of arthritis and panniculitis were in parallel, and the skin manifestation and arthritis responded concurrently to treatments for RA.

Conclusion: Although lobular panniculitis has not been previously described as manifestation of RA, the present study demonstrates that panniculitis may be a characteristic and notable skin manifestation in RA.

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Low Levels of Vitamin D Level Are Associated with Greater Disease Activity and Disability in Patients with Rheumatoid Arthritis. Uzma J. Haque[1], Kevin R. Fontaine[2], Clifton O. Bingham[3] and Susan J. Bartlett[4]. [1]Johns Hopkins Hospital, Baltimore, MD, [2]John Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD, [4]McGill University, Montreal, QC

Background/Purpose: Low vitamin D levels are prevalent among persons with rheumatoid arthritis (RA). Some studies have shown an association between low vitamin D and increased disease activity and pain. Our goal was to estimate the prevalence of low vitamin D levels in a cohort of RA patients and estimate relationships between 25(OH)D levels, clinical and patient reported indicators of disease activity and disability.

Methods: Data are drawn from the baseline visit of an RCT to assess the effect of vitamin D repletion therapy in RA patients (currently underway). Patients who met ACR criteria were consecutively approached during routine clinic visits from Jan 2009 through April 2011. Joint counts and evaluator disease activity assessments were performed. CDAI scores were calculated as an indicator of disease activity. Patients completed the HAQ, AIMS2-SF and other selected additional questionnaires. 25(OH)D measures were conducted by one laboratory using the DiaSorin radioimmunoassay.

Results: Participants ($N=139$) were mostly female (79.9%) and white (79,1%) with a mean $\pm$ SD age of 53.4 ± 12.3 yrs, BMI of 30.5 ± 6.9 kg/m^2 and disease duration of 10.0 ± 9.0 yrs. Mean 25(OH)2 levels were 28.3 ± 11.1 ng/mL (range 6.3 – 72.8); mean 25(OH)D was < 30 ng/mL in all seasons except summer when it increased to 31.9 ± 11.2 ng/ml ($p=.429$). Overall, 60.2% had 25(OH)D levels < 30 ng/mL, and 21% $\leq$ 20 ng/mL. Patients with the lowest 25(OH)D levels had higher BMIs (33.6 ± 9.5 vs. 31.2 ± 6.2 vs. 28.5 ± 5.6; $p<.01$) but did not differ by age, sex, race or education. Patients with Vitamin D $\leq$ 20 ng/mL had significantly higher clinical (swollen and tender joints, CDAI) and patient reported (morning stiffness, pain, fatigue) indicators of disease activity and higher HAQ scores as shown in table. In a subset of participants ($n=90$) who completed the AIMS2-SF, very low vitamin D status also was associated with significantly more symptom reports.

Table 1. Clinical and Patient-Reported Disease Indicators in Patients with Rheumatoid Arthritis by 25(OH)D Level.

25(OH)D Levels (ng/mL)	≤ 20 N=29	20–30 N=54	>30 N=56	P value
Clinical Disease Indicators				
Swollen Joints	7.4 ± 9.3^a	3.7 ± 4.8^b	3.6 ± 5.2^b	.016
Tender Joints	12.3 ± 12.1^a	6.2 ± 10.0^b	6.1 ± 8.1^b	.012
CDAI	19.1 ± 15.6^a	10.0 ± 11.1^b	9.3 ± 10.3^b	.003
Patient Reported Indicators				
Morning Stiffness (min)	160^a	74^b	27^b	.015
Pain (100 mm VAS)	39 ± 29^a	24 ± 24^b	25 ± 22^b	.020
Fatigue (SF12 Vitality)	42.2 ± 9.9^a	49.1 ± 10.2^b	47.6 ± 9.3^b	.010
AIMS2-Symptoms	4.4 ± 3.1^a	$2.9 \pm 2.9^{a\dagger}$	2.3 ± 2.0^b	.033
Disability				
HAQ	1.01^a	0.62^b	0.68^b	.026

Conclusion: Despite increasing awareness of the importance of vitamin D for overall health, low levels appear to be common in RA patients. Low vitamin D status is associated with significantly higher clinical and patient reported indicators of disease activity and greater disability. The effect of repleting and maintaining adequate levels of vitamin D on RA disease activity, symptoms and disability remains unknown.

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Predictors of Assymetric Dimethyl Arginine in Rheumatoid Arthritis. Theodoros Dimitroulas[1], Aamer Sandoo[1], Jet JJCS Veldhuijzen van Zanten[2], Jacqueline P. Smith[1], George Metsios[1], Peter Nightingale[3], Antonios Stavropoulos-Kalinoglou[1] and George Kitas[1]. [1]Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Dudley, West Midlands, UK, Dudley, United Kingdom, [2]School of Sport and Exercise Sciences, University of Birmingham, Birmingham, UK, Dudley, United Kingdom, [3]Dudley, United Kingdom

Background/Purpose: Rheumatoid arthritis (RA) is associated with endothelial dysfunction and increased cardiovascular mortality. Assymetric dimethylarginine (ADMA) is a competitive inhibitor of nitric oxide synthase and has emerged as a novel cardiovascular risk factor. Previous studies have shown that ADMA levels are elevated in patients with RA. The aim of the present study was to investigate if demographic, inflammatory, or metabolic factors predict elevated ADMA levels in RA and to define the potential relationship between ADMA and *in vivo* assessments of microvascular and macrovascular endothelial function.

Methods: We studied 67 patients (age (mean ± standard deviation): 56 ± 12 years, disease duration median (25^{th} – 75^{th} percentile): 8 (3 – 15) years, 48 women) and 29 healthy controls (age (mean ± standard deviation): 42 ± 12, 21 women). Routine biochemistry tests, lipid profile, glycemic profile and inflammatory markers were measured in all patients and controls. ADMA levels were measured by ELISA. Microvascular endothelial-dependent (Acetylcholine) and endothelial-independent (sodium nitroprusside) function were examined using Laser Doppler Imaging. Macrovascular endothelial dependent function was assessed using flow-mediated dilatation, and endothelial-independent function using glyceryl-trinitrate-mediated dilataion. Arterial stiffness was characterised using pulse wave analysis.

Results: ADMA levels were significantly higher (p=.004) in RA patients compared with healthy controls after adjustment for age (difference = 0.088, 95% confidence interval 0.029–0.147). Linear regression analysis revealed that Insulin (β=.33, t (65) = 2.80, p =.007), HOMA (β=.36, t (64) = 3.01, p =.004) and QUICKI (β= -.12, t (64) = 3.03, p =.004) were independent predictors of elevated ADMA. ADMA levels did not correlate with demographic or disease characteristics. No correlation was found between ADMA and non-invasive assessments of endothelial function or with arterial stiffness.

Conclusion: The present findings suggest that insulin resistance, rather than inflammation or other classical CVD risk factors, predict elevated ADMA levels in RA. ADMA was not associated with assessments of endothelial function and these assessments should therefore be used independently for global assessment of vascular health. Further longitudinal studies are required to assess the long-term effect of elevated ADMA level in RA.

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Disease Activity Levels and Treatment Patterns Amongst Ethnic Minority Rheumatoid Arthritis Consortium Patients. Yusuf Yazici[1], Christopher Swearingen[2], Yvonne R. S. Sherrer[3], Raj G. Nair[4], Edward L. Treadwell[5], Angelia D. Mosley-Williams[6], Luis R. Espinoza[7], Asia M. Mubashir[8], Jeffrey Huang[8] and Gail S. Kerr[9]. [1]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY, [2]University of Arkansas for Medical Sciences, Little Rock, AR, [3]Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, [4]Washington Hospital Center, Washington DC, DC, [5]E Carolina Univ Sch of Med, Greenville, NC, [6]John Dingell VAMC, Detroit, MI, [7]LSU Medical Center, New Orleans, LA, [8]Howard University Hospital, Washington, DC, [9]Washington DC VAMC and Georgetown University and Howard University Hospital, Washington, DC

Background/Purpose: Advances in therapeutic strategies for rheumatoid arthritis (RA) and focus on "treating to target" has led to increased use of disease activity measures in routine care. However, little data exists that examines disease activity in ethnic minorities. The Ethnic Minority Rheumatoid Arthritis Consortium (EMRAC) is a registry comprised of RA clinical measures obtained during routine care.

Methods: RA patients satisfying ACR diagnostic criteria, of self-reported ethnicity and seen at 8 US sites are enrolled. Collected data include patient demographics, comorbidities, disease characteristics and activity (MDHAQ, ESR, CRP, swollen and tender joint counts, composite disease activity indices). Patients enrolled in EMRAC were evaluated for treatment modalities, disease duration, and low/moderate/high disease activity as measured by RAPID3, CDAI, and DAS28. Ethnic groups were compared to Caucasians for each category of disease activity using Kruskal-Wallis for continuous variables and Chi-square test for qualitative variables; post-hoc pairwise comparisons between groups were adjusted using Bonferonni correction ($p<0.008$ for significance).

Results: More patients had data available for determination of RAPID3 than either CDAI or DAS28. Compared to Caucasians or Other racial category, Hispanic patients had significantly higher disease severity as measured by RAPID3; African Americans average RAPID3 was also higher, but was not statistically different from Caucasian or Other racial groups. No differences were seen in clinical remission by DAS28 or CDAI criteria, or in DMARD use between ethnic groups. However, significantly fewer African Americans were on biologic agents compared to Caucasians or Hispanics.

Table 1. Disease Severity and Treatments amongst Ethnic Groups in EMRAC

	African-American	Caucasian	Hispanic	Other	Total	p
N	102	105	82	49	338	
Dis Duration, mean yr (SD)	8.2 (9.3)	7.4 (10.0)	8.8 (9.4)	4.2 (5.1)	7.5 (9.2)	
RAPID3 (N=310)						**0.034**
High Severity [>12]	44 (48%)	34 (33%)	44 (59%)	13 (30%)	135 (44%)	
Moderate Severity [6.1–12]	20 (22%)	30 (29%)	16 (22%)	11 (26%)	77 (25%)	
Low Severity [3.1–6]	11 (12%)	13 (13%)	6 (8%)	8 (19%)	38 (12%)	
Near Remission [0–3]	16 (18%)	25 (25%)	8 (11%)	11 (26%)	60 (19%)	
Mean (SD) score [0–30]	11.2 (6.9)	9.5 (6.9)	13.1 (7.1)	8.9 (7.2)	10.8 (7.1)	**0.002**
DAS28 (N=56)						0.430*
High Severity [>5.1]	2 (6%)	2 (18%)	1 (14%)	0	5 (9%)	
Moderate Severity [3.21–5.1]	12 (34%)	5 (45%)	1 (14%)	1 (33%)	19 (34%)	
Low Severity [2.61–3.2]	9 (26%)	0	1 (14%)	0	10 (18%)	
Near Remission [0–2.6]	12 (34%)	4 (36%)	4 (57%)	2 (67%)	22 (39%)	
Mean (SD) score [0–10]	3.1 (1.1)	3.4 (1.9)	3.0 (2.0)	2.9 (0.8)	3.1 (1.4)	0.848
CDAI (N=87)						0.617*
High Severity [>22]	6 (11%)	2 (19%)	2 (17%)	0	10 (11%)	
Moderate Severity [10.1–22]	15 (27%)	3 (27%)	4 (33%)	3 (38%)	24 (29%)	
Low Severity [2.9–10]	24 (43%)	4 (36%)	3 (25%)	1 (13%)	32 (37%)	
Near Remission [0–2.8]	11 (20%)	2 (18%)	3 (25%)	4 (50%)	20 (23)%	
Mean (SD) score [0–76]	10.4 (11.0)	13.0 (13.2)	10.9 (9.7)	6.0 (5.6)	10.4 (1.7)	0.559
Prednisone (N, %)	41 (40%)	34 (32%)	28 (34%)	14 (29%)	117 (35%)	0.487
DMARD (N, %)	85 (83%)	78 (74%)	62 (76%)	41 (84%)	266 (79%)	0.294
Biologic (N, %)	22 (22%)	43 (41%)	40 (49%)	14 (29%)	119 (35%)	**0.001**

*Fisher's exact test reported instead of Chi-square test.

Conclusion: In a diverse ethnic cohort, significant differences in the patient-reported measure of RA disease activity and biologic treatment were noted. Further evaluation is needed to assess the reasons that may contribute to these differences among RA ethnic groups and their impact on long-term outcomes.

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The Impact of Morning Stiffness on Quality of Life in Early Rheumatoid Arthritis. Karin Britsemmer and Dirkjan van Schaardenburg. Jan van Breemen Research Institute / Reade, Amsterdam, Netherlands

Background/Purpose: In early rheumatoid arthritis (RA), joint stiffness and pain are often most severe in the morning hours. Morning stiffness (MS) could impair physical functioning and may impact the quality of life (QoL). The aim of this study was to evaluate the relationship between MS and QoL.

Methods: Data of 286 patients (71% female, age 53 (13)) fulfilling the ACR 1987 criteria for RA either at baseline or at 1 year follow-up that had

data available were used for the analysis. Patients were treated with conventional DMARDs or TNF-α inhibitors as prescribed by the treating rheumatologist. Univariate and multivariate correlation/regression was used to evaluate the relationship between MS and QoL, and between MS and physical functioning, with disease activity as covariate. MS was expressed as duration in minutes, disease activity was measured by the 28-joint count disease activity score (DAS28) and the Health Assessment Questionnaire (HAQ) measured physical functioning. EuroQol measured quality of life, expressed as visual analog scale (VAS, range 0–100) and as profile result. Profiles were calculated according to a scoring formula based on unweighted coefficient (range −0.59 – 1,00)[1]. Measurements were at baseline and after 1-year follow-up. Statistical tests were performed at a one-sided alpha of 0.05, given the known relationship of patient symptoms with quality of life, the moderate discriminative characteristics of both duration of MS and EuroQol as measure, and the relative low power of regression models to detect interaction effects. Thus all results with a $p<0.10$ are regarded as significant.

Results: At baseline 84% of patients had MS of 15 minutes or more (mean 79 (69) minutes). Patients had active disease with a mean DAS28 of 5,0 (1.2) and were significantly impaired in physical functioning (mean HAQ 1.21 (0,73)). Quality of life was significantly impacted with EuroQol profile scores of 0,37 (0,29) and VAS results of 55 (20). Most patients had improved scores after 1-year (table 1). In univariate analysis MS was significantly correlated to EuroQol at both time points. More importantly, improvement in MS correlated strongly with improvement in EuroQol. This relationship maintained when adjusted for DAS28 for the separate time points, but weakened for the change scores. In all models MS was strongly correlated to HAQ even after adjustment for DAS28 (table 1).

Table 1. Descriptives (mean (SD)) and the measures of correlation (adjusted for DAS) between morning stiffness and quality of life

	Baseline	1 year FU	Change scores
MS (minutes)	79 (69)	35 (55)	−44 (87)
DAS28	5.0 (1.2)	3.2 (1.2)	−1.9 (1.4)
HAQ	1.21 (0.73)	0.80 (1.25)	−0.55 (0.69)
EuroQol Profile*	0.37 (0.29)	0.60 (0.29)	0.23 (0.33)
EuroQol VAS*	55 (20)	69 (19)	14 (23)
Correlation/regression coefficient			
EuroQol Profile	−0.136 (p=0.005)	−0.146 (p=0.008)	−0.095 (p=0.086)
EuroQol VAS	−0.089 (p=0.006)	−0.148 (p=0.087)	−0.036 (p=0.514)
HAQ	0.187 (p=0.002)	0.157 (p<0.005)	0.150 (p=0.006)

* an higher score means a better health state

Conclusion: MS is a frequent feature of early RA. It has an impact on quality of life and physical function that is independent of disease activity. Interventions directed at reduction of MS may have added value.

References:

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Complementary and Alternative Medicine Use in African Americans with Rheumatoid Arthritis. Ashutosh Tamhane[1], Gerald McGwin[1], David T. Redden[1], Elizabeth Brown[2], Andrew Westfall[1], Richard J. Reynolds[1], Laura B. Hughes[1], Doyt L. Conn[3], Beth L. Jonas[4], Edwin A. Smith[5], Richard D. Brasington[6], Larry W. Moreland[7], S. Louis Bridges Jr.[8] and Leigh F. Callahan[9]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Univ of Alabama at Birmingham, Birmingham, AL, Birmingham, AL, [3]Emory Univ School of Medicine, Atlanta, GA, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]Med Univ of South Carolina, Charleston, SC, [6]Washington Univ School of Med, St. Louis, MO, [7]University of Pittsburgh, Pittsburgh, PA, [8]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [9]University of North Carolina, Chapel Hill, NC

Background/Purpose: Use of Complementary and Alternative Medicines (CAM) for rheumatoid arthritis (RA) has been increasing in the United States. Racial/ethnic differences with regard to CAM use have been reported but data on African-Americans (AAs) are limited. The study aimed to report the prevalence of CAM use in AAs with RA and compare the practices of those with late (>2 yrs) versus early (≤2 yrs) disease duration.

Methods: Self-reported data on CAM use (16 treatments, 9 activities, 5 providers) at enrollment was analyzed from the CLEAR registry.

Results: Of the 855 patients enrolled 85% were female and 418 (49%) had early disease. In late RA patients ever use of any of the CAM activities, treatments or providers was reported in 96%, 99%, and 51%, respectively and in early RA patients in 94%, 97%, and 51%, respectively. The most common treatment, activity, and CAM providers were heat treatment (80%), praying/attending church services (92%), and religious leaders (32%), respectively. Moderate (odds ratio ≥2) and significant ($p<0.05$) associations were observed for those with late disease and treatments such as ever using fish oils, or raisins soaked in gin while weak significant associations were observed for ever using household oils, heat treatments, gelatin, garlic, magnets, and special jewelry. Similarly, moderate significant association was observed for late disease and drinking alcohol. Those with late disease were significantly more likely to consult chiropractitioner but less likely to have visited religious leader.

Conclusion: Overall, CAM use was highly prevalent in this cohort.

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Effect of Treatment of Hypogonadism On Rheumatoid Arthritis In Male Veterans. Farah Mahmood, Robert W. McMurray and Dannette S. Johnson. G.V. Sonny Montgomery VA Medical Center and University of Mississippi Medical Center, Jackson, MS

Background/Purpose: It has been observed in previous studies that rheumatoid arthritis (RA) in male patients can affect the pituitary and hypogonadal axis. Men with RA have been shown to have a high incidence of testosterone deficiency. Low testosterone (T) can also predispose these patients to have more severe disease. We investigated the effect of hypogonadism therapy on rheumatoid arthritis activity in male patients.

Methods: In a subpopulation of the Veterans Affairs Rheumatoid Arthritis (VARA) registry, a group of men with a diagnosis of RA were previously found to be hypogonadal (total serum T < 250 ng/dl). Several of these men underwent treatment of their hypogonadism with testosterone replacement therapy (TRT) of testosterone cypionate 200mg IM every 8 weeks. Assessment of RA activity and treatment monitoring included: patient and physician global scores, tender and swollen joint counts, liver function tests, CBC, ESR and CRP. TRT monitoring assessments included: 30-second chair rise, 50-feet walk test, measurement of grip strength, Aging Male Symptoms (AMS) scale, as well as testosterone, prolactin, LH, and FSH measurements. The relationship of testosterone therapy on RA was evaluated using student's t-test and Wilcoxon matched-pairs test with Bonferroni correction ($\alpha=0.02$).

Results: The men with RA receiving TRT (n=14) had the following characteristics: 100% RF positive, age = 66.5 years (range 40–86 years), duration of disease = 14 years (range 2–31 years), mean T = 214 53 ng/dl. With TRT, 100% of patients had a decreased 50-foot walk time, 85% increased their 30-second chair rise, 92% decreased their DAS28, 50% had decreased CRP levels and 92% had decreased ESR. At 16 weeks of therapy, 50 % of patients met DAS28 remission criteria (DAS28<2.6). There was no significant change in RA therapy. There was a trend towards improvement in LH and FSH scores in almost 50% of patients. No adverse side effects of TRT were reported.

MEASURE (mean±SEM)	TIME (weeks) 0	8	16	P value (0–8 wks)	P value (0–16 wks)
Serum T (ng/dl)	213.4 ± 14.2	205 ± 25.9	310.9 ± 57.5	0.7	0.03
DAS28	3.8 ± 0.3	2.9 ± 0.3	2.6 ± 0.2	0.0002	0.0014
MD-HAQ	1.1 ± 0.1	1 ± 0.1	0.9 ± 0.1	0.5	0.3
Patient Global (mm)	44.2 ± 7.8	35.1 ± 4.8	33.8 ± 5.6	0.3	0.6
Physician Global (mm)	33.2 ± 6.4	23.7 ± 3	23.6 ± 3.9	0.15	0.3
ESR (mm/hr)	29.2 ± 5	22.2 ± 5	21.9 ± 6	0.4	0.017
CRP (ng/ml)	0.7 ± 0.2	0.4 ± 0.1	1.9 ± 1	0.09	0.9
HCT (%)	40.0 ± 1	41.2 ± 1.1	41.1 ± 1	0.09	0.1
50-Foot Walk (secs)	30 ± 2	22 ± 2	19.5 ± 2	0.0014	0.0011
30-sec chair (times)	8.3 ± 0.5	9.1 ± 0.5	10.8 ± 0.7	0.178	0.05
Grip–Right (mmHg)	55.5 ± 6.7	61.4 ± 6.6	86.07 ± 9.0	0.4	0.009
Grip–Left (mmHg)	56 ± 6.5	59.4 ± 6.4	78.9 ± 10.5	0.5	0.018
AMS Score	39 ± 3.4	31 ± 2.4	27.9 ± 2.7	0.0016	0.0017

Conclusion: In our population, TRT significantly improved RA disease activity and function in hypogonadal men with established RA. Symptoms of RA and hypogonadism overlap; men with RA should be screened for hypogonadism and TRT should be considered. Further investigation is needed to elucidate the aspects of immunoendocrine regulation of RA.

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Extra-Articular Manifestations of Rheumatoid Arthritis in An Ethnically Diverse Cohort: Prevalence and Clinical Associations. Nicole C. Richman[1], Jinoos Yazdany[1], Jonathan D. Graf[2], Vladimir Chernitskiy[1] and John B. Imboden[3]. [1]University of California San Francisco, San Francisco, CA, [2]Univ of Calif-San Francisco, San Francisco, CA, [3]University of California, San Francisco, CA

Background/Purpose: Prior studies report the prevalence of extra-articular manifestations of rheumatoid arthritis (ExRA) in predominantly Caucasian patients with rheumatoid arthritis (RA). The purpose of this study was to determine the prevalence and clinical associations of ExRA in an ethnically diverse, U.S. cohort of patients with RA.

Methods: This retrospective study analyzed 275 patients with RA seen at a public hospital between 2006 and 2010. All patients met the 1987 ACR criteria for RA. Outpatient records were reviewed to determine the presence of ExRA, including peripheral nodules, interstitial lung disease, serositis, scleritis, myocarditis, vasculitis, Felty's syndrome, large granular lymphocyte syndrome, and amyloid. A chi-squared test, t-test, or Fisher's exact test was used to determine whether or not there were differences in terms of sociodemographics (age at RA diagnosis, gender, and ethnicity), and clinical characteristics (rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and radiographic changes on radiographs of the hands and feet) in patients with and without ExRA. Multivariate logistic regression was then used to examine the association between the same sociodemographics, clinical characteristics, and the presence of ExRA.

Results: We studied 129 (47%) Hispanic, 97 (35%) Asian, 27 (10%) African American, and 20 (7%) Caucasian patients with RA. The prevalence of ExRA was 21%. Peripheral nodules and interstitial lung disease were seen in 16.9% and 3.2% of patients respectively. Scleritis, pleural effusions, and pyoderma gangrenosum were seen in ≤1% of our patients. Other forms of ExRA were not observed. The prevalence of ExRA was significantly higher amongst Hispanic patients compared to Asian patients (27% vs. 13% p< 0.001). Patients with ExRA were more likely to be male (24% vs 11% p= 0.007) and positive for serum rheumatoid factor (RF) (97% vs 79% p= 0.003). In the adjusted model, RF positivity was shown to be associated with ExRA (OR= 10.9; 95% CI 2.16 to 55). Hispanic and Asian ethnicity were not shown to be associated with ExRA in the adjusted model. Age at RA diagnosis (46.7 years vs. 45.7 years), the presence of anti-cyclic citrullinated peptide antibodies (79% vs 76%), and radiographic changes on radiographs of the hands and feet (77% vs. 68%) were not significantly different in patients with and without ExRA.

Conclusion: ExRA in an in our cohort had a prevalence of 21% and manifested largely as peripheral nodules and interstitial lung disease. While ExRA was significantly more prevalent amongst Hispanic patients compared to Asian patients in our cohort, ethnicity was not associated with the development of ExRA in our adjusted analysis. Patients with ExRA were more likely to be RF positive and male, compared to patients without ExRA.

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Frequency and Clinical Characteristics of Osteoporosis in Patients with Rheumatoid Arthritis - a Comparison with Healthy Subjects. Seung Geun Lee[1], Young Eun Park[1], Seong Hu Park[2], Sung Il Kim[3], Seung Hoon Baek[4], Geun Tae Kim[5], Joung Wook Lee[6] and Jun Hee Lee[7]. [1]Pusan National University Hospital, Busan, South Korea, [2]Pusan, South Korea, [3]Pusan National University Hospital, Busan, South Korea, [4]Pusan National University Yangsan Hospital, Yangsan, South Korea, [5]Kosin University Gopsel Hospital, Pusan, South Korea, [6]Busan St. Mary's Medical Center, Busan, South Korea, [7]Ilsin Christian Hospital, Pusan, South Korea

Background/Purpose: To compare bone mineral density (BMD) and the frequency of osteoporosis between patients with the rheumatoid arthritis (RA) and healthy subjects and to determine risk factors for bone loss in female patients with RA.

Methods: In a cross-sectional study, clinical and demographic data were collected retrospectively from 317 patients with seropositive RA and 264 age- and sex-matched healthy subjects. BMD in the lumbar spine, femoral neck and total hip was measured with Dual-energy x-ray absorptiometry. A T-score of −2.5 or lower in postmenopausal women and men age 50 and older was defined as "osteoporosis", and a Z-score −2.0 or lower in females prior to menopause and males younger than age 50 was defined as "below the expected range for age" by WHO classification.

Results: The frequency of osteoporosis in the patients with RA was 18.5% at the lumbar spine, 7.1% at the femoral neck and/or total hip, and 22.0% in at least one of the evaluated sites and was significantly higher than in healthy subjects (18.5% vs 9.7%; p-value = 0.026, 7.1% vs 1.3%; p-value = 0.010, 22.0% vs 10.4%; p-value = 0.005). The occurrence of below the expected range for age in the patients with RA was also significantly higher than in the healthy subjects (8.7% vs 0.9%; p-value = 0.006). In 299 female patients with RA, age and body mass index (BMI) were significantly associated with the lumbar spine, femoral neck, and total hip BMD (age: $\beta = -0.005$; p-value < 0.001, $\beta = -0.003$; p-value = 0.005, $\beta = -0.003$; p-value = 0.012, BMI: $\beta = 0.016$; p-value < 0.001, $\beta = 0.011$; p-value < 0.001, $\beta = 0.014$; p-value < 0.001). Postmenopausal status was also related to decreased lumbar spine BMD ($\beta = -0.067$; p-value = 0.009). Of disease-related variables, the use of glucocorticoids, not the cumulative dose of glucocorticoids, was independently associated with reduction of total hip BMD ($\beta = -0.037$; p-value = 0.040).

Table 1. Clinical characteristics of the patients with RA and the healthy subjects

	Healthy subjects (n=264)	RA patients (n=317)	p-value
Male: Female	18: 246	18: 299	0.570
Age (years)	51.3 ± 9.4	52.8 ± 9.9	0.060
BMI (kg/m^2)	22.8 ± 2.9	22.6 ± 3.2	0.559
Median Disease duration (months)	NA	25.0 (IQR 6.0–94.0)	–
Median ESR (mm/hour)	NA	41.0 (IQR 19.0–77.0)	–
Median CRP (mg/dL)	NA	0.49 (IQR 0.12–1.77)	–
Number of GCs ever users (%),	NA	34.1	–
Cumulative GCs of dose (mg) of ever user	NA	2303 (367.5–5355)	–
Number of DMARDs users (%)	NA	97.8	–
Number of biologic agents users (%)	NA	1.3	–
Number of bisphosphonate users (%)	NA	24.3	–
L2-4 Spine			
BMD (g/cm^2)	1.13 ± 0.18	1.02 ± 0.17	<0.001
Z-score	0.39 ± 1.19	−0.24 ± 1.20	<0.001
T-score	−0.02 ± 1.38	−0.79 ± 1.42	<0.001
Femoral neck			
BMD (g/cm^2)	0.89 ± 0.12	0.83 ± 0.14	<0.001
Z-score	0.49 ± 0.94	0.34 ± 1.00	0.065
T-score	−0.24 ± 1.04	−0.67 ± 1.20	<0.001
Total hip			
BMD (g/cm^2)	0.96 ± 0.13	0.85 ± 0.14	<0.001
Z-score	0.57 ± 1.02	0.26 ± 1.00	<0.001
T-score	0.09 ± 1.02	−0.41 ± 1.15	<0.001

RA = Rheumatoid arthritis; BMI = Body mass index; NA = not accessible; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein; GCs = Glucocorticoids; DMARD = Disease modifying anti-rheumatic drug; BMD = Bone mineral density

Table 2. Multivariable regression analysis of BMD in the 299 female patients with RA

	L2-4 spine BMD (g/cm^2)		Femoral neck BMD (g/cm^2)		Total hip BMD (g/cm^2)	
	β	SE	β	SE	β	SE
Age (years)	−0.005*	0.013	−0.003**	0.001	−0.003**	0.012
BMI (kg/m^2)	0.016*	0.003	0.011*	0.003	0.014*	0.003
Postmenopause	−0.067**	0.026	−0.031	0.020	−0.017	0.0002
ESR (mm/hr)	−0.0002	0.0002	0.0001	0.0002	−0.0002	0.0001
Disease duration (months)	0.0001	0.0001	−0.001	0.0001	6.66^{-6}	0.018
GCs ever user	−0.035	0.214	−0.032	0.017	−0.037**	0.022
Bisphosphonate use	−0.112*	0.026	−0.090*	0.021	−0.099*	0.073
R^2	0.406		0.310		0.307	

BMD = Bone mineral density; RA = Rheumatoid arthritis; BMI = Body mass index; ESR = Erythrocyte sedimentation rate; GCs = Glucocorticoids
* p-value < 0.001
** p-value < 0.005

Conclusion: The prevalence of osteoporosis in the patients with RA was 2.2 times higher than in the healthy subjects, and glucocorticoids use was a risk factor for generalized bone loss in the female RA patients.

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Low Vitamin D in Rheumatoid Arthritis Is Associated with Significant Limitations in Social Functioning. Susan J. Bartlett[1], Kevin R. Fontaine[2], Clifton O. Bingham[3] and Uzma J. Haque[4]. [1]McGill University, Montreal, QC, [2]John Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD, [4]Johns Hopkins Hospital, Baltimore, MD

Background/Purpose: Low vitamin D has been with linked increased disease activity, pain and disability in rheumatoid arthritis (RA). Little is known about the impact of low vitamin D in RA on participation in recreational and leisure activities (i.e., socializing and social function).

Methods: Data are drawn from the baseline visit of an RCT to assess the effect of vitamin D repletion in RA patients. Patients meeting 1987 ACR

criteria for RA and seen in a tertiary care clinic were consecutively approached during routine clinic visits from Jan 2009 through April 2011. Joint counts and evaluator disease activity assessments were performed and CDAI scores were calculated as an indicator of disease activity. Patients completed the HAQ, SF-12 and other selected questionnaires. 25(OH)D levels were measured by one laboratory using the DiaSorin radioimmunoassay. Multivariate linear regression was used to assess relationships among SF-12 social function (SF) and clinical and patient reported disease activity markers, disability and 25(OH)D.

Results: Participants (N=139) were mostly female (79.9%) and white (79.1%) with a mean ± SD age of 53.4 ± 12.3 yrs, body mass index (BMI) of 30.5 ± 6.9 m/kg^2 and disease duration of 10.0 ± 9 yrs. Mean 25(OH)2 levels were 28.3 ± 11.1 ng/mL (range 6.3 – 72.8); 60% had 25(OH)D levels < 30 ng/mL, and 21% ≤ 20 ng/mL. As compared with all others, patients with 25(OH)D ≤ 20 ng/mL had higher BMIs (29.8 ± 6.0 vs. 33.6 ± 9.5, respectively) and CDAI scores (9.6 ± 10.7 vs. 19.1 ± 15.6)(all p's<.03) but did not differ by age, sex, race or education. Mean SF was 48.2 ± 9.9 (range 16.2–56.6), significantly lower than population norms. In model 1 (adjusted for sex, BMI and disease duration), CDAI, HAQ, AM stiffness and pain were moderately and inversely related to SF; vitality and 25(OH)D were directly related to SF. In model 2 (fully adjusted), 25(OH)D remained a significant predictor of SF. Together, these factors accounted for a substantial amount of the variance in SF (F=13.97, p <.001; adj r^2=.56).

Table 1. Predictors of Social Function in Patients in with Rheumatoid Arthritis.

	Model 1* β	Model 2** β
CDAI	−.377†	−.167†
HAQ	−.572†	−3.286‡
25(OH)D (ng/mL)	.317‡	.135$^{\neq}$
SF12-Vitality	.573†	.349$^{\neq}$
Pain (100 mm VAS)	−.572†	−.109$^{\neq}$
Morning stiffness (min)	−.446†	−.008$^{\neq}$

*Adjusted for sex, BMI and disease duration; **Fully adjusted model; †p≤.001; ‡p≤.01; $^{\neq}$p≤.05.

Conclusion: Socializing and activity limitations have been previously reported in established RA. These data suggest that low vitamin D may also play an independent role in limiting normal social activities with friends, family, neighbors and other groups beyond disease activity, disability and patient-reported symptoms such as fatigue, pain and morning stiffness. The mechanism is unclear. Studies to evaluate the effect of repleting/maintaining adequate levels of vitamin D on RA on disease activity, symptoms and function are ongoing.

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Ocular Complication and Its Association with Disease Characteristics and Treatment Responses in a Cohort of 295 Rheumatoid Arthritis Patients. Zejin Zhu[1], Paul Maranian[2] and Harold E. Paulus[1]. [1]University of California, Los Angeles, Los Angeles, CA, [2]University of California, Los Angeles

Background/Purpose: To assess the prevalence of ocular complication and its association with disease characteristics and treatment responses over time in a disease-modifying antirheumatic drug (DMARD)-naive seropositive early rheumatoid arthritis (RA) cohort.

Methods: 295 patients with polyarticular disease who were DMARD-naive and had seropositive early RA (< 14 months) were recruited by the Western Consortium of Practicing Rheumatologists. Each patient was examined at study entry, 6 and 12 months, and yearly thereafter. Clinical, radiographic data, and ocular manifestation (keratoconjunctivitis sicca, xerostomia, episcleritis, scleromalacia, uveitis, salivary gland hypertrophy), presence of RA nodule, and serology markers were collected. We investigated the difference in baseline disease characteristics and treatment response in the presence or absence of eye manifestation.

Results: At baseline, 36 patients (12.2%) presented with ocular manifestation. Baseline disease characteristics were similar in the groups of RA patients with or without eye involvment. Patients with biologic DMARDs use was excluded from this study. Despite similar treatment, patients with ocular manifestations had worse disease progression over the 2-year follow up, as assessed by changes in Disease Activity Score 28/erythrocyte sedimentation rate (DDAS28-ESR4), changes in erosion score and joint space narrowing score. We also grouped the patients with Ksicca/xerostomia and/or salivary gland hypertrophy together to assume a diagnosis of secondary Sjogren's syndrome, and found this group of patients with worse disease progression and less response to DMARD therapy. The presence of rheumatoid nodules does not appear to predict the presence of ocular inflammation.

Conclusion: Ocular manifestation is not rare in rheumatoid arthritis; secondary sjogren's syndrome is by far the most prevalent ocular commorbidity. At baseline, early RA patients with or without eye manifestation had similar disease activity and joint damage. Responses to treatment over time were worse among patients with ocular manifestation in this cohort of patients treated with non-biologic DMARDs, despite similar treatment. We propose that aggressive treatment may be implicated in early RA patients with eye involvement to achieve better outcome.

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Role of Body Composition Phenotypes and Adiposity in Disease Activity, Endothelial Dysfunction and Radiological Damage in Rheumatoid Arthritis Patients. Esmeralda Delgado-Frías[1], Vanesa Hernandez-Hernandez[1], Ivan Ferraz-Amaro[1], Jose A. Garcia-Dopico[2], Lilian Medina[2], Antonieta Gonzalez-Diaz[3], Maria A. Gomez- Rodriguez-Bethencourt[3], Jose Ramon Muñiz[4], Ana I. Rodriguez-Vargas[1], M. Jesus Dominguez-Luis[1], M.Teresa Arce-Franco[1], M. Angeles Gantes-Mora[1] and Federico Diaz-Gonzalez[1]. [1]Servicio de Reumatología, Hospital Universitario de Canarias, La Laguna, Spain, [2]Servicio de Laboratorio Central, Hospital Universitario de Canarias, La Laguna, Spain, [3]Servicio de Medicina Nuclear, Hospital Universitario de Canarias, Spain, [4]Resonancia Magnética. IMETISA. Hospital Universitario de Canarias

Background/Purpose: The amount and distribution of fat and lean mass have important implications for health, and systemic inflammation may represent a risk for altered body composition. Rheumatoid arthritis (RA) is associated with changes in body composition and these changes may be factors potentially contributing to affect disease characteristics like endothelial dysfunction or radiological damage.

Methods: A total of 85 women, 44 RA patients and 41 age-matched controls were included in this cross-sectional study. Standards anthropometric measures were calculated. Demographic data, the 28-joint DAS (DAS-28) and disability using HAQ scores, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were collected. Quantification of visceral and subcutaneous abdominal fat area was determined using magnetic resonance imaging. Total and regional lean mass and fat mass were measured with dual energy X-ray absorptiometry. Lean mass of arms and legs, total body fat mass, truncal fat distribution, fat-free mass index, and presence or absence of sarcopenia and overfat were established. Radiological progression was defined in RA patients by the Sharp score. Endothelial dysfunction was assessed in patients and controls by brachial artery flow-mediated dilation (FMD) as the dilator response to 5 minutes distal cuff occlusion, and after sublingual nitroglycerine administration.

Results: RA patients showed endothelial dysfunction bias an inferior brachial artery FMD (6.3 vs 10.8 mm, p=0.03). Visceral and subcutaneous abdominal fat areas were not different between RA patients and controls when adjusted for age and body mass index. Abdominal fat through resonance imaging was not associated with endothelial dysfunction, DAS28, ESR, CRP or Sharp score. Only HAQ show a trend to be negatively related with subcutaneous abdominal fat (r^2=-0,358, p=0.07). Regard DEXA body composition parameters, overfat states tend to be more frequent in RA patients (chi^2=3.26, p=0.07). Disease duration was associated with an inferior fat mass (β coefficient −0.310 kg/years, p=0.03) and with changes in apendicular/truncal phenotypes: higher apendicular fat mass (r^2=0.41, p=0.01) and lower truncal fat mass (r^2=−0.40, p=0.02). Radiological damage through Sharp score was negatively correlated with fat free index and total lean mass (r^2=−0.39, p=0.04) showing that patients with fewer lean mass had higher radiological damage (adjusted for disease duration). This radiological damage was not associated with a specific apendicular or truncal fat mass phenotype. When patients were categorized as sarcopenic or not sarcopenic, radiological damage tends, in addition, to be high in the first group (26.0 vs 10.5 units, p=0.08). FMD was correlated with DAS28 but do not seem to be associated with any body composition phenotype. In our study endothelial dysfunction was not correlated with radiological damage.

Conclusion: Disease activity, radiological damage and disability scores are associated with unhealthy body composition in RA patients. Changes in body composition are partly explained by RA inflammation and these may influence the disease itself.

2135

Ultrasound Screening for Intestinal Lung Disease in Rheumatoid Arthritis. Sonja Kielhauser[1], Florentine Fuerst[1], Kerstin Brickmann[1], Peter Zechner[2], Norbert J. Tripolt[3] and Winfried B. Graninger[4]. [1]Med Univ Klinik Graz, Graz, Austria, [2]Cardiology, Graz, Austria, [3]Diabetology, Graz, Austria, [4]Medical University Graz, Graz, Austria

Background/Purpose: In rheumatoid arthritis (RA) patients, the occurrence of interstitial lung disease (ILD) is associated with an increased mortality due to loss of diffusion capacity and pulmonary hypertension. Thus regular screening for structural abnormalities of the lung is advised. In addition to standard radiological examination with computed x-ray tomography, ultrasound of the lung could serve as a non invasive and radiation-free ways of structural monitoring of the lung. We tested the reliability of lung sonography for the assessment of patients with RA who did not have clinical signs or symptoms of lung disease.

Methods: In a pilot study involving 64 patients with rheumatoid arthritis and 40 healthy volunteers, we screened the pleura and the pulmonary parenchyma for sonographic abnormalities. Patients with abnormal sonographic patterns were subjected to computed tomography of the chest.

Results: 28% of RA patients showed pleural nodules or B-line phenomena. In all of these patients CT scans showed signs of incipient interstitial lung disease. In 7% of the healthy controls, sporadic abnormalities were depicted by sonography. In this small study the use of methotrexate or TNF inhibitors was more frequent in the group of RA patients with radiographic and sonographic signs of interstitial lung disease.

Conclusion: Transthoracic ultrasound of the lung is suggested as a cheap and safe tool to screen patients with RA for incipient pulmonary structural changes.

2136

Genetic Predisposition of the Severity of Joint Destruction in Rheumatoid Arthritis; A Population Based Study. R. Knevel[1], Gerður Gröndal[2], Tom W.J. Huizinga[1], A. Willemien Visser[1], Helgi Jónsson[2], Arnór Víkingsson[2], Árni Jón Geirsson[2], Kristjan Steinsson[2] and Annette H.M. van der Helm-van Mil[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Landspítali, National University Hospital Center for Rheumatology Research, Reykjavik, Iceland, Reykjavik, Iceland

Background/Purpose: The severity of Rheumatoid Arthritis (RA), generally measured by joint destruction, is highly variable between patients. Factors driving these inter-individual differences are unknown. The susceptibility to RA is partly heritable, whether the severity of RA is also influenced by genetics is not determined. Evaluation on the heritability of the severity of RA is basic to further studies on genetic factors. Estimating this genetic predisposition requires accurate information on the family nature of the studied patients. The objective of this study was to evaluate whether the severity of joint destruction in RA is heritable.

Methods: Iceland has a nation-wide unique genealogical database of 10 centuries and genome wide genetic data available of a large part of the population. The majority of the Icelandic RA population lives in the area of Reykjavik. We studied RA patients included in the RA research cohort of the Reykjavik National Hospital. 325 patients had complete radiographs of hand and feet (median disease duration of 10 years) and genealogic information. Of 267 patients genome wide genetic data were present. Radiographs were scored using the Sharp-van der Heijde method blinded to clinical data or data of relatedness and the yearly progression rate was assessed. The degree of relatedness between patients was estimated two-folded. First kinship coefficients (KC) on the genealogic data were expressed. Second the identical-by-descent (IBD) was estimated applying long-range phasing on the genetic profile of the patients.

Results: Significant associations between degree of relatedness and similarity in joint destruction rates were observed, for both methods of determining relatedness (P_{KC}=0.018, P_{IBD}=0.003). The estimated heritability was 45% using KC and 58% using the estimated IBD data.

Conclusion: The severity of joint destruction in RA is influenced by genetic factors.

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Longitudinal Determinants of Disability in Vulnerable United States Hispanics with Rheumatoid Arthritis. George A. Karpouzas[1], Soha Dolatabadi[2], Ning Li[2], Rosalinda C. Moran[3], Perry M. Nicassio[4] and Michael H. Weisman[5]. [1]Harbor-UCLA, Torrance, CA, [2]Cedars Sinai Medical Center, Los Angeles, CA, [3]Harbor UCLA Medical Center, Carson, CA, [4]UCLA, Los Angeles, CA, [5]Cedars Sinai Med Ctr, Los Angeles, CA

Background/Purpose: United States Hispanics with Rheumatoid Arthritis (RA) experience worse functional outcomes and quality of life compared to Caucasians. The determinants of disability however are not well established in large cohorts. In the present report we identified predictors of disability in a cross-sectional design, and validated their significance and contributions in a longitudinal design.

Methods: Two hundred and fifty one US-based Hispanics with RA from a single center were cross-sectionally evaluated. Disease activity (DAS28-3v-ESR), serologies, radiographs, treatments, Irreversible articular damage (IAD-defined as subluxation, arthrodesis, fusion, or prosthesis) and joint replacement surgeries (JRS) were recorded. Self-reported disability (Health Assessment Questionnaire Disability Index- HAQ-DI), patient- pain by visual analogue scale (pain-VAS), and depression (Physician Health Questionnaire-PHQ-9) were collected. Predictors of disability were identified using exploratory linear regressions with a forward selection based on observed significance level. Their impact over time was validated longitudinally in 114 patients with a subsequent clinical visit 6 months later, using linear mixed effects models; the predictors entered into the model as time-dependent covariates.

Results: Seven parameters were identified in the cross-sectional phase as determinants of disability (table); in decreasing order of significance, those included pain, IAD, disease activity, depression, JRS, fibromyalgia and age. In the longitudinal analysis, five of the seven parameters remained predictive. Again, patient-reported pain was the most significant, followed by depression, IAD, disease activity, and age. Disease activity and Disability at time 1 were highly correlated with themselves at time 2 (correlation coefficient r=0.61 and 0.6 respectively, p<0.0001 for both), while such correlations were weaker for pain and depression (r=0.33 and 0.48 respectively, p<0.001 for both).

	b	95% CI	p-value
Cross-sectional Phase (N=251)- Multivariable analysis			
Pain-VAS	0.33	(0.21, 0.45)	<0.0001
IAD	0.37	(0.18, 0.56)	0.0001
DAS28-3v-ESR	0.14	(0.06, 0.21)	0.0003
PHQ-9	0.03	(0.01–0.04)	0.0005
JRS	0.48	(0.14–0.81)	0.0054
Fibromyalgia	0.3	(0.06, 0.54)	0.0129
Age	0.01	(0.002–0.02)	0.0178
Longitudinal Phase (N=114)- Multivariable analysis			
Pain-VAS	0.31	(0.21, 0.41)	<0.0001
PHQ-9	0.03	(0.02–0.05)	<0.0001
IAD	0.35	(0.12, 0.57)	0.0029
DAS28-3v-ESR	0.09	(0.02, 0.17)	0.0168
Age	0.01	(0.002–0.02)	0.0227

Conclusion: Self-reported pain is the most important longitudinal predictor of disability in vulnerable US Hispanics with RA, followed by depression, IAD, disease activity, and age. All, except age, are amenable to targeted interventions and should be addressed in an effort to limit disability in these patients.

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Smoking Impact on Radiographic Progression in An Early Rheumatoid Arthritis Cohort. Virginia Ruiz-Esquide[1], Jose Alfredo Gomez Puerta[2], S. Cabrera[1], J. D. Cañete[3], M. V. Hernandez[2], Eduard Graell[4], Guadalupe Ercilla[1], Odette Viñas[1], M. J. Gómara[5], Isabel Haro[5] and Raimon Sanmarti[2]. [1]Hospital Clinic of Barcelona, Barcelona, Spain, [2]Hospital Clinic of Barcelona, Barcelona, Spain, [3]Hospital Clínic de Barcelona,, Barcelona, Spain, [4]Hospital Parc Tauli, Sabadell, Spain, [5]IQAC-CSIC, Barcelona, Spain

Background/Purpose: Smoking is a known predictor of rheumatoid arthritis (RA), but its effect in radiographic progression is still controversial.

To investigate the effects of cigarette smoking on radiographic progression in an early RA cohort two years after the beginning of DMARD therapy.

Methods: One hundred and fifty six patients (83% female) with early RA (disease duration < 2 years) treated with a similar therapeutic strategy with DMARDs and low-dose glucocorticoids were included. Several demographic, genetic (DRB genotype), clinical, laboratory and radiographic data were obtained at baseline and after one and two years of follow-up. Smoking was evaluated at study entry and patients were classified as past smokers, current smokers and non-smokers. Radiographic progression after one and two years of follow-up was evaluated in hand and feet radiographs using the erosion joint count (EJC) and Larsen-Scott score. Multivariate lineal regression analysis was performed.

Results: The frequency of current, past and non-smokers were 30.1%, 12.2% and 57.7% respectively. Only 14% of patients were heavy smokers (> 20 pack/year). Radiographic damage at one and two years was higher in current smokers compared with non-smokers, although only in the EJC at two years the difference was statistically significant (1.2±1.7 vs. 0.7±1.7, p=0.04). The Larsen score at two years was higher in current smokers than in non-smokers although the difference was not significant (7.4±12.9 vs. 4.2±6.7, p>0.05). In the univariate analysis taking Larsen-Scott score as the measure of radiographic damage, female sex, higher HAQ at disease onset, the presence of anticitrullinated antibodies, the shared epitope (SE) and the HLA-DRB*04 had a significant effect on radiological score. In the multivariate regression analysis adjusted for baseline radiographic damage, female sex, HLA-DRB*04 genotype and current smoking were independently associated with two year radiographic damage measured by the Larsen Score as well as with the EJC (Table). No significant differences were seen in clinical disease activity or rates of EULAR response at one and two years of follow-up between smokers and non smokers.

Table. Multivariate regression linear analysis for radiographic progression

Larsen-Scot score at 2 years	**B**	**SE**	**95% CI**	**p-value**
Smoking (past vs non smoker)	0.486	2.529	−4.52–5.49	0.848
Smoking (current vs non smoker)	4.274	1.910	0.49–8.05	**0.027**
Women	7.142	2.217	2.75–11.53	**0.02**
HLA-DRB*04 +	5.097	1.624	1.88–8.31	**0.002**
ECJ score at 2 years	**B**	**SE**	**95% IC**	**p-value**
Smoking (past vs non smoker)	−0.065	0.372	−0.8–0.67	0.861
Smoking (current vs non smoker)	0.603	0.282	0.05–1.16	**0.034**
Women	0.792	0.327	0.14–1.44	**0.017**
HLA-DRB*04 +	0.632	0.239	0.16–1.11	**0.009**

EJC: erosion joint count. B: regression coefficient SE: standard error. CI: confidence intervals.

Conclusion: In our early RA cohort, current smoking emerges as an independent factor for radiographic progression after two years of DMARDs.

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Environmental and Genetic Contributions to Disease Severity in North American Natives with Early Inflammatory Arthritis. Carol A. Hitchon, Christine A. Peschken, Trevor Mailley, Jillian Dooley, Peter Nickerson and Hani S. El-Gabalawy. University of Manitoba, Winnipeg, MB

Background/Purpose: North American Native (NAN) populations present with severe inflammatory arthritis at an early age. We sought to determine the influence of genetic predisposition as reflected by HLA DRB1 alleles and environmental factors such as smoking and socioeconomic status on the development and outcome of early inflammatory arthritis (EIA) in this group.

Methods: Patients with EIA (less than 1 year symptom duration: NAN =46 and nonNAN=269 (Caucasian =222,Metis =13 others =34) were assessed at baseline clinic visit. One year followup was available for 206 (NAN n=26 other n=174). Baseline disease activity (DAS28CRP3), functional status (mHAQ) and environmental exposures including self reported current smoking status, current alcohol use, a history of vaccination, flu-like illness, bacterial infection, travel, or trauma occurring within 6 months of symptom onset and socioeconomic status (years of education) were recorded. HLA-DRB1 alleles were determined by DNA sequencing. One year clinical outcomes included treatment response (EULAR criteria) and remission (DAS28CRP3<2.6).

Results: NAN were more likely to be current smokers (14/25 (56%) vs 53/216 (25%) p<0.001), less likely to use alcohol (7/18 (38%) vs 127/182 (70%) p<0.008) and had less formal education (7.9 vs 12.7 years p<0.0001). There were no significant differences between NAN and non-NAN in reported exposure to vaccines (3/12 vs 22/104), flu-like illness (3/12 vs 29/102), bacterial illness (2/12 vs 15/100) travel (2/12 vs 46/105) or trauma (1/11 vs 20/100). NAN were more likely to have any SE (30/39 (77%) vs 124/225 (55%) p<0.01) and less likely to have DERAA protective alleles (1/39 (3%) vs 40/225 (18%) p<0.015) than non-NAN. Smoking associated with ACPA in SE +ve subjects. In linear regression models predicting baseline DAS28CRP3 (included variables: years of school, smoking. any SE and DERAA) SE (B=0.5 p=0.02) and years of school (B=−0.05 p=0.02) were significant. At one year NAN were less likely to be in remission (6/26(23%) vs 83/174 (48%) p<0.02).In multivariate models including ethnic group, smoking (ever), education, and SE and DERAA, the presence of DERAA alleles were associated with remission (OR 3.2 CI 1.18–8.86, p<0.05).

Conclusion: In this cohort, environmental factors especially socioeconomic status as reflected by years of education is an important contributor to baseline disease activity. The presence of protective DERAA alleles is associated with a better clinical outcome.

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Discrepancies Between Expert Reading and Standard Radiograph Report in Identifying Boney Erosions and Joint Space Narrowing in Patients with Rheumatoid Arthritis in the Veterans Affairs Rheumatoid Arthritis Registry. Maria P. Martes[1], Alan Erickson[2], Ted R. Mikuls[3], Alyse D. Mann[4], Liron Caplan[5], Dannette S. Johnson[6], J. Steuart Richards[7], Gail S. Kerr[7], Andreas M. Reimold[8] and Grant W. Cannon[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Omaha VA and University of Nebraska Medical Center, Omaha, NE, [3]Omaha VA and University of Nebraska, Omaha, NE, [4]Denver VA and University of Colorado, Denver, CO, [5]Denver VA and University of Colorado, Aurora, CO, [6]Jackson VA and University of Mississippi Medical Center, Jackson, MS, [7]Washington DC VAMC and Georgetown University, Washington, DC, [8]Dallas VA and University of Texas Southwestern, Dallas, TX

Background/Purpose: The identification of radiographic changes—specifically boney erosions (BE) and joint space narrowing (JSN)—impacts the diagnosis and management of rheumatoid arthritis (RA). Little data addresses the validity of standard radiograph reports read by radiologists in identifying these key abnormalities. We compared standard radiograph reports in the Veterans Affairs (VA) computerized patient record system (CPRS) to the assessment by an expert reader (ER) trained to use the modified Sharp Score.

Methods: Bilateral hand X-rays of 302 RA patients enrolled in the Veterans Affairs RA (VARA) registry, a multi-center observational cohort, were assessed by an ER who noted the presence and absence of BE and JSN and quantified these abnormalities if present. A blinded chart abstracter (CA) reviewed the CPRS radiology report for the same X-ray and noted if BE or JSN were reported. CPRS reports that were discordant with ER findings were subjected to a second chart review by a different blinded CA. This review showed strong agreement with original CPRS chart interpretations (>95% for BE and >90% for JSN). Discrepancies between the two CPRS report reviews were adjudicated by a third independent CPRS reading. Demographic, clinical and radiographic features were compared in patients with discrepancies to patients with concordant readings in patients with BE and JSN by ER.

Results: The patients mean age was 64±11 years, 88% were male, RA disease duration was 13±11 years, and the majority was sero-positive for rheumatoid factor (84%) and anti-CCP (80%). As noted below, the two reading were concordant in 199 (66%) cases for BE and 180 (60%) cases for JSN. Only 77 (45%) patients with BE by ER and 112 (48%) patients with JSN by ER were not identified in the CPRS report by radiologists.

	Expert Reading				**Expert reading**		
CPRS reading	**Erosion(s)**	**No erosion**	**Total**	**CPRS reading**	**Narrowing**	**No Narrowing**	**Total**
Erosion(s)	96	26	122	Narrowing	122	10	132
No Erosion	77	103	180	No Narrowing	112	58	170
Total	173	129	302	Total	234	68	302
Sensitivity		55.5%		Sensitivity	52.1%		
Specificity		79.8%		Specificity	85.3%		
Positive Predictive Value		78.7%		Positive Predictive Value	92.4%		
Negative Predictive Value		57.2%		Negative Predictive Value	34.1%		

Neither concordant nor discordant reporting of BE or JSN in the CPRS report was associated with patient age, gender, disease duration, ethnicity, smoking history, serology, nor with most measures for clinical disease activity. Only CPRS noted BE was associated with high joint swelling counts (6.0±6.6 versus 4.0±5.0, p<0.05) at the time of X-ray. Comparison of the quantitative reading by the ER showed a higher likelihood of BE reporting in CPRS in patients with more severe BE (Chi square 21.3 p<0.001) and JSN (Chi square 9.6, p<0.05) scores; however no association was noted for the reporting of JSN in CPRS with severity of BE or JSN noted by ER.

Conclusion: These data show that there is underreporting of BE and JSN in routine CPRS radiograph reports of RA patients. While a positive

report in the CPRS can be considered valid, the absence of these findings does not possess sufficient validity to exclude the presence of BE and/or JSN. While the causes of discrepancy in radiographic findings require further study, current use of electronic medical records appears to have significant limitations.

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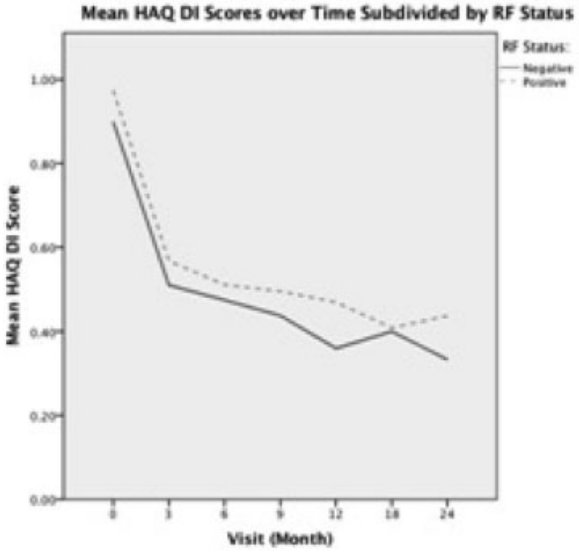
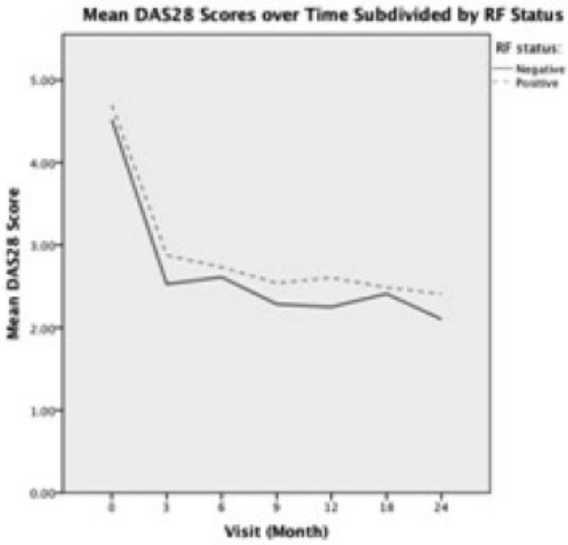
Function (HAQ) and Disease Activity (DAS) Varies by Rheumatoid Factor (RF) Status in Early Inflammatory Arthritis (EIA) with Stronger Associations in RF Positive Patients: Results From the CATCH Cohort. Tristan Boyd[1], Vivian Bykerk[2], Gilles Boire[3], Carol A. Hitchon[4], J. Carter Thorne[5], Edward Keystone[6], Boulos Haraoui[7], Diane S. Ferland[8], Janet E. Pope[9] and CATCH Investigators[10]. [1]University of Western Ontario, London, ON, [2]Brigham & Women's Hospital, Boston, MA, [3]CHUS - Sherbrooke University, Sherbrooke, QC, [4]University of Manitoba, Winnipeg, MB, [5]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [6]Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Mount Sinai Hospital, Toronto, ON, [7]Institut de Rhumatologie, Montreal, QC, [8]LaSalle, QC, [9]St. Joseph's Health Care, University of Western Ontario, London, ON, [10]Toronto, ON

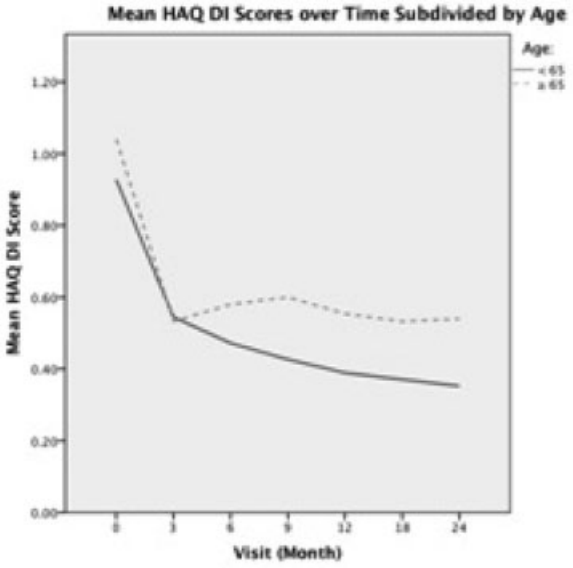
Background/Purpose: Our goal was to investigate the relationship between functional capacity and disease activity in early inflammatory arthritis (EIA) in a contemporary cohort and to determine if the correlations changed over time.

Methods: Data from patients (n=1,145) were collected from the Canadian Early Arthritis Cohort (CATCH), a multi-site observational cohort of EIA. HAQ and DAS28 were assessed at each visit. Correlations were done between HAQ and DAS every 3 months for the first year and then at 18 and 24 months. The relationship between HAQ and DAS in older and younger subjects (<65 versus ≥65) and in those who were RF positive or negative was studied.

Results: Mean symptom duration at first visit was 6.3 months. HAQ scores decreased over time from a baseline of 0.94 to 0.40 at 24 months (values were 0.55, 0.50, 0.47, 0.43, and 0.40 at 3, 6, 9, 12, and 18 months). Mean DAS28 scores also decreased over time from a baseline of 4.54 to 2.29 at 24 months (values were 2.72, 2.67, 2.44, 2.47, and 2.46 at 3, 6, 9, 12, and 18 months). Correlations between HAQ and DAS were significant at all time points ($p<0.01$) and varied over time. The strongest correlation between HAQ and DAS in the first 12 months occurred at the first visit (r=0.53, N=1,143), at which point many of the patients were untreated. At 6, 9, and 12 months the correlation was weaker (r=0.41, r=0.30, and r=0.40). Strong correlations were again noted at 18 months (r=0.57, N=321) and 24 months (r=0.59, N=214). The baseline correlation between HAQ and DAS was significantly different than correlations obtained at 3, 6, and 12 months ($p=0.02$, 0.01, and 0.01, respectively), but not statistically significantly different from values obtained at 18 and 24 months ($p=0.54$ and 0.43). Age did not change the association between HAQ and DAS {<65 years old (r=0.50, N=868) vs. ≥65 (r=0.48, N=254)}, but RF status did: RF+ relationship was larger than RF negative (r=0.63, N=636 vs. r=0.47, N=477).







Conclusion: Function and disease activity both improved after initiation of treatment and were related but in the first year most strongly linked at the first visit. Those with + RF had stronger associations.

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Progression of Joint Damage in a Rheumatoid Arthritis Cohort: Role of the HLA-DRB1 Shared Epitope. Jose Felix Restrepo[1], Inmaculada del Rincon[1], Daniel F. Battafarano[2] and Agustin Escalante[1]. [1]University of Texas Health Science Center, San Antonio, TX, [2]Brooke Army Medical Ctr, San Antonio, TX

Background/Purpose: A role for the HLA-DRB1 shared epitope (SE) in shaping the RA phenotype has long been suspected but not consistently observed. We used data from a large RA cohort to examine the association between the SE and the progression of joint damage, measured radiographically.

Methods: We recruited patients with RA attending a scheduled visit with a rheumatologist. We performed a comprehensive clinical evaluation, which include a radiograph of both hands and wrists. Patients were invited to attend annual follow-up visits which also included hand radiographs. These were scored for erosions and joint-space narrowing using the method developed by Sharp et al. We used generalized estimating equations (GEE) with the Sharp score as a dependent variable to examine association with joint damage. In particular, we tested SE × disease duration product terms to compare the rate of joint progression in patients with and without the SE.

Results: We recruited 779 RA patients. We obtained hand radiographs and typed for the SE in 718. Their median age was 57 (interquartile range 49, 64), disease duration 9 years (4, 17), and 509 were women (71%). These patients had 2,968 hand radiographs, or 4.1 films per patient, over 3,924 patient-years, or 5.5 years per patient. The mean Sharp score at the time of the

initial radiograph was 55 (range 0 to 294). It progressed at a rate of 4.5 Sharp units per year of RA duration (95% CI 4.3, 4.7). Among patients who did not have the SE, the rate of progression was 3.7 units per year (3.4, 4.1). In patients who were SE-positive patients, the progression rate was significantly more rapid, at 4.8 units per year (4.6, 5.0), $P \leq 0.001$.

Conclusion: These results suggest that joint damage progresses more rapidly among RA patients who have the SE than among patient who do not.

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Comparison of the Patient-Based Routine Assessment of Patient Index 3 in Usual Care of Rheumatoid Arthritis to the Physician-Based Disease Activity Score-28 Joint Count and Clinical Disease Activity Index. Daniel Lupash[1], Aarat M. Patel[2], Christine L. Amity[3], Lynne M. Frydrych[3], Derek Sippel[3], Donald M. Jones[3], Danielle Goudeau[3], Heather Eng[4], David Kyle[4], Melissa Saul[4], G.K. Balasubramani[4], Daniel H. Solomon[5], Stephen R. Wisniewski[4], Larry W. Moreland[1] and Marc C. Levesque[3]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr / Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [3]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [4]Univ of Pittsburgh, Pittsburgh, PA, [5]Brigham & Womens Hospital, Boston, MA

Background/Purpose: Studies support using quantitative measures of disease activity in the care of RA patients to improve patient outcomes. In addition, quantitative measures will soon be required by payers for full reimbursement for RA patient care. Despite Disease Activity Score-28 joint count's (DAS28) widespread use in clinical trials, it is challenging to use in clinical care because it requires a complex calculation, a blood test result (CRP or ESR), and a 28 joint assessment. Clinical Disease Activity Index (CDAI) avoids a complex calculation and ESR/CRP but still requires a 28 joint assessment. The Routine Assessment of Patient Index 3 (RAPID3) avoids these obstacles by assessing disease activity based on 3 patient-reported outcomes: physical function, pain, and global health status. This study compared RAPID3 as a measure of disease activity in the usual care of RA patients to DAS28 and CDAI.

Methods: 725 subjects in the University of Pittsburgh's Rheumatoid Arthritis Comparative Effectiveness (RACER) registry were evaluated. DAS28 was calculated using CRP. Correlations between DAS28, CDAI, and RAPID3 at a single visit were calculated. Next, comparisons of subjects classified by disease activity were performed. Finally, for 313 RA patients with follow-up visits, correlations were calculated for the change in DAS28, CDAI, and RAPID3 between visits.

Results: Spearman rank-order correlation results indicated that RAPID3 correlated with DAS28 (0.67, $p<0.001$) and CDAI (0.68, $p<0.001$) but not as strongly as CDAI correlated with DAS28 (0.93, $p<0.001$). RAPID3 and DAS28 categorization by disease activity were in agreement only 35% of the time, kappa score of 0.18. In contrast, CDAI and DAS28's categorization by disease activity were in agreement 54% of the time, kappa score of 0.41.

Table 1. DAS28 vs. RAPID3 Categorization of RACER Patients

	DAS28				
RAPID3	**Remission**	**Low**	**Moderate**	**High**	**Total**
Near Remission	102 (36%)	6 (6%)	9 (3%)	0 (0%)	117
Low	70 (24%)	15 (15%)	15 (6%)	4 (6%)	104
Moderate	74 (26%)	41 (42%)	85 (31%)	5 (7%)	205
High	41 (14%)	35 (36%)	161 (60%)	62 (88%)	299
Total	287	97	270	71	725

Kappa (95% CI) = 0.18 (0.17–0.19) (slight agreement)

Table 2. DAS28 vs. CDAI Categorization of RACER Patients

	DAS28				
CDAI	**Remission**	**Low**	**Moderate**	**High**	**Total**
Remission	96 (34%)	1 (1%)	0 (0%)	0	97
Low	174 (60%)	63 (65%)	27 (10%)	0	264
Moderate	17 (6%)	32 (33%)	164 (61%)	0	213
High	0	1 (1%)	79 (29%)	71 (100%)	151
Total	287	97	270	71	725

Kappa (95% CI) = 0.41 (0.37–0.44) (moderate agreement)

Of 287 subjects with a remission DAS28, only 102 had a near remission RAPID3 while 115 (40%) had a moderate or high RAPID3 (Table 1). When comparing these two groups, the 115 moderate to high RAPID3 patients had a higher Charlson Comorbidity Index (1.88 vs. 1.45, $p=0.002$) and lower SF-12 mental (47.38 vs. 52.03, $p<0.001$) and physical (34.5 vs. 49.1, $p<0.001$) health related quality of life than the 102 near remission RAPID3 patients; there were no differences in age, sex or disease duration between these groups. Pearson correlation results indicated that changes in RAPID3 between visits correlated significantly with changes in DAS28 (0.59, $P<0.001$) and CDAI (0.52, $p<0.001$) between visits, but not as strongly as changes in CDAI correlated with changes in DAS28 between visits (0.89, $p<0.001$).

Conclusion: DAS28 and CDAI were more strongly correlated than RAPID3 was correlated to CDAI or DAS28. Among subjects in DAS28 remission, 40% of subjects had discrepant RAPID3 and DAS28 associated with lower quality of life and more comorbidities. This suggests RAPID3 may lack specificity in a subset of RA patients as a measure of RA disease activity.

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Application of Ultrasound to Treat to Target Management of Rheumatoid Arthritis - Multicentre International Observational Experience. Sibel Aydin[1], Maya H. Buch[2], Sarah Horton[3], Kei Ikeda[4], Annamaria Iagnocco[5], Marwin Gutierrez[6], Walter Grassi[7], Esperanza Naredo[8], Eugenio De Miguel[9], Lene Terslev[10], Marina Backhaus[11], Maria-Antonietta D'Agostino[12], Alberto Batticciotto[2], Zunaid Karim[2], Richard J. Wakefield[13] and Paul Emery[14]. [1]Goztepe Training and Research Hospital, Istanbul, Turkey, [2]Leeds institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Disease Biomedical Research Unit, Leeds Teaching Hospitals, Leeds, United Kingdom, [3]Leeds institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Disease Biomedical Research Unit, Leeds Teaching Hospitals, United Kingdom, [4]Chiba University Hospital, Chiba, Japan, [5]Uni, Jesi, Italy, [6]Sapienza Universita di Roma, Rome, Italy, [7]Università Politecnica delle Marche, Jesi, Italy, [8]Hosptial Universitario Severo Ochoa, Madrid, Spain, [9]La Paz University Hospital, Madrid, Spain, [10]The Parker Institute, Copenhagen, Denmark, [11]Charite University Hospital, Berlin, Germany, [12]Versailles-Saint Quentin en Yvelines University-APHP, Ambroise-Paré Hospital, Boulogne-Billancourt, France, [13]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals, Leeds, United Kingdom, [14]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom

Background/Purpose: The recent formulation of 'treat to target' (T2T) recommendations on the management of rheumatoid arthritis (RA) (1) aim to improve patient outcomes. We aimed to investigate the additional role of ultrasound (US) to T2T clinical assessment.

Methods: An audit of 9 centres (8 countries) where musculoskeletal US is part of routine patient care was undertaken. Patients with active RA, requiring additional treatment and follow-up according to T2T recommendations were included. Clinical and US data were collected. US data from MCP 2–3, radiocarpal, intercarpal, MTP 5 joints and extensor carpi ulnaris tendon (where available) were analysed.

Results: At time of analysis, 93 patients had been audited. Baseline mean (SEM) characteristics included: Age 52.6 (15.5), disease duration 7.8 (11) years, DAS28 score 4.9 (1.5) and HAQ 2.4 (2.8). 78% were RF and 69%, ACPA positive. Thirty-five patients were on no DMARDS at baseline. At baseline, 81 % of patients had at least one joint PD signal.

The pre-defined disease activity target was achieved in 25% and 49% of patients at 3 and 6 months respectively. Therapy was modified in only 16–44 % of active patients; the main reason reported as "waiting for the previous treatment escalation to work" (13–76%) (Table 1).

At month 3, 50% of cases still had PD signal (38% PD≥2) in at least one joint despite achieving clinical target. Fifty percent of cases with clinical activity and PD signal did not receive any therapy modifications. Similarly at month 6, 53% of patients achieving clinical target still had PD signal in at least one joint with 20 % with PD≥2. Twenty-eight percent of patients received no treatment modification despite clinical disease activity and PD presence (Table 2).

Table 1. Summary of clinical assessments in each visit

CLINICAL ASSESSMENT	Month 1	M2	M3	M4	M5	M6
n	74	59	55	48	43	49
DAS28	3.8	3.5	3.4	3.1	3.1	3.2
HAQ	2.5	1.2	1	0.9	0.9	1
Clinical target achieved n (%)	11 (15)	17 (29)	14 (25)	22 (46)	17 (40)	24 (49)
Modification (in active group)	28/63 (44)	17/42 (40)	17/41 (42)	4/25 (16)	10/26 (39)	10/25 (40)
Type of modification						
Dose increase	25/28	10/17	8/17	2/4	4/10	1/10
Add DMARDS	1/28	2/17	4/17	2/4	3/10	7/10
Biologics	2/28	2/17	5/17	0/4	1/10	2/10
Additional steroids (n/active group)	4/63	6/42	4/41	2/25	3/26	2/25
Reason for no modification: Previous treatment to work n (%)	25/33 (76)	13/25 (52)	14/23 (61)	14/21 (67)	2/16 (13)	8/15 (53)

Table 2. PD findings according to clinical assessment at month 3 and 6.

Clinical target for disease activity	n	Any PD signal pos	Any PD signal neg	PD≥2 pos	PD≥2 neg
At month 3 (n=41)					
Achieved	8	4	4	3	5
Not-achieved	33	28	5	19	14
Modification	14	13	1	6	8
At month 6 (n=28)					
Achieved	15	8	7	3	12
Not-achieved	13	11	2	10	3
Modification	9	8	1	7	2

Conclusion: In this audit, therapy modifications were avoided in more than 50% of eligible RA patients at monthly visits, mainly due to waiting for the effect of previous treatments. A third to half of these cases also had PD signal, which has previously been demonstrated to be an independent risk factor for progression (2). US is a useful adjunct to clinical T2T approach and can inform patients who may particularly benefit from monthly treatment escalation.

Reference:

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Assessing the Individual Joint in Rheumatoid Arthritis (RA): Valid Detection of Synovitis in the MTP Joint Warrants Ultrasound Examination. Matthias Witt[1], Felix Mueller[1], Axel Nigg[1], Christiane Reindl[2], Hendrik Schulze-Koops[2] and Mathias Grunke[1]. [1]University of Munich, Munich, Germany, [2]Division of Rheumatology and Clinical Immunology, Med. Poliklinik, University of Munich, Munich, Germany

Background/Purpose: The clinical assessment of tender and swollen joints is a key outcome parameter in rheumatoid arthritis (RA). It has been shown recently, that the results of clinical joint examinations vary significantly among different examiners and depending on the joint region examined. Ultrasound examination has been proven to be more sensitive and reliable than clinical examination, but the sonographic evaluation of 68 joints is time-consuming and not feasible in daily clinical practice. The aim of this study was to compare the clinical and the ultrasonographic assessment of individual joints of patients with RA and to clarify, in which joints clinical examination alone is adequately reliable in the detection of arthritis and in which joints ultrasound confirmation is required.

Methods: 63 Patients with RA were clinically assessed for joint tenderness and swelling by performing a 66/68 joint count according to the EULAR technique. All patients were then independently examined by high resolution arthrosonography with an 18 MHz ultrasound probe and power doppler. For this analysis, clinical and ultrasonographic findings in each joint of the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and metatarsophalangeal (MTP) joints were compared and sensitivities and specificities for each joint was calculated with ultrasound as reference. Sonographic findings consistent with inflammation in greyscale (GS) or power doppler (PD) mode were classified on a semiquantitative 0–3 scale as specified before.

Results: 633 MCP-, 641 PIP- and 628-MTP joints of 63 RA patients were individually assessed for signs of arthritis by clinical examination and ultrasonography. Sensitivities of clinical examination for the individual joints ranged from 7,9 to 48,4% (overall 31,6%) for MCPs, from 34,1 to 70,7% (overall 40,8%) for PIPs and from 4,8 to 33,9% (overall 19,4%) for MTPs. Overall specificities for MCPs, PIPs and MTPs were 90,5%, 91,3 and 94,9%, respectively. Taking just grade 2 and grade 3 ultrasound findings as reference, overall sensitivities of clinical examination adjust to 53,0%, 62,9% and 30,5% for MCP-, PIP- and MTP joints, respectively, with corresponding adjustments of sensitivities on the level of the individual joint. In both settings, sensitivities for each individual MTP as well as for all MTPs were signifiantly lower than for MCP- and PIP-joints.

Conclusion: In this independent multirater study evaluating clinical joint examination only low and hence insufficient sensitivities for the individual joints were observed in general, underlining the limitations of clinical examination even for the experienced rheumatologist. In comparison to the joints evaluated, MTPs were significantly associated with the lowest sensitivities overall and in the individual joint, while PIPs were associated with the highest sensitivities. These differences remained significant even if grade 1 ultrasound findings were excluded from the analysis. This indicates that more articular effusion is necessary in MTP joints for clinical detection of joint swelling and therefore a comprehensive assessment of arthritis requires ultrasound evaluation at least of the MTP joints.

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Quantifying the Contributors to Global Assessment of Rheumatoid Arthritis Disease Activity by the Patient and the Physician. Paul Studenic[1], Josef Smolen[2] and Daniel Aletaha[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: The perception of disease activity in RA often differs between physicians and patients, as can be realized by a disconnect between patient and physician global assessments (PGA, MDGA). In previous studies, swollen joint count (SJC) and pain were identified as main determinants of a higher MDGA and PGA, respectively. It is unknown, however, to what extent patients relate higher pain levels, and physicians higher joint counts, to their global assessments. We aimed to investigate how much variability of the PGA and MDGA are explained by pain, SJC and other core set variables.

Methods: We identified RA patients from an observational, prospective RA outpatient database, and obtained visual analogue scores (VAS) for PGA and MDGA. We performed a stepwise linear regression model, using PGA as dependent variable, and other core set variables as independent variables: pain scores on VAS, swollen and tender joint counts (SJC and TJC), functional scores by the Health Assessment Questionnaire Disability Index (HAQ), morning stiffness in minutes (MST), as well as C-reactive protein (CRP) and rheumatoid factor in units/ml (RF). We identified the variability of PGA explained by the variables selected by the model using a $p<0.05$ cutpoint for entry and $p>0.10$ for removal. We then repeated the same analysis using MDGA as the dependent variable.

Results: We identified 634 RA patients (80% female, 68% RF positive, mean disease duration: 7.7 years). In the stepwise model pain, HAQ scores, and SJC remained significant ($p<0.001$ for each), explaining 79.3% of overall PGA variability mostly conveyed by pain (77.9%; see figure), while 20.7% of variability remained unexplained. For MDGA as dependent variable in the stepwise model SJC, pain, TJC and CRP were significant ($p<0.0001$ for each) explaining 65.2% of overall MDGA variability, mostly represented by SJC (58.1%, see figure), leaving 34.7% unexplained.

When all variables were included in a linear model, 93.1% of PGA was explained, indicating that the joint effects of these additional insignificant variables contributed another 14%, leaving only ~7% of PGA variability unexplained. For MDGA such model explained 84.2% of variability (further contribution of 19% by the insignificant variables), leaving 15.8% of MDGA variability unexplained.

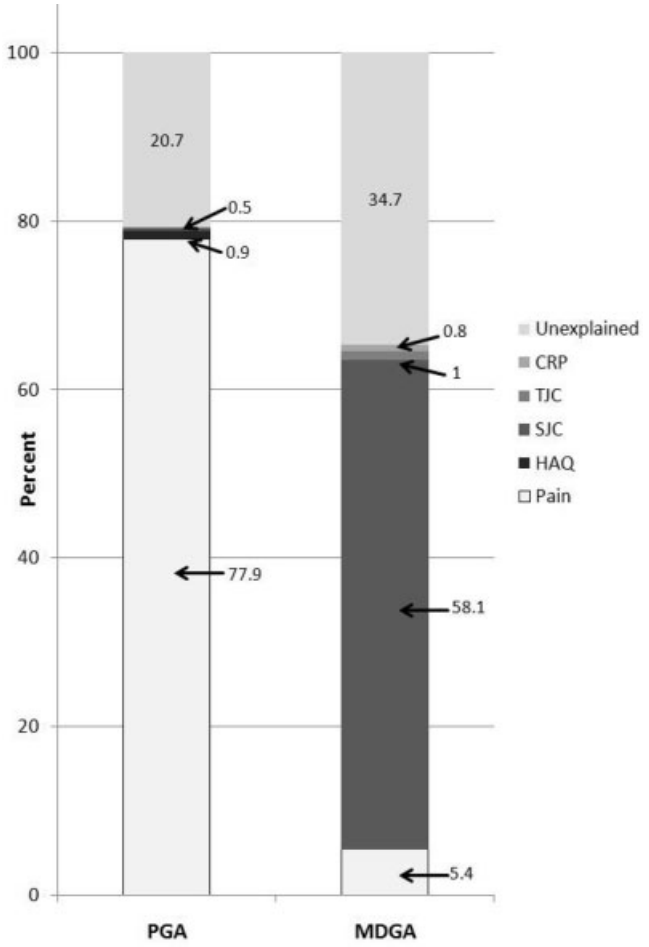

Figure 1. Components of patient global assessment (PGA) and physician global assessment (MDGA) in percent.

Conclusion: The single greatest determinant of patient global is pain, explaining ~80% of its variability. In contrast, the global assessment of disease activity by the MD, on the other hand, is largely a reflection of the number of swollen joints involved. The larger unexplained proportion of variability of the MDGA may indicate, that physicians take more aspects of RA disease activity into account than reflected in the core set measures, and supports its use as an additional measure of RA disease activity assessment.

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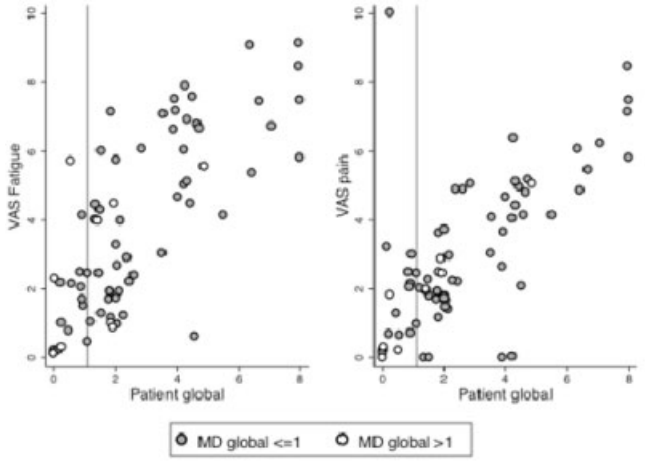
Validity and Reliability Problems with Patient Global As a Component of the American College of Rheumatology/European League Against Rheumatism Remission Criteria. Karim R. Masri[1], Frederick Wolfe[2], Timothy S. Shaver[3], Shadi H. Shahouri[4], Shirley Y. Wang[4], James D. Anderson[5] and Ruth E. Busch[6]. [1]Wichita, KS, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Arthritis & Rheum Clinics KS, Wichita, KS, [4]Arthritis & Rheum Clinic of KS, Wichita, KS, [5]Arthritis & Rheum Clinics KS, Leawood, KS, [6]Arthritis & Rheum Clinic, Wichita, KS

Background/Purpose: We have reported (A&R 2011) cross-sectional rates of remission in RA clinic patients of 7.5% using ACR/EULAR (AE) criteria, while 19.1% had Physician global scores $^{2}1$. AE clinical criteria require scores $^{2}1$ for tender and swollen joints and patient global (PtGlobal). Statistical analysis suggested that PtGlobal was the most important determinant of AE remission, but appeared to be unstable, shifting between observations. To understand the effect of PtGlobal, and what role it plays in AE remission, we studied its meaning and reliability and validity in consecutive patients who met AE joint criteria for remission.

Methods: We studied 73 consecutive RA clinic patients who met AE joint criteria for remission ($^{2}1$ swollen and $^{2}1$ tender joint), using the AE 28-joint count. Patients completed a VAS global, VAS fatigue and HAQ immediately before seeing the physician (MD), and completed a 2nd VAS global and questions about global severity immediately after the MD visit. MDs determined an MD global, clinical remission, and a complete tender and swollen joint count, including ankles and feet.

Results: Patient mean age was 60.0 (SD 15.1) years, and 41.7% were men. As expected, the VAS scores for pain, 2.9 (2.1), fatigue 3.7 (2.6) and patient global 2.7 (2.1) were low. Of patients meeting joint criteria for AE remission, 56 (76.7%) had PtGlobal >1, including 21.4% who reported no pain and 52.7% who indicated function or fatigue, not pain, were the main determinants of PtGlobal. Low back pain was also reported by 25% of this group. By contrast, 30.0% reported foot pain and 30.0% reported knee pain (compared with 7% on the MD examination) that may not have been identified in the physician's 28-joint count. There was no agreement beyond chance (kappa = 0.0, p=0.530) between ACR and MD remission, nor between high patient and physician global (global >1), kappa = −0.074, p=0.946. In addition to physician-patient disagreement (Figure 1), patients not meeting AE criteria frequently had high fatigue and high pain scores (Figure 1). Test-retest reliability of the patient global indicated an intraclass correlation coefficient (ICC) of 0.84.



Conclusion: PtGlobal has insufficient reliability for accurate measurement of remission in individual clinic patients. In addition, we identified problems with using PtGlobal as a measure of RA activity, for many patients who would otherwise be in AE remission were excluded because of non-RA activity factors, including low back pain, fatigue, functional limitations and low pain threshold. We also noted that physician joint counts may be biased downward by exclusion of foot and ankle pain that is not included in the 28-joint count or failure to identify knee joint activity. While the AE remission criteria appear to work well in clinical trials and groups of patients, problems with reliability and misclassification related to joint pain and patient global suggest caution in the use of the AE criteria in the individual patients.

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Changes and Sex Differences in Patient Reported Outcomes in Rheumatoid Factor Positive Rheumatoid Arthritis—Results From a Community Based Study. Korosh Hekmat, Lennart TH Jacobsson, Jan-Åke Nilsson, Ylva Lindroth and Carl Turesson. Lund University, Malmö, Sweden

Background/Purpose: Patient reported outcomes are important measures of the burden of rheumatoid arthritis (RA) in the community. In order to assess changes in such outcomes over time, cohorts from well defined catchment areas should be studied. A comprehensive register of patients with RA from all rheumatology care providers in a single city was established in 1997 and has been continually updated. This register includes virtually all the RA patients in the area**.** The aim of this study was to analyze patient reported outcomes, including health related quality of life (HRQoL) in surveys of this population conducted between 1997 and 2008. Furthermore, we wanted to assess differences in treatment and outcome in male and female patients.

Methods: In 1997, 2002, 2005 and 2008, questionnaires were sent to the RA patients in the register (n= 1016 in 1997; n=916 in 2002; n=1625 in 2005; n=1700 in 2008). Response rates varied between 62 % and 74 %, and 72–74 % were women. Questionnaire data included current and previous medication, visual analogue scales (VAS, 0–100) for global assessment of disease activity and pain, disability measured using the Health Assessment Questionnaire (HAQ), and HRQoL as measured by the Short Form (SF)-36 questionnaire. Data on rheumatoid factor (RF) tests were retrieved from the databases of the two clinical immunology laboratories in the area. In the

present comparison, only patients with at least one positive RF test were included. The analyses were stratified by sex.

Results: The number of RF positive responders was 668 in 1997, 438 in 2002, 517 in 2005 and 454 in 2008. Current treatment with biologics, corticosteroids and methotrexate was more frequent in 2008 compared to previous surveys (Table). Patients reported less severe outcomes for all measures in the later surveys compared to 1997, and patients' global disease activity assessment and self reported pain were further improved in 2008 compared to 2005 (Table). There was a similar trend for the physical component score of SF-36, but no change in HAQ between the surveys conducted in 2005 and 2008 (Table). Treatment was similar in men and women, but improvements were greater in men, in particular with regard to VAS for pain [mean (M) 29 (95 % CI 25–33) in 2008 vs M 40 (95 % CI 35–46) in 1997 for men; M 41 (95 % CI 38–44 in 2008 vs M 48 (95 % CI 45–51) in 1997 for women].

	1997	2002	2005	2008
N	668	438	517	454
Disease duration years, mean	15.0	16.7	15.8	17.2
Female sex	497 (74%)	321 (73%)	368 (71%)	331 (73%)
Age; years, mean	61.9	63.9	62.9	63.8
Current treatment (95 % CI)				
Corticosteroids	19% (16–22)	30% (26–35)	26% (23–30)	31% (27–35)
Biologic	0	16% (12–19)	23% (19–27)	29% (25–33)
Methotrexate	20% (17–23)	44% (40–49)	56% (52–60)	58% (54–63)
Patient reported outcomes mean (95% CI)				
HAQ*	1.12 (0.50–0.75)	1.00 (0.50–1.62)	0.88 (0.38–1.38)	0.88 (0.38–1.5)
VAS global	44.8 (42.3–47.4)	40.0 (37.6–42.4)	41.8 (39.6–44.1)	37.6 (35.2–40,0)
VAS pain	46.3 (43.7–48.9)	41.1 (38.8–43.5)	40.8 (38.6–43.0)	38.2 (35.8–40.7)
SF-36 PCS	32.1 (31.0–33.1)	33.2 (32.2–34.4)	34.6 (33.6–35.7)	35.2 (34.0–36.4)
SF-36 MCS	45.4 (44.0–46.7)	46.7 (45.4–48.1)	47.9 (46.7–49.0)	47.1 (45.9–48.3)

*median (IQR)
PCS=physical component score
MCS=mental component score

Conclusion: In this community based cohort of patients with RF positive RA, treatment was more extensive in later surveys, and there was improvement in all patient reported outcomes. Patients reported less pain and less severe global disease assessment in 2008 compared to 2005. Despite similar treatment, male patients reported better outcomes and more improvement, in particular regarding pain, compared to female patients. This suggests that patient reported outcomes should be assessed separately in male and female patients with RA.

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Assessment of Foot Structure in Rheumatoid Arthritis by a Foot Digitizer Reveals Marked Deformities, Even in the Absence of Radiographic Erosions. Sophie De Mits[1], Dirk De Clercq[1], Jim Woodburn[2], Philip Roosen[1] and Dirk Elewaut[3]. [1]Ghent University, Ghent, Belgium, [2]Glasgow Caledonian University, Glasgow, United Kingdom, [3]Gent University Hospital, Ghent, Belgium

Background/Purpose: Foot involvement is a major feature of rheumatoid arthritis (RA), yet the rheumatoid foot is often neglected. There seems to be limited clinical interest which could possible lead to insufficiencies in treatment. The DAS28, frequently used in daily clinical routine, even omits the feet and ankles in the joint count. However, it is clear that the feet need the proper attention and care. The Ritchie Articular Index includes the feet but groups the joints, eg the MTP joints. Its 0–3 graded evaluation of the severity of the joint tenderness may be somehow subjective and complicated.

A foot digitizer, based on an optical laser scanning procedure, is a quick, easy to use and non-invasive device to collect objective data of the feet. It is proven to be a valid and reliable tool to use (1). The aim of this study is to determine if a foot digitizer can be a valuable tool for daily clinical routine to examine the feet in RA patients.

Methods: 106 RA patients and 135 matched healthy controls participated in the study. All patients had a confirmed diagnosis of RA based on the ACR criteria. Their disease duration ranged between 1 and 55 years, their DAS28 score between 1.3 and 6.6 and 49% had swollen and/or tender foot joints. The patients were included in a consecutive manner, irrespective of foot complaints being present or not. Ethical Committee Approval was obtained and all participants signed an Informed Consent.

3Dscans of the foot were made with a foot digitizer (Infoot USB, standard type, I-Ware Laboratory Co., Ltd, Osaka, Japan). The routine radiographs of the patients feet were checked for the presence of erosions.

Linear Mixed Models (IBM SPSS Statistics 19) were applied to compare the Infoot data between the controls, the patients with and without erosions. Post hoc analyses were performed with a Bonferroni correction.

Results: A majority of RA patients (62%) had signs of erosions at the feet. The impact of presence or absence of erosions of the foot yielded some remarkable results. Ball girth circumference and height of top of ball girth were significant smaller the erosive group ($p=0.002$) versus non-erosive and controls. Foot width was significantly smaller for both subgroups of RA patients ($p=0.009$ and $p=0.05$ respectively). Fibular instep length was larger for both erosive and non-erosive RA patients ($p=0.03$ and $p=0.24$). Differences in toes were also apparent: toe 1 angle is smaller in erosive RA versus controls ($p= 0.007$). The height of toe 1 was higher for both erosive and non-erosive RA patients. These findings were independent of gender, age, body weight, disease duration, DAS28 or presence of tender or swollen foot joints.

Conclusion: The results of the present study highlight a previously underappreciated impact of RA on foot structure, even in the absence of clinical signs of swelling or radiographic erosions. The Infoot digitizer offers a valuable tool to screen for such foot deformities at an early stage, before the presence of erosions. Importantly, the observed deformities could have implications for the shoe behavior of the patients. Hence, the digitizer can help in giving the proper shoe advise and consequently help in the daily management of RA.

(1) De Mits S. et al. JAPMA 2011; 101(3):198–207.

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Comparison of Rheumatoid Arthritis Patient Characteristics From Randomized Controlled Trials to a Registry Designed for Rheumatoid Arthritis Comparative Effectiveness Research. Aarat M. Patel[1], Christine L. Amity[2], Lynne M. Frydrych[2], Derek Sippel[2], Donald Jones[2], Danielle Goudeau[2], Heather Eng[3], David Kyle[3], Melissa Saul[3], Daniel Hal Solomon[4], Stephen R. Wisniewski[3], Larry W. Moreland[5] and Marc C. Levesque[2]. [1]Univ of Pittsburgh Med Ctr / Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]Univ of Pittsburgh, Pittsburgh, PA, [4]Brigham & Womens Hospital, Boston, MA, [5]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: The US federal government and several medical societies have recently endorsed more research targeted to comparative effectiveness studies of existing medical therapies as a way to optimize medical care, to lower health care costs and to provide research results that are more generalizable to a broader population than those typically included in randomized controlled trials (RCTs). We developed a Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry at the University of Pittsburgh Medical Center (UPMC) to provide a platform for comparative effectiveness study designs that incorporate electronic health record information, improve patient care and incorporate aspects of both randomized studies and real world observation. We determined whether there were significant differences between the characteristics of RACER subjects versus subjects from published RCTs.

Methods: RACER was established in February 2010 and consists of patients ≥18 years with a rheumatologist diagnosis of RA (n=820). At each clinic visit, self-administered questionnaires including a routine assessment of patient index-3 (RAPID3), short-form-12 (SF12), work productivity and activity impairment (WPAI), DAS28, and physician and patient visual analogue scales (VAS) for arthritis-related pain and global health are collected from subjects. Blood samples for determination of C-reactive protein (CRP), RF and anti-cyclic citrullinated peptide (CCP) levels are collected. We compared RACER descriptive statistics to similar data from all RA patients seen in the UPMC health care system in 2010 (n=2,610) and to published biological therapy RCTs identified by PubMed searches. We also compared the descriptive statistics of RACER subjects initiating new therapies to subjects in RCTs.

Results: RACER subjects had characteristics similar to RA patients evaluated throughout the UPMC system in 2010. RACER subjects that initiated new biologic or DMARD therapies (n=185) had somewhat higher disease activity scores, more work impairment and a lower physical quality of life but were otherwise highly comparable to other RACER subjects (**Table 1**). When compared to subjects in RCTs of biologic therapies, RACER subjects were older, had longer disease duration and lower disease activity. However, RACER subjects and subjects in RCTs had several similar characteristics including sex, race, RF positivity, functional ability (HAQ or mdHAQ) and quality of life (SF-12 or SF-36).

Table 1. Demographics of RACER Subjects (n=820)

	All RACER subjects (n=820)	RACER subjects that began a new DMARD/Biologic (n=185)
Age, yrs	59.8 ± 13.5	58.6 ± 13.4
Female	78%	76%
Race Caucasian	88%	88%
African Am.	10%	11%
Other	1%	<1%
Duration, yrs	14.3 ± 12.4	14.2 ± 13.0
RA criteria Both 1987 and 2010	88%	94%
1987 ACR only	5%	4%
2010 ACR/EULAR only	4%	2%
Neither 1987 or 2010	2%	0%
ACR/EULAR Remission	17%	14%
Clinical Setting		
Academic	24%	29%
Private	76%	71%
RF, IU median	68	38
% Positive	77%	80%
Anti-CCP, IU median	46	60
% Positive	76%	79%
CRP, mg/dl	0.45	0.51
DAS28	3.2 ± 1.3	3.6 ± 1.5
SDAI	13.7 ± 11.8	17.9 ± 14.3
CDAI	12.9 ± 11.4	17.2 ± 13.9
RAPID3	3.5 ± 2.2	4.0 ± 2.2
WPAI Activity imp.	40.50%	48.60%
Time missed	6.20%	9.60%
Imp. working	27.60%	36.10%
Overall imp.	30.60%	39.30%
SF-12 MCS	36.1 ± 10.7	45.3 ± 11.7
PCS	46.7 ± 11.1	34.7 ± 9.8
Medications DMARD	47%	40%
Biologic	12%	15%
DMARD + Biologic	22%	29%
No DMARD or Biologic	8%	16%
NSAIDS	62%	56%
Corticosteroids	42%	45%
Opiates	36%	37%

All values are mean ± standard deviation unless otherwise written as median or percent. RACER: Rheumatoid Arthritis Comparative Effectiveness Research; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; RF: Rheumatoid factor; DAS28: disease activity score-28 joint count; SDAI: simplified disease activity index; CDAI: clinical disease activity index; RAPID3: routine assessment of patient index data 3; WPAI: Work Productivity and Activity Impairment; SF12: Short Form-12; DMARD: disease modifying anti-rheumatic Drug; MCS: mental component score; PCS: physical component score

Conclusion: The RACER cohort is representative of real world RA patients given the similarities between RACER subjects and non-RACER RA patients followed within the UPMC health care system. RACER subjects were typically older, had a longer disease duration and less disease activity than subjects in RCT's. This suggests that comparative effectiveness studies of different therapies tested in RACER subjects may yield different results compared to results from RCTs.

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The Accuracy of Patient Reported Current and Past Medications Used to Treat Rheumatoid Arthritis in An Academic Institutional Registry. Sergio Schwartzman[1], Dana E. Orange[2] and Stephen L. Lyman[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, The Rockefeller University, New York, NY

Background/Purpose: Academic institutional registries are a valuable tool for collecting patient information. They have focused on research, specific drug safety and efficacy, and quality improvement. Patient self report has frequently been used in some registries. Validating data collected from patient reported registries has not always been straightforward. In an attempt to validate data from an academic rheumatoid arthritis registry with patient reported data, we conducted a study to assess the agreement between patient reported currently used medications at time of entry into the registry and prior history of medications used. Specific types of medications reviewed included DMARDS, corticosteroids and glucocorticoids.

Methods: At the time of analysis, 1 1/2 years after the date of 1st enrollment, 223 RA patients were enrolled in the registry. The baseline registry questionnaire requested patients to note both current and prior medications used to treat rheumatoid arthritis. Sample size was approximately 1/3 of the cohort. 67 randomly selected charts from 5 different physicians and 7 charts from the fellow's clinic were reviewed. The chart review was conducted by two rheumatologists blinded to the patient questionnaire responses. Kappa statistics with 95% confidence intervals were calculated as well as sensitivity, specificity, and positive predictive value (PPV).

Results: The study cohort consisted of 52 Females and 22 Males and the mean age was 57.9. There were 5 Hispanic or Latino, 7 Black or African American and 59 White patients. Educational level: Grade school-2, High school-11, College-24, Post Graduate-34. There was very good agreement between patient self report and medical chart review for both current and previous medications. For current medications kappa was 0.849 (0.794, 0.904) with a sensitivity of 84%, specificity of 89%, and PPV of 89%. For prior medications, kappa was 0.838 (0.794, 0.882) with a sensitivity of 88%, specificity of 97%, and PPV of 86%.

Conclusion: Self-reported current and previous medication used to treat rheumatoid arthritis appears to have excellent validity in this cohort of patients. These results may reflect a unique patient and/or physician population possibly due to a high education attainment in the patient cohort and the effect of a specialty hospital environment on physician documentation.

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Discordant Autoantibodies and Clinical Outcomes In Rheumatoid Arthritis. Dannette S. Johnson[1], Alan Erickson[2], Grant W. Cannon[3], Gail S. Kerr[4], Liron Caplan[5], Andreas M. Reimold[6], John S. Richards[4], Pascale Schwab[7], Deana M. Lazaro[8], Nasim A. Khan[9], Bogdan Cherascu[10] and Ted R. Mikuls[11]. [1]G.V. Sonny Montgomery VA and University of Mississippi, Jackson, MS, [2]Omaha VA and University of Omaha, Omaha, NE, [3]Salt Lake City VA and University of Utah, Salt Lake City, UT, [4]Washington DC VA and Georgetown University, Washington, DC, [5]Denver VA and University of Colorado, Aurora, CO, [6]Dallas VA and University of Texas Southwestern, Dallas, TX, [7]Portland VA and Oregon Health & Science University, Portland, OR, [8]Brooklyn VA, Brooklyn, NY, [9]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, [10]Iowa City VA and University of Iowa, Iowa City, IA, [11]Omaha VA and University of Nebraska, Omaha, NE

Background/Purpose: Little attention has been given to the associations of discordant autoantibodies, RF and aCCP, with clinical outcomes in RA. We determined dual autoantibody status in a cohort of established RA patients and examined the associations of autoantibody status with RA disease characteristics.

Methods: U.S. Veterans in the Veterans Affairs Rheumatoid Arthritis (VARA) Registry with ≥ 2 clinical observations over 6 months had enrollment serum and DNA tested for aCCP, RF, and *HLA-DRB1* shared epitope (SE). Demographics, baseline and longitudinal clinical data were collected. Associations between aCCP, RF, and clinical outcomes were examined using linear and logistic regression adjusting for age and sex. Multivariate models also included demographics, disease activity and severity, comorbidity and therapies.

Results: Autoantibody status (n = 1097) was 81% RF positive and 76% aCCP positive (70% RF+/aCCP+, 11% RF+/aCCP-, 6% RF-/aCCP+ and 13% RF-/aCCP-). Patient characteristics based on dual autoantibody status are summarized in Table 1. SE, homozygous state, was more common in aCCP positive individuals than RF positive individuals regardless of whether patients were concordant for these values. Current smoking was lower among RF+/aCCP− patients than other patient groups. Multivariable associations of dual autoantibody status with measures of RA disease severity/activity are shown in Table 2.

Table 1. RA patient characteristics and prognostic factors based on autoantibody status

	Total (n = 1,097)	RF−/aCCP− (n = 146)	RF+/aCCP− (n = 115)	RF−/aCCP+ (n = 68)	RF+/aCCP+ (n = 768)	P-value
Age at enroll., yrs.	64 (11)	65 (12)	64 (10)	62 (12)	64 (11)	0.175
Male gender, %	91	89	90	85	92	0.323
Caucasian race, %	78	81	79	69	78	0.277
≥ H.S. education, %	83	84	83	87	82	0.755
Co-morbidity count (0–9)	1.9 (1.4)	1.9 (1.3)	1.9 (1.3)	1.6 (1.3)	1.9 (1.4)	0.313
Disease duration, yrs	12 (11)	10 (11)	11 (11)	11 (11)	13 (12)	0.070
Smoking status, %						
Never	20	24	23	28	18	0.002
Former	53	55	50	65	52	
Current	27	21	27	7	30	
HLA-DRB1 SE, %						
0 copies	28	47	44	22	23	<0.001
1 copy	51	47	50	48	52	
2 copies	21	6	6	30	25	
Prednisone, %	62	53	63	64	63	0.158
Methotrexate, %	69	71	72	79	67	0.157
Biologic DMARD, %	47	36	47	45	49	0.022

Table 2. Multivariate associations of autoantibody status with clinical outcomes

Autoantibody Status	Erosions	Nodules	Sustained Remission*	Proportion of Follow-Up in Remission·
	Odds Ratio (95% CI)			β-Coefficient (95% CI), p-value
RF neg./aCCP neg.	Referent	Referent	Referent	Referent
RF pos./aCCP neg.	1.60 (0.69 to 3.70)	1.78 (1.04 to 3.03)	0.56 (0.23 to 1.38)	−0.03 (−0.10 to 0.03), p = 0.281
RF neg./aCCP pos.	2.53 (0.94 to 6.82)	2.50 (1.34 to 4.66)	0.74 (0.28 to 1.98)	−0.01 (−0.09 to 0.06), p = 0.725
RF pos./aCCP pos.	3.41 (1.79 to 6.53)	3.39 (2.26 to 5.09)	0.50 (0.26 to 0.97)	−0.10 (−0.14 to −0.05), p <0.001

* Sustained Remission - at least 2 consecutive observations, separated by ≥ 3 months, with DAS28 % 2.6.
· Proportion of Follow-Up in Remission - (a continuous measure, range 0–1) to account for differences in follow-up duration (time in remission credited only when remission was maintained for at least 2 sequential visits)

Conclusion: In this cohort, RF+/aCCP+ patients had more severe disease and worse clinical outcomes with less time in remission than RF-/aCCP- patients. Discordant autoantibody groups generally demonstrated associations with disease outcomes that were intermediate or equivalent to those observed in the corresponding sero- negative / positive groups, suggesting that these autoantibodies play an additive and possibly synergistic role in RA disease progression.Bottom of Form

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Does Clinical Assessment of Swollen and Tender Joints Reflect Inflammatory Synovitis in Rheumatoid Arthritis? A Comparative Study of Physician, Nurse and Patient Clinical Assessments Versus Ultrasonography (US) As the Gold Standard. Peter Cheung[1], Laure Gossec[2], Adeline Ruyssen-Witrand[3], Catherine Le Bourlout[4], Maryse Mezieres[4] and Maxime Dougados[5]. [1]National University Hospital, Singapore, Singapore, [2]Cochin Hospital, Paris, France, [3]Hopitaux de Toulouse, Toulouse, France, [4]Hospital Cochin, Paris, France, [5]Paris-Descartes University, Cochin Hospital, Paris, France

Background/Purpose: Swollen and tender joints (SJ, TJ) enable physicians to detect and quantify synovitis in rheumatoid arthritis (RA). There are data indicating Power Doppler positive ("inflammatory") synovitis is predictive of damage. The aim was to assess if SJ and TJ derived by physician, nurse and patient are associated with synovitis that is "inflammatory" or "mechanical", and to assess if radiographic damage interferes in the assessment of joint counts.

Methods: A cross-sectional study of 50 RA patients was conducted, where joints were independently evaluated by patients themselves, a trained nurse and a physician for swelling and tenderness (presence or absence at each joint). The wrists, metacarpophalageal and proximal interphalangeal joints were analysed (22 joints). Separate assessments by US were performed with the following definitions as gold standards:

i) "Inflammatory" synovitis: B-mode (>/= Grade 1), PD signal (>/= Grade 1), or
ii) "Mechanical" synovitis: B-mode (>/= Grade 1), absence of PD signal

Radiographic damage was graded according to Larsen. Presence of swelling or tenderness at the joint level was compared with US-detected "inflammatory" or "mechanical" synovitis using sensitivities (Se), specificities (Spe) and positive likelihood ratios (LR).

Results: *Swollen joints (SJ)*: SJ reflected with a higher sensitivity, "inflammatory" than "mechanical" synovitis (Table 1). Physician and nurse-derived SJ best reflected "inflammatory" synovitis, with LR of 2.40 (95%CI 1.96–2.95) and 3.60 (95%CI 2.67–4.86) respectively, compared to patient-derived SJ (LR 1.84, 95%CI 1.46–2.32). *Tender joints (TJ)*: like SJ, TJ reflected more "inflammatory" than "mechanical" synovitis although the difference was not as great. Patient-derived TJ had the highest sensitivity for detecting "inflammatory" synovitis (Se=0.42). *Radiographic damage*: Physician and nurse-derived SJ continued to reflect "inflammatory" synovitis more than "mechanical" synovitis in joints with severe radiographic damage, while patient-derived SJ did not. Inversely, for TJ, patient-derived TJ has the best properties to reflect "inflammatory" synovitis in this situation (LR 2.31, 95%CI 1.37–3.88).

Table 1. Diagnostic performance of clinical synovitis compared to gold standard US for inflammatory synovitis and mechanical synovitis

	Inflammatory synovitis by US			Mechanical synovitis by US		
	Se	Spe	LR	Se	Spe	LR
Swollen Joint						
Physician	0.44	0.82	2.40 (1.96–2.95)	0.28	0.78	1.26 (1.00–1.60)
Nurse	0.29	0.92	3.60 (2.67–4.86)	0.09	0.86	0.66 (0.43–1.02)
Patient	0.32	0.82	1.84 (1.46–2.32)	0.20	0.79	0.92 (0.69–1.22)
Tender Joint						
Physician	0.25	0.86	1.87 (1.41–2.46)	0.17	0.84	1.09 (0.79–1.49)
Nurse	0.27	0.84	1.67 (1.28–2.16)	0.16	0.81	0.83 (0.60–1.14)
Patient	0.42	0.77	1.82 (1.50–2.21)	0.26	0.72	0.94 (0.74–1.19)

Conclusion: It appears clinical assessment in a way adjusts to "inflammatory" activity in RA. Physician and nurse-derived SJ, as well as patient-reported TJ (in severely damaged joints) reflect "inflammatory" synovitis rather than "mechanical" synovitis. Clearly a statistical significance is seen suggesting a relation between the clinical assessment and US derived inflammatory synovitis BUT the clinical relevance is questionable.

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Patient Tolerability of Arthroscopic Synovial Biopsy Compared to MRI. Maria J. H. de Hair, Marleen G. H. van de Sande, Mario Maas, Danielle M. Gerlag and Paul P. Tak. Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Arthroscopy is extensively used for research purposes in inflammatory arthritis. A relatively new tool for evaluating and quantitating synovial tissue abnormalities is dynamic contrast enhanced (DCE) MRI. Since the latter technique is less invasive and might therefore be experienced as more positive by study patients, we compared both procedures in terms of patient's preference.

Methods: Twenty-eight early arthritis patients and 34 individuals of our preclinical rheumatoid arthritis (RA) cohort who did not have any evidence of arthritis upon physical examination and were positive for IgM-rheumatoid factor and/or anti citrullinated protein antibodies were included in the study. All study subjects underwent both DCE-MRI (closed MRI n=24 for both study groups and open MRI n= 4 and 10, respectively) and arthroscopic synovial biopsy of the same joint within one week. In the early arthritis patients an inflamed wrist (n=1), knee (n=15) or ankle (n=11) joint was examined and in the preclinical RA subjects a knee joint in all cases. Before and after both procedures, patients filled in questionnaires with questions about patient expectations and experience with regard to the procedures.

Results: Eleven early arthritis patients did not complete the questionnaire after follow-up, of which 64% did not have a preference for one of the procedures at baseline and 18% had a preference for either MRI or arthroscopy before they had undergone the procedures. Fourteen individuals with preclinical RA did not complete the follow-up questionnaire, of which 64% did not have a preference, 22% preferred MRI and 14% preferred arthroscopy. Of 17 early arthritis patients and 20 preclinical RA subjects both baseline and follow-up questionnaires were available. Of these early arthritis patients 47% did not have a preference for one of the procedures at baseline, compared to 35% preferring MRI and 18% preferring arthroscopy. For the 20 preclinical RA subjects these percentages were 35% for 'no preference', 60% for MRI, and 5% for arthroscopy, respectively. After both procedures were performed, there was a shift of

35% in the early arthritis patients from 'no preference' and MRI in favour of arthroscopy. Also in the individuals with preclinical arthritis, there was a shift towards arthroscopy of 20%, coming from MRI in 75% of these individuals. In both groups, none of the subjects who preferred arthroscopy at baseline changed to MRI and only 6 and 10%, respectively, changed to 'no preference'. In the subset of subjects who underwent MRI in the open scanner, there was not a stronger preference for MRI than in the total group and nobody changed to having preference for MRI after both procedures.

Conclusion: In early arthritis patients who underwent both procedures, arthroscopy is preferred by 47%, compared to 24 and 29% for MRI and 'no preference', respectively. For some patients with active arthritis, being immobile during MRI is quite uncomfortable. In preclinical RA subjects who did not have any sign of arthritis, 25% preferred arthroscopy, compared to 55 and 20% for MRI and 'no preference', respectively. The results support previous studies showing that arthroscopic synovial biopsy is well tolerated.

ACR/ARHP Poster Session C
Rheumatoid Arthritis - Human Etiology and Pathogenesis II
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

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Polymorphisms in N-Acetyltransferase 2 Impact Rheumatoid Arthritis Risk Due to Cigarette Smoking in African Americans. Marshall Davis[1], Tricia LeVan[1], Karen Gould[1], Fang Yu[1], Geoffrey M. Thiele[1], Kimberly Bynote[1], Larry W. Moreland[2], Doyt L. Conn[3], Edwin A. Smith[4], Leigh F. Callahan[5], Beth L. Jonas[6], Richard Brasington[7], S. Louis Bridges Jr.[8] and Ted R. Mikuls[1]. [1]Univ of Nebraska Med Ctr, Omaha, NE, [2]University of Pittsburgh, Pittsburgh, PA, [3]Emory Univ School of Medicine, Atlanta, GA, [4]Med Univ of South Carolina, Charleston, SC, [5]University of North Carolina, Chapel Hill, NC, [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, [7]Washington Univ School of Med, St. Louis, MO, [8]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Cigarette smoking is associated with an elevated risk of rheumatoid arthritis (RA) in African Americans, a risk that is most striking for those with a cumulative exposure of 10 or more pack-years. Recognizing that the risk of developing other smoking-related conditions is impacted by genetic variation in genes encoding drug metabolizing enzymes (DMEs), we sought to examine whether the risk of RA attributable to smoking in African Americans differs based on the presence of select DME gene polymorphisms.

Methods: RA cases (n=727) and controls (n=268) were participants in the Consortium for the Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis (CLEAR) registry. Participants were categorized as either heavy smokers (≥ 10 pack-years) or other (< 10 pack-years including never smokers). Tagging single nucleotide polymorphisms (SNPs) encoding N-acetyltransferase 1 (*NAT1*), *NAT2*, and epoxide hydroxylase (*EPXH1*) and a homozygous deletion polymorphism in glutathione S-transferase Mu-1 (GSTM1-null) were genotyped. RA risk was evaluated for each polymorphism using logistic regression adjusting for age and gender. Evidence of gene-smoking interactions was examined by calculating the attributable proportion (AP; additive interaction) due to interaction and by modeling the polymorphism-smoking product term (multiplicative interaction). A Bonferroni correction was used to adjust for multiple comparisons (n = 30 polymorphisms) and the level of significance was set at a p-value < 0.0017 (0.05 / 30). Haplotype analyses were constructed for *NAT2* SNPs yielding at least borderline evidence of interaction (p < 0.05). A secondary analysis was conducted to evaluate the same outcomes in cases that were positive for anti-citrullinated protein antibody (ACPA).

Results: There were no associations of RA risk with any of the individual polymorphisms examined and there were no significant interactions between heavy smoking and the GSTM1-null, NAT1, or EPXH1 polymorphisms after adjusting for multiple comparisons. In contrast, there were 3 *NAT2* tagging SNPs with evidence of at least borderline interaction with heavy smoking in RA risk (Table 1). The *NAT2* rs9987109 and rs1208 SNPs demonstrated significant additive interactions with heavy smoking. *NAT2* haplotype analyses were consistent with the individual tagging SNP analyses and interactions were similar for overall disease risk compared to the risk of ACPA-positive RA.

Table 1. Association of NAT2 polymorphisms with RA based on smoking history

Gene/ polymorphism	Minor allele status	Smoking history	Cases (no.)	Controls (no.)	OR	95% CI	P-value
NAT2							
rs9987109	Absent	Never, < 10py	245 (38.1)	93 (36.3)	1.00	–	–
	Present	Never, < 10py	220 (34.2)	116 (45.3)	0.73	(0.52, 1.01)	0.06
	Absent	≥ 10py	85 (13.2)	31 (12.1)	1.07	(0.66, 1.73)	0.79
	Present	≥ 10py	93 (14.5)	16 (6.3)	2.42	(1.34, 4.38)	0.003
						P_{muk} = 0.003	
						AP (95% CI) = 0.67 (0.39 to 0.95)	
						P_{odd} = 0.000003	
rs1208	Absent	Never, < 10py	162 (23.6)	75 (28.7)	1.00	–	–
	Present	Never, < 10py	334 (48.8)	139 (53.3)	1.07	(0.76, 1.51)	0.69
	Absent	≥ 10py	60 (8.8)	26 (10.0)	1.10	(0.64, 1.90)	0.73
	Present	≥ 10py	129 (18.8)	21 (8.0)	3.03	(1.76, 5.23)	0.00006
						P_{muk} = 0.01	
						AP (95% CI) = 0.61 (0.34 to 0.89)	
						P_{odd} = 0.00001	
rs721399	Absent	Never, < 10py	156 (24.1)	85 (33.9)	1.00	–	–
	Present	Never, < 10py	313 (48.3)	120 (47.8)	1.45	(1.03, 2.03)	0.03
	Absent	≥ 10py	63 (9.7)	9 (3.6)	4.13	(1.94, 8.78)	0.0002
	Present	≥ 10py	116 (17.9)	37 (14.7)	1.83	(1.15, 2.91)	0.01
						P_{muk} = 0.008	
						AP (95% CI) = −1.50 (−3.35 to 0.35)	
						P_{odd} = 0.11	

Conclusion: These results show that the risk of RA in African Americans due to heavy smoking is mediated by genetic variation in *NAT2*. These results may provide important insight into disease pathogenesis and the constituents of cigarette smoke that may drive RA risk in this understudied population.

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Integrative Analyses Demonstrate That Rheumatoid Arthritis Risk Loci Impact Genes with CD4+ Effector Memory T-Cell Function. Xinli Hu[1], Hyun Kim[1], Eli A. Stahl[1], Robert M. Plenge[1], Mark Daly[2] and Soumya Raychaudhuri[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Massachusetts General Hospital, Boston, MA

Background/Purpose: Previous experimental animal model studies and observational human studies have implicated a wide range of immunological cell types ranging from mast cells to lymphocytes in rheumatoid arthritis (RA) pathogenesis. Now, with the recent discovery of a total of 39 RA risk-conferring single nucleotide polymorphisms (SNPs), there has been an increasing push to define how these loci relate to functional disease immunology. Here, we hypothesize that predisposing RA risk loci act upon a small number of pathogenic cell types and that the genes with critical functions in those cell types are likely to be near the identified disease loci. Utilizing a compendium of gene expression data in immune cell types as an objective proxy for cell-specific gene function, the present study seeks to identify the main immunological cell type that is implicated by these risk loci.

Methods: We implemented a statistical algorithm to identify potentially pathogenic tissue types, using a compendium of gene expression data; our algorithm evaluates each tissue for enrichment of specifically expressed genes within complex disease loci. First, our algorithm uses linkage disequilibrium properties to identify the potentially implicated genes by each associated SNP. Then, for each tissue, we assess the tissue specific expression of genes implicated by all associated SNPs. By comparison to randomly selected matched SNP sets, we are able to assign a significance score to each tissue.

Results: Using a gene expression data set of 223 murine immunological tissues from the Immunological Genome Consortium (http://www.immgen.org/) we demonstrate highly significant enrichment of four CD4+ effector memory T-cell genes within RA loci ($p<10^{-6}$). To independently validate the role of CD4+ effector memory T-cells in RA, we identified 436 loci with suggestive statistics in a recent GWAS meta-analysis ($p<0.001$) and completely independent from the 39 known RA loci. Separate analyses have shown that >5% of these loci are true RA loci (Stahl *et al* in review). We note enrichment for CD4+ effector memory T-cell genes within these loci as well ($p=1.25\times10^{-4}$); this enrichment can be explained by ~25 true RA risk loci. We further note that different cell types are implicated in other autoimmune diseases, for example we demonstrate enrichment of transitional B-cell genes in

systemic lupus erythematosus ($p=5.9\times10^{-6}$) and dendritic cells in Crohn's disease ($p=1.6\times10^{-5}$).

Conclusion: These results demonstrate that validated RA risk loci are near genes most specifically expressed in CD4+ effector memory T-cells more than other immune cell subsets. To understand how these loci act to confer risk of RA, functional studies must be conducted in the CD4+ effector memory T-cells to better elucidate disease mechanisms.

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The Hierarchy of HLA-DRB1 Shared Epitope Risk Genotypes Associated with Rheumatoid Arthritis in African-Americans Differs From That in Europeans. Altan F. Ahmed[1], Laura B. Hughes[1], Doyt L. Conn[2], Beth L. Jonas[3], Leigh F. Callahan[4], Edwin A. Smith[5], Richard D. Brasington[6], Larry W. Moreland[7], S. Louis Bridges Jr.[1] and Richard J. Reynolds[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Emory Univ School of Medicine, Atlanta, GA, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]University of North Carolina, Chapel Hill, NC, [5]Med Univ of South Carolina, Charleston, SC, [6]Washington Univ School of Med, St. Louis, MO, [7]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: HLA-DRB1 alleles encoding the shared epitope (SE) are associated with RA in persons of European ancestry (~60–70% of RA vs ~40% of controls have ≥1 SE allele). SE-containing alleles are also associated with RA in African-Americans (Af-Amer) but have a lower allele frequency than in Europeans (~43% of RA vs ~25% of controls). Several SE classification systems have been developed to define the relative contributions of individual SE alleles/combinations on susceptibility to RA, but these have not been tested in Af-Amer because of insufficient numbers of subjects. Here we evaluate the du Montcel classification system in 920 Af-Amer RA pts and 1,006 Af-Amer controls.

Methods: High-resolution HLA-DRB1 genotyping was performed in patients and controls from the CLEAR Registry and from local Birmingham controls. *HLA-DRB1* susceptibility (S) alleles are those with the amino acid sequence RAA at positions 72–74 (Table). S alleles are subdivided according to the amino acid at position 71 (S1: ARAA [S1A] or ERAA [S1E], S2: KRAA, S3: RRAA). The S3 alleles are subdivided further according to the amino acid at position 70 (S3D: DRRAA, S3P: QRRAA or RRRAA). S1A, S1E, and S3D are classified as low-risk (L) alleles. All other alleles are non-susceptibility alleles. To estimate the odds ratio of association of each genotype with RA, we fit log-linear models with case/control as the response, also stratified by autoantibody positivity, with levels of genotype as predictors.

HLA-DRB1 Alleles	Amino Acid Residue 70	71	72	73	74	Classification
0401, 1303		K	R	A	A	S2
0101, 0102, 0404, 0405, 0408, 10, 1402, 1406	Q/R	R	R	A	A	S3P
1501, 1502, 1503		A	R	A	A	L (S1A)
0103, 0402, 1301, 1302		E	R	A	A	L (S1E)
1102, 1103, 1202, 1305, 16	D	R	R	A	A	L (S3D)

Results: The genotype combination with the largest effect for Af-Amer RA was S2/S3P (OR 9.1, CI 3.4–24, $p=5.7\times10^{-6}$) followed by S3P/S3P (OR 3.2, CI 1.5–6.7, $p=1.9\times10^{-3}$), S2/L (OR 2.6, CI 1.9–3.6, $p=2.7\times10^{-9}$), S2/S2 (OR 2.3, CI 0.62–8.3, p=.20), S3P/L (OR 1.9, CI 1.5–2.4, $p=1.8\times10^{-8}$). When analyzing autoantibody positive patients only, the risk hierarchy was nearly identical, and the overall effect was slightly larger. In contrast, when stratifying by autoantibody negative patients, there was no association of genotype with RA ($c^2=1.9$, DF=5, p=0.86).

Conclusion: Among British RA the S2/S2 genotype provided the strongest association with RA, but was not associated with RA in Af-Amer. Therefore, the HLA-DRB1 risk hierarchy differs between Af-Amer and Caucasians. The much lower risk of the S2/S2 genotype is likely due to its low frequency (0.56%, both cases and controls) in Af-Amer. The lack of association among autoantibody negative patients further substantiates the role of the HLA in the pathogenesis of autoantibody positive RA. The results illustrate the importance of considering ethnic differences, which may include heterogeneous genetic admixture and/or allele frequency differences, when defining genetic susceptibility loci for RA and other complex diseases.

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Apolipoprotein M Polymorphism Is a Novel Risk Factor for Dyslipidemia in Rheumatoid Arthritis: A Possible Link Between Disease Susceptibility and Dyslipidemia. Yune-Jung Park[1], Jung-Hwa Lee[1], Hosung Yoon[2], Daejun Kim[1], Chul-Soo Cho[3] and Wan-Uk Kim[1]. [1]The Catholic University of Korea, St. Vincent's Hospital, Suwon, South Korea, [2]The Catholic University, Incheon, South Korea, [3]The Catholic University of Korea, Seoul

Background/Purpose: Chronic inflammatory diseases, including rheumatoid arthritis (RA), have been implicated in the increased risk of dyslipidemia. Apolipoprotein M (apoM) is a novel apolipoprotein predominantly associated with high-density lipoprotein cholesterol (HDL-C). In this study, we investigated the possible association of *APOM* polymorphism and dyslipidemia in Korean RA patients.

Methods: A genome-wide association scan (GWAS) was performed 100 RA patients and 600 controls using Affymetrix SNP array 5.0. Two-hundred fifteen well-characterized RA patients, who provided complete genotyping, were evaluated for this cross-sectional study. Fasting lipid profile, disease activity in 28 joints, inflammatory markers, and radiographic severity using modified Sharp method were also assessed.

Results: Through GWAS, APOM gene was identified as a novel SNP associated with RA (rs805297, odds ratio (OR)=2.28 [1.65–3.14], $P<0.001$). RA patients had increased frequency of *A* allele on apoM C-1065A compared to the controls (44.8 % versus 36.4 %, OR=1.40 [1.19–1.65], $P<0.001$). RA patients with APOM 1605 *A* carriers (*CA+AA*) had higher levels of total cholesterol and low-density lipoproteins, as well as lower levels of HDL-C and pre-b-HDL-C than those with CC genotype. After adjustment of gender, BMI, diabetes, medications, and inflammatory markers, APOM genotype was strongly associated with low HDL-C (OR=2.75 [1.17–6.5], $P=0.021$). Moreover, when subgroup analyses according to disease activity and Sharp score were performed, the association between APOM genotype and low HDL-C levels was still significant in all subgroups, indicating that APOM polymorphism may increase the risk of dyslipidemia, independent of disease activity and radiographic severity of RA.

Conclusion: The APOM C-1605A polymorphism is associated with an increased risk for developing RA and low HDL-C levels in RA patients. Reduced HDL-C level is independent of disease activity and severity, but it is significantly influenced by APOM genotype. These findings suggest that a certain genetic factor itself for RA could be fundamentally linked to dyslipidemia, increasing the risk of atherosclerosis.

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Increased Frequency of Complement *C4B* Deficiency in Rheumatoid Arthritis (RA): Interaction with the Shared Epitope (SE). William F. C. Rigby[1], Y.L. Wu[2], Moe T. Zan[3], Bi Zhou[2], Sanna Rosengren[4], Cheryl Carlson[5], Whitney Hilton[5], Jonathan D. Jones[6] and Chack-Yung Yu[7]. [1]Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [2]Nationwide Children's Hospital The Ohio State University, Columbus, OH, Columbus, OH, [3]Dartmouth-Hitchcock Clinic, Manchester, NH, [4]UCSD School of Medicine, La Jolla, CA, [5]Dartmouth Hitchcock Med Ctr, Lebanon, NH, [6]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [7]7Center for Molecular and Human Genetics, The Research Institute at Nationwide Children's Hospital and The Ohio State University, Columbus, OH

Background/Purpose: There is an increased frequency of complement *C4A* deficiency in Systemic Lupus Erythematosus (SLE). We assessed the Copy Number Variation (CNV) of complement *C4A* and *C4B* genes in patients with Rheumatoid Arthritis RA

Methods: DNA from 299 patients and volunteers were analyzed for CNV of total complement *C4, C4A,* and *C4B* genes by Southern blotting and real-time qPCR. These results were analyzed by chi-square analysis and odds ratios calculated. The presence or absence of the shared epitope (SE) was determined on all seropositive RA patients (n=113) as well as seronegative RA, non-RA controls and healthy volunteers with heterozygous deficiency (0–1 allele) for C4B (n=44).

Results: Chi-square analysis revealed similar distribution patterns of total *C4* alleles in RA (n=160), non-RA (n=88) rheumatology patients and in normal volunteers (n=51). There was no trend to *C4A* deficiency as seen in SLE. RA patients exhibited a ~2-fold increase in the frequency (40%) of homozygous and/or heterozygous *C4B* deficiency (0 or 1 allele) relative to non-RA patients (21%) or healthy controls (22%). This *C4B* deficiency concentrated in the seropositive RA patients relative to seronegative RA (44% vs 31%). The odds of *C4B* deficiency were 2.99 (C.I. 1.58–5.65 p=0.0006)

in the seropositive RA patient relative to non-RA controls. These findings were confirmed using a larger healthy control cohort (n=513) as a comparator, where an odds ratio of 1.83 (C.I. 1.21–2.76) p=0.0056 was observed. The shared epitope (SE) was present in 94/113 (83%) of seropositive RA patients (Table 1), similar to previous reports. In the 50 seropositive RA patients with C4B deficiency, the SE was present in 48/50 seropositive RA patients (96%) relative to seropositive RA patients with >2 *C4B* alleles (46/63, 73%, p<0.0009). In the 44 individuals with complement *C4B* deficiency that did not have seropositive RA, the frequency of the SE was 55% (24/44), which is similar to that seen in in the healthy volunteers/non-RA controls (17/30) and the general population. Thus, the frequency of the association of SE with C4B deficiency was significantly greater in the seropositive RA patient population relative to non-seropositive RA controls, 96% vs 55%, p<0.0001. The same level of statistical significance was seen using only the non-RA/healthy volunteers as a comparator (p<0.0001). Thus, while SE appears to be linked to heterozygous C4B deficiency, this linkage is further strengthened in seropositive RA, suggesting a functional interaction.

Table 1. Incidence of C4B Isotype Deficiency Increased in Sero+ and SE+ RA

Group	SE frequency (%)	p value
Seropositive RA	**94/113 (83%)**	
C4B (<2)	**48/50 (96%)**	
C4B (>2)	**46/63 (76%)**	**p=0.0009**
Non-Seropositive RA		
C4B (<2)	**24/44 (55%)**	**p<0.0001**
Non-RA/Volunteers	**17/30 (57%)**	**p<0.0001**

Conclusion: *C4B* CNV exhibits a clear relationship with RA that approximates that seen between *C4A* CNV and SLE. Given this frequency and the strength of this relationship, this finding has broad implications for our understanding of RA.

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The STAT4 rs7574865 Polymorphism Is Associated with Differences in Disease Activity and Disability in Patients Wirh Early Arthritis. Ana M. Ortiz[1], Amalia Lamana[1], Alejandro Balsa[2], Blanca Rueda[3], Laura Nuño[2], Maria Eugenia Miranda-Carus[2], María F. González-Escribano[4], Miguel A. López-Nebot[5], Dora Pascual-Salcedo[2], Javier Martin[6] and Isidoro González-Alvaro[1]. [1]Hospital Universitario de La Princesa. IIS Princesa, Madrid, Spain, [2]Hospital La Paz. IdiPaz, Madrid, Spain, [3]Facultad de Ciencias de la Salud. Universidad de Granada, Granada, Spain, [4]Hospital Universitario Virgen del Rocío, Sevilla, Spain, [5]Hospital Universitario Virgen de las Nieves, Granada, Spain, [6]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain

Background/Purpose: The presence of shared epitope and the minor allele of single nucleotide polymorphisms (SNPs) of STAT4 (rs7574865) and PTPN22 (rs2476601) have been associated with an increased risk of developing rheumatoid arthritis (RA). However, it is not well established whether these genetic markers could also determine a more severe clinical course of RA. The objective was to determine whether the genetic variants of *STAT4* rs7574865 and *PTPN22* rs2476601 and the number of copies of the shared epitope in *HLA-DRB1* affect disease activity or disability in patients with early arthritis (EA).

Methods: We studied 596 patients (75% female, median age at onset 51 years) of the EA registers of Hospital U La Paz and La Princesa in Madrid, who were followed up 2 years with visits every 6 months. Demographic and disease variables (rheumatoid factor, anti-CCP antibody [a-CCP, Euro-Diagnostica ELISA. Arnhem, Holland]), HAQ and variables needed to the estimation of DAS28 were collected. The HLA-DRB1 alleles were determined by medium-resolution technique (PCR-SSO) and sequencing was only done for the determination of certain subtypes of DR4. Genotyping of rs7574865 and rs2476601 was performed using real-time PCR and specific Taqman probes (Applied Biosystems). Multivariate analysis was performed using generalized estimating equations for repeated measures using the function xtgee of Stata 10.1 for Windows (StataCorp LP, College Station, TX, USA). We used the method "backward stepwise selection" to achieve the best fitting model, removing from the initial model, which included all independent variables, all those with $p > 0.15$.

Results: Female gender (β coefficient = 0.50 ± 0.13; $p < 0.001$), older age ([by 10 year] 0.22 ± 0.03; $p < 0.001$), a-CCP positivity (0.22 ± 0.21; $p = 0.056$) and TT genotype of rs7574865 in STAT4 (0.71 ± 0.32; $p = 0.024$) were associated with greater disease activity as measured by DAS28. A trend towards greater disease activity was detected in active smokers (0.25 ± 0.23; $p = 0.074$), whereas no association was found between the value of DAS28 and the presence of shared epitope and a tendency to lower activity in the homozygous minor allele of SNP in PTPN22 (−0.74 ± 0.92; $p = 0.132$) was also observed. There was no additive or synergistic effect between the presence of a-CCP and STAT4. On the other hand, female gender (0.1 ± 0.08; $p < 0.015$), older age ([by 10 year] 0.03 ± 0.02; $p = 0.003$) and heterozygosity (0.08 ± 0.07; $p = 0.035$) or homozygosity (0.17 ± 0.15; $p = 0.022$) for the T allele of rs7574865 in STAT4 were associated with functional capacity.

Conclusion: Our data suggest that EA patients with the minor allele of SNP rs7574865 in STAT4, in addition to a higher risk of developing RA, would have a more severe disease with increased activity and disability. These data have not been observed for the presence of shared epitope or PTPN22 variant that confers increased risk of RA.

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The Complexity of Anti-CCP Positive Rheumatoid Arthritis, in the Context of Gene-Environment Associations. Karin Lundberg, Camilla Bengtsson, Lena Israelsson, Nastya Kharlamova, Iskra Pollak-Dorocic, Rikard Holmdahl, Leonid Padyukov, Vivianne Malmström, Lars Alfredsson and Lars Klareskog. Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Risk factors for rheumatoid arthritis (RA), such as *HLA-DRB1* 'shared epitope' (SE) alleles, *PTPN22* and cigarette smoking, associate with anti-CCP positive disease. By subdividing CCP positive patients based on reactivity to CEP-1, the immunodominant B cell epitope on citrullinated alpha-enolase, we have previously shown that SE, *PTPN22* and smoking mainly constitute risk factors for CEP-1 positive, rather than CCP positive RA[1]. In this study, we investigate gene-environment associations with different subsets of RA, based on presence of anti-CCP and specific anti-citrullinated protein/peptide antibodies (ACPAs), including antibodies to CEP-1 and citrullinated peptides from vimentin (Cit-vim), fibrinogen (Cit-fib) and collagen type II (CII Cit-C1).

Methods: Presence of antibodies were analysed by ELISA (Immunoscan CCPlus (Euro-Diagnostica) and in-house peptide ELISAs) in 1985 RA patients from the Swedish population-based case-control study EIRA. One hundred and fifty healthy controls were used to determine the 98th percentile cut-off for positivity. A positive and a negative control serum and a standard of pooled antibody-positive sera were included on each plate. Different RA subsets were compared with regard to risk factors, by calculating odds ratios with 95% confidence interval by means of logistic regression.

Results: Antibody frequencies were: CCP (63%); CEP-1 (36%); Cit-vim (37%); Cit-fib (28%); CII Cit-C1 (37%). Most patients showed reactivity to multiple citrullinated antigens, though single-positive subsets of patients were also identified for each specific ACPA. Associations with the risk factors correlated with the number of ACPAs present, as well as anti-CCP antibody levels. However, SE, *PTPN22* and smoking associated specifically with CEP-1 positive and Cit-vim positive RA, but not with Cit-fib and Cit-C1 positive RA.

Conclusion: Our data show the complexity of CCP positive RA and that this subset can be further divided based on the fine-specificity of the ACPA response. SE, *PTPN22* and smoking seem to predispose for the development of ACPA with multiple reactivities, rather than one single specificity. However, clear differences with regard to gene-environment associations with specific ACPAs can also be identified, suggesting different etiological pathways in different subsets of anti-CCP positive RA patients.

Reference:

1. Mahdi et al, Nat Genet 41, 1319–1324 (2009).

2162

Genome-Wide Association Study and Comparison of Risk Alleles for Rheumatoid Arthritis in An Isolated Dutch Population. Joanne Nitiham[1], Kimberly E. Taylor[1], Yurii S. Aulchenko[2], Ben Oostra[2], Robert M. Plenge[3], Tom W.J. Huizinga[4], Peter K. Gregersen[5], Cornelia M. van Duijn[2] and Lindsey A. Criswell[1]. [1]University of California, San Francisco, San Francisco, CA, [2]Erasmus Medical Center, Rotterdam, Netherlands, [3]Brigham and Women's Hospital, Boston, MA, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Feinstein Institute Medical Reschearch, Manhasset, NY

Background/Purpose: Rheumatoid arthritis (RA) is a genetically complex autoimmune disease causing severe disability through joint destruction

and deformity. Alleles of the of the *HLA-DRB1* locus in the major histocompatibility complex (MHC) have long been known to increase risk of RA; recent genome-wide association studies (GWAS) have resulted in over 30 established loci associated with RA risk. However, effects of these loci are small and much of the heritability of RA is not explained. Isolated populations offer a unique opportunity for the study of genetic diseases, as certain disease-causing alleles may be enriched in such populations.

Methods: We performed Illumina 660W genotyping on 201 RA cases and 100 healthy controls from a genetically-isolated Dutch population, and utilized Illumina 317K genotyping on another 500 healthy controls from the isolate. After strict quality control, SNPs were imputed up to the HapMap2 using MACH, and SNPs retained with quality score > 0.8 and RSQ > 0.3. We also obtained genotypes for known RA risk SNPs from 2 cohorts: anti-CCP+ or RF+ cases (5,539) and healthy controls (20,169) from a pan-European study, and anti-CCP+ cases (157) and healthy controls (702) from a non-isolated Dutch population. First, we compared 49 RA risk SNPs in our anti-CCP+ cases (131) and controls (555) to those from the pan-European study, and to a subset of SNPs typed in the Dutch non-isolate. Second, we performed a GWAS of our full cohort using the software ProbABEL in order to account for imputed genotype probabilities and relatedness in the population. New SNP associations will be investigated in replication cohorts.

Results: Although 17 (35%) of the RA risk SNPs had evidence of different background (control) frequencies ($p<0.01$), only 6 SNPs had evidence of heterogeneity of odds ratios (ORs) ($p_{het}<0.1$) between the isolate and pan-European cohorts. A SNP of gene TNFRSF14/MMEL1 had a significantly stronger protective effect in the isolate, OR=0.62 (95% CI 0.44–0.87) versus OR=0.89 (0.85–0.94), $p_{het} = 0.037$. Comparison to the Dutch non-isolate supported that differences are due to isolate membership versus Dutch ancestry. In our GWAS, in spite of the relatively small size of this study, 58 SNPs in the MHC reached genome-wide significance ($p < 5\times10^{-8}$), with the top hit as expected in the *HLA-DRB1-HLA-DQA1* region. In addition there were 31 regions outside of the MHC with at least two signals with $p<5\times10^{-8}$, which have not been implicated previously.

Conclusion: For most established RA risk alleles this isolated Dutch population has similar risk distributions to that of a pan-European cohort, with some exceptions. Our GWAS has identified additional loci with preliminary evidence of association with RA in this population.

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Vitamin D Receptor Polymorphism rs2228570 (FokI) in North American Natives with Rheumatoid Arthritis and Their Unaffected First Degree Relatives. Carol A. Hitchon[1], Ye Sun[2], David B. Robinson[1], Christine A. Peschken[1], Charles N. Bernstein[1], Katherine A. Siminovitch[2] and Hani S. El-Gabalawy[1]. [1]University of Manitoba, Winnipeg, MB, [2]Mount Sinai Hospital, Toronto, ON

Background/Purpose: North American Natives (NAN) have high prevalence rates for rheumatoid arthritis. Our previous studies of a Cree/Ojibway population in Central Canada have shown an early age of onset, high prevalence and titers of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) and shared epitope alleles in the background population. 25 OH Vitamin D (VitD) has immune effects of potential importance to RA pathogenesis and low serum levels have been associated with RA and disease activity in other populations. We sought to examine association of the RS2228570 (FokI) polymorphism of the VitD receptor gene with RA susceptibility in the NAN population.

Methods: We tested NAN RA patients (n=458) and unrelated controls without autoimmune disease (n=715) were tested for the RS2228570 (FokI) single nucleotide polymorphism of the vitamin D receptor gene. The genotyping data were analyzed using genotypic (DD vs Dd vd dd), allelic (D vs d), dominant (DD, Dd vs dd), and recessive (DD vs Dd, dd) models.

Results: The minor allele frequency in the unaffected control group was 0.43. Significant differences between affected RA patients (90/240/118) and unaffected controls (157/307/241) were found using the genotypic model (ChiSq 11.83; p=0.0027). Using an allelic modle, there was no significant difference between the RA patients and controls (OR 1.12 p=NS, CI 0.95–1.32). Analysis using the dominant model was significant (RA=330/118 vs Controls=464/241 OR 1.45 p=0.006 CI 1.12–1.89). No interactions were seen between the presence of ACPA, RF and VitD receptor polymorphisms in the RA population.

Conclusion: The RS2228570 (FokI) VitD receptor polymorphism is associated with RA in the NAN population. Since VitD is important in maintaining dendritic cell tolerance, polymorphisms of the VitD receptor may contribute to loss of self tolerance in RA.

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The I50V *IL4R* SNP Is Associated with Increased Th17 Cell Frequency and Activity in Autoimmune Arthritis. Jan Leipe[1], Iryna Prots[2], Markus A. Schramm[1], Alla Skapenko[1] and Hendrik Schulze-Koops[1]. [1]Division of Rheumatology and Clinical Immunology, Med. Poliklinik, University of Munich, Munich, Germany, [2]Junior Research Group III, Nikolaus-Fiebiger Center for Molecular Medicine, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen

Background/Purpose: Th17 cells are increased in active rheumatoid and psoriatic arthritis (RA, PsA) and are thought to be the driving force of autoimmune inflammation in these diseases. On the other hand, a single nucleotide polymorphism (SNP) in the *IL-4R* gene (I50V, rs 1805010) has previously been associated with an aggressive destructive course of RA. In this regard, CD4 T cells expressing the V50 variant of the IL-4R are hyporesponsive to the activity of IL-4. Since Th17 cell development is negatively regulated by IL-4, here we investigated if the I50V *IL-4R* SNP is associated with the observed increase of Th17 cells in active RA.

Methods: *IL4R* genotypes for I50V SNP were determined in well-defined cohorts of patients with RA (n = 28) and PsA (n = 18); as well as in controls: healthy controls (n=21) and patients with osteoarthritis (OA, n=15) by TaqMan SNP assay. IL-17 serum levels and *ex vivo* Th17 cell frequencies were analyzed by multi-color flow cytometry and ELISA. To assess the inhibitory effect of IL-4 on Th17 cell development, we primed CD4 T cells for 72 h in the presence or absence of IL-4 and determined Th17 cell frequencies.

Results: Although the IL-17 serum level was not elevated in the overall cohort of RA or PsA patients, patients homozygous for the V50 allele variant demonstrated significantly higher IL-17 serum levels as compared to I50I or I50V patients and to healthy or OA controls. Accordingly, the frequencies of Th17 cells were significantly increased in the V50V groups of RA and PsA patients. When the IL-4 inhibitory effect on Th17 cell development was investigated *in vitro*, cells from V50V individuals responded weaker to IL-4 inhibition as compared to their I50I or I50V counterparts. In V50V cells, the diminished inhibitory effect of IL-4 on Th17 development was more pronounced in RA and PsA patients compared to controls and was even completely absent in some patients. Of note, clinical activity was consistently high in V50V patients during two years of follow-up despite similar treatment regimens.

Conclusion: Together, the data indicate that the V50 allele of the I50V *IL4R* SNP renders CD4 T cells insensitive to IL-4 *in vivo* and may thus contribute to the increased Th17 cell frequency and activity characteristic for RA and PsA.

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Gene Polymorphisms of Signal Transducers and Activator of Transcription 4 and Tumor Necrosis Factor Receptor-Associated Factor 1 Predict Clinical Response to Disease-Modifying Anti-Rheumatic Drugs in Japanese Patients with Rheumatoid Arthritis. Tetsuya Nishimoto, Noriyuki Seta, Ryusuke Anan, Tatsuya Yamamoto, Yuko Kaneko, Masataka Kuwana and Tsutomu Takeuchi. Keio university, Tokyo, Japan

Background/Purpose: Several single nucleotide polymorphisms (SNPs) associated with pathophysiology of rheumatoid arthritis (RA) have been identified in recent genome-wide association studies. Although disease-modifying anti-rheumatic drugs (DMARDs) including biologic agents, such as anti-tumor necrosis factor (TNF) drugs, have excellent efficacy against RA, a substantial number of patients still show inadequate responses. The aim of this study is to identify genetic predictors of response to non-biologic DMARDs, especially methotrexate (MTX), and anti-TNF drugs in RA patients using database of a single-centre prospective cohort study of Japanese patients with newly diagnosed and DMARDs-naïve RA (SAKURA study).

Methods: Fc receptor-like protein 3 (FCRL3) (-169A/G), signal transducers and activator of transcription 4 (STAT4) (+56293G/T), cytotoxic T lymphocyte antigen 4 (CTLA4) (+49G/A), peptidyl arginine deminase type IV (PADI4) (+163A/G), interferon regulatory factor 5 (IRF5) (+198G/T), and TNF receptor-associated factor 1 (TRAF1) (+16860A/G) were genotyped using TaqMan® SNP genotyping assay. We enrolled 114 untreated newly diagnosed Japanese RA patients, and prospectively analyzed the association between the SNPs and clinical response to treatment with DMARDs including biologics or MTX monotherapy as a first line treatment using the 28-joint Disease Activity Score (DAS28) at 24 weeks after registration. Moreover, in 28 RA patients treated with anti-TNF drugs in combination with MTX as a first biologic agent, such as infliximab, etanercept and adalimumab, we prospectively analyzed the association between SNPs and the clinical response using DAS28 and Simplified Disease Activity Index (SDAI) at 24 weeks of treatment.

Results: There was no association between each SNP and disease activity at baseline. Of 114 RA patients enrolled, 69 (60.5%) were treated with MTX, 41 (36.0%) with other non-biologic DMARDs, and 19 (16.7%) with biologic agents at 24 weeks after registration, although 34 (29.8%) patients were treated with more than one agent. Among them, 51 (44.7%) achieved a good response based on the DAS28 response criteria. FCRL3 (-169A/G) G allele (47.2% versus 30.8%, P=0.011, OR 2.01, 95%CI 1.17–3.45) and STAT4 (+56293G/T) G allele (76.9% versus 58.3%, P=0.003, OR 2.37, 95%CI 1.33–4.21) were increased in patients with a good response, compared with those with a moderate or no response. In 46 RA patients received MTX monotherapy for 24 weeks from diagnosis, 24 (52.2%) achieved a good response, and STAT4 (+56293G/T) G allele (75.0% versus 45.5%, P=0.003, OR 3.60, 95%CI 1.49–8.70) was also increased in patients with a good response. Interestingly, in 28 RA patients treated with anti-TNF drugs in combination with MTX as a first biologic agent, TRAF1 (+16860A/G) A allele was increased in patients with a good response based on DAS28 (88.9% versus 60.0%, P=0.012, OR 5.33, 95%CI 1.35–21.02), and a remission based on SDAI (92.3% versus 66.7%, P=0.020, OR 6.00, 95%CI 1.18–30.62).

Conclusion: STAT4 (+56293G/T) and TRAF1 (+16860A/G) are possibly useful in predicting the clinical response to MTX monotherapy as a first DMARD and anti-TNF drugs as a first biologic agent respectively.

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Fine-Mapping of Autoimmune Susceptibility Loci Using Immunochip Identifies Novel Susceptibility Loci for Psoriatic Arthritis. John Bowes[1], Pauline Ho[2], Eleanor Korendowych[3], Neil J. McHugh[3], Helena Marzo-Ortega[4], Jonathon Packham[5], Ian N. Bruce[1] and Anne Barton[1]. [1]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK, Manchester, United Kingdom, [3]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [4]University of Leeds, Leeds, United Kingdom, [5]Haywood Hospital, Stoke on Trent, United Kingdom

Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory joint disease that typically accompanies psoriasis vulagris (PsV). Both conditions are considered to be complex diseases with both genetic and environmental susceptibility factors. Genome-wide association studies (GWAS) have identified a number of genetic susceptibility loci for both diseases. Comparing GWAS results performed in many common autoimmune diseases has revealed an extensive overlap in the genetic liability between autoimmune diseases in general. Based on the observed sharing of susceptibility loci across autoimmune diseases, the aim of this project is to identify novel susceptibility loci for PsA by fine-mapping all the currently confirmed susceptibility loci for 12 autoimmune diseases.

Methods: Data was available for 929 PsA cases and 4537 healthy controls genotyped using the Immunochip Illumina iSelect array at the Sanger Centre (www.sanger.ac.uk). Control data was sourced from the WTCCC (www.wtccc.org.uk). This custom array was designed to comprehensively fine-map confirmed autoimmune susceptibility loci and contains 196,524 SNPs covering approximately 200 candidate regions. A strict SNP-focused quality control process was applied to the dataset followed by single point analysis using the Armitage test for trend.

Results: Association analysis of 182,883 high quality SNPs in 862 cases and 4306 controls robustly detected association to previously confirmed PsA risk loci; *HLA-C* ($p = 8.2\times10^{-35}$), *IL23R* ($p = 8.4\times10^{-8}$) and *TRAF3IP2* ($p = 2.8\times10^{-7}$), *IL12B* ($p = 6.5\times10^{-6}$). In addition we find convincing evidence to support association to a number of novel loci not previously reported for PsA, including; 17q21 ($p_{trend} = 3.3\times10^{-05}$, *SMARCE1)*, 18p11 ($p_{trend} = 2.0\times10^{-05}$, *PTPN2)*, 11q23 ($p_{trend} = 1.4\times10^{-05}$, *TREH)*, and 19p13 ($p_{trend} = 9.8\times10^{-05}$, *TYK2)*. Interestingly, we also find convincing evidence for association to the *CARD15* gene, supported by multiple SNPs.

Conclusion: The preliminary single point analysis of an autoimmune loci fine-mapping dataset identifies a number of potential novel loci for PsA susceptibility. Validation of these results is currently underway in an independent sample collection. Single-point analysis will be followed by analyses to indentify independent effects within the previously identified and newly discovered loci.

2167

The Potential Role of *PTPRD* Gene Copy Number Variation in Susceptibility to Rheumatoid Arthritis. Seung Cheol Shim, Donghyuk Sheen, Mi-Kyoung Lim, Jiyoung Kim, Soyoung Lee and Sangkwang Lee. Eulji University Hospital, Daejeon, South Korea

Background/Purpose: Since it is important to explore genetic variations associated with rheumatoid arthritis (RA), genome-wide association studies (GWAS) have led to the identification of RA genetic variants putatively associated with susceptibility. Recently, copy number variation (CNV) may also affect susceptibility to diseases, which have been already observed in diverse autoimmune diseases. Protein tyrosine phosphatase receptor D (PTPRD) is a member of the receptor-like PTP which expresses in the B cell lines and thymus and could be involved in the pathogenesis of autoimmune diseases. In this study, we investigated whether the variation of the *PTPRD* gene copy number related with susceptibility to RA.

Methods: To investigate whether the variation of the *PTPRD* gene copy number influence the pathogenesis to RA, blood samples and clinical records were obtained from 217 RA patients (184 females, 33 males) and 205 healthy controls. The genomic DNA of RA patients and healthy controls was extracted from leukocytes in peripheral blood using the Genomic DNA Extraction kit (iNtRON Biotechnology, Korea). To measuring the copy number of *PPTRD* gene, the quantitative real-time PCR (QPCR) was carried out using Mx3000P QPCR system (Stratagene, La Jolla, CA) and each sample for each gene was assayed in triplicate.

Results: The copy number of *PTPRD* gene in RA patients was compared with that in healthy controls. The proportion of the individuals with <2 copy of *VPREB1* was significantly higher in patients than in controls, while that of the individuals with >2 copy was lower in patients than in controls. The average relative copy number of the *PTPRD* gene in RA patients (1.14, 95 % CI (1.12–1.16)) was significantly lower than that in healthy controls (1.65, 95 % CI (1.12–1.16), $p < 0.0001$) (Figure 1). Furthermore, we also investigated association between copy number of *PTPRD* and RA phenotype such as RF factor and anti-CCP levels, which showed no association between copy number of *PTPRD* and both RA phenotypes.

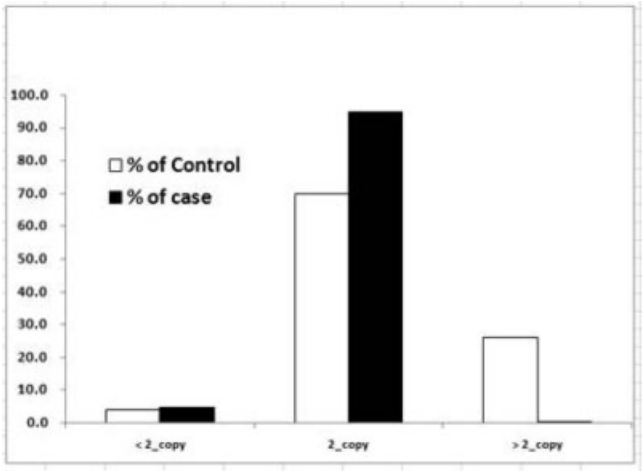

Figure 1. Relative gene copy numbers of *PTPRD* in RA patients and healthy controls. Relative amount of gene copy numbers of *PTPRD* in RA patients (n = 217) was compared to that in healthy controls (n = 205) by Quantitative PCR. Each of gene copy number was normalized to *HS6ST3* gene used as an internal control. The mean copy number of *PTPRD* in RA patients (1.14, 95 % CI (1.12–1.16)) was significantly lower than that in healthy controls (1.65, 95 % CI (1.12–1.16)) ($P<0.0001$). Bar show the mean ± SD for each group.

Conclusion: This is the first evidence showing the association between low copy number of the PTPRD gene and susceptibility to RA, which may help understanding the pathogenesis of RA and other autoimmune disorders like affecting maturation and differentiation of T cell and B cells.

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Exposure to Environmental Tobacco Smoke and the Risk of Rheumatoid Arthritis Among Nonsmoking Women. So-Young Bang, Hye-Soon Lee, Jae Hoon Kim, Joo-Hyun Lee, Jin Ju Kim, Young Bin Joo and Sang-Cheol Bae. Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

Background/Purpose: Smoking is the major known environmental risk factor for rheumatoid arthritis (RA). International meta-analyses have indicated that exposure to environmental tobacco smoke (ETS) results in significantly higher risks for many diseases as well as smoking. Although ETS may play an important role in the development of RA who never smoked, the association between exposure to ETS and RA has never been investigated.

The objectives of this study are to examine the prevalence of ETS in

nonsmoking women with RA, and to investigate whether ETS contribute to the development of RA.

Methods: A total of 1,450 women patients from BAE RA cohort, who fulfilled the American College of Rheumatology 1987 classification criteria for RA, and 897 healthy women were recruited in a Korean population. The RA patients (n =1,330) and controls (n = 868) were nonsmoking women. Four-digit HLA-DRB1 typing was performed by a conventional PCR-SBT method. Information about smoking and ETS history was obtained through a questionnaire by face-to-face interviews. Odds ratios (OR) with a 95% confidence interval (CI) were calculated by multivariate logistic regression.

Results: The frequency of smokers in Korean women (RA 8.3%, control 3.2%) was much lower than in Caucasian. The prevalence of ETS at home (> 3 day/week) was 21.0 % (n=279) in our RA cohort. The exposure to ETS (> 3 day/week) at home was associated with RA [OR 1.36 (95% CI: 1.05 1.75), p = 0.02] compared with the risk among nonsmokers exposed to ETS (< 3 day/week), when adjusted for age and HLA-DRB1 shared epitope alleles. Furthermore, the daily exposure to ETS at home [OR 1.68 (95% CI: 1.27 – 2.21), $p = 2.51 \times 10^{-4}$] increased the risk for RA compared with the risk among nonsmokers exposed to ETS (< 3 day/week) by multivariate logistic regression.

Conclusion: Exposure to ETS at home may confer an increased risk of RA among women who never smoked.

2169

Smoking and Oxidative Stress Interaction Is Associated with Rheumatoid Arthritis Risk. A Case–Control Study. Victoria Navarro Compán, Enrique Melguizo Madrid, Blanca Hernández Cruz, Christian Leyva Prado, Teresa Arrobas Velilla, Federico Navarro Sarabia and Concepción González Rodríguez. Hospital Universitario Virgen Macarena, Sevilla, Spain

Background/Purpose: The main objective of this study is to establish an association between smoking, oxidative stress and the development of rheumatoid arthritis (RA).

Methods: A case-control study, including disease-modifying antirheumatic drugs (DMARD) and glucocorticoids naïve early RA patients (1987 criteria) and healthy age, sex and smoke habit matched controls. Smoking was recorded by current habit and pack-year index. Oxidative stress was determined by measuring of plasmatic levels of malonildialdehyde (MDA), carbonyl protein (CP) and lipid hidroperoxide (LOOH). Statistical analysis was performed using the STATA 10.0.

Results: A total of 65 RA patients and 65 controls were included. Statistically significant differences between groups were found in antibodies and genetic variables associated with the disease. Pack-year index was associated with RA risk, OR of 4.0 and 6.5 for amount higher to 20.1 and 34 pack-year, respectively. Association was also observed between plasma LOOH and CP levels and RA risk, increased for levels higher than 27.1 mM (OR 2.4) for LOOH and 67 mM (OR 2.2) and 120 mM (OR 3.1) for CP. Negative association was observed between MDA levels and RA risk, OR 4.7 for MDA<7.7 mM.

Table 1. OR and corresponding 95% CI, adjusted by age, sex and smoking habit

	RA patients			Controls			
Pack-years	**Medium**	**IQR**	**n**	**Medium**	**IQR**	**n**	**OR (95% CI)**
0	0		30	0		39	0.77 (0.48–123)
0.1–8.0	4.5	1.6–5.5	7	2.5	1.2–5.0	10	0.70 (0.27–1.83)
8.1–20.0	15.0	13.0–16.0	7	10.5	9.2–17.8	12	0.58 (0.23–1.45)
20.1–34.0	25.8	23.2–30.8	8	25.0	21.0–29.0	2	4.00 (0.85–18.83)
>34.0	50.0	40.2–73.2	13	35.0	34.5–40.0	2	6.50 (1.47–28.80)
LOOH (μM)	**Medium**	**IQR**	**n**	**Medium**	**IQR**	**n**	**OR (95% CI)**
0–13.0	4.9	3.7–7.4	5	6.2	1.3–9.4	25	0.20(0.08–0.52)
13.1–27.0	21.0	17.2–23.5	13	17.7	15.5–21.4	21	0.62 (0.31–1.23)
27.1–43.0	36.1	30.2–40.2	24	31.9	29.2–35.6	10	2.40 (1.15–5.02)
>43.0	54.3	49.5–64.3	23	64.3	47.2–72.8	9	2.56 (1.18–5.52)
CP(μM)	**Medium**	**IQR**	**n**	**Medium**	**IOR**	**n**	**OR(95% CI)**
0–40.0	29.5	14.0–38.0	5	23.6	16.1–30.7	29	0.17 (0.07–0.44)
40.1–67.0	53.5	48.3–59.1	15	51.6	46.3–57.2	19	0.79 (0.40–1.55)
67.0–120.0	106.2	87.8–115.2	20	90.2	75.0–99.1	9	2.22 (1.01–4.88)
>120.0	167.2	138.6–201.1	25	139.9	126.7–164.9	8	3.12 (1.40–6.93)
MDA (μM)	**Medium**	**IQR**	**n**	**Medium**	**IQR**	**n**	**OR (95% CI)**
0–7.7	6.5	6.0–7.2	28	7.47	7.1–7.7	6	4.66 (2.16–14.5)
7.8–8.6	8.2	8.0–8.3	20	8.3	8.1–8.5	17	1.18 (0.68–2.60)
8.6–10.0	9.1	9.0–9.9	7	9.1	8.7–9.8	22	0.32 (0.15–0.83)
>10.0	11.6	10.3–13.0	10	10.6	10.4–11.3	20	0.50 (0.22–1.11)

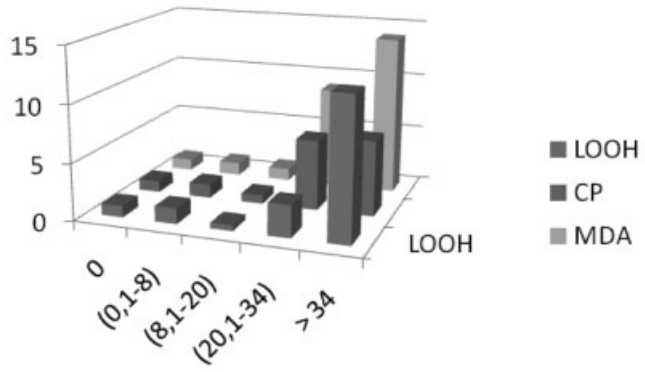


Figure 1. OR and corresponding 95% CI due to interaction for different amount of smoking (pack-years) and plasmatic levels of oxidative stress biomarkers (LOOH and CP).

The interaction of smoking and LOOH or CP increased RA risk, OR 12.3 for pack-years>34 for LOOH and OR 6.2 for pack-year>20.1 for CP. The interaction of smoking and MDA was associated with RA risk, OR 9.0 and 13.4 for pack-year>20.1 and >34 respectively.

Conclusion: The interaction between oxidative stress and smoking is associated with the RA risk.

2170

Smoking and Periodontal Status Are Associated with ACPA Fine Specificity and Levels of Inflammatory Cytokines in Rheumatoid Arthritis: The ARIC Study. Reuven Bromberg[1], Jeremy Sokolove[1], Lauren J. Lahey[1], Alvaro Alonso[2], Mark H. Wener[3], Vivian H. Gersuk[4], Jane Hoyt Buckner[4], James D. Beck[5], Bryan S. Michalowicz[6], Aaron A. Folsom[2], William Robinson[7] and Jerry A. Molitor[8]. [1]Stanford University, Palo Alto, CA, [2]Minneapolis, [3]University of Washington, Seattle, WA, [4]Benaroya Research Institute, Seattle, WA, [5]Chapel Hill, NC, [6]Minneapolis, MN, [7]Stanford Univ School of Med, Stanford, CA, [8]Univ of MN MMC108, Minneapolis, MN

Background/Purpose: Environmental factors predisposing to the development of rheumatoid arthritis (RA) include tobacco exposure (TE) and possibly periodontal disease (PD). Only TE has been clearly associated with risk for anti-citrullinated protein antibodies (ACPA). We sought (i) to determine whether periodontal disease (PD) was associated with an increased risk for development of APCA, (ii) to assess for interaction between TE and PD in the development of APCA, and (iii) whether this interaction was affected by presence of the HLA-DR4 shared epitope (SE).

Methods: We performed serum profiling of 16 putative RA-associated autoantibodies and 47 cytokines in 44 participants of the Atherosclerosis Risk in Communities (ARIC) study with a hospital discharge diagnosis of RA. Participants underwent detailed periodontal assessment (PD status: none or mild; moderate or severe). We evaluated levels of anti-cyclic citrullinated peptide antibodies by a second generation assay (CCP2) as well as breadth, amplitude, and specificity of ACPA targeted by RA patients with current or prior TE; moderate to severe PD; TE with PD; or neither TE or PD.

Results: The average number of ACPA subtypes closely paralleled the average CCP2 value and was higher among RA participants with TE and concurrent PD (Table 1). Small numbers particularly in non-smokers without PD (n=1), limited assessments to qualitative analysis.

Table 1.

	Average CCP2 titer (AU)	**Average # ACPA subtypes**	**n**
Tobacco exposure (TE)	7.55	1.1	11
Periodontal disease (PD)	53.4	2.0	12
TE and PD	224.3	11.5	20

Evaluation of individual ACPAs again suggested an interaction among smokers with PD as demonstrated by much higher levels of most ACPA subtypes among those with TE and PD compared with subjects with TE or PD alone. In most cases there were minimal differences between subgroups with TE or PD alone. An exception was anti-cit-fibrinogen autoantibodies which were elevated in both the TE and PD subgroups; with levels among those with TE approaching average levels of those with TE and PD combined. Among subjects positive for both TE and PD, HLA-DR4 status (7 positive, 12

negative) was associated with ACPA targeting citrullinated enolase, clusterin, and histone 2B.

Levels of 18 serum cytokines including TNFα, IL1β, IFN-γ followed a similar pattern to ACPA and were markedly elevated in the subgroup with combined TE and PD compared with TE or PD alone.

Conclusion: The presence of PD and TE was associated with increased breadth and amplitude of ACPA subtypes. This suggests a possible interaction between the presence of both TE and PD resulting in further increase in CCP2 titer, number of ACPA subtypes represented, and level of most individual ACPA subtypes. HLA-DR4 SE status appears to further influence the development of only a subgroup of ACPA subtypes. The relative lack of a combined effect between smoking and PD for anti-citrullinated fibrinogen antibodies supports a model in which these autoantibodies are formed in response to airway inflammation-induced citrullination of fibrinogen predisposing to autoantibody formation.

2171

Relationships Between Smoking, HLA-DRB1 Risk Alleles and the Fine Specificity of Anti-Citrullinated Peptide Antibodies in Korean Patients with Rheumatoid Arthritis. Benjamin A. Fisher[1], So-Young Bang[2], Hye-Soon Lee[2], Joo-Hyun Lee[2], Muslima Chowdhury[3], Peter J. Charles[4], Patrick Venables[5] and Sang-Cheol Bae[6]. [1]Kennedy Institute of Rheumatology, Imperial College London, London, United Kingdom, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Imperial College London, London, United Kingdom, [4]Kennedy Institute of Rheumatology, Imperial College, London, United Kingdom, London, England, [5]Kennedy Institute, Imperial College London, London, United Kingdom, [6]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea

Background/Purpose: In North European RA cohorts there is a gene-environment interaction between the HLA-DRB1 shared epitope (SE) and smoking as risk factors for development of disease-specific anti-citrullinated protein/peptide antibodies (ACPA). This is particularly strong for antibodies to citrullinated α-enolase and vimentin peptides. East Asian populations have a differing HLA-DRB1 profile and the aim of this study was to examine such associations in a large Korean cohort where the main risk alleles are *0405 and *0901.

Methods: Levels of antibodies were determined to citrullinated peptides from α-enolase (CEP-1), vimentin (cVim) and fibrinogen (cFib), in addition to CCP2, in 513 South Korean patients. Cut-offs were the 95th percentile of 75 healthy controls. Smoking was defined as never (n=417) or ever (n=96). The Mann Witney U Test was used to compare antibody levels. Logistic regression, adjusted for age and sex, generated odds ratios for RA in a case-control analysis with 1101 controls.

Results: Antibodies to CEP-1, cVim, cFib and CCP2 were positive in 46%, 64%, 75% and 87% respectively. The number of citrullinated peptides recognised, as well as the antibody level against each peptide, significantly increased with the number of copies of the SE. This effect was seen with the most prevalent DR4 allele, 0405, as well as for 0101/1001. However it was not observed with the major non-SE HLA risk allele in this population, 0901, or with smoking. In this population there was also a statistically significant association between the SE and anti-CCP2 negative RA. The SE conferred the strongest risks for subsets positive for both anti-CCP2 and either anti-CEP-1 or anti-cVim antibodies, in non-smokers (OR 14.5 and 17.7 respectively with 2 copies of the SE) as well as smokers (OR 17.6 and 30.8 respectively with 2 copies of the SE). However a gene-environment interaction between the SE and smoking was not limited to these subsets. Moreover, combinations of the SE and DRB1*0901 alleles (SE+*0901) were significantly associated with RA risk for subsets with anti-CCP2 and either anti-CEP-1, anti-cVim or anti-cFib antibodies, in the absence of smoking.

Conclusion: Within this population the SE governed the magnitude and breadth of the anti-citrullinated peptide antibody response. However the SE and smoking gene-environment interaction in relation to ACPA subsets differed from that seen in North European populations.

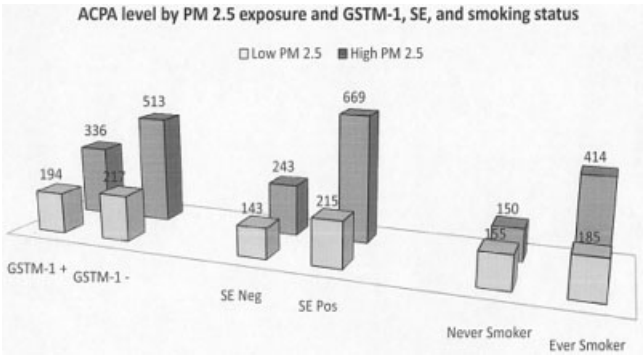
2172

Association of Particulate Air Pollution Exposure with Anti-Citrullinated Protein Antibody Elevation in Rheumatoid Arthritis Patients. Gary A. Kunkel[1], Ryan L. Ragle[1], Daniel O. Clegg[1], Ted R. Mikuls[2] and Grant W. Cannon[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Omaha VA and University of Nebraska, Omaha, NE

Background/Purpose: Cigarette smoking is the major environmental risk factor associated with anti-citrullinated protein antibodies (ACPA) positive rheumatoid arthritis (RA), but other inhalational exposures have also been implicated. The purpose of this study was to explore the association of fine particulate air pollution exposure less than 2.5 micrometers in diameter (PM 2.5) with ACPA and to assess whether smoking history, homozygosity for the deletion allele in the enzyme *glutathione S-transferase Mu-1(GSTM-1 null),* and *HLA-DRB1 shared epitope (SE)* status impacted PM 2.5 association on ACPA.

Methods: PM 2.5 exposure was determined for 320 Salt Lake City RA patients enrolled in the Veterans Affairs Rheumatoid Arthritis (VARA) registry residing throughout the intermountain west. Yearly average PM 2.5 values from the nearest (as measured by patient zip code) State and Local Air Monitoring Station (SLAMS) were recorded from the United States Environmental Protection Agency (EPA) website. Associations of high versus low PM 2.5 exposure with ACPA level (as measured by second generation anti-CCP ELISA) were examined, with reference to smoking history, *GSTM1-null,* and *SE* status.

Results: Patients were greater than 90% male and Caucasian, age 65±10 years, positive for ACPA (78.2%) and rheumatoid factor (RF) (77.1%). The low and high exposure group's average yearly PM 2.5 exposures were 6.59±1.14 ug/m3 and 10.61±1.34 ug/m3, respectively. Significantly higher levels of ACPA were seen in the high PM 2.5 exposure group compared to the low exposure group (199±320 u/mL versus 342±665 u/mL, $p<0.02$). Analyses stratified by traditional risk factors including *GSTM-1 null* status, *SE* positivity, and never/ever smoking (figure below) suggest the possibility of interactions between pollution and these genetic and environmental factors. Former smokers constituted the group with the most apparent variation due to air pollution. The analysis of ACPA positivity, RF positivity, and RF showed similar trends but were not statistically significant with this small number of patients.



Conclusion: Particulate air pollution exposure appears to influence ACPA level in this small cohort, particularly in patients with genetic and/or environmental risk for ACPA positivity. Future plans will expand this work to involve other VARA sites to confirm these associations and expand the potential to further explore these genetic and environmental interactions.

2173

Childhood Residential Pesticides and Other Environmental Exposures in Relation to Rheumatoid Arthritis (RA) in Adulthood. Christine G. Parks, Aimee D'Aloisio, Lisa DeRoo and Dale Sandler. NIH/NIEHS, Research Triangle Park, NC

Background/Purpose: Experimental studies show important effects of immunotoxic exposures on the developing immune system, but few studies have addressed childhood environmental risk factors for RA. Here we examine whether childhood residential characteristics and proximity to potential environmental hazards are related to prevalence of rheumatoid arthritis (RA) in adult women.

Methods: The study sample included 50,884 women (ages 35 to 74; median age 55 years; 84% non-Hispanic white, 9% black, 8% Hispanic/other) enrolled 2004–2009 in the Sister Study, a national cohort study of environmental factors and health. Data were obtained from baseline questionnaires. Cases were defined as women reporting doctor-diagnosed RA with onset after age 16 years, who had a history of current or past use of disease modifying anti-rheumatic drugs (DMARDs) or steroids for RA, and bilateral joint swelling lasting 6 weeks or longer. Early life factors included characteristics of longest childhood residence up to age 14,

residential insecticide use and proximity of residence to of a variety of potential environmental hazards. Odds Ratios (OR) and 95% Confidence Intervals (CI) were estimated by logistic regression, adjusting for age and race/ethnicity. We also considered potential confounding by a previously developed score reflecting lower childhood socioeconomic status (SES), pack-years of smoking, and adult education level.

Results: We identified 424 (0.8%) women reporting RA diagnosed after age 16 (median = 47 years at diagnosis) who reported DMARD use or steroids for RA and bilateral joint swelling. Compared to 48,927 women without RA, cases were more likely to report frequent residential pesticide use (8% cases vs. 5% non-cases reported use at least every 1–3 months), personally applying pesticides (4% of cases vs. 2% non-cases reported applying them at least some of the time). After adjusting for age and race, a significant trend was seen for more frequent use of residential pesticides ($p=0.007$), with a strong, though imprecise, association for personally applying them all or most of the time (OR=5.2; 95%CI 2.4, 11.3). In adjusted models, cases also had significantly ($p<0.05$) higher odds of living near an oil refinery (OR=2.2), slaughterhouse or poultry processing plant (OR =1.9), landfill (OR=1.8), drycleaners (OR=1.4) or gas station (OR=1.4). The observed associations were not confounded by childhood SES score, smoking history, or adult educational attainment. No significant differences were seen for urban, town, rural, or farm residence, or water source.

Conclusion: These results suggest residential pesticide use and potential exposure to other environmental hazards in childhood are related to risk of DMARD-treated RA in adulthood. These results add to previous studies on residential insecticide use and RA, and suggest other relevant exposures may include hydrocarbons/solvents, animals/infections, or other types air or water pollutants. Future work will explore the extent to which the observed associations may also be related to ongoing adult exposures.

2174

Periodontal Disease Is Associated with Increased Risk of Incident Rheumatoid Arthritis in Never-Smokers: Results From the First National Health and Nutrition Examination Survey and Its Epidemiologic Follow-up Study. Ryan T. Demmer[1], David R. Jacobs Jr.[2], Bryan S. Michalowicz[2] and Jerry A. Molitor[3]. [1]New York, [2]Minneapolis, MN, [3]Univ of MN MMC108, Minneapolis, MN

Background/Purpose: Periodontal infections have been proposed as rheumatoid arthritis (RA) risk factors. This putative risk is typically confounded by tobacco smoking, which is a known environmental risk for both RA and Periodontitis. We examined whether signs of periodontal infection including gingivitis, periodontitis, and progressive tooth loss were associated with RA development in NHANES I & NHEFS, among never-smokers.

Methods: In 1971–1974, 9,702 men and women, aged 25–74 were enrolled and surveyed longitudinally at four time points (1982, 1986, 1987, and 1992). Of the total, there were 4,424 never smoking individuals without a baseline diagnosis of RA. Periodontal infection was defined by baseline tooth loss or the presence of gingivitis or periodontitis based on periodontal index values. Incident (n=218) RA cases were defined via self-report physician diagnosis, ICD-9 codes (714.0–714.9), death certificates, and/or RA hospitalization. Results were adjusted for age, gender, race and education.

Results: Missing $^{3}5$ teeth was positively associated with increased odds of incident RA. Relative to participants missing 0–4 teeth, the odds ratios(95%CI) for incident RA among never-smoking participants missing 5–8, 9–14, 15–31 or 32 teeth were 1.28(0.69,2.41), 1.56(0.81,3.01), 1.87(0.91,3.86) and 1.92(1.00,3.66), respectively (p for linear trend = 0.04). Odds ratios (OR) for incident RA among participants with gingivitis, periodontitis or those who were edentulous relative to periodontally healthy participants were 0.97(0.53, 1.77), 1.58(0.92, 2.74) and 1.47(0.87, 2.46), respectively (p for linear trend = 0.06).

Conclusion: Among never smokers, periodontal infection surrogates demonstrated weak, positive associations with incident RA, suggesting that periodontal infection may be a risk for RA, independent of smoking.

2175

Prevalence of Periodontitis Is High in Rheumatoid Arthritis Patients and Correlated to Disease Activity. Menke J. de Smit, Johanna Westra, Arjan Vissink, Berber Doornbos-van der Meer, Pieter A. Roelofs, Elisabeth Brouwer and Arie Jan van Winkelhoff. University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: In a general population, the prevalence of severe periodontitis in adults is 10–15%. Co-existence of periodontitis and rheumatoid arthritis (RA) has been reported. These diseases have similarities in etiology, pathogenesis and risk factors. They are possibly linked by protein citrullination and subsequent ACPA response in genetically susceptible individuals. *Porphyromonas gingivalis* is a periodontal pathogen with the unique ability to citrullinate endogenous and human proteins, and human fibrinogen and alpha-enolase, which are auto-antigens in RA. This study aimed to assess the prevalence of periodontitis and the occurrence of *P. gingivalis* in RA patients, together with the correlation between markers of disease activity of RA.

Methods: In a cohort of 95 subsequent dentate RA patients attending our RA out patient clinic, the condition of the periodontium was investigated using the Dutch periodontal screening index for treatment needs (DPSI), which divides patients into category A (patients that require only oral hygiene instruction and calculus removal), category B (patients that require limited periodontal examination), and category C (patients that require extensive periodontal examination). RA disease activity was scored with the DAS28. Smoking and presence of HLA-SE (shared epitope) was determined. Serum was investigated for CRP-, IgMRF- and ACPAlevels. IgG- and IgM antibody titers to *P. gingivalis* were measured by ELISA. Subgingival microbial samples were taken to test for presence of *P. gingivalis*. In addition, ACPA titers in gingivocrevicular fluid (GCF) were measured.

Results: Twenty-seven % of the RA patients belonged to DPSI category C, which is significantly higher than the 12.5% DPSI category C subjects reported in a normal adult population (n=1503) of the same geographic area in the Netherlands ($p<0.0001$). The DAS score of the RA DPSI category C subjects was significantly higher compared to DPSI category A and B RA patients ($p<0.0001$), as were the CRP and IgMRF levels ($p=0.02$ and $p=0.01$). No significant differences in DAS scores between smokers and non- or former smokers were observed, neither when limiting this comparison to RA DPSI category C patients only. Likewise, no significant differences were found between these groups in presence or absence of the HLA-DR shared epitope, a known genetic risk factor for RA and a possible genetic risk factor for periodontitis. Subsequently, between these groups, no significant difference was found in ACPA titer.

Seventeen % of the RA patients were positive for *P. gingivalis,* of which 56 % belonged to DPSI category C. Patients positive for *P. gingivalis* had significant higher IgG anti- *P. gingivalis* titres ($p=0.002$). Also there was a positive correlation between ACPA and IgM anti-*P. gingivalis* levels ($p=0.017$), ACPA and IgMRF titer ($p<0.0001$), and ACPA titer in serum and GCF ($p<0.0001$).

Conclusion: In RA patients the prevalence of patients with periodontitis is significantly higher than a comparable normal adult population. Most strikingly, we found significantly higher DAS28 scores in RA patients with periodontitis, suggesting that periodontitis might attribute to disease activity in RA.

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Lung Changes Detected by High Resolution Tomography Are Present in ACPA Positive Rheumatoid Arthritis Patients Already At Disease Onset. Gudrun Reynisdottir[1], Sven Nyren[2], Anders Harju[1], Magnus Skold[3], Anders Eklund[1], Marianne Engström[1], Johan Grunewald[3], Lars Klareskog[4] and Anca Irinel Catrina[5]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [2]Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [3]Respiratory Medicine Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [4]Karolinska Institutet, Stockholm, Sweden, [5]D2:01, Stockholm, Sweden

Background/Purpose: We have previously shown that smoking increases citrullination in the lungs of healthy smokers and hypothesized that this process is an important step in the early development of rheumatoid arthritis (RA). To test this we investigated lung function in a cohort of RA patients with very early disease, already at the time of diagnosis and compared it with an aged, smoke and gender matched cohort of individuals without RA.

Methods: 82 patients, 56 female and 26 male, median age 60 (range 22–84) with symptom duration less than 1 year at the time of diagnosis and naive to DMARD treatment were included in the RA cohort. A second cohort of age, smoking and gender matched non RA individuals (n=43) were investigated with

an identical protocol. Lung function (X-ray, HRCT and dynamic spirometry) was tested in both RA and controls at baseline and repeated after 6 months in the RA group. All patients were started on anti rheumatic treatment according to clinical practice with 90% of the patients started on methotrexate. In a subgroup of patients bronchoscopy was performed at inclusion (n=18) and 6 months later (n=11) and BAL samples as well as mucosal large bronchial biopsies were retrieved. Presence of peptydilamino deiminase (PAD) enzymes were evaluated by immunohistochemistry

Results: 63% of the patients were ACPA positive, 26% were current smokers and 22% have reported a previous lung pathology. All patients had active disease with a mean DAS of 5.5±0.1 at inclusion that decreased significantly to 3.3±0.2 after 6 months. A majority of the patients (55%) had any type of changes on HRCT either focal or diffuse. Lung changes of any type were more frequent in RA as compared to non RA individuals (35%) with a higher prevalence of lung fibrosis (15/82 in the RA cohort and 0/43 in the control cohort). In the RA cohort 1 patient (1.2%) was diagnosed with lung cancer following HRCT screening while none in the control cohort. ACPA and RF but not smoking status associated with the presence of changes on HRCT. Immunohistochemistry demonstrated a significant increase in expression of both PAD2 and PAD4 in the lungs of current smokers independent of the ACPA status with no significant changes following 6 months of treatment.

Conclusion: Presence of ACPA associates with early lung HRCT changes in RA. We suggest that smoking (and other yet unidentified factors) promotes site specific citrullination (such as in lungs) leading to generation of ACPA immunity and lung changes very early in the disease process.

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Investigating the Cellular Composition of Lymph Nodes in Preclinical and Early Inflammatory Arthritis: A Feasibility Study. Lisa G.M. van Baarsen[1], Maria J. H. de Hair[1], Tamara H. Ramwadhdoebe[1], Marleen G. H. van de Sande[1], IJsbrand A.J. Zijlstra[2], Mario Maas[2], Danielle M. Gerlag[1] and PP. Tak[1]. [1]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease of unknown etiology. To ultimately cure or prevent this chronic disease, it is critical to understand the earliest changes in the immune system that cause RA. Recent work has shown that systemic autoimmunity precedes inflammation in the synovium of RA patients. Animal models have suggested that changes in the lymph nodes may precede those in the synovial tissue. To provide insight into the immunological mechanisms involved in the pathogenesis of RA, we developed a method allowing us to obtain lymph node biopsies under local anaesthesia and investigated the cellular composition and distribution within lymph node tissue in individuals at risk of developing RA compared to early arthritis patients and healthy controls.

Methods: Six individuals without any evidence of arthritis upon physical examination who were positive for IgM rheumatoid factor and/or anti-citrullinated protein antibodies were included. For comparison 12 early arthritis patients (1x systemic lupus erythematosus, 1x psoriatic arthritis, 1x gout, 5x undifferentiated arthritis and 4x RA; disease duration <1 year, DMARD naïve), and 4 autoantibody negative healthy controls without joint complaints were included in the study. All study subjects underwent ultrasound-guided inguinal lymph node biopsy. Different T lymphocyte subsets were analysed by multi-color flow cytometry using labelled antibodies specific for CD3, CD4, CD8, CD45 and CD69.

Results: The procedure was well tolerated; no complications occurred. Different T cell subsets could be distinguished and differences between autoantibody positive individuals at risk of developing RA, early arthritis patients and healthy controls could be observed (Table 1). Interim analysis of these small study groups indicate an increase of activated CD69+ T cells in the early arthritis as well as in the at risk group compared to the control group. Interestingly, the CD4/CD8 distribution within the activated T cells was significantly changed in the early arthritis patients compared to healthy controls and the same trend was observed for the at risk group.

Table 1. Distribution of activated CD4+ and CD8+ T cells

CD45+CD3+	% CD69+	% CD4+ of CD69+	% CD8+ of CD69+
Subjects at risk of RA	14.80 (12–21)	78.45 (55–83)	12.55 (10–28)
Early arthritis	18.40 (9–48)	77.45 (84–94)*	15.00 (10–22)*
Healthy controls	10.70 (6–13)	91.20 (84–94)	4.4 (3–13)

Median (IQR); * $p<0.05$ Kruskal-Wallis test plus post Dunn's Multiple comparison test

Conclusion: Flow cytometry analysis of ultrasound-guided inguinal lymph node biopsies is a feasible method for investigating the cellular composition of lymph nodes in the earliest phases of inflammatory arthritis. These preliminary results suggest increased CD8+ T cell activation within lymph nodes of early arthritis patients as well as in autoantibody positive individuals at risk of developing RA. This method provides a unique tool to investigate the immunological changes in the lymph node compartment in the earliest phases of inflammatory arthritis. These data support the rationale for larger studies using more extensive panels of cellular markers.

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Type 1 Interferon Signature Predicts Development of Rheumatoid Arthritis. Joyce Lubbers[1], Mikael Brink[2], Lotte A. van de Stadt[3], Saskia Vosslamber[1], John G. Wesseling[1], Dirkjan van Schaardenburg[3], Solbritt M. Rantapaa-Dahlqvist[2] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Umeå University, Umea, Sweden, [3]Jan van Breemen Research Institute / Reade, Amsterdam, Netherlands

Background/Purpose: Early recognition of development of rheumatoid arthritis (RA) allows timely start of treatment. It is known that antibodies against citrullinated proteins (ACPA) and rheumatoid factor (RF) have a predictive value for development of RA within 5 years. Since only 20–40% of $ACPA^+$ and/or RF^+ arthralgia patients develop RA better prognostic markers are warranted. Recently, we reported gene signatures in the peripheral blood that are relevant to the development of arthritis after a median of 7 months (van Baarsen, A& R, 2010). Gene signatures that are significantly associated with arthritis development involved interferon (IFN) activity. In this study we validate these findings and determine the predictive value of increased IFN activity in arthritis development.

Methods: For independent validation RNA was isolated from peripheral blood mononuclear cells (PBMC) from individuals of the Northern Sweden Health and Disease Study and the Maternity cohorts of Northern Sweden. RNA samples from 22 pre-onset RA patients (median disease duration before RA diagnosis was 3 years), 25 RA patients and 48 age and sex matched healthy individuals were analyzed. In addition, whole peripheral blood RNA of 106 $ACPA^+$ and/or RF^+ arthralgia patients who are clinically followed at Reade, Amsterdam, every year for RA development were used for diagnostic analysis. Gene expression levels of 6 IFN response genes were measured using the BioMark™ Dynamic Array system. An IFN score was determined by averaging the expression levels of these genes. Differences in IFN response score between the healthy controls, pre-onset RA and RA patients were analyzed using Mann-Whitney U test. The diagnostic potential was analyzed using Receiver Operating Characteristics (ROC)-curve analysis.

Results: To validate the presence of the IFN signature in an independent pre-onset RA cohort we analyzed the IFN score in pre-onset RA patients from the Northern Swedish Repository. Analysis of the IFN score in PBMCs from both pre-onset RA and RA samples revealed higher scores compared to HC (Mann-Whitney U test $p=0.0064$ and $p=0.0075$, respectively). No significant difference in the IFN score between pre-onset RA and RA samples was observed. To determine the diagnostic value of the IFN score for the development of arthritis we measured the IFN score in whole blood of $ACPA^+/RF^+$ arthralgia patients from the Amsterdam cohort after a median follow-up of 40 months. Out of 106 patients included 38 arthralgia patients had developed arthritis. Comparison of the IFN score at inclusion, between the arthritis converters and non-converters, confirmed the increased score in the arthritis converters (Mann-Whitney U test $p=0.0435$). ROC-curve analysis revealed an area under the curve of 0.601 ($p=0.043$), indicative for diagnostic potential of the use of the IFN score for diagnosing the pre-onset phase of RA.

Conclusion: Our results confirm the increased IFN response gene expression in the pre-onset stage of RA in an independent pre-onset RA cohort. Furthermore, we demonstrate the potential of using the IFN score for diagnosing the pre-onset stage of RA. Altogether, these results support the potential of using the IFN signature as a biomarker for early diagnosis of RA.

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Identification of Shared Citrullinated Potentially Immunological Targets in the Lungs and Joints of Patients with Rheumatoid Arthritis. Jimmy Ytterberg[1], Gudrun Reynisdottir[1], Elena Ossipova[1], Aase Haj Hensvold[2], Anders Eklund[3], Magnus Skold[3], Johan Grunewald[3], Karin Lundberg[4], Vivianne Malmström[4], Per Johan Jakobsson[5], Roman Zubarev[4], Lars Klareskog[4] and Anca Irinel Catrina[1]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [2]Rheumatology unit, 171 76 Stockholm, Sweden, [3]Respiratory Medicine Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [4]Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology Unit, Karolinska Institutet; Karolinska University hospital, Stockholm, Sweden

Background/Purpose: We have previously demonstrated that smoking induces citrullination in the lungs of healthy smokers and we know that anti citrullinated protein antibodies (ACPA) develop in rheumatoid arthritis (RA) patients many years before disease onset. We hypothesized that shared citrullinated targets are present in the lungs and joints of RA affected individuals and sought to investigate this by full-proteome analysis of synovial and lung biopsies of RA patients.

Methods: Proteins were extracted from synovial (n=7, 5 females and 2 males, median age 58, 66.7% ACPA positive) and lung (n=6, 4 females and 2 males, median age 63, 66.7% ACPA positive) biopsies of RA patients. Synovial biopsies were obtained at the time of open surgery from patients with longstanding RA (mean disease duration 24 years). Large bronchi biopsies were obtained by bronchoscopy from patients with newly diagnosed RA (3 smokers and 3 non smokers) with symptom duration less than 1 year. The proteins were reduced, alkylated and digested with Lys-C, separated by reverse phase nanoflow chromatography and analyzed by LTQ Velos Orbitrap using multiple fragmentation methods. The data were searched against the human IPI database using the Mascot search engine and all citrullinated peptides were manually verified. Relative protein levels were quantified by label free approach using in-house written programs (Quanti), while the degree of modification was quantified manually. The final results were expressed as ratios of citrullinated versus non-modified peptides.

Results: Over 3300 peptides and 500 proteins were identified and quantified in the different samples. The overall protein profiles varied between patients. 5 of the identified proteins in the synovium (in total 8 sites) and 4 in the lungs (in total 4 sites) contained citrullinated residues. Two vimentin derived citrullinated peptides were present in a majority of synovial and lung biopsies with slightly higher citrullinated/unmodified peptides ratios in the smokers as compared to non-smokers (median ratio of 0.03 in smokers and 0.02 in non smokers for one of the peptides and a median ratio of 4.5 in the smokers and 0.04 in the non smokers for the second vimentin peptide). While non-modified and citrullinated fibrinogen a chain derived peptides were present in various amounts in the synovium, only the unmodified sites could be detected in the lungs of a subset of the patients (3 out of 6)

Conclusion: We demonstrate the presence of shared in vivo citrullinated proteins in the joints and lungs of RA individuals, providing further support for the important pathogenic link between joints and lungs in development of RA.

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A Disease-Modifying Role for Mucosal IgA Antibodies to Citrullinated Antigens? Anna Svärd[1], Alf Kastbom[2], Yngve Sommarin[3] and Thomas Skogh[4]. [1]Linköping University, Falun, Sweden, [2]Linköping University, Linköping, Sweden, [3]Euro-Diagnostica AB, Malmö, Sweden, [4]Linkoping University, Linkoping, Sweden

Background/Purpose: The aim of this pilot study was to investigate whether IgA antibodies to cyclic citrullinated peptides (CCP) can be detected in saliva of patients with established rheumatoid arthritis (RA) and if it relates to clinical manifestations.

Methods: Salivary samples were collected (by 'passive drewling') from 63 consecutive patients with established RA at a visit to the rheumatology outpatient clinic (Falun, Sweden), and from 20 healthy persons (hospital staff). The samples were centrifuged and kept frozen at −20°C until analysis. IgA-class anti-CCP antibodies in saliva were analysed by adaptation of a commercial ELISA (Immunoscan RA, *Euro-Diagnostica* AB, *Malmö*, Sweden) using polyclonal rabbit antihuman alpha-chain specific antibodies conjugated with horseradish peroxidase (DakoCytomation, Glostrup, Denmark) as secondary antibody.To ensure specificity of the reaction, a corresponding ELISA was set up to analyse IgA antibodies to control antigen (cyclic arginine peptide, CAP), and anti-CCP/anti-CAP ratios were calculated. Also, inhibition studies were performed by preincubation of sera with soluble CCP or CAP. Clinical and laboratory data on disease activity, *i.e.* C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and 28-joint count disease activity score (DAS28) as well as radiological outcome (occurrence or absence of erosions as judged by a radiologist in diagnostic routine) were achieved retrospectively via the patients' medical records.

Results: Background reactivity against CCP was found in virtually all patients and healthy subjects, whereas a positive anti-CCP/anti-CAP ratio (≥1.5) was found in 14 out of 63 RA patients (22%) and in one healthy subject (5%). Salivary IgA-reactivity with CCP was dose-dependently inhibited by soluble CCP (but not with CAP) in sera with anti-CCP/anti-CAP ratios ≥1.5. No IgG-reactivity to CCP was found in saliva, although all patients with salivary IgA anti-CCP tested IgG anti-CCP-positive in serum. Furthermore, less than half of those testing IgA-positive in saliva were IgA anti-CCP positive in serum, strongly arguing against passive leakage of anti-CCP antibodies from blood to saliva. The patients testing positive for salivary IgA antibodies had lower average disease activity measures (CRP, ESR, DAS28) at presentation and fewer developed bony erosions within six years after presentation (p=0.043, Fisher's exact test).

Conclusion: Salivary IgA antibodies to citrullinated proteins were found in a subset of IgG anti-CCP positive RA patients. In contrast to their serum counterparts, salivary IgA antibodies may associate with a milder/less destructive disease course. This accords with the notion that secretory IgA antibodies exert anti-inflammatory actions, and that they may be associated with induction of systemic tolerance (oral tolerance). The possible disease-modifying role of mucosal immunity to citrullinated proteins needs further investigation!

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The ACPA Recognition Profile and Sub-Grouping of APCA Positive Rheumatoid Arthritis Patients. Annemiek Willemze, Stefan Böhringer, Rachel Knevel, E.W. Nivine Levarht, Gerrie Stoeken-Rijsbergen, Jeanine J. Houwing-Duistermaat, Annette H.M. van der Helm-van Mil, Tom W.J. Huizinga, René E.M. Toes and Leendert A. Trouw. Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are the most predictive factor for the development of rheumatoid arthritis (RA). Epitope spreading towards more citrullinated epitopes occurs before the onset of RA. Here, we investigated whether specific subsets of RA patients can be distinguished on the basis of specific epitope recognition and determined the association of the ACPA fine specificity with clinical features of RA.

Methods: The reactivity of 661 RA patients, from the Leiden Early Arthritis Clinic (EAC), against several citrullinated antigens was determined by enzyme-linked immunosorbent assay (ELISA). Cluster analyses were performed to identify subgroups of patients on the basis of their ACPA-recognition profile and principal component analyses were performed to reduce data complexity. The association of the specific reactivities with clinical characteristics was studied.

Results: ACPA-positive patients displayed a heterogeneous ACPA-recognition profile. After performing a cluster analysis and a principal component analysis no apparent clustering of patients was found and on the basis of the reactivities analyzed, already 64 different subgroups could be identified. The extent of epitope recognition was associated with anti-CCP2-levels. The recognition of specific citrullinated epitopes was not associated with baseline characteristics. Likewise, patients with an extended fine specificity repertoire did not display differences in baseline characteristics or joint damage after 7 years of follow up using anti-CCP2 levels as a proxy, compared to ACPA-positive patients recognizing fewer peptides.

Conclusion: These data show that the ACPA-response is highly diverse with respect to recognition of specific epitopes. This diversity hampers further 'subgrouping' of ACPA-positive patients to define more homogenous patients groups that share baseline characteristics or radiological outcome.

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Total Protein, Citrullination and Autoantibodies Are Elevated in Lungs of Patients with Established Rheumatoid Arthritis Compared to Controls: Pilot Study Results. Van Willis[1], Mark Parish[1], Lezlie A. Derber[2], M. Kristen Demoruelle[3], Jason R. Kolfenbach[4], Chris Striebich[3], Peter Sachs[3], David Lynch[5], Russell Bowler[5], Kevin K. Brown[6], V. Michael Holers[4] and Kevin D. Deane[3]. [1]University of Colorado Anschutz Medical Campus, Aurora, CO, [2]University of Colorado AMC, Aurora, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]Univ of Colorado School of Med, Aurora, CO, [5]National Jewish Health, Denver, CO, [6]National Jewish Hospital, Denver, CO

Background/Purpose: Autoantibodies (Abs) to citrullinated proteins and other antigens may be a key part of the pathogenesis of articular as well as extra-articular disease in rheumatoid arthritis (RA). To evaluate the potential role of citrullination, antibodies to citrullinated protein antigens (ACPAs) and rheumatoid factor (RF) in RA-related lung disease, herein we evaluated levels of total and citrullinated proteins, anti-cyclic citrullinated peptide-2 (aCCP2) antibodies and RF isotypes in bronchoalveolar lavage (BAL) and sputa samples from subjects with established RA and interstitial lung disease (ILD), early RA with asymptomatic airways disease, and several control groups.

Methods: BAL samples from 5 patients with established RA-ILD (3 smokers), 5 with scleroderma (SSc)- ILD (2 smokers) and 32 healthy controls (20 smokers) were tested for levels of total protein (TP) (Pierce BCA method, Thermo Fischer Scientific Inc, USA) and citrullinated protein (CP) (colorimetric method, Knipp et al 2000). All BAL samples were tested by ELISA methods for aCCP2 (Axis-Shield, UK) and RF isotypes IgA, G, and M (INOVA, USA). aCCP2 testing was also performed on sputa samples from 5 additional patients with early seropositive RA (<8 mos. duration of symptoms) with asymptomatic airways disease without ILD per research-related lung high-resolution computed tomography, as well as sputa from 8 healthy controls.

Results: TP levels were increased in BAL from patients with RA-ILD and SSc-ILD compared to healthy controls ($p<0.01$) (Table). CP were present to some degree in most subjects, including controls; however, the highest median levels of CP were observed in subjects with RA-ILD ($p<0.05$) (Table). Patients with RA-ILD also had higher BAL aCCP2 and RF isotype levels compared to controls ($p<=0.03$) (Table). Finally, in the 5 patients with early RA and asymptomatic airways disease the median level of aCCP was significantly elevated compared to the 8 controls (35 vs. <1; $p<0.01$).

Median levels of total and citrullinated protein and rheumatoid arthritis (RA)-related autoantibodies in broncho-alveolar lavage (BAL) fluid

	RA-ILD (N=5)	SSc-ILD (N=5)	Healthy controls, never smokers (N=12)	Healthy controls, smokers (N=20)	P-value*
Total protein (pg/mL)	232	135	28	57	<0.01
Citrullinated protein (uM)	70	26	7	11	<0.01
aCCP2 (units)	100	<1	<1	<1	<0.01
RF-IgA (units)	62	3	7	29	<0.01
RF-IgG (units)	19	5	4	6	0.03
RF-IgM (units)	16	<1	<1	<1	<0.01

* Kruskal-Wallis testing comparing median BAL levels of autoantibodies across all groups

Conclusion: Levels of TP and CP are increased in the BAL of patients with RA-ILD compared to controls. This may represent increased protein generation in the lungs of these patients, and increased citrullination related to the inflammation of RA-ILD. Also, aCCP2 and RF isotype levels are increased in the BAL in patients with RA-ILD, and aCCP2 is increased in the sputa from patients with early RA and asymptomatic airways disease, suggesting that these autoantibodies may play a role in the pathogenesis of lung injury. Further studies are necessary in order to evaluate the types and citrullination status of lung proteins in RA patients, mechanisms of citrullination, and the potential pathogenic roles of aCCP2 and RF in lung injury.

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A Serological Proteome Approach for Screening of Autoantigens From Korean Rheumatoid Arthritis Patients. Sung-Hoon Park[1], Ji Hun Kim[1], Seong-Kyu Kim[2], Jung-Yoon Choe[3], Sang-Hyon Kim[4], Yong-Hak Kim[5], Yeonkyung Park[5] and Mina Choi[5]. [1]Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegu, South Korea, [2]Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegue, South Korea, [3]Arthritis and Autoimmunity Research Center, Catholic university of Daegu, School of mediine, Daegu, [4]Dongsan Medical Center, Keimyung University, Daegu, South Korea, [5]Catholic univeristy of Daegu, School of Medicine, Daegu, South Korea

Background/Purpose: Rheumatoid Arthritis (RA) is a chronic, autoimmune, systemic inflammatory disease. An immunogenic autoantigen or antibody is still not clearly elucidated. We used a serological proteome approach in order to screen RA antigens and overview the underlying disease mechanism.

Methods: A whole cell extract of human osteosarcoma Cybrid rho(0) cells was used as a source of human antigens. Total proteins were analyzed by 2D gel electrophoresis and Western blotting with two pools of sera of female RA patients ($n = 6$; age = 35 ~ 59, mean ± SD = 46.2 ± 8.7) and healthy control women ($n = 6$, age = 30 ~ 58, mean ± SD = 43.3±11.1). Antigen spots showing >2-fold differences in Western blot data were identified from 2D gels, and trypsin-digested peptide extracts were analyzed on an LC-mass instrument. Proteins were identified by the X!Tandem search of mass data against a non-redundant database of human female (http://ppp.thegpm.org/) with high probability of $\log(e) < -2$ and false discover rate < 0.01, and were enlisted to analyze proteins associated with disease pathways.

Results: 2D gel and Western blot analysis with the sera of RA patients and healthy controls distinguished a total of 91 antigen spots, in which 49 spots were highly detected with the RA sera, and 42 spots with the normal sera. Protein entities were obtained from mass data of 46 RA and 39 normal spots, which accounts for 93.4% of the isolated spots from 2D gels. From identified spots, 25 RA and 17 normal spots had single proteins identified by two or more unique peptides. Analyses of protein association network (http://string-db.org/) and KEGG pathway database (http://www.genome.jp/kegg/pathway.html) showed that serologically identified RA factors were most probably related to a p53-signaling pathway leading to the control of cell cycle and apoptosis. In contrast, normal antigens were common components of glycolysis, DNA complex assembly, and splicesome.

Conclusion: A serological proteome approach was useful for screening of specific autoimmune factors associated with RA patients. The success rate of this approach was roughly 93.4% (85/91) from the mass data. However, it was accurately 46.2% (42/91) based on high resolution 2D gel and blot imaging system for identification of true antigens from single spots. Our study shows that RA factors may associate with some components of a p53-signaling pathway triggering cell cycle arrest and apoptosis. Further studies for verification and validation of these factors remain to be done.

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Could Presence of Antibodies to Citrullinated Proteins Be More Strongly Associated to Bone Than Cartilage Destruction? Results From a 10-Year Prospective Study. Silje Watterdal Syversen[1], Pernille Bøyesen[2], Guro Løvik Goll[1], D. Van Der Heijde[3] and Tore K. Kvien[2]. [1]Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: A more destructive disease course is a key feature of antibody positive RA. Although the strong association between ACPA status and radiographic progression is well established, the underlying mechanisms for this association are not known. The slightly higher disease activity in antibody positive patients can not alone ex-

plain this difference, but whether the antibodies are causually related to destruction of either bone or cartilage remains to be clarified. The aim of this study was to take advantage of clinical data from a long-term prospective study to establish whether ACPA status is related to joint destruction in general, or to either bone or cartilage destruction in particular.

Methods: The study population consists of patients included in the 10-year prospective EURIDISS study (n=238, disease duration <4 yrs. mean 2.3 yrs, 61% ACPA positive). A longitudinal data collection was performed including clinical data, serum sampling, conventional radiographs and assessment of bone mineral density (BMD). The radiographs were scored according to the vdH Sharp score with separate scores for erosions and joint space narrowing (JSN). Change in erosion score and JSN score over ten years are used as outcomes of bone and cartilage destruction. ACPA was measured by anti-CCP2 (INOVA®). Biomarkers of bone- (CTX-I (Nordic Biosience®)) and cartilage destruction (COMP (Anamar®) and C2C (Ibex®)) were assessed in baseline samples. Total and percentage change in BMD over 5 yrs were used as outcomes of generalised bone loss. Linear regression was performed both to assess the relation between ACPA status and progression in erosion and JSN score and change in BMD. Comparions between groups were performed by Mann-Whitney test.

Results: A positive ACPA status predicted 10-year progression both in the erosion and the JSN component of the vdHSS, but was more strongly associated to the change in the erosion component than to the change in the JSN score (standardized β 0.40 versus 0.26). ACPA positivity explained 16% of the change in erosion score, whereas only 6% of the change in JSN score could be attributed to ACPA status. Results remained when adjusting for markers of systemic inflammation. ACPA positive patients had higher baseline levels of the bone degradation marker CTX-I (0.43 ng/ml versus 0.33 ng/ml, $p < 0.01$), whereas levels of the two cartilage degradation markers (COMP, C2C) were similar in ACPA positive and negative patients. Furthermore, the generalised bone loss was higher in ACPA positive patients (6.8% loss in BMD versus 2.1% loss in BMD over 5 year, $p < 0.001$). A positive ACPA status explained 15% of the change in BMD, and remained the strongest predictor of long-term generalized bone loss, also when adjusting for gender and markers of systemic inflammation.

Conclusion: This study suggests that ACPA status might be more strongly associated to bone degradation than cartilage destruction, and furthermore raises the hypothesis that ACPA might act pathogeneic in the osteoclast mediated destruction of the joints by other mechanisms than just amplification of inflammation.

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Rheumatoid Arthritis Patients Have Anti-Homocitrullinated Fibrinogen Antibodies. Mathias Scinocca[1], David A. Bell[1], Janet Pope[2], Ewa Cairns[1] and Lillian J. Barra[1]. [1]Schulich School of Medicine and Dentistry, London, ON, [2]Univ of Western Ontario, London, ON

Background/Purpose: Homocitrulline is generated by the chemical modification of lysine and is structurally similar to citrulline, the latter has been detected in the joints of RA patients using antibodies to modified citrulline (AMC). A recent study indicates that AMC cannot distinguish citrulline from homocitrulline. Antibodies to citrullinated peptides (ACPA), including citrullinated fibrinogen, are thought to be specific to RA and strongly linked to the Shared Epitope (SE), the major genetic risk factor for this disease. However, it is unclear whether RA patients also have antibodies to homocitrullinated peptides. Our specific objective was to determine the presence of anti-homocitrullinated fibrinogen antibodies (AHFA) in patients with RA and other rheumatic conditions and whether homocitrullinated peptides of fibrinogen are predicted to bind to the SE.

Methods: A commercial preparation of human fibrinogen (CalBiochem™) was homocitrullinated via a reaction with potassium isocyanate and confirmed by mass spectrometry. It was used in ELISA to detect AHFA and anti-citrullinated fibrinogen antibodies (ACFA) from patient serum (RA, Systemic Lupus Erythematosus (SLE) and Psoriatic Arthritis (PsA) meeting ACR criteria). All RA patients were anti-CCP2 positive.

Results: 85/103 lysines showed evidence of homocitrullination present in all three chains of fibrinogen, comprising 34 peptides predicted to bind to the SE using a modified algorithm by *Hammer et al.* Of these 34 peptides, 5 homocitrullinated peptides were previously shown to be capable of being citrullinated. Antibodies to this homocitrullinated fibrinogen were found in 16/46 RA patients (mean 12.73+/− 38.6 RU/ml), but only 1/37 PsA patients (mean 1.16+/−2.56 RU/ml), 1/37 age-matched normals (mean 1.43+/−2.37 RU/ml) and no SLE patients (n=37, mean 0.56+/−3.0 RU/ml); $p<0.0001$ for RA compared to others. 36/46 RA patients were also positive for ACFA and of these 14/36 were AHFA positive. All of the ACFA negative patients were also AHFA negative.

Conclusion: Fibrinogen can be extensively homocitrullinated and citrullinated. Both citrullinated and homocitrullinated fibrinogen appear to be autoantigens specific to RA.

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Heterogeneity in the Memory B Cell Compartment in the Bone Marrow in Human Rheumatoid Arthritis. Arumugam Palanichamy, Christopher A. Cistrone, Jennifer Hossler, Teresa Owen and Jennifer H. Anolik. University of Rochester, Rochester, NY

Background/Purpose: In addition to being the site of B cell development, the bone marrow (BM) contains mature lymphocytes that may participate in secondary immune responses including formation of germinal centers. However, the detailed phenotype, function, and regulation of mature B cell subsets in the BM microenvironment in humans is largely unexplored, particularly in the setting of autoimmunity.

Methods: BM aspirates and paired peripheral blood (PB) samples were collected from RA patients and age-matched normal controls (NC) (n=10). B cell subsets and effector molecules were defined using multiparameter flow cytometry by the expression of markers including CD19, IgD, CD27, Mitotracker G, CD10, CD38, CD24, B220, CD95, CXCR3 and CD21. In select experiments, B cells were enriched by rosette separation and single memory B cells from the switched (SM: IgD-, CD27+), unswitched (USM: IgD+, CD27+) and double negative memory (DN: IgD-, CD27-) subsets were sorted. Sorted naïve (IgD+, CD27-) B cells served as controls. B cell mRNA was reverse transcribed, immunoglobulin (Ig) genes were amplified by a nested PCR and products sequenced. Rearranged Ig gene products were compared to the closest germline fit on JoinSolver and a detailed mutational analysis was performed.

Results: Both NC and RA contained diverse mature memory B cell populations in the BM. The USM population in RA BM was decreased compared to NC BM (P=0.02) Analysis of activated, effector phenotype molecules on BM memory subsets showed significant levels of B220+, CD95+ and CXCR3+, with some RA subjects displaying a profound expansion of effector memory. Interestingly, the expression level of these molecules between BM and PBL subsets were closely comparable. However, in the RA DN compartment, the CD24- effector subset was larger in the BM (P=0.04, BM Vs. PB) and CXCR3+, CD95+ subsets represented in lower levels (P=0.001, BM Vs. PB). On the molecular level, the overall mutational frequencies in the SM, USM and DN Ig genes were similar between RA and NC BM. However, detailed mutational analysis revealed that all memory subsets in RA BM showed increased transversions compared to NC counterparts (P=0.001). Of note, SM and DN fractions from RA PB showed an elevated mutational frequency compared to NC PB (SM: 7.7% vs. 5.8%, DN: 4.5% vs. 2.8%). Moreover, similar to BM, RA PB also had elevated levels of transversions compared to NC PB ($P<0.05$ in all cases). Further analysis revealed a distinct pattern of nucleotide substitutions in RA BM and PB memory B cells compared to NC counterparts (e.g. predominant T/A to G substitutions in the RA BM SM B cells and T to C substitutions in RA PB SM B cells).

Conclusion: Tissue specific differences in the effector molecule expression on B cell subsets in RA suggests preferential homing or in-situ generation of these B cells in the BM. Elevated transversions in RA memory B cells may indicate increased activity of Uracil DNA glycosylase and warrants further investigation to understand the precise mechanisms underlying the mutational machinery in an autoimmune setting.

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Tocilizumab and Tumor Necrosis Factor Inhibitors in Biologic Switchers: Similar Drug Survival and Safety with Different Infection Profile in Routine Practice. Kazuki Yoshida[1], Kazuo Matsui[1], Hiroto Nakano[1], Hideto Oshikawa[1], Masako Utsunomiya[1], Tatsuo Kobayashi[1], Makiko Kimura[1] and Mitsumasa Kishimoto[2]. [1]Kameda Medical Center, Kamogawa City, Japan, [2]St Luke's International Hospital, Chuo-ku, Tokyo, Japan

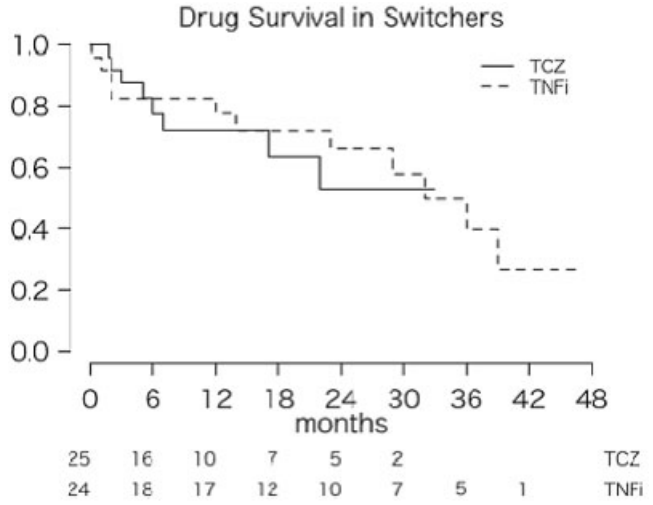
Background/Purpose: To compare the difference between tocilizumab (TCZ) and tumor necrosis factor inhibitors (TNFi) on safety and drug survival time.

Methods: We studied rheumatoid arthritis (RA) patients in the Cohort of Arthritis Biologic Users at Kameda Institute (CABUKI) registry from Jul/2003 to Apr/2011. Kaplan-Meier drug survival estimates of second-line TCZ and TNFi were analyzed with log rank test, and baseline predictors of poor drug survival were determined using multivariable-adjusted Cox regression models. We also examined the rates of serious adverse events (SAE; defined as hospitalization or IV antibiotic use) per 100 person-years (PY) of drug usage.

Results: We identified 260 patients who received TCZ (n=51) and TNFi (n=209, infliximab 102, etanercept 101, adalimumab 6). Among these patients, 49 patients who received second-line TCZ (n=25) and TNFi (n=24, infliximab 3, etanercept 19, adalimumab 2) were included for drug survival analysis. For multivariate models and SAE analysis, in addition to the second-line biologic users, 200 first-line (TCZ 19 and TNFi 181) and 11 third-line (TCZ 7 and TNFi 4) biologic users were also included.

No baseline characteristics were significantly different although second-line TCZ users had a shorter mean follow-up duration (TCZ 12.47 mo vs TNFi 19.71 mo, p=0.053) and a higher mean age (TCZ 60.68 yr vs TNFi 54.17 yr, p=0.118). Disease activity score-28 (DAS28) did not significantly differ between the groups (TCZ 5.1 ± 1.3 and TNFi 4.8 ± 1.1, p=0.423).

Drug survival was also comparable (p=0.732) between the second-line TCZ (77.5% at 6 mo; 72.3% at 12 mo) and TNFi (82.5% at 6 mo; 77.6% at 12 mo) users (Figure 1).



The reasons for drug discontinuation were: ineffectiveness (TCZ 50.0% vs TNFi 36.4%), side effects (12.5% vs 27.3%), patient preference (12.5% vs 9.1%), MD preference (12.5% vs 0%), and good response (12.5% vs 27.3%). Baseline factors affecting drug survival were BMI (HR1.06, [1.01, 1.10]), previous exposure to biologics (HR0.44, [0.27, 0.73]), and NSAIDs (HR0.59, [0.41, 0.84]).

Mean rates of SAEs were not significant different: 46.9/100PY for the TCZ group and 36.0/100PY for the TNFi group (p=0.621, t-test). Serious soft tissue infections, some requiring surgical interventions, occurred in 4 patients receiving TCZ (mediastinitis, orbital cellulitis, dog bite infection, joint injection site infection, and elbow bursitis), whereas only 3 patients receiving TNFi experienced such infections (vertebral osteomyelitis, septic arthritis, and cellulitis) although a larger number of patients were present in the TNFi group.

Conclusion: Drug survival was comparable between second-line TCZ and TNFi in routine practice. Although SAE rate was similar for both drugs, serious soft tissue infections may be more common among TCZ users. Both physicians and patients should be vigilant about this type of infection.

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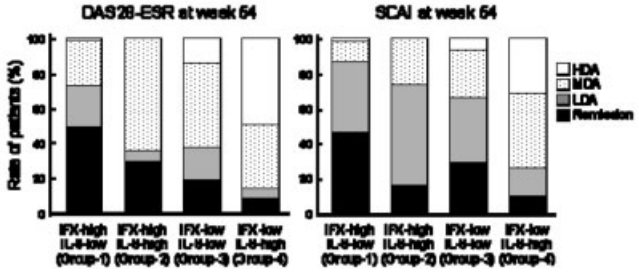
Clinical Efficacy of Infliximab Is Maximized When Both Circulating TNF and IL-6 Are Suppressed In the Treatment of Rheumatoid Arthritis—Results From the RISING Study. Tsutomu Takeuchi[1], Yoshihiko Tatsuki[2], Toshiro Yano[2], Toru Yoshinari[2], Nobuyuki Miyasaka[3], Tohru Abe[4] and Takao Koike[5]. [1]School of Medicine, Keio University, Tokyo, Japan, [2]Mitsubishi Tanabe Pharma Corporation, Osaka, Japan, [3]Tokyo Med & Dent Univ, Tokyo, Japan, [4]Saitama Medical School, Kawagoe-shi Saitama, Japan, [5]Sapporo Medical Center NTT EC, Sapporo, Japan

Background/Purpose: We have previously reported the practicability of the dose escalation of infliximab (IFX), an anti-TNF antibody, in MTX-refractory patients with rheumatoid arthritis (RA) in the RISING study (NCT00691028)*. Here, we show the analysis of the clinical response from the viewpoints of serum IFX level and plasma IL-6 level.

Methods: After the patients with RA refractory to MTX received 3 mg/kg IFX infusion at weeks 0, 2, and 6, they were randomly assigned for the administration of 3, 6, or 10 mg/kg IFX, every 8 weeks from week 14 to 46 in a double-blind manner (n=307). Disease activity was evaluated at week 54 by using DAS28-ESR or SDAI. Serum IFX and plasma IL-6 levels were measured by ELISA. Because the circulating TNF level could not be measured correctly in the presence of IFX, we used IFX level as the surrogate marker of the TNF level. For an index in TNF and IL-6 level, we stratified all patients who had complete data at week 54 (disease activity, IFX level and IL-6 level, n=271) into four groups: Group-1 (IFX-high/IL-6-low: suppression seen in both TNF and IL-6); Group-2 (IFX-high/IL-6-high: suppression in TNF only); Group-3 (IFX-low/IL6-low: suppression in IL-6 only); Group-4 (IFX-low/IL6-high: neither TNF nor IL-6 were suppressed). The cut-off values of IFX and IL-6 levels were determined as <1 μg/ml (the threshold level for clinical response of IFX) and <10 pg/ml (below the third quartile at week 54).

Results: Immediately after starting IFX treatment, the IL-6 level was markedly decreased. Median (IQR) IL-6 level at baseline (week 0) and at week 54 were 28.9 (12.8, 65.0) and 2.4 (0.9, 16.3) pg/ml, respectively, and the median reduction rate was 87%. IFX level closely and negatively correlated with the IL-6 level (rho=-0.58, p<0.001). Both IFX and IL-6 levels were closely correlated with disease activity as well as various components such as tender/swollen joint counts and patient global assessment. The number of patients in Group-1, 2, 3 and 4 were 134, 31, 48, and 58, and approximately half of the patients were in Group-1 (both TNF and IL-6 were suppressed). There is a significant difference in the clinical responses among Groups-1, 2, 3 and 4, and Group-1 exhibited the highest clinical response, especially clinical remission. Meanwhile, Group-4 (neither TNF nor IL-6 were suppressed) showed the lowest rate of response. Clinical response in Group-2 and Group-3 were intermediate values between those of Group-1 and Group-4 (Fig.). Similar results were obtained in the other components of disease activity.

Fig. The influence of serum IFX level and plasma IL-6 level on the disease activities at week 54.



Conclusion: IFX therapy remarkably suppressed not only TNF, but also the IL-6 level in RA patients. The clinical efficacy of IFX therapy was maximized when both circulating TNF and IL-6 were suppressed by the treatment.

*T Takeuchi, et al. Mod Rheumatol 2009;19:478.

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Combination Therapy with Adalimumab+Methotrexate Significantly Improved Work Ability, Physical Function, Fatigue, and Other Patient-Reported Outcomes in Early Rheumatoid Arthritis: Results From a 26-Week Analysis. Paul Emery[1], Arthur F. Kavanaugh[2], Josef Smolen[3], Mary A. Cifaldi[4], Leonardo Chaves[4], Benoit Guerette[5], Vipin Arora[4] and Ronald F. van Vollenhoven[6]. [1]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [2]University of California San Diego, San Diego, CA, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [4]Abbott Laboratories, Abbott Park, IL, [5]Abbott, Rungis, France, [6]The Karolinska Institute, Stockholm, Sweden

Background/Purpose: To compare work ability assessments and other patient-reported outcomes (PROs) in early rheumatoid arthritis (RA) patients treated with adalimumab (ADA)+methotrexate (MTX) vs. MTX+placebo (PBO) over 26 weeks.

Methods: OPTIMA (Optimal Protocol for Treatment Initiation With MTX and ADA in Patients With Early RA) was a Phase IV, double-blind, randomized, placebo-controlled trial. The overall study design has been described elsewhere[1]. This analysis evaluated the Period 1 (26 weeks) PRO, comparing ADA+MTX vs. MTX+PBO. Work outcomes were assessed with the Work Productivity and Activity Impairment (WPAI) questionnaire, percentage of employed patients, and Work Instability Scale (WIS). Other PROs evaluated included: Patient's Global Assessment of disease activity (PaGA; 100-mm visual analog scale (VAS]), Patient Assessment of Pain (PAP; 100-mm VAS), EuroQOL (100-mm VAS), Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Patient Assessment Acceptable State (PASS; yes/no). The intent-to-treat population was analyzed and data were imputed using last observation carried forward. For continuous variables, treatment group homogeneity was assessed using 1-way ANOVA. Discrete variables were analyzed using chi-square or Kruskal-Wallis tests.

Results: There were no significant differences between treatment groups with respect to baseline demographics and disease characteristics or baseline PRO assessments, with the exception of employment status. Fewer patients in the ADA+MTX group compared with the MTX+PBO group were employed at baseline (49% vs. 55%; p=0.046). Significant differences between the ADA+MTX and PBO+MTX groups were observed for all PROs as early as Week 4. Improvements were maintained through Week 26. The table summarizes HAQ, PAP, FACIT-F, and WPAI results.

Patient-Reported Outcomes: Change From Baseline to Weeks 4 and 26

	ADA+MTX (N=515)	PBO+MTX (N=517)	P-Value
HAQ			
Change at Week 4 (mean±SD)	−0.64±0.61 (n=511)	−0.31±0.54 (n=512)	p<0.001
Change at Week 26 (mean±SD)	−0.89±0.74 (n=512)	−0.66±0.73 (n=512)	p<0.001
PAP			
Change at Week 4 (mean±SD)	−28.9±26.15 (n=512)	−15.6±22.70 (n=513)	p<0.001
Change at Week 26 (mean±SD)	−37.9±28.61 (n=513)	−28.0±29.33 (n=513)	p<0.001
FACIT-F			
Change at Week 4 (mean±SD)	8.1±10.28 (n=502)	4.4±8.70 (n=508)	p<0.001
Change at Week 26 (mean±SD)	10.5±11.82 (n=506)	8.3±11.12 (n=512)	p=0.001
WPAI Total Work Productivity Impairment			
Change at Week 4 (mean±SD)	−13.9±29.39 (n=205)	−5.4±24.32 (n=220)	p<0.001
Change at Week 26 (mean±SD)	−23.4±33.1 (n=215)	−16.5±31.20 (n=232)	p=0.002

Importantly, for those employed at baseline, more patients in the ADA+MTX group compared with the PBO+MTX group were still employed at Week 26 (85.9% vs. 76.3%; p=0.005). No differences were observed at Week 26 between the 2 groups among patients unemployed at baseline.

Conclusion: Patients who received ADA+MTX combination therapy were more likely to remain employed, be less impaired at work, and have less instability for future employment. They were also more satisfied with their health state, were less fatigued, and had better physical functioning than MTX-monotherapy patients. These data suggest that treatment with ADA+MTX for patients with early RA may improve their ability to retain employment and improve daily functionality and overall quality of life.

Reference: Smolen JS, et al. *Ann Rheum Dis* 2010;69(Suppl3):102.

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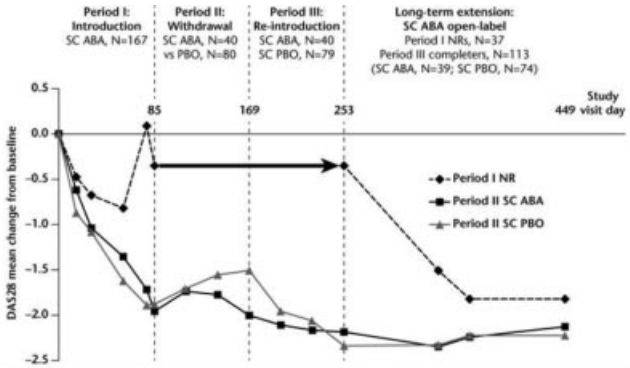
SC Abatacept Is Effective and Well Tolerated with Low Immunogenicity Following Temporary Withdrawal and Reintroduction in the ALLOW LTE (Evaluation of ABA Administered SubcutaneousLy in AduLts With Active Rheumatoid Arthritis: Impact of Withdrawal and Reintroduction). Jeffrey L. Kaine[1], Geoffrey S. Gladstein[2], Ingrid Strusberg[3], Manuel Robles[4], Ramesh Pappu[5], Ingrid Delaet[5], Miranda Pans[5] and Charles L. Ludivico[6]. [1]Sarasota Arthritis Center, Sarasota, FL, [2]New England Research Associates, Trumbull, CT, [3]Instituto Reumatológico Strusberg, Cordoba, Argentina, [4]Centro Médico Toluca, Metepec, Mexico, [5]Bristol-Myers Squibb, Princeton, NJ, [6]East Penn Rheumatology Association, East Stroudsburg, PA

Background/Purpose: Patients (pts) may temporarily stop rheumatoid arthritis (RA) biologic therapy, leading to reduced drug concentration and immunogenicity, with possible effects on safety and efficacy. We assess the impact of withdrawal and re-introduction of subcutaneous (SC) abatacept on safety, immunogenicity and efficacy up to Mth 15 of the ALLOW trial.

Methods: Pts with mild-to-moderate RA (receiving MTX for ≥3 mths) were enrolled in this randomized, double-blind, Phase III withdrawal trial. During Period I (3-mth, open-label [OL]) pts received 125 mg/week SC abatacept, plus an IV load (~10 mg/kg) on Day 1. Pts achieving DAS28-CRP reduction of ≥0.6 at Mth 3 (Period I responders) were randomized (1:2) in Period II to 3 mths SC abatacept or placebo (PBO). In Period III (3-mth, OL) all pts completing Period II received SC abatacept. Period III completers could enter the OL long-term extension (LTE) at the end of Mth 9, Period I non-responders (NR) could directly enter the OL LTE at the end of Mth 3. Pts continued to receive SC abatacept in the LTE. Safety was monitored in pts who received ≥1 dose of abatacept in the LTE. Immunogenicity (on-treatment and ≤85 days post-treatment by electrochemiluminescence) and disease activity (DAS28) are for pts entering the LTE (as-observed data), presented for 6 mths of the LTE up to Mth 15.

Results: Of 167 pts who entered Period I, 89.8% (n=150) entered the LTE: 113 Period III completers and 37 pts from Period I; 138 pts remained at time of reporting (Period I NRs=30; Period II SC abatacept=38, Period II PBO=70). 12 pts discontinued the LTE (seven Period I NRs, one Period II SC abatacept and four Period II SC PBO), the most common reasons being consent withdrawal (n=3) and other (n=4). Median (range) SC abatacept exposure was 18.9 (5–24) mths for Period I NRs and 18.7 (12–25) and 17.5 (11–22) for Period III SC abatacept and PBO groups, respectively. For pts entering the LTE, mean (SD) baseline (BL) RA duration was 7.3 (7.9) yrs and DAS28 was 4.7 (0.8). In the LTE, 12 (8.0%) SAEs occurred (none led to discontinuation) and one pt died (upper gastrointestinal bleeding). No serious infections or malignancies occurred; one pt had mild psoriasis. Local injection site reactions occurred in two (1.3%) pts. Immunogenicity was low: 4/142 (2.8%) pts treated in the LTE had positive immunogenicity (Period I NR, 1/36 [2.8%], Period II SC abatacept, 1/38 [2.6%] and PBO, 2/68 [2.9%]). Reduction in disease activity was maintained through the LTE (from Mth 9–15) in Period II SC abatacept and PBO groups, with increasing reductions from BL seen for Period I NRs (Fig). DAS28 remission rates (DAS28<2.6) at Mth 15 were 56.3 (18/32), 50.0 (19/38) and 57.1% (40/70) for Period I NRs, Period II SC abatacept and PBO.



	Number of patients with data available for DAS28 analysis			
	Month 3	Month 6	Month 9	Month 15
Period I NR	36	NA	36	32
Period II SC abatacept	39	37	38	38
Period II SC placebo	73	71	71	70

*Period I non-responders who achieved a clinical response (decrease in DAS28 of ≥0.6 from baseline) during the first 12 weeks of the long-term extension could then add a non-biologic DMARD if required

Conclusion: In ALLOW, 3-mth interruption and subsequent re-introduction of SC abatacept had no adverse impact on safety, immunogenicity or efficacy over 15 mths and was well-tolerated by the high proportion of pts continuing treatment in the LTE.

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Immunogenicity Is Low and Transient with Intravenous (IV) Abatacept Therapy: Results From a Large Pooled Analysis of 3985 Patients (pts) with Rheumatoid Arthritis (RA) and up to 8 Years' Exposure. Michael E. Weinblatt[1], Mark C. Genovese[2], Michael H. Schiff[3], Rene Westhovens[4], Rieke Alten[5], Ingrid Delaet[6], Marleen Nys[6], James Manning[6] and Joel M. Kremer[7]. [1]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Stanford University, Palo Alto, CA, [3]Rheumatology Division, University of Colorado, Denver, CO, [4]University Hospital KU Leuven, Leuven, Belgium, [5]Rheumatology Schlossparkklinik, Berlin, Germany, [6]Bristol-Myers Squibb, Princeton, NJ, [7]Albany Medical College and The Center for Rheumatology, Albany, NY

Background/Purpose: Immunogenicity with some biologics has been associated with loss of efficacy and occurrence of adverse events (AEs)[1,2]. IV abatacept (ABA) has demonstrated low and transient immunogenicity in clinical trials (~3%) that does not impact safety or efficacy[3]. We further explore immunogenicity to ABA using a large dataset of pts with up to 8 years' ABA exposure.

Methods: Data from seven ABA RA clinical trials were included in immunogenicity assessments, including the short-term (ST) periods (6- or 12-months) of six double-blind, placebo-controlled studies (AIM, ATTEST, ATTAIN, ASSURE, 101 and 100) and one non-randomized, open-label study (ARRIVE), and their open-label long-term extensions. Pts had active RA, inadequate response/intolerance to MTX/DMARDs or biologics and were treated with monthly IV ABA (~10 mg/kg). Samples on or before the day of first ABA dose were excluded. Anti-ABA antibodies were detected using two ELISAs: one to the whole ABA molecule (CTLA4 and IgG1), and one to the CTLA4 region (T). Positive samples had titers ≥400 for anti-ABA or ≥25 for anti-CTLA4-T. Immunogenicity was defined as proportion of pts with antibody response while on-treatment (≤42 days post-last dose) or post-treatment. Persistent immunogenicity was defined as positive response on ≥2 consecutive visits. Data are as-observed for all ABA-treated pts.

Results: 3985 pts were included with up to 8 years' ABA exposure; 252/3985 (6.3%) pts demonstrated antibody response (Table). Antibody titers in positive pts were generally low (in the majority of pts, titers were less than 5000 for anti-ABA and less than 100 for anti-CTLA4-T) and did not appear to increase with continued treatment. Persistent immunogenicity and immunogenicity with missed doses was infrequent (Table); titers in these pts were also generally low. Serious adverse events (SAEs) related to study drug occurred in 32/252 pts who experienced immunogenicity, with no relationship identified between immunogenicity and SAEs, peri-infusional, acute infusional or autoimmune events, or hypersensitivity reactions. No consistent relationship with efficacy was identified; 83% (55/66) of ACR20 responders maintained this following positive antibody response, while 36% (10/28) of non-responders achieved ACR20 following positive antibody response.

Immunogenicity, n/N (%) patients with positive antibody response

	Total	Anti-abatacept	Anti-CTLA4-T
Overall	252/3985 (6.3)	178/3868 (4.6)	82/3985 (2.1)
On-treatment	187/3877 (4.8)	160/3762 (4.3)	32/3877 (0.8)
Persistent on-treatment	77/3214 (2.4)	74/3050 (2.4)	3/3212 (0.1)
Post-treatment follow-up	103/1888 (5.5)	52/1685 (3.1)	53/1887 (2.8)
Persistent post-treatment follow-up	31/1298 (2.4)	22/1149 (1.9)	9/1297 (0.7)
Patients with no missed doses	68/2272 (3.0)	60/2229 (2.7)	9/2272 (0.4)
Patients with one missed dose	28/742 (3.8)	27/707 (3.8)	1/742 (0.1)
Patients with ≥two missed doses*	40/863 (4.6)	29/826 (3.5)	13/863 (1.5)

* Includes patients who missed two or more doses (with one missed dose within 365 days) prior to any on-treatment serpositive antibody result; CTLA4-T= cytotoxic T-lymphocyte antigen-4-Tip

Conclusion: ABA demonstrated low immunogenicity; any immunogenicity was transient and with low titer that did not increase upon continued dosing. No consistent association was observed between antibody response and safety or clinical efficacy, with previous observations in a pooled dataset demonstrating no association with pharmacokinetics[3]. These findings confirm previous observations[3] in a large pt population with up to 8 years' exposure.

[1]Bartelds GM, et al. *JAMA* 2011;**305**:1460–68
[2]Pascual-Salcedo D, et al. *Rheumatology* 2011;DOI: 10.1093/rheumatology/ker124
[3]Haggerty HG, et al. *J Rheum* 2007;**34**:2365–73

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Tofacitinib (CP-690,550), An Oral Janus Kinase Inhibitor, As Monotherapy in Japanese Patients with Active Rheumatoid Arthritis: A 12-Week Phase 2b Study. Y. Tanaka[1], T. Takeuchi[2], H. Yamanaka[3], M. Suzuki[4], H. Nakamura[4], S. Toyoizumi[4], J. D. Bradley[5] and S. H. Zwillich[5]. [1]University of Occupational & Environmental Health, Kitakyushu, Fukuoka, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [4]Pfizer Inc., Tokyo, Japan, [5]Pfizer Inc., Groton, CT

Background/Purpose: To compare efficacy, safety, and tolerability of 5 doses of tofacitinib monotherapy vs placebo (PBO) for treatment of rheumatoid arthritis (RA) in Japanese pts with inadequate response to DMARDs.

Methods: This study was a 12-week (wk), double-blind, PBO-controlled Phase 2b study. Pts with active RA (≥6 tender/swollen joints, C-reactive protein [CRP] >7 mg/L or ESR > upper limit of normal [ULN]) were randomized to tofacitinib 1, 3, 5, 10, 15 mg twice daily (BID) or PBO. Continuation of stable doses of NSAIDs and corticosteroids ≤10 mg prednisone equivalent was permitted.

Results: 317 pts received at least one dose of study medication. Baseline demographics and disease characteristics were comparable across treatment groups: mean ages were 52.6 to 54.7 years (y); mean duration of RA was 6.4 to 11.0 y; mean tender joint count was 13.6 to 18.6; mean swollen joint count was 11.3 to 15.3; mean DAS28-4(ESR) was 5.9 to 6.4.

The primary endpoint, ACR20 response rate at Wk 12, was statistically superior for all tofacitinib doses compared with PBO and a clear dose-response was observed. ACR50 and ACR70 response rates at Wk 12 also showed a dose-response. Tofacitinib dosed ≥5 mg BID was statistically superior in rates of DAS28-4(ESR) <2.6 at Wk 12 with maximum effect observed at doses of 10 mg and 15 mg BID (Table 1).

Table I. ACR response rates. HAQ-DI and rates of DAS28-4(ESR)<2.6 at Wk 12

	Tofacitinib					
	1 mg BID N = 51	3 mg BID N = 49	5 mg BID N = 50	10 mg BID N = 49	15 mg BID N = 52	PBO N = 48
ACR20[a]† (%)	37.7**	67.9**	73.1**	84.9**	90.7**	15.4
ACR50† (%)	13.2	26.4*	46.2**	69.8**	72.2**	7.7
ACR70† (%)	7.6	13.2*	26.9*	49.1**	51.9**	1.9
HAQ-DI‡ (change from baseline)	−0.19**	−0.38**	−0.55**	−0.67**	−0.68**	0.18
DAS28-4[§] (ESR)<2.6 (%)	5.9	2.0	16.0*	42.9**	40.4**	2.1

For ACR20, ACR50 and ACR70, a step-down procedure was used with a significance level of 0.05 based on chi-square test
* p<0.05, **p<0.0001 vs PBO
[a] primary endpoint
† last observation carried forward; ‡longitudinal linear model; [sc]no imputation

The most common adverse events (AEs) were nasopharyngitis, hyperlipidemia, and increased LDL; most were mild in severity. Fifteen serious AEs (SAEs) were reported in 9 pts. Nine treatment-related SAEs were observed in 6 pts. There were no deaths in this study.

There were dose-dependent decreases in neutrophil counts. There was no severe anemia (hemoglobin value 7.0–8.0 mg/dL decrease from baseline). Dose-dependent increases in total, HDL, and LDL cholesterol and small increases in serum creatinine were also observed in this study. AST levels >3x ULN were observed in 1 pt in the PBO group, and ALT levels >3x ULN were observed in 1 and 2 pts in 1 mg BID and PBO treatment groups, respectively (Table 2).

Table 2. Summary of safety AEs. (SAEs and laboratory values)

	Tofacitinib					
	1 mg BID N = 53	3 mg BID N = 53	5 mg BID N = 52	10 mg BID N = 53	15 mg BID N = 54	PBO N = 52
Incidence of AEs (%)	21 (39.6)	23 (43.4)	29 (55.8)	32 (60.4)	28 (51.9)	23 (44.2)
Incidence of SAEs (%)	0	3 (5.7)	2 (3.8)	2 (3.8)	1 (1.9)	1 (1.9)
Incidence of severe AEs (%)	0	2 (3.8)	1 (1.9)	1 (1.9)	0	0
Incidence of discontinuation due to AEs (%)	0	1 (1.9)	2 (3.8)	3 (5.7)	0	2 (3.8)
LSM change from baseline at Week 12:						
Neutrophil counts ($10^3/\mu L$)	0.06	−0.98	−1.44	−2.10	−1.66	0.47
LDL cholesterol (mg/dL)	3.21	11.77	16.43	21.45	24.69	−0.24
HDL cholesterol (mg/dL)	5.04	10.81	17.73	21.94	21.11−0.94	
Number (%) of pts with abnormalities and normal baseline:						
AST > 3 × ULN	0	0	0	0	0	1 (2.0)
ALT > 3 × ULN	1 (1.9)	0	0	0	0	2 (3.9)

LSM, least squares mean

Conclusion: When used as monotherapy, tofacitinib dosed >1 mg BID demonstrated superior ACR20 response rates compared with PBO at Wk 12. Doses of tofacitinib 5, 10, and 15 mg BID demonstrated superiority to placebo in DAS28-4(ESR) < 2.6. The safety profile of tofacitinib monotherapy was manageable in Japanese pts with long-standing active RA.

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Use of Disease-Modifying Anti-Rheumatic Drugs for Rheumatoid Arthritis in Quebec, Canada. Jean-Pascal Roussy[1], Louis Bessette[2], Sasha Bernatsky[3], Elham Rahme[3], Jean Légaré[4] and Jean Lachaine[1]. [1]University of Montreal, Montreal, QC, [2]CHUL, Quebec, QC, [3]McGill UHC/RVH, Montreal, QC, [4]Arthritis Alliance of Canada, Neuville, QC

Background/Purpose: Disease-modifying anti-rheumatic drugs (DMARDs) are the cornerstone of rheumatoid arthritis (RA) pharmacotherapy and should be initiated promptly following RA diagnosis. Our objectives were 1) to describe the characteristics of RA subjects in Quebec, 2) to evaluate trends in DMARD use, and 3) to assess potential factors associated with DMARD use in newly diagnosed RA.

Methods: Data from the Quebec public healthcare system databases (RAMQ and MED-ECHO) were used to identify RA subjects and their claims for medical and pharmaceutical services between January 1st 2002 and December 31st 2008. Descriptive statistics were used to characterize the RA population. To describe the patterns of DMARD use and their evolution over time, cross-sectional analyses were performed on November 1st of each year. Finally, for the newly diagnosed subgroup, multivariable logistic regressions were used to identify potential correlates of DMARD initiation at 12 months, and Kaplan-Meier curves to define the probability of initiating a DMARD over time.

Results: A total of 32,533 subjects were included. The mean age was 67.5 years; 70.4% were female. Over the study period, the percentage of subjects on a DMARD increased from 42.0% (Nov 2002) to 43.2% (Nov 2008). In multivariable analyses, being followed by a rheumatologist (vs. a general practitioner) was shown to be the strongest predictor of DMARD initiation (OR=4.39; 95%CI: 3.80–5.08). The use of NSAIDs, corticosteroids, and opioids in the year prior to cohort entry and the calendar year of the cohort entry were also increasing the likelihood of DMARD initiation. Increasing age, comorbidity score, and the use of acetaminophen had a negative effect on DMARD initiation. When specifically looking at initiation of biologic DMARDs, the strongest predictor was calendar year of cohort entry (OR 2007 vs. 2002=10.78; 95%CI: 2.45–47.37). Of subjects newly diagnosed in 2002, 0.1% had a biologic initiated within one year, while for those newly diagnosed in 2007, the percentage was 1.3%. Being followed by a rheumatologist increased the likelihood of biologic initiation, whereas increasing age reduced that likelihood. At 12 months after RA diagnosis (i.e., after cohort entry), the probability of having initiated any DMARDs was 38.5%. That probability was higher (47.8%) in the subgroup followed by a rheumatologist. Over time, the probability of DMARD initiation improved. In 2008, the median time to DMARD initiation was 288 days.

Conclusion: From 2002 to 2008, the use of RA treatment in Quebec has evolved. Despite indications that practice is moving toward earlier and more aggressive management of the disease, initiation of DMARD therapies still appears sub-optimal. Improving access to rheumatologists could be an area of focus in order to enhance the quality of RA care.

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Remission Induction by Etanercept (ETN) Plus Methotrexate (MTX) Combination Therapy Versus ETN Monotherapy in Patients with Active Rheumatoid Arthritis Despite MTX Treatment. Hideto Kameda[1], Ukitaka Ueki[2], Kazuyoshi Saito[3], Shouhei Nagaoka[4], Toshihiko Hidaka[5], Tatsuya Atsumi[6], Michishi Tsukano[7], Tsuyoshi Kasama[8], Shunichi Shiozawa[9], Yoshiya Tanaka[3], Katsuaki Kanbe[10], Eri Sato[11], Hisashi Yamanaka[12] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Rheumatic and Collagen Disease Center, Sasebo, Japan, [3]U Occupa & Environ Hlth, Kitakyushu, Japan, [4]Yokohama Minami Kyosai Hospital, Yokohama, Japan, [5]Zenjinkai Shimin-No-Mori-Hospital, Miyazaki, Japan, [6]Hokkaido University, Sapporo, Japan, [7]Kumamoto Hospital, Kumamoto, Japan, [8]Showa University School of Med, Shinagawa-ku Tokyo, Japan, [9]Kobe University Graduate School of Health Science and Medicine/ TThe Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan, [10]Medical Center East, Tokyo Women's Medical University, Tokyo, Japan, [11]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [12]Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan

Background/Purpose: The JESMR study suggested clinical and radiographic superiority of ETN+MTX combination therapy to ETN monotherapy in patients with active rheumatoid arthritis (RA) despite MTX treatment.

Methods: To examine the difference in ACR/EULAR/OMERACT remission rates (Boolean and simplified disease activity index; SDAI) at 52 weeks between ETN+MTX combination versus ETN monotherapy.

Results: Demographic and clinical features between groups at baseline were similar. The rates of tender joint count ≤ 1, swollen joint count ≤ 1, physician's global assessment ≤ 1 and serum C-reactive protein (CRP) ≤ 1 mg/dl were significantly higher in the E+M group than the E group at week 52. The Boolean and the simplified disease activity index (SDAI) remission rates were 11.6% and 21.7% in the E group, respectively, while those were 21.9% and 32.9% (p=0.12 and p=0.19, respectively, versus the E group) in the E+M group. Non-remission by the Boolean or SDAI in the E group was identified as a high-risk group for radiographic progression by modified total Sharp score (ΔTSS), while remission in the E+M group resulted in radiographic non-progression.

	ETN	ETN+MTX	p value
% tender joint count ≤ 1	35	64	0.0007
% swollen joint count ≤ 1	39	59	0.02
% patient's global assessment ≤1	22	33	0.19
% physician's global assessment ≤1	35	56	0.012
% CRP ≤ 1 (mg/dL)	51	82	<0.0001
% Boolean remission	12	22	0.12
% SDAI remission	22	33	0.19
ΔTSS in Boolean remission; mean ± SD	1.1 ± 2.4	0.0 ± 2.9	0.16
ΔTSS in Boolean non-remission; mean ± SD	4.0 ± 11.1	1.0 ± 7.2	0.065
ΔTSS in SDAI remission; mean ± SD	1.8 ± 3.0	−0.4 ± 3.8	0.027
ΔTSS in SDAI non-remission; mean ± SD	4.2 ± 12.0	1.4 ± 7.5	0.11
% HAQ-DI ≤ 0.5 in baseline TSS ≤ 100	67	62	0.63
% HAQ-DI ≤ 0.5 in baseline TSS > 100	21	47	0.054

Conclusion: It is indicated that the continuation of MTX at the commencement of ETN and subsequent remission induction are associated with beneficial clinical and radiographic outcomes even in patients with active RA despite MTX treatment.

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Celecoxib, a Selective Cyclooxygenase-2 Inhibitor, Improves a Bone Resorption Marker in Postmenopausal Women with Rheumatoid Arthritis. Shigeyoshi Tsuji[1], Tetsuya Tomita[2], Takao Iwai[1], Takanobu Nakase[1], Masayuki Hamada[1], Hideo Kawai[1] and Hideki Yoshikawa[2]. [1]Hoshigaoka Koseinenkin Hospital, Hirakata city, Japan, [2]Osaka University Graduate School of Medicine, Suita Osaka, Japan

Background/Purpose: Celecoxib (CEL), a selective COX-2 inhibitor, has been reported to suppress osteoclastogenesis in vitro, reduce bone resorption in ovariectomized mice, and prevent bone destruction in adjuvant-induced arthritic rats. However, the effects of CEL on bone metabolism have not been demonstrated in clinical setting. Here, we prospectively investigated the effects of CEL on bone metabolism and inflammation in patients with rheumatoid arthritis (RA) who switched from nonsteroidal anti-inflammatory drugs (NSAIDs) to CEL.

Methods: RA patients who had been treated with NSAIDs for more than 12 weeks were switched to CEL without any other changes in previous medications. All patients gave informed consent before enrollment. Urinary type I collagen cross-linked N-telopeptide (uNTX), serum bone alkaline phosphatase (BAP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3 (MMP-3) were evaluated before and 16 weeks after switching to CEL. Data are expressed as the mean ± SD, and Wilcoxon signed rank test was used in a statistical analysis with the significance level set at 0.05.

Results: Eighty-five patients were included in the study, and seventy-three of those were eligible for the efficacy analysis. Sixty-one were female, and the average age and affected period were 62.5 ± 10.3 and 17.2 ± 10.4 years, respectively. The most prevalently-used NSAID was loxoprofen sodium (49.3%), followed by diclofenac sodium (15.1%), meloxicam (13.7%), and etodolac (13.7%).

Sixteen weeks after switching to CEL, uNTX was significantly reduced to 34.9 ± 18.9 nmol BCE/mmol·Cr, compared with pre-treatment value of 41.0 ± 27.6 nmol BCE/mmol·Cr ($p = 0.042$) in female patients ($n = 60$). There was also a significant reduction in uNTX in postmenopausal females (from 39.0 ± 24.7 to 33.1 ± 18.6 nmol BCE/mmol·Cr, $p = 0.033$, $n = 52$), and postmenopausal females who did not use bisphosphonates (from 59.1 ± 28.3 to 46.2 ± 22.3 nmol BCE/mmol·Cr, $p = 0.011$, $n = 14$,). However, uNTX was not significantly altered in premenopausal females (from 53.8 ± 42.1 to 46.7 ± 17.1 nmol BCE/mmol·Cr, $p = 0.844$, $n = 8$) or males (from 26.1 ± 12.6 to 34.5 ± 33.9 nmol BCE/mmol·Cr, $p = 0.925$, $n = 12$). There were no significant changes in BAP, a bone formation marker, in any of these subgroups. Among various inflammatory markers, CRP was significantly decreased in the patients switched from NSAIDs to CEL (from 1.00 ± 1.36 to 0.92 ± 1.28 mg/dL, $p = 0.007$, $n = 73$), while ESR and MMP-3 remained unchanged (Table).

Table.

Changes in bone turnover and inflammatory markers after switching to celecoxib	n	Before switching	After switching	p value
Urinary NTX (nmolBCE/mmol·Cr)				
Female	60	41.0 ± 27.6	34.9 ± 18.9	p=0.042
Premenopause	8	53.8 ± 42.1	46.7 ± 17.1	p=0.844
Postmenopause	52	39.0 ± 24.7	33.1 ± 18.6	p=0.033
Bisphosphonate (+)	38	31.6 ± 18.7	28.3 ± 14.7	p=0.320
Bisphosphonate (−)	14	59.1 ± 28.3	46.2 ± 22.3	p=0.011
Biologics (+)	7	42.6 ± 20.7	34.8 ± 17.8	p=0.031
Biologics (−)	45	38.5 ± 25.4	32.8 ± 18.9	p=0.092
Corticosteroid (+)	25	43.4 ± 29.0	34.6 ± 21.2	p=0.068
Corticosteroid (−)	27	35.0 ± 19.7	31.7 ± 16.2	p=0.272
Male	12	26.1 ± 12.6	34.5 ± 33.9	p=0.925
BAP (U/L)				
Female	60	21.6 ± 9.3	20.8 ± 6.9	p=0.214
Male	12	21.3 ± 5.6	20.7 ± 4.0	p=0.925
CRP (mg/dl)	73	1.00 ± 1.36	0.92 ± 1.28	p=0.007
ESR (mm/hour)	52	35.7 ± 29.7	35.4 ± 27.7	p=0.996
MMP-3 (ng/ml)	72	168 ± 158	156 ± 123	p=0.483

MEAN±SD, Wilcoxon singed rank test

Conclusion: This is the first report to demonstrate that CEL significantly reduces uNTX, a bone resorption marker, in postmenopausal RA patients who switched from traditional NSAIDs to CEL, suggesting that CEL may suppress bone resorption through mechanisms other than cyclooxygenase inhibition. Further studies will be needed to determine whether CEL can prevent the long-term loss of bone mass in postmenopausal women.

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Safety of Rituximab in Combination with Other Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis: 48-Week Data From SUNDIAL. William Rigby[1], Philip J. Mease[2], Ewa Olech[3], Mark Ashby[4] and Swati Tole[4]. [1]Dartmouth Medical School, Lebanon, NH, [2]Swedish Medical Center, Seattle, WA, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Genentech, Inc., South San Francisco, CA

Background/Purpose: Combination biologic therapy may be used in selected patients (pts) with an inadequate response (IR) to a single biologic. In addition, pts with an IR to rituximab (RTX) may receive other biologics while B-cell depleted. The objective of SUNDIAL (stage II) was to characterize the safety of RTX (single and repeat dose) in combination with biologic DMARDs in pts with RA.

Methods: An open-label study of adult pts with active RA and an IR to ≥1 biologic. Pts who received a biologic for ≥12 wks at a stable dose for ≥4 wks prior to baseline were treated with RTX (500 mg IV ×2) plus their current biologic (etanercept, adalimumab, infliximab, or abatacept) and non-biologic DMARD treatment at a stable dose. After 24 wks, pts with a DAS ≥2.6 were offered retreatment with RTX. Primary endpoint: proportion of pts developing a serious adverse event (SAE) within 24 wks of receiving the first course of RTX. Secondary endpoints included additional safety endpoints and efficacy at 24 and 48 wks. Missing values due to pt discontinuation were handled as non-responders. Some imputation was done for missing ACR components if the pt continued on study.

Results: The safety analysis population comprised 176 pts (mean age 53.6 yrs; 88% female, mean RA disease duration 10.6 yrs; mean baseline DAS28-ESR 6.21; baseline oral steroid use 39.2%; mean number of prior anti-TNFs 1.5). Pts received RTX with 18 different biologic/DMARD combinations: 110 (62.5%) biologics alone and 66 (37.5%) biologics with non-biologic DMARDs. The most common combinations were with adalimumab alone (n=46; 26.1%) and etanercept alone (n=37; 21.0%). Of the 176 pts, 160 (90.9%) completed 24 wks and 134 (76.1%) completed 48 wks. Between wks 24 and 40, 147 (83.5%) pts were retreated with RTX. Among the 147 retreated pts, rates of SAEs, infections, and serious infections were not increased compared with the overall study population at 24 or 48 wks (Table). No SAEs occurred during/within 24 h of any RTX infusion.

Table. Summary of safety data (Event rate/100 pt-yrs [95% CI])

	Safety population up to wk 24 (n=176) (Total pt-yrs=78.2)	Safety population up to wk 48 (n=176) (Total pt-yrs=147.1)	Retreated population up to wk 48 (n=147) (Total pt-yrs=134.5)
SAEs	21.7 (13.5–35.0)	22.4 (15.9–31.6)	16.4 (10.8–24.8)
Infections	165.0 (138.8–196.1)	144.8 (126.6–165.6)	145.7 (126.7–167.6)
Serious infections[a]	3.8 (1.2–11.9)	2.7 (1.0–7.2)	2.2 (0.7–6.9)

[a]SAE or any infection treated with an IV antibiotic.

ACR responses increased from wk 24 to 48 (ACR20: 30.1 to 47.2%; ACR50: 10.2 to 21.6%; ACR70: 5.1 to 9.1%). At wk 48, 61.4% of pts achieved EULAR moderate/good response; 22.1 and 7.0% achieved DAS28 low disease activity and remission, respectively. Mean HAQ-DI score improved by −0.32 from baseline at wk 48.

Conclusion: The overall safety profile of RTX used in combination with a biologic DMARD at 48 wks was consistent with that previously reported for RTX + methotrexate[1] and RTX + nonbiologic DMARDs.[2] Despite patterns consistent with clinical benefit, conclusions regarding efficacy results cannot be drawn due to the lack of a control group and differences in baseline characteristics compared with previous studies.

References:

1. Cohen et al. Arthritis Rheum 2006;54:2793–806.
2. Loveless et al. Arthritis Rheum 2009;60(Suppl 10):1660.

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Switching of Biologic Disease-Modifying Antirheumatic Drugs During the First Year in Patients with Rheumatoid Arthritis in a Real-World Setting. Brian Meissner, Digisha Trivedi, Min You and Tony Hebden. Bristol-Myers Squibb, Plainsboro, NJ

Background/Purpose: Biologic disease-modifying antirheumatic drugs (bDMARDs) are commonly used to treat rheumatoid arthritis (RA). Although switching between bDMARD therapies is an accepted practice, there is a paucity of data describing the switching that occurs with these agents. Objective: To characterize bDMARD switching in a real-world RA population in the first year following initiation of therapy.

Methods: This observational, retrospective study utilized administrative medical and pharmacy claims from 01/01/2004 through 03/31/2010 of RA patients who were newly initiated on abatacept, etanercept, infliximab, or adalimumab. Switching of bDMARD therapy was characterized during the 12-month period following biologic initiation (post-index date). Switching was defined as a different bDMARD claim within a 100% gap in days' supply from the prior bDMARD claim. Days' supply for the bDMARD identified within the medical file was imputed based on the dosing frequency stated in the product label. Bivariate and multivariate statistical analyses were conducted to examine the characteristics of bDMARD switchers versus non-switchers.

Results: Of 10,281 patients initiated on one of the four bDMARDs studied, 7.8% switched from their index bDMARD to another within 1 year, specifically 8.9% of adalimumab, 8.5% of etanercept, 5.2% of infliximab, and 2.0% of abatacept patients. Those patients who initiated treatment with etanercept or adalimumab and switched within the first year primarily switched to a second anti-tumor necrosis factor agent (94.8%, 90%, respectively), although this was less frequent with infliximab initiators (44.6%). Among patients who switched to adalimumab, etanercept, infliximab, or abatacept as their second biologic, 18.1%, 12.9%, 12.8%, and 6.0% of patients switched to a third bDMARD, respectively, within the first year of therapy. Compared with non-switchers, bDMARD switchers incurred more hospitalizations (9.5% versus 7.2%; $p=0.015$), and higher monthly healthcare costs ($1,025 versus $796; $p<0.001$) prior to bDMARD initiation.

Conclusion: Less than 10% of RA patients who initiated therapy on adalimumab, etanercept, infliximab or abatacept switched to a second bDMARD in their first year of therapy, with switching associated with significantly more hospitalizations and healthcare costs than not switching. Further studies are required to determine why abatacept-treated patients had a lower frequency of switching than the other three biologics studied.

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Real-World Switching Patterns in Rheumatoid Arthritis Patients Receiving Abatacept, Adalimumab, Etanercept or Infliximab As Second-Line Biologic Therapy. Brian Meissner, Lisa Rosenblatt, Digisha Trivedi, Min You and Tony Hebden, Bristol-Myers Squibb. Plainsboro, NJ

Background/Purpose: A number of patients with rheumatoid arthritis (RA) switch from one biologic disease-modifying antirheumatic drug (bDMARD) to another, having previously switched from their initial bDMARD. There is a paucity of data characterizing this second-line bDMARD switch in these patients.

Objectives: To characterize, in a real-world RA population, bDMARD switching in the first year following initiation of second-line abatacept, adalimumab, etancercept or infliximab.

Methods: This observational, retrospective study utilized administrative medical and pharmacy claims from 01/01/2004 through 03/31/2010 of RA patients who were newly initiated on abatacept, etanercept, infliximab, or adalimumab. Patients were then followed forward to identify the first bDMARD claim (index date) that deviated from their initial bDMARD. Patients were required to have 6 months of continuous eligibility before, and 12 months after, the first bDMARD switch. The 12-month follow-up period was used to identify the rate of bDMARD switching among patients on second-line bDMARD therapy. Bivariate and multivariate statistical analyses were conducted to examine the characteristics of second-line abatacept versus second-line anti-tumor necrosis factor (TNF) patients.

Results: Of 3158 patients on a second-line bDMARD, 2478 (78.5%) had switched from one anti-TNF agent to another, 599 (20.0%) from anti-TNF to abatacept, and 81 from abatacept to anti-TNF (2.6%). Of these, 21.9% switched to a third bDMARD within 1 year, with 23.3% of second-line anti-TNF patients switching to a third agent compared with 15.9% of abatacept patients ($p<0.01$). Logistic regression demonstrated that patients on a second-line anti-TNF were more likely to switch to a third agent than patients on abatacept (odds ratio=1.69, 95% confidence interval: 1.33, 2.16), after controlling for age, gender, and pre-index comorbidity, hospitalization, and healthcare costs.

Conclusion: The majority of RA patients who switched from initial bDMARD stayed within the anti-TNF class. Approximately 20% of patients who switched to a second-line bDMARD subsequently switched to a third bDMARD, with those on an anti-TNF agent being significantly more likely to switch than those receiving abatacept. Further research is required to determine why abatacept-treated patients had a lower switching frequency than patients receiving an anti-TNF agent.

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Long-Term Safety of Rituximab in Rheumatoid Arthritis: Pooled Analysis of Patients in Clinical Trials with up to 9.5 Years of Treatment. Ronald F. van Vollenhoven[1], Paul Emery[2], Clifton O. Bingham[3], Edward Keystone[4], Roy M. Fleischmann[5], Daniel E. Furst[6], Nicola Tyson[7], Neil Collinson[7] and Patricia B. Lehane[7]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [3]Johns Hopkins University, Baltimore, MD, [4]University of Toronto, Toronto, ON, [5]University of Texas, Dallas, TX, [6]UCLA, Los Angeles, CA, [7]Roche Products Limited, Welwyn Garden City, United Kingdom

Background/Purpose: To evaluate the long-term safety profile of rituximab (RTX) in rheumatoid arthritis (RA).

Methods: A pooled observed case analysis of safety data from patients (pts) treated with RTX + methotrexate (MTX) in clinical trials. RTX re-treatment was based on clinical need and evidence of active disease (SJC and TJC ≥8 or DAS28 ≥2.6). Pts with >5 yrs' follow-up were analyzed as a subgroup (long-term population). Pooled data from pts treated with placebo (PBO) during the PBO-controlled phases of the trials were used to provide the PBO group.

Results: As of Sep 2010, 3194 pts (11962 pt-yrs) had received up to 17 courses of RTX over a period of 9.5 yrs. Repeat treatment data from pts exposed for >5 yrs were available for 627 pts (4418 pt-yrs). The PBO group comprised 818 pts (1107 pt-yrs) with a mean duration of follow-up of 1–1.5 yrs. The most frequent adverse event (AE) in RTX-treated pts was infusion-related reaction (IRR); 23.0% pts (734/3194) experienced IRR at first infusion of the first course; most were CTC grade 1 or 2 and were rarely serious. Other than IRR, the safety profile of RTX was similar to PBO and that of general RA populations.[1] Rates of AEs, serious AEs (SAEs), and infections remained stable over time and with multiple RTX courses. The rate of serious infection in RTX-treated patients, including pts through >5 yrs' follow-up, was comparable to that observed in the PBO population (Table). The most frequent serious infection was pneumonia (2% RTX pts). Serious opportunistic infections were rare (RTX 0.06/100 pt-yrs vs PBO 0.09/100 pt-yrs). There was no evidence of an increased risk of malignancy over the duration of follow up or with repeat RTX treatment courses. The rate of myocardial infarction (0.41/100 pt-yrs) was consistent with rates observed in the general RA population (0.48–0.59/100 pt-yrs).[1]

Table. Summary of adverse event rates per 100 pt-yrs

	RTX All-Exposure (n=3194; 11962 pt-yrs)	RTX Long-term (>5 yrs) (n=627; 4418 pt-yrs)	Pooled placebo (n=818; 1107 pt-yrs)
AE rate (95% CI)	263.10 (260.21–266.02)	254.12 (249.46–258.86)	315.43 (305.14–326.06)
SAE rate (95% CI)	14.40 (13.73–15.09)	14.30 (13.23–15.46)	13.82 (11.79–16.19)
Infection rate (95% CI)	81.64 (80.04–83.27)	75.41 (72.89–78.02)	90.39 (84.96–96.17)
Serious infection rate (95% CI)	3.94 (3.60–4.31)	3.26 (2.77–3.84)	3.79 (2.80–5.13)

CI = confidence interval.

Conclusion: Pooled long-term safety data from 3194 pts exposed to RTX in clinical trials for up to 9.5 yrs (11962 pt-yrs) show that RTX has remained well tolerated over time and over multiple courses. Increased duration of exposure to RTX treatment was not associated with any new safety signals, including in pts with >5 yrs' follow-up. The overall safety profile of RTX remains similar to that of the pooled PBO population and is consistent with published data for moderate to severe RA.

Reference: 1. British Society for Rheumatology Biologics Register, 2007

2200

Eight Year Results of Disease Activity Steered Treatment in a Large Recent Rheumatoid Arthritis Cohort: Clinical and Radiological Outcomes.

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Background/Purpose: To compare 8-year clinical and radiological outcomes of four dynamic DAS steered treatment strategies (BeSt study) in recent onset rheumatoid arthritis (RA) patients.

Methods: 508 patients with recent onset RA were randomized to four treatment strategies: 1. sequential monotherapy, 2. step up combination therapy, 3. initial combination with prednisone, 4. initial combination with infliximab. Every three months, treatment adjustments were made based on DAS measurements (DAS >2.4: next treatment step; DAS ≤ 2.4 during ≥6 months: taper to maintenance dose, next if DAS <1.6 during ≥6 months: stop anti-rheumatic treatment). Functional ability (HAQ) was analyzed with a linear mixed model (LMM) with time, treatment and time*treatment as independent variables. Joint damage progression (Sharp-van der Heijde Score (SHS)) was assessed on X-rays of baseline and year 1, 2, 3, 4, 5, 6, 7 and 8 and scored by two independent readers (LD and MvdB), blinded for patient identity and in random order.

Results: After 8-years follow-up, 161 patients (32%) dropped out the study. Seventy-nine percent of the completers had a DAS ≤2.4 and 52% DAS <1.6 (remission), equally distributed among the four groups (table). Eighteen, 19, 17 and 15% of the patients in groups 1–4 were in drug free remission with a median (mean) duration of 45 (39) months. Six patients lost and twelve new patients achieved drug free remission in year 8, while eight patients with prolonged drug-free remission dropped out. The initial improvement of function, which occurred earlier in groups 3 and 4 than in groups 1 and 2, was maintained without deterioration over 8 years time in all groups. Over time (LMM), patients in group 4 have significantly better functional ability compared to group 2 (mean HAQ: 0.57 and 0.71). After initial differences in years 1 and 2 between the 4 groups, yearly radiological damage progression rates were low and similar between all groups, reflecting the efficacy of DAS-steered therapy. Differences in total damage after 8 years are no longer statistically significant. Mean SHS progression in patients in sustained drug free remission was 0.1 (median (IQR) 0 (0–0.03)) per person year drug-free. Toxicity was comparable between the groups.

Table. 8-year results of the BeSt study.

	Group 1 n=126	Group 2 n=121	Group 3 n=133	Group 4 n=128	p-value
DAS ≤2.4, (%)†	79	76	84	76	0.49
DAS <1.6, (%)†	49	56	57	47	0.48
DAS <1.6 drug free, %†	18	19	17	15	0.90
Still on initial treatment step, %†	29	22	45	66	<0.001
Mean HAQ during 8 years‡	0.69	0.71	0.63	0.57	<0.05*
IFX current use, (%)†	21	10	13	24	0.06
Lost to follow-up, n (%)‡	41 (33)	43 (36)	47 (35)	30 (23)	0.13
Missing data, no.	8	12	9	4	
SHS progression, median (mean)†					
Total, year 0–8	3.0 (14.6)	4.3 (13.9)	2.0 (8.5)	2.0 (8.3)	0.567
year 1	0.3 (4.9)	0.5 (2.3)	0 (1.1)	0 (1.0)	0.005
year 2	0 (2.6)	0 (1.1)	0 (0.8)	0 (0.6)	0.028
year 3	0 (1.2)	0 (1.5)	0 (1.1)	0 (0.6)	0.841
year 4	0 (1.1)	0 (1.3)	0 (1.1)	0 (0.8)	0.898
year 5	0 (1.3)	0 (1.6)	0 (1.3)	0 (1.2)	0.593
year 6	0 (1.5)	0 (1.2)	0 (1.4)	0 (0.9)	0.841
year 7	0 (0.6)	0 (1.7)	0 (1.6)	0 (0.7)	0.066
year 8	0 (0.4)	0 (1.0)	0 (1.3)	0 (0.7)	0.527

†completers analysis, ‡intention to treat. *LMM: group 2 vs 4, $p < 0.05$, group 1 vs 4, $p = 0.055$, all other, $p > 0.05$.

Conclusion: After a clinically relevant earlier functional improvement with initial combination therapy than with initial monotherapy, improvement was maintained in all groups without deterioration over time with continued DAS steered treatment aiming at DAS ≤ 2.4. In addition, radiological damage was very low, even after 8 years. The percentages of patients in clinical remission and in drug free remission were stabilized.

2201

A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Dose Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of BIIB023 (Anti-TWEAK) in Subjects with Rheumatoid Arthritis.

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Background/Purpose: TNF-like weak inducer of apoptosis (TWEAK) and its sole signaling receptor FGF-inducible molecule 14 (Fn14) are highly upregulated locally in the end organ targets of inflammatory and autoimmune diseases. Inhibition of the TWEAK/Fn14 pathway has proved to be efficacious in multiple experimental models of these diseases by reducing inflammatory responses and pathological tissue remodelling. BIIB023 is a humanised anti-TWEAK monoclonal antibody currently in development for the treatment of lupus nephritis.

The objectives of this first in man study were to evaluate the safety, tolerability, PK and immunogenicity of single administration of BIIB023 in subjects with rheumatoid arthritis (RA). Exploratory objectives included the analysis of biomarkers for the assessment of target engagement and pharmacologic effect.

Methods: This was a multicenter, randomized double-blind, placebo-controlled, dose escalation study in subjects with RA. Fifty three subjects on stable regime of methotrexate received a single intravenous dose of BIIB023 of 0.03 to 20 mg/kg (n=38) or placebo (n=15) and were followed up for 70 days. Safety assessment included adverse events (AEs), serious adverse events (SAE), physical examination and laboratory analysis. Serum samples were collected for PK, immunogenicity and exploratory biomarker assessments.

Results: Single dose IV administration of BIIB023 demonstrated a favourable safety and tolerability profile with no dose-dependent safety finding observed in any of the dose groups. There were no severe or serious AEs or any subject discontinuation or withdrawal and no difference in infection rate between groups. No notable laboratory or physical exam/ECG findings were observed. The PK profile of BIIB023 revealed a t1/2 of approximately 24 days in the high doses of 10 and 20 mg/kg. A single subject (3%) tested positive for anti-drug antibody.

Serum soluble TWEAK concentrations, an indicator of target engagement, were suppressed to below the level of quantitation at the first timepoint assessed (6 hours after dosing) and returned to baseline levels at 3 to 4 weeks following a single dose of 10 mg/kg or 20 mg/kg BIIB023. Multiplex analysis of biomarkers revealed a trend toward down modulation in MCP-1, ICAM-1, A-SAA, BAFF, E-Selectin, IL-6, and IP-10 in the high dose cohorts (3 to 20 mg/kg) and was consistent with dose dependent activity of BIIB023 upon administration of a single dose.

Conclusion: Single dose administration of BIIB023 (Anti-TWEAK) showed a favourable safety and tolerability profile in subjects with RA and suppressed serum soluble TWEAK, a biomarker of target engagement, for up to 4 weeks. The PK profile of BIIB023 supports further development in inflammatory and autoimmune diseases and is currently being pursued for the treatment of Lupus Nephritis.

Response to Second-Line DMARDs and TNFi in Seropositive and Seronegative Patients in Early and Late Rheumatoid Arthritis Are Not the Same: Results From the CATCH Cohort and a Large, Established Rheumatoid Arthritis Database. Yang Cao[1], Ashley Bonner[2], Lillian J. Barra[3], J. Carter Thorne[4], Boulos Haraoui[5], Gilles Boire[6], Carol A. Hitchon[7], Nicole G. H. Le Riche[8], Andrew E. Thompson[9], Edward Keystone[10], Vivian Bykerk[11], Janet E. Pope[12] and CATCH Investigators[13]. [1]University of Western Ontario, London, ON, [2]McMaster University, Hamilton, ON, [3]Schulich School of Medicine and Dentistry, London, ON, [4]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [5]Institut de Rhumatologie, Montreal, QC, [6]CHUS - Sherbrooke University, Sherbrooke, QC, [7]University of Manitoba, Winnipeg, MB, [8]St. Joseph's Hospital, London, ON, [9]St. Josephs Health Ctr, London, ON, [10]University of Toronto, Toronto, ON, [11]Brigham & Women's Hospital, Boston, MA, [12]St. Joseph's Health Care, University of Western Ontario, London, ON, [13]Toronto, ON

Background/Purpose: To investigate differences in treatment response to second-line DMARDs and biologics (TNFi) in seropositive versus seronegative RA patients in early and established RA.

Methods: Patients from the CATCH ERA Cohort who had failed first line DMARD therapy and continued to second-line therapy were selected. These were defined as those on first-line therapy with DAS28>2.6 who added new DMARD(s). Patients treated with DMARDs before inclusion in the CATCH cohort were excluded from the analysis. The proportion achieving DAS<2.6 in next 6 months after the first addition of DMARD(s) were compared with regards to RF status and anti-CCP status. Similarly, patients with DAS28>2.6 adding biologic therapy were selected and the proportion achieving DAS<2.6 in the next 6 months were compared with regards to RF and anti-CCP status using Pearson Chi-square analyses. In an established RA Cohort[1] from an outpatient rheumatology practice, RA patients using TNFi were studied by response to treatment by RF status on HAQ-DI and pain change (on a 0 to 3 scale).

Results: CATCH Cohort: No significant difference was found in second-line DMARD response between RF+ and RF- groups as well as in anti-CCP+ and − groups. Proportion achieving DAS<2.6 at follow-up after initiating biologic therapy was significantly higher in anti-CCP− patients (14/22=63.6%) versus Anti-CCP+ patients (11/32=34.4%); p=0.034. The ERA changes in HAQ were not different in post DMARD and post TNFi when studying RF and CCP status (Table 1). Established RA Cohort: Mean one year HAQ-DI change was found to be significantly greater in 90 RF+ patients at −0.356 versus 38 RF- patients at −0.126 (p=0.043). Mean pain change was also found to be significantly greater in 77 RF+ patients at −0.725 versus 32 RF- patients at −0.332 (p=0.03) (Table 2).

Table 1.

Established RA TNFi Treatment	RF+	RF-	P value
N	178	60	
% Female	82%	72%	0.7
Age (SD)	57 (14)	56 (12)	0.6
Disease duration {years} (SD)	12 (8)	9 (8)	0.017
Baseline HAQ (SD) (0=3) prior to TNFi	1.44 (0.63)	1.41(0.63)	0.8
HAQ change Baseline to Year 1	**−0.356 (0.60)**	**−0.126 (0.54)**	**0.04**
Baseline PAIN (SD) (0–3)	1.92 (0.67)	1.93 (0.67)	0.9
PAIN change Baseline to Year 1	**−0.725 (0.86)**	**−0.332 (0.82)**	**0.03**
Mean treatment duration for first TNFi {Years} (SD)	2.8 (2.0)	2.3 (1.6)	0.1
Proportion of patients still on same TNFi after 1 year	68%	62%	0.5

Table 2. ERA Cohort

	DMARD Added				TNFi Added		
	RF +	RF −	P Value		RF +	RF −	P Value
Patients adding first DMARD(s)	108	62		Patients adding first TNFi	39	30	
% achieving DAS<2.6 at 1st FU	32.4%	30.6%	0.812	**% achieving DAS<2.6 at 1st FU**	**28.2%**	**46.7%**	**0.114**
% achieving DAS<2.6 at 2nd FU	61.1%	50.0%	0.159	% achieving DAS<2.6 at 2nd FU	43.6%	53.3%	0.422
HAQ Baseline (Adds)	0.853	0.752	0.389	HAQ Baseline (Adds)	0.914	0.618	0.136
HAQ 1st Follow up (Adds)	0.780	0.679	0.395	HAQ 1st Follow up (Adds)	0.750	0.660	0.650
HAQ 2nd Follow up (Adds)	0.731	0.619	0.424	HAQ 2nd Follow up (Adds)	0.891	0.581	0.181
Change in HAQ after 1st Follow up (Adds)	−0.122	−0.076	0.622	Change in HAQ after 1st Follow up (Adds)	−0.162	0.074	0.203
Change in HAQ after 2nd Follow up (Adds)	−0.259	−0.115	0.165	Change in HAQ after 2nd Follow up (Adds)	−0.103	0.092	0.221

	CCP +	CCP −	P Value		CCP +	CCP −	P Value
Patients adding first DMARD(s)	81	50		Patients adding first DMARD(s)	32	22	
% achieving DAS<2.6 at 1st FU	38.3%	24.0%	0.091	% achieving DAS<2.6 at 1st FU	31.2%	40.9%	0.465
% achieving DAS<2.6 at 2nd FU	60.5%	48.0%	0.162	% achieving DAS<2.6 at 2nd FU	**34.4%**	**63.6%**	**0.034**
HAQ Baseline (Adds)	0.821	0.794	0.835	HAQ Baseline (Adds)	0.830	0.607	0.348
HAQ 1st Follow up (Adds)	0.705	0.694	0.934	HAQ 1st Follow up (Adds)	0.680	0.613	0.776
HAQ 2nd Follow up (Adds)	0.647	0.686	0.813	HAQ 2nd Follow up (Adds)	0.647	0.722	0.778
Change in HAQ after 1st Follow up (Adds)	−0.144	−0.107	0.704	Change in HAQ after 1st Follow up (Adds)	−0.073	0.0875	0.418
Change in HAQ after 2nd Follow up (Adds)	−0.266	−0.160	0.331	Change in HAQ after 2nd Follow up (Adds)	−0.131	0.111	0.212

Conclusion: RF+ patients with established disease may be more responsive to TNFi therapy as measured by changes in HAQ and pain. Perhaps in established RA with DMARD failure, any biologic may have a blunted response in RF negative patients. However, anti-CCP negative patients may also be more responsive to TNFi therapy in ERA but other datasets may be needed to confirm these results. This may also be due to chance.

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Better Retention Rate of Rituximab Vs Anti-Tnf Agents As Second Line therapy in RA Patients Failing a First Anti-Tnf Agents: Results From the Rhumadata® Registry. D. Choquette. Institute of Rheumatology of Montreal, Montreal, QC

Background/Purpose: A significant proportion of patient with rheumatoid arthritis treated with a first anti-tnf agent will eventually be exposed to a second biologic agent. The actual knowledge as to the best choice is another anti-TNF agent or an agent with a different mode of action such as rituximab remains controversial and often only explores the first three to six month after initiating the second agent.

Methods: We report three year follow-up of treatment with either a second anti-tnf agents, abatacept or rituximab in a cohort of RA patients having failed a first anti-tnf agent. Data initial extraction date is January 1st 2007. Data is extracted from the prospective Rhumadata ®electronic data collection system which compile over time demographics, diagnosis information, disease duration, anti-CCP and RF status, ESR &CRP, all DAS score, CDAI and SDAI, commonly used PRO's such as the HAQ, Patient global, fatigue evaluation, pain score at all visits. It also compiles all medications used for the treatment of RA with dose, frequency, duration, adverse events and reason for stopping.

Results: 119 patients are included in this analysis. All have failed a first anti-tnf agents. 34 received adalimumab (ADA) as second agent only, 17 rituximab (RTX), 25 etanercept (ETA), 15 infliximab (INF), and 28 abatacept(ABA). Baseline variables are shown in the table 1 (MEAN). % of patient still on treatment at 36 months in table 2.

Table 1. Baseline variables

TX	#PTS	RA/ YEAR	FEMALE	TJC	SJC	DAS28-4-ESR	DAS28-4-CRP	CDAI	FATIGUE (0–10 VAS)
ADA	34	14	74	5	6	3.12	3.47	16.84	5
RTX	17	20	82	8	9	3.79	4.23	23.15	6
ETA	25	15	80	11	10	3.90	4.36	24.85	5
INF	15	14	87	10	9	3.91	4.51	25.27	6
ABA	28	15	82	9	9	3.84	4.12	26.50	7

Table 2. % of patients still continuing therapy at 36 months

Biologic agents	% (p value)
Adalimumab	50% (p=0.03)*
Rituximab	76.5% (ref)
Etanercept	52% (p=0.05)*
Infliximab	33.3% (p=0.01)*
Abatacept	57.1% (p=0.1)*

* Fischer exact test –rituximab vs comparator

Conclusion: In this small sample of patients failing a first anti-tnf, rituximab at usual dosage seems to have better retention rate at 36 months than a second anti-tnf statistically and abatacept numerically.

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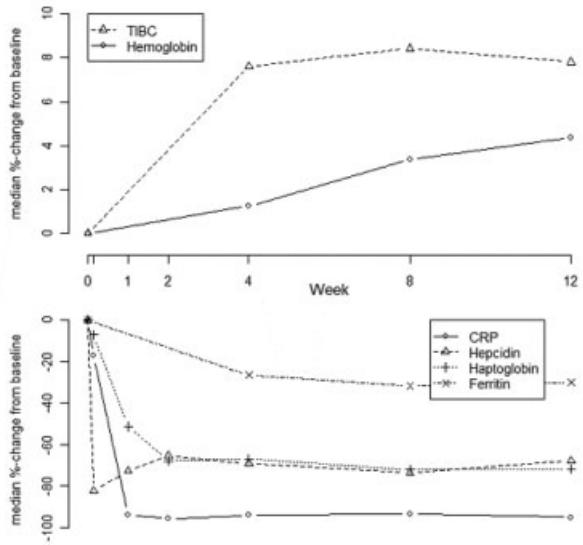
Effect of Tocilizumab on Hematologic Markers Implicates Interleukin-6 Signaling in the Anemia of Rheumatoid Arthritis. John D. Isaacs[1], Olivier Harari[2], Uwe Kobold[3], C. Bernasconi[4] and Janet S. Lee[5]. [1]Newcastle University, Newcastle Upon Tyne, United Kingdom, [2]Roche, Welwyn, United Kingdom, [3]Roche Diagnostics GmbH, Penzberg, Germany, Germany, [4]Roche, Basel, Switzerland, [5]Roche, Nutley, NJ

Background/Purpose: Infections trigger mechanisms that reduce iron availability to invading pathogens. The putative master regulator of this phenomenon is hepcidin, which inhibits intestinal absorption as well as mobilization from reticuloendothelial stores. Hepatic hepcidin expression is largely IL-6-signaling dependent.[1] These mechanisms also underlie chronic anemia in rheumatoid arthritis (RA).[2] Trials of tocilizumab (TCZ), an IL-6 receptor (IL-6R) inhibitor, show suppression of inflammation and increases in hemoglobin (Hb) in RA patients. We probed for associations between increases in Hb and hepcidin levels in RA patients treated with TCZ.

Methods: In the MEASURE study, patients with active RA and inadequate response to methotrexate (N=132) were randomized to TCZ 8 mg/kg IV or placebo (PBO) every 4 weeks (wks), both with weekly MTX. Serum hepcidin (HPLC–tandem mass spectroscopy assay[3]), markers of inflammation, and iron homeostasis were measured at screening, baseline, and through wk 12 of study. Descriptive methods and simple and multiple regression were used to evaluate data.

Results: Low Hb at baseline exhibited moderate correlation with acute phase reactants (C-reactive protein [CRP] and haptoglobin; Spearman rank correlation [P] −0.20 and −0.25, $P<0.023$ and $P<0.004$, respectively). Pre-treatment hepcidin was highly variable (0 – 63.1 fmol/uL), and levels correlated with acute phase reactants (CRP, HPT, ferritin [P: 0.34–0.64, $P<0.001$]), but not with Hb ($P=0.03$; $P=0.70$). Through 12 wks of treatment with TCZ (n=70) (but not PBO; n=62), increases in Hb and early and marked reductions in hepcidin and inflammation markers (CRP, haptoglobin, and ESR) were observed (Figure). Ferritin levels were reduced, reflecting the role of ferritin as an acute phase reactant; total iron binding capacity increased, reflecting an increased capacity of the blood compartment to store available iron. In TCZ-treated patients, an early drop in hepcidin (wks 1 and 2) correlated with a late increase in Hb (wks 4, 8, and 12) ($P>0.28$, $P<0.02$ for all comparisons). In multivariate analyses including all variables, the strongest predictor for TCZ-induced Hb increase through wks 4, 8, and 12 was fall in haptoglobin (multiple $R^2=0.26$, 0.31, and 0.45, respectively; $P<0.0001$).

Figure: Time course of median %-change in haematologic and inflammatory markers in the TCZ group,exclude early withdrawals (n=5) and patients who received escape therapy (n=12). CRP=C-reactive protein; TIBC= total iron binding capacity.



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Conclusion: TCZ induced a rapid and sustained fall in hepcidin, in association with suppression of inflammation markers. Association of early reductions in hepcidin with subsequent Hb increases is compatible with role of hepcidin in inflammatory anemia of RA.[4] These findings highlight the need for comparative data on the resolution of inflammatory anemia in RA pts, with TCZ vs. other therapies.

2205

Comparison of Disease Characteristics of rheumatoid arthritis patients in Remission According to the DAS Criteria Versus the New ACR/EULAR Criteria in a Real-World Patient Population. Denis Choquette[1], William G. Bensen[2], Maqbool K. Sheriff[3], John T. Kelsall[4], Milton F. Baker[5], John S. Sampalis[6], Susan M. Otawa[7] and Heidi Imhoff[7]. [1]University of Montreal Hospital Research Centre (CRCHUM), Notre Dame Hospital Montreal, Montreal, QC, [2]McMaster University, Hamilton, ON, Hamilton, ON, [3]Nanaimo Regional General Hospital, Nanaimo, BC, [4]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, [5]University of Victoria, Victoria, BC, [6]McGill University & JSS Medical Research, Montreal, QC, [7]Merck Canada Inc, Kirkland, QC

Background/Purpose: The commonly used remission criteria DAS-ESR and DAS-CRP rather define minimal disease activity than remission. ACR/EULAR recently developed new definitions of remission[1] (A/E criteria) that reflect more accurately a patient population in clinical remission. ACR/EULAR also endorses the definition of remission according to the SDAI (SDAI≤ 3.3). The purpose of this analysis is to compare the performance of the different remission criteria in a real-world Canadian patient population treated with infliximab (IFX).

Methods: BioTRAC is an ongoing, non-interventional study of patients (pts) starting IFX as first biologic or after having been treated with a biologic for less than six months. Pts with rheumatoid arthritis (RA) who have been enrolled for at least 6 months (mo) ago are included in this analysis. Remission rates at 6 mo are based on a modified ITT analysis, including all pts with sufficient information reported.

Results: A total of 775 established RA patients were included in this analysis. At 6 mo 33%, 28%, 17% and 8% of the pts achieved remission as defined by DAS28-CRP (≤2.6), DAS28-ESR (≤2.6), SDAI (≤3.3) or the A/E criteria, respectively.

In general, mean clinical parameters at 6 mo were higher in pts in DAS-CRP and in DAS-ESR remission compared to pts in SDAI or in A/E remission. The only exceptions were CRP, which was lowest in pts in DAS-CRP remission, and ESR, which was lowest in pts in DAS-ESR remission, reflecting the high weighing of the acute phase reactants in the DAS criteria. When comparing clinical characteristics at 6 mo between pts in SDAI and pts in A/E remission, mean CRP, ESR, Phys. Global Assess., DAS28-ESR, DAS28-CRP and SDAI score were comparable, while morning stiffness, HAQ, TJC, SJC, Pat Global Assess. were lower in pts in A/E remission (table 1). Pts in A/E remission at 6 mos consistently had the lowest HAQ over a 4 year period (as observed analysis), with mean HAQ<0.5, suggesting that pts achieving stringent remission criteria regain normal function and maintain it over 4 years.

Multivariate regression analysis showed that baseline characteristics predicting remission according to the different criteria at 6 mo did not differ greatly. Male gender and HAQ were the major prediction factors for remission.

Table 1. Clinical parameters at 6 mos according to remission criteria

Clinical parameters at 6 mos	DAS28 ESR > 2.6	DAS28 ESR <= 2.6	DAS28 CRP > 2.6	DAS28 CRP <= 2.6	SDAI > 3.3	SDAI <= 3.3	No ACR/ EULAR remission	ACR/ EULAR remission	All patients
	N/Mean	N/Mean	N/Mean	N/Mean	N/Mean	N/Mean	N/Mean	N/Mean	N/Mean
Morning Stiffness (min)	319/38.38	123/23.22	248/42.44	124/18.36	412/39.14	86/16.66	439/38.39	39/12.23	498/35.26
HAQ	317/1.26	121/0.60	249/1.27	121/0.66	412/1.21	81/0.48	437/1.17	39/0.32	493/1.09
ESR (mm/hr)	324/29.12	123/10.37	239/26.64	119/18.16	371/25.76	79/14.58	396/25.24	37/14.92	450/23.80
CRP (mg/L)	261/12.74	94/6.84	252/14.38	124/4.66	312/12.80	64/3.26	332/12.21	39/3.62	376/11.17
TJC (out of 28)	324/7.23	123/0.76	252/8.03	124/0.60	420/6.51	86/0.33	447/6.14	39/0.18	506/5.46
SJC (out of 28)	324/4.89	123/0.92	252/5.49	124/0.81	420/4.61	86/0.27	447/4.36	39/0.13	506/3.87
Pat GA (mm)	296/42.12	112/21.34	230/43.44	112/23.38	391/42.71	72/6.72	411/41.27	39/3.72	463/37.11
Phys GA (mm)	319/37.02	123/16.75	249/39.08	124/16.45	411/36.03	86/11.05	438/34.38	39/11.54	497/31.71
DAS28 CRP	261/3.74	94/1.89	252/3.96	124/1.86	312/3.61	64/1.60	332/3.49	39/1.60	376/3.27
DAS28 ESR	324/4.29	123/1.84	237/4.29	118/2.19	369/3.99	78/1.82	394/3.87	37/1.70	447/3.61
SDAI	324/18.90	123/4.31	252/20.50	1234/4.15	420/18.54	86/1.51	447/17.55	39/1.16	506/15.64

Conclusion: The results of this real-world study show that pts in DAS remission have higher disease activity than pts in SDAI or A/E remission. Although ACR/EULAR endorses both the SDAI as well as the A/E criteria, disease activity in pts in SDAI versus A/E remission was different in this real world pt population, with pts in A/E remission having lower disease activity. Stringent remission 6 mo after IFX initiation was associated with a normal functional outcome (mean HAQ<0.5) over 4 years.

1: Felson et al. Arthritis Rheum. 2011. 63(3): 573

2206

Golimumab Treatment Inhibits Progression in Joint Damage in Patients with Psoriatic Arthritis Regardless of Baseline Disease Severity. Arthur Kavanaugh[1], Dafna D. Gladman[2], Anna Beutler[3], Chenglong Han[4] and GO-REVEAL Clinical Investigators. [1]University of California San Diego, San Diego, CA, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA, [4]Johnson & Johnson Pharmaceutical Services, LLC, Malvern, PA

Background/Purpose: To identify variables associated with radiographic joint damage in pts PsA treated with golimumab (GLM) or placebo (PBO) (standard therapy with MTX or/and NSAIDs) in a Ph3 randomized, PBO-controlled study (GO-REVEAL).

Methods: Adult PsA pts with ≥3 swollen & ≥ 3tender joints were randomized to subcutaneous placebo(PBO) or GLM(50 or 100mg) q4wks. At wk16, pts with <10% improvement in swollen & tender joint counts entered early escape in blinded fashion to GLM50mg (PBO pts) or GLM100mg (GLM 50mg pts). Starting at wk 24, pts remaining on PBO crossed over to GLM50mg. Changes from baseline in PsA modified vdH-S scores of hands and feet were compared at wks24&52 by stratification of baseline disease activity (DAS28>5.1 vs. ≤5.1) or CRP level (>0.6 vs. ≤0.6 mg/dL). Logistic regression model was used to adjust for covariates(age, gender, disease duration, body weight, baseline MTX use) when examining association of baseline DAS28 with joint progression from baseline to wk24 or from wk24 to 52. In logistic regression model, only patients who had no missing X-ray data were evaluated.

Results: 405pts were enrolled with mean(SD) total PsA modified vdH-S scores of 18.15(27.76) to 23.85(35.41) and baseline DAS28 score of 4.9 (1.0) to 5.0 (1.1). At wk24, GLM-treated pts had significantly less radiographic damage than PBO(mean change from baseline −0.09±1.32 vs. 0.27±1.26, p=0.015) or had no progression (change≤0) than PBO-treated pts (77.7% vs. 62.7%, p=0.003). These differences were greater among pts with high disease activity (DAS28>5.1) (p<0.01) or elevated CRP(CRP>0.6 mg/dL) (p=0.01) than pts with moderate disease activity or normal CRP. After adjusting for baseline characteristics using a regression model, higher baseline disease activity was significantly associated with radiographic progression at wk24 in PBO group (p<0.01), but baseline disease activity was not associated with radiographic progression in the GLM group. Similarly, disease activity at wk24 in all pts randomized to GLM or switched to GLM at wk24 was not associated with radiographic progression from wk24 to 54, suggesting that irrespective of disease activity at wk24, there was absent or nominal progression in joint damage at wk52.

Table. Pts with no radiographic progression (vdH-S score ≤0) at wk24 by baseline disease severity (DAS28) or baseline CRP concentration

Baseline DAS28	PBO N=109	GLM (50 or 100mg) N=285	Baseline CRP (mg/dL)	PBO N=112	GLM (50 or 100mg) N=290
<5.1	76.7%	81.2% (p=0.45)	≤0.6	71.7%%	81.3% (p=0.15)
≥5.1	53.1%	76.7% (p<0.01)	>0.6	61.0%	77.6% (p=0.01)

Conclusion: PsA pts with high arthritis disease activity or CRP level at baseline experience more joint damage if treated with standard therapy only. Adding GLM provides additional benefit in inhibiting radiographic progression, especially for pts with more severe disease activity. The beneficial effect of GLM on joint damage was also observed in pts with baseline DAS28 <5.1 or CRP ≤0.6 mg/dl but to a lesser degree than in pts with high disease activity.

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Optimism and Depressive Scores in Early Arthritis Patients Before and After Treatment with Methotrexate and a Tapered High Dose of Prednisone in the IMPROVED Study. L. Heimans[1], K.V.C. Wevers-de Boer[1], K. Visser[1], Tom W.J. Huizinga[1], H.K Ronday[2], M.L. Westedt[3], T.H.E. Molenaar[4], R.C. van der Mast[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Haga Hospital, The Hague, Netherlands, [3]Bronovo Hospital, The Hague, Netherlands, [4]Groene Hart Hospital, Gouda, Netherlands

Background/Purpose: To assess depression and optimism scores in patients with recent onset arthritis, before and after four months of induction therapy with methotrexate and prednisone.

Methods: Patients with recent onset rheumatoid and undifferentiated arthritis were treated with MTX 25mg/week and 60 mg/day of prednisone immediately tapered to 7.5mg/day in seven weeks in the IMPROVED-study. At baseline and four months after start of treatment, patients filled out the Beck Depression Inventory (BDI-II) to assess depression symptom severity (range 0–63) and the Life Orientation Test Revised (LOT-R) to measure optimism (range 0–24). Comparisons were made between scores before and after treatment and between patients who did or did not achieve clinical remission, defined as a Disease Activity Score (DAS) <1.6. Linear multiple regression analysis was used to investigate the relationship between the two questionnaires, DAS and DAS components, visual analogue scales (VAS) for pain, general wellbeing and global health, age, sex, marital status, children, educational level, work, and previous medical history.

Results: 210 patients completed the LOT-R and 215 patients completed the BDI-II at both time points. Optimism and depression are related at baseline, but not after four months. Optimism significantly decreased, independent of whether remission was achieved. There was no significant difference in scores at baseline or after four months between both groups (p=0.823). Regression analysis revealed no significant relationship between disease activity and optimism scores. Only (higher) age was an independent predictor of (higher) absolute optimism scores after 4 months of treatment (p<0.001). Overall, the depression scores significantly improved. In patients who achieved remission, the scores after four months treatment were significantly lower than at baseline (from 6.9 to 4.8, p<0.001). In the non-remission group depression scores before and after treatment were similar (baseline 11.2 and 4 months 11.0, p=0.826). Independent predictors of depression scores after four months were a high depression score at baseline (B 0.48, p<0.001), a high DAS (B 2.17, p<0.001) and a history of metabolic disease (B 2.55, p=0.03). A higher baseline score predicted a smaller delta-BDI-II (B-0.51, p<0.001), higher VAS scores for general health (B 0.07, p=0.020) and general wellbeing (B 0.10, p<0.001) predicted a slightly increased delta-BDI-II.

Conclusion: Depression severity scores decrease in early RA and UA patients who achieve remission after 4 months of treatment with methotrexate and prednisone. However, optimism scores also decreased independent of whether remission was achieved and without strong predictors. This suggests that the change in optimism is not related to change in disease activity but maybe to shared characteristics related to diagnosis, trial participation or medication.

2208

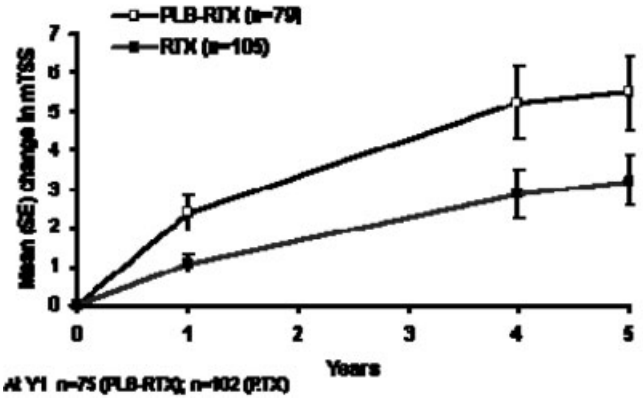
Sustained Inhibition of Structural Damage in Patients with Rheumatoid Arthritis and An Inadequate Response to Tumor Necrosis Factor Inhibitors Prior to Rituximab Treatment: 5-Year Data From the REFLEX Study. Edward Keystone[1], Stanley B. Cohen[2], Paul Emery[3], Joel M. Kremer[4], Maxime Dougados[5], James E. Loveless[6], Carol Chung[7], Patricia B. Lehane[8] and Helen Tyrrell[8]. [1]University of Toronto, Toronto, ON, [2]Metroplex Clinical Research Center, Dallas, TX, [3]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [4]Albany Medical College, Albany, NY, [5]Rene Descartes University, Paris, France, [6]St. Luke's Rheumatology, Boise, ID, [7]Genentech, Inc., South San Francisco, CA, [8]Roche Products Limited, Welwyn Garden City, United Kingdom

Background/Purpose: Rituximab (RTX) in combination with methotrexate (MTX) has been shown to inhibit progressive joint damage (PJD) in RA patients (pts) with an inadequate response to TNF inhibitors (TNF-IR) at 2 yrs (Cohen SB, et al. Ann Rheum Dis 2010;69:1158–61). This analysis assessed the impact of RTX treatment over 5 yrs on PJD in TNF-IR pts in the REFLEX open-label extension study.

Methods: In REFLEX, TNF-IR pts received background MTX and were randomized to placebo (PLB; n=209) or RTX (2 × 1000 mg, 2 wks apart; n=311). The study design has been described previously (Cohen SB, et al. Arthritis Rheum 2006;54:2793–806). Pts subsequently transferred to an open-label extension study to receive RTX repeat treatment as clinically required. This post-hoc analysis was conducted on ITT pts with an X-ray at baseline (BL) and at the 5-yr timepoint. Pts who were randomized at BL to PLB who may have subsequently received RTX as rescue therapy (PLB-RTX group) and pts originally randomized to RTX (RTX group) were included. X-rays of the hands and feet were read at BL and yrs (Y) 1, 4, and 5. All X-rays were rescored for this analysis using the Sharp-Genant method by trained radiologists who were blinded to treatment group assignment and order of the X-rays. Missing data were imputed using linear extrapolation of the progression observed from BL to the last value prior to the missing value. Linear interpolation was used between Y1 and Y4.

Results: The ITT population for this analysis comprised 79 PLB-RTX and 105 RTX pts. Among PLB-RTX pts, 71 were rescued with RTX during Y1, with an additional 6 pts rescued after Y1. BL demographics and disease characteristics were balanced between the groups, with the exception of RA disease duration (PLB-RTX 10.5 yrs; RTX 13.5 yrs). Pts in both groups received up to 12 RTX courses (mean = 5 courses over the 5 yrs). In both groups, the mean (SE) change in modified Total Sharp Score (mTSS) continued to decrease to Y5 (figure): change from BL at Y5 was 5.51 (0.95) for PLB-RTX pts and 3.21 (0.64) for RTX pts. Similar effects were observed for erosion scores and joint space narrowing. The annualized progression rate decreased from 2.08 (BL to Y1) to 0.89 (Y1 to Y4) and 0.25 (Y4 to Y5) in PLB-RTX pts, and from 0.91 to 0.56 and 0.33 for the same periods in RTX pts. Between Y4 and Y5, PLB-RTX pts showed similar rates of PJD to those originally randomized to RTX.

Figure: Mean change from baseline in mTSS



Conclusion: This 5-yr analysis of the REFLEX study demonstrates that RA pts with an IR to TNF inhibitors originally randomized to RTX treatment had enhanced inhibition of PJD at 5 yrs compared with pts originally randomized to PLB and later rescued with RTX. Both groups showed continued improvement in PJD inhibition over time, with pts originally randomized to PLB progressing more rapidly than pts originally randomized to RTX. A 1-yr delay in initiating RTX appears to lead to an increased rate of PJD. Differences between the groups remained out to 5 yrs.

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Evaluation of Remission Over 1 Year in Patients (pts) with Early Rheumatoid Arthritis (RA) Treated with Abatacept (ABA) Plus Methotrexate, According to Simplified Disease Activity Index (SDAI). Josef Smolen[1], J. Wollenhaupt[2], Juan J. Gomez-Reino[3], Walter Grassi[4], Manuela Le Bars[5], Corine Gaillez[5], Coralie Poncet[6], Ayanbola Elegbe[7] and Rene Westhovens[8]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]Schön Klinik Hamburg-Eilbek, Hamburg, Germany, [3]Hospital Clinico Universitario, Santiago de Compostela, Spain, [4]Università Politecnica delle Marche, Ancona, Italy, [5]Bristol-Myers Squibb, Rueil Malmaison, France, [6]Docs International, Sèvres, France, [7]Bristol-Myers Squibb, Princeton, NJ, [8]UZ Gasthuisburg, Leuven, Belgium

Background/Purpose: In the AGREE study, a large proportion of pts with early RA and poor prognostic factors achieved DAS28 remission over 1 yr[1]. However, there is evidence that RA pts in DAS28 remission may experience residual disease activity as evidenced by tender/swollen joint counts (TJC/SJC) which, in turn, can lead to radiographic progression over time[2,3]. Recent ACR/EULAR recommendations advise the use of more stringent criteria, such as SDAI to define remission. SDAI does not have such heavy weighting for acute phase reactants as DAS28, but encompasses both physician and patient global assessments[4]. Here, we assess outcomes for ABA + MTX-treated early RA pts in SDAI remission through 1 yr.

Methods: During the 1-yr double-blind (DB) period of AGREE, MTX-naïve pts with early erosive RA (≤2 yrs), high disease activity (TJC ≥12, SJC ≥10 and CRP >0.45 mg/dL), and positivity for RF or anti-CCP were randomized 1:1 to ABA (~10 mg/kg) + MTX or placebo + MTX (MTX alone). DAS28 (C-reactive protein [CRP]) remission (co-primary Yr 1 endpoint) was defined as <2.6 (pts who discontinue considered non-responders) and SDAI remission as ≤3.3. All SDAI analyses were *post-hoc* (as-observed data). Clinical outcomes for patients in SDAI remission at Mth 6 and Yr 1 were determined.

Results: In total, 256 and 253 pts were treated with ABA + MTX vs MTX alone; 232 and 227 pts, respectively, completed Yr 1. Baseline demographics were similar between groups[1]; mean (SD) DAS28 (CRP) 6.3 (1.0) [n=256] vs 6.2 (1.0) [n=252] and SDAI 48.7 (14.9) [n=255] vs 48.1 (14.5) [n=252] for ABA + MTX vs MTX alone. At Mth 6, 72/256 (28.1% [95% CI: 22.6–33.6]) vs 39/253 (15.4% [11.0–19.9]) pts achieved DAS28 remission and 44/235 (18.7% [13.7–23.7]) vs 22/228 (9.6% [5.8–13.5]) SDAI remission, for ABA + MTX vs MTX alone. At Yr 1, 106/256 (41.4% [35.4–47.4]) vs 59/253 (23.3% [18.1–28.5]) achieved DAS28 remission and 70/219 (32.0% [25.8–38.1]) vs 21/215 (12.6% [8.1–17.0]) achieved SDAI remission for ABA + MTX vs MTX alone, respectively. For pts only achieving SDAI remission at Yr 1 but not Mth 6, mean (SD) SDAI at Mth 6 was 11.6 (11.3) for ABA + MTX (n=36) vs 11.9 (11.8) for MTX alone (n=18), suggesting low disease activity and improvements from baseline. Mth 6 and Yr 1 outcomes for ABA + MTX-treated pts in SDAI remission are shown (Table); pts in remission at Mth 6 and Yr 1 experienced low TJCs, SJCs, and HAQ-DI scores, among other SDAI components.

Table 1. Outcomes for abatacept plus methotrexate treated patients

Mean score (SD)	Patients in SDAI Remission at Month 6* (n=44)	Patients in SDAI Remission at Year 1†(n=70)
SDAI	1.53 (0.83)‡	1.63 (0.90)
TJC	0.18 (0.39)	0.19 (0.43)
SJC	0.14 (0.41)	0.11 (0.36)
PGA (0–10 cm VAS)	0.55 (0.45)	0.63 (0.57)
EGA (0–10 cm VAS)	0.35 (0.32)§	0.34 (0.34)
CRP (mg/dL)	0.32 (0.34)	0.36 (0.40)
ESR (mm/hour)	18.60 (11.95)#	19.10 (17.68)¶
HAQ-DI (0–3)§	0.18 (0.23)**	0.20 (0.34)††

Based on patients with both baseline and post-baseline data; *Outcomes at Month 6; †Outcomes at Year 1; ‡n=43; §n=43; #n=20;¶n=30;**n=42; ††Last observation carried forward; SD=standard deviation; SDAI=Simplified Disease Activity Index;TJC=28-joint tender joint count; SJC=28-joint swollen joint count; HAQ-DI=Health Assessment Questionnaire-Disability Index; PGA=Patient Global Assessment; VAS=visual analog scale; EGA=Physician Global Assessment; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate

Conclusion: A large proportion of ABA + MTX-treated pts (32%) with early RA achieved stringent SDAI remission by Yr 1. Pts in SDAI remission at Mths 6 and 12 had little residual activity, as evidenced by SJC, TJC and HAQ-DI. Pts in SDAI remission at Yr 1 but not Mth 6 had low disease activity at Mth 6 suggesting that pts experiencing improvements can reach treatment goals with continued therapy.

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2210

GLPG0634 Shows Selective Inhibition of JAK1 and Maintained JAK-STAT Suppression in Healthy Volunteers. Frédéric Vanhoutte[1], René Galien[2], Eva Vets[3], Florence Namour[2], Béatrice Vayssière[2], Luc Van Rompaey[1], Bart Smets[1], Reginald Brys[1], Piet Wigerinck[1] and Gerben van 't Klooster[1]. [1]Galapagos NV, Mechelen, Belgium, [2]Galapagos SASU, Romainville, France, [3]SGS, Antwerp, Belgium

Background/Purpose: The four members of the Janus kinase (JAK) family of kinases, JAK1, JAK2, JAK3 and TYK2, are involved in signal transduction of inflammatory mediators, implicated in the pathogenesis of rheumatoid arthritis (RA). Small-molecule inhibitors of JAK1/2 and JAK1/3 have demonstrated therapeutic efficacy in clinical trials in RA.

GLPG0634 inhibits JAK1 with an IC_{50} of 10 nM in biochemical assays and shows efficacy in the therapeutic rat collagen-induced arthritis (CIA) model at 1 mg/kg once-daily oral dosing.

The JAK selectivity profile of GLPG0634 was further characterized using cellular- and human whole blood assays (WBA). The safety, tolerability and pharmacokinetic/pharmacodynamic (PK/PD) profile were evaluated in healthy volunteers. These data are presented here.

Methods: JAK inhibition by GLPG0634 was evaluated in a range of cellular assays with phosphorylation of STATs (pSTAT1, 5 and 6) induced by various ligands (IL, IFN, OSM and EPO) as read-outs.

Phase I clinical evaluation included single and multiple ascending oral dosing as capsules in 6 panels of 8 male healthy volunteers (2 on placebo). Two alternating panels took single doses from 10 to 200 mg, and 10-day dosing was performed in 4 consecutive panels for doses from 25 mg twice daily up to 200 mg once-daily. Safety was monitored continuously, and PK and PD (upon *ex vivo* stimulation, extent of STAT phosphorylation and/or JAK-STAT target gene expression) were evaluated at various timepoints on Days 1 and 10.

Results: In contrast to JAK2 pathways (EPO/pSTAT5, $IC_{50} > 10\ \mu M$), JAK1/JAK3 pathways were potently inhibited (IL4/pSTAT6, IC_{50}: 160 nM) in cells. Furthermore, GLPG0634 demonstrates 30-fold selectivity for JAK1 over JAK2 in cellular assays and WBA (IL-6/pSTAT1 over GM-CSF/pSTAT5).

In healthy volunteers, GLPG0634 was safe and well-tolerated for up to 10 days at 200 mg/day. Treatment-emergent adverse events (AEs) over all dose groups were mild and transient with a comparable incidence in GLPG0634- and placebo-treated subjects. Main AEs were headache, somnolence and abdominal discomfort. There were no relevant findings on hematology (including reticulocytes), biochemistry (including cholesterol and lipids) or other safety parameters (ECG and vital signs). A maximal tolerated dose was not reached. After both single and repeated dosing, PK was dose proportional, with an average elimination half-life of 6 hours. At 50 mg and higher doses, exposures were similar to or exceeded active exposures in rat CIA studies. Up from this dose level, dose-related PD effects on JAK1-related biomarkers (IL6-induced pSTAT1 and IFN-induced SOCS3 gene expression) were observed in blood from subjects exposed to GLPG0634. After once-daily dosing of 200mg, IL6-induced pSTAT1 still tended to be suppressed at pre-dose trough.

Conclusion: GLPG0634 potently inhibits JAK1 with a 30-fold selectivity over JAK2 in WBA. In healthy volunteers, GLPG0634 is well tolerated in the pharmacological active dose range, with a PK/PD relationship consistent with once-daily dosing. No signs indicative of anemia were observed after 10-days of dosing. These results support the progression of GLPG0634 into efficacy evaluation in RA patients.

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Evaluation of Anti-Tumor Necrosis Factor Levels and Anti-Tumor Necrosis Factor Antibodies in Rheumatic Diseases Treated with Infliximab and Adalimumab; Preliminary Results From a Local Registry.

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Background/Purpose: To analyse the clinical relevance of serum levels of infliximab (INF) and adalimumab (ADA) and the production of anti-INF (INF-Abs) or anti-ADA antibodies (ADA-Abs) from a local registry of patients with rheumatic diseases on treatment with INF or ADA.

Methods: We included 55 consecutive patients receiving treatment for more than 6 months with INF (25 patients) and ADA (30 patients). Clinical characteristics, clinical activity index (DAS in 28 joints for rheumatoid arthritis -RA- and psoriatic arthritis -PsA-; BASFI, BASDAI for ankylosing spondylitis -AE-) were recorded. Serum levels of INF or ADA and INF-Abs or ADA-Abs (ELISA kit. Promonitor®-INF, ADA. Proteomika, Derio. Vizcaya. Spain) were evaluated. Cut-off level for serum Abs for INF was >15 U/mL, and for ADA >8 U/mL and cut-off level for serum level of INF and ADA were <0.04 mg/L and <0.002 mg/L respectively.

Serum samples were collected at the time of infusion of INF or before injection of ADA, and stored frozen until analysis. Infusion reactions with INF were defined as any event appearing during infusion requiring either arrest of drug infusion or the administration of parenteral medication.

Patients were considered responders if they had at the same time of extraction, DAS28-ESR≤3 in RA or PsA patients; BASDAI≤4 in AE patients.

Results: We enrolled 55 patients, 36 were women; the mean age was 55±14 years. The diagnosis of patients was: RA (49%), AE (31%), PsA (15%) and others (5%). The average time of treatment for the whole population was 33.63 months and for INF and ADA was 41.5 months (range: 6–127) vs 25 months (range: 8–51) respectively. INF was the first anti-TNF received in 24 (96%) of the patients, and ADA was the first in 25 (83%) of the patients.

Antibodies were detected in 9 patients (18%): 5/25 patients (20%) INF-Abs and 4/30 patients (13%) ADA-Abs. In the ADA-Abs patients: all of them had low level of ADA, with a range level of Abs between 132–717.824 U/mL. Table 1 showed the characteristics in responders and non-responders patients. In the INF-Abs patients, only one patient had normal level (1.3 mg/L), and the range level of Abs was between 20–121.840 U/mL. Three patients had infusion reaction with INF, 2 of them with high level of Abs (1.282, 121.849 U/mL), and one patient without Abs.

Table 1. Characteristics in responders and non-responders patients.

	Responders (n: 17)	Non Responders (n: 8)	P
INF level, mean (range)	22.98±18,25 (3.60–73.21)	0.17±0.39 (0.04–1.14)	<0.005
INF-Abs	0%	62.5%	<0.001
DAS28-ESR	2.56	3.60	<0.001
	Responders (n: 15)	**Non Responders (n: 15)**	
ADA-level mean (range)	8,44±5.0 (2.42–21.30)	2,93±3,39 (0.002–11.28)	<0.005
ADA-Abs	0%	27%	0.02
DAS28-ESR	2.52	4.37	<0.01*

* Less than 5 values in same categories.

Conclusion: 1. Serum antibodies were detected in 20% of patients receiving treatment with INF and 13% of patients with ADA. 2. Patients responders have absence of Abs and significantly higher serum concentrations of anti-TNF than non-responders. 3. Immunogenicity can induce inefficacy in patients on treatment with anti-TNF.

2212

Open-Label, Pilot Study of the Safety and Clinical Effects of Rituximab in Patients with Rheumatoid Arthritis-Associated Interstitial Pneumonia.

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Background/Purpose: Clinically overt interstitial lung disease (ILD) is prevalent in 10–20% of patients with rheumatoid arthritis (RA) and has a significant impact on mortality. We sought to investigate the clinical effect of rituximab (RTX) in the management of progressive RA related ILD over a 48 week period of observation.

Methods: A total of 10 patients with RA ILD (4 with UIP, 6 with NSIP) were enrolled into this 48 week, open label treatment study. Treatment was with RTX at 1000 mg at time 0, and then repeated at week 2 and then again at weeks 24 and 26, with concomitant MTX. The primary endpoint was the safety of rituximab therapy, with secondary endpoints progression-free survival at 48 weeks.

Results: The study included 4 men and 6 women with mean age 64.7 years (min: 43, max: 80) who had RA (mean duration 13.8 years; min: 0.4, max: 43) and ILD (mean duration 3.2 years; min:0.2, max 7.5). Baseline pulmonary function included mean FVC 68% (min: 47%, max: 89%), mean DLco 47.6% (min: 28%, max: 73%), mean FEV1/FVC ratio 86.5 (min: 68.8, max 101), mean St. George's score 54.7 (min: 4.0, max 92.5). ILD changes were present in all patients at baseline. Mean SF-36 physical component score (PCS) was 23.2 (min: 11.4, 43.5), and the mean mental component score (MCS) was 47.8 (min: 324, max: 57.3).

Safety: One patient had an infusion reaction at week 0 and withdrew from the study. One patient was hospitalized for congestive heart failure at week 5, unlikely to be related to study drug, and later died at week 32 (complications following a traumatic hip fracture). Another patient died at week 6 (possible pneumonia).

Efficacy: By week 48, the DLco had worsened by at least 15% (at least ≥ 3 ml/min/mm Hg) in 1 patient, was stable in 4 patients, and increased by >15% of baseline in 2 patients. The FVC declined by at least 10% (and at least ≥ 200ml) in 1 patient, was stable in 4 patients, and increased by at least 10% in 2 patients. HRCT showed improvement in 1 patient and there were no changes noted on HRCT for the other 6 patients assessed at week 48. There was no clinically meaningful change in the St. George's respiratory score or SF36 parameters at week 48.

Conclusion: In this pilot study of 10 patients with RA associated advanced ILD treated with rituximab, there were significant adverse events including two deaths. Given the small number of patients, the relationship of these events to treatment vs. underlying disease is unclear. However, we didnot find a signal for clinical efficacy of this treatment for RA-ILD. Further research is needed to clarify whether this treatment has a role in management of RA-ILD in less advanced disease, or in specific histopathologic patterns of disease.

2213

Efficacy and Safety of Tocilizumab As Monotherapy or in Combination with Nonbiologic Disease-Modifying Antirheumatic Drugs: A 24-Week Randomized Study in a United States Population. Michael E. Weinblatt[1], Joel M. Kremer[2], John J. Cush[3], William F. C. Rigby[4], Lichen Teng[5], Natasha Singh[5] and Raymond L. Malamet[6]. [1]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Albany Medical College and The Center for Rheumatology, Albany, NY, [3]Baylor Research Institute, Dallas, TX, [4]Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [5]Roche, Nutley, NJ, [6]Genentech, South San Francisco, CA

Background/Purpose: The efficacy and safety of tocilizumab (TCZ) were studied in 5 pivotal randomized controlled trials (RCTs). We evaluated the benefit-risk profile of TCZ in patients (pts) with rheumatoid arthritis (RA) in an open-label, clinical practice study (ACT STAR).

Methods: This phase 3b, 24-wk, open-label, randomized, multicenter US study evaluated adults with active RA who had an inadequate clinical response or safety/tolerability issues with prior DMARD therapy. Patients on monotherapy (MONO) with biologic DMARD prior to baseline (BL) had biologic discontinued and replaced with TCZ MONO (8 mg/kg). Patients on MONO or combination (COMBO) with nonbiologic DMARDs were randomized to TCZ 4 mg/kg or 8 mg/kg and continued their current nonbiologic DMARD (discontinuing any prior biologic). At wk 8, pts on TCZ 4 mg/kg + nonbiologic DMARD who did not achieve ≥20% improvement in joint counts had TCZ dose increased to 8 mg/kg; beginning at wk 12, TCZ dose could be increased to 8 mg/kg per physician judgment. Study visits occurred at BL and 4 wks after each infusion; safety was primary study endpoint.

Results: The safety population included 883 pts (364 TCZ 4/8 mg/kg + nonbiologic DMARD; 381 TCZ 8 mg/kg + nonbiologic DMARD, and 138 TCZ 8 mg/kg). Over half of TCZ 4 pts were switched to TCZ 8 (n=211; 142 at wk 8). In the 3 groups, BL mean RA duration was 11.5, 10.5, and 13.5 years, respectively; pts using previous biologic DMARD were 65.4, 71.7, and 92.0%, respectively; pts using ≥2 previous anti-TNF agents were 25.8, 34.6, and 44.2%, respectively; and pts with normal CRP (≤0.3 mg/dL) were 28.3, 31.8, and 17.4%, respectively. AEs/SAEs/lab results are summarized in **Table**. SAEs/100 Pt-Yrs (95% CI) were comparable [29.1% (21.0, 39.2), 30.3% (22.2, 40.2), and 20.6% (10.3, 36.9)] for TCZ 4/8+DMARD, TCZ 8+DMARD, and TCZ 8 groups. The most common SAE was serious infections (SIEs, 3.6% [n=32]); tuberculosis was not reported. GI perforation was noted for TCZ 4+DMARD (n=3). At wk 24, CRP values were decreased 0.66, 0.91, and 1.54 mg/dL (all $P<0.0001$) from BL in the 3 groups, respectively. Efficacy outcomes (ACR20/50/70 response: 44.8/24.3/8.8%, 49.7/27.1/10.3%, and 47.9/24.5/7.4%, respectively; DAS28 remission: 20.6, 25.2, and 19.8%, respectively; and joint count response [≥20% improvement in tender and swollen joint counts] for BL CRP normal/elevated pts: 59.2/58.7%, 61.7/61.3%, and 46.7/59.4%, respectively) were similar for all groups in ITT population.

Table. AEs, SAEs, and Laboratory Abnormalities

Pts with ≥1 event/result, %	TCZ 4/8*+ DMARD n=364	TCZ 8+DMARD n=381	TCZ 8 n=138
AEs, %	80.8	81.1	82.6
SAEs, %	8.0	8.4	5.8
SAEs leading to TCZ discontinuation, %	3.0	1.0	2.2
Death, % (n)[†]	0.5 (2)	(0)	(0)
SIEs, %	3.6	3.9	2.9
Neutropenia (CTC Grade 3[‡])[µ], %	0.8	2.4	5.1
Platelet count (CTC Grade 3[‖]), %	0.6	–	–
ALT elevations (≤ULN at BL), %			
>1.5–3 × ULNM	7.9	13.2	6.1
>3 × ULN	2.1	1.9	1.5
TCZ or DMARD dose reduced/ interrupted/stopped after second ALT elevation, n/N (%)	18/33 (54.5)	34/60 (56.7)	9/13 (69.2)
Normalization following highest ALT elevation			
≥1–3 × ULN, n/N (%)	64/103 (62.1)	68/115 (59.1)	14/26 (53.8)
≥3–5 × ULN, n/N	3/8	2/6	0/4
≥5 × ULN, n/N	0	2/2	0
LDL-C ≥130 mg/dL (<100 at BL), %	8.0	6.7	3.2

* 211 pts switched from TCZ 4 to 8; [†]Cardiac death; cerebrovascular accident; [‡]ANC ≥0.5 – <1.0 × 10^9/L; no Grade 4 neutropenia; [µ]No apparent relationship between neutropenia and SIEs; [‖]Platelets ≥25.0 – <50.0 × 10^9/L; no Grade 4 thrombocytopenia.

Conclusion: The safety of TCZ MONO and COMBO therapy observed in this US clinical practice study was consistent with that seen in TCZ RCTs. Overall, similar rates of SAEs, SIEs, and laboratory abnormalities were observed among the 3 treatment groups. Efficacy among MONO and COMBO treatment groups was similar and comparable with the pivotal RCTs, suggesting a similar risk-benefit profile of TCZ MONO and COMBO therapy is observed in real-world practice.

2214

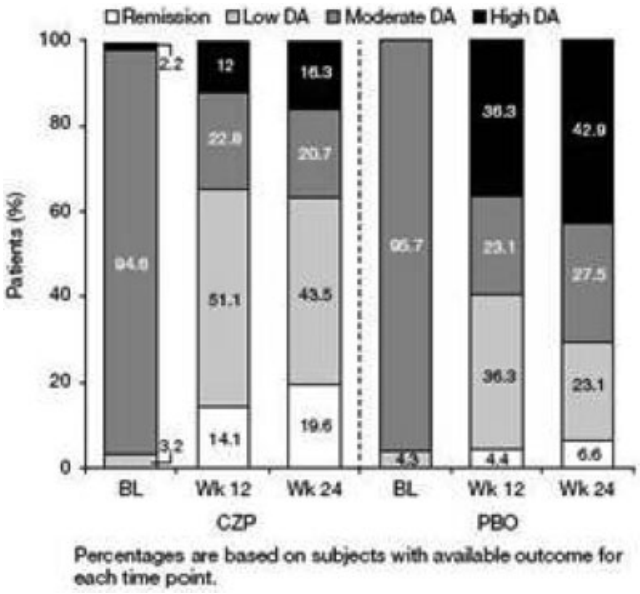
Efficacy, Safety, and Improvements in Work Productivity and Daily Activities with Certolizumab Pegol After Incomplete Response to Disease-Modifying Anti-Rheumatic Drugs in Patients with Low to Moderate Disease Activity. Josef Smolen[1], Paul Emery[2], Gianfranco Ferraccioli[3], Francis Berenbaum[4], Owen Davies[5], Oana Purcaru[5], Johann Ambrugeat[5], Barbara Bennett[6] and Harald Burkhardt[7]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [3]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [4]Pierre and Marie Curie University, AP-HP St-Antoine Hospital, Paris, France, [5]UCB, Brussels, Belgium, [6]UCB, Smyrna, GA, [7]Johan Wolfgang Goethe University, Frankfurt am Main, Germany

Background/Purpose: We evaluated the efficacy, safety, and effects on work productivity and daily activity of certolizumab pegol (CZP) in combination with nonbiologic DMARDs in RA patients (pts) with low to moderate disease activity (DA).

Methods: CERTAIN (**CERT**olizumab pegol in the treatment of R**A**: remission **IN**duction and maintenance in pts with low DA) was a 52-wk, double-blind, Phase IIIb trial that enrolled pts with low to moderate DA (CDAI >6 and ≤16). Pts were randomized (1:1) to CZP (400 mg at Wks 0, 2, and 4, then 200 mg every other wk) or placebo (PBO) + existing DMARDs for an initial 24-wk phase (NCT00674362). Primary efficacy end point was % of pts in CDAI remission (≤2.8) at both Wks 20 and 24. CDAI/SDAI/DAS remission was assessed using NRI. Pts with CDAI remission at Wks 20 and 24 stopped CZP and were followed until Wk 52. Work productivity and daily activities were assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI:RA). We report data for efficacy, safety, and WPAI:RA up to Wk 24.

Results: A total of 194 pts were randomized (mean age 54 y; 80% female) and 164 (84.5%) completed 24 wks. At BL, mean RA duration was 4.6 y and >90% of pts had moderate DA. Mean BL scores were SJC = 3.3, TJC = 3.8, CDAI = 13.4, HAQ-DI = 1.1, and DAS28(ESR) = 4.5. Significantly more CZP pts had CDAI remission at both Wks 20 and 24 than PBO pts (18.8% vs 6.1%, p=0.013 by logistic regression). At Wk 24, more CZP pts had CDAI remission/low DA (63.1% vs 29.7%) (Figure). CZP was associated with prevention of disease worsening; fewer CZP pts had moderate/high DA (37.0% vs 70.4%). Most of the effect of treatment with CZP was already seen at Wk 12, with similar numbers of pts in CDAI remission/low DA as at Wk 24. Mean CDAI/SDAI/DAS28 scores worsened in PBO pts (mean change from BL at Wk 24 CZP vs PBO: –4.01/–4.4/–1.12 vs 3.38/3.4/–0.07). Safety results at Wk 24 indicated that CZP was well tolerated with AE, serious AE, and serious infection rates comparable between CZP and PBO

(68.8% vs 67.3%; 5.2% vs 7.1%; 2.1% vs 1.0%). At BL, 32.4% pts were employed (29% in PBO vs 35.9% in CZP). Increased WPAI:RA mean scores at BL indicated an economic burden of low to moderate RA, especially in terms of overall work and daily activities (Table). Over the 24 wks, CZP pts reported on average greater improvements in absenteeism, presenteeism, overall work impairment, and daily activity, than PBO (Table).



Conclusion: In RA pts with longstanding low to moderate DA, the addition of CZP to nonbiologic DMARDs was well tolerated and associated with increased rates of remission, prevention of disease worsening, and improved work productivity and daily activity.

2215

Improved Quality of Life and Productivity in Patients with Moderate or Severe Rheumatoid Arthritis Actively Switched to Treatment with Infliximab From Adalimumab or Etanercept Therapy. Roy M. Fleischmann[1], Rebecca Bolce[2], Jim Wang[3], Mike Ingham[2], Raphael J. DeHoratius[2], Dennis Decktor[2] and RESTART Clinical Investigators. [1]MCRC, University of Texas, Dallas, TX, [2]Janssen Services, LLC, Horsham, PA, [3]Johnson & Johnson Pharmaceutical Research and Development, LLC, Belle Mead

Background/Purpose: The results from the RESTART study have shown that RA pts with active disease, despite treatment with SC anti-TNFα inhibitors, respond to infliximab (IFX). The dosing flexibility allowed in the IFX prescribing information allows for the treatment of continued active disease by adjusting dose for achievement of specific targeted clinical outcomes. The purpose of this study was to evaluate the effect of IFX on quality of life(Qol) and productivity in pts with moderate or severe RA actively switched from adalimumab (ADA) or etanercept (ETN).

Methods: This is a Ph4, multicenter, open-label, assessor-blinded, active switch study of IFX in pts with active RA who received MTX and had inadequate response (DAS28 score$\geq$ 3.6 and $\geq$6 swollen and $\geq$6 tender joints) to ADA/ETN. Pts were on stable dose of $\geq$7.5 mg/wk of MTX for $\geq$4 wks prior to screening. Pts receiving ETN were switched no less than 1wk and no more than 2wks after the last dose; pts receiving ADA were switched no less than 2wks and no more than 4wks after the last dose. Pts received open-label 3mg/kg IFX infusions at wks0, 2&6. Pts who either achieved/maintained EULAR response at wks14/22 remained on current IFX dose. IFX dose was increased by 2mg/kg for pts who did not achieve/lost response. Evaluations occurred at wk10 post induction and at wk26 following 2additional IFX doses at wk14&22. Pt functional status was assessed using the HAQ-DI at wk10&26. Health Status was evaluated using EQ-5D & SF-36. The EQ-5D includes a descriptive 5-dimensional system for evaluating current health status (each dimension has 3 response levels) and an alternative method using a standard 20cm VAS "feeling thermometer". Available algorithms allow scores on either dimension responses or the VAS to be converted to a pt quality adjusted life year(QALY) "utility" score. SF-36 requests pt health status over the prior 4wks and reports on 8 dimensions and2 summary component scales (Mental and Physical Health). Health economics data included medical resource utilization, time lost from work/school &employability at wk30.

Results: Data for 197/203pts enrolled were evaluable. 60.9% and 39.1% pts were previously treated with ETN or ADA, respectively. Baseline demographics and efficacy were reported previously. Mean HAQ score significantly improved from baseline (1.334,CI:1.252, 1.415) at both wk10 (-0.173,CI:-0.242,-0.105; $p<0.001$) and wk26 (-0.223,CI: -0.303,-0.143; $p<0.001$). % of pts who achieved significant improvement ($\geq$0.22 units) in HAQ score were 39.1% (CI:32.2%, 46.3%) at wk10 and 40.1% (CI:33.2%, 47.3%) at wk26. Change from baseline on all SF-36 domain scores significantly improved at both wk 10&26. Change in pt QALYs, taken from theEQ-5D also significantly improved over baseline (mean change of 0.106, CI: 0.073 to 0.140); $p<0.001$). Number of physician visits in previous 8wks decreased at wk30 from baseline. At wk30, no pts reported emergency room visits in the past 8wks. Pts assessed their productivity as significantly improved at wk30 vs. baseline (-1.42, CI:-1.86, -0.98; $p<0.001$).

Conclusion: RA pts actively switched from ADA or ETN to IFX, without a washout period, demonstrated a statistically significant & clinically important improvement in QoL, health status and productivity.

2216

Safety and Effectiveness of Adalimumab in Patients with Rheumatoid Arthritis During More Than 5 Years of Therapy Observed in a Phase 3b and Post-Marketing Observational Study. Gerd-Rüdiger Burmester[1], Marco Matucci-Cerinic[2], Xavier Mariette[3], Francisco Navarro-Blasco[4], Uemit Oezer[5], Sonja Kary[5], Kristina Unnebrink[5], Theresa Peterson[6] and Hartmut Kupper[5]. [1]Charité - University Medicine, Berlin, Germany, [2]University of Florence, Florence, Italy, [3]Université Paris-Sud Hôpital Bicêtre, Le Kremlin Bicêtre, France, [4]Universitario de Elche, Alicante, Spain, [5]Abbott, Ludwigshafen, Germany, [6]Abbott, Abbott Park, IL

Background/Purpose: In the phase 3b ReAct study, adalimumab (ADA) was added to pre-existing, inadequate, DMARD therapies in patients (pts) with long-standing, severely active rheumatoid arthritis (RA).[1] ReAlise was established to evaluate the long-term safety and effectiveness of ADA in pts who had completed ReAct. The objective of this analysis was to examine the long-term safety and effectiveness of ADA from the first injection in ReAct until the last observation (LO) in ReAlise (ie, >5 yrs).

Methods: Pts were eligible to enroll in ReAlise within 12 months of concluding participation in ReAct. Adverse events (AEs) were tabulated by 5 time windows after the first ADA injection. Standardized Mortality Rates (SMR) and Standardized Incidence Ratios (SIR) for malignancies were calculated for the completed treatment periods of all patients. For the calculation of SIR, the study results were compared with the NCI SEER database for all malignancies and lymphomas. For the calculation of SMR, study results were compared to an age- and sex-matched European cohort (WHO statistics, 2001). Effectiveness measures included the number (%) of pts with low disease activity (LDA) or remission (REM) as determined by simplified disease activity index (SDAI) $\leq$11 and $\leq$ 3.3, respectively, at 0.5, 1, 3, and 5 yrs and at LO after the first ADA injection using observed values.

Results: Among pts from ReAct, 52% (3435 of 6610) enrolled in ReAlise. In ReAct, the median age, DAS28, and HAQ-DI were 55 yrs, 6.1, and 1.73, respectively, at baseline. The median treatment duration was 2045 days (5.7 yrs); the minimum/maximum was 129 and 2681 days. The SIR was 0.64 (95% CI = 0.53–0.76) for all malignancies, and 1.99 (95% CI = 1.11–3.28) for lymphomas. The SMR was 0.71 (95% CI = 0.57–0.87). AEs are displayed in time windows after the first injection of ADA (**Table 1**). The number (%) of patients who achieved and maintained LDA and REM are shown in **Table 2**.

Table 1. Overview of Adverse Events (E[E/100PYs]) During More Than 5 years of Therapy with ADA

	Time windows after first injection of ADA					
	Overal N=6610 18272 PYs)	≤0.5 yr N=6610 (3059 PYs)	>0.5 to 1 yr N=5922 (2256 PYs)	>1 to 3 yrs N=4283 (6149 PYs)	>3 to 5 yrs N=2623 (4549 PYs)	>5yrs N=2000 (2260 PYs)
Serious AEs	2529 (13.8)	838 (27.4)	419 (18.6)	661 (10.7)	417 (9.2)	194 (8.6)
Fatal AEs	102 (0.6)	29 (0.9)	19 (0.8)	27 (0.4)	17 (0.4)	10 (0.4)
Serious Infections	518 (2.8)	162 (5.3)	83 (3.7)	154 (2.5)	81 (1.8)	38 (1.7)
TB[a]	35 (0.2)	11 (0.4)	11 (0.5)	8 (0.1)	4 (0.1)	1 (<0.1)
Sepsis	35 (0.2)	13 (0.4)	4 (0.2)	7 (0.1)	7 (0.2)	4 (0.2)
Malignancies[b]	121 (0.7)	19 (0.6)	16 (0.7)	45 (0.7)	25 (0.5)	16 (0.7)
Lymphoma	15 (0.1)	1 (<0.1)	0	9 (0.1)	4 (0.1)	1 (<0.1)
NMSC	43 (0.2)	8 (0.3)	2 (0.1)	17 (0.3)	11 (0.2)	5 (0.2)
Serious CHF	47 (0.3)	15 (0.5)	6 (0.3)	12 (0.2)	13 (0.3)	1 (<0.1)
Cerebrovascular AEs	56 (0.3)	13 (0.4)	5 (0.2)	16 (0.3)	15 (0.3)	7 (0.3)
Serious hematologic AEs	13 (0.1)	4 (0.1)	2 (0.1)	1 (<0.1)	3 (0.1)	3 (0.1)
Serious hepatic events	58 (0.3)	10 (0.3)	13 (0.6)	16 (0.3)	13 (0.3)	6 (0.3)

CHF, congestive heart failure; E, events; NMSC, non-melanoma skin cancer; PYs, patient-years; TB, tuberculosis. [a]Including 2 pts with a positive test for latent TB during ADA therapy. [b]Excluding lymphoma and NMSC.

Table 2. Number (%) of Patients with LDA or REM During ADA Treatment

	Time points after first injection of ADA				
	0.5 yr	1 yr	3 yrs	5 yrs	Last Observation
LDA	2372 (49)	1899 (56)	1364 (69)	062 (75)	3176 (50)
REM	781 (16)	747 (22)	616 (31)	503 (36)	1321 (21)

Conclusion: Long-term data from observational studies or registries are subject to bias since continued treatment often occurs in patients for whom the drug is efficient and well tolerated. However, in a setting that represents routine clinical practice, no new safety concerns, no increased risk of malignancy, and the expected risk of lymphoma were observed during a median follow-up of more than 5 years of treatment with ADA, representing approximately 20,000 PYs. Effectiveness of ADA was maintained during long-term observation.

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2217

Long-Term Safety of Tocilizumab in Rheumatoid Arthritis Clinical Trials. Mark C. Genovese[1], Anthony Sebba[2], Andrea Rubbert-Roth[3], Juan Scali[4], Moshe Zilberstein[5], Liz Thompson[6] and Ronald F. van Vollenhoven[7]. [1]Stanford University Medical Center, Palo Alto, CA, [2]University of South Florida, Palm Harbor, FL, [3]University of Cologne, Cologne, Germany, [4]Durand University Hospital, Buenos Aires, Argentina, [5]Roche, Nutley, NJ, [6]Roche, Welwyn, United Kingdom, [7]Karolinska University Hospital, Stockholm, Sweden

Background/Purpose: Inhibiting interleukin-6 receptor (IL-6R) signal transduction by tocilizumab (TCZ) has been shown to effectively improve signs and symptoms and reduce joint damage in patients with rheumatoid arthritis (RA). The purpose of this analysis was to assess the long-term safety of TCZ in adult patients with RA.

Methods: Pooled data were assessed from clinical trials (OPTION, TOWARD, RADIATE, AMBITION, and LITHE), a clinical pharmacology study, and long-term extension studies (GROWTH95 and GROWTH96) as pertaining to patients who received ≥1 TCZ dose from initial exposure through February 17, 2010.

Results: A total of 4009 patients received TCZ; the median (mean [range]) duration was 3.6 (3.1 [0.0–5.1]) years, and the total observation time was 12,293 patient-years (PY). Rates of adverse events (AEs), serious adverse events (SAEs), and serious infections (Table) were consistent with those reported in the RA population.[1–5] The overall AE rate was 314.6/100 PY (95% CI: 311.5, 317.7); infections were the most frequent AE (103.7/100 PY, 95% CI: 101.9, 105.5), and the most common infections were upper respiratory tract infections and nasopharyngitis. The rate of AEs leading to withdrawal was 5.2/100 PY; the most common AEs leading to withdrawal were laboratory abnormalities (1.1/100 PY, transaminase elevations), infections (1.0/100 PY), and neoplasms (benign, malignant, or unspecified, 0.7/100 PY). The overall SAE rate was 14.7/100 PY (95% CI: 14.0, 15.4); infections were the most frequent SAE (4.6/100 PY; 95% CI: 4.3, 5.0). The rate of GI perforations was 0.24/100 PY (95% CI: 0.17, 0.37) and has remained consistent with that previously reported. Most of these events (59%, 17/29) were colonic diverticular perforations. Rates of myocardial infarction (MI) and stroke were 0.3/100 PY (95% CI: 0.2, 0.4) and 0.2 (95% CI: 0.1, 0.3), respectively, were stable over time (Table), and were similar to expected rates in the RA population.[3–5] Eight patients (0.1/100PY) experienced anaphylactic reactions and withdrew.

Table. Event Rate/100 PY (95% CI) Over 12-Month Periods

	0–12	13–24	25–36	37–48
AEs	418.4 (411.6, 425.2)	297.9 (291.8, 304.1)	273.3 (267.1, 279.6)	251.4 (244.8, 258.0)
SAEs	15.7 (14.4, 17.1)	13.9 (12.6, 15.2)	15.2 (13.7, 16.7)	14.4 (12.8, 16.0)
Serious infections	4.6 (3.9, 5.4)	3.9 (3.2, 4.7)	5.2 (4.3, 6.1)	4.9 (4.0, 5.9)
MI	0.3 (0.1, 0.5)	0.2 (0.1, 0.4)	0.3 (0.1, 0.6)	0.5 (0.3, 0.9)
Stroke	0.3 (0.1, 0.5)	0.1 (0.0, 0.3)	0.2 (0.1, 0.4)	0.1 (0.0, 0.3)

Conclusion: Rates of SAEs, serious infections, and cardiovascular events have remained stable with continued exposure to TCZ in long-term clinical trials.

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2218

Comparison of Tocilizumab As Monotherapy or with Add-on Disease-Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis and An Inadequate Response to Previous Treatments. Vivian Bykerk[1], Andrew Östör[2], José Andrés Román Ivorra[3], Jürgen Wollenhaupt[4], Andrea Stancati[5], Corrado Bernasconi[5] and Jean Sibilia[6]. [1]Brigham & Women's Hospital, Boston, MA, [2]University of Cambridge, Cambridge, United Kingdom, [3]Hospital Universitario La Fe, Valencia, Spain, [4]Schön Klinik, Hamburg, Germany, [5]Roche, Basel, Switzerland, [6]CHU Hautepierre, Strasbourg, France

Background/Purpose: Although combination therapy with a biologic agent plus a traditional disease-modifying antirheumatic drug (DMARD) is a well-established approach for the treatment of rheumatoid arthritis (RA) patients, little data exist on biologic monotherapy for patients for whom combination (biologic plus DMARD) therapy may not be appropriate (eg, due to methotrexate [MTX] intolerance). In the AMBITION trial, tocilizumab (TCZ) monotherapy showed significantly superior efficacy compared with MTX alone in patients who had not been exposed to or who never failed MTX. However, comparative data of TCZ monotherapy versus TCZ plus add-on DMARDs within the same study are limited. The objective of this analysis was to compare safety and efficacy measures in patients who received TCZ monotherapy versus patients who received TCZ plus DMARDs in the ACT-SURE study.

Methods: ACT-SURE was a phase 3b, open-label, single-arm, 6-month study in patients with inadequate responses to DMARDs (DMARD-IR) or tumor necrosis factor (TNF) inhibitors (TNFi-IR) who were receiving TCZ 8 mg/kg every 4 weeks, alone or in combination with 1 or more DMARDs at the investigator's discretion.

Results: Of 1681 patients in the safety and intent-to-treat populations, 14% (n=239) received TCZ monotherapy. Of monotherapy patients, 72% were TNF-IR; 37% of patients with add-on DMARDs were TNF-IR, and 22% of patients with add-on DMARDs received >1 DMARD. The most commonly used DMARD was MTX (79% of DMARD patients, of whom 74% had a weekly dose >10 mg and 47% >20 mg), followed by hydroxychloroquine (17%), leflunomide (13%), and sulfasalazine (13%). Baseline DAS28 was similar in both groups (6.2, 5.9). Safety in monotherapy/add-on DMARDs: withdrawal, 5%/5%; adverse event (AE), 82%/77%; serious AE (SAE), 8%/8%; AE leading to withdrawal, 5%/5%; infection, 38%/35%; serious infection (most common SAE), 2%/2%; grade 3 neutrophil decrease on at least 1 time point, 1.7%/3.3% (grade 4 decreases; only 1 case in add-on DMARDs, 0.1%); ALT elevation >60 U/L at any time point, 6%/9%; AST elevation >50 U/L at any time point, 1.7%/2.4%. At week 24, efficacy end points were comparable between groups (Table).

Week 24 Results, n/n (%)	TCZ Monotherapy	TCZ + DMARDs	p
EULAR good + moderate response	196/239 (82.0)	1206/1442 (83.6)	0.65
ACR50 response	104/239 (43.5)	680/1442 (47.2)	0.80
ACR70 response	57/239 (23.8)	386/1442 (26.8)	0.76
HAQ-DI reduction from baseline ≥0.22	143/209 (68.4)	912/1242 (73.4)	0.037
DAS28 <2.6	102/205 (49.8)	724/1250 (57.9)	0.70
CDAI remission	42/205 (20.0)	231/1243 (18.6)	0.18
SDAI remission	44/205 (21.5)	260/1218 (21.3)	0.31

p values are for the test of the "TCZ monotherapy = TCZ + DMARDs hypothesis" using logistic or linear regression models adjusted for previous treatment (DMARD-IR/TNF-IR) and baseline DAS28, CDAI, or SDAI. n/n = patients who responded/evaluable patients at week 24.

Conclusion: In a setting close to real life, TCZ monotherapy was highly efficacious at week 24; TCZ plus DMARDs provided similar results, suggesting that TCZ may be an appropriate treatment for patients who cannot tolerate MTX. The safety profile was similar for both groups.

2219

Effects of Tocilizumab Dose Escalation on Disease Activity in Adult Rheumatoid Arthritis Patients with Inadequate Response At 16 Weeks. Jeffrey R. Curtis[1], Sarika Ogale[2], Jenny Devenport[2] and Denise Lepley[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Genentech, South San Francisco, CA

Background/Purpose: In the United States, current recommendations are to start tocilizumab (TCZ) at 4 mg/kg and to increase to 8 mg/kg, depending on clinical response. The objective of this analysis was to evaluate whether rheumatoid arthritis (RA) patients with inadequate response (IR) to TCZ after the first 16 weeks benefit from dose escalation (from TCZ 4 mg/kg [TCZ4] to TCZ 8 mg/kg [TCZ8]) or maintenance on their initial dose (TCZ8).

Methods: This post hoc analysis of clinical trial data included DMARD-IR (LITHE and OPTION) and TNF-IR (RADIATE) patients randomized to weekly methotrexate plus either TCZ4 or TCZ8 every 4 weeks for 24 weeks. Patients with inadequate response to treatment at week 16 (TJC and SJC improvement <20%) received blinded (LITHE) or open-label (OPTION and RADIATE) rescue treatment per protocol (TCZ4 to TCZ8, TCZ8 remained on TCZ8). Patients were grouped by initial TCZ dose and response at week 16: TCZ4 responders (no rescue); TCZ4 patients who dose-escalated to TCZ8 (TCZ4 rescue); TCZ8 responders (no rescue); TCZ8 rescue patients who received continued TCZ8 (TCZ8 rescue). Mean changes in DAS28 and CDAI from baseline to week 16 and from week 16 to week 24 were assessed, and paired within-person differences in DAS28/CDAI change between these 2 intervals were estimated. These analyses included patients with evaluable end points at baseline, week 16, and week 24.

Results: For TCZ4 patients who met criteria to receive rescue therapy/dose escalation to TCZ8 at week 16, significant improvements in DAS28 occurred between rescue and week 24 and exceeded pre-rescue improvements from baseline (Table). In contrast, TCZ8 rescue patients showed some improvement in DAS28 from baseline to rescue and had a numerically smaller magnitude of improvement from rescue to week 24 with continued therapy at the same TCZ dose (Table). Patients on both TCZ4 and TCZ8 doses who did not require rescue experienced the greatest improvements in DAS28 during the first 16 weeks (Table). Results from LITHE, in which week 16 rescue treatment remained blinded, showed patterns similar to the other two trials, which had open-label rescue. A pattern similar to that of TCZ4 rescue patients for DAS28 was seen for CDAI in all trials (data not shown).

Mean (95% CI) Change in DAS28	TCZ4 Rescue to TCZ8	TCZ8 Rescue to TCZ8	TCZ4 Responders	TCZ8 Responders
OPTION (DMARD-IR)	**n = 24**	**n = 17**	**n = 152**	**n = 168**
Change from baseline to week 16(D1)[a]	−0.22 (−0.70, 0.26)	−1.53 (−2.03, −1.04)	−2.57 (−2.80, −2.34)	−3.21 (−3.43, −3.00)
Change from week 16 to 24 (D2)[a]	−1.75 (−2.23, −1.28)	−0.99 (−1.95, −0.02)	−0.11 (−0.29, 0.07)	−0.23 (−0.39, −0.06)
Difference in change scores pre- and post-week 16 (D2-D1)[b]	−1.53 (−2.20, −0.86)[c]	0.55 (−0.79, 1.89)[d]	2.46 (12.13, 2.79)[c]	2.99 (2.68, 3.30)[c]
RADIATE (TNF-IR)	**n = 28**	**n = 17**	**n = 99**	**n = 119**
Change from baseline to weak 16 (D1)[a]	−0.30 (−0.61, 0.01)	−0.92 (−1.4l, −0.43)	−1.84 (−2.05, −1.64)	−3.10 (−3.34, −2.85)
Change from week 16 to 24 (D2)[a]	−2.04 (−2.44, −1.64)	−0.78 (−1.34, −0.23)	−0.09 (−0.30, 0.13)	0.14 (−0.37, 0.10)
Difference in change scores pre- and post-week 16 (D2-D1)[b]	−1.74 (−2.32, −1.16)[c]	0.14 (−0.57, 0.85)[d]	1.76 (1.45, 2.06)[c]	2.96 (2.56, 3.36)[c]
LITHE (DMARD-IR, blinded rescue)	**n = 47**	**n = 34**	**n = 292**	**n = 301**
Change from baseline to week 16 (D1)[a]	−0.39 (−0.60, −0.19)	−0.81 (−1.20, −0.42)	−2.33 (−2.48, 2.18)	−2.95 (−3.10, −2.8)
Change from week 16 to 24 (D2)[a]	−1.83 (−2.12, −1.55)	−0.96 (−1.40, −0.51)	−0.16 (−0.28, −0.05)	−0.33 −0.45, −0.21)
Difference in change scores per- and post-week 16 (D2-D1)[b]	−1.44 (1.85, −1.03)[c]	−0.15 (−0.79, 0.50)[d]	2.17 (1.95, 2.38)[c]	2.63 (2.41, 2.84)[c]

[a] At week 16, patients with IR could receive rescue. [b]Paired *t* test of differences, baseline-week 16 vs week 16–24. [c]$p<0.0001$, [d]$p>0.10$.

Conclusion: DMARD-IR and TNF-IR RA patients who did not achieve adequate response to TCZ4 and dose-escalated to TCZ8 at week 16 had significant improvements in DAS28 and CDAI scores at 24 weeks. For patients who fail to achieve adequate response to TCZ 4 mg/kg, physicians should consider dose escalation to TCZ 8 mg/kg. Patients who started on TCZ8 and who did not achieve adequate response at week 16 showed some incremental improvements in DAS28 and CDAI with continued TCZ8 treatment.

2220

Long Term Anti Tnfa Therapy for Inflammatory Rheumatic Disease Is Associated with Increased Bone Mineral Density and Paradoxical Elevation of TRAP5b Serum Levels. Eric Toussirot[1], Laurent Mourot[2], Emilie Grandclement[3], Daniel Wendling[4] and Gilles Dumoulin[3]. [1]Rheumatology and CIC Biotherapy 506 and EA 4266 Pathogens and Inflammation, Besançon, France, [2]University of Franche Comté, Besançon, France, [3]Department of Physiology, France, [4]Minjoz University Hospital, Besancon, France

Background/Purpose: Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are inflammatory rheumatic diseases associated with increased risk of fractures, low bone mineral density (BMD) and increased levels of markers of bone resorption with normal or decreased values for bone formation markers. Anti-TNFa agents are very effective in treating clinical symptoms of RA and AS and suppressing inflammation. We evaluated the long term changes in bone mass and metabolic bone markers in patients with RA or AS while receiving anti-TNFa agent.

Methods: 20 patients (6 F) were evaluated (12 AS [modified NY criteria], age [mean ± SD]: 40.7 ± 16.1 yrs; and 8 RA [ACR criteria], age 60.5 ± 9.7 yrs; disease duration: 9.6 ± 9.8 yrs). They all received anti-TNFa agent (adalimumab: 12; etanercept: 6; infliximab: 2). At baseline and at 1, 3, 6, 12,18 and 24 months (M) after initiating anti-TNFa treatment, we measured both serum tartrate resistant acid phosphatase isoform 5b (TRAP5b, EIA, Quidel) and bone alkaline phosphatase (BAP, RIA, Beckman), as enzymatic markers of osteoclast and osteoblast, respectively, as well as serum beta CTX-I (EIA, IDS Nordic Bioscience), as marker of bone resorption. Serum osteocalcin (OC; RIA, Cisbio) and P1CP (Quidel) were measured as markers of bone formation. Osteoprotegerin (OPG, EIA, Quidel), an inhibitor of bone resorption was also evaluated. BMD at the lumbar spine and the hip was measured at baseline and after 6,12 and 24 M by DEXA (iDXA, Lunar). No patients had bisphosphonate treatment. Nine patients were under low dose corticosteroids (< 10 mg prednisone).

Results: All the patients responded to the treatment with clinical improvement and decline in erythrocyte sedimentation rate ($p=0.006$) and CRP levels ($p=0.003$). Compared to baseline, lumbar spine and hip BMD at M24 increased (+ 6.3% and + 2.4% respectively), with significant changes at the spine ($p< 0.001$). Beta CTX-I and OPG remained stable over the 24 M period while we observed a progressive and marked increase in TRAP5b (baseline: 1.21 ± 0.74; M24: 2.44 ± 1.05 U/L) ($p<0.001$). BAP also increased at M3 but not significantly. OC and P1CP similarly increased at M1 and M3 with significant change for P1C P ($p = 0.04$), then returning to baseline values.

Conclusion: This study confirms the beneficial effects of anti-TNFa agents on BMD, mainly at the lumbar spine. On the contrary of previous study, we did not observe a decrease in bone resorption markers (beta CTX-I) but we found a paradoxical increase in TRAP5b. By contrast, bone formation markers (BAP, OC) were unchanged or transciently increased (P1CP). These results suggest that anti-TNFa agents may increase osteoclast activity, but without stimulation of bone resorption since there was no parallel increase of beta CTX-I and no deleterious effect on BMD. We conclude that prolonged treatment with TNFa blocking agents has a favorable effect on bone mass in patients with RA or AS.

2221

12 Month-Retrospective Analysis of Two Different Rituximab Retreatment Regimens in Rheumatoid Arthritis: Retreatment At Clinical Relapse Vs 6th Month Fixed Retreatment. Luca Quartuccio[1], Franco Schiavon[2], Domenico Biasi[3], Valeria Carraro[2], Viviana Ravagnani[4], Ilaria Dal Forno[4], Paola Masolini[1], Elisa Mansutti[1], Laura Corazza[1], Leonardo Punzi[5], Silvano Adami[4] and Salvatore De Vita[1]. [1]Rheumatology Clinic, DSMB, University of Udine, Udine, Italy, [2]Rheumatology Clinic, University of Padova, Padova, Italy, [3]Rheumatology Unit, University of Verona, Verona, Italy, [4]Rheumatology Clinic, University of Verona, Verona, Italy, [5]Rheumatology Unit, University of Padova, Padova, Italy

Background/Purpose: to describe two treatment regimens, retreatment at clinical relapse or fixed retreatment at 6th month with rituximab in rheumatoid arthritis (RA), focusing on clinical efficacy and costs at month +12.

Methods: 76 longstanding RA patients treated with rituximab at standard dose of 1 g ×2 were studied; 47 patients were retreated with rituximab (1 g ×2) at clinical relapse (retreatment at relapse group, ReR group), while 29 patients were retreated (rituximab 1 g ×2) at the end of the 6th month after the first standard cycle of rituximab (6 month fixed retreatment group, 6-R group). There were not differences as concerns the age and sex distribution between the two groups.

Results: There were significant differences as concerns the number of patients anti-TNF naïve (ReR>6-R, p=0.04), baseline DAS28 (ReR>6-R, p=0.01) and baseline HAQ (6-R>ReR, p<0.0001).

No differences were observed between the two groups as concerns DAS28 (p=0.6), EULAR moderate/good (ReR vs 6-R: 34/47 vs 20/29 (p=0.8), and ACRn response (ReR vs 6-R, 37/47 vs 26/29, p=0.3) at month +12.

Baseline HAQ was statistically associated with both EULAR good response [p=0.004 (OR 0.3, CI95% 0.1–0.7)], and ACR≥50 response at month +12 [p=0.001 (OR 0.3, CI95% 0.2–0.6)], independently from the retreatment regimen employed, by multivariate analysis.

Globally, a significant increase in utility (QoL) at month +12 vs baseline (p>0.0001) was observed, with mean QALY of 0.35 at month +12. Mean QALY at month+12 was 0.44 and 0.25 in ReR and 6-R group, respectively (p=0.01). A major QALY gain was observed in 6-R group than in ReR group (0.13 vs 0.07, p=0.006). Cost/QALY gain at month +12 was similar (p=1.0).

Conclusion: In RA patients, the identification of the best rituximab retreatment regimen remains an open question. Patients in the ReR group were more often TNF naïve, had a lower HAQ and higher DAS28. Similar results may be obtained with less intensive retreatment regimen in the first 12 months (i.e., retreatment at clinical relapse) in patients 1) naïve for TNF inhibitors, 2) with lower disability and 3) with higher disease activity.

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The Comparative Efficacy and Toxicity of Initial Disease-Modifying Anti-Rheumatic Drug Choices for Patients with Moderate-Severe Early Rheumatoid Arthritis: A Bayesian Network Meta-Analysis. Glen S. Hazlewood[1], Cheryl CM Barnabe[2], George A. Tomlinson[1], Deborah Marshall[3] and Claire Bombardier[4]. [1]University of Toronto, Toronto, ON, [2]Univ of Calgary Foothills Hosp, Calgary, AB, [3]University of Calgary, Calgary, AB, [4]Institute for Work & Health, Toronto, ON

Background/Purpose: The choice of initial DMARD therapy in patients with early rheumatoid arthritis (ERA) is controversial. A systematic review of international clinical practice guidelines used to inform the 2011 Canadian Rheumatology Association Recommendations for the Management of RA identified four treatment options for patients with moderate-severe ERA: oral methotrexate (MTX) monotherapy, subcutaneous (sc) MTX monotherapy, combination therapy with MTX + other DMARDs, or MTX + anti-TNF therapy (TNF). The objective of this study was to compare the relative efficacy and toxicity of these treatment choices.

Methods: A systematic review of MEDLINE, EMBASE, Cochrane Central and 2009–2010 ACR/EULAR abstracts was performed to identify any randomized controlled trial evaluating the 4 treatment choices in adult patients with RA. The comparator arm was any DMARD or DMARD combination, as long as another trial was available to link the comparator to other trials within the network. Trials without an active comparator arm were excluded (i.e.- trials comparing the continuation of a failed DMARD to the addition of another DMARD). The primary efficacy and toxicity outcomes were ACR50 response and withdrawal (WD) due to toxicity. Secondary outcomes included WD due to inefficacy, total WD due to inefficacy or toxicity, ACR20 and ACR70 responses. Treatment effects relative to oral MTX were calculated through a Bayesian random-effects network meta-analysis, incorporating both direct and indirect treatment comparisons. Comparisons were made to estimates derived from Bayesian direct effect (non-network) meta-analyses.

Results: 16 trials were identified with the following treatment arms: oral MTX, sc MTX, combination therapy with MTX [MTX+ hydroxychloroquine/chloroquine (HCQ/CQ); MTX+sulphasalazine (SSZ); MTX+SSZ+HCQ] and MTX+TNF. There was a 99% and 100% probability that MTX+SSZ+HCQ and MTX+TNF respectively were superior to oral MTX monotherapy for ACR50 responses [MTX+SSZ+HCQ: OR 1.8 (95% Credible Interval (CrI): 1.1–3.0); MTX+TNF: OR 1.9 (95%CrI:1.4–2.7)]. Other DMARD combinations and scMTX monotherapy were not more effective than oral MTX. Similar results were found for ACR20 and ACR70 responses, although the ACR70 response for MTX+SSZ+HCQ showed only a trend towards superiority [OR: 1.6 (95%CrI: 0.8–3.7)]. MTX+SSZ+HCQ and MTX+TNF were associated with 64% and 92% probabilities respectively that treatment was associated with more withdrawals due to toxicity than oral MTX. No treatment was superior to oral MTX for total WD. Results were similar in analyses of direct treatment comparisons, however credible intervals were wider and an evaluation of ACR responses for MTX+SSZ+HCQ and MTX+HCQ relative to oral MTX was not possible due to a lack of studies directly comparing these treatment options.

Conclusion: Amongst currently recommended treatment choices for initial DMARD therapy in RA, there is a high probability that both MTX+SSZ+HCQ and MTX+TNF are more effective than oral MTX for clinically relevant outcomes. The incorporation of indirect treatment comparisons through the network meta-analysis permits inferences about ACR responses for MTX+SSZ+HCQ that are not possible through a traditional meta-analysis.

2223

Impact of Comorbidities on TNF Inhibitor Persistence in Rheumatoid Arthritis Patients: An Analysis of Korean National Health Insurance Claims Data. Soo-Kyung Cho[1], Yoon-Kyoung Sung[1], Chan-Bum Choi[2], Jae Hoon Kim[3], Jin Ju Kim[4], Joo-Hyun Lee[4], Young Bin Joo[4] and Sang-Cheol Bae[1]. [1]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Disease, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Hanyang University Hospital for Rheumatic Disease, Seoul, South Korea, [4]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

Background/Purpose: The tumor necrosis factor (TNF) inbibitors have been shown to be effective in treating rheumatoid arthritis (RA) in several randomized controlled trials (RCTs). However, patients with RA in clinical practice might be different from those patients selected for clinical trials; for example, they may have different comorbidities, economic problems, and be taking other drugs at the same time. These differences may influence the efficacy and safety profile of TNF inhibitors. Comorbidity in particular increases the complexity of patient care and makes treatment decisions more challenging. Therefore, in clinical practice, it is important to recognize such comorbidities in RA patients and to consider them before initiating TNF inhibitor treatment. We conducted this study to evaluate TNF inhibitor persistence and the impact of comorbidity on treatment persistence in patients with RA.

Methods: In a Korean National Health Insurance claims database, patients with a diagnosis code of RA (M05 or M06) who started TNF inhibitor therapy between July 1, 2007 and June 30, 2008were enrolled. The study cohort was followed until December 31, 2009. Persistence was examined using Kaplan-Meier survival analysis, and multivariate Cox proportional hazard models were developed to examine the potential impact of comorbidities on drug persistence.

Results: A total of 388 patients were enrolled in the study cohort. The mean persistence rate in the overall population was 61% at 18 months. Drug survival rates for adalimumab and etanercept at 6 months were 82% and 85%, respectively, and 73% and 78%, respectively, at 12 months. Charlson comorbidity index (CCI) scores and comorbidities such as diabetes, chronic pulmonary disease, mild liver disease, and depression at initiation were not related with drug persistence, while peptic ulcer disease (PUD) lowered the risk of discontinuation of TNF inhibitors (HR 0.73, 95% CI: 0.55 to 0.97). Old age (HR 1.59, 95% CI: 1.09 to 2.33) and

prescription of inhibitors by an internist (HR 1.59, 95% CI: 1.02 to 2.48) were other factors associated with early discontinuation of TNF inhibitors.

Conclusion: The persistence rate of TNF inhibitors was 61% at 18 months. CCI score and other comorbidities were not related with early discontinuation of TNF inhibitors, while PUD was an independent contributing factor to TNF inhibitor persistence.

2224

Perioperative Use of Anti-TNF Medications in Patients with Rheumatoid Arthritis Undergoing Total Knee Replacement. Beverly Johnson, Susan M. Goodman, Michael Alexiades and Lisa A. Mandl. Hospital for Special Surgery, New York, NY

Background/Purpose: Anti-TNF medications are increasingly used in patients with rheumatoid arthritis (RA), and current guidelines recommend holding preoperatively. However, few studies examine actual practice and perioperative safety of TNF inhibitors. This study assesses the preoperative use of anti-TNF medications in RA patients undergoing total knee replacement (TKR), and examines if anti-TNF use increases six month adverse post-operative events or disease flares.

Methods: This is a retrospective chart review with follow-up. RA patients who had a TKR between June 2007 and May 2010 were identified from a large prospective single institution joint replacement registry. RA cases were identified by ICD-9 code (714.0) or self-report, and then confirmed by chart review. All registry patients receive a six month adverse events questionnaire which is validated by chart review or phone. For this study, patients received a RA focused questionnaire; medications were confirmed by chart review. We examined self-reported RA flare within one month of surgery and six month adverse events, including surgical site infection (SSI), pulmonary embolus (PE), deep venous thrombosis (DVT), pneumonia, any other infection or re-operation. We evaluated patterns of preoperative anti-TNF use, and compared differences in short term adverse events and post-operative flares between those on anti-TNF and non-users using a Chi-squared analysis. Analysis done with SAS version 9.2. This study was IRB approved.

Results: Of 728 cases reviewed, 194 patients were confirmed as RA (208 cases). Mean age was 61.7 years (SD+/− 11.9), female 86.6%, Caucasian 78.7% and 69.6% had some college education Anti- TNF was used in 86 cases (41.4%): etanercept 59.3%; adalimumab 20.9% infliximab 18.6% and golimumab 1.2%. 86% of the charts documented that anti-TNF should be held and of these, 54 (74%) recommended a specific stop time: mean of 2.4 (SD 2.4) weeks for etanercept (t ½ = 3–5.5 days), 4.6 weeks (SD 6.2) for adalimumab (t ½ = 10–20 days), and 4.9 (SD 2.15) weeks for infliximab (t ½ = 7–12 days). In anti-TNF vs. non-anti-TNF cases, non-biologic DMARDs or prednisone were used in 67.4% vs. 65.6%. 160 cases (77%) had six month data, and 120 (57.4%) responded to the RA questionnaire. There were 7 confirmed adverse events: 2 PEs, 1 DVT, 2 SSIs, and 2 re-operations. 4 / 7 were in the anti-TNF group (all SSIs and re-operations) and all of these were on etanercept. There was no significant difference between the anti-TNFs and non-anti TNF groups (p-value=.51). Self-reported RA flare was higher in the anti-TNF groups (22.4% vs. 16.9%), but the difference was not significant (p-value=.47).

Conclusion: Anti-TNF medication use was not associated with an increased risk of short term adverse postoperative events, though adverse events were rare. Anti-TNFs were held 2 to 4 weeks before TKR, without apparent regard for their pharmacologic half-lives. There appeared to be a non-significant trend towards increased post-operative flares in anti-TNF users. Larger studies should be done to examine if more pharmacologically based timing of anti-TNF withdrawal prior to surgery might minimize the risk of post-operative RA flare while maintaining the excellent safety of these medications.

2225

Undetectable Rheumatoid Factor Following Treatment with Rituximab- What Is Clinical Significance? Pravin Patil[1], Julia Flint[1], Elena Becerra-Fernandez[1], Inmaculada de la Torre[2], Geraldine Cambridge[1], Maria J. Leandro[1] and Jonathan CW Edwards[1]. [1]University College of London, London, United Kingdom, [2]Hospital Gregorio Maranon, Madrid, Spain

Background/Purpose: It is well established that rheumatoid arthritis (RA) patients with positive rheumatoid factor respond better to rituximab therapy. However, little is known whether the RF titre before or following rituximab therapy correlates with clinical response. In our cohort we observed that in a group of seropositive RA patients, RF as measured by agglutination assays can become undetectable following treatment with rituximab (seronegative). We studied the baseline characteristics of this group and their response to rituximab therapy in comparison to those patients who remained seropositive after the first cycle of rituximab.

Methods: All seropositive RA patients treated with rituximab in our centre from 2008 with at least one year follow up were included. Patients who lost seropositivity after the first cycle of rituximab were compared to patients who remained seropositive at this stage. Patients were assessed before treatment, 1 and 3 months after treatment and every 2 to 3 months thereafter. Serial assessments included CRP levels, CD19 counts, total immunoglobulin levels and RF by agglutination assay (RAPA). Anti-CCP antibodies were measured at baseline.

Results: Eighty-one patients were included in the study. The mean age was 56 years (range 20–86 years). 98% patients were anti-CCP positive at baseline. 23% of patients lost seropositivity after the first cycle of Rituximab, all within a year (n=19). These patients had lower baseline RF titres ($p<0.001$). There was no significant difference in number of patients being on concomitant DMARD in both groups. However, percentage of patients on steroids was significantly higher (13%) in those who remained with RF than those who lost seropositivity (5 %).

There was no significant difference between the groups in the baseline levels of C-reactive protein (CRP), total IgM and CD19 count. While all who lost seropositivity responded to rituximab therapy and achieved complete depletion of CD19 ($<0.005\times10^9$/L), six who remained with RF (9.5%) did not respond and required switching to another agent. Eight remaining with RF did not deplete well (CD19 count $>=0.005$). Nadir levels of CRP and total IgM following treatment were also similar.

The average number of months until B cell repopulation and clinical relapse was 5.4 and 7.33 respectively in patients who lost seropositivity compared to those who retained RF was 4.5 and 8.76.

Conclusion: This study suggests that those with low baseline RF titres are significantly more likely to lose seropositivity following treatment with rituximab. There was also a tendency towards a shorter and less robust response to rituximab in patients retaining seropositivity. However, larger studies are required to establish whether there is any correlation between the loss of seropositivity to RF with clinical response to treatment.

2226

Definition of Treatment Response in Rheumatoid Arthritis Based on the Simplified and the Clinical Disease Activity Index. Daniel Aletaha[1], José Martinez-Avila[2], Tore K. Kvien[3] and Josef S. Smolen[4]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna, Austria, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Krankenhaus Lainz, Vienna, Austria

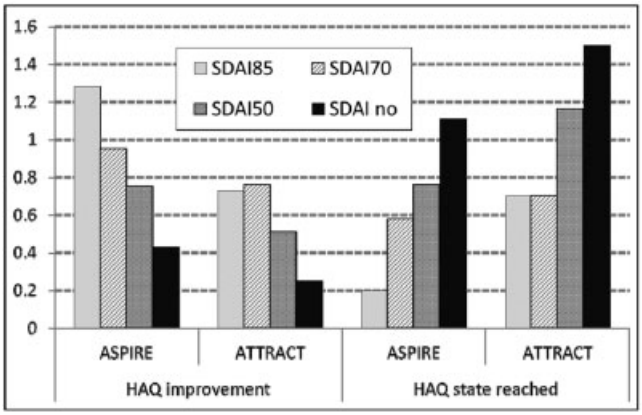
Background/Purpose: The Simplified and the clinical disease activity indices (SDAI, CDAI) have been introduced to assess disease activity in a simple way and have shown their merits in clinical practice. In clinical trials of rheumatoid arthritis (RA), however, treatment efficacy has traditionally been assessed through response rates. Currently, no validated response definitions for the SDAI and CDAI are available.

We aimed to define minor, moderate, and major response criteria for the SDAI based on the agreement with the traditional way of response assessment by the American College of Rheumatology (ACR) 20%, 50%, and 70% improvement definition.

Methods: We used data from two clinical trials on infliximab plus methotrexate (MTX) vs placebo plus MTX in early (ASPIRE) or established (ATTRACT) RA, and identified the three SDAI cutpoints based on the best agreement (by Kappa statistics) with the ACR20/50/70 responses. These cutpoints were then tested for face validity, construct, and discriminant validity in the trial datasets, and for construct validity and validity in regards to patients' reported perception of improvement in an observational dataset (NOR-DMARD).

Results: Based on agreement with the ACR response, the minor, moderate, and major responses were identified as SDAI 50%, 70%, and 85% improvement. These cutpoints had good face validity, with major response bringing the majority of patients into remission or near remission, moderate response bringing the majority into at least low disease activity, and minor response essentially warranting that no patient remains in a high disease activity state. Construct validity was shown by a clear association of increasing SDAI response categories with increasing levels of functional improvement, and better functional states reached (see

Figure). Also, the annual radiographic progression was greatest in SDAI non responders and increased across thes SDAI 50/70/85 response groups (mean: 5.9 vs. 3.9/2.2/-0.3). Across SDAI50/70/85 the sensitivities regarding patients' perceived improvement in NOR-DMARD decreased (73%/39%/22%) and the specificities increased (61%/89%/96%). Further, the identified cutpoints discriminated well between treatment arms in ASPIRE and ATTRACT. Results for the CDAI were not different to the SDAI, and thus the same cutpoints for definition of response were used.



Conclusion: New cutpoints for response have been defined for the SDAI and the CDAI, and have been assessed for their validity. These criteria expand the usefulness of the SDAI and CDAI for their application as endpoints in clinical trials beyond the definition of disease activity categories.

2227

Golimumab 3-Year Safety Update: An Analysis of Pooled Data From the Long Term Extensions of Randomized, Double-Blind, Placebo-Controlled Studies in Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis. Jonathan Kay[1], Roy Fleischmann[2], Edward Keystone[3], Elizabeth C. Hsia[4], Mittie K. Doyle[4], Benjamin Hsu[4], Michael Mack[5], Anna Beutler[5], Jürgen Braun[6] and Arthur Kavanaugh[7]. [1]University of Massachusetts Memorial Medical Center/University of Massachusetts Medical School, Worcester, MA, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]University of Toronto, Toronto, ON, [4]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC/Univ. of Pennsylvania School of Medicine, Malvern/Philadelphia, PA, [5]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]University of California San Diego, San Diego, CA

Background/Purpose: Golimumab (GLM) has been assessed in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) in randomized controlled trials. The purpose of this study was to present analysis of pooled data (cumulative control and uncontrolled periods) through approximately 3 yrs of follow-up from 5 ongoing GLM Phase 3 subcutaneous (SC) trials across rheumatological indications and through 1 yr in a completed Phase 2 RA trial.

Methods: SC placebo (PBO) or GLM (50mg or100mg) was administered q4wks in Phase3 and q2/4wks in Phase 2 clinical trials. After wk24/52, pts in the Phase 3 studies entered long term extensions (LTE) and received GLM 50mg or 100mg q4wks in an unblinded fashion. Dose escalation from 50mg to 100mg was allowed; no dose reduction was permitted. Concomitant medications included DMARDs, most frequently MTX. Adverse events (AE) were analyzed based on treatment received prior to the occurrence of the AE. Because pts could cross-over from PBO to GLM or increase GLM dose from 50mg to 100mg in cases of inadequate response in the Phase 3 trials, a pt may appear in more than one column. Due to the short duration of the PBO-controlled portion, comparisons between the GLM and PBO groups are limited.

Results: In combined Ph2/3 trials, 674 pts received PBO, 1317 GLM 50mg, and 1571 GLM100mg through 3 yrs. In Phase 3, 4.9%, 7.4%, and 10.5% of PBO, GLM50, GLM100mg pts, respectively, discontinued due to adverse events (AE) through 3yrs. In Phase 2, 5.9% of PBO and 8.0% of GLM pts discontinued due to AE through 1 yr. The incidences per 100 PY of deaths, serious infections (including tuberculosis and opportunistic infections), demyelination, and malignancies are presented (Table). Overall occurrence of injection site reactions was low; most were mild, and only 2 cases led to discontinuation. No GLM SC-treated pt developed anaphylaxis or a serum sickness-like reaction. Malignancies occurring during the 5 Phase 3 and 1 Phase 2 trials included skin cancers, solid tumors, and lymphoma. In comparison to the Surveillance Epidemiology and End Results (SEER) database for malignancies, the overall incidence of malignancies in GLM-and PBO-treated pts was similar to that expected in the general US population. The incidence of lymphomas per 100 pt-years of follow-up was greater in the GLM100mg dose group through 3yrs and higher than that expected in the general US population.

	PBO +/− MTX	GLM50mg +/− MTX	GLM100mg +/− MTX
Pts treated (n)	674	1317	1571
Total pt/yrs of follow-up	358	2313	3401
Deaths			
Incidence/100 pt yrs 95% CI	0.28 (0.01, 1.56)	0.3 (0.12, 0.62)	0.41 (0.23, 0.69)
All serious infections			
Incidence/100 pt yrs 95% CI	5.31 (3.20, 8.30)	3.03 (2.36, 3.82)	5.09 (4.36, 5.90)
Tuberculosis			
Incidence/100 pt yrs 95% CI	0 (0.00, 0.84)	0.17 (0.05, 0.44)	0.35 (0.18, 0.62)
Opportunistic infections other than tuberculosis			
Incidence/100 pt yrs 95% CI	0 (0.00, 0.84)	0.13 (0.03, 0.38)	0.24 (0.10, 0.46)
Demyelination*			
Total pt/yrs of follow-up	357	2426	3644
Incidence/100 pt yrs 95% CI	0 (0.00, 0.84)	0 (0.00, 0.12)	0.14 (0.04, 0.32)
Malignancy			
Nonmelanoma skin cancers (NMSC)			
Total pt/yrs of follow-up	356	2305	3379
Observed # of pts with event	5	10	18
Incidence/100 pt yrs (95%CI)	1.40 (0.46, 3.28)	0.43 (0.21, 0.80)	0.53 (0.32, 0.84)
Lymphoma			
Total pt/yrs of follow-up	358	2313	3400
Observed # of pts with event	0	1	6
Incidence/100 pt yrs (95% CI)	0.00 (0.00, 0.84)	0.04 (0.00, 0.24)	0.18 (0.06, 0.38)
Expected # of pts with event	0.09	0.58	0.9
SIR (95% CI)	0.00 (0.00, 31.98)	1.71 (0.04, 9.55)	6.69 (2.45, 14.56)
Other malignancies			
Total pt/yrs of follow-up	357	2308	3398
Observed # of pts with event	2	18	14
Incidence/100 pt yrs (95% CI)	0.56 (0.07, 2.02)	0.78 (0.46, 1.23)	0.41 (0.23, 0.69)
Expected # of pts with event	2.05	12.32	19.34
SIR (95% CI)	0.98 (0.12, 3.53)	1.46 (0.87, 2.31)	0.72 (0.40, 1.21)

Includes GLM SC Phase2b in addition to 3RA, PsA, AS studies
* Based on data cut off as of Jan 25, 2010
SIR=standardized incidence ratio (observed/expected)

Conclusion: The safety profile of continued SC GLM exposure in this pooled analysis demonstrates that GLM was generally well-tolerated with overall low rates of discontinuation due to AEs. Safety profiles were generally similar between GLM dose groups with the exception of higher rates of serious infections, including tuberculosis and opportunistic infections, and lymphoma in the GLM100mg group. Results are confounded by LTE design in which pts could receive GLM100 mg after being exposed to GLM50mg with higher GLM dose used for pts with more active disease, and by limited exposure to PBO making the comparisons between PBO and active treatment groups of less value.

2228

Initial Combination Therapy with Adalimumab Plus Methotrexate Leads to Better Long-Term Outcomes in Patients with Advanced Rheumatoid Arthritis: Analysis of the Final 10-Year Results of An Open-Label Extension of a Phase 3 Trial. Edward Keystone[1], Désirée van der Heijde[2], Michael E. Weinblatt[3], Neelufar Mozaffarian[4], Benoit Guerette[5], Hartmut Kupper[6], Shufang Liu[4], Benjamin Wolfe[4] and Arthur Kavanaugh[7]. [1]University of Toronto, Toronto, ON, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [4]Abbott, Abbott Park, IL, [5]Abbott, Rungis, France, [6]Abbott GmbH & Co KG, Ludwigshafen, Germany, [7]University of California San Diego, San Diego, CA

Background/Purpose: DE019 was a phase 3, randomized, controlled trial (RCT) in which patients (pts) with active, advanced rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX) were randomized to 1 year (yr) of adalimumab (ADA) 40 mg every other week (eow), ADA 20 mg weekly, or placebo (PBO) injections; all received concomitant MTX. RCT results demonstrated the clinical and radiographic superiority of

ADA+MTX over PBO+MTX[1]. All pts completing the RCT were eligible to receive open-label (OL) ADA 40 mg eow +MTX for an additional 9 yrs. This post hoc analysis evaluated observed pt data to determine whether a 1 yr delay in initiation of ADA treatment results in differences in clinical, functional, or radiographic efficacy after up to 10 yrs of treatment.

Methods: Clinical and functional outcomes were assessed by the 28-joint disease activity score [DAS28(CRP)] and the disability index of the health assessment questionnaire (HAQ-DI), respectively. Radiographic damage was assessed using the modified total Sharp Score (mTSS) at baseline (BL) and yrs 1, 8, and 10; progressors were defined as pts with a change (Δ) in mTSS from BL >0.5. Differences in mean ΔmTSS between initial treatment arms were assessed using a constrained longitudinal data analysis. Safety was assessed in terms of adverse events for all pts exposed to ADA.

Results: Of the 619 pts initially randomized, 202 (32.6%; 80, 66, and 56 pts from the initial ADA 40 mg eow, ADA 20 mg weekly, and PBO arms, respectively) continued on OL ADA+MTX treatment through yr 10. Efficacy outcomes at yr 10 were not different between the 2 ADA arms; therefore, results for the ADA 40 mg eow arm are presented as representative of both ADA arms. Following the switch to OL ADA+MTX, the significant differences in clinical and functional responses observed during yr 1 (DAS28 =3.4 and 4.5; HAQ-DI =0.8 and 1.1 for ADA and PBO arms, respectively) were largely resolved following an additional 9 yrs of OL ADA+MTX treatment (DAS28 =2.4 and 2.7; HAQ-DI =0.7 and 0.8 for initial ADA and PBO arms, respectively). In addition, rates of radiographic progression became comparable between the treatment arms during OL ADA+MTX treatment (P =.22). However, pts initially randomized to ADA had significantly lower mean ΔmTSS compared with pts initially randomized to PBO (0.7 vs 6.2; P =.005), as well as a lower percentage of pts with radiographic progression (49.4% vs 61.1%). No new safety signals arose following up to 10 yrs of ADA exposure, and there was perhaps a trend towards fewer deaths than would be expected from a matched population [SMR (95% CI) =0.77 (0.52, 1.10)].

Conclusion: Following up to 10 yrs of treatment with ADA+MTX, pts with long-standing RA experienced safe and effective disease control. Initial treatment with ADA led to better outcomes than initial treatment with PBO, but the disparities in clinical and functional response rates observed during the RCT were largely ameliorated after treatment with OL ADA+MTX. Notably, radiographic damage remained lower in pts initially randomized to ADA, owing to the more extensive damage accrued during the RCT in PBO-treated pts.

[1]Keystone, et al. *Arthritis Rheum*. 2004; 50(5):1400–11.

2229

Patients with Early Rheumatoid Arthritis (RA) Who Respond Well to Methotrexate Monotherapy Have Less Metacarpal Bone Loss, Measured by Digital X-Ray Radiogrammetry (DXR), Than Those Who Need Add-on Therapy. Findings From a Randomized Trial. Hamed Rezaei[1], Saedis Saevarsdottir[1], Kristina Forslind[2], Pierre Geborek[3], Ingemar F. Petersson[3], Sofia Ernestam[4], Johan Bratt[4] and Ronald F. van Vollenhoven[1]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Helsingborgs Lasarett and Lund University, Lund, Sweden, [3]Lund University, Lund, Sweden, [4]Karolinska University Hospital, Stockholm, Sweden

Background/Purpose: The aim of this study was to investigate metacarpal bone loss measured by digital X-ray radiogrammetry (DXR) in patients with early rheumatoid arthritis receiving different treatment regimens, and to evaluate if DXR-change rates during the first year correlate with radiological damage after 24 months.

Methods: In the SWEFOT trial, 487 patients (symptom duration <12 months) started methotrexate (MTX) 20 mg/week. After 3–4 months, patients with DAS28>3.2 were randomized to either sulfasalazine and hydroxychloroquine ("triple therapy") or infliximab ("anti-TNF"). Those with DAS28 ≤3.2 were followed in regular care ("MTX-responders"). Radiographic progression over 24 months was scored according to the van der Heijde modified Sharp score (SvdH). Metacarpal bone loss from 0–12 months was measured by DXR (Sectra, Linköping, Sweden), a method developed to allow measurement using routinely obtained digital x-rays. DXR bone loss >2.5 mg/cm2/month (10× upper limit of normal) is considered highly elevated and was used as cut-off in this study.

Results: Out of the whole SWEFOT population (n=487), the X-rays from 159 patients were of sufficient quality and correctly timed to be analyzed with the DXR method: MTX-responders 49 (31.0%), triple therapy 55 (34.5%), and anti-TNF 55 (34.5%).

The proportions of patients with DXR-change rate ≥ 2.5 mg/cm2/month in MTX responders, triple therapy, and anti-TNF were 4.1%, 22.2% and 16.4%, respectively (p=0.01).

Mean (SEM) radiological progression over 24 months according to SvdH-score was 6.72 (1.01), 7.40 (2.01) and 4.55 (0.66) for MTX monotherapy, triple therapy and anti-TNF, respectively (p=0.06 between triple therapy and anti-TNF).

Mean (SEM) radiological progression over 24 months in patients who did and who did not have a highly elevated DXR-change rate during the first 12 months was 10.38 (4.60) and 3.86 (0.58), respectively (p=0.006), and a significant difference was also seen for progression in the erosion score, 3.81 (1.98) vs. 1.23 (0.32) (p=0.02). Patients with highly elevated DXR change rate during the first 12 months had statistically significantly greater risk for a ≥5 increase in SvdH after 24 months (odds ratio 3.09, 95% CI =1.20–7.79, p=0.02). More progression occurred in the triple therapy group. (odds ratio 4.15, 95% CI=1.05–16.35, p=0.04).

Conclusion: DXR provides information on metacarpal bone loss in patients with RA. Non-responders to MTX (who went on to randomization in this trial) had a significantly greater risk for highly elevated BMD loss than MTX-responders despite the add-on therapies; and patients with highly elevated metacarpal bone loss had significantly greater x-ray damage after 24 months. Information from DXR may be complementary to that obtained by clinical assessments and standard radiography.

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Relevance of Involvement of Tofacitinib in T Cell Subsets to Clinical Courses in Patients with Rheumatoid Arthritis. Koshiro Sonomoto, Kunihiro Yamaoka, Satoshi Kubo, Keisuke Maeshima, Ippei Miyagawa, Kazuhisa Nakano, Norifumi Sawamukai, Kazuyoshi Saito and Yoshiya Tanaka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Background/Purpose: Tofacitinib, a Janus kinase (JAK) inhibitor, has demonstrated clinical efficacy on rheumatoid arthritis (RA). However the exact mechanism of action remains unclear especially in patients treated with tofacitinib. It is a key issue to elucidate the biological function of tofacitinib in RA patients, in order to increase not only the benefit but also safety. The purpose of this study is to clarify the mechanism of tofacitinib in clinical use of RA patients.

Methods: Twenty nine patients (24 women, mean age; 55.6 years, mean disease duration 73.9 months) with RA were enrolled in clinical studies of tofacitinib (6 treated with tofacitinib alone, 23 treated with tofacitinib with MTX) and were randomized to different doses of tofacitinib or placebo for the first 3 to 6 months and subsequently advanced to 5 mg or 10 mg BID of tofacitinib open label. Lymphocyte population analysis and proliferation of Carboxyfluorescein succinimidyl ester (CFSE) labeled CD4+ T cells at baseline (0 week) and 52 weeks were performed by flow cytometry.

Results: 25 patients out of 29 completed 52 weeks treatment with tofacitinib. MTX was administered in 23 patients and the average dose was 9.2 mg/week, oral corticosteroid was administered in 5 patients and the average dose was 4.4 mg/day. Four patients discontinued the treatment because of malignancy (n=2), bacterial infection (n=1) or incidental trauma (n=1). Tofacitinib improved disease activity measured by SDAI (36.0+-14.5 to 7.1+-7.2), and 12 out of 29 reached SDAI remission (<3.3), 9 patients fulfilled the Boolean remission criteria, and 14 patients reached DAS28-ESR <2.6. There was no change in the total lymphocyte counts nor lymphocytes subset profile at week 52. However, proliferation of CD4+ T cells induced by stimulation with anti-CD3 and CD28 antibodies *in vitro* was significantly reduced by administration of tofacitinib (p=0.02) and the decrease of proliferation of CD4+ T cells significantly correlated with both ΔCRP (p=0.02) and ΔSDAI (p=0.03). There was no statistical correlation between the decrease of CD4+ proliferation and incidence of the infections, although 21 events of infection (17 viral infection including 8 herpes zoster, 3 bacterial infection and 1 local fungus infection) were observed. In contrast, it is noteworthy that the number of CD8+ T cells at baseline was extracted as a predictive factors affecting incidence of infections by ROC analysis (odds ratio 5.33, 95% CI 1.02–27.8). Cut off value of CD8+ cells at baseline was <210/μl (sensitivity 0.67, specificity 0.82) to predict at least one infection per year. Moreover, all three patients who showed multiple infections had less than 141/μl CD8+ T cells at baseline.

Conclusion: Tofacitinib has demonstrated efficacy for the treatment of RA. These results indicate that the suppression of CD4+ T cell proliferation *in vitro* after the treatment with tofacitinib appears to contribute to the its mechanism of action in RA patients. In contrast, our results also suggest that patients with lower CD8+ T cell counts should be considered to possess a higher risk of infections.

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Improvement in Disease Activity and Treatment Response Over 2 Years of Abatacept Treatment and Shifts to Improved Disease States in Patients with Early Rheumatoid Arthritis Who Switch From MTX. Rene Westhovens[1], Juan J. Gomez-Reino[2], Walter Grassi[3], Corine Gaillez[4], Manuela Le Bars[4], Coralie Poncet[5], Ayanbola Elegbe[6] and Jurgen Wollenhaupt[7]. [1]UZ Gasthuisburg, Leuven, Belgium, [2]Hospital Clinico Universitario, Santiago de Compostela, Spain, [3]Università Politecnica delle Marche, Ancona, Italy, [4]Bristol-Myers Squibb, Rueil Malmaison, France, [5]Docs International, Sèvres, France, [6]Bristol-Myers Squibb, Princeton, NJ, [7]Schön-Klinik Hamburg-Eilbeck, Hamburg, Germany

Background/Purpose: Remission is the primary RA treatment target; guidelines state the importance of maintaining the target disease state and measuring disease activity with validated, composite indices.[1] Biologics are recommended for early intensive treatment of early RA pts with poor prognostic factors; abatacept (ABA) has demonstrated significant clinical efficacy and reduction in irreversible structural damage progression vs MTX alone in these pts.[2,3] Using 3 composite disease activity indices, we explore if target disease states achieved with ABA + MTX are maintained/improved with continued treatment, and if MTX-treated pts can improve their disease state with addition of ABA.

Methods: Pts with erosive RA (≤2 yrs) were randomized to ABA + MTX (~10 mg/kg) or placebo + MTX (MTX alone) in the 1 yr double-blind (DB) period of AGREE. All DB-completing pts received open-label (OL) ABA (~10 mg/kg) in Yr 2. These *post-hoc* analyses of as-observed pt-level data include all pts who received ≥1 ABA dose in the OL period according to DB period treatment group (ABA + MTX vs MTX alone). Disease activity was defined by DAS28, SDAI and CDAI as High, Moderate and Low Disease Activity states (HDAS, MDAS and LDAS, respectively), and remission.

Results: Overall, 459 pts (232/256 ABA + MTX, 227/253 MTX alone) completed the DB period. All 459 pts were treated in the OL period; 433 pts completed Yr 2. At Yr 1, 32.1 and 33.2% of ABA + MTX pts achieved SDAI and CDAI remission, respectively, vs 12.5 and 16.1% of MTX alone pts. A similar trend was observed for DAS28 remission: 46.8 of ABA + MTX pts vs 26.9% of MTX alone pts at Yr 1. For MTX alone pts who switched to ABA + MTX at Yr 1, 51.9, 36.5 and 38.1% achieved DAS28, SDAI or CDAI remission at Yr 2, respectively, similar to pts from the original ABA group (56.9, 37.5, 39.0%, respectively). DAS28 and SDAI disease states at Yr 2 are shown for pts in LDAS or remission at Yr 1 (Table); ≥75% of pts achieving LDAS/remission at Yr 1 maintained or improved their disease status at Yr 2, regardless of initial treatment group. Addition of ABA at Yr 1 corresponded to a shift in 57 and 46% of MTX alone pts from LDAS to remission at Yr 2, according to DAS28 and SDAI, respectively. Similar trends to SDAI were observed for CDAI (data not shown).

Table. Abatacept plus methotrexate

		Year 1 DAS28 State, n (%)		Year 2 DAS28 State, n (%)	
	Total* (n=197)	HDAS DAS28 >5.1	MDAS DAS28 >3.2–5.1	LDAS DAS28 2.6–3.2	Remission DAS28<2.6
LDAS	31 (15.7)	0 (0)	6 (19.4)	9 (29.0)	26 (51.6)
Remission	89 (45.2)	0 (0)	4 (4.5)	8 (9.0)	77 (86.5)
		Year 1 SDAI State, n (%)		Year 2 SDAI State, n (%)	
	Total* (n=192)	HDAS SDAI >26	MDAS SDAI>11–26	LDAS SDAI>3.3–11	Remission SDAI ≤3.3
LDAS	65 (33.9)	0 (0)	6 (9.2)	38 (58.5)	21 (32.3)
Remission	58 (30.2)	0 (0)	1 (1.7)	13 (22.4)	44 (75.9)
Methotrexate	alone				
		Year 1 DAS28 State, n (%)		Year 2 DAS28 State, n (%)	
	Total* (n=181)	HDAS DAS28 >5.1	MDAS DAS28 >3.2–5.1	LDAS DAS28 2.6–3.2	Remission DAS28<2.6
LDAS	28 (15.5)	0 (0)	7 (25.0)	5 (17.9)	16 (57.1)
Remission	50 (27.6)	1 (2.0)	3 (6.0)	6 (12.0)	40 (80.0)
		Year 1 SDAI State, n (%)		Year 2 SDAI State, n (%)	
	Total* (n=178)	HDAS SDAI >26	MDAS SDAI>11–26	LDAS SDAI>3.3–11	Remission SDAI ≤3.3
LDAS	56 (31.5)	2 (3.6)	3 (5.4)	25 (44.6)	26 (46.4)
Remission	23 (12.9)	0 (0)	1 (4.3)	7 (30.4)	15 (65.2)

*Includes patients with data at both Year 1 and Year 2; DAS28=Disease Activity Score 28; HDAS=High disease Activity State; MDAS=Moderate Disease Activity State; LDAS=Low Disease Activity State; SDAI=Simplified Disease Activity Index

Conclusion: At Yr 1, greater proportions of ABA-treated pts achieved remission vs MTX alone according to DAS28, SDAI and CDAI criteria. Regardless of initial treatment group, the majority of pts in LDAS or remission at Yr 1 maintained or improved their disease state at Yr 2. According to all three indices, addition of ABA at Yr 1 to MTX corresponded to a shift in disease activity from LDAS to remission in ~50% of pts by Yr 2. These findings support the use of ABA + MTX in treating to target pts with early RA and poor prognostic factors.

[1]Smolen et al. *ARD* 2010;**69**:631–7
[2]Westhovens et al. *ARD* 2009;**68**:1870–7
[3]Bathon et al. *A&R* 2009;**60**(S10):Abs639

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Rate of Anti-Cyclic Citrullinated Peptide Antibody and Rheumatoid Factor Seroconversion in Patients with Undifferentiated Arthritis or Early Rheumatoid Arthritis Treated with Abatacept. Tom W.J. Huizinga[1], Paul Emery[2], Rene Westhovens[3], Manuela Le Bars[4], Corine Gaillez[4], Coralie Poncet[5], Ayanbola Elegbe[6] and Josef S. Smolen[7]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University of Leeds, Leeds, United Kingdom, [3]UZ Gasthuisberg, Leuven, Belgium, [4]Bristol-Myers Squibb, Rueil Malmaison, France, [5]Docs International, Sévres, France, [6]Bristol-Myers Squibb, Princeton, NJ, [7]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Autoantibodies are continuously generated in RA and the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies or rheumatoid factor (RF) in early RA suggest poor prognosis. Disrupting antigen presentation may interfere with autoantibody formation. As such, co-stimulation modulation with abatacept may lead to seroconversion. We evaluated anti-CCP and RF seroconversion in patients (pts) treated with abatacept or placebo in ADJUST (undifferentiated arthritis [UA] or very early RA) and AGREE (early RA), and assessed the clinical relevance of seroconversion.

Methods: In ADJUST, pts were DMARD-naïve, anti-CCP positive with UA/very early RA and had clinical synovitis of ≥2 joints; pts were treated with abatacept monotherapy or placebo to Mth 6, then withdrawn for 18 mths. In AGREE, MTX-naïve pts who had RA ≤2 yrs, were RF/anti-CCP positive with joint erosions on X-rays were treated with abatacept + MTX or MTX alone. RF and anti-CCP seroconversion was assessed at Mths 6 and 12 and data are presented for pts with positive results at baseline and the visit of interest. RF ≥15–20 IU/mL (dependent on assay) and anti-CCP >5 U/mL were considered positive. Efficacy subanalyses were performed for AGREE, but not for ADJUST due to low pt numbers.

Results: At baseline, 100 and 89% of all pts in ADJUST and AGREE, respectively, were positive for anti-CCP; 79 and 97% were positive for RF. Seroconversion from RF and anti-CCP positive to negative is shown for both studies (Table). For the overall abatacept + MTX population in AGREE, mean (SE) change in RF titers from baseline to Mth 6 was –133 (38.4) and to Mth 12 was –111 (45.2); change from Mth 6 to Mth 12 was 16.5 (12.7). For abatacept + MTX-treated pts in AGREE who converted from RF positive to negative from baseline to Mth 12, mean percentage reductions in tender and swollen joint counts were –75 (95% CI: –85, –66) and –76 (–87, –65) compared with –79 (–84, –73) and –84 (–87, –80) for those who remained positive at Mth 12. Mean changes in DAS28-CRP at Mth 12 were –3.0 (95% CI: –3.5, –2.6) vs –3.4 (–3.7, –3.2) for pts who seroconverted at Mth 12 vs those who remained positive.

		Month 6		Month 12	
		Seroconversion from aseline, n/N (%)	Treatment difference (95% CI)	Seroconversion from baseline, n/N (%)	Treatment difference (95% CI)
Proportion of patients with RF seroconversion (Positive to negative)					
ADJUST*	ABA	5/18 (27.8)	20.1 (−12.7, 48.5)	0/11 (0.0)	−12.5 (−52.7, 17.9)
	PBO	1/13 (7.7)		1/8 (12.5)	
AGREE	ABA + MTX	39/230 (17.0)	7.4 (0.8, 14.1)	41/222 (18.5)	3.9 (−3.5, 11.2)
	MTX alone	22/231 (9.5)		32/219 (14.6)	
Proportion of patients with anti-CCP seroconversion (Positive to negative)					
ADJUST*	ABA	2/22 (9.1)	9.1 (−9.3, 29.2)	2/15 (13.3)	13.3 (−19.6, 41.0)
	PBO	0/19 (0.0)		0/10 (0.0)	
AGREE	ABA + MTX	15/227 (6.6)	3.7 (−0.8, 8.2)	15/212 (7.1)	2.5 (−2.5, 7.6)
	MTX alone	6/208 (2.9)		9/198 (4.5)	

* Monotherapy (treatment withdrawn at Month 6); ABA=abatacept; PBO=placebo

Conclusion: Treatment with abatacept + MTX resulted in a greater proportion of pts with RF seroconversion vs MTX alone in early RA[1,2]. In pts with UA/very early RA, a similar effect on anti-CCP seroconversion was seen up to Mth 12, 6 mths after abatacept withdrawal, suggesting that abatacept may impact autoantibody formation. Pts experienced disease activity benefits with abatacept + MTX in the short-term regardless of RF seroconversion, although AGREE was not powered to evaluate this. Positivity for RF and anti-CCP is a prognostic marker of rapid progression of disease; therefore, further long-term analyses in larger populations are needed to determine whether seroconversion results in better long-term clinical and radiographic outcomes.

[1]Westhovens R, et al. *Ann Rheum Dis* 2009;**68**:1870–7
[2]Kremer J, et al. *Ann Intern Med* 2006;**144**:865–76

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Comparative Effectiveness and Time to Response Among Abatacept, Adalimumab, Etanercept and Infliximab for the Treatment of Rheumatoid Arthritis in a Real World Routine Care Registry. Yusuf Yazici[1], Maria T. Filopoulos[2] and Christopher J. Swearingen[3]. [1]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY, [2]NYU Hospital for Joint Diseases, New York, NY, [3]University of Arkansas for Medical Sciences, Little Rock, AR

Background/Purpose: With the availability of multiple biologic agents with different modes of action, and no head to head trials, it is of use to examine comparative effectiveness of these agents in real world registries to inform physicians how they might be used for the treatment of rheumatoid arthritis (RA).

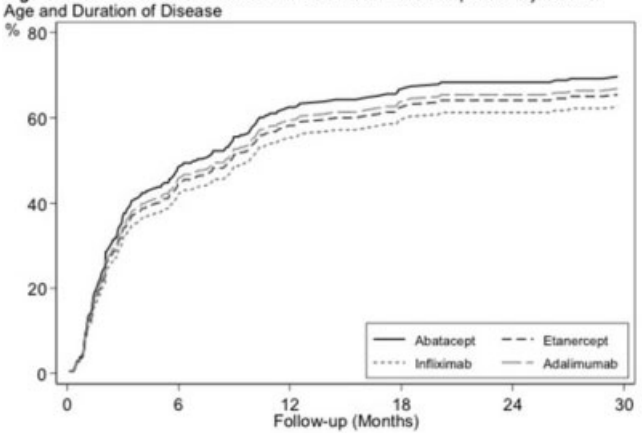
Methods: Arthritis Registry Monitoring Database (ARMD) has been collecting prospective patient data since 2005 in all patients seen in routine care at New York University. For this analysis usage of the biologic medications abatacept, adalimumab, etanercept and infliximab along with self-reported disease activity and clinic measures were abstracted. Time to first response defined as an improvement in RAPID3 of at least 3.6 (clinically important difference) was calculated; change from biologic medication initiation to first response for self-reported disease activity and clinic measures was estimated. Differences in time to first response between biologic medications were estimated using Cox proportional hazards model.

Results: 3574 encounters were reviewed for this analysis. A total of 385 treatment courses were determined. 272 of the 385 courses represent the only biologic medication used by an individual; 40 individuals used two biologic medications at different times, while 11 had used three biologics. Abatacept had more patients achieve response (65%) characterized by a reduction in RAPID of 3.6 points or greater than adalimumab (64%), etanercept (62%) or infliximab (45%). Those patients treated with abatacept had 82% increased likelihood than those treated with infliximab to achieve response (HR=1.82, 95% CI: (1.00, 3.32), p=0.050) in an unadjusted Cox model; no other statistically significant differences between treatments were found. The difference between abatacept and infliximab was not maintained in a Cox model adjusting for age and duration. Increased duration of disease was associated with decreased likelihood of achieving a RAPID3 response. No difference in time to response among biologics was seen (Figure).

Table 1. Demographics and Outcome Measures at Initiation and Follow-up by Biologic Medication

	Abatacept Initiation	Change RAPID3 >=3.6 Present	Absent	Etanercept Initiation	Change RAPID3 >=3.6 Present	Absent	Infliximab Initiation	Change RAPID3 >=3.6 Present	Absent	Adalimumab Initiation	Change RAPID3 >=3.6 Present	Absent
N	114	61 (65%)	33 (35%)	148	77 (62%)	48 (38%)	38	13 (45%)	16 (55%)	85	42 (64%)	24 (36%)
Age (Years)	52.2 (14.6)			50.6 (13.3)			55.4 (14.9)			52.6 (15.3)		
Durataion (Years)	8.0 (7.8)			5.5 (7.1)			9.4 (12.1)			5.5 (6.0)		
Education (Years)	13.7 (3.9)			14.0 (3.7)			14.2 (3.5)			13.1 (4.0)		
Female [N (%)]	102 (90%)			127 (88%)			30 (81%)			66 (80%)		
Function [0–10]	3.4 (2.1)	2.8 (2.1)	3.9 (2.2)	2.9 (2.3)	2.5 (2.0)	2.9 (2.3)	2.9 (2.2)	2.6 (2.3)	3.0 (2.3)	3.4 (2.6)	2.1 (1.9)	3.8 (2.4)
Pain [0–10]	5.6 (2.4)	3.8 (2.4)	6.1 (2.2)	5.6 (2.9)	3.9 (2.5)	5.6 (3.1)	5.4 (2.6)	4.5 (2.6)	5.8 (3.4)	5.8 (2.9)	3.9 (3.0)	6.3 (2.5)
Global [0–10]	5.2 (2.1)	3.7 (2.2)	5.8 (2.4)	5.2 (2.8)	3.1 (2.2)	5.8 (3.0)	5.0 (2.9)	3.9 (2.5)	5.5 (3.0)	5.6 (2.8)	3.6 (2.7)	5.8 (2.6)
RAPID3 [0–30]	14.3 (5.6)	9.9 (5.5)	15.7 (6.1)	13.6 (7.2)	9.0 (5.4)	14.2 (7.6)	13.2 (6.8)	10.3 (6.9)	14.3 (8.0)	14.8 (7.6)	8.5 (6.5)	15.9 (6.8)
Fatigue [0–10]	5.5 (2.9)	4.1 (3.0)	5.6 (2.9)	5.5 (3.0)	4.2 (3.0)	5.6 (3.0)	5.5 (3.0)	4.3 (2.5)	5.6 (3.3)	5.4 (3.2)	4.5 (3.2)	6.1 (2.8)
MD GLobal [0–10]	3.7 (1.3)	2.3 (3.8)	2.3 (1.2)	2.7 (1.6)	1.6 (1.3)	3.4 (2.4)	3.8 (0.9)	3.8 (2.6)	4.0 (3.1)	3.1 (1.9)	2.2 (1.8)	2.7 (1.6)
Swollen [0–28]	1.8 (2.9)	0.0 (0.0)	2.3 (3.2)	4.3 (5.7)	1.3 (3.2)	4.0 (6.4)	4.0 (2.2)	0.7 (1.2)	4.3 (4.9)	4.1 (5.8)	2.0 (3.7)	2.7 (3.8)
Tender [0–28]	7.4 (3.9)	0.4 (0.9)	4.3 (4.0)	6.8 (5.4)	2.7 (3.8)	7.1 (7.0)	5.5 (0.6)	1.7 (2.9)	6.3 (4.0)	7.6 (5.7)	3.5 (4.8)	5.0 (4.5)
ESR(mm/hr)	23.0 (18.3)	27.5 (11.8)	8.0 (1.4)	26.9 (27.2)	27.2 (26.0)	22.6 (25.7)	26.8 (26.1)	20.5 (13.4)	14.0 (15.6)	25.8 (27.5)	20.0 (14.2)	31.3 (29.6)
CRP (mg/dL)	8.8 (25.9)	1.6 (2.2)	1.1 (1.1)	5.4 (25.4)	2.3 (6.0)	17.9 (53.3)	1.8 (1.5)			2.1 (3.5)	2.7 (5.4)	2.2 (3.9)
DAS28 [0–10]	4.3 (0.7)			4.3 (1.8)	2.4 (1.1)	3.8 (1.9)				4.3 (1.6)	2.9 (2.0)	4.6 (2.6)
CDAI [0–76]	19.7 (7.3)	7.1 (4.9)	16.8 (8.5)	19.7 (13.2)	7.0 (6.7)	20.3 (14.6)	18.8 (2.5)			20.9 (13.0)	11.1 (2.3)	16.6 (10.1)
Follow-up (Months)		4.7 (6.0)	13.1 (12.9)		6.2 (8.0)	13.2 (18.9)		2.9 (3.4)	18.7 (4.0)		5.2 (6.6)	18.8 (38.1)

Figure 1. Cumulative Incidence of Time to RAPID ⌑3.6 Response Adjusted for Age and Duration of Disease



Conclusion: Our data suggest that overall efficacy of abatacept, adalimumab, etanercept and infliximab was similar. In addition no differences in time to response was shown among these biologic agents when treating RA patients. With no difference in clinical outcomes or response time, most treatment decisions may be based on ease of use, safety data and longterm survival of respective biologics agents when they are being considered for RA treatment.

2234

Switching From Rituximab to Abatacept: Tolerance Data of 203 Patients Prospectively Followed up in the (Orencia) and Rheumatoid Arthritis (ORA) Registry. Jacques-Eric Gottenberg[1], Thierry Schaeverbeke[2], Philippe Gaudin[3], Liana E. Euller-Ziegler[4], Thao Pham[5], Rene-Marc Flipo[6], Alain G. Cantagrel[7], Eric Houvenagel[8], S. Redecker[9], Xavier X. Le Loet[10], Pascal Claudepierre[11], Isabelle Pane[12], Philippe Ravaud[13] and Xavier Mariette[14]. [1]Strasbourg University Hospital, Strasbourg, France, [2]Pellegrin Hospital, Bordeaux, France, [3]CHU Hôpital Sud, Grenoble Teaching Hospital, Echirolles, France, [4]L Archet Hospital (University), Nice CEDEX 3, France, [5]Sainte Marguerite Hospital, Marseille, France, [6]Hopital R Salengro CHRU, Lille CEDEX, France, [7]Hopital Purpan, Toulouse CEDEX 9, France, [8]St Philibert Hospital, Lomme 59462, France, [9]Hospital University Abbeville, France, [10]CHU de ROUEN, Rouen CEDEX, France, [11]Université Paris Est, Laboratoire d'Investigation Clinique (LIC) EA 4393, AP-HP, Hôpital Henri-Mondor, Rheumatology department, Creteil, France, [12]France, [13]Hopital Hotel Dieu, Paris Descartes University, Paris, France, [14]Université Paris-Sud, Le Kremline Bicetre, France

Background/Purpose: No tolerance data are available in patients with rheumatoid arthritis (RA) who switched from rituximab (RTX) to abatacept (ABA). RTX may have a persistent effect after its discontinuation, until B-cell repopulation, while the patients are already treated by ABA. This may result in some patients to a period of dual targeting of both B and T lymphocytes. We investigated tolerance of the switch from RTX to ABA using data from the "Orencia and Rheumatoid Arthritis" (ORA) registry.

Methods: The French Society of Rheumatology has developed the independent ORA registry, available on-line (www.ora-cri.org), in which data of tolerance and efficacy of ABA in refractory RA are currently being collected every 6 months for 5 years.

Results: From June 2008 to January 2010, 1st, 1000 RA patients have been prospectively included in the ORA registry. Among them, 203 patients (20.3%) received RTX as the last biologic before ABA initiation.

Median age of patients (74.9% of women, 73.5% RF-positive) was 59 years, median disease duration was 13 years. 5.0% of patients had a record of cancer and 35.2% had previously had severe or recurrent infections. Median number of prior synthetic DMARDs was 3. 85.2% of patients had been previously treated with anti-TNF.

Baseline disease activity and medications: before ABA, median DAS28ESR (assessed in 139 patients) was 5.5. 81.9% of patients were also treated with oral prednisone, with a median dosage of 10 mg/day. 30.2 % of patients were treated with ABA in monotherapy and 69.8% with a concomitant DMARD (methotrexate: 78.0%).

Follow-up: 190 patients have already had at least 1 follow-up visit. Median current follow-up duration is 1.8 years (342 patient/years).

Tolerance: 3 severe infusion-reactions resulted in ABA discontinuation. 6 deaths, including 2 resulting from a serious infection, occurred. 4 cancers

were observed (1.2/100 patient/years). 17 serious infections occurred corresponding to 5.0 serious infections/100 patient/years. In patients who did not receive RTX as a last biologic, the rate of serious infections was 6.1/100 patient/years.ABA was discontinued in 95 (46.8%) patients (10.5 % for severe adverse events, 73.7% for inefficacy and 15.8% for other reasons [adverse event and inefficacy, patient's wish, . . .])

Conclusion: In real life, switching from rituximab to abatacept is not unfrequent. In ORA registry, no increased risk of serious infections has been observed until now when RTX was the last biologic used before ABA, but a larger number of patients and a longer follow-up are required to confirmed these data.

2235

First Year Radiological Erosive Progression Is a New Predictor of Further Erosive Progression in Early Arthritis: Results of the ESPOIR Cohort. Gabriel Tobon[1], Alain Saraux[2], Cédric Lukas[3], Frédérique Gandjbakhch[4], Xavier Mariette[5], Bernard G. Combe[6] and Valerie Devauchelle-Pensec[7]. [1]Unit of immunology, Brest, France, [2]Brest Occidentale University, Brest, France, [3]Montpellier 1 University, Lapeyronie Hospital, 371, Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France, Montpellier, France, [4]Hopital Pitié Salpétrière, Paris, France, [5]Université Paris-Sud, Le Kremlin Bicetre, France, [6]Hopital Lapeyronie, Montpellier, France, [7]Brest Occidentale University, Brest, France

Background/Purpose: One of a major goal in the treatment of recent arthritis is to prevent articular destruction. Several factors exist to predict joint destruction, but the rapidity of progression is never taken account.

Our objective was to determine if the first year radiological erosive progression (FIRE) is a predictor of further erosive progression (FURE) during the next two years in a cohort of early arthritis.

Methods: 813 patients with a diagnosis of recent arthritis of less than 6 months were included in the prospective French "ESPOIR" cohort. Standardized radiographs of hand wrist and foot in postero-anterior view (PAV) were performed at inclusion, one, two and three years. Inter and intraobserver variabilities were assessed. All the radiographs were examined by a blinded reader for modified Sharp score. The speed of progression was defined at one year (between M0 and M12) and after the next two years (between M12 and M36). The patients with a speed of annual progression of more than 2.5 in the erosion Sharp score were considered as high progressors.

Results: 535 patients have a complete set of radiographs. Among them 7% (35/500) received biological treatment before one year. None of them was FURE. For the 500 remaining patients without biologics, 55/500 (11%) were FIRE. During the first year, 37/500 (7.4%) did not have radiographic progression, 25% (124/500) were rapid progressor (> 5pts) Concerning classification criteria, only the presence of RF and the item 7 of the ACR criteria, or the serological item and the ACR/EULAR score of the ACR/EULAR criteria were associated with a FURE. Using logistic regression, the presence of RF or ACPA ($p = 0.023$), erosion at inclusion ($p=0.001$), the level of IL-6 ($p = 0.043$) and FIRE ($p = 0.002$) were associated with FURE. When items were combined, the FIRE criteria performed better than other criteria to predict further rapid progression.

Conclusion: The first year radiological erosive progression should be considered as a new predictor of further erosive progression in early arthritis None.

2236

New, Provisional American College of Rheumatology and European League Against Rheumatism Remission Criteria: Results From 2 Randomized, Controlled Golimumab Trials in Patients with Rheumatoid Arthritis. Paul Emery[1], Edward Keystone[2], R. M. Fleischmann[3], M. C. Genovese[4], Lars Klareskog[5], Stephen Xu[6], Chenglong Han[7] and Elizabeth C. Hsia[8]. [1]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [2]University of Toronto, Toronto, ON, [3]University of Texas Southwestern Medical Center and Metroplex Clinical Research Center, Dallas, TX, [4]Stanford University Medical Center, Palo Alto, CA, [5]Karolinska Institutet, Stockholm, Sweden, [6]Centocor R & D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, [7]Johnson & Johnson Pharmaceutical Services, LLC, Malvern, PA, [8]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA

Background/Purpose: To assess wk24 remission rates from GO-BEFORE and GO-FORWARD using new, "provisional" criteria proposed by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) (Felson et al).[1]

Methods: This is a retrospective analysis from GO-BEFORE (methotrexate (MTX)-naïve RA pts) and GO-FORWARD (RA pts with inadequate response to MTX) through wk24. In GO-BEFORE (N=637) MTX-naïve pts and in GO-FORWARD (N=444) pts with active RA despite MTX were randomized to PBO+MTX, GLM100mg+PBO, GLM50mg+MTX, or GLM100mg+MTX, grps 1–4, respectively. In GO-FORWARD, pts with <20% improvement in SJC/TJC at wk16 entered early escape: PBO+MTX→GLM50mg+MTX, GLM 100mg+PBO→GLM100mg+MTX, GLM 50mg+MTX→GLM 100mg+MTX. GLM/PBO was injected q4wks. New ACR/EULAR remission was defined as follows: Definition A [Def A]-(TJC/SJC [28 joints], CRP mg/dL, and pt global assessment, each score ≤1) and Definition B [Def B]-SDAI score is the sum of (TJC/SJC [28 joints], pt global assessment, physician global assessment, and CRP mg/dL), scoring ≤3.3. Data handling rules were applied to wk24 analysis of data (Table).

Table. GO-BEFORE (MTX-naïve) and GO-FORWARD (MTX-inadequate response) Week 24 results using new, provisional ACR/EULAR remission criteriaμ

	Group 1 PBO+MTX	Group 2 GLM 100mg+PBO	Group 3 GLM 50mg+ MTX	Group 4 GLM 100mg+MTX	GLM 50 and 100mg + MTX
GO-BEFORE Wk 24-All pts*					
Definition A†	6.3 (10/160)	6.9 (11/159)	15.7** (25/159)	10.7 (17/159)	13.2** (42/318)
Definition B‡	8.1 (13/160)	7.5 (12/159)	15.1 (24/159)	15.7** (25/159)	15.4** (49/318)
GO-FORWARD Wk 24-All pts*					
Definition A†	1.5 (2/133)	6.0 (8/133)	12.4** (11/89)	10.1** (9/89)	11.2** (20/178)
Definition B‡	2.3 (3/133)	8.3** (11/133)	13.5** (12/89)	12.4** (11/89)	12.9** (23/178)

*% (n/N), ** p< 0.05, †Definition A-(TJC/SJC [28 joints], CRP mg/dL, and patient global assessment are all ≤1); ‡Definition B-Simplified Disease Activity Index score is the sum of (TJC/SJC [28 joints], patient global assessment, physician global assessment, and CRP mg/dL) is ≤3.3. μEarly escape (EE), pts wk16 values carried forward to wk24, last observation carried forward (missing data) and treatment failure rules applied. For GO-FORWARD-at wk16, pts in Grps 1, 2, and 3 with <20% improvement in SJC/TJC entered EE. Grp1: includes pts on PBO+MTX→EE to GLM 50mg+MTX (N=41); Grp2: GLM 100mg+PBO→EE to GLM 100mg +MTX (N=36); Grp3 GLM 50mg+MTX→EE GLM 100mg+MTX (N=15).

Results: Using new ACR/EULAR remission criteria (Def A and B), a significantly greater proportion of pts achieved remission in the combined GLM+MTX treatment grps vs grp 1 in GO-BEFORE and GO-FORWARD. A comparison between new criteria and previously published DAS28 remission criteria for the combined GLM+MTX treatment grps show: GO-BEFORE (13.2% (Def A)/15.4% (Def B) vs 26.7% (prev pub'd) and GO-FORWARD (11.2% (Def A)/12.9% (Def B) vs 28.7% (prev pub'd). As expected, the new, more stringent criteria resulted in lower remission rates vs DAS28 remission criteria. Def A and B had generally similar remission rates in both studies, with slightly lower numbers for Def A vs B. A comparison between individual treatment grps using the new criteria show: GO-BEFORE remission rates significantly greater in grp 3 for Def A and grp 4 for Def B, with grp 3 approaching statistical significance ($p=0.052$) (Def B) vs grp 1. In GO-FORWARD, significantly greater remission rates using Def A were achieved in grps 3 and 4, with grp 2 approaching statistical significance ($p=0.053$) vs grp 1, while significantly greater proportions of pts achieved remission in all GLM treatment grps vs grp 1 using Def B.

Conclusion: Significantly greater remission rates were achieved in the combined GLM grp vs grp 1 in GO-BEFORE and GO-FORWARD through wk24 based on new, more stringent ACR/EULAR criteria. Remission rates were generally slightly lower using Def A vs Def B.

[1]Felson D, Smolen J, Wells G, et al. American College of Rheumatology/ European League Against Rheumatism Provisional Definition of Remission in Rheumatoid Arthritis for Clinical Trials. *Arthritis & Rheumatism*, 63 (3)573–586.

2237

A Twelve-Week Exploratory Phase II Trial of GLPG0259 Versus Placebo in Patients with Active Rheumatoid Arthritis and Inadequate Response to Methotrexate. Rene Westhovens[1], Filip De Keyser[2], Dmitro Rekalov[3], Evgeny L. Nasonov[4], Johan Beetens[5], Annegret Van der Aa[5], Piet Wigerinck[5], Florence Namour[6], Frédéric Vanhoutte[5] and Patrick Durez[7]. [1]University Hospital KU Leuven, Leuven, Belgium, [2]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [3]Zaporizhzhia Regional Hospital, Zaporozhe, Ukraine, [4]Institute of Rheumatology, Moscow, Russia, [5]Galapagos NV, Mechelen, Belgium, [6]Galapagos SASU, Romainville, France, [7]Université Catholique de Louvain, Brussels, Belgium

Background/Purpose: GLPG0259, an inhibitor of the kinase MAP-KAPK5, blocked the release of mediators of inflammation (IL-6, TNFa) and cartilage erosion (MMPs) in disease-relevant cells and in synovial

cultures. In the mouse collagen-induced arthritis model, GLPG0259 reduced paw inflammation and prevented bone and cartilage erosion. Given these pre-clinical results, we explored the clinical development of GLPG0259 for the treatment of rheumatoid arthritis (RA). In Phase I trials GLPG0259 showed a favorable safety and a pharmacokinetic (PK) profile that supported once daily dosing. A Phase II dose-finding trial was then initiated to evaluate the efficacy and dose levels of GLPG0259 in RA patients.

Methods: This exploratory, Phase II, double-blind, placebo-controlled, multicenter trial was designed to be performed in a maximum of 200 randomized subjects with active RA who had an inadequate response to methotrexate (MTX). The trial consisted of two parts:

In Part A, thirty eligible subjects were randomized in a 2:1 ratio to receive either a once-daily 50 mg dose of GLPG0259 or placebo, in addition to a stable dose of MTX.

An interim analysis was performed at the end of Part A to assess the efficacy and tolerability of GLPG0259 versus placebo.

If the interim analysis at the end of Part A showed a clinical advantage of GLPG0259 over placebo, Part B would be initiated, with an additional 150 subjects randomized to GLPG0259 (50, 25 or 12.5 mg/day), or placebo.

Results: Here we present the results from Part A of the trial. In total 31 patients were randomized; one patient dropped-out before administration of study medication. The 30 remaining patients were allocated to 50 mg GLPG0259 q.d. (19 patients) or to placebo (11 patients) for 12 weeks. Both patient populations were comparable: they had an RA diagnosis established on average 7 years prior to participation in the trial, were on an average dose of MTX of 10–11 mg weekly for at least 12 weeks, had never taken biologics before and had comparable RF and anti-CCP seropositivity.

After 12 weeks of treatment 26% and 27% of GLPG0259 and placebo recipients, respectively, showed an ACR20 response. Sub-analysis of the ACR components showed no marked difference between the two treatment populations. A modest drop in CRP (26%) in the GLPG0259 group did not result in an improved ACR20 response.

Overall 9 patients (30%) presented with treatment-emergent adverse events (AEs); 8 (42%) on GLPG0259 and 1 (9%) on placebo. The GLPG0259-related AEs mainly affected the gastrointestinal tract (nausea, vomiting, gastrointestinal discomfort and xerostomia), consistent with the Phase I results.

Plasma concentrations of GLPG0259 were within the range observed in healthy volunteers dosed at 50 mg q.d. for 14 days.

Conclusion: The interim analysis of the results of Part A of this exploratory Phase II trial, involving 12 weeks of treatment with 50 mg q.d. GLPG0259 or placebo in patients with active RA and insufficient response to MTX, did not show any clinical benefit from GLPG0259. Therefore, Part B of the trial will not be initiated. This innovative trial design did, however, enable a quick determination of the lack of GLPG0259's efficacy in RA patients.

2238

Safety and Efficacy of Abatacept in Eight Rheumatoid Arthritis Patients with Chronic Hepatitis B. Paul S. Kim[1], Gerald Y. Ho[2], Pamela E. Prete[3] and Daniel E. Furst[4]. [1]University of California, Irvine, Orange, CA, [2]Arthritis/Osteoporosis Med Ctr, La Palma, CA, [3]Long Beach VA Med Ctr, Long Beach, CA, [4]UCLA, Los Angeles, CA

Background/Purpose: There are no previous studies on the use of abatacept in patients with chronic hepatitis B. This medical record review assesses the safety and efficacy of abatacept in eight patients with rheumatoid arthritis (RA) and chronic hepatitis B.

Methods: A retrospective analysis of 8 patients with RA and chronic hepatitis B treated with abatacept was conducted. The primary outcome was DAS 28 at each follow-up visit along with markers of hepatitis B reactivation including liver function tests as measured by aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hepatitis B viral load.

Results: A total of 47 visits were recorded. Mean duration of follow-up of patients on abatacept was 19.1 months (SD 12.7, range 3–33). Analysis was limited to 18 months of follow-up (included 77% of all visits: 36/47). Four patients were started on antiviral prophylaxis for hepatitis B (3 on entecavir and 1 on tenofovir) with the initiation of abatacept while four patients were not. Among the 4 patients who received antiviral prophylaxis, RA improved as evidenced by a statistically significant decrease in DAS 28 scores from 5.2 (SD 1.7) at baseline to 2.9 (SD 1.4) at 18 month follow-up, $p = 0.025$. Also these 4 patients had no reactivation of hepatitis B with viral titers remaining within 1 log of baseline in the 2 where it was obtained. In the 4 patients without antiviral prophylaxis there was no significant decrease in the DAS 28 scores going from 4.8 (SD 0.9) at baseline to 3.9 (SD 0.34) at 18 month follow-up, $p = 0.318$, and all 4 experienced reactivation of hepatitis B with viral titers increasing more than 10-fold. There were no adverse events other than the hepatitis B reactivation.

Conclusion: In these preliminary data, the use of abatacept in patients with RA and chronic hepatitis B appears feasible if antiviral prophylaxis for hepatitis B is given concurrently. In these patients there were no non-hepatitis-related adverse effects. These data are encouraging and should lead to initiation of controlled trials of abatacept in hepatitis B.

2239

Higher Proportion of Rheumatoid Arthritis Patients Achieve Low Swollen and Tender Joint Counts and No Radiographic Progression with Etanercept Plus Methotrexate Versus Methotrexate Alone. Eustratios Bananis, Tahmina Ferdousi, Ronald Pedersen, Andrew S. Koenig and Thomas V. Jones. Pfizer Inc., Collegeville, PA

Background/Purpose: ACR/EULAR remission criteria for rheumatoid arthritis (RA) include achievement of 0 or 1 swollen joints (SJ) and 0 or 1 tender joints (TJ).[1] Recent studies have identified SJ count as a potential predictor of radiographic progression.[2,3] The Combination of Methotrexate (MTX) and Etanercept (ETN) in Active Early Rheumatoid Arthritis (COMET) trial demonstrated that treatment of early RA with MTX and ETN led to superior rates of DAS clinical remission and radiographic non-progression compared with MTX alone. This post hoc analysis of data from the COMET trial examines rates of achieving ≤1 SJ, ≤1 TJ and inhibition of radiographic progression (change in mTSS ≤0) at years 1 and 2 in response to treatment.

Methods: Overall trial methods have been previously described.[4,5] For this analysis, LOCF data, utilizing the DAS28 joint counts from the COMET trial, was assessed at years 1 and 2. Inhibition of radiographic progression was calculated for patients with valid radiographs that achieved ≤1 SJ and ≤1 TJ by treatment group.

Results: At year 1, a significantly higher proportion of patients achieved ≤1 SJ (70.9% vs 46.0%, P<0.02) or ≤1 TJ (64.2% vs 40.7%; P<0.02) when treated with ETN+MTX versus MTX alone, respectively (Table). Furthermore, a higher proportion of patients receiving ETN+MTX treatment that achieved ≤1 SJ (76.3% vs 65.5%, P=0.06) or ≤1 TJ (78.5% vs 55.9%, P<0.02) had no radiographic progression compared to MTX monotherapy at year 1 (Table). At 2 years, a significantly higher proportion of patients with continuous ETN+MTX therapy than MTX monotherapy had ≤1 SJ (80.6% vs 53.2%, P<0.02) or ≤1 TJ (70.4% vs. 53.2%, P<0.02), respectively. Similar to year 1 results, a higher proportion of patients receiving continuous ETN+MTX versus continuous MTX who achieved ≤1 SJ (87.7% vs 69.9%, P<0.02) or ≤1 TJ (85.5% vs 70.2%, P=0.062) had no radiographic progression at year 2 (Table). The proportion of patients with ≤1 SJ at year 1 and who had no radiographic progression after 2 years of continuous ETN+MTX therapy was significantly higher compared to those with ≤1 SJ at year 1 receiving 2 years of continuous MTX monotherapy (89.9% vs 65.2%, P=0.002). Similar results were seen in patients who achieved ≤1 TJ at year 1 after 2 years of continuous treatment (87.0% vs 62.8%, P=0.005).

Table. Patients who achieved ≤1 swollen joint or ≤1 tender joint and no radiographic progression at years 1 and 2 by treatment group

	Year 1		Year 2	
	ETN + MTX	MTX	ETN + MTX	MTX
≤ 1 swollen joint	188/265 (70.9)*	121/263 (46.0)	87/108 (80.6)*	50/94 (53.2)
≤ 1 swollen joint and mTSS ≤0†	135/177 (76.3)	74/113 (65.5)	71/81 (87.7)*	32/46 (69.6)
≤ 1 tender joint	170/265 (64.2)*	107/263 (40.7)	76/108 (70.4)*	50/94 (53.2)
≤ 1 tender joint and mTSS ≤0†	128/163 (78.5)*	57/102 (55.9)	59/69 (85.5)	33/47 (70.2)

All values n/N (%); *P<0.02 versus MTX monotherapy; †Includes only patients with valid radiographs

Conclusion: In this analysis, a significantly higher proportion of patients who were treated with ETN+MTX had ≤1 swollen joint or ≤1 tender joint at year 1 and 2 as compared to patients receiving MTX alone. Of the patients achieving ≤1 swollen joint or ≤1 tender joint, a higher proportion of patients receiving ETN+MTX had no radiographic progression versus MTX monotherapy. Combination treatment increases the proportion of patients achieving 2 major components of the new remission criteria and inhibits radiographic progression.

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2240

Efficacy of TNF Switch After Failure of One TNF Inhibitor – Results From a Nation-Wide Observational Study. Katerina Chatzidionysiou[1], Jonas Eriksson[2], Johan Askling[3] and Ronald F. van Vollenhoven[1]. [1]Karolinska Institute, Stockholm, Sweden, [2]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Solna, Sweden

Background/Purpose: The purpose of this study was to determine whether patients who failed one anti-TNF benefit from switching to another anti-TNF and whether the specific order of agents and reason for switch is significant.

Methods: Data from the ARTIS registry were used. Patients with RA, who received an anti-TNF [etanercept (ETA), adalimumab (ADA) or infliximab (INF)] as first biologic and subsequently switched to an alternative anti-TNF, were included in the analysis. Treatment segments were analysed according to DAS28 and HAQ reduction and EULAR response at 6 months after baseline. Treatment results were analysed for each biologic, by type of previous anti-TNF and reason for discontinuation (primary and secondary inefficacy or intolerance). Multiple treatment segments with the same anti-TNF were disregarded for this analysis.

Results: A total of 1080 patients were included. Of these, 520 switched to ETA, 466 to ADA, and 94 to INF. Complete data were available for appr. 50% of patients and were evenly distributed between groups. At baseline (BL= start of 2nd anti-TNF) no differences in age, sex, disease duration, RF, HAQ and concomitant NSAIDs were observed between groups. BL DAS28 (mean±SD) was significantly lower for ADA (4.79±1.32) than ETA (5.15±1.32, p<0.0001) and INF (5.13±1.22, p=0.04). INF was more often combined with DMARDs (81.9%) than ETA (69.3%, p=0.007) and ADA (65.7%, p=0.001), but less often with glucocorticoids (39.4%) than ETA (51.2%, p=0.02) and ADA (50.6%, p=0.03).

Significant clinical improvements were observed for the whole cohort of patients. DAS28 improvement at 6 months was 1.59±1.47 for ETA, 1.17±1.35 for INF and 1.00±1.32 for ADA (p=0.002 ETA vs. ADA, p=0.29 ETA vs. INF; p values adjusted for age, sex, BL DAS28, conc. DMARDs and glucocorticoids). HAQ improvement at 6 months = 0.26±0.52 for ETA, 0.14±0.50 for INF and 0.14±0.43 for ADA (adjusted p=0.42 ETA vs. INF, p=0.23 ETA vs. ADA). The percentages of EULAR Good/Moderate/Non-responders were 28/43/29% for ETA, 21/46/33% for INF and 17/45/38% for ADA (p=0.02 between groups). In table 1 the effectiveness of each anti-TNF by type and reason for discontinuation of the previous anti-TNF is summarized.

Table 1. Efficacy of the 2nd antiTNF assessed by DAS28 (mean±SD) and HAQ (mean±SD), reductions at 6 months from baseline, accordning to the type of previous antiTNF and reason for discontinuation. ([Number of patients])

1st antiTNF	2nd antiTNF	DeltaDAS28 6m mean±SD	p-value*	DeltaHAQ 6m mean±SD	p-value*
ETA	ADA	0.93 ± 1.21 [154]	0.34	0.12 ± 0.43 [164]	0.70
	INF	1.24 ± 1.40 [36]		0.18 ± 0.44 [36]	
ADA	ETA	1.39 ± 1.46 [121]	0.88	0.25 ± 0.44 [127]	0.25
	INF	0.91 ± 1.16 [10]		−0.02 ± 0.67 [10]	
INF	ETA	1.75 ± 1.47 [145]	0.30	0.26 ± 0.57 [145]	0.82
	ADA	1.16 ± 1.56 [63]		0.19 ± 0.43 [68]	
Reason discontinuation 1st antiTNF					
Intolerance	ETA	1.68 ± 1.47 [62]	0.85	0.30 ± 0.46 [61]	0.17
	INF	1.32 ± 0.90 [6]		0.20 ± 0.11 [5]	
	ADA	1.24 ± 1.79 [46]		0.06 ± 0.42 [53]	
Primary inefficacy	ETA	1.56 ± 1.45 [82]	0.13	0.25 ± 0.58 [87]	0.86
	INF	1.23 ± 1.33 [17]		0.13 ± 0.66 [19]	
	ADA	1.02 ± 1.03 [63]		0.16 ± 0.40 [65]	
Secondary inefficacy	ETA	1.65 ± 1.41 [83]	**0.02****	0.25 ± 0.48 [86]	0.92
	INF	1.04 ± 1.11 [12]		0.14 ± 0.50 [10]	
	ADA	0.99 ± 1.16 [59]		0.20 ± 0.45 [62]	

* Adjusted for BL age, sex, DAS28, conc. DMARDs and glucocorticoids.
** ETA vs. ADA p=0.005

Conclusion: In this large observational cohort, patients who failed anti-TNF therapy do benefit from switching to other TNF inhibitors. ETA as 2nd anti-TNF yielded significantly greater DAS28 reductions than INF and ADA, but due to the relatively large number of incomplete data this finding must be interpreted with caution. For patients who discontinued anti-TNF because of secondary inefficacy, switching to ETA appeared more effective than switching to ADA.

2241

A Safety Analysis of Oral Prednisone As a Pre-Treatment for Rituximab in Rheumatoid Arthritis. John D. Carter[1], Nancy Albritton[1], S. Alireza Zarabadi[2], Louis R. Ricca[3], Joanne Valeriano-Marcet[1], Frank B. Vasey[4] and Anthony Sebba[5]. [1]University of South Florida, Tampa, FL, [2]Tampa Arthritis Center, Tampa, FL, [3]University of South Florida College of Medicine, St Petersburg, FL, [4]Wayne State Univ. Health Ctr., Detroit, MI, [5]University of South Florida, Palm Harbor, FL

Background/Purpose: The administration of 100mg of methylprednisolone intravenously (IV) ½ hour prior to rituximab decreases the incidence and severity of acute infusion reactions (AIRs). However, the recommended pretreatment with IV methylprednisolone adds considerable time to the medication administration protocol; it also conveys potential risk. We present preliminary results of an assessment of oral prednisone as a pretreatment to rituximab.

Methods: This is a 6-month open-label assessment of 40mg of oral prednisone given ½ hour prior to rituximab as a prophylaxis against acute infusion reactions in patients with rheumatoid arthritis (RA). Subjects are ages 18–80 and either methotrexate (MTX) or TNF-antagonist inadequate responders and naïve to rituximab. All subjects have to be on concomitant methotrexate. Standard safety and laboratory exclusions applied. All subjects were treated with 40mg of oral prednisone ½ hour prior to their rituximab infusions. Rituximab was administered as per the standard RA protocol; i.e. 1000mg IV twice at days #1 and #15. The primary endpoint is AIRs in the first 24 hours after the initiation of their day #1 infusion. The severity, timing, and treatment (including rituximab dose modifications) of any AIRs are also recorded. Secondary endpoints include AIRs during the 24 hours following the day #15 infusion and any adverse events experienced during the 6 month study; efficacy measures (DAS-28 and HAQ-DI) were also followed as secondary endpoints.

Results: 65 subjects were screened and 50 subjects qualified. Baseline demographics include 42 females and 8 males, with 39/50 (78%) Caucasians, 5 (10%) Hispanics, 3 African-Americans (6%), and 3 other. The subjects' mean age was 52.2 years (range 27–80) and disease duration was 11.2 years (range 1–49). The average MTX dose was 16.2mg weekly and 30/50 (60%) have failed previous anti-TNF therapy (average number of TNF-antagonists used was 1.5). 22/50 (44%) subjects were on glucocorticoids at baseline with an average dose of 7.1mg prednisone daily; 36/50 (72%) subjects were seropositive. The mean DAS28 at screening was 5.64 and their HAQ-DI was 1.39. Regarding the primary endpoint, 15/50 (30%) of the subjects had AIRs within 24 hours of their day #1 infusion; 13 were mild in severity and 2 were moderate. There were only 6 (12.2%) AIRs within 24 hours of their day #15 infusion; all were mild. One of the day #1 AIRs required drug discontinuation (wheezing). Of the 47 subjects who have completed the entire 6 months of the study, 37 (79%) experienced an AE at some point during the trial. There were 3 SAE's (a-fib, asthma, suicide attempt) deemed not to be study-drug related. The DAS28 and HAQ-DI all improved significantly at weeks 8, 16, and 26 compared to baseline.

Conclusion: Historical controls demonstrate that 27–33% of RA subjects experience AIRs with their first rituximab infusion. Our data suggest a smaller dose of oral prednisone is an effective alternative to IV methylprednisolone as a pretreatment for rituximab in patients with RA.

2242

Characterization of Long-Term Responders to First Treatment Course of Rituximab (RTX)—Results From the CERERRA Collaboration. Elisabeth Lie[1], Katerina Chatzidionysiou[2], Evgeny L. Nasonov[3], Galina Lukina[3], Karel Pavelka[4], Dan C. Nordström[5], Matija Tomsic[6], Cem Gabay[7], Ioan Ancuta[8], Piet LC van Riel[9], Juan J. Gomez-Reino[10], João E. Fonseca[11], Merete L. Hetland[12], Ulrik Tarp[13], Tore K. Kvien[1] and Ronald F. van Vollenhoven[2]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Karolinska Institute, Stockholm, Sweden, [3]Institute of Rheumatology, Moscow, Russia, [4]1Institute of Rheumatology, Department of Experimental Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [5]ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, [6]University Medical Centre Ljubjana, Ljubljana, Slovenia, [7]University Hospitals of Geneva, on behalf of the SCQM registry, Geneva, Switzerland, [8]Cantacuzino Hospital, Bucharest, Romania, [9]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [10]Hospital Clinico Universitario, Santiago, Spain, [11]Lisbon Academic Medical Center, on behalf of Rheumatic Diseases Portuguese Register (Reuma.pt), Lisbon, Portugal, [12]Copenhagen University Hospital at Glostrup, on behalf of DANBIO, Copenhagen, Denmark, [13]Aarhus University Hospital, Aarhus, Denmark

Background/Purpose: Most rheumatoid arthritis (RA) patients (pts) who respond to the first course of RTX need retreatment with a second course after 6 to 12 months due to increase in disease activity. However, some pts show a sustained clinical response for a longer period. Our objective was to characterize pts who showed a sustained response after the 1st course of RTX and compare them to those who were not long-term responders.

Methods: 10 European biologics registries provided anonymized data sets of RA pts treated with RTX in clinical practice for analysis of pooled data. Pts with available retreatment data were eligible for the current analyses. Long-term response was defined as no retreatment during the 1st year AND sustained response (ΔDAS28 < -1.2 vs. baseline) at months 6–12, in pts with at least 9 months follow-up. The comparator groupincluded pts retreated during the 1st year and/or without sustained response. Baseline (BL) characteristics, and year 1 and year 2 DAS28 states and changes were compared. Due to heterogeneity in timing of follow-up visits, overall mean DAS28 was calculated for the period 3–12 months and for year 2. The main effectiveness outcome was mean DAS28 during year 2. Predictors of long-term response were identified by univariate and multivariate logistic regression analysis.

Results: 209 pts were classified as long-term responders (LTRs) and 867 were non-long-term responders (NLTRs) (79% of NLTRs were retreated during the 1st year); 93% vs. 88% had >18 months follow-up time. In both groups, 83% were female, 81% received concomitant DMARDs and mean disease duration was 12 years. 84%/82% were RF pos. LTRs were significantly older (mean 55.1 vs. 52.2 years, p=0.005), were more often biologics naïve (51.0% vs. 40.4%, p=0.006) and had higher BL DAS28. Despite higher BL DAS28, % in low disease activity state (LDA) and remission (rem) were higher for LTRs through year 1, and mean DAS28 was lower (Table 1). The difference in mean DAS28 was more or less sustained through year 2, but % in LDA/rem. were similar for most time points. 34% of LTRs were retreated during year 2. Mean(SD) total number of RTX courses from baseline through year 2 was 1.6(1.0) for LTRs vs. 2.6(0.8) for NLTRs (p<0.001). Older age, biologics naivety, higher BL DAS28 and lower HAQ-DI were independent predictors of LTR (Table 2).

Table 1.

	Long-term responders	Non-long-term responders	p-value
BL DAS28	6.26	5.91	<0.001
Mean DAS28 months 3–12	3.66	4.39	<0.001
DAS28 ≤ 3.2 (LDA) months 6/12	36.4%/45.3%	19.8%/22.0%	<0.001/<0.001
DAS28 <1.6 (rem.) months 6/12	19.2%/22.7%	9.7%/11.5%	0.001/<0.001
Mean DAS28 year 2	3.78	4.13	0.01
ΔDAS28 BL to year 2	−2.37	−1.85	0.001
DAS28 ≤ 3.2 (LDA) months 18/24	28.3%/54.5%	25.8%/36.0%	0.70/0.02
DAS28 < 2.6 (rem.) months 18/24	13.2%/31.8%	13.1%/17.5%	0.98/0.03

Table 2.

	OR (95% CI)	p-value
Age	1.08 (1.00–1.16)*	0.051
Biologics naivety	1.58 (1.08–2.30)	0.018
BL DAS28	1.44 (1.19–1.73)	<0.001
BL HAQ-DI	0.70 (0.52–0.95)	0.024

* Per 5-year increase. Multivariate model, adjusted for sex and BL pain VAS. Hosmer-Lemeshow goodness-of-fit p=0.88.

Conclusion: Biologics naïve pts who were older and who had higher disease activity and less functional impairment at baseline were more likely be long-term responders to the 1st course of RTX, and these pts generally sustained a good clinical response through year 2.

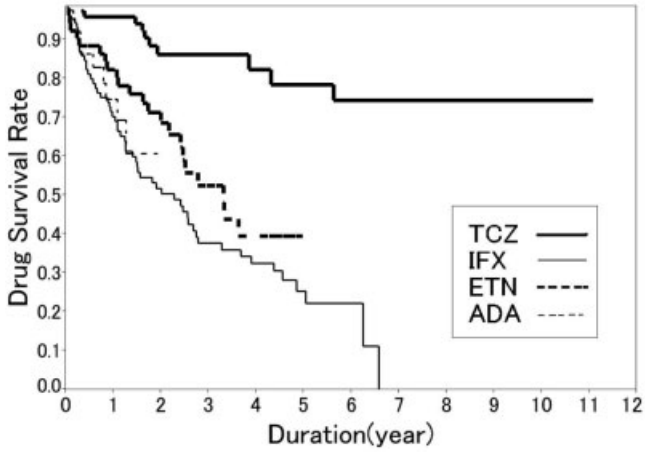
2243

Long-Term Tolerability of Tocilizumab for the Treatment of Rheumatoid Arthritis. Yoshihiro Hishitani, Toru Hirano, Yoshihito Shima, Atsushi Ogata, Masashi Narazaki, Keisuke Hagihara and Toshio Tanaka. Osaka University Graduate School of Medicine, Suita, Japan

Background/Purpose: Tocilizumab(TCZ),a humanized monoclonal anti-IL-6 receptor antibody, has been shown to have definite efficacy in patients with rheumatic arthritis(RA). However, long term utility of TCZ has not been well documented. And there are few reports comparing TCZ with anti-TNFα drugs. We observe patients with RA who are administered TCZ for up to 11 years. So we examined the tolerability of biologics, especially TCZ.

Methods: We retrospectively reviewed the medical charts of RA patients who were administered biologics from 1999 to 2010. We examined continuation rate andcause of discontinuation of biologics for the treatment of RA.

Results: We administered biologics to 200 RA patients by September 2010. And we were able to follow 192 cases to September 2010. TCZ,infliximab(IFX),etanercept(ETN),adalimumab(ADA) were administered to 78(51), 87(80), 53(43), 44(26) cases respectively (as the 1st biologics). TCZ and ADA were administered to elder patients than ETN. TCZ and ETN were administered to patients who had higer DAS-28 score than ADA. Concomitant dosage of methotrexate(MTX) was more in patients who were administered IFX (IFX group) compared to other groups. Disease duration and concomitant prednisolone dosage were not significantly different among the 4 groups. Median duration of administration of TCZ, IFX, ETN, ADA were 704,545,714,248days, respectively. The Kaplan-Meier curves of the continuation rate of the 4 drugs are shown in Figure. TCZ showed significantly higher continuation rate than anti-TNFα drugs (p<0.001). The cause and number of discontinuation of these 4 biologics are shown in Table. The rate of discontinuation due to lack of efficacy or loss of efficacy was significantly less in TCZ group than other groups. The rate of infusion reaction was significantly more in IFX group than other groups. The rate of discontinuation due to severe infection was not significantly different among the 4 groups.



Cause of discontinuation	TCZ	IFX	ETN	ADA
no efficacy	1	9	4	4
loss of efficacy	2	12	12	3
infusion reaction	1	12	2	0
severe infection	5	5	1	1
remission	0	5	1	1
miscellaneous	2	14	3	1
overall discontinuation	11	57	23	10
(Total cases)	(78)	(87)	(53)	(44)

Conclusion: In our cohort, TCZ showed long-term tolerability for the treatment of RA.

2244

A Multi-Biomarker Disease Activity Score (Vectra™DA algorithm score) Reflects Clinical Disease Activity and Tracks Response in a Japanese Rheumatoid Arthritis Population Treated with Anti-TNF Therapy. Shintaro Hirata[1], Douglas J. Haney[2], Guy Cavet[2], Lyndal K. Hesterberg[2], Norifumi Sawamukai[1], Kunihiro Yamaoka[3], Kazuyoshi Saito[1] and Yoshiya Tanaka[1]. [1]University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, [2]Crescendo Bioscience, Inc., South San Francisco, CA, [3]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Background/Purpose: Effective management of rheumatoid arthritis (RA) patients involves regular quantitative disease activity assessment. We set out to determine whether a multi-biomarker disease activity algorithm (MBDA), developed and validated in predominantly Caucasian populations, could assess disease activity and track changes in a Japanese RA cohort treated with anti-TNF therapy.

Methods: Patients were enrolled at the University of Occupational and Environmental Health, Kitakyushu, Japan. Each received anti-TNF treatment (50 adalimumab, 49 etanercept, 50 infliximab) in the course of their routine clinical care. Twelve biomarkers were measured using custom immunoassays on the Meso Scale Discovery MULTI-ARRAY platform and combined in a pre-specified algorithm to generate a MBDA score between 1 and 100. The association between MBDA score and DAS28 was evaluated by Spearman correlation and by area under the receiver operating characteristic (AUROC) curve for distinguishing DAS28 $\leq$ 3.2 from DAS28 $>$ 3.2. These analyses used a single randomly selected visit for each patient. MBDA score was evaluated as an independent predictor of disease activity in ordinary least squares regression with DAS28 as response variable and CRP and MBDA score (using only biomarkers other than CRP) as predictor variables. The ability of change in MBDA score to track clinical response was assessed by AUROC for good EULAR response at 1 year.

Results: At baseline, patients had median age of 60 (interquartile range (IQR) 50–68), median DAS28 of 5.7 (IQR 5.0–6.5) and disease duration of 60 months (IQR 18–168). MBDA scores distinguished low and moderate/high disease activity categories (AUROC = 0.80, 95%CI 0.72–0.87, $p < 0.001$) and were correlated with DAS28 (rho = 0.64, 95%CI = 0.54–0.73, $p < 0.05$). The MBDA score (with CRP removed) was independently predictive of DAS28 in a model including CRP (MBDA: $p < 0.001$, CRP: $p = 0.001$). 56% of patients had good EULAR responses at 1 year. Change in MBDA score from baseline to 1 year distinguished these responders from non-responders (AUROC = 0.68, 95%CI 0.58–0.76, $p < 0.001$).

Conclusion: The MBDA score reflects clinical disease activity and changes in the score are associated with clinical response in Japanese patients initiating anti-TNF therapy. The contributions of MBDA biomarkers other than CRP are independently predictive of clinical disease activity in a model also including CRP. These results are similar to those observed in predominantly Caucasian populations, suggesting that the behavior of the MBDA biomarkers is generally consistent between Japanese and Caucasian ethnic groups.

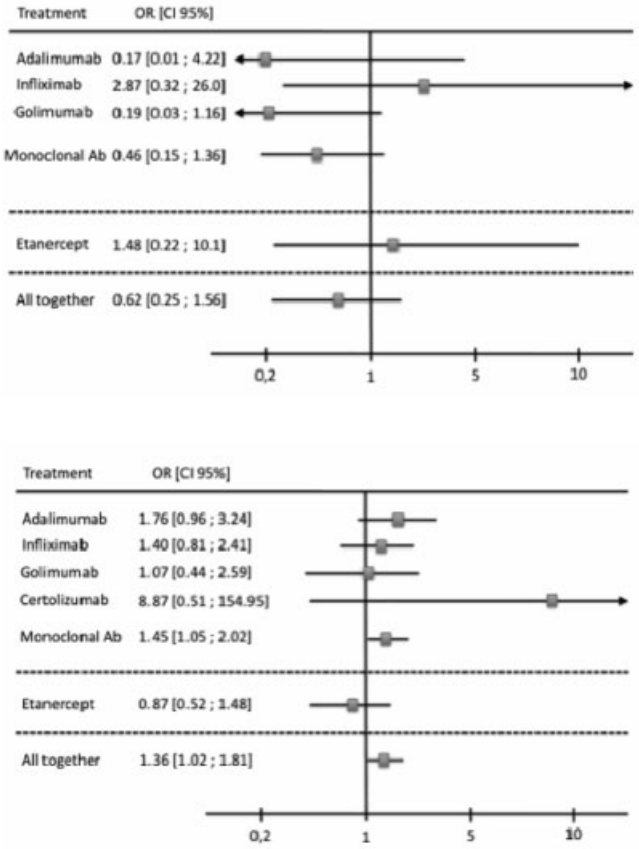
2245

The Risk of Serious Infection with and without Anti-TNF Therapy in Rheumatoid Arthritis and Ankylosing Spondylitis: A Meta-Analysis. Hélène Cormier, Thomas Barnetche and Thierry Schaeverbeke. Pellegrin Hospital, Bordeaux, France

Background/Purpose: In 2006, a meta-analysis of Bongartz et al. indicated that the rate of severe infections in rheumatoid arthritis is higher in patients treated with adalimumab and infliximab compared with patients treated with placebo. The difference was found to be not significant in ankylosing spondylitis with adalimumab, infliximab and etanercept (Fouque-Gombert et al.) Many randomized controlled trials have been published since 2006, included new anti-TNF: golimumab and certolizumab. Our objective was to assess the risk of infection with and without TNF blockers, with more power in RA and AS.

Methods: A systematic literature search was performed on Medline for randomized controlled trials from 1994 to December 2010. We included studies evaluating the five anti-TNF agents in rheumatoid arthritis and four anti-TNF agents in ankylosing spondylitis, using standard dosing regimens. The primary clinical outcome was the frequency of serious infections (infections requiring intravenous antibiotics and/or hospitalization). Statistical analyses were based on odds ratio for risk. We calculated a pooled odds ratio (Mantel-Haenszel methods) for serious infections in anti-TNF-treated patients vs placebo patients. We estimated effects for standard doses. Using these combined estimates, we calculated the absolute risk of serious infections for each product in RA and AS.

Results: 36 studies were included (9707 patients), 24 in RA (7702 patients) and 12 in AS (2005 patients). The frequency of serious infection is 2.2% (78/3487) in RA and 0.9% (7/707) in AS in patients not exposed to TNF blockers. The frequency of serious infection is 3% (125/4215) in RA and 0.6% (8/1298) in AS in patients exposed to TNF blockers. The pooled ratio for serious infection was 1.36 ($CI_{95\%}$= [1.02–1.81]) in RA and 0.62 ($CI_{95\%}$= [0.25–1.56]) in AS. Nevertheless, in RA, metanalysis of RCTs with etanercept compared with placebo shows that the increase in serious infections was not significant (OR=0.87; $CI_{95\%}$= [0.52–1.48]). In metanalysis of RCTs with monoclonal antibody therapy compared with placebo in RA, the difference is significant (OR=1.45; $CI_{95\%}$= [1.05–2.02], see Figure 1).



This difference of risk between etanercept and monoclonal antibodies is not observed with SA patients (see Figure 2).

Conclusion: There is an increased risk of serious infections in patients with RA treated by monoclonal antibodies. This difference is not significant in patients receiving etanercept. The risk of severe infections is low in patients with AS who receive placebo or TNF blockers, and no significant difference was demonstrated between these two groups.

2246

Rebalancing the IL-23/Th17 Axis and Regulatory T Cells in Arthritis by Depleting IRF5 $^{+}$ IL-23^{+} M1 Macrophages Using An Anti-Human DR5 Antibody. Jun Li[1], Hui-Chen Hsu[1], PingAr Yang[1], Qi Wu[1], Hao Li[1] and John D. Mountz[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham and Birmingham VAMC, Birmingham, AL

Background/Purpose: The abundance and activation of macrophages in the inflamed synovium significantly correlate with the severity of rheumatoid arthritis (RA). Macrophages are one of the major sources of IL-23 which potentially contributes to T cell subset plasticity including

Th17 cells and regulatory T cells (Tregs). Dysregulation of macrophages, the IL-23/Th17 axis, and Tregs have been implicated in the pathogenesis of RA. However, therapeutic strategies that can restore the homeostasis of these factors in RA are unknown. Death receptor 5 (DR5) is a pro-apoptotic protein, which mediates apoptosis upon cross-linking by a novel anti-human DR5 antibody, TRA-8. The purpose of this study was to investigate the immunomodulatory and therapeutic effects of TRA-8 by using macrophage targeted expression of a humanized DR5 transgenic (Tg) mouse with arthritis.

Methods: A humanized DR5 Tg mouse was generated using a 3kb mouse promoter/*Floxed* STOP/humanized mouse DR5 construct. Macrophages specific expression was achieved by crossing the DR5 Tg mice with lysozyme M-Cre mice. Arthritis was induced by intradermal injection of CII in CFA/IFA. TRA-8 (0.2 mg/mouse; I.V. weekly) was initiated on day 30 until mice were sacrificed 3 months post CII. Macrophages, Th17 and Tregs T cell subpopulations in the draining lymph nodes (LN) of DR5 Tg mice with and without TRA-8 treatment was analyzed by flow cytometry. *In vivo* joint macrophage activity was quantitated using an infrared cathespin imaging system. Expression of IRF5 and IL-23 protein in the $F4/80^+$ macrophages of draining LN was determined by 4-color imaging on Zeiss 710 confocal microscope. Clinical scoring and histological assessments of the joints were performed to evaluate the severity of arthritis.

Results: TRA-8 treatment resulted in a ~65% reduction of $CD11b^+$ macrophages in the draining LN of Tg^+ mice. Within the $CD11b^+$ cells, ~75% of the $Ly6C^+$ activated macrophages and ~90% of the $IL\text{-}23^+$ macrophages were eliminated by TRA-8 (2.4% to 0.23%, $P<0.05$). The depletion also leads to elevation of $CD4^+Foxp3^+$ Tregs (3.6% to 5.9%, $P<0.05$) and reduction of the $CD4^+IL\text{-}17^+$ Th17 cells (6.8% to 3.2%, $P<0.05$). Confocal imaging showed that there was a significant reduction of IL-23 and IRF5 expression (~85% and ~55% respectively) in macrophages after TRA-8 treatment, which suggested that TRA-8 specifically depleted M1 inflammatory macrophages. After TRA-8 treatment, joint histopathology showed a significantly decreased $MAC3^+$ macrophage infiltration, synovial hyperplasia, cartilage damage, and bone erosion (arthritis score: 9.8 versus 1.5, $P<0.01$). TRAP staining indicated that osteoclast formation in joints was inhibited by TRA-8 treatment. Cathepsin activity was significantly decreased (~62%) in DR5 Tg mice that received TRA-8 treatment. Neither systematic toxicities nor increased infection were found.

Conclusion: This study demonstrated that anti-human DR5 antibody (TRA-8) can specifically deplete the IL-23 secreting inflammatory M1 macrophages restoring the balance between Th17 and Tregs. Thus, anti-human DR5 antibody, currently in phase II cancer clinical trails, is a novel immunomodulatory agent and potentially effective for treatment of RA.

2247

Systematic Review and Network Meta-Analysis of Combination Therapy for Methotrexate-Experienced, Rheumatoid Arthritis Patients: Analysis of American College of Rheumatology Criteria Scores 20, 50 and 70.
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Background/Purpose: To determine the relative effectiveness of all UK licensed biological disease-modifying anti-rheumatic drugs (bDMARDs) for the treatment of rheumatoid arthritis (RA), in particular the concomitant use of bDMARDs with methotrexate (MTX) after failure of one or more DMARD.

Methods: A comprehensive systematic review was conducted to identify randomised controlled trials of bDMARDS for the treatment of RA in MTX experienced patients (defined as patients with an inadequate response to at least 1 cycle of MTX (6 months) or withdrawn from MTX due to adverse events). This analysis covers combination therapy (biological DMARD + other DMARD) in MTX experienced patients and:

Excludes studies in MTX naïve patients.

Excludes study arms evaluating biologic monotherapy, except if this results in only one remaining study arm for the meta-analysis (the biologic monotherapy arm is then included as the control for this study).

MTX monotherapy controls are included in the network and MTX is the reference treatment for the network meta-analysis (NMA).

Structured literature searches were conducted in MEDLINE, EMBASE, and the Cochrane Library, as well as hand searches of conference proceedings and reference lists. From this 13,649 citations were identified, of which 12,984 were excluded based on the title/abstract. After reviewing 665 full-text papers, there were 26 eligible studies that reported endpoints based on ACR criteria reported between 12 and 30 weeks. A network meta-analysis was conducted to estimate the relative effectiveness of treatments whilst preserving the randomised comparisons within each trial. A Bayesian network meta-analysis was conducted using a random-effects, logit model fitted to the binomial ACR20/50/70 trial data and was coded in WinBUGS. Direct probability statements are based on results from two chains of 20,000 samples.

Results: The table below summarise the network meta-analysis results for ACR 20/50/70.

Treatment	Log-OR vs MTX (95% CrI)	% pts achieving ACR20/50/70 (95% CrI)	Probability best
ACR70			
Etanercept 2×25mg/week + MTX	3.34 (1.11, 6.55)*	55.3% (12.8%, 97.3%)	62.59%
Certolizumab Pegol 200mg/2 weeks + MTX	2.61 (1.38, 3.96)*	41.4% (15.8%, 73.8%)	27.17%
Tocilizumab 8mg/kg/month + MTX	1.93 (0.76, 3.1)*	27.3% (9.2%, 54.5%)	5.2%
Golimumab 50mg/month + MTX	1.64 (0.26, 3.03)*	22.9% (5.8%, 52.6%)	3.48%
Abatacept 10mg/kg/month + MTX	1.49 (0.62, 2.41)*	19.3% (7.9%, 37.8%)	0.57%
Rituximab 2×1000mg + MTX	1.1 (−0.13, 2.39)	14.9% (4%, 36.9%)	0.51%
Adalimumab 40mg/2 weeks + MTX	1.34 (0.51, 2.19)*	17.1% (7%, 33.1%)	0.25%
Infliximab 3mg/kg/2 months + MTX	1.3 (0.49, 2.21)*	16.7% (6.9%, 33.2%)	0.24%
MTX	–	4.9% (3.2%, 7.1%)	0%
ACR50			
Etanercept 2×25mg/week + MTX	3.04 (1.65, 4.65)*	71.8% (40.9%, 93.6%)	77.79%
Certolizumab Pegol 200mg/2 weeks + MTX	2.29 (1.41, 3.22)*	57.1% (34.6%, 78.1%)	17.54%
Golimumab 50mg/month + MTX	1.65 (0.67, 2.63)*	42.1% (20.3%, 66.8%)	2.21%
Tocilizumab 8mg/kg/month + MTX	1.55 (0.65, 2.45)*	39.8% (19.9%, 62.6%)	1.27%
Rituximab 2×1000mg + MTX	1.42 (0.49, 2.38)*	37% (17.6%, 60.8%)	0.89%
Adalimumab 40mg/2 weeks + MTX	1.4 (0.77, 2.05)*	36.1% (21.5%, 53.2%)	0.15%
Infliximab 3mg/kg/2 months + MTX	1.34 (0.73, 1.97)*	34.8% (20.8%, 51.4%)	0.09%
Abatacept 10mg/kg/month + MTX	1.3 (0.65, 1.96)*	33.8% (19.5%, 51%)	0.08%
MTX	–	12.1% (9%, 15.9%)	0%
ACR20			
Etanercept 2×25mg/week + MTX	2.35 (1.34, 3.41)*	80.1% (60.6%, 92.8%)	44.94%
Certolizumab Pegol 200mg/2 weeks + MTX	2.42 (1.7, 3.16)*	81.7% (68.2%, 91.2%)	52.89%
Tocilizumab 8mg/kg/month + MTX	1.43 (0.68, 2.19)*	63% (43.9%, 79.7%)	0.89%
Golimumab 50mg/month + MTX	1.21 (0.38, 2.04)*	58% (36.7%, 77.1%)	0.45%
Abatacept 10mg/kg/month + MTX	1.16 (0.61, 1.71)*	56.9% (41.6%, 71.3%)	0.05%
Rituximab 2×1000mg + MTX	1.33 (0.56, 2.11)*	60.7% (40.8%, 78.4%)	0.61%
Adalimumab 40mg/2 weeks + MTX	1.26 (0.71, 1.81)*	59.3% (44.3%, 73.2%)	0.1%
Infliximab 3mg/kg/2 months + MTX	1.32 (0.81, 1.84)*	60.8% (46.5%, 73.9%)	0.08%
MTX	–	29.6% (23.7%, 36%)	0%

Abbreviations: CrI, credible interval (Bayesian probability interval); * $p<0.05$

Conclusion: In conclusion, in these selected studies, concomitant bDMARDs were significantly more effective than MTX alone in improving ACR 20/50/70 outcomes in MTX experienced patients. Out of the studies that met inclusion in our analysis, Etanercept had the highest probability of being the most effective concomitant bDMARD for achieving ACR 70 and 50 responses, whilst certolizumab pegol had the highest probability of achieving ACR 20 response.

2248

Fucosylation Inhibitor, 2-D-Gal, Promotes Human Synovial Fibroblast Apoptosis and Is a Potent Suppressor of Arthritis in a TNF-α Tg Mouse Model *In Vivo*.
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Background/Purpose: Apoptosis plays a pivotal role in the pathogenesis of rheumatoid arthritis (RA). Resistance to cell death leads to the hyperplasic synovium and progressive joint destruction. Fucosylation is one of the most important glycosylation processes and altered fucosylation is involved in regulation of cancer cell death. However, the role of fucosylation in RA has not been extensively studied. The purpose of this study is to determine if fucosylation is involved in regulation of apoptosis of RA synovial fibroblasts (RASF) and to determine the therapeutic effects of fucosylation inhibition.

Methods: Thirty RA and 16 osteoarthritis (OA) subjects were recruited in this study. The study was approved by IRB, UAB. Synovial fibroblasts were isolated from synovial tissues obtained at the time of joint replacement surgery and synovial fragments of synovial fluid. Fucosylation of RASFs was labeled using the Click-it metabolic labeling kit. Apoptosis was measured by ATPLite and visualized by MitoTracker Deep Red FM staining. Total RNA was isolated from the synovial fibroblasts using Trizol reagent. Real-time PCR was performed using a Bio-Rad IQ5 thermocycler. For mouse study, the human TNF-α Tg mouse was obtained from Taconic. An α1–2-Fucosyltransferase (FUT1) inhibi-

tor, 2-Deoxy-D-Galactose (2-D-Gal, 200mg/kg body weight, every 3 days), Etanercept (5mg/kg body weight, every week), and combined therapy was administered via I.P. initiated at the age of 12 weeks. Clinical scoring and histological assessments of the joints were performed.

Results: There was no significant difference of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (*Trail*), its receptors including *Dr4*, *Dr5*, *Dcr1*, *Dcr2* and regulators of TRAIL apoptosis $Flip_l$ and *ciap* between RASF to OASF. However, there is a higher expression level of α1–2-Fucosyltransferase (*Fut1*, P=0.016), α1–3/1–4-Fucosyltransferase (*Fut3*, P=0.018) and α1–3-Fucosyltransferase (*Fut6*, P=0.038), but not α1–6-Fucosyltransferase (*Fut8*, P=0.910) in RA compared to OA synovial tissues and fibroblasts. Interestingly, there is a very high correlation between *Tnf*α and *Fut1, Fut2* and *Fut3* (P=0.0001). *Fut1* also correlated with *IL-17a* (P=0.003) in synovial tissues. *Fut1* transcript abundance in synovial fibroblasts was highly correlated with the cell viability after TRAIL or anti-human DR5 treatment determined by ATPLite (R^2=0.81, P=0.00026), which was also confirmed by Click-it fucose labeling and MitoTracker confocal imaging. The human TNF-α Tg mice with established arthritis were treated with 2-D-Gal, Etanercept, and both for 4 weeks. 2-D-Gal treatment resulted in a significant ($p<0.05$) early decrease of joint swelling and sustained suppression of arthritis as determined by clinical scoring and histology, which was equivalent to that of Etanercept (P>0.05).

Conclusion: Our studies suggest that fucosylation is strongly correlated with TNF-α and IL-17, contributing to the inflammation and apoptosis resistance of RASF. Fucosylation inhibitor, 2-D-Gal, exhibited a compelling anti-arthritic effect which was equivalent to that observed with Etanercept. Fucosylation inhibition is a potential novel therapeutic strategy for RA.

2249

Infliximab Is Associated with Improvement in Arterial Stiffness in Patients with Early Rheumatoid Arthritis—a Randomized Trial. Lai Shan Tam[1], Qing Shang[1], Edmund K. Li[1], Ka Lai Lee[2], Ying Ying Leung[3], King Yee Ying[4], Cheuk-Wan Yim[5], Emily W. Kun[6], Alexander M. Leung[7], Martin Li[1], Tena K. Li[1], Tracy Y. Zhu[1], Ricky K. Chui[1], Lorraine Tseung[1], Shui Lian Yu[1], Woon Pang Kuan[8] and Cheuk-Man Yu[1]. [1]The Chinese University of Hong Kong, Hong Kong, Hong Kong, [2]Pamela Youde Nethersole Eastern Hospital, Hong Kong, Hong Kong, [3]North District Hospital, Hong Kong, Hong Kong, [4]Princess Margaret Hospital, Hong Kong, Hong Kong, [5]United Christian Hospital, Hong Kong, Hong Kong, [6]Tai Po Hospital, Hong Kong, Hong Kong, [7]Queen Elizabeth Hospital, Hong Kong, Hong Kong, [8]Hospital Selayang, Kuala Lumpur, Malaysia

Background/Purpose: Chronic inflammation is probably a driving force for premature atherosclerosis in Rheumatoid arthritis (RA). Whether effective suppression of inflammation could prevent progression of atherosclerosis would be worth studying. This study aimed to ascertain the efficacy of methotrexate (MTX) with infliximab compared with MTX alone in the prevention of atherosclerosis in patients with early RA.

Methods: A randomized, open-labeled study in which early RA patients (symptom onset < 2 years) with moderate to severe disease severity were treated with MTX with (Group 1, n=20) and without (Group 2, n=20) infliximab according to a standard treatment protocol for 12 months. Patients were assessed every 3 month. The main goal of treatment was to achieve remission (Disease activity score in 28 joints [DAS28] £ 2.6). Therapeutic regime was adjusted at each visit if the patient failed to achieve remission within 3 months according to the protocol. Progression of subclinical atherosclerosis will be measured by carotid ultrasound and arterial stiffness indexes as determined by pulse wave velocity (PWV) and augmentation index (AIx) at baseline and 12 months.

Results: Baseline clinical, demographic, cardiovascular risk factors and vascular assessment parameters (intima-media thickness [IMT], PWV and AIx) were similar between the 2 groups except Group 1 had a higher DAS28 score. At months 12, there was a significant decrease in PWV in Group 1 compared to baseline (15.3 $\pm$ 2.3 m/s versus 14.5 $\pm$ 2.6 m/s, $p<0.05$), while no significant changes were observed in Group 2 (14.6 $\pm$ 2.5 m/s versus 14.9 $\pm$ 3.2 m/s, p=0.341). Other vascular assessment parameters including the mean and maximum IMT and AIx remain unchanged in both groups. A higher proportion of patients in Group 1 achieved remission compared to Group 2 (4/20 [20%] versus 10/20 [50%], $p<0.05$). Most of the clinical and laboratory parameters of disease activities improved significantly in both groups compared to baseline, but there were no significant differences between the 2 groups at month 12. At month 12, the lipid profile was similar between the 2 groups although the fasting sugar level was significantly higher in Group 2 (4.9 $\pm$ 0.4 mmol/L 5.6 $\pm$ 0.6 mmol/L, $p<0.05$). Compared with baseline, the total cholesterol increased significantly in both groups and patients in Group 2 also had significant increase in LDL-cholesterol level. Fasting sugar and other lipid profile remained unchanged in both groups.

Conclusion: PWV, a marker of arterial stiffness, improved significantly in patients with early RA after 12-month treatment with MTX plus infliximab, compared to MTX alone, suggesting that effective suppression of inflammation using TNF-α inhibitors may prevent progression of atherosclerosis by improving vascular function in patients with early RA.

2250

Golimumab Use and Sustained Clinical Response in Patients with Active Rheumatoid Arthritis Previously Treated with Anti-Tumor Necrosis Factor Alpha Agents. Josef Smolen[1], Jonathan Kay[2], Robert Landewe[3], Eric L. Matteson[4], Norman B. Gaylis[5], J. Wollenhaupt[6], Frederick T. Murphy[7], O. Zamani[8], Yiying Zhou[9], Elizabeth C. Hsia[9] and Mittie K. Doyle[9]. [1]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [2]University of Massachusetts Medical School, Worcester, MA, [3]Academic Medical Center, Amsterdam, Netherlands, [4]Mayo Clinic, Rochester, MN, [5]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [6]Eilbeck Hospital, Hamburg, Germany, [7]Altoona Ctr for Clinical Research, Duncansville, PA, [8]Rheumazentrum Favoriten, Wien, Austria, [9]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, PA

Background/Purpose: To assess sustained clinical response in patients with active rheumatoid arthritis (RA) and previously treated with anti-TNF agent(s) who received treatment with golimumab (GLM) through wk100 in the GO-AFTER study.

Methods: GO-AFTER is a randomized, Phase 3, double-blind, PBO-controlled study of GLM in active RA ($\geq$4 tender and $\geq$ 4 swollen joints [TJC/SJC]) anti-TNFα experienced patients. Patients were randomized to PBO (Grp1), GLM 50 mg (Grp 2) or GLM 100 mg (Grp 3); injections were administered q4wks. Patients in Grps1 and 2 with <20% improvement in wk16 TJC/SJC escaped to GLM 50 mg and 100 mg, respectively. During the long-term extension, starting at wk24, all Grp1 patients crossed over to GLM 50 mg, Grp 2 patients continued GLM 50 mg or 100 mg per early escape status, and Grp 3 pts maintained dosing. After the wk24 database lock, patients were permitted to dose-escalate from GLM 50 mg to 100 mg at the investigator's discretion.

Results: From wk24 to wk100, ACR20 response was sustained in approximately 70% and 73% of patients in Grps 2 and 3, respectively and HAQ $\geq$0.25 improvement was sustained in approximately 81% and 75% of patients in Grps 2 and 3, respectively (Table). In addition, approximately 80% and 58% of pts in Grps 2 and 3, respectively achieved ACR 50 response and 71% and 55% of patients in Grps 2 and 3, respectively achieved ACR 70 response from wk24 through wk100, albeit with a smaller patient population. EULAR good and moderate response by DAS28 CRP was sustained in approximately 78% and 84% of patients in Grps 2 and 3 and by DAS28 ESR was found in 82% and 82% of patients in Grps 2 and 3, respectively from wk24 to wk100.

Table. Summary of results for sustained clinical response to golimumab from wk 24 through wk 100

	Group 1*	Group 2**	Group 3
No of randomized pts	150	147	148
ACR 20 response at wk 24 and at wk 100***,† ‡	–	38/54 (70.4)	40/55 (72.7)
ACR 50 response at wk 24 and at wk 100***,† ‡	–	20/25 (80.0)	15/26 (57.7)
ACR 70 response at wk 24 and at wk 100***,† ‡	–	10/14 (71.4)	6/11 (54.5)
EULAR response using CRP at wk 24 and at wk 100***,† ‡		55/71 (77.5)	62/74 (83.8)
EULAR response using ESR at wk 24 and at wk 100***,† ‡		55/67 (82.1)	63/77 (81.8)
HAQ improvement ≥0.25 at wk 24 and 100***,†‡	–	55/68 (80.9)	55/73 (75.3)

(n/N) %*Includes pts who early escaped at wk16 or crossed over at wk24 to GLM50 mg or dose escalated after the wk24 database lock to GLM100mg.**Includes pts who early escaped at wk16 or dose escalated after the wk24 database lock to GLM100mg.***excludes 16 pts from site 7465 (5 PBO, 6 GLM 50mg, 5 GLM 100mg) due to violations at the study site identified during the Sponsor's standard audit process. †observed data, ‡based on wk 24 responders who remained in the study at wk 100 for response rates at wk 100

Conclusion: Patients with active RA who received GLM 50mg or 100mg had sustained clinical response from wk24 through wk100.

2251

Methotrexate Every Day Is Safe and Effective As Weekly Dosage. Ricardo Moreno-Valdes[1], Marco Ulises Martinez-Martinez[1], Enrique Cuevas-Orta[1], Jorge Alcocer-Varela[2] and Carlos Abud-Mendoza[3]. [1]Hospital Central,, San Luis Potosí, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico city, Mexico, [3]Hospital Central y Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosi, Mexico

Background/Purpose: Most of rheumatologists, under established guides with poor scientific support, emphasized that methotrexate (MTX), in rheumatoid arthritis, should be given weekly at low doses in one day (OD), with apparent less liver toxicity and better tolerance than given every day (ED). Studies have described that C reactive protein levels were lower and more constant with ED dosage. Objective: To compare patients with rheumatoid arthritis (RA) treated with MTX under OD with patients with RA treated with ED scheme.

Methods: We analyzed the files of consecutive patients with diagnosis of rheumatoid arthritis according ACR criteria, seen in two Mexican hospital centers. Patients with at least 1 year of disease evolution, treated with stable doses of methotrexate at least in the last 12 weeks were evaluated. Patients were divided into two groups, 80 patients were treated with methotrexate weekly in one day once or in two times with 12 hours between doses (OD or group 1) and 100 patients with low doses every day (ED or group 2). None of our patients were under another DMARD and patients continued taking low doses of steroids (equivalent to 7.5 mg of prednisone or less) and NSAID. We analyzed demographic characteristics, ACR response and disease activity, laboratory tests and adverse events.

Results: We did not find statistical demographic differences in the analyzed groups. Methotrexate dosage was the double in the group 2 with administration every day (equivalent to 2.5 mg/d vs. 1.3 mg/d). Group 2 achieve a better ACR 20, 50 and 70 responses vs. group 1, 81% vs. 60%, 55% vs. 32% and 42% vs. 15% respectively. Hemoglobin levels increased in group 2, and remain in same levels in group 1, C reactive protein and erythrosedimentation rate did not show modifications in group 1 patients, but C reactive protein and ESR diminished 25% and 18.3% respectively. Patients had similar elevation of liver function tests (24 patients in each group, none with 3x or more). Relapses occurred in 47% of patients under OD (Group 1) and in 14% of those with ED therapy (Group 2) ($p<0.01$). Methotrexate therapy was stopped in 18% of group 1 and in 2% of group 2 because adverse events. We did not find any differences related with glucocorticoid and NSAID doses.

Conclusion: Methotrexate given every day is associated to similar or better efficacy than weekly doses. Lower acute toxicity is founded in every day administration of MTX than when is used weekly. We recognized that is convenient a long and large randomized clinical trial, to define or ratify if methotrexate to diary dosage is as safe and effective as when is used weekly.

2252

B Cell Biomarkers Allow Prediction of Improving Response on Repeat Cycles of rituximab. Sudipto Das[1], Edward M. Vital[2], Shouvik Dass[2], Maya H. Buch[3], Andrew Rawstron[2] and Paul Emery[4]. [1]NIHR Leeds Musculoskeletal Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [2]NIHR Leeds Biomedical Research Unit, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]University of Leeds, Leeds, United Kingdom, [4]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom

Background/Purpose: Rituximab is effective in rheumatoid arthritis but many patients do not achieve EULAR Good response. Previous studies have shown that repeat cycles of rituximab can improve responses in patients with non-response (NR) to the first cycle (C1). We therefore investigated the effect of repeat cycles of rituximab in C1 responders and the ability of known biomarkers to predict changing patterns of response.

Methods: 124 patients pooled from three clinical trials were treated with 2 × 1000mg of rituximab at baseline and then, in initial responders, on clinical relapse. DAS28 and EULAR response were calculated at baseline and 6 months after each cycle, compared to the original baseline. B cell naïve, memory and plasmablast subsets were measured by high flow assay as previously described.

Results: As previously reported, patients with NR after C1 were retreated at 6mo and most responded. Patients with EULAR MOD or GOOD in C1 were retreated following clinical relapse. Overall responses were better in C1 (see table).

Cycle 1 response	DAS28 at baseline (SD)	DAS28 after C1 (SD)	DAS28 after C2 (SD)	P (DAS28 after C1 vs. after C2)	EULAR response after C2		
					Non	Mod	Good
Moderate (n=44)	5.95 (1.02)	4.10 (0.77)	3.68 (1.08)	0.013	11.4%	54.5%	34.1%
Good (n=30)	5.53 (0.92)	2.31 (0.53)	2.71 (1.38)	0.118	16.7%	13.3%	70.0%

In MOD, B cell numbers were significantly lower at weeks 2–14 compared to C1, but in GOOD no difference was observed between cycles. Of 78 patients with positive RF at baseline, 28% became negative after C1 (seroconversion), and of these 90% remained positive after C2, although the titre was signicantly lower. There was no association between RF and B cell subsets at baseline, but seroconversion was associated with significantly lower B cell numbers at weeks 2–26.

Seroconversion was not associated with response in C1, but was associated with improving response in C2. In patients with C1-MOD and positive RF at baseline, 11/33 had seroconversion in C1, of whom only 1(9%) improved to GOOD in C2. Of 22/33 without seroconversion, 9(41%) improved to GOOD in C2 ($p=0.012$).

We compared DAS28 components, HAQ, RF and B cell subsets between patients with C1-GOOD who maintained (GOOD) or worsened (NR/MOD) response in C2. Patients with worsening response had lower baseline CRP ($p=0.002$) and higher memory B cells at repopulation ($p=0.094$) with no difference in severity of flare at relapse or time to retreatment.

Conclusion: Patients with potential for improved response on retreatment with rituximab may be identified by persistent RF. Greater repopulation of memory B cells before retreatment was associated with loss of response in C2.

2253

Pulmonary Adverse Events in a Cohort of Patients with Rheumatoid Arthritis Under Tnfa Blockers. Juan Antonio Martinez-Lopez[1], Fredeswinda Romero[1], Sandra Bermudez[1], Jorge J. González López[1], María Pérez Ferro[1], Sheila Recuero[1], Gema Díaz Moya[1], Maria A. Contreras[1], Gabriel Herrero-Beaumont[2] and Olga Sanchez-Pernaute[1]. [1]Jiménez Díaz Foundation University Hospital, Madrid, Spain, [2]Jiménez Diaz Foundation University Hospital, Madrid, Spain

Background/Purpose: Post-marketing surveillance of TNF blockers has confirmed an overall good safety profile. However, there have been increasing reports of either de novo developed or progression of pre-existent intersticial lung disease (ILD) in patients with rheumatoid arthritis (RA) treated with TNF blockers. They raise the concern of whether these therapies should be avoided in specific subsets of patients. Our aim was to analyse the occurrence of pulmonary events in our cohort of RA patients treated with TNF blockers.

Methods: All patients with RA from our Rheumatology clinics started on TNF blockers before April 2010 were included. A retrospective study of their clinical record was done.

Results: We evaluated 106 patients, with a total exposure to TNF blockers of 369 patient-year (median: 3.1 years). 17 patients developed a total of 31 relevant pulmonary events. Pulmonary events were classified as lung infections (18 cases), acute non-infectious pneumonitis (2 cases), ILD with fibrosis (5 cases), bronchospasm (1 case) and chronic obstructive lung disease (5 cases). The outcome was permanent disease in 9 patients and there was 1 death. In 6 cases, pulmonary symptoms led to discontinuation of TNF therapy. Both the disease duration (18 years, range 3–48) and the exposure to TNF blockers (74.6 patient-year, median: 3.8 years) were longer in the group suffering pulmonary events. Pre-existent lung disease was identified as a risk factor for the development of pulmonary events (RR 2.36, CI 0.79 – 6.89). The percentage of patients exposed to methotrexate was similar in both groups (88% compared to 81%, respectively). In the same way, no differences were found in the number of DMARD used, erosive arthritis, positive autoantibodies and smoking. The subgroup with pulmonary events had a higher rate of extra-articular manifestations (41% vs 24%) and Sjögren syndrome (41% vs 28%).

Conclusion: In our cohort, pulmonary events were a major cause of anti-TNF discontinuation. The pre-existence of lung disease and longstanding RA were the major risk factors for the occurrence of pulmonary complications. Since pulmonary processes can remain subclinical in early stages, we underline the importance of specifically seeking for respiratory lung diseases prior to the initiation of anti-TNF therapies in patients with RA.

2254

Electrocardiographic Abnormalities in a Large Systemic Lupus Erythematosus Inception Cohort. Josiane Bourré-Tessier[1], Murray B. Urowitz[2], Mori J. Krantz[3], Lawrence Joseph[4], SLICC investigators[5] and Christian A. Pineau[6]. [1]McGill University Health Center, Montréal, QC, [2]Toronto Western Hospital and University of Toronto, Toronto, ON, [3]University of Colorado, Denver, CO, [4]McGill University Health Centre, Montreal, QC, [5]Toronto, [6]McGill Univ Health Center, Montreal, QC

Background/Purpose: Cardiovascular involvement is common in systemic lupus erythematosus (SLE) and can cause considerable morbidity and mortality. Myocardial ischemia, rhythm disturbances, and repolarization abnormalities including QT prolongation and increased QT dispersion (QTd) may be associated with an increased risk of sudden death. This study aimed to determine the early prevalence of electrocardiographic abnormalities in a large inception cohort of SLE patients.

Methods: We studied adult patients from 23 centers participating in the Systemic Lupus International Collaborating Clinics (SLICC) Prospective Inception Cohort for Atherosclerosis. Patients are followed prospectively and undergo a yearly assessment where demographics, disease activity (SLEDAI), disease damage (SLICC/ACR DI), laboratory data and 12-lead resting ECGs are collected. Baseline ECGs were manually interpreted by board certified cardiologists. QTd was defined as the difference between maximal and minimal QT-intervals. Proportions with QTc-prolongation crossing categorical regulatory thresholds (International Conference on Harmonization) and increased QTd (defined as $>$ 40 ms) were assessed.

Results: Of 785 patients evaluated at study entry, 744 had an interpretable ECG. At the time of their ECG, mean (SD) age was 35.6 years (13.8), 88.4% were women, and mean disease duration was 10.5 months (14.4). Mean SLEDAI was 5.41 (5.60) and mean SLICC/ACR DI was 0.50 (1.00). ST-segment changes were frequent: 30.9% were nonspecific and 3.5% had changes compatible with acute or chronic myocardial infarction. QTc prolongation, defined as $\geq$ 440 ms, was observed in 15.4%, while a QTc $\geq$ 480 ms was found in 1.1%. Mean (SD) QTd was 34.2 ms (14.7) and increased QTd, defined as greater than 40 ms, was found in 20.2%. A total of 5.4% manifested abnormalities compatible with left ventricular hypertrophy and 0.1% with right ventricular hypertrophy. Ventricular conduction disturbances were seen in a total of 4.3% of the patients. Other findings included supraventricular arrhythmias (1.5%; the majority were atrial flutter), premature ventricular contractions (1.5%), and atrioventricular heart block (0.7%).

Conclusion: Electrocardiographic abnormalities were frequent in this large SLE inception cohort. Despite a short disease duration, a significant proportion of patients manifested repolarization abnormalities possibly representing early signs of cardiac involvement. Performing ECGs in SLE patients may identify patients at a potentially higher cardiovascular risk, though additional studies assessing the utility of this strategy are needed.

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Initial Results for the LFA Collective Data Analysis Initiative (LFA CDAI): How Do Subjects From Lupus Clinical Trials Randomized to Standard of Care Respond Over Time? Kenneth C. Kalunian[1], Mimi Kim[2], Leslie M. Hanrahan[3], Jean-Claude P. Becker[4], Sabine Bongardt[5], Paul Brunetta[6], David Close[7], Jorn Drappa[7], Richard Furie[8], Bevra H. Hahn[9], Matthew Linnik[10], Jane E. Salmon[11], Neil Solomons[12] and Joan T. Merrill[13]. [1]UCSD School of Medicine, La Jolla, CA, [2]Albert Einstein College of Medicine, Bronx, NY, [3]Lupus Foundation of America, Washington, DC, [4]Becker Clinical Reearch Consulting LLC, New York, NY, [5]UCB Biosciences, [6]Genentech, So San Francisco, CA, [7]MedImmune Inc., [8]North Shore-LIJ Health System, Lake Success, NY, [9]UCLA David Geffen School of Medicine, Los Angeles, CA, [10]Lilly Research Laboratories, [11]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [12]Vifor Pharma, [13]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: In the past two decades, more than a dozen investigational products have entered phase II/III clinical trials for lupus and failed despite adequate proof of concept studies in animal models and in vitro human studies. The Lupus Foundation of America (LFA) formed the LFA Collective Data Analysis Initiative (CDAI) to better understand these failures. Working and steering committees were formed, comprised of academic and industry lupus experts and an independent biostatistician with lupus expertise. Industry partners contributed blinded and deidentified data from their clinical trials. The first LFA CDAI project was to address the hypothesis that in the course of clinical trials in lupus, background medications may mask the effect of an investigational agent. To understand response rates of different background medications, pooled data from 5 industry sponsored clinical trials in lupus were utilized.

Methods: Data from the standard of care arms of 5 industry sponsored clinical trials (Total N=620) were combined to estimate response rates by background medication at different time points during follow up. Response was defined as an improvement by at least 1 step in any BILAG A and B at baseline without any new BILAG A. Background medications were classified into the following five groups: azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), cyclophosphamide (IVC), and other (including treatments such as antimalarials alone); corticosteroids usage was calculated for each treatment group. Separate subgroup analyses were also performed of nephritis patients only. The chi-square test was used to evaluate the null hypothesis that response rates are equivalent across treatment groups.

Results: Estimated response rates across background treatment groups ranged from 34%–65% at 12 weeks (p=0.06) and 28%–52% at 52 weeks (p=0.05). At both time points, the lowest response rate occurred in the MTX group. Mean steroid doses were 12.3–23.5mg at 12 weeks and 8.2–13.3 mg at 52 weeks and were significantly lower in responders compared to non-responders at 52 weeks (p=0.01) but not at 12 weeks (p=0.68). When the lupus nephritis trials were analyzed separately, using a more stringent response definition that required improvement in renal BILAG scores to C or better, response rates were 21% on IVC and 26% on MMF at 12 weeks and 34% on IVC and 42% on MMF at 24 weeks, the maximum duration of follow-up.

Conclusion: Lupus patients enrolled in clinical trials and randomized to standard of care arms are a proxy for real-life experiences of lupus patients who receive these standard therapies. The results of these analyses therefore provide a basis both for expected outcomes of lupus patients receiving standard of care in clinical practice and for lupus subjects in clinical trials randomized to these therapies. In addition, these data may be useful for investigators designing future clinical trials.

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Incidence and Standardized Incidence Ratio (SIR) of Suicide in Southern Chinese Patients with Rheumatic Diseases in Hong Kong, China: 1999–2010. Chi Chiu Mok[1], Raymond Kwok[2], Ling Yin Ho[3] and Paul Yip[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]University of Hong Kong, Hong Kong, Hong Kong, [3]Tuen Mun Hospital, Hong Kong SAR, Hong Kong

Background/Purpose: Suicide is one of the most devastating complications of chronic medical illnesses, including rheumatological disorders. We studied the absolute incidence of suicide and its standardized incidence ratio (SIR) in six rheumatic diseases in Hong Kong as compared to the general population.

Methods: Patients with the diagnostic codes of systemic lupus erythematosus(SLE), rheumatoid arthritis(RA), ankylosing spondylitis(AS), psoriatic arthritis(PSA), systemic vasculitides(SV) and systemic sclerosis(SSc) registered in 37 public hospitals between 1999 and 2010 were identified from the hospital registry database. Patients who died of suicidal attempts within the same period were also retrieved. The SIRs were calculated by comparing the suicidal rate of patients with each disease with that of the general population, adjusted for age, with the 95% confidence intervals obtained by the exact Poisson method.

Results: In 2010, data on 10996 RA, 6296 SLE, 3034 AS, 2108 SV, 1192 PSA and 569 SSc patients were available in our registry. Between 1999 and 2010, 25 patients with these diseases committed suicide and died (15 SLE, 5 RA, 3 AS, 1 PSA, 1 SV and 0 SSc patients). There were 19 women and 6 men. The mean age of these patients at the time of suicidal acts was 48.8 $\pm$16.3 years. The methods of suicide were: jump from height (60%), overdose of medications (20%); hanging or strangulation (8%); drowning (4%); and uncertain method (8%). Three patients (12%) had documented history of suicidal attempts in the past. Of patients who committed suicide by overdose of medications, two were SLE patients who died of overdosage of hydroxychloroquine. The incidence of suicide per 100,000 patients was 31.6 for SLE, 17.1 for AS, 16.7 for PSA, 7.5 for SV and 6.9 for RA. The age-adjusted SIRs in female patients were 3.13 (95%CI [1.75–5.16]) in SLE, 2.72 (95%CI [0.07–15.2] in AS and 0.34 (95%CI [0.07–1.00]) in RA. The age-adjusted SIRs in male patients were 0.59 (95%CI [0.07–2.14]) in AS,

0.50 (95%CI [0.06–1.82]) in RA, 1.29 (95%CI [0.03–7.21]) in PSA and 0.82 (95%CI [0.02–4.56]) in SV.

Conclusion: Among the rheumatic diseases studied, only female patients with SLE have significantly increased relative risk of suicide by 2-fold as compared to the general population. More attention should be paid to mood problems in SLE patients and screening for depression should be performed during clinical visits.

2257

Support Vector Machines Classification of Texture Parameters of White Matter Lesions in Systemic Lupus Erythematosus. Possible Mechanism to Distinguish Between Demyelination and Ischemia. Aline Lapa[1], Mariana P. Bento[1], Letcia Rittner[1], Gabriela Castellano[1], Heloisa Ruocco[2], Benito Damasceno[3], Lilian Costallat[4], Roberto Lotufo[4], Fernando Cendes[1] and Simone Appenzeller[5]. [1]State University of Campinas, Campinas, Brazil, [2]Medical Faculty of Jundiai, Campinas, Brazil, [3]Medical Faculty of Jundiai, Campinas, United Kingdom, [4]State University of Campinas, Campinas, United Kingdom, [5]State University of Campinas, São Paulo, Brazil

Background/Purpose: Texture analysis (TA) is a branch of image processing which seeks to reduce image information by extracting texture descriptors from the image. White matter hyperintensities (WMH) are frequently observed in systemic lupus erythematosus (SLE), however the etiology is still unknown. Ischemic and demyelination have been proposed as possible etiologies. Support vector machines (SVM) are a group of supervised learning methods that can be applied to classification or regression. SVM performs classification by constructing a set of hyperplanes in a high dimensional space that optimally separates the data into different categories. A classification task usually involves separating data into training and testing sets. The goal of SVM is to produce a model based on the training data which predicts the target values of the test data given only the test data attributes. Objective: To produce a training model that accurately differentiates WMH of multiple sclerosis (MS) and stroke from normal white matter. To determine attributes that best characterizes WMH in SLE and to analyze clinical and laboratory features that may differentiate SLE patients with demyelination from ischemic WMH.

Methods: TA was applied to axial T2-weighted magnetic resonance images (MRI) of 30 SLE, 30 MS, and 10 stroke patients and 30 normal controls, all age and sex-matched. The TA approach used was based on the Gray Level Co-occurrence Matrices (GLCM). The WMH were manually segmented for each subject, classified in periventricular and subcortical WMH and 256 texture parameters were computed for each lesion. A SVM classifier was developed based on texture features of normal white matter and WMH in MS and stroke patients. The classifier was then used to classify WMH in SLE patients. Nature of the classified WMH, demographic, clinical and laboratory features were included in a regression model to determine which variables could help to predict the nature of WMH in clinical practice.

Results: We achieve a accuracy rate of 0.9 on a database of 97 ROIs to training procedure, and 41 ROIs to testing procedure. Of the 24 periventricular WMH, 18 (75%) were classified as ischemic and 6 (25%) as demyelination. Of 44 subcortical lesions, 26 (59%) were classified as ischemic and 18 (41%) as demyelination. Age (odds ratio [OR] 1.7, 95% confidence interval [95% CI] 1.58–6.72), hypertension (OR=2.6; 95%CI 1.9–5.3) and positive antiphospholipid antibodies (aPL) (OR=1.9; 95%CI 1.2–7.3) were variables associated with stroke, whereas shorter disease duration (OR=3.1; 95%CI 2.2–7.5) and new onset of neurologic symptoms (OR=1.8; 95%CI 1.2–3.5) were associated with demyelination.

Conclusion: Although 75% of WMH were classified as ischemic in nature, we identified approximately 25% of demyelinating WMH in SLE. SMV of TA is a useful method to help to determine etiology of WMH in SLE. Age, hypertension and aPL were variables associated with ischemic; shorter disease duration and new onset neurologic symptoms were associated with demyelinating lesions in this cohort.

2258

sIL-7R Is a Novel Marker of Disease Activity in Systemic Lupus Erythematosus Nephritis, Which Reflects Target Organ Involvement. Valérie Badot[1], Geneviève Depresseux[2], Frédéric. A. Houssiau[2] and Bernard Lauwerys[2]. [1]CHU-Brugmann & Université catholique de Louvain, Brussels, Belgium, [2]Université catholique de Louvain, Brussels, Belgium

Background/Purpose: The soluble form of the interleukin-7 receptor (sIL-7R) results from an alternative splicing of the full-length IL-7R mRNA. It is produced by fibroblasts, and, to a lesser extent, CD4 T cells, after stimulation with pro-inflammatory cytokines (TNF-alpha, IL-1beta alone or in combination with IL-17). We also previously demonstrated that sIL-7R serum levels are higher in rheumatoid arthritis patients compared to controls. We wondered whether sIL-7R production is dysregulated in systemic lupus erythematosus (SLE).

Methods: Serum sIL-7R titers were measured by sandwich ELISA, and transcriptomic studies were performed in PBMC from SLE patients and controls. IL-7R immunostaining was performed on frozen kidney sections from SLE nephritis patients.

Results: sIL-7R titers are significantly higher in the sera of patients with SLE nephritis (n = 17) compared to controls (n = 75) (mean SLE +/− SEM: 3,646.6 +/− 793.9 pmol/ml; mean controls +/− SEM: 688.1 +/− 60.5 pmol/ml; $p < 0.0001$). sIL-7R serum concentrations correlate significantly with SLEDAI scores ($r = 0.53$, $p < 0.05$), and significantly decrease under therapy, in parallel with disease activity scores (mean +/− SEM sIL-7R from 3,897.7 +/− 1,050.1 pmol/ml down to 967.4 +/− 129.0 pmol:ml, $p < 0.05$; mean +/− SEM SLEDAI from 22.9 +/− 2.3 down to 6.9 +/− 1.4, $p < 0.0001$ in 10 patients with follow-up measurements).

Strikingly, IL-7R gene expression is lower in SLE PBMC compared to controls, which indicates that the source of elevated serum sIL-7R titers is not to be found in SLE circulating cells. By contrast, we found a positive perivascular IL-7R immunostaining signal in kidney biopsies from patients with SLE nephritis.

Conclusion: sIL-7R is a novel marker of SLE disease activity. By opposition to conventional disease activity markers, sIL-7R is not produced by circulating cells, but by the target organ in SLE nephritis.

2259

High-Sensitivity C-Reactive Protein As An Independent Risk Factor for Coronary Artery Disease in Systemic Lupus Erythematosus. Mandana Nikpour[1], Dafna D. Gladman[2], Dominique Ibanez[3], Paula Harvey[4] and Murray B. Urowitz[3]. [1]The University of Melbourne, Fitzroy, Australia, [2]Toronto Western Hospital, University of Toronto, Toronto, ON, [3]Toronto Western Hospital and University of Toronto, Toronto, ON, [4]Women's College Hospital, Toronto, ON

Background/Purpose: In the general population, high sensitivity C-reactive protein (hsCRP), a non-specific marker of inflammation, is a predictor of coronary artery disease (CAD). Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with accelerated CAD. In SLE, hsCRP varies markedly over time due to changes in disease activity and treatment, casting doubt over its usefulness as marker of CAD in this patient population. We sought to determine whether hsCRP is an independent predictor of CAD among patients with SLE.

Methods: In a prospective cohort design, patients with serial measurements of hsCRP were followed for the occurrence of CAD events including angina and myocardial infarction (MI), which were defined based on a combination of clinical features, electrocardiographic and enzyme changes. Time-dependent proportional hazards regression models were used to determine the ability of hsCRP to predict CAD

Results: Four hundred and seventy two patients comprising 2,523 hsCRP measurements were included. HsCRP was significantly predictive of the twenty CAD events observed over a mean follow-up of 3.8 ± 5.4 years. The hazard ratio (HR) for each quartile increase in hsCRP level was 1.57, 95% confidence interval (CI): 1.02, 2.43, p=0.04. This association was independent of the Framingham ten-year risk score (HR 1.15, 95% CI: 1.05, 1.27, p=0.003) and time-adjusted SLE disease activity score (AMS; HR 1.12, 95% CI: 1.02, 1.22, p=0.01), which were also associated with CAD. Cut-point analysis using regression modeling revealed that an hsCRP level of 1.6 mg/L or greater was associated with significantly increased CAD risk.

Conclusion: Despite marked variability over time, even among patients with SLE, hsCRP level is significantly predictive of CAD, independently of the Framingham risk score and SLE disease activity score. This finding highlights the pivotal role of inflammation in the development of CAD in SLE, and makes a case for measuring hsCRP in routine CAD risk assessment of patients with SLE. SLE patients with hsCRP level ³ 1.6 mg/L are at significantly increased risk of CAD and represent a group in whom measures to prevent CAD events may include the use of statins.

2260

Effect of Raloxifene, a Selective Estrogen Receptor Modulator, on Disease Activity, Flare and Vascular Biomarkers in Patients with Systemic Lupus Erythematosus (SLE): A 12-Month Double-Blinded Randomized Controlled Trial. Chi Chiu Mok[1], King Yee Ying[2] and Kwok Man Ma[1]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Princess Margaret Hospital, Hong Kong, Hong Kong

Background/Purpose: To examine the effect of raloxifene on disease activity, flares, traditional risk factors and bone mineral density (BMD) in patients with SLE.

Methods: Subgroup data of postmenopausal female SLE patients who participated in a 12-month double-blinded randomized controlled trial of the effect of raloxifene on bone turnover and BMD in glucocorticoid-induced osteoporosis were extracted. Patients were randomized to receive either raloxifene (60mg/day) or matched placebo (one tab/day) on top of calcium and vitamin D. Disease activity was assessed by the SELENA-SLEDAI and physicans' global assessment (PGA; 0–3) every 3 months. Lupus flares were assessed by the SELENA flare instrument. The SLEDAI and PGA area under the curve (AUC) over 12 months and number of flares was compared between the raloxifene and placebo groups. In addition, the effect of raloxifene on homocysteine, soluble thrombomodulin (sTM), interleukin(IL)-6, high-sensitivity C-reactive protein (hsCRP) level and changes in traditional atherosclerotic risk factors was also evaluated.

Results: Sixty-two patients were studied (mean age 52.5±6.7 years; disease duration 9.3±7.6 years). The mean duration of menopause was 7.2±6.6 years. The mean duration of prednisolone treatment was 87±68 months and mean daily dose was 6.8±5.6mg. The mean SLEDAI score at entry was 1.8±2.3 and only 5(8%) patients had SLEDAI score of >=6. Thirty patients were randomized to raloxifene and thirty-two were randomized to placebo. Basic clinical characteristics were similar between the two groups. After 12 months, a significant gain in BMD at the lumbar spine was observed in raloxifene-treated patients (0.883±0.125 to 0.897±0.116g/cm^2; +1.6%,p=0.02) but not in the placebo group. Bone resorption and formation markers (urine DPD, P1NP, CTX and osteocalcin) decreased significantly in the raloxifene but not in the placebo group. The SLEDAI AUC (18.7±23 in raloxifene vs 20.3±19 in placebo; p=0.76) and PGA (2.2±3.5 vs 2.3±2.6; p=0.94) scores over 12 months were not significantly different between the two groups of patients. There were 3 episodes of mild / moderate flares of SLE (33% musculoskeletal, 33% dermatological) in the raloxifene group, compared to 9 episodes of mild / moderate flares (27% musculoskeletal, 45% dermatological) in the placebo group (p=0.11). The total and LDL cholesterol level of placebo-treated patients increased significantly but there were no significant changes in the raloxifene group. The systolic and diastolic blood pressure values did not change significantly in both groups of patients. The homocysteine level showed a trend of decrease in raloxifene-treated patients, but no statistically significant changes in hsCRP levels in both groups of patients were observed. Levels of IL-6 and sTM did not change significantly in either the raloxifene or placebo groups of patients. Treatment was well tolerated, with no thromboembolic complications reported.

Conclusion: Raloxifene is safe and well tolerated in stable SLE patients with no hypercoagulability factors. Raloxifene significantly improves lumbar spine BMD but does not cause an increase in lupus activity or flares.

2261

Transcriptional Patterns in Whole Blood Diagnostic of Systemic Lupus Erythematosus. Tracy Costello and Cole Harris. Exagen Diagnostics, Houston, TX

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease of heterogeneous presentation. As SLE can present with a wide range of symptoms, severity, and organ involvement, diagnosis can be difficult. Current laboratory tests suffer either from poor specificity or sensitivity. Improved laboratory tests are needed for earlier and more accurate diagnosis.

Methods: With the aim of providing a basis for development of improved tests, we sought to identify diagnostic gene expression patterns in whole blood from publicly available data. Two relevant datasets in the GEO repository (http://www.ncbi.nlm.nih.gov/geo) are described in the table below. Our analysis employed proprietary data mining software to identify diagnostic expression patterns in small subsets of genes. As shown in the table, a portion of GSE22098 data was used for identifying these patterns (training) and the balance for blinded validation (test). GSE8650 data was used primarily to confirm the results. Regression analyses investigated the relationship between the expression of the confirmed genes and SLEDAI in the SLE patients in GSE8650.

Results: In the pattern identification phase, 10,000 significant ($p<.05$ Bonferroni-corrected) 3-gene combinations were identified. A total of 5191 gene probes appear at least once in these combinations, however relatively few appear frequently. We identified the set of 38 gene probes, representing 35 unique genes, that appeared in more than 1% of the patterns. The combination utilizing the three most frequent genes (RH3HDM4, IFI44L, IFI27) achieved 95% sensitivity and 98% specificity in the training data, and 92% sensitivity and 100% specificity in the test data.

Across all 3-gene combinations from the 38-probe set, the means (range) of sensitivity and specificity in the training data were 96% (92–100) and 97% (90–100) respectively. In the blinded data, mean (range) sensitivity and specificity were 90% (76–96) and 97% (84–100).

In distinct analyses of GSE8650, we identified gene sets consisting of those genes frequently represented in significantly diagnostic 3-gene combinations for both SLE vs control and SLE vs SoJIA. Five genes appeared in frequent gene lists from GSE22098 and GSE8650 analyses: HERC6, LY6E, IFI44, IFI44L, and EPSTI1.

Univariately, all five genes were significantly associated with SLEDAI. In a multivariate linear regression analysis, we found that HERC6, LY6E, and EPSTI1 provide significant independent information.

GEO ID	Gene Probes	Controls (train/test)	SLE (train/test)	SoJIA (train/test)	SLEDAI
GSE22098	N=48803 Illumina	164 (115/49)	110 (85/25)	0	No
GSE8650	N=44928 Affymetrix	21 (14/7)	38 (26/12)	58 (39/19)	Yes

Conclusion: If validated in subsequent studies, patterns of expression in the listed genes can provide a basis for development of improved SLE diagnostics.

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Adjusted Framingham Risk Factor Scoring for Systemic Lupus Erythematosus. Murray B. Urowitz[1], Dominique Ibanez[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: There is a high prevalence of premature atherosclerosis among patients with SLE, with a risk 50 times of the general population. The traditional Framingham risk factor underestimates the risk for coronary artery disease (CAD) in patients with SLE. There has been discussion as to whether SLE should be considered equivalent to diabetes and therefore automatically be high risk, or whether some other adjustment to the scoring system is more appropriate. The aim of this study was to determine whether an adjustment to the Framingham risk factor scoring (FRS) algorithm would more accurate reflect the higher prevalence of CAD among patients with SLE.

Methods: Patients with SLE are followed regularly according to a standard protocol in an observational cohort study. Patients were included from the first visit where all the data required to calculate the FRS were available. Only patients without previous CAD or diabetes were included. Several modifications to the Framingham risk score were considered: 1) increasing the value of specific item (e.g. age, cholesterol values), 2) adding SLE as its own item with variable weights, or 3) enhancing the value of all items equally by multiplying each by 2. The latter was considered most appropriate since it retains the relative contribution of each of the various components. FRS was calculated for all patients with this modification. Patients with subsequent CAD were compared to those without CAD using the original and the modification. Descriptive statistics were used to characterize the patient population. T-tests were evaluated to compare the original and modified FRS between patients with and without subsequent CAD.

Results: 858 patients were included. There were 775 (90.3%) women, age at visit 38.2 ± 14, disease duration 9.5 ± 8.8. Total cholesterol 4.9 ± 1.4, HDL 1.5 ± 0.5, systolic blood pressure 119.8 ± 17.5 diastolic 74.9 ± 10.7, smokers 116 (13.5%). The overall FRS 10 year risk was 2.3 ± 3.6%. Table shows the calculated classic FRS and the modified FRS for the whole group.

	Classic FRS		Modified FRS	
Risk Category	**Number**	**%**	**Number**	**%**
Very low risk	806	93.9	678	79.0
Low risk	37	4.3	63	7.3
Moderate risk	11	1.3	23	2.7
High risk	4	0.5	94	11.0
Mod + high	**15**	**1.7**	**117**	**13.6**

Of the 858 patients 38 subsequently developed CAD and 787 did not. Of those who developed CAD the Classic FRS classified only 7.8% in the Moderate/High risk group and 1.4% in those without CAD. Using the modified FRS, this increased to 42.1% and 12.3% in patients with and without CAD respectively. The 10-year risk using the Classic FRS was 6.4 ± 7.2 in patients with CAD compared to 1.9 ± 3.5 in patients without CAD (p=0.0006). Using the modified FRS, the 10 year risk was 14.6 ± 14.9 for patients with CAD compared to 4.7 ± 9.0 for those without subsequent CAD (p=0.0003)

Conclusion: The modified Framingham risk score where each item is multiplied by 2 more accurately identifies patients at Moderate/High Risk of CAD (13.6%) and more accurately predicted subsequent coronary artery disease (Score of 14.6 vs 4.7) Therefore the modified Framingham risk score should be used to identify SLE patients for more intensive risk factor modification.

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Damage Accrual in Patients with Systemic Lupus Erythematosus Is Associated with Endothelial Function Detriment: A Prospective Cohort Study. Chiara Tani[1], R. Bruno[1], Anna d'Ascanio[2], Lorenzo Ghiadoni[1], Y. Plantinga[1], Rossella Neri[1], Antonio Tavoni[3], Linda Carli[1], Stefano Taddei[1], Stefano Bombardieri[2] and Marta Mosca[1]. [1]University of Pisa, Pisa, Italy, [2]Rheumatology Unit, Pisa, Italy, [3]AOUP, Pisa, Italy

Background/Purpose: Endothelial dysfunction is considered an initial step in the pathogenesis of atherosclerosis and an important predictor of future cardiovascular events. Flow-mediated dilation (FMD) is a reliable and non invasive technique to assess endothelial function (EF) Our aim was to study EF in a cohort of systemic lupus erythematosus (SLE) patients prospectively followed at our unit and to investigate its relation with disease activity and damage over time.

Methods: 38 female SLE patients without overt cardiovascular involvement were enrolled (mean age 35.8±8; 21– 55 years) and clinically followed-up for a mean of 4.45±1.5 years. Clinical history, traditional cardiovascular risk factors, laboratory parameters as well as a complete serological profile were recorded. Disease activity was evaluated with the ECLAM global score (a score >2 were arbitrarily used to defined "active disease") while SLICC/ACR-DI was used for scoring disease damage. An increase in SLICC/ACR DI or death were defined as poor outcome. FMD was assessed in the brachial artery by high-resolution ultrasound and computerized edge detection system (Quipu s.r.l., Pisa, Italy); FMD was defined as maximal % change in brachial artery diameter after reactive hyperemia induced by 5-min forearm ischemia. In addition, endothelium-independent dilation after administration of glyceryl trinitrate (25 μg s.l.) was also assessed. FMD assessment was performed at study entry and was repeated in a subgroup of 21 patients after a follow-up of 4.45±1.5 years.

Results: At enrolment, 18 patients (47%) presented an active disease and 7 (15%) an active renal involvement; 20 (53%) were inactive; mean FMD was 7.9±3.1% with no statistically significant differences between active (8.7±1) and inactive group (7.9±0.8; p=0.53), even after correction for age and disease duration. During the follow-up, 3 patients died and 12 accrued organ damage with cardiovascular complications in eight patients (21%) and progression to renal failure in 6 (15%). Interestingly, while basal EF did not predict the poor final outcome (death or damage accrual), its decline over time did. In fact, in the follow-up FMD showed a significant decline over time (from 8.0±3.2 to 5.9±3.3, P=0.04) while endothelial-independent dilation did not (from 9.2 ±3.5 to 8.6±4.9; p= 0.63). The decline was not different between active and inactive group; however, patients with poor outcome (n=7) showed a greater worsening in FMD over time (−4.1% vs −2.0%).

Conclusion: This study shows that in SLE patients damage accrual is associated with progressive loss of FMD, with preserved response to glyceryl trinitrate, suggesting a progressive detriment in EF. On the other hand, disease activity does not appear to influence EF. Rapid progressive worsening of EF over time could represent an early marker of poor outcome and its assessment by repeated measurement of FMD could allow its early and non invasive identification. In this perspective, EF preservation may be important in preventing damage accrual and life-threatening consequences and therefore could be viewed as a therapeutic goal.

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Transverse Myelitis and Its Relationship with Neuromyelitis Optica in the Michigan Lupus Cohort. Malini Venkatram[1], Patricia C. Cagnoli[1], Diana Gomez-Hassan[2] and W. Joseph McCune[1]. [1]University of Michigan, Ann Arbor, MI, [2]Univ of Michigan, Ann Arbor, MI

Background/Purpose: Background: Transverse myelitis (TM) is an infrequent but serious manifestation of Systemic Lupus Erythematosus (SLE) with a reported incidence of 1–2 % and significant morbidity and mortality. TM complicating SLE has been variously reported to be associated with optic neuritis, anti-phospholipid antibodies, and antibodies to Ro/SSA and more recently with antibodies to aquaporin 4.

Neuromyelitis optica (NMO) is a relapsing, autoimmune, demyelinating condition characterized by TM and ON & at least two of the following: 1)Brain MRI, non-diagnostic for multiple sclerosis; 2) Spinal cord lesion extending over >=3 vertebral segments 3) NMO Ig-G antibody.

NMO spectrum disorders refer to inflammatory conditions of spinal cord & optic nerve, associated with anti-NMO Ig-G that do not fulfill the classic definition for NMO.

We present the largest study of TM in SLE including testing for anti-NMO antibodies in patients who had stored sera from the time of onset of neurologic symptoms. We also try to investigate the relationship of TM in lupus with NMO/NMO spectrum disorders.

Methods: We conducted a retrospective study of all the patients satisfying 4 ACR criteria for SLE within the Michigan Lupus Cohort (MLC) & evaluated the clinical, laboratory & Imaging features in 23 patients with a history of TM. Available stored sera from the time of onset of TM were tested for IgG NMO antibodies.

Results: 2.7% (23/ 856) of patients in the MLC had TM of whom 9.5 % (2/ 23) had optic neuritis. Only 81.8% of all the pts demonstrated ANA positivity. At the time of the event, serologic markers for lupus activity were normal in 50 %of the patients. We did not observe the previously reported increased frequency of anti-phospholipid antibodies (8/23, 34.7%)%) or anti Ro/SSA antibodies (39.13%) compared to the general lupus population.

Sensory involvement was the commonest manifestation (93.7%) followed by motor (62.5%) and bladder involvement (50%). Paraplegia occurred in 21.05% & 17.6% were catheter dependent. All the pts received steroids & 81.25% received Cytoxan. Overall recovery was good mostly due to aggressive immunotherapy.

2/23 (9.5) % of pts with TM had optic neuritis and fulfilled criteria for NMO. 30% of pts with available serum samples demonstrated NMO Ig-G. Overall 36.3% were categorized as NMO disease (inclusive of NMO and NMO spectrum). Contrary to our expectation, none of the pts in NMO category had a severe involvement such as paraplegia or catheter dependency. There were no statistically significant differences between the two groups in imaging or serological characteristics. Recurrences were seen in 75%of NMO group vs none in non-NMO group (P<0.024).

Conclusion: In a large prospective cohort, TM occurred in 2.7% of patients & was not associated with antibodies to phospholipids or Ro/SSA. Majority of patients recovered after aggressive immunosuppression. There were no significant differences between the NMO and NMO groups. Recurrences of TM, but not severity of onset, were associated with NMO spectrum disorders.

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Evaluation of Treatment Success in Systemic Lupus Erythematosus Clinical Trials: Development of the British Isles Lupus Assessment Group-Based Composite Lupus Assessment Endpoint. D. Wallace[1], V. Strand[2], R. Furie[3], M. Petri[4], K. Kalunian[5], M. Pike[6], L. Kelley[7] and C. Gordon[8]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]Stanford University, Palo Alto, CA, [3]North Shore-LIJ Health System, Lake Success, NY, [4]Johns Hopkins University School of Medicine, Baltimore, MD, [5]UCSD School of Medicine, La Jolla, [6]Massachusetts General Hospital, Fort ashington, PA, [7]UCB, Symrna, GA, [8]Medical School, Birmingham, United Kingdom

Background/Purpose: The evaluation of disease activity in systemic lupus erythematosus (SLE) clinical trials is challenging due to the multi-organ presentation of SLE, interindividual variability, unpredictability of disease course, medication effects, and interobserver rating differences. While composite endpoints have been widely adopted to study other diseases, single disease activity indices (DAIs) have been the

norm in SLE. The purpose of this study was to develop a composite responder index for use in SLE clinical trials.

Methods: An expert panel was consulted to review the characteristics of DAIs commonly used in SLE trials. These included the British Isles Lupus Assessment Group index (BILAG-2004), the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and the Physician's Global Assessment (PGA). Characteristics considered included basis of scoring and the number and types of items assessed. Following this review, the BILAG-based Composite Lupus Assessment (BICLA) was developed as a composite of multiple DAIs based on early epratuzumab clinical trial data. The BICLA requires patients to meet response criteria across three assessment tools.

Results: BICLA responders must achieve BILAG disease activity improvement with no worsening in BILAG or other DAIs and no treatment failure at any time point (Table). The BICLA was used to evaluate response in the EMBLEM™ phase II study (SL0007), a 12-week, randomized, double-blind, placebo-controlled study that recruited 227 patients with moderate to severe SLE. BICLA was sensitive to epratuzumab treatment response (epratuzumab 600 mg QW 45.9% response at 12 weeks; epratuzumab 1200 mg EOW 40.5%; epratuzumab 2400 mg cumulative dose 43.2%) with a limited placebo response rate (21%; p = 0.02 vs 2400 mg at 12 weeks). The use of BILAG as the primary component of the BICLA requires simultaneous improvement across all body systems with severe or moderate disease activity at baseline. BILAG gives balanced weight to all affected body systems and can reflect incremental improvements within a body system. The BICLA is also the 48-week primary efficacy variable in the EMBODY™ phase III studies (SL0009 [NCT01262365] and SL0010 [NCT01261793]) of epratuzumab in patients with moderate to severe SLE.

Table. Requirements for BICLA treatment response.

Improvement and	1. All BILAG level A scores at study entry improved to B/C/D and
	2. All BILAG level B scores at study entry improved to C/D
No worsening and	1. No single new BILAG A or two new BILAG B scores and
	2. No worsening of baseline SLEDAI total score and
	3. No worsening in PGA (< 10% worsening relative to baseline)
No treatment failure	Treatment failure defined as non-protocol treatment, e.g. new or increased immunosuppressants or antimalarials

Conclusion: The BICLA is a sensitive, clinically meaningful composite measure of SLE disease activity that requires disease improvement across all body systems with moderate or severe baseline activity without worsening or change in background medication, and which has discriminated between placebo and treatment responses in a phase II clinical trial. The three DAIs included in the BICLA require clinical assessment, physician assessment, laboratory assessment, and recording of medication use. Further analysis of data from studies using the BICLA composite endpoint may help to guide the design of future trials in SLE.

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Inpatient Mortality Related to Cerebrovascular Disease in Systemic Lupus Erythematosus: The Impact of Delay in Diagnosis of Neuropsychiatric Lupus. Jamal A. Mikdashi, Univ of Maryland Schl of Med. Baltimore, MD

Background/Purpose: Despite improvements in the process of care of stroke patients, mortality related to cerebrovascular disease (CVD) in systemic lupus erythematosus (SLE) patients during the first- ever stroke remains high when compared to patient with other causes for their first-ever stroke.

Purpose: To examine the predictors of inpatient mortality related to CVD in SLE and determine whether mortality associated with first-ever stroke is related to the disease effects, comorbidities or quality of care.

Methods: Inpatient mortality was examined in 143 SLE patients admitted to a tertiary care stroke center with validated first-ever stroke between January 2000 and January 2011. Mortality was defined as all-cause fatal event from day of first-ever stroke through the 28 day of follow up. Demographics, clinical manifestations and processes of care were compared between those who died (n= 14) and age- and gender –matched controls who survived the stroke event [3 controls for every patient] (N= 42). Risk factors predictive of mortality were determined using univariable analyses between survivals and non survivals. Multivariate analyses and Cox proportional hazards analyses of significant variables were examined to determine their contribution to mortality related to CVD. Severity of SLE disease activity (SLEDAI), damage (SDI) and stroke severity were adjusted for during analyses.

Results: Intractable disease activity and cumulative damage involving pulmonary and renal organs were higher in patients who died compared to those who survived the first-ever stroke. Both groups had comparable disease duration, ethnicity, socioeconomic features, smoking and alcohol use, stroke type (ischemic, hemorrhagic) and Charlson comorbidity score. Death related to cerebral vasculitis (50 %) appeared to be more common than death related to hemorrhagic (29 %) or ischemic stroke (21 %). The median time to diagnosis of neuropsychiatric SLE (NPSLE) was longer for patients who died as compared to patients who survived the stroke event [7days v 3 days; $p < 0.026$].

Table 1. Univariable analyses and Cox hazard analyses of factors associated with mortality related to CVD

Factors	Univariable Model Odds Ratio (95% Confidence Interval)	Proportional Hazard Model Hazard Ratio (95% Confidence interval)
Seizure	3.6 (1.1 – 12.3)	2.7 (1.0 – 7.6)
Cognitive impairment	3.7 (0.9 – 19.3)	2.1 (0.7 – 6.4)
Thrombocytopenia	4.8 (1.3 – 17.6)	3.3 (1.2 – 9.3)
Lupus anticoagulant	3.3 (0.9 – 15.4)	2.5 (0.8 – 7.0)
C Reactive Protein	1.2 (0.48 – 3.1)	0.9 (0.3 – 2.9)
Delay in NPSLE diagnosis	7.0 (1.8 – 27.1)	4.2 (1.4 – 11.6)

Conclusion: Despite the admission to a designated stroke center, mortality related to CVD in SLE remains significantly high. Quality improvement strategies targeting early diagnosis and timely intervention of neuropsychiatric SLE may reduce the associated morbidity and mortality among SLE patients.

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Predictors of Outcome in Peripheral Nervous System Manifestations of Systemic Lupus Erythematosus. Brandusa Florica[1], Jiandong Su[2] and Paul R. Fortin[1]. [1]Toronto Western Hospital, Toronto, ON, [2]The Toronto Western Hospital, Toronto, ON

Background/Purpose: Peripheral neuropathies (PN) in patients with systemic lupus erythematosus (SLE) are diverse and may cause significant functional impairment. The identification of factors that influence the outcome of PN is essential in decision regarding the timely treatment of potentially reversible nerve degeneration.

Methods: Data collected prospectively from the University of Toronto Lupus Clinic cohort was used to identify factors associated with improved neurological deficit (no need for assistance in self care). Potential predictors of improvement in PN were considered in univariate and multivariate logistic regression models. Also, the univariate and multivariate Cox proportional regression models were used to ascertain the results. The analysis included two groups of patients: those with SLE-related and those with PN not thought to be related to SLE. The statistical software used was SAS 9.13

Results: From 1533 SLE patients, 184 patients had PN diagnosed within 6 months of their first visit, with 105 patients with SLE-related PN and 79 with non SLE-related PN. Mean duration of follow up after PN diagnosis was 18.8 ± 11.0 years for SLE-related PN and 21.2 ± 11.0 years for non SLE-related PN. Patients with SLE-related PN had significantly higher SLEDAI at time of PN diagnosis ($p<0.0001$) and used more often steroids in the first year after PN diagnosis ($p=0.023$). SLE duration at PN onset and SLICC score were positively associated with improved outcome in patients with SLE-related PN, in the univariate logistic regression model, with OR (95%CI) of 0.949(0.909, 0.991) p =0.017 and of 0.730 (0.546, 0.977). Using multivariable Cox proportional model, the use of steroids in the first year after PN onset was the only factor that was independently associated with improved outcome in SLE-related [HR (95%CI) of 4.181 (1.254, 13.940) $p=0.019$] and with negative association for non-SLE related PN [HR (95%CI) 0.306 (0.127, 0.739) $p=0.008$]. Similar results were replicated using the multivariate logistic regression for non-SLE related PN [OR (95%CI) 0.137 (0.035, 0.538) p =0.004].

Conclusion: Clinical and laboratory characteristics of SLE patients at the time of PN diagnostic are not helpful to predict the outcome of the peripheral neurological manifestations. Steroid treatment in the first year after PN onset was associated with more patients improving in SLE related PN group and inversely in non-SLE related PN. Correct delineation of PN etiology is critical for timely intervention on nerve damage.

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Mortality Causes and Associated Factors in a Systemic Lupus Erythematosus Monocentric Cohort: Is the Systolic Pulmonary Artery Pressure a Risk Factor for Death? I. Rua-Figueroa, C. Erausquin, MD Fiuza, F. Francisco-Hernández, S. Ojeda, A. Naranjo, JC Quevedo, A. Acosta, R. Lopez -R and C. Rodriguez-Lozano. Hospital de GC Dr Negrin, Las Palmas GC, Spain

Background/Purpose: Despite improved prognosis, patients with SLE remain at increased risk for early death. Limited data are available in our country regarding the mortality of patients with SLE.

Objectives: To examine the mortality and associated factors in a monocentric Spanish

Methods: We studied 254 SLE (ACR 1997 criteria) patients under protocolized follow up in a rheumatology service. Acumulated clinical characteristic and damage accrual (ponderated SLICC/ACR/DI) (SDIp) and severity (Severity Katz Index) (SI) were recorded. The standardized mortality ratio (SMR), ROC analysis, with Hanley and McNeil contrast' for area under curve (AUC) comparisons and a multivariable analysis (logistic regression) were carried out.

Results: Mean age: 44.2±13.6; 92.1% female. The mean time (±S.D.) since the lupus diagnosis was 13.3 years (± 8.5); 19 patients (7.5%) died, 12 by SLE (63.2%). The most common cause of death was of respiratory origin (31.6%), followed by infection (26.3%), cancer (21%) cardiovascular (10.5%) and others (10.5%). SMR: 1.84 (1.48 females).The ROC curve cutoff for SDIp was >4 (sensitivity 66.6%; specificity 73.8% and + likelihood ratio (LR) 2.54 and for SI was >3 (S: 94.4%; E: 59.3%; +LR 2.31). There were no differences in AUC between SDIp (0.756; IC95% 0.698–0.808) and SI (0.820; IC95% 0.767–0.866) (p=0.632).The variables associated with mortality in the bi-variable analysis were: hospitalization by SLE, any time (66% vs 100% in deaths, OR 1,1; 95%CI:1.06–1.18; p=0.003), tobacco use (24.3 vs 47.4% OR 3.4; 95%CI:1.3–9.3; p=0.011), vasculitis (13.6 vs 42.1% OR 4.5; 95%CI: 1.7–12.1; p=0.001), severe thrombocytopenia (10.6% vs 26.3%; OR: 3.1; 95%CI: 1.04–9.6; p=0.033), hematocrit <30% (24.7% vs 73.7%; OR: 10.1; 95%CI: 3.2–32; p<0.0001), elevated **s**ystolic pulmonary artery pressure (SPAP) (2.6% vs 31.6%; OR:18.8; 95%CI: 5.2–67; p=0.0001), ischemic event (10.6% vs 26,3%; OR: 4,5; 95%CI: 1.4–14.2; p=0.005), cutaneus ulcers (4.3 vs 21.1 OR: 6.3; 95%CI: 1.7–22.7; p=0.002), major organ (52.8 vs. 84.2 OR: 6.9; 95%CI: 1.5–30.7; p=0.004), severe infection (29.8 vs. 78.9;OR: 8.7; 95%CI: 2.7–27.2; p=0.0001), antimalarials use (16.7% vs. 4.7%;OR: 0.2; 95%CI: 0.09–0.6; p=0.002), SI >3(OR: 24.6; 95%CI: 3.2–28.3; p<0.0001) and SDIp >0 (OR: 6.4; 95%CI: 1,4–28,3; p=0.006). Only hematocrit <30% (OR 10.3; 95%CI: 1.86–57.67, p=0.008) and elevated SPAP (OR 23.1; 95% CI: 3.24–165, p=0.002) were proven as independent factors in multivariate analysis.

Conclusion: Consistent with previous data, a strong association was found between anemia and mortality in SLE. However, the association with elevated SPAP, whatever cause, has not been previously recorded. We could not demonstrate a protective effect of antimalarials in the final model, perhaps by the very definition of the variable and/or the high percentage of patients treated with these drugs in our cohort. However, the protection against mortality was independent of severity, minimizing bias due to confounding by indication. This point needs to be explored further. Finally, our analysis doesn't reveal any differences between SDIp and SI as predictors of mortality.

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Anti-Nucleosome Antibodies Correlate with Temporal Fluctuations in Disease Activity in Systemic Lupus Erythematosus. Li Timothy[1], Stacey Morrison[2], Wendy Lou[3], Heather Reich[2], Ellie Aghdassi[4], D. D. Gladman[5], Murray B. Urowitz[1], James Scholey[2], Paul R. Fortin[1], Joan E. Wither[6] and Carolina Landolt-Marticorena[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]The Toronto Western Hospital, Toronto, ON, [3]University of Toronto, Toronto, ON, [4]University Health Network, Toronto, ON, [5]The Arthritis Program, Toronto Western Hospital and Division of Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON, [6]Toronto Western Research Institute, University Health Network, Toronto, ON

Background/Purpose: The clinical course of SLE is characterized by unpredictable disease exacerbations. Current biomarkers (anti-dsDNA antibodies and complement (C3)) function poorly in forecasting these events. This limits their utility as reliable markers of disease activity, generating interest in the identification of novel biomarkers. Anti-nucleosome antibodies are increased in SLE patients and are associated with disease activity. The aim of this study was to examine the utility of anti-nucleosome antibodies as a flare-specific biomarker in SLE.

Methods: 51 SLE patients satisfying ≥ 4 ACR criteria and 49 healthy controls were recruited. Patients were followed over a 14-month period with at least 3 clinical and biochemical assessments over that time. Clinical data and blood samples were collected at the time of recruitment and at subsequent assessments to determine the SLEDAI-2K (S-2K). A modified S-2K (mS-2K) was calculated by subtracting the contribution of anti-dsDNA antibodies and complement from the global score. An ELISA was utilized to determine IgG anti-nucleosome antibody levels in patients and control with a threshold for anti-nucleosome positivity defined as values 3 SD above the mean for controls. Spearman's (non-parametric) rank correlation analysis was used to determine the correlation coefficient between variables. Logistic regression analysis was performed with outcome parameters defined as activity (mS-2K > 0) or no activity (mS-2K = 0). Analysis of longitudinally correlated data was assessed by mixed effects models. p values of less than 0.05 were considered statistically significant.

Results: Anti-nucleosome antibodies were significantly elevated in SLE patients versus controls ($p < 0.0001$). Anti-nucleosome antibody levels show a statistically significant positive correlation with anti-dsDNA antibodies ($r = 0.72$, $p < 0.0001$) and a negative correlation with C3 levels ($r = -0.42$, $p = 0.002$). A moderate positive correlation ($r = 0.32$, $p = 0.02$) was found between anti-nucleosome antibodies and disease activity. The ability of anti-nucleosome antibodies to discriminate between patients with active (mS-2K > 0) and inactive disease was determined using an ROC curve analysis. Examination of the area under the curve (AUC) for C3 (0.63), anti-dsDNA (0.69) and anti-nucleosome (0.61) antibodies demonstrated that all 3 biomarkers functioned in a comparable fashion. To determine the utility of these 3 parameters to mirror changes in disease activity a mixed effects regression analysis was performed. Models combining C3 and anti-nucleosome antibodies (AIC = 1188.6) outperformed models with C3 and anti-dsDNA antibodies (AIC = 1191.4). In a model (AIC = 1185.8) incorporating all 3 parameters only anti-nucleosome antibodies ($p < 0.0001$) remained statistically significant.

Conclusion: Anti-nucleosome antibodies outperform traditional biomarkers in tracking with changes in SLE disease activity supporting the incorporation of this serological marker in the monitoring of SLE. The current shift towards multiplex platforms for autoantibody determination will facilitate the inclusion of this parameter into clinical practice.

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The Substantial Negative Impact of Systemic Lupus Erythematosus on the Working Lives of Patients: Results of the Lupus European Online Survey. M. Schneider[1], C. Gordon[2], K. Lerstrøm[3], M. Govoni[4], E. Nikai[4] and D.A. Isenberg[5]. [1]Heinrich-Heine-University, Duesseldorf, Germany, [2]University of Birmingham, Birmingham, United Kingdom, [3]LUPUS EUROPE, Farum, Denmark, [4]UCB, Brussels, Belgium, [5]University College of London, London, United Kingdom

Background/Purpose: Previous studies have shown that SLE has a significant impact on patients' health-related quality of life (HRQoL). A significant proportion of employed SLE patients miss days of work or are permanently unemployed due to SLE.[1] An online survey was developed to understand better the impact of SLE on patients' daily lives and career. The survey used lupus-specific, validated patient-reported outcome (PRO) instruments.

Methods: The LEO survey was developed by a steering committee of SLE medical experts and a LUPUS EUROPE board patient representative. UCB representatives provided support and coordination. The survey was available between May and August 2010 in five European languages. It included patient-designed questions and lupus-specific, validated PROs assessing fatigue (Fatigue Severity Scale [FSS]: scores 1–7; higher score = greater fatigue; < 4 = normal), HRQoL (LupusQoL questionnaire: 8 domains; scores 1–100; higher score = better HRQoL), and work impairment (Work Productivity and Activity Impairment Questionnaire, Lupus V2.0 [WPAI]: 4 domains; higher percentage = greater loss of productivity). LUPUS EUROPE made the survey available to patients via e-mail, social media, patient organization websites and national SLE magazines. Responses were anonymous. Participants were not required to answer all questions.

Results: The survey was completed by 2070 respondents with self-reported SLE; of 1796 providing information about the effect of lupus on their career, most were aged < 45 years (67%) and were female (94%). Most respondents reported that SLE adversely affected their careers; among those aged 26–45 years, only one-third reported no effect. Among those whose careers were affected by SLE, mean total FSS was 6.2 in those requiring social or disability allowance (n = 330), 5.8 in patients requiring sick leave (n = 309), 5.7 in those who needed to

work flexible hours (n = 336) and 5.6 in those who had changed career (n = 183) compared with 4.5 (n = 565) in those whose career had not been affected. Among respondents receiving social or disability allowance, 95% reported fatigue (FSS score > 4 points). HRQoL was higher among respondents whose careers were not affected by SLE and lowest in those receiving social or disability allowance (Table). A negative impact of SLE on work productivity was seen in all 4 WPAI domains, and greater impairment was reported in respondents whose careers were affected by SLE (Table).

Table. Relationship between LupusQoL ad WPAI domains and self-reported effect of SLE on career

	Did SLE affect your career?				
LupusQoL domains (mean score ± SD)	**No influence on career**	**Sick leave**	**Social or disability allowance**	**Change career**	**Work flexible hours**
Physical health	n = 544 76.7 ± 20.8	n = 298 52.6 ± 24.0	n = 327 37.7 ± 22.7	n = 179 58.1 ± 20.3	n = 328 57.2 ± 20.4
Pain	n = 535 75.1 ± 24.8	n = 293 49.8 ± 28.9	n = 323 38.3 ± 27.8	n = 178 54.4 ± 25.1	n = 324 57.2 ± 27.8
Planning	n = 536 80.4 ± 24.1	n = 295 47.4 ± 30.3	n = 323 37.5 ± 27.8	n = 177 55.7 ± 27.8	n = 323 56.3 ± 29.3
Intimate relationship	n = 530 78.6 ± 28.7	n = 290 53.9 ± 32.8	n = 320 47.4 ± 33.6	n = 175 65.4 ± 29.8	n = 323 64.5 ± 30.1
Burden to others	n = 536 60.4 ± 30.4	n = 294 35.2 ± 30.4	n = 322 33.6 ± 30.4	n = 179 41.2 ± 29.5	n = 324 43.9 ± 31.0
Emotional health	n = 536 70.4 ± 22.9	n = 291 54.6 ± 24.0	n = 315 53.7 ± 24.3	n = 179 59.2 ± 24.0	n = 320 59.8 ± 24.1
Body image	n = 342 70.2 ± 25.6	n = 133 55.6 ± 30.2	n = 266 54.1 ± 28.2	n = 125 65.4 ± 28.0	n = 218 59.7 ± 30.1
Fatigue	n = 540 62.1 ± 25.5	n = 295 39.2 ± 24.8	n = 320 33.3 ± 23.3	n = 179 41.7 ± 23.6	n = 325 43.6 ± 23.0
WPAI dimensions (mean % of time impaired ± SD)					
Absenteeism	n = 268 3.8 ± 12.4	n = 82 35.0 ± 37.7	n = 37 31.3 ± 35.6	n = 91 10.0 ± 17.3	n = 193 16.6 ± 22.4
Presenteeism	n = 354 25.2 ± 19.4	n = 104 55.9 ± 27.4	n = 49 53.3 ± 26.3	n = 109 44.2 ± 22.3	n = 238 47.3 ± 23.0
Work productivity loss	n = 265 27.5 ± 20.5	n = 66 58.1 ± 28.4	n = 32 59.2 ± 28.4	n = 91 48.7 ± 25.0	n = 188 52.3 ± 24.9
Activity impartment	n = 552 39.2 ± 25.8	n = 300 64.7 ± 24.5	n = 325 70.6 ± 21.2	n = 178 57.9 ± 23.7	n = 327 58.4 ± 23.3

Conclusion: The LEO survey demonstrates that SLE adversely affects patients' careers and levels of productivity at work. Respondents who had to change work commitments because of SLE reported greater fatigue levels, worse HRQoL and greater loss of productivity. These results demonstrate the extensive burden of disease for patients, in terms of both quality of life and lost productivity.

Reference

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Is the Heightened Lung Cancer Risk in Systemic Lupus Erythematosus Decreasing Over Time? Data From a Very Large International Multi-Centre Cohort. Sasha Bernatsky[1], Ann E. Clarke[2], C. Gordon[3], Jeremy Labrecque[1], Rosalind Ramsey-Goldman[4] and Systemic Lupus International Collaborating Clinic (SLICC).[5]. [1]McGill UHC/RVH, Montreal, QC, [2]Research Institute of the McGill Univ. Health, Montreal, QC, [3]University of Birmingham, Birmingham, United Kingdom, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Toronto

Background/Purpose: Previously we have demonstrated a small over-all increased cancer risk in SLE, with particularly heightened risk for non-Hodgkin's Lymphoma (NHL) and lung cancer. We recently updated our data, and present figures for over-all, NHL, and lung cancer risk in SLE versus the general population, for the years prior to 2000, and the period from 2000 onward.

Methods: We studied a very large multi-centre international cohort of clinically confirmed SLE patients. Patients at each center were linked to regional tumor registries to determine cancer occurrence. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected cancers. Cancers expected were determined by multiplying person-years in the cohort by the geographically matched age, sex, and calendar year-specific cancer rates, and summing over all person-years.

Results: We studied a total of 16, 263 lupus patients from 1976 to 2009, from 53 centres. The total cohort was 90% female and the average follow-up was 9.3 years (a total of 150,984 patient-years). From the 1970's to 2000, there were 101,237 patient-years of follow up and from 2000 onward there were 49,747 patient-years of follow-up. The SIRs for prior to the year 2000, versus after 2000, are presented below.

	Prior to the year 2000					From the year 2000 onward				
	Observed	**Expected**	**SIR**	**95% CI**		**Observed**	**Expected**	**SIR**	**95% CI**	
Lung	73	54.6	1.34	1.05	1.68	28	29.5	0.95	0.63	1.37
NHL	50	14.1	3.54	2.63	4.67	30	8.3	3.63	2.45	5.18
All	550	457.5	1.20	1.10	1.31	302	254.8	1.19	1.06	1.33

Conclusion: The clear increase in lung cancer risk in SLE compared to the general population, which was demonstrated prior to 2000, was not as evident in more recent data. In contrast, the risk in SLE (compared to the general population) remained heightened for total malignancy incidence and NHL incidence. However, since our case ascertainment (and the general population cancer rates) rely on cancer registry records, the apparent trend could possibly also be related to systematic differences in classification of lung cancers, with a shift from ICD-9 to ICD-10 coding, if there is increasing non-differential misclassification of both lung cancers in SLE and the general population. Changes over time in race/ethnicity mix, smoking, and medication use are additional considerations, and these will be examined in future analyses.

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Risk Factors Associated with Cataracts in Systemic Lupus Erythematosus Patients. An inception-Cohort Study. Mariana Chávez-Villa, Juanita Romero-Diaz, Claudia Recillas-Gispert, Carmen Lizana, Francisco Cárdenas and Jorge Sánchez-Guerrero. Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubirán, Mexico, Mexico

Background/Purpose: Cataracts have been reported as common finding in SLE patients. Its characteristics and lupus related risk factors are still poorly known. We aimed to identify the prevalence, time of onset, subtypes and risk factors associated with cataracts in an inception-cohort of SLE.

Methods: We included 123 patients (90% females) with SLE of recent-onset at enrollment. At entry, a standardized medical evaluation was done assessing lupus characteristics, medications, cardiovascular risk factors, and laboratory tests. Patients were seen every 3–6 months, and assessed for disease activity and medications. Every year, information was updated and a blood sample drawn.

At 4.9(3.0) years of follow-up, the patients were screened for ocular manifestations by 2 certified ophthalmologists who performed a full standardized ophthalmic examination. A composite slit-lamp evaluation based system for the clinical classification and grading of cataracts was performed. Cataracts features were classified morphologically by Lens Opacities Classification System (LOCS) III, and individual features were graded by comparison with standard diagrams mounted adjacent to the slit-lamp. The image degrading effect of the cataract was assessed using a resolution target projection ophthalmoscope.

Results: At enrollment into the cohort, mean (SD) age of lupus patients was 27.9 (8.9) years, lupus duration 5.4 (4.0) months, number of SLE criteria 5.7(1.3) and SLEDAI-2K score 6.5 (6.1). At ocular screening mean age of patients was 32.8 (8.6) years. Thirty nine patients (32%) were identified with cataract, females (90%). NC0NO0C0P1 (posterior subcapsular) was the most common subtype (41%). Cataracts were observed as early as age 21–30 years, and since the first years of diagnosis. Comparing patients with and without cataract, only hypertension was more often observed in patients with cataracts, no difference was observed in body mass index, diabetes mellitus, lipid profile, glucose, homocystein and hsCRP. Regarding SLE characteristics, patients with cataract had more often renal criterion, and higher modified SLICC/DI score. Photosensitivity was more frequent in patients without cataract. Age at diagnosis, disease duration, and autoantibodies profile did not differ between groups. The cumulative dose of prednisone was 28.2(17.8) and 19.1(13.8) grams, between patients with and without cataract, respectively (P=0.005), cyclophosphamide use 62% vs 32%, (P=0.003) and cumulative dose of cyclophosphamide was 9.6(17.7) and 4.6(9.9), (P=0.006). No difference was observed with the use of antimalarials and low-dose aspirin. Logistic regression analysis showed an independent association of cumulative dose of prednisone (OR 1.04, 95%IC1.0–1.07, p=0.02) and photosensitivity (OR 0.14, 95%IC 0.4–0.45,p=0.001) with cataract.

Conclusion: In this inception cohort of young lupus patients, at 4.9 years of follow-up, cataracts were observed in 32% of patients, from age 21–30 years, and since the first year of lupus. Cumulative dose of prednisone is an independent risk factor for cataract. Photosensitivity seems to be a protective factor in patients with lupus.

2273

Clinical and Psychosocial Factors Are Associated with Current Work Status and Missing Days At Work in a Large Population of Patients with Systemic Lupus Erythematosus (SLE). Stacey Morrison, Jiandong Su and Paul R. Fortin. Toronto Western Hospital, Toronto, ON

Background/Purpose: Our aim is to describe the work status of patients with systemic lupus erythematosus (SLE) and test for associations with (1) current work; and (2) missing days from work due to SLE in a North American registry of SLE patients.

Methods: A large registry collects information from (a) consenting SLE patients (age, gender, race, education, insurance, troublesome symptoms and work-related factors); and (b) their rheumatologist [ACR criteria, SLE duration, disease activity (SLEDAI, range 0–24), SLICC damage index (SDI, range 0–15)] at each visit. Descriptive statistics and univariate and multivariate (MV) regression analyses were performed.

Results: Data was collected from 1,242 individuals: mean (sd) age of 40.5 (13.2), 92% female, 48% Caucasian, 34% African American, 12% Hispanics, 74% with a college degree or higher. Four or more ACR criteria were met in 90% of the group with [median (IQR)] disease duration of 11.0 (11.0); SLEDAI of 2.0 (4.0); and SDI of 1.0 (2.0). Private insurance was reported in 60% of patients, 27% were work-disabled. There were 570 (48%) not working: 80% of these had worked previously with 20% having lost their job since their last visit and 14% looking for a job. Current work was reported by 52% of participants, 70% of these full time. One hundred and ninety (30%) had missed work due to illness since their last visit and 51% worried that SLE made it difficult for them to perform their job. Variables independently associated with work status and missing work are reported in Tables 1 and 2.

Table 1. Variables independently associated with current work

Variable	OR	95% CI	
Age (years)	0.99	0.98	1.00
Gender (male)	2.00	1.23	3.26
Private insurance	4.30	3.27	5.66
Race (African American)	1.39	1.04	1.87
Education	1.15	1.07	1.22
SDI	0.79	0.73	0.86

Further MV analysis of individual SDI items revealed that retinal damage, pulmonary hypertension and fibrosis, cardiomyopathy, osteoporosis, avascular necrosis and extensive skin scarring were adverse contributors to work status.

Table 2. Variables independently associated with missing days at work

Variable	OR	95% CI	
SLE duration (years)	1.03	1.00	1.05
Race (African American)	1.52	1.01	2.28
SLEDAI	1.07	1.01	1.12
Fatigue	2.81	1.85	4.26
Weakness	2.51	1.58	4.01
Difficulty thinking	2.03	1.23	3.36
Other troublesome symptoms	1.60	1.03	2.49

Conclusion: Work is a marker of vulnerability and is important in measuring health status. Factors independently associated with current work in SLE are younger age, male gender, African American race, higher education and less damage. Longer SLE duration, higher disease activity and several dimensions important to patients but often ignored by physicians (fatigue, weakness, difficulty thinking and other troublesome symptoms) are predictors of missing work. Improving work-related interventions, especially those focused on presenteeism may make this population less vulnerable to becoming work-disabled.

2274

The WHO Fracture Risk Assessment Tool ($FRAX^R$) Under-Estimates the 10-Year Fracture Risk in Chinese Patients with Systemic Lupus Erythematosus (SLE). Chi Chiu Mok, Chi Hung To and Kwok Man Ma. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: The WHO $FRAX^R$ tool was developed to evaluate the fracture risk of patients based on data derived from different ethnic groups so as to guide treatment decision. We compared the actual observed 10-year fracture incidence in a group of Chinese patients with long-standing SLE with the risk estimated by using the WHO $FRAX^R$ tool.

Methods: All patients who fulfilled ^{3}4 ACR criteria for SLE, aged ^{3}50 years and had disease duration of ^{3}10 years in the year 2008 were recruited. The 10-year risk of major fracture (without data on bone mineral density) was estimated by entering the WHO $FRAX^R$ tool covariates / risk factors described in our medical records in the year 1998. All these patients were screened for compression fracture of the thoracic and lumbar spine in the year 2008 using plain radiograph of the spine (antero-posterior and lateral). The grading of vertebral fracture as suggested by Genant was used to assess vertebral fractures (stage I, II and III). Data on non-vertebral fragility fracture in the same year were also collected by direct patient interview and medical record review. The actual observed incidence of vertebral and non-vertebral fractures in year 2008 was compared with the risk estimated by the WHO $FRAX^R$ tool based on the risk factors in the year 1998.

Results: 65 SLE patients were studied (92% women, age 56.6±6.3 years, disease duration 17.3±7.2 years in 2008). Thirteen patients (20%) had major fractures in 2008 (11 vertebral fractures – 5 Genant stage I, 4 stage II, 2 stage III; 3 multiple vertebral fractures; 2 fibular fractures). Six patients (9%) had symptomatic fractures at these sites. The frequency of risk factors for fragility fractures in 1998 used for the $FRAX^R$ tool in these patients was: chronic smoking (9%), use of glucocorticoids for more than 3 months (65%), premature menopause (6%), body mass index $<18 kg/m^2$ (5%), habitual drinking (0%) and history of parental fracture or personal fracture (0%). From the FRAX program, the mean 10-year fracture risk of this group of patients was estimated to be 2.0±2.1% (range 0.7% to 16%). The median 10-year fracture risk was 1.5% (IQR 1.2–2.4%). Even when symptomatic major fractures were considered only, the actual incidence (9%) was much higher than that estimated by the WHO $FRAX^R$ tool (2%).

Conclusion: The WHO $FRAX^R$ tool greatly under-estimates the 10-year incidence of fragility fractures in Chinese patients with SLE.

2275

Insulin Resistance and Its Association with Phospholipid Profile, Carotid Intimal- Medial Thickness and Carotid Plaque Area in Women with Systemic Lupus Erythematosus. Ellie Aghdassi[1], David WL. Ma[2], Lihi Eder[3], Amaris K. Balitsky[4], Stacey Morrison[5], Michael Frattasi[5], Jiandong Su[5], Shayan Ezatollahpour[5], D. D. Gladman[6] and Paul R. Fortin[7]. [1]University Health Network, Toronto, ON, [2]University of Guelph, Guelph, ON, [3]Toronto Western Hospital, University of Toronto, Toronto, ON, [4]The University of Toronto, Toronto, ON, [5]The Toronto Western Hospital, Toronto, ON, [6]The Arthritis Program, Toronto Western Hospital and Division of Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON, [7]Toronto Western Hospital, Toronto, ON

Background/Purpose: Insulin resistance (IR) is associated with the metabolic syndrome and has been linked to inflammation and an increased risk for cardiovascular disease (CVD). The ratio of Phosphatidylcholine (PC) to Phosphatidyl-ethanolamine (PE) and the composition of PC and PE are important determinants of the cell membrane integrity and PC/ PE ratio may be a novel inflammatory marker. The purpose of this study was to estimate the prevalence of insulin resistance (IR) in women with Systemic Lupus Erythematosus (SLE) and to determine whether there are associations between IR and: PC/PE ratio, carotid intimal-medial thickness (cIMT) and carotid plaque area (cPA).

Methods: Consecutive SLE women, meeting the ACR criteria for classification of SLE were enrolled into this study. Data on demographic variables, cardiovascular risk profile, SLE disease activity index-2000 (SLEDAI-2K) and SLICC (Systemic Lupus International Collaboration Clinic)-damage index (SDI) were collected. Blood was collected after 12-hr fast and analyzed for glucose and insulin. Insulin resistance was calculated using the homeostatic model assessment formula (HOMA: {glucose (mmol/l) × insulin (mU/l}/22.5). HOMA >3 was considered IR. Phospholipid profile was determined in red blood cells (RBC) using thin layer and gas chromatography. cIMT and cPA were determined using B-mode ultrasonography only in a subset of patients (n=36). cIMT, cPA, SDI, SLEDAI-2K, demographic variables and CVD risk profiles were compared between patients with and without IR using student's t-test. Pearson correlation was used to determine associations.

Results: Among 78 subjects, 53 (67%) had IR (HOMA>3). Compared to those with HOMA<3, subjects with IR had higher: BMI [24.3 (6.5) vs. 27.2 (7.3) kg/m^2, p=0.09], systolic blood pressure [113.7 (8.5) vs. 123.0 (19.8) mmHg, p=0.02], waist circumference [76.2 (11.6) vs. 86.2 (15.0) cm, p=0.003], cPA [0.06 (0.06) vs. 0.19 (0.25) cm^2 p= 0.02] and were older [40.7 (13.9) vs. 50.6 (12.3) year, p=0.004]. PC to PE ratio was significantly

lower in those with IR compared to those without IR [1.37 (0.21) vs. 1.27 (0.17), p=0.024). SLEDAI, SDI and cIMT were similar between the two groups. However, there was a significant negative correlation between RBC PC content and: cIMT (r= − 0.35, p=0.03) and cPA (r= −0.32, p=0.46).

Conclusion: IR is prevalent in SLE patients and is accompanied by alterations in RBC phospholipid profile. Alteration in RBC phospholipids profile was associated with a higher cIMT and cPA. The data suggest that IR and alterations in phospholipids profile play a role in the pathophysiology of atherosclerosis in patients with SLE and warrants further investigations.

2276

Vitamin D Deficiency As Marker for Disease Activity and Organ Damage in Systemic Lupus Erythematosus: A Comparison with Anti-dsDNA and Anti-C1q. Chi Chiu Mok[1], Daniel Birmingham[2] and Brad H. Rovin[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Ohio State University Medical Center, Columbus, OH

Background/Purpose: Vitamin D has been shown to have in-vitro inhibitory effects on T and B cell functions. Low levels of 25-hydroxyvitamin D3 were found in patients with SLE and correlated with active disease. The objective of this study is to examine the sensitivity and specificity of vitamin D deficiency for predicting disease activity and damage of systemic lupus erythematosus (SLE) in comparison with anti-dsDNA and anti-C1q.

Methods: Consecutive patients who fulfilled ^{3}4 ACR criteria for SLE were recruited from an out-patient clinic during the summer months (May to August, 2008). Levels of 25-hydroxyvitamin D3 (enzyme immunoassay; Immunodiagnostic Systems Inc, Fountain Hills, AZ, USA), anti-C1q (ELISA kits, Euroimmun, Lubeck, Germany) and anti-dsDNA (ELISA kit, Eurodiagnostica, Arnhem, Netherlands) antibodies were measured. Relationship among these markers, concurrent disease activity and damage scores of SLE was studied by Spearman's rank correlation method.

Results: 290 SLE patients were studied (95% women; mean age 38.9±13.1years; SLE duration 7.7±6.7years). Clinical or serological lupus activity (SLEDAI^{3}1) was present in 225 (78%) patients at the time of venepuncture. Thirty-seven (13%) patients had SLEDAI score of 12 or more. The mean 25-hydroxyvitamin D3 level was 19.1±6.2 ng/mL (range 6.2–53.0). Vitamin D insufficiency (level <30ng/mL) was present in 277 (96%) patients. More serious vitamin D deficiency (level <15ng/mL) was found in 78 (27%) patients. Levels of 25-hydroxyvitamin D3 correlated inversely with the clinical SLE disease activity score (Rho=-0.26;p<0.001). The mean titers of anti-C1q and anti-dsDNA were 23.4±33 RU/mL (NR<20) and 143±153 RU/mL (NR<50), respectively. Levels of 25-hydroxyvitamin D3 correlated significantly and inversely with titers of anti-C1q (Rho= −0.14; p=0.02) and anti-dsDNA (Rho= −0.13; p=0.02). However, there was no significant relationship between levels of 25-hydroxyvitamin D3 and complement C3 (Rho=0.09; p=0.12) or C4 (Rho=0.09; p=0.13). Both 25-hydroxyvitamin D3 deficiency (specificity 0.78 and 0.79; sensitivity 0.44 and 0.38, respectively) and anti-C1q (specificity 0.82 and 0.82; sensitivity 0.59 and 0.45, respectively) were more specific but less sensitive than anti-dsDNA (specificity 0.47 an 0.47; sensitivity 0.86 and 0.76, respectively) for concurrent clinical renal and non-renal SLE activity. Levels of 25-hydroxyvitamin D3, anti-dsDNA or anti-C1q did not correlate significantly with the SLE damage scores.

Conclusion: 25-hydroxyvitamin D3 correlated inversely and significantly with clinical SLE activity, anti-C1q and anti-dsDNA titers, but not with complement levels or damage scores. Deficiency of 25-hydroxyvitamin D3 was as specific as anti-C1q, but less sensitive than anti-dsDNA, for detecting concurrent renal and non-renal clinical activity of SLE.

2277

Number of Breastfed Babies Inversely Related to Development of Systemic Lupus Erythematosus Compared to Controls. April Barnado[1], Lee Wheless[2], Anna K. Meyer[2], Gary S. Gilkeson[3] and Diane L. Kamen[4]. [1]Duke University Medical Center, Durham, NC, [2]Medical University of South Carolina, Charleston, SC, [3]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [4]Medical University of SC, Charleston, SC

Background/Purpose: Given the strong female predominance in Systemic Lupus Erythematosus (SLE), hormonal factors may play a role in its pathogenesis. Prior studies on breastfeeding and the development of SLE have found inconsistent results. Utilizing data from a longitudinal study of Gullah African Americans, we examined the effect of parity and breastfeeding on the development of SLE by comparing cases to controls.

Methods: Gullah African American cases and controls with at least one live birth were drawn from a longitudinal observational cohort started in 2002. In-person interviews, examination, labwork determination, and chart reviews confirmed the case/control status of each subject. We collected demographic, socioeconomic, and reproductive data, specifically live births occurring before SLE diagnosis in cases and all live births for controls. Weeks of breastfeeding were summed across all pregnancies. Categorical variables were examined by chi-square tests. Differences in the means of continuous variables were tested using Student's t-test. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI), adjusting for age and education. Two-sided p-values < 0.05 were significant.

Results: Mean age at SLE diagnosis was 34.6 years. Compared to controls (n = 207), cases (n = 120) had significantly fewer mean live births (2.3 vs 2.8, p<0.01). Cases had a similar mean age at first live birth (21.3 vs 22.3, p=0.13) and years of education (13.0 vs 13.0, p=0.97). Cases were as likely as controls to have breastfed (30.8% vs 24.2%, p=0.19) with similar mean weeks of breastfeeding (11.9 vs 15.4, p=0.54) and mean number of babies breastfed (0.5 vs 0.8, p=0.06). Number of live births was not associated with risk of developing SLE (Table 1, p for trend=0.70). There was a non-significant trend for a decreased risk of SLE with longer duration of breastfeeding (vs 0: 2–12 weeks OR 1.35, 95% CI 0.67–2.71; 13–51 weeks OR 0.50, 95% CI 0.19–1.26, p for trend=0.20). However, the number of babies breastfed was associated with a significantly lower risk of SLE (Table 1, p for trend= 0.02).

Table 1. Odds ratios (OR) and 95% confidence intervals (CI) for development of SLE compared to controls in an African American population. All estimates are adjusted for age and education.

	# of live births before diagnosis (p for trend = 0.70)	**# of babies breastfed before diagnosis (p for trend = 0.02)**
# of events	OR (95% CI)	OR (95% CI)
0	–	1.00
1	1.00	0.59 (0.31–1.13)
2	0.96 (0.52–1.75)	1.21 (0.47–3.12)
3	0.86 (0.43–1.72)	0.33 (0.06–1.73)
≥ 4	0.57 (0.24–1.36)	0.13 (0.02–1.03)

Conclusion: Number of live births was not associated with risk of developing SLE, with rates of breastfeeding low among both cases and controls in this cohort. Number of babies breastfed was protective against development of SLE. However, duration of breastfeeding was not associated with a significantly decreased risk of SLE, possibly because prolactin levels peak early in lactation and may offer a protective role that is less significant as levels slowly decline after a few months. These results suggest that early breastfeeding may be more clinically important than duration and need further investigation.

2278

Predictors of Preterm Birth and Preeclampsia in Systemic Lupus Erythematosus. Megan E. B. Clowse, Lisa G. Criscione-Schreiber and David S. Pisetsky. Duke University Medical Center, Durham, NC

Background/Purpose: Women with systemic lupus erythematosus (SLE) are at increased risk for preterm delivery and preeclampsia. While increased SLE activity is the best known predictor of adverse pregnancy outcome, markers of inflammation (CRP and ferritin), placental health (estradiol and alpha-fetoprotein), and renal function (uric acid) are good predictors of pregnancy complications in the general population. In this study, we investigated whether these markers could predict adverse pregnancy outcomes in women with SLE.

Methods: We prospectively enrolled pregnant women with SLE by the 1997 ACR criteria to assess SLE activity markers, inflammation, and placental health between 20 and 29 weeks gestation. SLE activity was measured using the SLE pregnancy disease activity index (SLEPDAI) and the physician's global assessment (PGA), as well as the anti-dsDNA antibody titer, C3, C4, blood counts, creatinine, and urine spot protein: creatinine ratio. The sedimentation rate (ESR), C reactive protein (CRP) and ferritin were used to measure inflammation. Measures of placental health were alpha-fetoprotein (AFP) and estradiol. Correlation analyses were used to examine the bivariate relationship between potential predictors with the gestational week of delivery and preterm birth; a p-value<0.05 was considered statistically significant.

Results: We enrolled 33 women, none of whom had antiphospholipid syndrome, and evaluated 33 pregnancies. One pregnancy resulted in a stillbirth. Of the live births, 10 (31%) were delivered preterm (<37 weeks gestation) and 5 (16%) were complicated by preeclampsia.

In this cohort, no markers of SLE activity correlated with gestational age at delivery. Low complement (C3) (r=-0.39), elevated urine protein: creatinine ratio (r=0.41), and SLEPDAI (r=0.35) all correlated with preeclampsia.

The renal changes associated with preeclampsia can lead to an increase in serum uric acid. In this cohort, the presence of an elevated uric acid at mid-pregnancy correlated with early delivery (r=-0.42) and preeclampsia (r=0.43).

Since estradiol levels can increase dramatically in pregnancy due to production by the placenta, a lower than expected estradiol level may indicate placental dysfunction. In this cohort, having a lower estradiol level at the mid-pregnancy visit correlated with an earlier delivery (r=0.52). AFP, also a marker of placental health, was not associated with gestational age at delivery in this study.

While CRP and ESR did not correlate with pregnancy outcomes, elevated ferritin was correlated with lower gestational age at delivery (r=-0.51) and preeclampsia (r=0.45).

Conclusion: In women with SLE, low estradiol or an elevated ferritin or uric acid level at mid-pregnancy may predict preterm birth. Furthermore, preeclampsia may be predicted by an elevated ferritin or uric acid, in addition to markers of SLE activity, including low complement, elevated proteinuria, and elevated SLEPDAI score. Although levels of estradiol, ferritin, and uric acid have not been previously associated with pregnancy complications in women with SLE, these markers may prove to be clinically useful in identifying pregnancies at particularly high risk for adverse outcomes.

2279

Nitrated Nucleosome Levels in Patients with Systemic Lupus Erythematosus – Associations with Ethnicity and Autoantibody Status. Sara Croca, Charis Pericleous, Karim Alber, Harry Yong, Ian Giles, David A. Isenberg, Anisur Rahman and Yiannis Ioannou. University College London, London, United Kingdom

Background/Purpose: Many different autoantibodies have been described in patients with SLE and serological assays have concentrated mainly on measuring autoantibody levels. Measuring levels of modified autoantigens may also be valuable. Nucleosomes from apoptotic debris are known to play a key role in pathogenesis of SLE, especially lupus nephritis. Nitration of histones within nucleosomes may be enhanced in patients with SLE by the presence of increased serum levels of reactive nitrogen species characteristic of inflammatory states. We developed a novel assay for measuring serum nitrated nucleosome (NN) levels. Here we report on results of this assay in patients with SLE and associations with ethnicity and autoantibody profile.

Methods: Multiple stored serum samples (mean 8 per patient) from a cohort of 49 patients with SLE were tested. The samples had been obtained over a mean (SD) follow-up period of 89 (46) months. NN levels were measured using a novel capture ELISA: serum added to a streptavidin plate pre-coated with a biotinylated anti-nitrotyrosine antibody followed by detection with a rabbit anti-histone-3 antibody and then an anti-rabbit IgG HRP conjugated antibody. OD values were converted to standard absorbance units (AU) by comparison to a positive control sample loaded on every plate. The mean absorbance value for each of the patients was calculated. Univariate analysis was used to investigate association between these levels and age, gender, ethnicity, disease duration and autoantibody status.

Results: The assay yielded reproducible results with an intra and inter-plate coefficient of variation of <10%. The mean age of the patients was 36 years (SD 13) and 81% were female. 23 were Caucasian, 18 Afro-Caribbean (A-C) and 8 other ethnicities. 17 patients had no NN at any time-point. In the other 34 patients, NN levels varied over time (mean 32.4 AU; SD 62.2; min 0; max 270.4). Age, gender and disease duration were not associated with NN level. A-C patients had significantly higher NN than other ethnic groups (p=0.03). Anti-Sm positivity was strongly associated with higher NN levels. Mean NN was 103.5 AU in anti-Sm positive and 7.75 AU in anti-Sm negative patients (p<0.0001). The apparent effect of ethnicity may be mediated via anti-Sm positivity since A-C patients were significantly more likely than other ethnic groups to be anti-Sm positive (p=0.04) and within the A-C group, anti-Sm positive patients had significantly higher NN levels than anti-Sm negative patients (p= 0.0004). There was no relationship between NN levels and positivity for anti-La, anti-Ro, anti-RNP or antiphospholipid antibodies.

Conclusion: NN were found in the serum of 65% of patients with SLE. Anti-Sm positivity and Afro-Caribbean ethnicity were associated with significantly higher NN levels. Studies to investigate the possible association of NN with anti-nucleosome antibodies are under way.

2280

Free Fatty Acids Are Associated with Metabolic Syndrome and Endothelial Activation but Not Inflammation in Lupus. Michelle J. Ormseth[1], Larry L. Swift[1], Sergio Fazio[1], MacRae F. Linton[1], Cecilia P. Chung[1], Paolo Raggi[2], Young Hee Rho[1], Joseph F. Solus[1], Annette M. Oeser[1], Aihua Bian[1], Tebeb Gebretsadik[1], Ayumi Shintani[1] and C. Michael Stein[1]. [1]Vanderbilt Medical Center, Nashville, TN, [2]Div.of Cardiology, Emory University, Atlanta, GA

Background/Purpose: Free fatty acids (FFAs) affect insulin signaling and are implicated in the pathogenesis of insulin resistance and atherosclerosis. Inflammatory cytokines increase lipolysis and thus raise levels of FFAs. Elevated FFAs can promote endothelial dysfunction, which may increase atherosclerosis risk. We hypothesized that increased inflammation is associated with increased FFAs resulting in insulin resistance and atherosclerosis in patients with systemic lupus erythematosus (SLE).

Methods: Clinical variables, serum FFAs, homeostasis model assessment for insulin resistance (HOMA-IR), and coronary artery calcium were measured in 167 patients with SLE and 90 controls. Inflammatory cytokines and markers of endothelial activation were measured in 115 of the SLE patients and 83 of controls. We compared FFAs in SLE and controls using Wilcoxon rank sum tests and further tested for independent association by adjusting for age, race, sex and BMI using multivariable regression models. Among patients with SLE, we assessed the relationship between FFAs and inflammatory cytokines, HOMA-IR, markers of endothelial activation and coronary artery calcium scores using Spearman correlation and multivariable regression analysis. Continuous variables are described as median [IQR].

Results: Patients with SLE and controls (both groups 87% female) were of similar age (40 years [30–48] and 42 [30–49], P=0.93), but BMI was higher in SLE (27.3 [23.6–32.6] vs 25.2 [22.5–30.1]. FFAs levels were higher in patients with SLE than controls (0.56 mmol/l [0.38– 0.71] vs. 0.44 mmol/l [0.32– 0.60], P=0.008), but association was not significant after adjustment for age, race, sex and BMI (adjusted P=0.074). Metabolic syndrome was present in 25.1% (42/167) of SLE patients. In univariate analysis, FFAs were increased among SLE with metabolic syndrome (0.665 mmol/l [0.47–0.80] vs. 0.52 mmol/l [0.37– 0.66], P<0.001). FFAs levels did not differ by current immunosuppressive medication use (all P value>0.05). In patients with SLE, FFAs were not associated with insulin resistance (HOMA-IR), inflammation (IL-6, TNFα), or atherosclerosis (coronary calcium score) (all adjusted P values >0.2), but were positively associated with levels of triglycerides (adjusted P=0.018), E-selectin (adjusted P<0.001) and ICAM-1 (adjusted P=0.004).

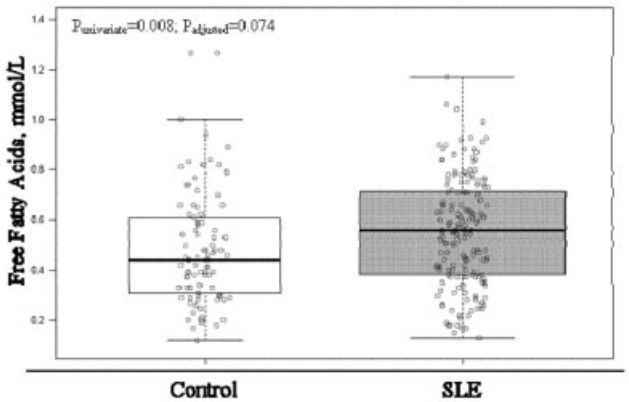

Figure 1. Free fatty acids concentration (mmol/L) in SLE and control subjects. *P univariate: Wilcoxon rank sum test; P adjusted: Multivariable linear regression was used for adjustment of age, race, sex and BMI.

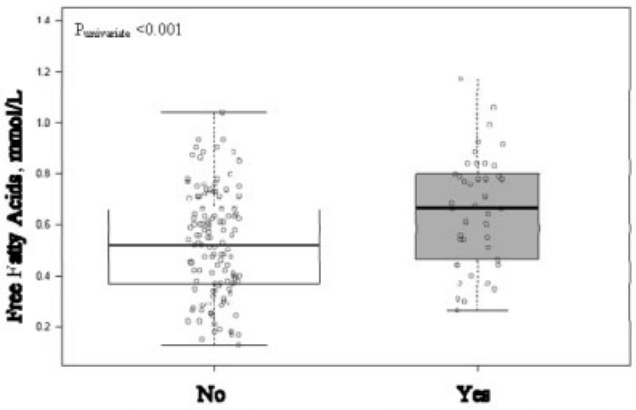

Figure 2. Free fatty acids concentration (mmol/L) in SLE patients without (No) and with (Yes) metabolic syndrome as defined by WHO criteria. *P univariate: Wilcoxon rank

Conclusion: FFAs are elevated in patients with SLE, particularly those with metabolic syndrome. FFAs in SLE are not associated with markers of generalized inflammation but are independently associated with triglycerides and markers of endothelial activation.

2281

B Cell Depletion therapy and Pregnancy Outcome in Severe Refractory Autoimmune Disease. Pamela M.K Lutalo[1], Shirish Sangle[1], Rachel J. Davies[1], Munther A. Khamashta[2] and David P. D'Cruz[1]. [1]Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom, [2]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom

Background/Purpose: Pregnancy is often associated with severe flares in active autoimmune diseases such as systemic lupus erythematosus (SLE) and ANCA positive vasculitis. Maternal and foetal outcomes are often poor if disease activity is not controlled prior to conception. We present an observational study of the antenatal and post-natal period of five women with severe, refractory autoimmune disease who received B-cell depletion therapy - Rituximab.

Methods: Four women with SLE and 1 woman with ANCA positive vasculitis fulfilling the ACR classification criteria who conceived following rituximab therapy were studied retrospectively. Three women had SLE complicated by aggressive crescentic WHO class IV lupus nephritis, 1 had SLE and immune thrombocytopenia (ITP) and 1 had ANCA positive vasculitis with an intra-orbital mass. All patients had previously failed or were intolerant to 3 or more immunosuppressive therapies. All received Rituximab (1gram) infusions on day 1 and day 15 after written informed consent. All immunosuppressive drugs, except oral corticosteroids and Hydroxychloroquine were stopped 2 weeks before the first infusion.

B-cell depletion was monitored by circulating CD19+ cell count on flow cytometry and patients were considered to have achieved B- cell depletion if absolute CD19 counts were $<$ 5 cell/ μL.

Results: Table 1. Baseline characteristics and pregnancy outcome

Table 1. Baseline characteristics and pregnancy outcomes

Pt	Age (yrs)	Race	Disease Duration (yrs)	AutoAb profile	Indication for BCDT	Previous therapy	Time of exposure before pregnancy (months)	Complications during pregnancy	Gestation age at birth (weeks)	Mode of delivery	BW (kg)	Neonatal Health
1	38	C	5	cANCA	WG, Intra orbital mass	Steroids HCQ, MTX, AZA, MMF, CyC, IVIG	10	Nasal septal perforation	40	C/S	2.9	Healthy neonate
2	39	C	10	dsDNA, Ro, La	SLE, Nephritis (IV+V)	Steroids HCQ, AZA, MMF, CyC, IVIG	18	Proteinuria > 3g/day at 21/40	31	C/S	1.17	Preterm low birth weight neonate
3	34	C	15	dsDNA	SLE, Nephritis (IV +V)	Steroids HCQ, AZA, MMF,	10	None	38	NVD	3.25	Healthy neonate
4	32	C	16	dsDNA	SLE, ITP	Steroids HCQ, AZA, IVIG, PE	22	None	40	C/S	3.2	Healthy neonate
5	32	AC	6	dsDNA, Sm, RNP, La, aCL	SLE, Nephritis (IV) APS	Steroids HCQ, AZA, CyC	8	Cutaneous lupus flare	38	NVD	3.3	Healthy neonate

Key: AC, Afro Caribbean; aCL anticardiolipin antibody; AutoAb autoantibody; AZA Azathioprine; BCDT, B-cell depletion therapy; BW (kg)birth weight in kilograms; C Caucasian; C/S Caesarean section; CyC Cyclophosphamide; dsDNA anti-double-stranded DNA antibody; HC Hydroxychloroquine; ITP, Immune thrombocytopenia; IVIG, Intravenous immunoglobulin; La anti-La antibody; MMF, Mycophenolate Mofetil; MTX, Methotrexate; NVD normal vaginal delivery; PE, plasma exchange NVD; RNP anti-RNP antibody; Ro anti-Ro antibody

Four women were Caucasian and 1 was Afro-Caribbean with a median age of 34 (range 32–39) years, median disease duration of 10 (range 5–16) years. All women responded to Rituximab therapy with a depleted B-cell count $<$ 1 cell/μL at 1 month and $<$ 5 cells/ μL 6 months post treatment. All women conceived within 22 months of treatment. Four women remained B-cell depleted throughout the course of their pregnancy. Median gestation period was 38 (range 31–40) weeks. Median birth weight of new born babies was 3.25 (range1.17–3.3) kg. All women had successful pregnancies with no congenital abnormalities. One new born (mother SLE with nephritis) needed observation in paediatric ITU for low birth weight.

Conclusion: A favourable pregnancy outcome is possible in women following B-cell depletion therapy with rituximab who have had previous refractory autoimmune diseases.

2282

Treatment of Hypertension and Hypercholesterolemia Is Not Successful in the Majority of Patients with Systemic Lupus Erythematosus. Elizabeth A. Pek[1], Dafna D. Gladman[2], Dominique Ibanez[1] and Murray B. Urowitz[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Patients with SLE demonstrate accelerated atherosclerosis and are at an increased risk of coronary artery disease. Previous quality improvement studies have demonstrated that increasing numbers of patients are being treated for hypertension and hypercholesterolemia. The objective of this study was to determine whether the initiation of treatment with antihypertensive or lipid lowering medications led to successful control of these risk factors.

Methods: Patients from the Toronto lupus cohort presenting within 1 year of SLE diagnosis and who received treatment with antihypertensive medications since 1985 and/or lipid lowering medications since 1995 were included. Success was defined as having met target blood pressure (BP), systolic BP $\leq$ 140 and diastolic BP $\leq$90 mmHg), serum total cholesterol (TC), TC $\leq$ 5.2 mmol/L or serum LDL, LDL $\leq$ 3.2 mmol/L during at least 90% of follow-up). Adjusted mean blood pressure and serum cholesterol values were calculated for one year prior to treatment initiation and for the duration of follow-up after treatment initiation.

Results: There were 441 inception patients seen after 1985 of which 234 (53%) had hypertension. Of these patients, 182 (78%) were initiated on anti-hypertensive therapy. 115 were included in our study (86% female, mean$\pm$SD age at treatment was 43.2$\pm$15.5, mean$\pm$SD disease duration at treatment was 2.8$\pm$4.2years). There were 287 inception patients seen after 1995 of which 195 (68%) had hypercholesterolemia. Of these patients, 56 (28%) were receiving appropriate treatment. 49 patients were included in our study (82% female, mean$\pm$SD age at treatment was 42.9$\pm$13.3, mean$\pm$SD disease duration at treatment was 3.2$\pm$3.6 years). Overall the adjusted mean systolic pressure decreased from 146.600$\pm$18.6 mmHg to 131.7$\pm$14.2 mmHg following treatment and the adjusted mean diastolic pressure decreased from 90.3$\pm$11.8 mmHg to 80.8$\pm$7.6 mmHg. However, only 39 of 110 patients (35%) met our criteria for successful treatment of hypertension. The adjusted mean total serum cholesterol and LDL decreased from 6.29$\pm$1.48 mmol/L to 4.76$\pm$1.01 mmol/L and 3.65 $\pm$ 1.29 to 2.56 $\pm$ 0.81 respectively. However, only 19 of 48 patients (40%) attained target total cholesterol levels while 25/40 (63%) attained target LDL levels during over 90% of follow-up.

Conclusion: Treatment of hypertension and hypercholesterolemia does not necessarily result in successful control of these risk factors in the majority of SLE patients. Further analysis will be important to discern the reasons for unsuccessful treatment and to compare CAD outcomes in patients who were successfully treated and those who were not.

2283

Systematic Review and Meta-Analysis of the Association of Systemic Lupus Erythematosus and Malignancy. I.D. Dey[1] and David A. Isenberg[2]. [1]University College London Hospital, London, United Kingdom, [2]University College London, London WC1E 6JF, United Kingdom

Background/Purpose: There is a perceived increase risk of malignancy especially of Non-Hodgkin's lymphoma (NHL) in patients with Systemic Lupus Erythematosus (SLE). Many studies have investigated this association and the verdict is still open to debate. Also unclear is the possible role of immunosuppressive therapy and its contribution to this

risk. Previous studies have been limited by small cohort numbers and heterogeneous study groups. There have been new studies with larger cohorts of patients addressing these limitations but no systematic review has been done on the subject.

Methods: A systematic review of all relevant literature was conducted using Excerpta Medica Database (EMBASE), MEDLINE and PubMed databases, references of retrieved articles. Using keywords and MeSH terms relating to SLE, immunosuppressive medications and neoplasms. Cohort studies on SLE patients fulfilling the American College of Rheumatology (ACR) criteria were selected and data collated for review and meta-analysis. Meta-analysis was done using Relative risks (RR) with 95% confidence intervals to look for an association with malignancy with Comprehensive Meta-analysis software (CMA). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was used.

Results: 232 studies were identified after an initial search. 40 full text articles were selected after review of abstracts and application of inclusion and exclusion criteria. Of the 40 articles, final analysis was undertaken on 17 cohort studies selected for homogeneity after exclusion of case control, clinical series and duplicate centre studies.

The study review covers a period of 18 years from 1992 to 2010.

Out of 64135 patients, 2736 (4.26%) developed malignancy. Of the 17 cohort studies reviewed, eight reported significant association between malignancy and SLE. Nine of them did not show any association. Only one study revealed an association of overall malignancy with immunosuppressive medication. Seven did not show any association with medication use and nine studies were inconclusive or did not investigate this.

Meta-analysis indicates an association between malignancy and SLE.

Conclusion: Cohort studies to date seem to be equally divided on the issue of whether there is an increased incidence of malignancy in SLE patients. Meta-analysis of these studies however implies a positive association between malignancy and SLE.

Evidence of a link between malignancy in SLE and the role of immunosuppressive therapy in increasing that risk is inconclusive.

Keywords: Systemic Lupus Erythematosus, Lupus, Neoplasm's, Malignancy, Immunosuppressive therapy, Systematic Review, Meta-analysis.

Disclosure of Interest: Dr Ida Dey's fellowship training was supported partly by scientific training bursary from the European League against Rheumatism (EULAR).

2284

Late Versus Early Development of Lupus Nephritis. Debra Dye-Torrington[1], Murray B. Urowitz[1], Dominique Ibanez[1] and Dafna D. Gladman[2]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Renal involvement is a common complication of Systemic lupus erythematosus, occurring in 50–60% of patients. A proportion of these patients will develop lupus nephritis as an initial presentation. The remaining patients will develop lupus nephritis later in the course of the disease. A recent longitudinal observational study of an inception cohort showed that of 107 patients who developed lupus nephritis 48(45%) did so after the first three years. 9% of these patients developed lupus nephritis after 10 years. In this study we compare the baseline characteristics of patients who developed early nephritis (within 3 years of entry into the clinic) with those who developed late nephritis (after 3 years) to determine predictors of late development of lupus nephritis.

Methods: Inception patients seen in clinic within one year of diagnosis of SLE were selected from a single centre cohort followed in an observational cohort study. Lupus nephritis was defined as sterile hematuria and/or pyuria, granular casts, proteinuria (>500mg/24hr), or elevated serum creatinine (defined as greater than 120μmols/l) on two or more consecutive visits attributed to SLE, or dialysis, transplant or WHO renal biopsy ≥ class 2. We identified patients who developed lupus nephritis after entry into the cohort. Early lupus nephritis was defined as those developing nephritis in the first 3 years. Patients developing lupus nephritis after three years were defined as having late lupus nephritis. The comparisons were done using t-test and chi-square test. Included in the model were sex, age at SLE diagnosis, race, SLEDAI-2K, steroids, antimalarial, immunosuppressant, complement and dsDNA at inclusion.

Results: 107 patients were identified from an inception group as having developed lupus nephritis in the course of their follow-up. This group was comprised of 89% female, 80% Caucasian. Mean (SD) age at SLE diagnosis was 34(13.9), mean (SD) SLEDAI -2K was 8.1 (7.4) and mean (SD) serum creatinine was 73.8(16.9). 51.0% had low complement and 49.5% had dsDNA antibodies. From this group, 59(55%) developed lupus nephritis within the first three years (early), while 48(45%) developed nephritis after three years. (Late). Comparison between early and late groups at first clinic visit showed that age at SLE diagnosis was younger in the early group Mean(SD) =30.9(12.2) compared to the late group.

Conclusion: Among patients who developed Lupus Nephritis after three years, age at diagnosis was the only significant predictor. Thus ongoing observation regarding renal involvement in SLE is important in all patients.

2285

Hospitalization in Patients with Systemic Lupus Erythematosus. Alhussain Asiri[1], Dafna D. Gladman[2], Anne G. MacKinnon[1] and Murray B. Urowitz[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: Patients with SLE may require frequent admission to hospital. Understanding the characteristics and risk factors of hospital admission of lupus patients would allow effective planning of services and resources utilization. We aimed to identify the causes and risk factors for hospital admissions and re-admissions of lupus patients to a network of three large teaching hospitals, and the outcomes of those admissions.

Methods: Patients who were admitted to the between January 2009 and December 2010, who had a diagnosis of SLE were identified and their information collected from electronic patient record. Simple calculations for percentages and means and P-values were performed.

Results: We identified a total number of 77 SLE patients admitted to hospital over the two year period with a total number of 165 admissions. SLE admissions represented 54% of total rheumatology admissions and 0.26% of total UHN admissions. The mean length of hospital stay in SLE patients was 14 days. When compared to patients in the lupus cohort seen during the same time period and not admitted to hospital, those admitted were more often Black, of younger age, shorter disease duration had a higher SLEDAI-2K and ACR/SLICC damage index. The main causes of admissions were disease flare 55 patients (71%) and infection in 16 patients (21%). Hospitalization outcome showed that in 27 patients (35%) the problem remained unresolved, 34 patients (46%) partially resolved and 14 patients (18%) had complete resolution of the primary problem. 22% had admission to ICU and 4% of patients died. 43 patients (56%) had re-admissions at least twice over 2 years. Mean hospital stay was 14 days for all admissions. Readmission causes were infections and non-resolved lupus flare in 44 % and 24 % respectively. Re-admissions for other medical or surgical causes accounted for 18% and 14% of the re-admissions respectively.

Conclusion: Admissions for SLE patients accounted for 54% of all rheumatology admissions. Major causes for admission are SLE flare and infection. There is a high rate of re-admission within a 2 year period. The major causes for re-admissions were infections and unresolved SLE flare. SLE patients utilize a significant proportion of rheumatology inpatient resources and services.

2286

Few Pregnancies After Cyclophosphamide Treatment Despite Preserved Ovarian Function. Lindsey E. Harward[1], Kate Mitchell[2], Lisa G. Criscione-Schreiber[2] and Megan E. B. Clowse[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Duke University Medical Center, Durham, NC

Background/Purpose: Cyclophosphamide (CYC), an alkylating agent used to treat severe autoimmune diseases, causes ovarian insufficiency. Our aims were (1) to retrospectively measure rates of ovarian protection used by women who underwent CYC therapy; (2) to measure the rate of ovarian failure in these women, (3) to measure how frequently women treated with CYC were able to complete their families and (4) compare pregnancy outcomes before and after CYC.

Methods: We enrolled women who had received CYC for rheumatologic disease before the age of 35. Participants completed a questionnaire about their reproductive health including information about their CYC treatment, desire for future children at the time of diagnosis, use of ovarian protection methods (leuprolide or oral contraceptives), current menstrual patterns, and information about each woman's pregnancy outcomes before and after CYC therapy. Additional information about dates of CYC treatment and cumulative dose was obtained from via chart review.

Results: This analysis included 23 women, mean age 32.9 years (range 21–45), who received CYC treatment at a mean age of 25.1 years (range 12–35). Diagnoses included SLE (19), scleroderma (1), granulo-

matosis with polyangiitis (Wegener's granulomatosis) (2), and SLE/scleroderma (1). The study group received an average cumulative CYC dose of 21,000mg (range 500 to 87,750 mg). CYC was given orally to 3 women, intravenously to 16, and by both routes to 4. CYC treatment lasted less than 6 months in 5 subjects (21.7%), 6–12 months in 7 (30.4%), and over 12 months in 11 (47.8%).

A form of ovarian protection was used by 10 subjects (leuprolide (7), oral contraceptives (3)). Cessation of menses occurred in 2 women prior to CYC and following CYC in 8 who had a mean age of 32.9 years at menopause, or 7.75 years (range 0 – 25) after CYC treatment. Of the remaining 13 women, 8 (34.8%) resumed regular menstrual cycles and 5 resumed irregular menstrual cycles following CYC. Women who had used ovarian protection had a higher rate of continuing regular menses (60%) than women who did not (15.4%, $p=0.02$).

The opportunity to have the number of children desired was limited by diagnosis prior to the completion of childbearing: 6% had the number of children desired when diagnosed prior to the completion of childbearing, compared to 57% diagnosed after childbearing ($p<0.01$) 10 women had never been pregnant. The remaining 13 women had 41 pregnancies (average 3.15 +− 1.8). Data was acquired for 39 pregnancies. Thirty-three pregnancies occurred before and 6 after CYC treatment. There were no significant differences in the number of live births, miscarriages, elective terminations, preterm births, or episodes of preeclampsia before and after CYC. No birth abnormalities were reported after CYC treatment.

Conclusion: The use of ovarian protective methods appears to improve the rate of regular menstruation in the years following treatment. However, menstruation may not indicate fertility, as despite menstruation, very few pregnancies occurred after treatment with CYC. Most participants in this study were unsuccessful in having the number of children they desired. This study highlights the need to study methods ovarian protections to determine whether they preserve fertility.

2287

Urinary Exosomal Microrna-192 and -195 As Potential Biomarkers of Renal Disease Activity in Lupus Nephritis. Hua Zhou[1], Gema Souto-Adeva[2], Donna Hardwick[2] and Gabor G. Illei[1]. [1]NIDCR/ NIH #10 1N110, Bethesda, MD, [2]NIH/NIAMS, Bethesda, MD

Background/Purpose: Urinary exosomes contain useful bioinformation and may serve as a novel source of biomarkers for kidney diseases. Renal microRNA (miR)-192 was increased in an animal model of diabetic nephropathy and increased expression of miR-195 was reported in kidney biopsies from class II lupus nephritis by microarray. The aim of the present study, was to explore whether miR-192 or miR-195 can reflect renal disease activity in lupus nephritis (LN) patients treated with Cytoxan.

Methods: Urine samples were collected from nine patients with active proliferative LN at baseline, 6 and 9 months post Cytoxan treatment. Urinary exosomes were isolated from 8 ml of urine sample in each urine collection by differential ultracentrifugation (520 × g for 10 min, 17,000 × g for 15min and 200,000 × g for 1hr at 4C). Total RNA was extracted from urinary exosomes with miRNeasy Kit. 25ng of total RNA were used in Taqman RT-PCR for analysis of miR-192, -195, and -27b (as the control of glomerular miRs due to abundant expression of miR-27b in renal medulla). The correlation among miRs and clinical parameters were analyzed by the Spearman correlation test, using the Prism 5 software package.

Results: The excretion of three urinary exosomal miRs significantly decreased at 6 and 9 months after cytoxan treatment compared to pretreatment in active LN patients. The level of urinary exosomal miRs did not correlate with urine concentration determined by urinary creatinine concentration. However, urinary exosomal miR-192 levels significantly correlated with urinary protein/creatinine (P/C, $r=0.56$, $p=0.031$) and so was urinary exosomal miR-195 ($r=0.60$, $p=0.018$). Albeit not significant, a similar trend was seen with urinary exosomal miR-27b and P/C ($r=0.31$, $p=0.26$). All three miRs correlated strongly with each other ($r=$ 0.68–0.8, $p<0.05$).

Conclusion: Urinary exosomes contain abundant miRs which can serve as a useful source for biomarkers. All three miRs decreased after cytoxan treatment. The difference in correlation between the level of miRs previously linked to diabetic nephropathy or lupus nephritis and miR-27b, which was used as a control, suggests a qualitative and not just quantitative change in exosomal miRs. However, the strong correlation among the three miRs tested supports the contrary and suggests that the correlation between miRs and proteinuria is a mere reflection of the improvement in the filtering function of the glomerular basement membrane. Further studies with a larger number of miRs are needed to assess the biomarker potential of urinary exosomal microRNAs in lupus nephritis.

2288

Nitrated Nucleosome Levels in Patients with Systemic Lupus Erythematosus—Associations with Disease Activity. Sara Croca[1], Charis Pericleous[1], Karim Alber[1], Harry Yong[1], Ian Giles[1], David A. Isenberg[2], Anisur Rahman[1] and Yiannis Ioannou[1]. [1]University College London, London, United Kingdom, [2]University College London, London WC1E 6JF, United Kingdom

Background/Purpose: Many different autoantibodies such as anti-nucleosome antibodies have been described in patients with SLE and serological assays have concentrated mainly on measuring autoantibody levels. Measuring levels of modified autoantigens may also be valuable. Since levels of reactive nitrogen species that promote nitration may rise with levels of systemic inflammation, we hypothesised that nitrated nucleosome (NN) levels may vary in parallel with disease activity. This abstract describes the result of longitudinal studies of NN levels and measures of disease activity in patients with SLE.

Methods: Longitudinal serum samples ($n=$ 398) were selected retrospectively from a cohort of 49 patients with SLE with a mean of 8 samples per patient (SD 2.16; min 3; max 14) and a mean follow-up of 89 months (SD 46; min 14; max 180). NN levels were measured using a capture ELISA. For all samples where data were available, we obtained anti-dsDNA and complement C3 levels and disease activity from a matching date and from the previous 3 assessments if these had occurred in the preceding 12 months. Using the British Isles Lupus Assessment Group (BILAG) index, we categorized the samples by disease activity as follows.

Current activity (on the date of the sample) was defined as high if global BILAG score was ≥5 and low if it was <5). Disease activity over the most recent 4 assessments was characterized as persistently low activity (all systems BILAG C, D or E) or persistently moderate-high activity (A or ≥1 B in any BILAG system on at least 2/4 occasions). 90% of all samples fell into one of those two categories and the rest were excluded.

Anti-dsDNA was defined as high or normal based on a cut-off of 50IU/ml. C3 was defined as low or normal based on a cut-off of 0.9g/l.

Results:

	Number of samples (*n*)	Mean (SD) NN level	*p*-value (high vs. low)
Persistently moderate-high activity	188	40.50 (51.7)	0.038
Persistently low activity	154	24.8 (72.3)	
BILAG< 5	204	25.6 (57.3)	0.045
BILAG≥ 5	171	37.9 (69.3)	
Anti-dsDNA			
High (>50IU/ml)	171	29,0 (48.1)	0.035
Normal(≤50IU/ml)	177	21.9 (38.6)	
C3			
Normal (≥0.9g/l)	207	20.8 (40.6)	<0.0001
Low (<0.9g/l)	138	31.6 (47.0)	

Conclusion: High NN levels were associated with high disease activity, high anti-dsDNA and low complement. In addition, flares in different organ systems may be associated with different levels of NN.

2289

Expression of Interferon-Inducible Genes Are Regulated by Sex Hormones and Gender in Systemic Lupus Erythematosus. Ravi Dinesh[1], Awlad Hossain[1], Bevra H. Hahn[1] and Ram P. Singh[2]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]David Geffen Schl of Med/UCLA, Los Angeles, CA

Background/Purpose: The goal of the present study was to determine the role of gender and the effect of sex hormones on the regulation of interferon genes in healthy individuals and in SLE patients, with particular attention to CD4+ regulatory T cells, which are fewer in number in women than in men in both the general population and in SLE patients.

Methods: Levels of interferon genes, sex hormones (17 b-estradiol, testosterone), cytokines, and chemokines were measured by real time PCR in peripheral blood cells, by ELISA in the serum/plasma of healthy donors, and

from the culture supernatant of peripheral blood mononuclear cells (PBMC) isolated from SLE patients and healthy controls. PBMC were immunophenotyped by flow cytometry, and mRNA gene expression studies were performed by real time PCR. Protein expression was analyzed by intracellular staining and by Western blot analysis. The *in vitro* effect of sex hormones 17 b-estradiol (60–100, 500pg/ml), and testosterone (100pg/ml) were studied by addition to cultures of sorted $CD4^{+}CD25^{hi}CD127_{lo}$ regulatory T cells for 24–72 hours. FACS/Western blot analyses of the cells were performed after culture.

Results: 1. Healthy women have significantly higher interferon related genes in PBMC ($p<0.02$) than healthy men.

2. Similarly, female BWF1 lupus mice have increased expression of interferon genes in spleen cells compared to age and sex- matched males.

3. Estradiol regulates interferon-inducible genes differentially in healthy controls and in SLE, with higher induction of IFN-inducible genes in the SLE population.

4. Estradiol increases proinflammatory cytokine generation, including positive correlation between plasma levels of estradiol and IL-21.

5. Plasma 17b-estradiol levels are significantly increased in female SLE patients compared to healthy females ($p<0.01$).

6. Testosterone (100 pg/ml) significantly increased FoxP3 expression in $CD4+CD25^{hi}$ cells from women with SLE ($p< 0.03$).

Conclusion: Women may be more susceptible than men to SLE and other autoimmune diseases in part because many healthy women have fewer CD4+ regulatory T cells, with less expression in PBMC of FoxP3 and more of interferon-regulated genes. In addition, women with SLE, compared to healthy women, have less ability to generate CD4+ Treg in response to physiologic concentrations of 17 b- estradiol, whereas testosterone metabolite increases the generation of Tregs. These data suggest that gender and sex hormones may influence susceptibility to SLE in part via their effects on regulatory T cells and interferon genes.

2290

The Lupus Damage Index Questionnaire and Its Correlation with the SLICC/ACR Damage Index and the LupusQoL in a Spanish Multicenter Lupus Cohort. Is It Really Measuring Damage? José M. Pego-Reigosa[1], Íñigo Rúa-Figueroa[2], Teresa Otón-Sánchez[1], Manuela Fontanillo-Fontanillo[1], María Galindo-Izquierdo[3], Esther Uriarte-Isacelaya[4], Bruno Aspe-de la Iglesia[5], Laura Cáceres-Martín[2] and Félix Francisco-Hernández[2]. [1]Hospital do Meixoeiro, Vigo, Spain, [2]Hospital Universitario Dr Negrín, Las Palmas de Gran Canaria, Spain, [3]Hospital 12 de octubre, Madrid, Spain, [4]Donosti, Spain, [5]Vigo, Spain

Background/Purpose: Survival in patients with systemic lupus erythematosus (SLE) has improved over the last decades. Consequently, outcome measures such as accumulated damage and health-related quality of life (HRQOL) are gaining relevance. A self-assessed lupus organ damage instrument, the Lupus Damage Index Questionnaire (LDIQ), has been recently developed.

To study the correlation of accumulated lupus damage measured using the LDIQ with that measured using the SLICC/ACR damage index (DI). To analyze the correlation of both measures with SLE HRQOL measured using LupusQoL.

Methods: Multicenter cross-sectional study evaluating 156 patients with SLE. All patients completed the LDIQ and the LupusQoL. Four rheumatologists reviewed the clinical charts in order to calculate accumulated damage using SLICC/ACR DI. The correlation of the levels of damage measured using both instruments was calculated (Spearman's rho correlation coefficient). The correlation of damage with HRQoL measured using LupusQoL was calculated employing the same statistical test.

Results: One hundred and fifty-six patients (146 women and 10 men) were included in the study. The mean age (±S.D.) was 45.4 years (± 12.3). The mean time (±S.D.) since the lupus diagnosis was 15.5 years (± 8.9). The mean number (±S.D.) of lupus criteria was 5.6 (± 1.6) per patient. The mean time of years of study of the patients (±S.D.) was 11.1 (± 4.1).

The mean SLICC/ACR DI score was 1.1 (range 0–12) and the mean LDIQ score was 4.5 (range 0–18). The worst degree of agreement between SLICC/ACR DI and LDIQ was for renal damage (Spearman's $r = 0.13$, $p =$ n.s.). There was an important overestimation of neuropsychiatric damage (particularly neuropathy) by LDIQ compared to SLICC/ACR DI capturing 21 (15%) and 74 (49%) of the patients, respectively. The mean difference (±S.D.) between both damage scores was 2.7 (±2.5) and a clear trend towards lower differences was seen in the subgroup of patients with a longer period of education (>12 years) compared to that with <8 years. We found significant association of both damage scores with the number of lupus criteria and with the time since diagnosis of lupus. The global level of HRQoL was measured calculating the mean value of the eight domains that form the LupusQoL (the value ranges from 0–100 being 0 the minimum value and 100 the maximum value of HRQoL). The mean LupusQoL score was 64.0 (range 4.7–100). We did not find significant association of the LupusQoL scores with the time since the diagnosis and the number of lupus criteria that the patient fulfilled. The LDIQ scores had a significant correlation with the SLICC/ACR DI scores (Spearman's $r = 0.44$, $p < 0.001$) but a stronger significant negative correlation with LupusQoL scores (Spearman's $r = -0.48$, $p = 0.001$).

Conclusion: The correlation between the self-assessed LDIQ and SLICC/ACR DI is moderately high. The LDIQ tends to overestimate accumulated lupus damage (particularly renal and neuropsychiatric damage) compared with SLICC/ACR DI. This overestimation may be associated with a shorter period of education. The correlation of LDIQ scores with a HRQoL instrument scores such as LupusQoL is stronger than that with the traditional damage index scores (SLICC/ACR DI).

2291

Anti-Dense Fine Speckled 70 Antibodies: Initial Study of Clinical and Laboratory Associations in a US Laboratory Patient Population. Gurpreet Rawat, Kathleen Hutchinson and Mark H. Wener. University of Washington, Seattle, WA

Background/Purpose: The recently recognized nuclear dense fine speckled immunofluorescence (IF) ANA pattern is associated with antibodies to the dense fine speckled 70 (DFS70) antigen. Presence of antiDFS70 may identify populations with a low prevalence of autoimmune rheumatic disease. A systematic evaluation of the associations of antiDFS70 has not been described previously in a U.S. clinical lab population.

Methods: Serum samples sent for ANA tests to our clinical laboratory were tested for ANA by a multiplex bead assay and HEp2 IF. Specimens with a positive IF ANA but negative for tested ANA subsets were identified. Randomly selected samples from that population were tested using a commercial anti-DFS70 ELISA and chart reviews were done on positive samples.

Results: 110 sera that were IFA positive but negative for ANA subsets were tested for anti- DFS70. Of those, 26 (24%) samples were positive.

Clinical data were available for 10 of the 26 DFS70-positive sera: 5 of the 10 were eventually referred to rheumatology. The IF ANA pattern was most commonly a mixed homogenous-speckled pattern (7/10). Three ANAs were homogenous alone. One serum had an ANA titer of 1:40, 4 had a 1:80 titer, 2 had 1:160 titer and 2 had 1:320 titer. One serum had an indeterminate RNP antibody, but no other ENA serologic abnormalities were present. Common clinical symptoms were arthralgias (6/10) and myalgias (3/10) with normal creatine kinase. 1 subject had documented synovitis. No other symptoms or signs of a connective tissues disease were present in the 10 subjects. One subject had transient lymphopenia and one subject had benign large granular lymphocytes. The ESR was elevated in 1/5 tested at 25 mm/hr. C-reactive protein was elevated in 3/5 tested, at 10.3, 14.3 and 20.9 mg/L. 2 subjects had echocardiograms: 1 normal, 1 with moderate diastolic dysfunction. One subject had pulmonary function tests showing mild restrictive disease. Diagnoses in the patients with DFS70 antibodies included 1 with multiple sclerosis, 1 with a history of ITP and 1 with hypothyroidism. There were no other autoimmune diseases noted. Other diagnoses included type II diabetes mellitus (2/10); obstructive sleep apnea (2/10); fibromyalgia (3/10); and polymorphic light eruption, migraines, and asthma in one subject each. There was no recorded history of atopic dermatitis, cystitis or malignancy (diagnoses previously reported with antiDFS70).

Conclusion: We found a moderate prevalence of antiDFS70 in sera ANA-positive by IF but without identified routine ANA subsets. Most of the positive samples were reported as having a combined homogenous-speckled pattern, similar to the recently described dense fine speckled pattern. Our positive sera had a range of ANA IF titers. None of our subjects had an identified autoimmune rheumatic disease. From this U.S. population, although small, we provide additional support for the proposal that sera with only DFS70 antibodies may help identify patients who do not have a rheumatologic disease despite a positive ANA IF test.

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The Workplace Activity Limitations Among Lupus Patients. Ali Al-Dhanhani[1], M. A. Gignac[2], Dorcas E. Beaton[3], Jiandong Su[4] and Paul R. Fortin[5]. [1]UAE University, Al Ain, United Arab Emirates, [2]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [3]Ontario Workers Comp Institute, Toronto, ON, [4]The Toronto Western Hospital, Toronto, ON, [5]Toronto Western Hospital, Toronto, ON

Background/Purpose: Evidence in the literature suggests that people with lupus are at risk of work loss soon after diagnosis, but little is known about the experience of those people while at work. The objective of this study was to examine the extent of workplace activity limitations among persons with lupus and to determine factors associated with workplace activity limitations.

Methods: This is a cross sectional study using a mail survey of persons with lupus who attend a large single outpatient lupus clinic. We combined the survey data with the clinical data available for those patients from the clinic database. Eligible patient were those who read and wrote English and who were seen in the clinic in the previous two years. We used the workplace activity limitations measure (WALS), a 12-items scale that measures difficulty related to different activities at work. Through the survey, we collected data on demographics and health, work factors and psychosocial measures. Descriptive statistics, followed by univariate and multivariate (MV) regression analyses were performed.

Results: There were 604 eligible patients who were sent the survey. We had 362 responders (60% response rate). The mean age of respondents was 47.7 ± 15.0 and disease duration was 17.7±11.0. Eighty eight percent of responders were females. There were only 50% of respondent who were in the workforce. Among those who were not working, 52% reported not working because of lupus. In all the items of the WALS with one exception those who recently left the workforce had statistically significant more difficulty with work tasks compared to those who are currently at work table 1. Among working groups, 12% had difficulty in 9 items or more, compared to 43% among those who recently left the workforce. Those who left the work force had more difficulty in lifting, carrying or moving objects. Among those working, we document more difficulty crouching, bending, kneeling or working in awkward positions. In the multivariate analysis, factors associated with workplace activity limitations were age, disease activity, fatigue, health status measured by SF-36, job control, job strain, and working more than 40 hours/week.

Table 1. Percentage of people reporting difficulties in WALS items, a comparison between employed and not employed participants (but recently left the workforce in the previous five years) on the workplace activity limitations scale (WALS).

	Not employed (N = 65) %	Employed (N = 180) %	Difference (p-value)
1. How much difficulty would you have getting to and from work (e.g., subway, bus, car, walking) and getting to and from work on time?	32.3	17.9	0.0157*
2. How much difficulty would you have getting around the workplace (e.g., stairs, hallways, furniture)?	41.5	17.2	<0.0001*
3. How much difficulty would you have sitting for long periods of time at your job (e.g., more than 20 minutes)?	43.1	28.3	0.0293*
4. How much difficulty would you have standing for long periods of time at your job (e.g., more than 20 minutes)?	56.9	33.9	0.0012*
5. How much difficulty would you have lifting, carrying or moving objects?	64.6	42.2	0.0020*
6. How much difficulty would you have working with your hands (e.g., writing, typing, grasping small objects, holding a phone)?	52.3	27.2	0.0002*
7. How much difficulty would you have crouching, bending, kneeling or working in awkward positions?	60.0	57.8	0.7554
8. How much difficulty would you have reaching?	46.9	23.0	0.0003*
9. How much difficulty would you have with the schedule or hours of work that your job requires?	62.5	36.1	0.0003*
10. How much difficulty would you have with the pace of work that your job requires?	63.1	37.4	0.0004*
11. Overall, how much difficulty would you have meeting your current job demands?	60.3	36.7	0.0011*
12. As a result of your lupus, how much difficulty would you have concentrating or keeping your mind on your work?	63.1	38.6	0.0007*

Conclusion: People with lupus experience significant limitations and difficulty at work. Determinants of workplace activity limitations are mainly those related to health, and workplace related factors.

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Shrinking Lung Syndrome is a Multifactorial Process Featuring Reduced Lung Compliance and Extrinsic Ventilatory Restriction. Lauren A. Henderson[1], Stephen H. Loring[2], Ritu R. Gill[3], Katherine P. Liao[3], Matthew L. Stoll[4], Susan Kim[1], Paul F. Dellaripa[3], Deborah Rothman[5], Lawrence S. Zemel[6], Mary B. Son[1] and Peter A. Nigrovic[3]. [1]Children's Hospital Boston, Boston, MA, [2]Beth Israel Deaconess Medical Center, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Shriners Hosptials for Children, Springfield, MA, [6]Connecticut Childrens Med Ctr, Hartford, CT

Background/Purpose: The pathogenesis of shrinking lung syndrome (SLS) is poorly understood. We sought to identify the locus of pathology in SLS through detailed study of pulmonary physiology in affected patients.

Methods: SLS was defined to encompass patients with a systemic rheumatic disease who presented with dyspnea and all of the following: (1) decreased lung volumes on chest imaging; (2) pulmonary function tests demonstrating a restrictive ventilatory defect with normal diffusing capacity for carbon monoxide (DLCO), corrected for alveolar volume and hemoglobin concentration; and (3) absence of lung parenchymal pathology on chest computed tomography (CT). Patients who met these criteria and underwent pulmonary evaluation with esophageal manometry were identified. Demographic and clinical data were obtained from the medical records. Parameters examined included maximal inspiratory pressures measured by an esophageal balloon catheter (MIP_{es}) at defined lung volumes and static and dynamic lung compliances. Chest CT scans were reformatted to allow assessment of lung densities.

Results: Six SLS patients who underwent pulmonary evaluation were identified. All patients presented with dyspnea and had evidence of pleuritis manifested by pleuritic chest pain and/or pleural effusions. Chest imaging was free of parenchymal disease. Total lung capacities (TLC) ranged from 39% to 50% of predicted; however, corrected DLCOs were normal. Static and dynamic lung compliances were reduced in all patients. MIP_{es} were normal or near normal at functional reserve capacity (FRC), excluding overt respiratory muscle myopathy. In contrast, MIP_{es} at higher lung volumes were impaired in 5 patients, ranging from 12.2 to 23.7cm H_20 (normal: 25 to 35cm H_20), a finding consistent with an inability to fully expand the chest wall. Chest CT reformatting to assess lung density was available in 5 patients and showed increased lung densities. Re-evaluation after successful therapy in 1 patient showed improved MIP_{es} at FRC and TLC with no change in lung compliance.

Conclusion: In all patients studied, SLS manifested at least 2 concomitant pulmonary abnormalities: (1) reduced expansion of the chest wall upon inspiration, likely reflecting respiratory muscle inhibition by neural reflexes initiated by pleuritis; and (2) decreased lung compliance in the absence of radiographically evident interstitial lung disease, a well-recognized but poorly understood effect of chronic hypoventilation. Together, these findings suggest that SLS is primarily an unusual manifestation of pleural inflammation. Why some patients with pleurisy progress to SLS while others do not remains to be defined, but propensity to develop changes in lung parenchyma with hypoventilation is one intriguing candidate.

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Socioeconomic Status Is Associated with Disability in Pediatric Systemic Lupus Erythematosus. Mary Beth F. Son[1], Aimee O. Hersh[2], Hermine Brunner[3], B. Anne Eberhard[4], Emily von Scheven[5] and CARRAnet Investigators[6]. [1]Children's Hospital Boston, Boston, MA, [2]University of Utah, Salt Lake City, UT, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [5]UC San Francisco, San Francisco, CA, [6]Durham

Background/Purpose: To evaluate socioeconomic status (SES), demographics, use of cyclophosphamide, and disease activity as predictors of disability in a diverse cohort of patients with pediatric-onset systemic lupus erythematosus (pSLE).

Methods: Cross-sectional data were obtained from the CARRAnet registry, a United States pediatric rheumatology database. Subjects included in the database were diagnosed with SLE at ≤18 years of age and were ≤ age 21 at enrollment. Disability was defined as a Childhood Health Assessment Questionnaire (CHAQ) score > 0 at enrollment. Multivariate logistic regression was used to determine predictors of disability. Gender, ethnicity, annual household income as a principal measure of SES, disease duration, previous or current treatment with intravenous cyclophosphamide as proxy for nephritis or cerebritis, and disease

activity at enrollment according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), were included as predictors.

Results: Data from 306 subjects enrolled at 44 sites were analyzed. Mean age at onset of symptoms was 12 ± 3 yrs (range 2.6–19.3 yrs). Mean disease duration was 3.6±2.7 years; 82% were female. Race/ethnicities included African American (33%), Caucasian (27%), Hispanic/Latino (22%), Asian (10%) and other (8%). 21% of the cohort had a household income of <$25,000/year. The median SLEDAI score at the time of enrollment was 4 (range 0–38). 32% had a current or prior history of treatment with intravenous cyclophosphamide. 131/306 (43%) subjects had disability defined as a CHAQ score>0; the mean CHAQ score was 0.23±0.43 and the median CHAQ score was 0 (range 0–3). In multivariate logistic regression analysis, low income was associated with disability (pseudo R2 = 0.088, Table 1).

Table 1. Regression-adjusted odds ratios for disability in the CARRAnet pediatric systemic lupus erythematosus cohort

Variable	Adjusted Odds Ratio (95% CI)
Disease Duration	1.00 (0.89–1.12)
Female	0.47 (0.21–1.07)
Ethnicity	
Caucasian	Referent
African American	1.23 (0.57–2.62)
Latino/Hispanic	1.30 (0.56–3.01)
Asian	0.49 (0.13–1.80)
Other	0.84 (0.23–3.1)
Household Income (in USD)	
≥75,0000	Referent
25,000–74,999	1.51 (0.69–3.30)
<25,000	2.69 (1.15–6.29)
SLEDAI	1.08 (1.01–1.15)
Cyclophosphamide Use	0.63 (0.33–1.22)

Conclusion: Disability was common in this cohort of pSLE subjects; the strongest predictor was SES as measured by household income. Additional studies are needed to better understand the relationship between SES and outcomes in pSLE.

2295

Performance of Complement C3, C4 and Anti-dsDNA Antibody in Predicting Disease Flare in Systemic Lupus Erythematosus: An Analysis of Data From 6035 Clinical Visits. Chi Hung To, Ka Lung Yu and Chi Chiu Mok. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: To examine the performance of complement C3, C4 and anti-ds DNA antibody in predicting clinical disease flare in systemic lupus erythematosus(SLE).

Methods: SLE patients who were followed up in our clinics between 2000 and 2008 were studied. The date and clincial details of all visits during this period were retrieved from the electronic medical records. Disease flares (mild/moderate or severe), as defined by the SELENA-SLE flare instrument, were recorded. Disease activity scores during the flare episodes were measured by the SELENA-SLEDAI. The complements level C3, C4 and anti-dsDNA antibody titer checked within 4 weeks before the flare episodes (mild/moderate or severe) and the non-flare episodes were retrieved. Low C3 (LC3), very low C3 (VLC3), low C4 (LC4), and very low C4 (VLC4) were defined as 0.5–0.74g/L, <0.5g/L, 0.1–0.13g/L and <0.1g/L, respectively. Positive anti-dsDNA (PdsDNA) and highly positive anti-dsDNA (HPdsDNA) assay were defined as 50–300 IU/ml and >300 IU/ml respectively. The sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of C3, C4 and anti-dsDNA in predicting disease flares were calculated.

Results: 218 SLE patients were studied. There were a total of 6035 clinical visits recorded. Among these, there were a total of 238 mild / moderate lupus flares, 178 severe lupus flares and 5778 non-flare episodes. The results were shown in table 1.

Table 1. Sensitivity, specificity, PPV and NPV of C3, C4 and anti-dsDNA antibody in predicting mild/moderate and severe lupus flares.

	Mild/Moderate Flares				Severe Flares			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
LC3	34.8%	63.2%	3.7%	95.9%	29.2%	63%	2.3%	96.7%
VLC3	43.1%	**87.5%**	12.3%	97.4%	51.1%	**87.4%**	11%	98.3%
LC4	19.1%	78.9%	3.7%	95.8%	19.2%	79%	2.8%	96.9%
VLC4	**49.1%**	74%	7.4%	97.2%	**52.9%**	73.9%	5.9%	98%
PdsDNA	**51.8%**	57.1%	5.1%	96.4%	**56.1%**	57.1%	4.1%	97.5%
HPdsDNA	28.4%	**89.1%**	10.3%	96.5%	26%	**88.8%**	7.1%	97.3%

Conclusion: The combination of complement C3, C4 and anti-dsDNA antibody is reasonably specific for predicting lupus flares in the preceding 4 weeks, especially for HPdsDNA and VLC3. However, these conventional markers are not sensitive for predicting lupus flares.

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Performance of Complement C3, C4 and Anti-dsDNA Antibody in Predicting Disease Flare in Individual Organ Systems in Systemic Lupus Erythematosus: An Analysis of Data From 6035 Clinical Visits. Chi Hung To, Ka Lung Yu and Chi Chiu Mok. Tuen Mun Hospital, Hong Kong, Hong Kong

Background/Purpose: To examine the performance of complement C3, C4 and anti-ds DNA antibody in predicting disease flare in individual organ systems in systemic lupus erythematosus(SLE).

Methods: SLE patients who were followed up in our clinics between 2000 and 2008 were studied. The date and clinical details of all visits during this period were retrieved from the electronic medical records. Disease flares in the five organ systems (cutaneous and musculoskeletal, serositis, hematologic flare, renal and neuropsychiatric) were defined by using the individual components of SLEDAI and the SELENA-SLE flare instrument and were recored during flare episodes. The complements level C3, C4 and anti-dsDNA antibody titer checked within 4 weeks before the flare episodes and the non-flare episodes were retrieved. Low C3 (LC3), very low C3 (VLC3), low C4 (LC4), and very low C4 (VLC4) were defined as 0.5–0.74g/L, <0.5g/L, 0.1–0.13g/L and <0.1g/L respectively. Positive anti-dsDNA (PdsDNA) and highly positive anti-dsDNA (HPdsDNA) assay were defined as 50–300 IU/ml and >300 IU/ml respectively. The sensitivity, specificity of C3, C4 and anti-dsDNA in predicting disease flare of individual organ systems were calculated respectively.

Results: 218 SLE patients were studied. A total of 6035 clinical visits were recorded. There were a total of 257 cutaneous and musculoskeletal flares, 119 hematologic flares, 108 renal flares, 26 serositis flares, 27 neuropsychiatric flares and 5778 non-flare episodes recorded. The results were shown in table 1.

Table 1. Sensitivity, specificity of C3, C4 and anti-dsDNA antibody in predicting disease flare of individual organ systems

	Cutaneous and musculoskeletal flare		Serositis flare		Hematologic flare		Renal flare		Neuropsychiatric flare	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
LC3	35.9%	63.2%	23.1%	63.2%	34.5%	63.2%	28.7%	63.1%	28.6%	63.2%
VLC3	43.4%	**87.2%**	46.2%	**86.4%**	52.1%	**87.1%**	57.4%	**87.1%**	33.3%	**86.4%**
LC4	16%	78.9%	26.9%	79.1%	17.5%	78.9%	19.4%	79%	14.8%	79%
VLC4	**52.5%**	73.8%	34.6%	73.1%	**57%**	73.7%	55.3%	73.6%	34.6%	73.1%
PdsDNA	48.7%	56.9%	**66.6%**	56.8%	54.6%	56.9%	**61.1%**	57%	**60%**	56.8%
HPdsDNA	30.7%	**88.9%**	9.5%	**88.3%**	29.1%	**88.7%**	27.7%	**88.6%**	5%	**88.3%**

Conclusion: Anti-dsDNA lacks sensitivity in predicting serosal and neuropsychiatric lupus flares. Specificity for flares in any organ system is high for HPdsDNA and VLC3. The sensitivity of these conventional markers in picking up a lupus flare in any system is not impressively high. More sensitive novel biomarkers for predicting lupus flares are necessary.

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Digital Image Analysis Results Show High Reproducibility and Agreement with Human Interpretation on HEp-2 Cells. Gabriella Lakos, Carol E. Buchner, Cassandra C. Bryant, Pieter A. Baker, Rachel A. Rosenblum and Rufus W. Burlingame. INOVA Diagnostics, Inc., San Diego, CA

Background/Purpose: Evaluate the precision of the NOVA View® automated digital microscope system for anti-nuclear antibody (ANA) testing on HEp-2 cells based on nuclear light intensity units (LIU) and endpoint titration data. Additionally, compare the NOVA View results generated on 204 clinically defined sera to human interpretation of the same image captured by an automated camera and archived as a digital image.

Methods: For assessing intra-assay precision, four specimens with established patterns were assayed in the same run in 12 replicates. For inter-assay precision, five serum samples were tested in 25 runs that included two lots of HEp-2 slides, two lots of conjugates, and three operators. The %CV values were calculated based on nuclear LIU values generated by the NOVA View. Moreover, endpoint titers of four positive sera were established in 25 separate runs. To evaluate agreement, 204 clinically defined sera were processed for ANA testing on HEp-2 cells and then analyzed on the NOVA View automated system. A comparision of the nuclear LIU of the NOVA View with the reactivity obtained by human interpretation of the archived images was performed.

Results: The intra-assay and inter-assay precision was <20%. In the titration experiments, the same endpoint was found on average 15 times out of 25 runs

(range: 8–18), and the endpoint was one dilution lower or higher in the rest of the cases. Therefore, the 25 runs resulted in the same ± one dilution endpoint for all 25 runs for all four sera.

The qualitative discrimination by NOVA View was compared to the operator reactivity grading of the archived images. Depending on the chosen LIU cut-off values, the agreement between the automated and the human interpretation was 95.1% with a 100 LIU cut-off, and 96.1% with a 200 LIU cut-off, respectively. In the first setting there were 10 NOVA View positive/human interpretation negative results, while in the second setting there were 8 NOVA View negative/human interpretation positive results in the cohort.

Conclusion: Indirect immunofluorescence (IIF) testing on HEp-2 cells is considered the reference method for ANA detection. Lack of standardization of this method, however, still remains a concern. Sources of variability include the microscope and the interpretation by the operator. The NOVA View system offers automated evaluation of the IIF images, thereby decreasing sources of variability. Our results show that ANA detection by the NOVA View automated system is reproducible and reliable. The archived images can be stored and viewed or shared at any time. NOVA View provides the capability to quantify results which, in combination with high reproducibility, could provide the basis for ANA testing standardization.

2298

Serological and Clinical Associations of Anti-PCNA Antibodies in Systemic Lupus Erythematosus Detected by a Novel Chemiluminescence Assay. Michael Mahler[1], Marvin J. Fritzler[2] and John G. Hanly[3]. [1]INOVA Diagnostics, Inc., San Diego, CA, [2]University of Calgary, Calgary, AB, [3]Dalhousie University, Halifax, NS

Background/Purpose: Autoantibodies targeting proliferating cell nuclear antigen (PCNA) occur rarely in patients with systemic autoimmune rheumatic diseases, but are most commonly associated with systemic lupus erythematosus (SLE). The primary antigenic target is a 34 kDa protein that is part of the DNA polymerase delta multi-protein complex. The objective of the present study was to analyze the prevalence of anti-PCNA antibodies in SLE and various other diseases and healthy controls using a novel chemiluminescence immunoassay (CIA) and to evaluate a putative association with neuropsychiatric manifestations in SLE patients.

Methods: Sera or plasma from SLE patients (n=251), from individuals with various other diseases (n=257), and from apparently healthy blood donors (n=188) were tested for anti-PCNA antibodies by QUANTA Flash PCNA (research use only, INOVA Diagnostics) using commercially available recombinant human PCNA (Diarect AG, Freiburg, Germany) coupled to magnetic beads. SLE patient samples were also tested for other autoantibodies using the respective QUANTA Lite® ELISAs (INOVA Diagnostics). Statistical analysis (Fisher exact test, receiver operating characteristics (ROC) analysis) was done with ANALYSE-IT Version 2.03.

Results: Anti-PCNA antibodies were detected in 6% (15/251) of SLE patients, in 2.6% (1/38) of systemic sclerosis samples and in 4.3% (2/47) of rheumatoid arthritis patients. All other control samples were negative. Thus, the sensitivity for SLE was 6% (95% Confidence interval, CI 3.4–9.7%) with a specificity of 98.9% (95% CI 97.4–99.6%). The positive and negative likelihood ratios were 5.32 and 0.95, respectively. When SLE patients were compared to controls by ROC analysis, the area under the curve value was 0.88 (95% CI 0.85–0.90). Anti-PCNA antibodies were associated with anti-dsDNA (p=0.0250), anti-chromatin (p=0.0017) and anti-Ribosomal P antibodies (p=0.0058), but not with anti-RNP, anti-Sm, anti-SS-A (Ro60 and Ro52/TRIM21 mixture) or anti-SS-B.

Anti-PCNA antibodies, but none of the other autoantibodies were associated with lupus psychosis (p=0.0063). When NPSLE patients were compared to SLE without psychosis by ROC analysis, the AUC value was 0.83 (95% CI 0.65–1.00). At a cut-off of 20,000 RLU the sensitivity for NPSLE was 50.0% (95% CI 11.8–88.2%) and the specificity 95.1% (95% CI 91.6–97.4%). The positive likelihood ratio (LR) was 10.21 and the native LR 0.53.

Conclusion: Anti-PCNA antibodies are present in 6% of SLE patient sera, and are associated with anti-dsDNA, anti-chromatin and anti-ribosomal P antibodies as well as with lupus psychosis. In all of our samples, anti-PCNA antibodies were accompanied by at least one other autoantibody. Further studies using defined clinical subsets are required to verify the association between anti-PCNA antibodies and NPSLE.

2299

LupusPRO and Responsiveness to Changes in Health Status and Disease Activity Over Time. Meenakshi Jolly, Jessica Cornejo, Rachel A. Mikolaitis and Joel A. Block. Rush University Medical Center, Chicago, IL

Background/Purpose: LupusPRO is a disease targeted patient reported outcome measure for patients with Systemic Lupus Erythematosus (SLE). It has been developed from and validated among US patients with SLE. Herein, we sought to determine if LupusPRO domains (a) changed with changes in heath status and Disease activity and (b) if the direction of the changes observed paralleled the direction of changes in disease activity or health status longitudinally in SLE.

Methods: We utilized our observational longitudinal repository data of 69 SLE patients meeting ACR classification criteria. The data were collected as part of routine outpatient care of SLE patients at our center. wherein patients complete the LupusPRO along with a change in health status since previous visit (Likert responses range from −7 to 7). Disease activity was ascertained using the Physician Global Assessment (PGA) and the Lupus Foundation of America definition of Flare (Yes/No). Two visits data was available on all patients, while 28 and 13 patients had additional data from visit 3 and 4. Random Regression Model was used to analyze the relationship between LupusPRO domains and changes in disease and health related variables. Estimates of changes in domain scores were reported. P values less than 0.05 were considered as significance.

Results: The mean age (SD) of the patients was 43.9 (12.8) yrs. Ninety-Seven percent were women and 53% African-American, 21% Caucasian, 20% Hispanic and 6% Asian. Mean (SD) PGA and SLEDAI were 0.7 (0.8) and 3.6 (4.4). Mean (SD) SDI was 1.4 (1.8). Eighteen percent of patients were classified as having flare (LFA). Most of the domains seemed to be responsive to changes in disease and self reported changes in health over time. The changes in domains scores occurred in the expected directions (Table) and are summarized below.

Table. Estimates of Changes in the LupusPRO domains

LupusPRO Domain	PGA	LFA Flare	Change in Health Status
Symptom Scale	Unit Increase −9.99 p 0.0001	Yes −13.0 p 0.0001	Extremely Worse −10.7 p 0.03 Moderately Worse −13.0 p 0.0006 Minimally Worse −8.2 p 0.01 Extremely Better −9.6 p 0.06
Cognition			Moderately Worse −7.7 p 0.04
Lupus Medications	Unit Increase −4.9 p 0.04	Yes −8.5 p 0.02	Extremely Worse −16.9 p 0.004
Physical Health	Unit Increase −7.8 p 0.001		Extremely Worse −30.2 p 0.0001 Moderately Worse −16.2 p 0.003 Extremely Better 11.2 p 0.05
Pain Vitality	Unit Increase −9.7 p 0.002	Yes −13.5 p 0.004	Extremely Worse −37.6 p 0.0001 Moderately Worse −23.2 p 0.001 Minimally Worse −15.1 p 0.001 Extremely Better 14.9 p 0.03
Emotional Health			Extremely Worse −17.3 p 0.0006 Moderately Worse −8.3 p 0.02
Body Image			Extremely Worse −10.1 p 0.04
Desires & Goals			Extremely Worse −21.2 p 0.002 Moderately Worse −15.2 p 0.003 Minimally Worse −10.4 p 0.03
Social Support		Yes 10.2 p 0.04	Moderately Worse 10 p 0.08
HRQOL Summary	Unit Increase −3.7 p 0.003	Yes −3.8 p 0.04	Extremely Worse −10.9 p 0.0004 Moderately Worse −5.8 p 0.007 Extremely Better 8.5 p 0.03

Conclusion: LupusPRO domains seem to be sensitive to changes in disease and health status over time and in the expected directions in this observational non clinical trial non intervention based data repository from SLE patients. We did not experience the full spectrum of changes in disease activity and health status to better assess the responsiveness of the tool. However within the constraints of the study design data support responsiveness of the domains. Its inclusion into clinical trials for further responsiveness evaluations are now indicated. None.

2300

Analysis of Risk Factors for Relapses and Chronic Renal Failure in Lupus Nephritis: Long Term Follow-up of Biopsy Proven 172 Patients Followed at a Single Center. Bahar Artim-Esen[1], Yasemin Özlük[2], Isin Kilicaslan[2], Ahmet Omma[1], Özlem Pehlivan[1] and Murat Inanç[1]. [1]Istanbul University, Istanbul Faculty of Medicine,Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey, [2]Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, Istanbul, Turkey

Background/Purpose: Renal involvement is a major cause of mortality and morbidity in systemic lupus erythematosus (SLE) and carries a 10–25 % risk of chronic renal failure (CRF). In this study, we aimed to analyse the

characteristics and course of lupus nephritis (LN), determine the risk factors for flares and CRF.

Methods: An analysis of 172 patients with histopathologically proven LN registered and followed-up in our clinic (lupus clinic after 1993) between 1980 and 2010 was performed. Patients with adequate histopathologic and clinical data were selected for analysis. Biopsies were classified by both WHO and ISN/RPS 2003 systems by an experienced nephropathologist(IK). The association of clinical characteristics of the cohort with renal flares and outcome was investigated. Logistic regression analysis was done and Kaplan-Meier's method was used for survival analysis.

Results: Eighty-one % of the cohort was female. Duration of renal disease was 103±66 and follow-up was 100±67 months. Class IV nephritis was the most frequent (55%) followed by class V (15%), class III (11%), class II (10,5 %) and combined(6,6%). Cyclophosphamide was used for remission induction in 80 %. Remission was achieved in 90 %. CRF developed in 25 patients (14,5 %), 4 of whom were transplanted and 8 stayed on permanent dialysis. There were 53 flares in 38 patients and the most common type was proteinuric (60,4%). Comparison of patients with and without a flare revealed that in non-relapsing patients, cyclophosphamide was more significantly used for remission induction (85 % vs 60%, p<0,001) and more patients were on mycophenolate mofetil (MMF) for maintenance (38 vs 12%, p=0,004). When active and chronic lesions at renal biopsies were compared, the presence of fibrous crescents was significantly prevalent in the relapsing group (17 vs 2%, p<0,001). At multivariate analysis not being on MMF at maintenance, fibrous crescents at biopsy, lack of exposure to cyclophosphamide at remission induction and anti-Sm positivity were found to be risk factors for flare. Of patients with a flare, 31,6% developed CRF (vs 6,6 % in non-relapsing group, p<0,001). Comparison of patients who developed CRF to others, revealed that presentation with acute renal failure (ARF), hypertension and increased creatinine, occurrence of a flare, fibrous crescents at biopsy were more frequent in CRF + group (60 vs 19 %, p <0,001; 28 vs 10 %, p=0,009, 47 vs 8 %, p<0,001; 33 vs 12 %, p=0,03; 30 vs 2 %, p<0,001 respectively). Significantly less number of patients were on MMF at maintenance in CRF + patients (16 % vs 38%, p0,03). At logistic regression analysis, hypertension followed by fibrous crescents at biopsy and maintenance without MMF were found as risk factors for the development of CRF. Comparison of survival between patients with CRF to others showed significantly reduced survival in patients with CRF after 20 years (64 vs 90%; p=0,02).

Conclusion: Flares and chronic renal failure have a negative impact on the outcome. Cyclophosphamide usage for remission induction, MMF for maintenance and tight control of hypertension may reduce the risk of flares and development of CRF. Renal histopathologic features can be a predictive tool for renal outcome.

2301

Clinical Impact of Frequency of Visits in Systemic Lupus Erythematosus. Dafna D. Gladman[1], Dominique Ibanez[2] and Murray B. Urowitz[2]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: The ACR committee on SLE guidelines recommends that patients with SLE be reviewed on a regular basis, with the frequency of visits based on the activity and severity of the disease and its complications. The aim of this study was to determine the optimal frequency of follow up visits in patients with SLE.

Methods: Patient selection: Patients followed in a large observational cohort lupus clinic from January 1, 2009 to December 31, 2010 who had at least 3 visits and at least 18 months of follow up were included. At each visit patients undergo a complete history, physical examination and laboratory evaluation. The following variables of interest that would not have been recognized by the patient were identified: proteinuria, hematuria, pyuria, casts, low haemoglobin, leucopenia, thrombocytopenia, elevated serum creatinine, positive anti-DNA antibodies and low complement. At each visit when one of these variables was detected, it was determined whether it was new, and whether other features of activity were present. Thus isolated new variables of interest were identified. Descriptive statistics were used.

Results: 515 patients met the inclusion criteria of having at least 3 visits and 18 months of follow up for a total of 3126 visits. The average length of time between visits was 3.8±1.0 months. There were 461 (89.5%) female, 315 (61%) Caucasian, 82 (16%) Black, 54 (11%) Asian, and 64 (12%) other. Age at SLE diagnosis 28.0± 12.6 (range = 6.0 to 79). At 1st clinic visit within the study period the mean age was 42.2 ± 15.1, disease duration was 14.2 ± 10.6 years (range = 0 to 56), SLEDAI-2K score was 4.1 ± 4.5 (range 0 to 34), with an adjusted mean SLEDAI of 3.87 ± 3.44 during the study period (range 0 to 180. The SLICC ACR damage index score was 1.51 ± 1.89 (range 0 to 11). Of the 515 patients, the variables of interest were the sole manifestation of SLE (ie SLEDAI-2k excluding new variable = 0) in 127 (24.7%) of the patients (in a total of 173 visits). Table 1 shows the frequency of the new isolated variables of interest in the patients and visits.

Variable	Number of visits with "new" (out of 173)	Number of patients with ≥1 visit with "new" (out of 127)
Cast	16	16
Hematuria	10	9
Proteinuria	15	15
Pyuria	42	35
Low complement	55	45
DNA antibodies	36	32
Thrombocytopenia	8	7
Leukopenia	7	7
Serum creatinine	9	8
hemoglobin	6	6

The commonest manifestations were renal, low complement and DNA antibodies but important manifestations such as thrombocytopenia, low haemoglobin and elevated creatinine were also seen.

Conclusion: 1 in 4 patients with SLE seen over a 2-year period will have a solitary silent variable of interest that could only be detected by routine laboratory follow –up. All patients with SLE should be followed with clinical and laboratory measures at 3 month intervals.

2302

Quality of Life Measures Are Not Associated and Have No Discriminative Validity in Lupus Patients for Different Levels of Disease Activity. Zahi Touma[1], Dafna D. Gladman[2], Dominique Ibanez[1], Shahrzad Taghavi-Zadeh[1] and Murray B. Urowitz[1]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, University of Toronto, Toronto, ON

Background/Purpose: A previous study showed that there is no superiority of LupusQoL over Short Form-36 in assessing lupus patients' quality of life with mild disease activity over 12 months. The utility of SF-36 and LupusQoL needs to be evaluated in patients with moderate to severe disease activity.

The objective of this study is to determine if among active lupus patients with moderate to severe disease activity, SF-36 and LupusQoL are associated with and have discriminant validity for different levels of disease activity.

Methods: This is a cross-sectional study conducted on lupus patients seen in a single center between September 2009–April 2011. At the baseline visit all patients had SLEDAI-2K ≥6. Patients completed both questionnaires on the baseline and follow-up visits.

We included the last available visit for each patient in the analysis. At the follow-up visit patients were grouped as follows: improved (if SLEDAI-2K decreased by ≥4) or same/worse.

We studied the association for each of the 8 domains of both questionnaires with SLEDAI-2K at the baseline and at the follow-up visit.

Discriminative validity was determined separately in the group who improved or was worse/same by comparing the mean scores for each of the 8 domains in both questionnaires at the baseline and the follow-up visit using t-test.

Results: 55 patients with SLEDAI-2K≥6 were indentified and included in the study. The demographics of the 55 patients are presented in table 1.

Table 1. Patients' characteristics

Sex	Female 48 (87%)/7 (13%)
Age at diagnosis (years)	28.1 ± 12.2
Age at 1st visit in the study (years)	39.1 ± 12.7
Disease Duration at 1st visit in the study (years)	10.9 ± 7.8
Race	
Caucasian	20 (36%)
Black	22 (40%)
Asian	6 (11%)
Others	7 (13%)
SDI at 1st visit in the study	1.5 ± 1.6
Prednisone at baseline visit: patients number (%)	46 (84%)
Anti-malarial number: patients number (%)	40 (73%)
Immunosuppressants: patients number (%)	40 (73%)

Mean SLEDAI-2K was 10.8±4.6 at the baseline visit and 8.4±5.0 at the follow-up visit. The length of the study was 4.8±2.3 months.

No association could be found between the 8 domains of both questionnaires and disease activity at both baseline and follow-up visits (Table 2) (all $p>0.05$).

Table 2. Association of LupusQoL and SF-36 with SLEDAI2K at baseline and follow-up visits

Domains	Baseline visits	Follow-up visits	Domains	Baseline visits	Follow-up visits
LupusQoL	**Correlation (p)**			**SF-36**	**Correlation (p)**
Physical Health	−0.02 (0.98)	0.06 (0.68)	**Bodily Pain**	−0.11 (0.43)	−0.01 (0.92)
Emotional Health	−0.20 (0.14)	−.020 (0.14)	**General Health**	0.14 (0.30)	0.18 (0.20)
Body Image	−0.11 (0.44)	−0.21 (0.12)	**Mental Health**	−0.16 (0.23)	−0.05 (0.70)
Pain	0.06 (0.66)	0.06 (0.65)	**Physical Functioning**	0.17 (0.22)	−0.02 (0.87)
Planning	0.04 (0.76)	0.04 (0.78)	**Role Emotional**	−0.16 (0.26)	0.02 (0.89)
Fatigue	−0.07 (0.61)	−0.005 (0.97)	**Role Physical**	−0.002 (0.99)	−0.12 (0.40)
Intimate Relationships	0.17 (0.27)	−0.06 (0.71)	**Social Functioning**	−0.16 (0.25)	−0.13 (0.34)
Burden to others	−0.25 (0.07)	−0.12 (0.40)	**Vitality**	−0.10 (0.48)	0.06 (0.65)
			PCS	0.13 (0.35)	−0.04 (0.77)
			MCS	−0.25 (0.07)	0.00 (0.95)

Both questionnaires showed no discriminative validity to different levels of disease activity; improved and same/worse (Table 3).

Table 3. Follow-up means comparing patients who improved (n=21) to patients who worsened/same (n=34)

	Improved n=21	Same/ worsened n=34	p values		Improved n=21	Same/ worsened n=34	p values
Disease Activity	**SLEDAI-2K**						
Baseline	12.7 ± 5.7	9.7 ± 3.4	0.04	Baseline	12.7 ± 5.7	9.7 ± 3.4	0.04
Follow-up	5.0 ± 4.3	10.4 ± 4.2	<0.001	Follow-up	5.0 ± 4.3	10.4 ± 4.2	<0.001
Domains				**Domains**			
LupusQoL	**Mean scores**				**SF-36**	**Mean scores**	
Physical Health	71.9 ± 26.0	62.2 ± 24.3	0.17	**Bodily Pain**	68.3 ± 27.3	61.8 ± 28.3	0.41
Emotional Health	77.8 ± 18.9	71.6 ± 25.0	0.34	General Health	48.4 ± 16.1	50.5 ± 23.7	0.72
Body Image	72.2 ± 21.8	66.0 ± 29.5	0.41	Mental Health	66.0 ± 15.2	68.3 ± 25.0	0.67
Pain	76.2 ± 26.1	69.1 ± 29.2	0.36	Physical Functioning	68.2 ± 28.3	58.8 ± 29.2	0.25
Planning	78.6 ± 28.5	73.8 ± 29.2	0.52	**Role Emotional**	60.0 ± 44.1	66.7 ± 43.2	0.59
Fatigue	64.7 ± 18.9	61.7 ± 26.8	0.67	Role Physical	50.0 ± 45.2	44.5 ± 45.7	0.67
Intimate Relationships	81.3 ± 21.4	56.3 ± 37.7	0.01	Social Functioning	73.2 ± 29.9	63.2 ± 29.3	0.23
Burden to others	64.5 ± 28.1	55.6 ± 26.6	0.25	Vitality	47.1 ± 18.1	52.2 ± 23.1	0.40
				PCS	43.1 ± 11.0	39.1 ± 11.7	0.22
				MCS	44.8 ± 11.0	47.6 ± 14.0	0.47

Conclusion: SF-36 and the LupusQoL are not associated with disease activity in this group of patients with moderate to severe disease activity. SF-36 and the LupusQoL have no discriminative validity to different levels of disease activity.

2303

The Influence of Age of Onset of Systemic Lupus Erythematosus and Disease Duration on Lupus Manifestations. Nayef Al Ghanim[1], Jiandong Su[2], Ellie Aghdassi[3], Wendy Lou[1] and Paul R. Fortin[4]. [1]University of Toronto, Toronto, ON, [2]The Toronto Western Hospital, Toronto, ON, [3]University Health Network, Toronto, ON, [4]Toronto Western Hospital, Toronto, ON

Background/Purpose: To investigate the influence of age of Systemic Lupus Erythematosus (SLE) onset and disease duration on the SLICC damage index (SDI).

Methods: Patients were identified from a single large lupus registry if they met four of the American College of Rheumatology classification criteria or 3 criteria and lupus histology on skin or kidney tissue. Patients were divided into two groups based on age of onset at diagnosis of SLE with Early onset (EOS) defined as those with SLE diagnosis between the ages 18 and 47 and Late onset SLE (LOS) at age 48 and more. We limited this study to an inception cohort defined as all those entered into the registry within one year of SLE diagnosis. Data on demographics, age at enrollment, SDI items and total score were collected. Chi-square tests were used to compare categorical variables. SLICC items were summarized by organ systems and then converted to a binary variable (0= negative, 1= score of 1 or more). The total SLICC scores in the two groups were compared using Wilcoxon Rank Sum test.

Results: Our sample included 653 patients with 514 EOS and 139 LOS. The majority of patients were female in both groups (88.1% in EOS vs. 82.0% in LOS; p=0.058). Caucasians were represented more in LOS (82.0% in LOS vs 69.9% in EOS; p=0.005). At 5 years follow-up, LOS patients were more likely to have cardiovascular manifestations (18% in LOS vs 6% in EOS. p=0.005). At 10 years follow-up, LOS patients have higher rate of ocular (28.9% vs 13.2%. p=0.01) and cardiovascular manifestations (23.7% vs 7.9%. p=0.005). There was no statistically significant difference in renal manifestations. Total mean SDI score was 1 in both groups at 5 and 10 years follow-up (p=NS). Comparing SDI manifestations over time (at the fifth versus the tenth year), EOS developed significantly more damage at the tenth year in ocular (9.8% vs 15.2%, respectively; p=0.01), cardiovascular (7.1% vs 10.7%; p=0.04), musculoskeletal (17% vs 26.8%; p=0.0009) and dermatological (3.6% vs 8%; p=0.02) organ systems. Similarly, LOS developed significantly more damage at the tenth year in musculoskeletal (9.1% vs 27.3%; p=0.04). In both groups, the total SLICC score increased from 0 to 1 over ten years (p=0.0005) and as expected, patients with longer follow-up have higher SLICC scores.

Conclusion: SLE damage reflects age of SLE onset diagnosis and disease duration.

2304

Prescribing Practices of Hydroxychloroquine World Wide. Seema Malani. SUNY Downstate Medical Center, Brooklyn, NY

Background/Purpose: Hydroxychloroquine (HCQ) has been used for the treatment of systemic lupus erythematosus (SLE) and other autoimmune diseases. Maculopathy is the most feared complication limiting its use. Our purpose with this survey was to determine if there is any correlation between the dosing practices of rheumatologists for HCQ and the incidence of maculopathy.

Methods: Approximately 1800 rheumatologists worldwide were invited to participate in an electronic survey with 20 questions pertaining to the use of HCQ. The survey included questions regarding use for various manifestations of SLE, side effects most noted and risk factors for maculopathy considered important by prescribers, and whether renal or hepatic function, ideal or actual body weight were taken into consideration while dosing HCQ.

Results: 582 physicians responded to the survey with 252 from North America, 151 from Europe, 109 from Asia, 66 from South America and Australia.

96% of respondants start HCQ at the time of diagnosis of SLE, 28.9% at the time of a flare and 51.6% would start even in established patients with SLE who were not on HCQ in the past. 98% of rheumatologists prescribed HCQ for arthritis with SLE, while 97.3% for cutaneous manifestations, 65.9% for fatigue, 39% for hematological indications and 26.7% for lupus nephritis (45.6% from Asia vs 22.5% from remaining respondants; p=0.000003). 52.1% would start HCQ in women planning pregnancy if symptomatic, while 31.2% even if no disease activity was present while 16.6% would not start at all. 79.8% and 61.3% stated that they would, however, continue HCQ if a patient with SLE becomes pregnant or is nursing while on it.

About 81% agreed that HCQ was beneficial for the overall survival of lupus patients. Of risk factors known for maculopathy, 79.1% considered underlying retinal or macular problems as the most significant, 49% a daily dose of more than 6.5 mg/kg actual or ideal body weight and about 32% each - age greater than 60 years, cumulative dose more than 1000 grams exposure, impaired renal function. Obesity and impaired hepatic function were not considered important by the majority.

54.2% used a fixed daily dose of 400 mg, while 31.1% adjusted the dose to actual body weight, 14.6% to ideal body weight. 33.3% and 23% adjusted for impaired renal and hepatic functions, respectively. However, there was no significant difference in maculopathy reported worldwide based on the dosing regimens with 86.6% reporting the incidence as less than 1%. GI side effects were the most common reported adverse events (74.8%) followed by skin pigmentation (72.4%), muscle weakness (27%), hematologic (11.6%) and cardiac (7.4%) effects. 94.8% of respondents from Asia and South America reported skin pigmentation vs 64.4% from the other continents ($p=1.38\times10^{-11}$).

Conclusion: The use of HCQ among rheumatologists worldwide did not differ and the dosing regimens did not affect the incidence of maculopathy. The indications and side effects appear to differ amongst the treating physicians especially from Asia and South America.

2305

Cluster Analysis of Autoantibodies in 852 Patients with Systemic Lupus Erythematosus From a Single Center: Four Main Clusters with Prognostic Implications. Bahar Artim-Esen[1], Erhan Çene[2], Yasemin Sahinkaya[1], Semra Ertan[1], Özlem Pehlivan[1], Sevil Kamali[1], Ahmet Gül[1], Lale Öcal[1], Orhan Aral[1] and Murat Inanç[1]. [1]Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey, [2]Yildiz Technical University, Department of Statistics, Faculty of Arts and Sciences, Istanbul, Turkey

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease with various serological and clinical manifestations. Associations between autoantibodies and clinical features have been described. Herein, we aimed to define autoantibody clusters and their clinical correlations in a large cohort of lupus patients.

Methods: We analysed 852 patients who attended our clinic (lupus clinic after 1993) between 1980 and 2010. Mean duration of disease was 115±85,9 months and 87% was female. Seven autoantibodies, namely anti-DNA, anti-Sm, anti-RNP, anticardiolipin IgG or IgM (aCL IgG/M), Lupus anticoagulant (LAC), anti-Ro, anti-La were selected for cluster analysis to identify subsets of lupus patients with similar autoantibody patterns. K-means cluster and Kaplan-Meier survival analyses were used.

Results: The frequencies of the selected autoantibodies in the cohort were as follows: anti-dsDNA 70%, anti-Sm 19%, anti-RNP 15%, Anti-Ro 24%, anti-La 11%, LAC 11%, aCL IgG/M 29%. Four clusters were identified by cluster analysis. Cluster 1 consisted of anti-Sm and anti-RNP, cluster 2 of anti-dsDNA only, cluster 3 of anti-Ro and anti-La and cluster 4 of aCL IgG/M autoantibodies. Although it did not reach statistical significance, LAC was more prevalent in cluster 4. Patients in cluster 1 when compared to 3 other clusters had significantly higher incidence of pulmonary hypertension (11%) and lower incidence of renal (12%) and neuropsychiatric involvement (7,9%). Cluster 2 had the highest incidence of renal involvement (43,2%) with diffuse proliferative nephritis dominating. In cluster 4, there were significantly more patients with neuropsychiatric involvement (42,9%), arterial (53,6%) and venous (54%) thrombotic events and autoimmune hemolytic anemia (33,3%). According to SLICC damage index, the highest frequency of damage was in cluster 2 (32,7%). Among SLICC damage items, there were significantly more patients with renal damage (43,1%) in cluster 2 compared to other clusters (11,1%, 15,3% and 30,6% in clusters 1, 3 and 4 respectively). Patients in cluster 4 had the highest percentage of damage due to arterial and/or venous thrombotic events. This cluster also had significantly more neuropsychiatric (40,2%) and cardiovascular (32,6%) damage compared to 3 other clusters. Comparison of 10 (98%, 92%, 95%, 88%) and 20 (98%, 87%, 88%, 80%) years survival in four clusters shows a trend towards reduced survival in Cluster 4 but the analysis did not reveal any statistical difference.

Table 1. Frequency of autoantibodies in clusters, n (%)

Autoantibody	Cluster 1 (n=136)	Cluster 2 (n=293)	Cluster 3 (n=240)	Cluster 4 (n=183)
Anti dsDNA	69 (50,7)	293 (100)*	98(40,8)	141 (77)
Anti Sm	135 (99,2)*	9 (3)	14 (5,8)	5 (2,7)
Acl IgG/IgM	43 (31,6)	0 (0)	21 (8,7)	183 (100)*
LAC	12 (8,8)	10 (4)	15 (6,2)	55 (30)
Anti RNP	121 (88,9)*	2 (0,8)	4 (1,6)	4 (2,1)
Anti RO	36 (26,4)	0 (0)	152 (63,3)*	17 (9,2)
Anti LA	14 (10,2)	2 (0,8)	71 (29,5)*	4 (2,1)

Conclusion: This study confirms the prognostic importance of autoantibodies and shows that disease subsetting according to autoantibody clusters may be useful in predicting the outcome of the disease. The cluster with only anti-dsDNA positivity in the absence of other important autoantibodies carries the highest risk for a major organ involvement and damage in our cohort.

2306

Urine Protein-to-Creatinine Ratio in a Random Spot Urine Collection Is a Reliable Measure of Proteinuria in Lupus Nephritis. In Ah Choi, Eun Young Lee, Yeong Wook Song and Eun Bong Lee. Seoul National University Hospital, Seoul, South Korea

Background/Purpose: The accurate measurement of proteinuria is critical to the clinical management of lupus nephritis. The 24-hour urine collection has been commonly used to objectively measure the amount of proteinuria but is a laborious procedure for patients and is prone to cause collection error. Alternatively, spot urine ratio of protein to creatinine (P/Cr) has been introduced as an alternative representation of the 24-hour urine collection in various kinds of kidney diseases with proteinuria. However, it is not known whether spot urine P/Cr can replace 24hr urine protein in lupus nephritis.

Methods: This is a retrospective study investigating the association of random spot urine P/Cr and 24-hour urine protein in patients with biopsy-proven lupus nephritis. A total of 286 samples of random spot urine and concurrent 24-hour urine collections from 120 patients were analyzed. All the patients were diagnosed as systemic lupus erythematosus according to the revised criteria of American College of Rheumatology and were enrolled from Seoul National University Hospital between May 2004 and July 2010.

Results: In 286 selected samples, 24-hour urine protein excretion ranged from 42 mg/day to 36,080 mg/day. The range of 24-hour urine P/Cr was 0.04 to 49.72. Random urine P/Cr ranged from 0.06 to 51.40. There was a strong correlation between 24-hour urine protein excretion and random urine P/Cr ($r= 0.774$, $P<0.001$). A strong correlation ($r= 0.939$, $P<0.001$) was also found between 24-hour urine P/Cr and random P/Cr.

The spot urine P/Cr was correlated well with 24-hour urine protein when 24-hour urine protein was less than 8 g/day ($r=0.742$, $p<0.001$). However, the correlation was poor when it was more than 8 g/day ($r=367$, $p=0.134$).

Conclusion: This study shows that random spot urine P/Cr is well correlated with 24-hour urine protein when the 24-hour urine protein is less than 8 g/day. The result supports the use of random spot urine P/Cr in screening and monitoring of proteinuria in patients with lupus nephritis.

2307

***Quasi*-homogeneous ANA-HEp-2 Pattern Reflects An Autoantibody Profile Intermediate to the Homogeneous and Dense Fine Speckled Nuclear Patterns.** Natália R. França[1], Alessandra Dellavance[2], Sílvia H. Rodrigues[3], Sandro F. Perazzio[4], Neusa P. Silva[5] and Luis Eduardo C. Andrade[3]. [1]Federal University, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo and Fleury Health and Medicine Laboratories, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo and Fleury Health and Medicine Laboratories, Sao Paulo Brazil, Sao Paulo, Brazil, [4]Federal University of Sao Paulo, Sao Paulo, Brazil, [5]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil

Background/Purpose: The indirect immunofluorescence assay on HEp-2 cells (ANA-HEp-2) yields different morphological patterns that reflect the distribution of the autoantigens recognized by a given sample. Thus the ANA-HEp-2 pattern may reflect the autoantibody profile present in the sample. We have recently observed a novel ANA-HEp-2 pattern, herein designated *Quasi-Homogeneous* (QH) pattern, which presents intermediary morphological features between the previously characterized nuclear homogeneous (Ho) and nuclear dense fine speckled (DFS) patterns. These three patterns have a common feature of staining the mitotic chromosome plates, what may induce misinterpretation. This study aimed to perform the clinical and immunological characterization of the QH pattern.

Methods: Serum samples were consecutively selected from the ANA-HEp-2 routine as follows: 60 samples displaying the QH pattern, 30 samples displaying Ho pattern, and 30 samples displaying the DFS pattern. All samples were tested for the presence of antibodies against native DNA, nucleosome, histones, cardiolipin, and extractable nuclear antigens (ENA). QH samples were processed in four different ANA-HEp-2 slide brands, in home-made slides with HEp-2 cells fixed with either methanol/acetone or paraformaldehyde, and tested in western blot against MOLT-4 cell total extract. Systemic autoimmune rheumatic diseases (SARD) were defined according to ACR criteria after clinical chart review and interview with clinicians.

Results: The QH pattern was reproducible in the four ANA-HEp-2 slide brands and in home-made HEp-2 cell slides fixed with the two different protocols. QH samples showed an intermediate frequency of antibodies against native DNA (7%), ENA (5%), nucleosome (35%) and histones (16.7%), in contrast with Ho samples, which showed high frequency of these autoantibodies (36.7%, 23.3%, 96.7% and 60%, respectively), and DFS samples in which these autoantibodies were consistently absent. In western blot, QH samples depicted heterogeneous reactivity with no apparent common band. QH serum samples were associated with heterogeneous clinical conditions, including SARD, non-inflammatory diseases, non-specific complaints, and even apparently healthy subjects. Association with SARD was higher for QH samples

(87.5%) than QH samples (41.6%) (p=0.004). The latter samples were more frequently associated with SARD than DFS samples (4%) (p=0.009). Therefore, QH samples held an intermediate position between the two other patterns in that the Ho pattern was strongly associated with SARD and the DFS pattern that held no association with SARD.

Conclusion: The QH ANA-HEp-2 pattern reflects a heterogeneous profile of autoantibodies and clinical manifestations intermediate to those represented by the Ho and DFS patterns, respectively. The distinction among these patterns is important for the appropriate interpretation of the ANA-HEp-2 results.

2308

Cognitive Differences in Systemic Lupus Erythematosus Patients From the Western (Denver, CO) and Eastern (New York, NY) Regions of the United States. Elizabeth Kozora[1], Doruk Erkan[2], Sterling G. West[3], Christopher Filley[3], Aziz Ulug[4], Glendalee Ramon[2], Emily Duggan[1], Lening Zhang[1], JoAnn Vega[2] and Michael D. Lockshin[2]. [1]National Jewish Health, Denver, CO, [2]Barbara Volcker Center for Women and Rheumatic Diseases: Hospital for Special Surgery, New York, NY, [3]University of Colorado School of Medicine, Aurora, CO, [4]The Feinstein Institute for Medical Research, Manhasset, NY

Background/Purpose: Cognitive dysfunction can occur in over 50% of systemic lupus erythematosus (SLE) patients. During the analysis of two independent studies of SLE completed at two different regions of United States (US), we noticed significant differences in the cognitive test results. Thus, we decided to investigate the potential causes of this inconsistency.

Methods: SLE patients without prior or overt neuropsychiatric (NP) disorders from Western (Denver, CO) and Eastern (New York, NY) regions of the US were enrolled in two different but parallel cognition studies. Participants at both sites were screened similarly and evaluated with the same battery of cognitive tests recommended by the ACR (ad hoc ACR committee, 1999). Cognitive impairment was calculated using a reliable and valid index (range 0–12) with global impairment defined as impairment in four or more of the 12 scores (Kozora et al, 2004). The continuous variables were compared using a non-parametric Wilcoxon Rank Sum test and categorical variables with Fisher's Exact Test. Additional correlations were performed using Spearman coefficient.

Results: There were 84 patients enrolled from Western and 20 from Eastern regions with cognitive impairment rates of 24% and 60%, respectively (mean number of impaired cognition tests 2.6+2.3 versus 4.4+2.7, $p=0.005$). There were no significant differences between the groups in the demographics, depression level, SLE characteristics, and other co-morbidities except that Eastern participants had: a) significantly longer disease duration and higher ACR SLE criteria score (Table); and b) higher rates of malar rash, renal involvement, and immunologic disorder ($p<0.001$). There were no significant differences between the groups on measures of verbal memory/fluency, information processing, and visual learning/memory; however, Eastern participants were more commonly impaired in semantic fluency ($p=0.005$), visuomotor speed ($p=0.013$), and motor sequencing ($p=0.001$). We found a trend correlation between cognitive impairment and SLE disease duration ($p=0.07$) but not with total ACR SLE criteria score ($p=0.38$).

	Western (n: 84)	Eastern (n: 20)	P
Female (%)	94	100	Ns
Caucasian (%)	63	40	Ns
Mean Age (years)	36.7+8.7	36.5+11.7	Ns
Mean Education (years)	15.6+2.5	15.6+2.4	Ns
Mean ACR SLE Criteria	4.7+1.1	6.2+1.5	<0.001
Mean Diagnosis Duration (months)	90.2+78.7	154.8+122.9	0.005
Mean SLEDAI Score	4.2+6.3	3.7+4.6	Ns

Ns: not significant

Conclusion: SLE patients in the Eastern US, with significantly longer disease duration, showed greater cognitive impairment compared to patients in the Western US. The higher prevalence of medical complications in Eastern SLE patients might contribute to this difference. Although results should be interpreted cautiously due to varying sample size and baseline characteristics, our study provides a staring point to investigate different cognitive dysfunction patterns that may exist in different parts of the country.

2309

Hypophosphatemia Is Associated with Nephrogenic Systemic Fibrosis: A Case-Control Study. Elana J. Bernstein[1], Tamara Isakova[2], Mary E. Sullivan[3], Lori B. Chibnik[4], Hasan Bazari[3], Myles Wolf[2] and Jonathan Kay[5]. [1]Hospital for Special Surgery, New York, NY, [2]University of Miami, Miami, FL, [3]Massachusetts General Hospital, Boston, MA, [4]Brigham & Women's Hospital, Boston, MA, [5]University of Massachusetts Medical School, Worcester, MA

Background/Purpose: Nephrogenic systemic fibrosis (NSF) manifests as hardening, tethering, and hyperpigmentation of skin; flexion contractures of joints; and extracutaneous fibrosis in individuals with chronic kidney disease (CKD) following exposure to gadolinium-based contrast agents (GBCA) during imaging procedures. Given that not all patients with CKD exposed to GBCA develop NSF, additional factors must be involved in its pathogenesis. Preliminary evidence suggests that there may be derangements of calcium and phosphorus metabolism in patients with NSF. Fibroblast growth factor 23 (FGF23) is a phosphorus and vitamin D regulating hormone. FGF23 levels increase markedly as glomerular filtration rate (GFR) decreases. Whether FGF23 excess contributes to the development of NSF is unknown.

This study investigated potential factors in addition to GBCA exposure that may be involved in the pathogenesis of NSF. We hypothesized that, compared to patients with stage 5 CKD who do not have NSF, those with NSF would manifest greater alterations in calcium, phosphorus, and FGF23 levels.

Methods: Twenty-nine adult subjects with stage 5 CKD undergoing hemodialysis or peritoneal dialysis were recruited from outpatient nephrology and rheumatology practices. Subjects were excluded if they had a history of a phosphate wasting disorder or untreated primary hyperparathyroidism. Cases consisted of 10 patients with stage 5 CKD and biopsy-proven NSF. Controls consisted of 19 patients with stage 5 CKD without NSF, 9 of whom had never previously been exposed to GBCA. Cases and controls were matched for age and sex. Blood was collected from all 29 subjects and analyzed for phosphorus, calcium, FGF23, and 25-hydroxy-vitamin D levels, in addition to other routine laboratory tests. Statistical analysis was performed using the student's t-test for differences in phosphorus, calcium, and 25-hydroxy-vitamin D levels between the 2 groups, and the Wilcoxon test for differences in FGF23 levels.

Results: Subjects were predominantly male (62%), and the majority identified themselves as Caucasian (79%). The mean age of subjects was 63 years (SD 12). Patients with NSF had significantly lower phosphorus levels compared to controls (3.4 ± 0.87 mg/dL vs. 4.49 ± 1.05 mg/dL, p = 0.01). Accounting for the use of phosphate binders did not alter these results. There were no significant differences in calcium (9.53 ± 0.92 mg/dL vs. 9.64 ± 0.58 mg/dL, p = 0.70), 25-hydroxy-vitamin D (29.53 ± 23.90 ng/mL vs. 26.90 ± 15.00 ng/mL, p = 0.74), or FGF23 (8468 ± 8560 RU/mL vs. 6956 ± 4785 RU/mL, p = 0.79) levels between NSF patients and controls.

Conclusion: This case-control study suggests that differences in phosphorus metabolism may exist between patients with stage 5 CKD and NSF compared to patients with stage 5 CKD without NSF. Further study of the possible pathogenic role of altered phosphorus handing in the development of NSF is therefore needed.

2310

HLA-DRB5*01:05 Is a Risk Factor for Systemic Sclerosis with Interstitial Lung Disease. Toshio Odani, Shinsuke Yasuda, Ayaka Kubota, Hisako Nakagawa, Yuichiro Fujieda, Kotaro Otomo, Masaru Kato, Tetsuya Horita, Tatsuya Atsumi and Takao Koike. Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Background/Purpose: Interstitial lung disease (ILD) is a serious complication of Systemic Sclerosis (SSc). Recently, a variety of markers including cytokines, disease-specific autoantibodies and genetic backgrounds have been reported to be associated with SSc. However, few studies have focused on association between specific markers and SSc-related ILD. We aimed to elucidate markers associated with ILD in patients with SSc.

Methods: This study was approved by the ethical committee of Hokkaido University Graduate School of Medicine. RNA was prepared from peripheral blood mononuclear cells (PBMCs) from 14 SSc patients. Fourteen samples were divided into 4 sets of RNA pools according to the presence or the absence of ILD, and to the treatment (conventional or hematopoietic stem cell transplantation), then were subjected to DNA microarray. The expression levels of *HLA-DRB5* in each individual were evaluated by real-time qPCR for 43 SSc patients (25 with ILD, 18 without ILD), 42 patients with other autoimmune diseases and 10 healthy controls. Genomic DNA samples were collected from147 healthy controls and 70 SSc patients who received high-resolution CT scan for the evaluation of ILD. *HLA-DRB5* genotype was analyzed by sequence specific primers method.

Results: Microarray analysis revealed that *HLA-DRB5* was the only gene commonly up-regulated in patients with ILD compared to those without in both treatment groups. *HLA-DRB5* gene expression was significantly higher in PBMCs from SSc with ILD patients, than in those without ILD ($P = 0.007$). Although the frequencies of *HLA-DRB5* carriers were not significantly frequent in all SSc patients compared to controls, *HLA-DRB5* carriers were significantly more frequent in SSc patients with ILD (52.4 %) compared to those without ILD (25.0 % $P = 0.022$). Detailed genotyping of *HLA-DRB5* gene revealed that HLA-*DRB5*01:05* allele was significantly more frequent in SSc patients (22.9 %; $P < 0.001$), Especially *DRB5*01:05* allele was significantly more frequent in SSc patients with ILD (31.7 %, $P < 0.001$), compared to controls (5.4 %). (Table1)

Table 1. Frequencies (%) of *HLA-DRB5* alleles in patients with SSc with ILD, without ILD and in healthy controls

		SSc total N=70	ILD(+) N=41	ILD(−) N=29	Controls N=147	SSc vs controls	ILD(+) vs controls	ILD(−) vs controls
HLA-DRB5	**alleles**		(%)				OR (95% CI)	
*DRB5*01*	**01:01*	12.9	9.8	17.2	14.3	0.89 (0.38–2.05)	0.65 (0.21–2.01)	1.25 (0.43–3.64)
	**01:02*	18.6	22.0	10.3	14.9	1.30 (0.61–2.75)	1.83 (0.79–4.27)	0.66 (0.18–2.35)
	**01:05*	**22.9**	**31.7**	10.3	5.4	**5.15 (2.08–12.73)**	**8.07 (3.06–21.28)**	2.00 (0.50–8.06)
*DRB5*02*	**02:02*	4.29	4.88	–	2.0	2.15 (0.42–10.93)	2.46 (0.40–15.25)	

Numbers (%) Chi-square test or Fisher's exact test

Conclusion: *HLA-DRB5*01:05* allele is a risk factor for the development of ILD in patients with SSc.

2311

***Transforming Growth Factor-β Receptor One* Variant Is Associated with Constitutively Decreased Transforming Growth Factor-β Signaling and Risk for Systemic Sclerosis.** Monique E. Hinchcliff[1], Michael Pennison[2], Jacquelyn Zimmerman[2], Naresh Bellam[2], Qinghua Zeng[2], Chiang-Ching Huang[1], Richard M. Pope[1], Maureen Sadim[1], Wendy Wolf[3], Jeffrey C. Edberg[4], Robert P. Kimberly[2], Kui Zhang[5], Jun Li[5], Nengjun Yi[5], Canadian Scleroderma Research Group (CSRG)[6], Scleroderma Registry Investigators[7], Maureen D. Mayes[7], John Varga[1] and Boris Pasche[2]. [1]Northwestern Univ Med School, Chicago, IL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Harvard Medical School, Boston, MA, [4]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [5]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [6]SMBD Jewish General Hospital, Montreal, QC, [7]University of Texas Health Science Center at Houston, Houston, TX

Background/Purpose: The Transforming Growth Factor Beta (TGF-μ) signaling pathway plays a central role in the pathogenesis of systemic sclerosis/scleroderma (SSc) as a potent contributor to the fibrotic process. Only a few underpowered studies have investigated the association between genetic variants of TGF-β1 (*TGFB1*) and the risk for developing SSc, and the results have been inconsistent. Thus, there is no known association between naturally occurring variants of the TGF-β signaling superfamily and risk for SSc. We hypothesized that variants of the type I TGF-β receptor (*TGFBR1*) may be associated with risk for SSc given the central role of TGFBR1 as the initiator of SMAD- and non-SMAD-mediated signaling.

Methods: Using phase II HapMap data for the HapMap European (CEU) sample for *TGFBR1*, we selected 14 haplotype tagging single nucleotide polymorphisms (SNPs) in addition to *TGFBR1**6A, a functionally-relevant variant associated with cancer risk. Using a PCR-based protocol, we genotyped the 15 variants in 212 clinic-based patients with a diagnosis of SSc and 426 clinic-based individuals without a diagnosis of SSc or cancer who were well matched for age, sex, race, and smoking history. SNPs associated with risk for SSc were validated in 1373 patients and 744 control Caucasian, non-Hispanic subjects from the Scleroderma Registry and DNA Repository and from the University of Texas Medical School, Houston. The functional relevance of SNPs associated with risk for SSc in the combined analysis of both cohorts was assessed using lymphoblastoid cell lines from healthy individuals.

Results: The majority of the discovery cohort subjects were Caucasian (70.8% cases and 72.5% controls). One hundred and twenty (56.6%) and 84 (39.6%) had the diffuse and limited forms of SSc, respectively. Four hundred ninety-five (36.1%) and 789 (57.5%) patients in the validation cohort had diffuse and limited SSc respectively. One of the three *TGFBR1* SNPs associated with risk for SSc in the discovery cohort was also associated with risk for SSc in the validation cohort.

Combined logistic regression analyses of the two cohorts adjusted for race, gender, smoking and age shows OR 1.67, 95% CI 1.16–2.41 for rs2026811 and OR 0.62, 95% CI 0.45–0.86 for rs334348. Disease subset analysis shows that rs10733710 is associated with diffuse disease, rs2026811 is associated with limited disease, and rs334348 with both limited and diffuse disease. Functional analysis shows that lymphoblastoid cell lines that carry the two-SNP (rs2026811 x rs334348) *TGFBR1* haplotype associated with risk for SSc in the combined analysis have significantly reduced TGF-β signaling.

Conclusion: These findings provide the first evidence that the *TGFBR1* locus is associated with risk for SSc and suggest that constitutively altered TGFBR1 signaling contributes to the pathogenesis of this disease.

2312

Anti-AT(1)R and Anti-ET(A)R Autoantibodies in Systemic Sclerosis: Indication of Possible Involvement in Disease Pathology. Angela Kill[1], Mike O. Becker[2], Jeannine Guenther[1], Harald Heidecke[3], Duska Dragun[2] and Gabriela Riemekasten[1]. [1]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [2]Charité University Hospital, Berlin, Germany, [3]CellTrend GmbH, Luckenwalde, Germany

Background/Purpose: Recently identified functional autoantibodies simultaneously targeting the angiotensin-II type-1 receptor (AT1R-Abs) and the endothelin-1 receptor type A (ETAR-Abs) were linked with vascular and fibrotic complications in patients with systemic sclerosis (SSc). Presence of both autoantibodies moreover predicted mortality due to cardiopulmonary complications implicating their contribution in SSc pathogenesis. Here, different autoantibody- and ligand-mediated effects and their blockade by receptor inhibitors were studied.

Methods: HMEC-1 were treated with IgG from SSc patients containing anti-AT(1)R and anti-ET(A)R autoantibodies, with IgG from healthy donors, and with the natural receptor ligands. In parallel, cells were pre-treated with various receptor antagonists alone and in combination. The effect on different cytokines, growth factors, cell signaling molecues, and cell viability was measured by e.g. toxicity test, qRT-PCR, and ELISA.

Results: Exposure of endothelial cells to SSc- IgG led to a strong upregulation of several mediators. In case of IL-8 mRNA and on protein expression levels, expression of mRNA was downregulated and partially reduced on the protein levels using pre-treatment with receptor inhibitors. There was a high variability in the response to the blockers exhibiting responders and non-responders. Interestingly, treatment with natural ligands did not result in IL-8 up-regulation.Treatment with SSc-IgG led also to a significantly reduced cell viability compared to N-IgG treatment. These effects were partially abolished by pre-treatment with AT(1)R- inhibitor, but completely abolished using by one but not by another ET – inhibitor. MCP-1 was also up-regulated by IgG from SSc patients but not from controls, but was not blockable using receptor inhibitors.

Conclusion: Our results suggest an autoantibody-driven cytotoxicity and inflammatory activation of endothelial cells by angiotensin/endothelin-receptors *in vitro*. The data also suggest a heterogeneity of the antibody-mediated effects, the role of other possible autoantibodies, and different responses to inhibitors and the natural ligands. Whether these *in vitro* data could be used to identify responders or non-responsers to therapy, remain to be studied. *In vivo* experiments are underway to give better insight into the complex nature of the SSc-antibody-mediated effects.

2313

Identification of Major Histocompatibility Complex Class II Alleles Associated with Systemic Sclerosis Through Imputation Strategy. Jose Ezequiel Martin[1], International Scleroderma Group[2], Timothy RD Radstake[3], Filemon K. Tan[4], Frank C. Arnett[4], Maureen D. Mayes[4], Paul de Bakker[5], Bobby P.C. Koeleman[6] and Javier Martin[7]. [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, [2]Granada, Spain, [3]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [4]University of Texas Health Science Center at Houston, Houston, TX, [5]Brigham and Women's Hospital, Boston, MA, [6]University Medical Center Utrecht, Utrecht, Netherlands, [7]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain

Background/Purpose: Different alleles of MHC class II molecules (namely, HLA-DRB1, DPB1 and DQB1) have been described to be associated either with risk to systemic sclerosis (SSc) or its subphenotypes. Due to the high cost of HLA typing, studies have been limited to small sample sizes, preventing definitive statements as to which HLA alleles are likely causal.

Methods: We have imputed the MHC class I and II alleles of 2,296 cases and 5,356 controls from the US, Spain, Germany and The Netherlands with a method previously developed, which uses genotype data from ~2000 SNPs in the MHC region and an independent reference panel of dense SNP and classical HLA typing data in >2700 unrelated Europeans. We obtained actual HLA typing data for both class I and II molecules for the Spanish and US cohorts, and compared the accuracy of the imputation. Besides classical HLA alleles, we also imputed amino acid changes encoded by genetic variants within the different MHC molecules. We compared the frequencies of the different alleles between cases and controls for SNPs, amino acids and classical HLA alleles.

Results: The accuracy of the imputations ranged from 90% to 98% depending on the alleles being imputed with an average of 93% for all alleles in both populations. We confirmed previous associations of HLA alleles with SSc or its auto-antibody positive subgroups (HLA-DRB1*0701, HLA-DPB1*1301, HLA-DRB1*1104, HLA-DQB1*0501). We define in deeper detail some of these associations down to the level of aminoacidic positions which affect epitope binding. Furthermore, we describe new associations of HLA alleles with auto-antibody positive subgroups, HLA-DRB1*0801, with the presence of anti-centromere auto-antibodies and HLA-DQB1*0301 with the presence of anti-topoisomerase I auto-antibodies. No associations in the MHC class I molecules was found.

Conclusion: Our data indicate that most associations of HLA alleles (and more precisely aminoacidic positions within them) are specific to the presence of auto-antibodies. Also, only MHC class II alleles are associated and not MHC class I.

2314

FLOW Cytometric Analysis of Circulating Microparticles In Systemic Sclerosis. Line V. Iversen. Statens Serum Institut, Copenhagen S, Denmark

Background/Purpose: Microparticles (MPs) are small membranous vesicles released by apoptotic or activated cells. MPs exert regulatory functions in inflammation, thrombosis, vascular reactivity and angiogenesis. All these processes are involved in the disease manifestations of Systemic Sclerosis (SSc). SSc autoantigens have been identified in blebs released from cells undergoing apoptosis in vitro. This may link MPs to the development of systemic autoimmunity. Here, we characterize the circulating MPs a large group of clinically well-defined patients with SSc.

Methods: One hundred and twenty one (n = 121) unselected SSc patients, 49 sex- and age-matched healthy controls and 29 systemic lupus erythematosus (SLE) patients were included in the study. All samples were analyzed for MPs directly in citrated platelet poor plasma (PPP). A subset was also analyzed using washed MPs. MPs were characterized by a double labeling procedure using AnnexinV (AnxV) together with antibodies to platelet, leukocyte or endothelial cell surface markers. The reproducibility varied up to experiments and 12 % in day to day experiments.

Results: The total concentration of MPs and AnxV-binding MPs was significantly reduced in SSc and SLE patients compared to healthy controls. The concentration of MPs derived from platelets and leukocytes was reduced in patients while endothelial cell-derived MPs were not altered in SSc. The results from direct analysis in PPP and analysis of washed MPs from the same samples were significantly correlated with the exception of MPs derived from endothelial cells. No difference was found in the total MP concentration or cell-derived MP concentrations comparing diffuse and limited cutaneous systemic sclerosis.

Conclusion: The concentration of MPs was found to be reduced in patients with SSc and in patients with SLE compared to healthy controls. No differences in MP concentrations was found comparing limited and diffuse cutaneous systemic sclerosis.

2315

A Peptide Derived From Endostatin Ameliorates Fibrosis Induced by TGF–β and Bleomycin in Multiple Pre-Clinical Models. Yukie Yamaguchi[1], Takahisa Takihara[2], Roger Chambers[2], Adriana T. Larregina[2] and Carol A. Feghali-Bostwick[2]. [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Systemic sclerosis (SSc) results in significant morbidity and mortality due to organ fibrosis characterized by increased deposition of extracellular matrix (ECM). There are currently no effective therapies for fibrosis. Endostatin, a 20-kDa internal fragment of the carboxy terminus of collagen XVIII, has anti-cancer properties due to its endogenous angiogenesis inhibitory effect. In this study, we evaluated the potential of endostatin and endostatin-derived peptides to ameliorate fibrosis in several pre-clinical models: *in vitro* using primary human fibroblasts, *ex vivo* using human skin, and *in vivo* in TGF-β and bleomycin-induced dermal and pulmonary fibrosis. We also identified the mechanisms mediating the anti-fibrotic effects of endostatin peptides.

Methods: Levels of ECM components in primary human fibroblasts stimulated with recombinant endostatin (rE) or synthetic peptides of human endostatin were evaluated by immunoblotting. The effects of endostatin-derived peptides were also assessed in TGF-β-induced dermal fibrosis *in vivo* in a mouse model, *ex vivo* in human skin, and in bleomycin-induced dermal and pulmonary fibrosis *in vivo*. Levels of lysyl oxidase (LOX) and matrix metalloprotease (MMP)-2 were evaluated using immunoblotting, immunohistochemistry, and zymography.

Results: rE suppressed production of fibronectin and type I collagen *in vitro* in primary human fibroblasts and reduced skin thickness induced by TGF-β *ex vivo* in human skin. A C-terminal endostatin peptide (E4) of rE, but not an amino-terminal domain (E1), prevented TGF-β- and bleomycin-induced fibrosis *in vitro*, *in vivo* in mouse skin and lung, and *ex vivo* in human skin. E4 exerted potent anti-fibrotic effects in all the pre-clinical models used. In addition to preventing fibrosis, E4 significantly reduced existing fibrosis when administered a few days following the fibrotic trigger. Furthermore, E4 exerted its anti-fibrotic effects via multiple mechanisms that included reducing LOX levels and activating MMP-2. A reduction in LOX results in reduced cross-linking of collagen, rendering the ECM more susceptible to degradation by activated MMPs.

Conclusion: A peptide corresponding to the C-terminal domain of endostatin displays anti-fibrotic activity and is a novel and effective therapeutic agent for organ fibrosis.

2316

Thymic Stromal Lymphopoietin (TSLP) Is Overexpressed in Scleroderma Skin and It Is Induced by TLR3 Activation in Dermal Fibroblasts. Alicia Usategui, Manuel J. Del Rey, Elena Izquierdo, Patricia E. Carreira, Pablo Ortiz and Jose L. Pablos. Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain

Background/Purpose: Th2 responses are associated to the production of pro-fibrotic mediators such as IL-4 and IL-13. Contrarily, Th1 effectors such as IFN-gamma or TNF-α are anti-fibrotic. Thymic stromal lymphopoietin (TSLP) is a potent inducer of Th2 polarization in skin and lung allergic inflammation. TSLP is expressed by resident cells and can be regulated by activation of toll like receptors (TLR). Although T-cells participate in the pathogenesis of systemic sclerosis (SSc), the mechanisms of T-cell polarization and their relevance to fibrosis are unclear. The aim of this study was to analyze the expression and potential regulation of TSLP in human SSc and in the bleomycin model of scleroderma.

Methods: We analyzed by immunohistochemistry (IHC) the expression of TSLP in involved skin from 18 patients with diffuse SSc (mean disease duration 2.8±0.5 years), and in the bleomycin mouse model of scleroderma, compared to normal control tissues. Dermal fibrosis was induced in female C3H mice aged 6 wk by subcutaneous injections of bleomycin (1mg/ml) into the shaved back skin every day for 4 weeks. TSLP mRNA expression was analyzed by quantitative RT-PCR in bleomycin induced skin lesions and in cultured fibroblasts. Normal human and mouse dermal fibroblasts were cultured from healthy skin and treated with bleomycin or specific TLR-2, −3 and −4 agonists (LPS, Pam3Cys and poly(I:C) respectively). Data are

expressed as mean±SEM. Quantitative data were analysed by Mann-Whitney U-test and p-value<0.05 was considered significant.

Results: TSLP protein was detected by IHC in 14 of 18 (78%) human SSc skin sections whereas it was undetectable in normal skin from 3 healthy individuals. TSLP expression was observed in keratinocytes, mast cells and fibroblasts of involved SSc skin. In fibrotic lesions of bleomycin-injected mouse skin, we also observed an increase in TSLP expression in mast cells, keratinocytes and fibroblasts by IHC. We confirmed a 4.6±0.7 fold increase of the TSLP mRNA level in bleomycin-injected skin ($p<0.05$). In human fibroblasts, TLR-3 agonist induced a strong increase in TSLP mRNA expression (8.4±5.4, $p<0.05$), whereas TLR-2 and -4 agonists and bleomycin did not significantly modify TSLP mRNA expression. In mouse fibroblasts, all TLR-2, -3 and -4 agonists but not bleomycin induced TSLP mRNA expression. The strongest effect was observed for TLR-3 agonist (17.8±7.7, $p<0.05$).

Conclusion: We demonstrate overexpression of TSLP in resident cells of human SSc and mouse bleomycin-induced scleroderma. Among TLR agonists, TLR-3 was the most potent inducer of TSLP expression in human and mouse fibroblasts. These observations suggest that in scleroderma skin, Th2 differentiation may be induced by TSLP in response to TLR-3 activation in resident cells.

2317

Oxidation of Protein Tyrosine Phosphatase-1B Leads to Pronounced PDGFR Activation in Scleroderma Fibroblasts. Pei-Suen Tsou[1], Adam J. Pinney[1], Nadin N. Talia[1], Sonsoles Piera-Velazquez[2], Sergio A. Jimenez[3], James R. Seibold[4], Kristine Phillips[1] and Alisa E. Koch[5]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]Thomas Jefferson University, Philadelphia, PA, [3]Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA, [4]Scleroderma Research Consultants LLC, Avon, CT, [5]Department of Veteran's Affairs and University of Michigan, Ann Arbor, MI

Background/Purpose: Skin fibrosis is a main characteristic of systemic sclerosis (SSc). Platelet-derived growth factor (PDGF) and its receptor (PDGFR) have been shown to play key roles in promoting fibrosis in SSc. Upon PDGF stimulation, the PDGFR is phosphorylated (p-PDGFR), and its downstream signaling pathways, such as ERK1/2, are activated. The PDGFR is dephosphorylated by phosphatases, including protein tyrosine phosphatase 1B (PTP1B), and the signaling cascade is hence terminated. We previously following PDGF stimulation, ERK1/2 was phosphorylated (p-ERK1/2) to a greater extent in SSc dermal fibroblasts. Moreover, increased oxidative stress was observed in SSc cells compared to normal (NL) fibroblasts, and PTP1B was inactivated. In this study we hypothesize that the p-PDGFR profile in SSc fibroblasts is affected by the inactive PTP1B, and the mechanism of PTP1B inactivation is due to oxidation of its active site. The effect of the thiol antioxidant n-acetylcysteine (NAC) on p-PDGFR, p-ERK1/2, tyrosine-phosphorylated proteins, collagen I (Col I) production, and PTP1B mRNA expression was investigated.

Methods: SSc and NL dermal fibroblasts were isolated from skin biopsies. Cellular thiol content was measured by using 5,5'-dithiobis (2-nitrobenzoic acid). Tyrosine phosphorylated proteins were immunoprecipitated, and p-PDGFR was probed with rabbit anti-human PDGFR antibodies. Oxidized PTPs and p-ERK1/2 were measured by Western blotting. Col I was detected by immunofluorescence and quantitative PCR.

Results: Col I expression was significantly higher in SSc fibroblasts, accompanied by significantly lower amounts of free thiol compared to NL fibroblasts (464 ± 18 in NL vs. 344 ± 15 μM/mg protein in SSc cells, $n=3$, $p<0.01$). After PDGF stimulation, multiple proteins including the PDGFR, were phosphorylated to a greater extent in SSc fibroblasts. Moreover, the significantly lower PTP1B activity in SSc fibroblasts resulted from cysteine oxidation at its active site by higher levels of ROS, since oxidation of multiple PTPs, including PTP1B, was observed. NAC improved the profile of p-PDGFR and p-ERK1/2, decreased the number of tyrosine-phosphorylated proteins, and decreased both Col I protein and mRNA expression. The PTP1B mRNA level did not change in the presence of NAC in NL fibroblasts when stimulated with PDGF, but PTP1B mRNA significantly increased in SSc fibroblasts after 2 hr of PDGF stimulation (0.0023 ± 0.0005 vs. 0.0036 ± 0.0002 arbitrary unit in the absence or presence of NAC, $p<0.05$, $n\geq5$).

Conclusion: The inactivation of PTP1B was caused by oxidation of its active site due to the excess oxidative stress in SSc fibroblasts, as indicated by the lower cellular free thiol levels. This led to pronounced and prolonged activation of the PDGFR and ERK1/2 pathways and therefore the increase in Col I production. NAC treatment, by reducing oxidative stress and restoring the low PTP1B activity and expression, decreased Col I production in SSc dermal fibroblasts. We introduce a new mechanism by which ROS promote a profibrotic phenotype in SSc fibroblasts through oxidative inactivation of PTP1B leading to pronounced PDGFR activation and thus increased Col I production.

2318

The Expression and Activities of Protein Tyrosine Phosphatases in Scleroderma Dermal Fibroblasts: Impact of Oxidative Stress on DEP-1 and SHP-2. Pei-Suen Tsou[1], Adam J. Pinney[1], Ann Kendzucky[2], Sonsoles Piera-Velazquez[3], Sergio A. Jimenez[4], Kristine Phillips[1] and Alisa E. Koch[5]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]Grand Valley State University, MI, [3]Thomas Jefferson University, Philadelphia, PA, [4]Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA, [5]Department of Veteran's Affairs and Unversity of Michigan, Ann Arbor, MI

Background/Purpose. We and others have shown that the platelet-derived growth factor receptor (PDGFR) is crucial for promoting fibrosis in systemic sclerosis (SSc). The PDGFR is activated via its ligand PDGF, and phosphorylation of the receptor occurs. Protein tyrosine phosphatases (PTP), such as PTP1B, SHP-2, and DEP-1, have been suggested to be able to dephosphorylate the PDGFR, and therefore terminate the initiation of the downstream signaling pathways. We previously showed that the increased oxidative stress in SSc dermal fibroblasts inactivates PTP1B, and that the ability to generate more PTP1B is hampered when cells are stimulated with PDGF. The loss of activity results from oxidation of its active site. Since PTP1B is not the only phosphatase that dephosphorylates the PDGFR, in this study we sought to determine the expression and activity of two other crucial phosphatases, namely SHP-2 and DEP-1, in SSc dermal fibroblasts. The impact of a thiol antioxidant, n-acetylcysteine (NAC), was also examined.

Methods: SSc and normal (NL) dermal fibroblasts were isolated from skin biopsies. Cells were stimulated with 30 ng/ml PDGF and the expression of DEP-1 and SHP-2 was determined by qPCR and Western blotting. Phosphate release assays were used to determine DEP-1 and SHP-2 activity.

Results: DEP-1 had higher protein expression in SSc dermal fibroblasts compared to NL ($p<0.05$, $n=7$), and NAC significantly increased DEP-1 expression in both NL and SSc cells. However, following PDGF stimulation DEP-1 mRNA decreased significantly in SSc cells compared to NL. There was no difference in DEP-1 activity in NL and SSc cells, but following NAC treatment the activity in SSc cells increased about 2 fold ($p<0.05$, $n=6$). On the other hand, the SHP-2 protein and mRNA levels in SSc fibroblasts were lower compared to NL. While NAC increased mRNA expression following PDGF stimulation, it had no significant effect on SHP-2 protein expression in SSc cells. The lower expression of SHP-2 in SSc dermal fibroblasts led to lower SHP-2 activity ($p<0.05$, $n=6$), while NAC had no effect on SHP-2 activity.

Conclusion: In SSc dermal fibroblasts, the pronounced and prolonged activation of the PDGFR pathway is likely due to the lower expression and activities of SHP-2 and PTP1B, which we showed previously. The increased DEP-1 expression might be a defense mechanism to overcome the lower expression of PTP1B and SHP-2. In addition, the susceptibility of these phosphatases to oxidative stress is different. While NAC restored PTP1B and DEP-1 activity in SSc cells, it had no effect on SHP-2 activity. Besides its thiol antioxidative effect, NAC also affects the expression of PTPs. This study suggests that the irregular expression and inactivated enzyme activity of PTPs in SSc dermal fibroblasts might contribute to the fibrotic phenotype seen in SSc patients.

2319

Atorvastatin Attenuates Skin Fibrosis Through the PI3K Pathway. Yuko OTA, Yasushi Kawaguchi, Kae Takagi, Hisae Ichida, Takahisa Gono, Masanori Hanaoka and Hisashi Yamanaka. Tokyo Women's Medical University, Tokyo, Japan

Background/Purpose: Atorvastatin, a member of the statin class of drugs, is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This drug offers several beneficial effects in treating conditions with vascular involvement, such as Raynaud's phenomenon and digital ulcers in patients with systemic sclerosis (SSc), by recruiting circulation endothelial progenitor cells. In addition to their well-known effects in down-regulation of serum cholesterol, statins induce pleiotropic effects at the cellular level, regulating intracellular signaling systems. Recently, it was reported that statins ameliorated liver and heart fibrosis. The aim of the present study was to investigate the antifibrotic effects of atorvastatin on skin fibroblasts from patients with SSc.

Methods: Skin fibroblasts from five patients with diffuse cutaneous SSc were cultured with increasing concentrations of atorvastatin for various times. The resulting supernatants were collected and stored at −80 °C. Procollagen type I C-peptide and IL-6 levels were then measured using commercial ELISA kits. In addition, mRNA levels of collagen 1α(II) and IL-6 were

estimated using real-time PCR. The phosphorylation of Akt (Thr308) was evaluated by Western blot analysis using specific monoclonal antibodies.

Results: In the supernatants of fibroblasts cultured with 10 μM of atorvastatin for 72 h, the levels of procollagen type I C-peptide and IL-6 were significantly suppressed ($p < 0.001$, Figure 1) as compared with those in supernatants obtained from cultures lacking atorvastatin. In skin fibroblasts cultured with LY294002 (PI3K inhibitor), procollagen type I C-peptide and IL-6 production were significantly suppressed ($p < 0.05$, and $p < 0.01$ respectively). IL-6 production was significantly suppressed ($p < 0.01$) upon the administration of Y27632 (Rho kinase inhibitor), although procollagen type I C-peptide levels were not suppressed. Treatment with U0126 (Erk1/2 inhibitor) did not affect the levels of collagen or IL-6. The results from Western blot analyses indicated that atorvastatin inhibited the phosphorylation of Akt (Thr308), which is regulated by the PI3K signaling pathway.

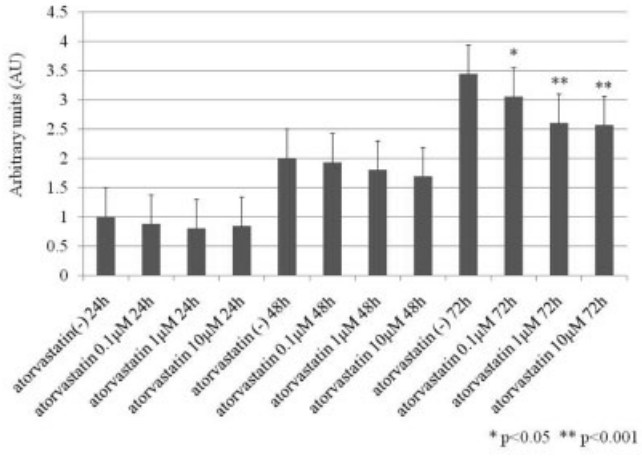

Figure 1. The effect of atorvastatin for collagen production on SSc fibroblasts.

Conclusion: Our results showed that atorvastatin attenuates, via the PI3K pathway, collagen and IL-6 production in skin fibroblasts from patients with SSc. Atorvastatin may represent a novel therapy not only for vasculopathy but also for fibrosis in patients with SSc.

2320

The Role of Adiponectin in the Pathogenesis of Dermal Fibrosis in Systemic Sclerosis. Yoshihide Asano, Yuri Masui, Takafumi Kadono and Shinichi Sato. The University of Tokyo, Tokyo, Japan

Background/Purpose: Adiponectin has been demonstrated to be one of anti-inflammatory and anti-fibrotic factors, suggesting the potential of this cytokine to be involved in the developmental process of systemic sclerosis (SSc). The purpose of this study is to investigate the clinical significance of serum adiponectin levels in patients with SSc and to examine if adiponectin affects the pro-fibrotic phenotype of SSc fibroblasts.

Methods: Serum adiponectin levels were determined by enzyme-linked immunosorbent assay in 32 patients with diffuse cutaneous SSc (dcSSc), 28 with limited cutaneous SSc (lcSSc), and 27 healthy controls. No significant difference between these groups existed in terms of sex, age, and body mass index. Normal and SSc fibroblasts were stimulated with adiponectin and mRNA levels of human α2(I) collagen and matrix metalloproteinase 1 genes were determined by real-time PCR. mRNA levels of adiponectin receptor 1 and adiponectin receptor 2 genes in those cells were also evaluated by real-time PCR.

Results: Serum adiponectin levels in dcSSc patients (4.93 ± 6.48 μg/ml) were significantly lower than those in lcSSc patients (9.69 ± 7.61 μg/ml, $P < 0.01$) and healthy controls (9.36 ± 5.57 μg/ml, $P < 0.01$). dcSSc patients with disease duration of ≤ 5 years had significantly decreased serum adiponectin levels (2.15 ± 1.69 μg/ml) than those with disease duration of > 5 years (13.29 ± 8.36 μg/ml, $P < 0.01$), lcSSc patients with disease duration of ≤ 5 years ($8.07 \pm 7.98$$\mu$g/ml, $P < 0.05$), lcSSc patients with disease duration of > 5 years (10.9 ± 7.34 μg/ml, $P < 0.01$), and healthy controls (9.36 ± 5.57 μg/ml, $P < 0.01$). Longitudinal studies in 5 patients with early dcSSc treated with oral prednisone demonstrated that serum adiponectin levels inversely correlate with the activity of progressive skin sclerosis in dcSSc patients. In normal fibroblasts, adiponectin stimulation decreased mRNA levels of human α2(I) collagen gene, while increasing mRNA levels of matrix metalloproteinase 1 gene. In SSc fibroblasts, mRNA levels of adiponectin receptor 1 and adiponectin receptor 2 genes were decreased compared with normal fibroblasts. Consistently, SSc fibroblasts were less sensitive to anti-fibrotic effect of adiponectin than normal fibroblasts.

Conclusion: Serum levels of adiponectin may serve as a useful marker to evaluate the activity of progressive skin sclerosis in dcSSc. As well as the decrease in serum levels of adiponectin, the decreased expression of adiponectin receptors contributes to the establishment of pro-fibrotic phenotype in SSc fibroblasts.

2321

Platelet Derived Growth Factor Receptor Inhibitor ARRY-768 Prevents Experimental Dermal Fibrosis and Induces Regression of Pre-Established Dermal Fibrosis. Michal Tomcik[1], Nicole Reich[2], Katrin Palumbo[2], Pawel Zerr[2], Jérôme Avouac[3], Alfiya Akhmetshina[2], Clara Dees[2], Christian Beyer[4], Radim Becvar[1], Ladislav Senolt[5], Oliver Distler[6], Georg Schett[2] and Jorg HW Distler[2]. [1]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [4]University of Erlangen-Nuremberg, Erlangen, Germany, [5]Institute of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [6]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Platelet derived growth factor (PDGF) is one of the key profibrotic cytokines in pathogenesis of systemic sclerosis. ARRY-768 is a highly selective, orally active, small molecule inhibitor of PDGF receptors, which targets PDGFR more potently than imatinib (IC_{50} of 3 vs. 69 nM, respectively). The aim of this study was to investigate the efficacy of ARRY-768 in prevention of dermal fibrosis and treatment of pre-established dermal fibrosis induced by bleomycin.

Methods: Design for prevention of dermal fibrosis (A) comprised 3 treatment groups injected with bleomycin s.c. for 3 weeks: group I was treated with ARRY-768 50mg/kg p.o., group II and III with imatinib mesylate 50 and 200mg/kg i.p., respectively, twice a day. Control groups, injected with NaCl (IV) and bleomycin (V) s.c., were treated p.o. with a vehicle (water). Design for the treatment of pre-established dermal fibrosis (B) consisted of 4 treatment groups injected with bleomycin s.c. for 6 weeks. During the last 3 weeks, groups I and II were treated with ARRY-768 30 and 100mg/kg p.o., whereas groups III and IV with imatinib mesylate 50 and 200mg/kg i.p., respectively, twice a day. Control groups, injected s.c. with NaCl (V) or bleomycin (VI) for 6 weeks or bleomycin for the first 3 and NaCl the last 3 weeks (VII), were treated p.o. with water for the last 3 weeks. A total of 40+56 (A+B) DBA/2 mice were examined weekly for weight, activity and the texture of the fur.

Results: In the standard model of bleomycin-induced dermal fibrosis (A), treatment with ARRY-768 50mg/kg (I) reduced dermal thickening by $67\pm2\%$ ($p<0.001$), hydroxyproline content by $23\pm6\%$ ($p=0.642$) and myofibroblast count by $47\pm5\%$ ($p<0.001$). Control treatment with imatinib (II, III) demonstrated comparable reduction of dermal fibrosis. Similarly in the model of bleomycin-induced pre-established dermal fibrosis (B), treatment with ARRY-768 30 (I) and 100mg/kg (II) decreased dermal thickening by $45\pm2\%$ ($p<0.01$) and $56\pm1\%$ ($p<0.01$), hydroxyproline content by $52\pm4\%$ ($p<0.001$) and $55\pm5\%$ ($p<0.001$), and myofibroblast count by $75\pm6\%$ ($p<0.001$) and $88\pm8\%$ ($p<0.001$), respectively. Control treatment with imatinib (III, IV) showed similar regression of pre-established dermal fibrosis. ARRY-768 demonstrated significant antifibrotic effects in both prevention and treatment of pre-established dermal fibrosis. The treatment with ARRY-768 was well tolerated for 3 weeks at all dosing regimens (30, 50 or 100mg/kg) and no signs of toxicity such as weight loss, decreased activity or changes in the texture of the fur were observed.

Conclusion: This is the first study on the anti-fibrotic effects of the selective PDFGR inhibitor ARRY-768. ARRY-768 did not only prevent experimental fibrosis, but also induced regression of pre-established bleomycin-induced fibrosis without toxic side effects. The efficacy of ARRY-768 was comparable to that of imatinib, suggesting that the effects of imatinib might be mediated primarily via inhibition of PDGFR, whereas inhibitory effects on c-abl, a downstream mediator of TGFβ, seem to be less relevant. These data highlight the importance of PDGF signaling in fibrotic diseases.

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Adenosine A_{2A}Receptor Activation Stimulates Collagen1 and Collagen3 by Different Signaling Pathways in Normal Human Dermal Fibroblasts (NHDF). Miguel Perez-Aso and Bruce N. Cronstein. New York Univ Medical Center, New York, NY

Background/Purpose: Prior studies have demonstrated that adenosine, acting at A_{2A} receptors, promotes wound healing and plays a role in dermal fibrosis, such as occurs in scleroderma, as well. The intracellular signaling pathways by which adenosine receptor activation stimulates collagen production have not previously been explored in dermal fibroblasts. We therefore examined the signaling mechanisms by which adenosine A_{2A} receptors, members of the $G_{\alpha S}$-linked family of receptors that generally signal via increased cAMP, promote collagen production in normal human dermal fibroblasts (NHDF).

Methods: Collagen1α1 (Col1α1) and Collagen3α1 (Col3α1) expression in Normal Human Dermal Fibroblasts (NHDF) was determined by Western blot for protein content.

Results: Stimulation of NHDF for 24h with the A_{2A}R agonist CGS21680 stimulated a biphasic increase in Col1α1 production (0.1μM: 160$\pm$11% of control, $p<0.05$; 1μM: 135$\pm$10% $p>0.05$; 10μM: 133$\pm$11% $p>0.05$ versus control, n=11), while the maximum increase of Col3α1 was at 1μM (0.1μM: 111$\pm$10% $p>0.05$; 1μM: 172$\pm$19% $p<0.05$; 10μM: 166$\pm$17% $p>0.05$ versus control, n=11). Interestingly, two different activators of Protein kinase A 8-Cl-cAMP and 6-Bnz-cAMP (0.1μM), both stimulated Col1α1 production, (8-Cl-cAMP, 280$\pm$74% of control, $p<0.01$; 6-Bnz-cAMP 157$\pm$6% of control, $p<0.01$, n=3). Stimulation with 8-Cl-cAMP did not affect Col3α1 production at 0.1μM, but decreased Col3α1 content at higher concentrations (1μM: 66$\pm$7% of control, $p>0.05$; 10μM: 32$\pm$11% of control, $p<0.01$; 100μM:48.2$\pm$24 $p<0.05$ versus control, n=4). Stimulation with the specific Epac activator 8-CPT-2'-O-Me-cAMP from 0.1 to 100μM did not affect Col1α1, but increased Col3α1 production in a dose-dependent fashion by as much as 260$\pm$70% (n=3, $p<0.05$). Blockade of Epac signaling by Brefeldin A (10μM) dramatically increased Col1α1 production (287$\pm$35% of control, $p<0.01$, n=3), but diminished Col3α1 to 32$\pm$15% of control ($p<0.01$, n=3). Inhibition of p38MAPK by SB203580 (1μM) abrogated the CGS21680 (1μM)-stimulated increase of Col3α1 from 170$\pm$21% to 73$\pm$9 of control ($p<0.05$, n=3).

Conclusion: These results demonstrate that adenosine A_{2A} receptor stimulation promotes collagen production by two different pathways. Adenosine A_{2A} receptors promote Col1α1 secretion via activation of a cAMP-PKA-dependent pathway whereas these receptors stimulate Col1α3 secretion via activation of a cAMP-Epac-p38Mapk pathway.

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Adenosine-Mediated Dermal Fibrosis and Fli-1 Expression in CD39 and CD73 Knockout Mice. Edwin SL Chan[1], Gideon Smith[1], Patricia Fernandez[2], Hailing Liu[1], Andrew G. Franks[2], Maria Trojanowska[3] and Bruce N. Cronstein[4]. [1]New York University School of Medicine, New York, NY, [2]New York University, New York, NY, [3]Boston University, Boston, MA, [4]New York Univ Medical Center, New York, NY

Background/Purpose: Genetic deletion of CD39/73 results in vastly decreased adenosine in tissues, protecting against bleomycin-induced pulmonary fibrosis. To characterize the contribution of endogenous adenosine to fibrogenesis in the skin, we determined its impact on murine bleomycin-induced dermal fibrosis.

Methods: Male CD39/CD73-double deficient mice (CD39/73KO) were injected with bleomycin (0.1U sc qodx18d) and compared to wild-type littermates. Dermal morphometry was assessed on 6mm skin punch biopsies. Hydroxyproline levels were determined and adenosine levels assessed by HPLC. To further characterize the contribution of endogenous adenosine to skin fibrosis and the key parts of this pathway, we also looked at individual knockouts of CD39 and CD73.

Finally, we examined the expression of the transcription factor Fli1 (Friend leukemia integration-1), a repressor of key matrix-producing genes, in our mice. Deficiency of Fli1, downregulated in SSc fibroblasts, has been shown to reproduce the fibrotic changes of systemic sclerosis (SSc) in animals.

Results: CD39/CD73KO mice showed lower dermal thickness (0.29$\pm$0.05 vs. 0.36$\pm$0.10mm), skin-fold thickness (0.79$\pm$0.16 vs. 0.97$\pm$0.37mm), tensile strength (198.2$\pm$7.3 vs. 248.7$\pm$7.0g) and hydroxyproline content (21.7$\pm$1.2 vs. 26.5$\pm$1.1μg/mg tissue) (n=6, $p<0.01$ for each) compared to controls after bleomycin treatment; correlating with a decrease in adenosine levels, and associated with a mild increase in Fli-1 immunostaining.

CD73KO mice showed no statistically significant difference in dermal thickness (0.59$\pm$0.26 vs. 0.52$\pm$0.62mm), skin-fold thickness (1.08$\pm$0.06 vs. 1.07$\pm$0.09mm), or tensile strength (270.2$\pm$72.9 vs. 248.0$\pm$38.3g) (n=3, $p>0.05$ for each) compared to controls without bleomycin treatment, with no detectable changes in Fli-1 staining.

Conclusion: This work shows that extracellular adenosine, possibly acting in part through Fli-1, is necessary for the sclerosing effects of bleomycin. Blockade of adenosine or its receptors may be useful in the treatment of diseases such as scleroderma where dermal fibrosis is a prominent manifestation.

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Enhanced IL-6 Trans-Signalling in Early dcSSc May Drive Fibrotic Response Via JAK2/STAT3 Signalling Pathways. Korsa Khan[1], Xu Shiwen[2], David J. Abraham[3], Christopher P. Denton[4] and Voon Ong[5]. [1]UCL medical School, London, United Kingdom, [2]Royal Free Hospital, London, United Kingdom, [3]Centre for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom, [4]UCL Medical School, London, United Kingdom, [5]UCL Medical School, London, England

Background/Purpose: We have reported that a subgroup of diffuse cutaneous systemic sclerosis (dcSSc) with elevated serum IL-6 levels is associated with high modified Rodnan skin score (mRSS). In this study, we examine its potential profibrotic effects and downstream signalling pathways in patients with early dcSSc.

Methods: Using skin biopsies obtained from patients with early dcSSc (n=10, mean disease duration, Mean$\pm$SEM: 35$\pm$9.5 months) and healthy controls (n=5), colocalisation of IL-6 with aSMA and phospho-STAT3 were determined with immunohistochemical techniques. The effect of IL-6 trans-signalling on extracellular matrix(ECM) production was assessed on fibroblasts grown by explant culture from skin of SSc patients and healthy controls. Downstream signalling pathways regulated by IL-6 and soluble IL-6 receptor was examined using pharmacological inhibitors. These were stimulated overnight with IL-6 (0–50ng/ml) and sIL-6R (20ng/ml).

Results: There was greater dermal IL-6 expression in patients with early dcSSc compared to healthy controls. IL-6 accumulation was strongly associated with vascular structures and perivascular inflammatory infiltrate in 8/10 patients. Compared to controls, immunostaining for downstream IL-6 signaling molecules showed an increased expression of pSTAT3 in all cases with early dSSc particularly in the perivascular inflammatory foci and vascular structures. Similar co localisation of IL-6 and aSMA was observed in all skin sections with early dcSSc.

To explore the effect of IL-6 trans-signalling on ECM synthesis, incubation of dermal fibroblasts from healthy controls with either IL-6 alone (25–50 ng/ml) or sIL-6R (20ng/ml) alone had no effect on collagen, aSMA and CTGF production. However, there was upregulation of collagen synthesis in normal fibroblasts(34.3$\pm$2.45 vs 9.88$\pm$1.54 Densitometry Image Unit (DIU) controls, $p < 0.05$) in response to IL-6 (25ng/ml) and sIL-6R (20ng/ml). Similar induction of aSMA and CTGF by 12-fold and 15-fold ($p<0.01$) respectively were observed in normal fibroblasts incubated with a combination of IL-6 and sIL-6R. The IL-6 trans-signalling activation of collagen synthesis in normal fibroblasts was abrogated by AG490 (3.6-fold) and S3I-201 (3.5-fold, $p<0.02$), that targets JAK2 and STAT3 signalling pathways respectively.

Time-course analysis indicates that IL-6 trans-signalling induces maximal activation of pJAK2 and pSTAT3 at 45 min and this was diminished by 2 hours in normal fibroblasts. Constitutive activation of both JAK2 and STAT3 pathways was observed in SSc fibroblasts and further activation by the addition of IL-6 and sIL-6R occurred at 15 minutes and this was sustained at 1 hour.

Conclusion: Our results confirm overexpression of IL-6 in dcSSc and demonstrate a potent profibrotic effect of IL-6 trans-signalling via the JAK2/STAT3 pathways. The data also provide rationale that targeting the IL-6 trans-signalling as a potential fibrotic therapy in SSc.

2325

Estimation of Cellular States From SSc Gene Expression Reveals Heterogeneity of Pathway Expression. J. Matthew Mahoney and Michael L. Whitfield. Dartmouth Medical School, Hanover, NH

Background/Purpose: Genome-scale gene expression profiles for SSc and healthy control skin biopsies have identified molecularly distinct subsets of SSc. These subsets have been linked to disease severity and may respond differently to therapy. It is less clear which biochemical pathways are dysregulated to produce the different disease states. Due to the cost and

complexity of perturbative experiments in disease models, bioinformatics approaches in SSc must use inference tools based on "static" gene expression profiles from patient skin biopsies to build hypotheses to test in models. Given the heterogeneity of scleroderma, we hypothesized that multiple canonical pathways would be dysregulated and that meaningful patterns of co-regulation could be statistically identified from gene expression in whole tissue.

Methods: We collected a database of canonical gene pathways comprised of KEGG, BioCarta, and Reactome annotated pathways and analyzed two independent gene expression datasets that analyzed SSc skin. To identify pathways that showed differential regulation, we employed a clustering method called "Pathway-based Clustering" on a publicly available SSc skin microarray data set (Milano et al. 2008 PLoS One) and a second, unpublished dataset. To infer the cellular state corresponding to the identified modes of regulation, we fit Gibbs distributions, which allow for the identification of gene-gene interactions and novel co-regulation, to the expression profiles of the clusters. Components of deregulated pathways in each subset are used to create a network diagram.

Results: Over 100 of the 880 pathways used in this study, including disease implicated pathways like TGFbeta, sphingolipid metabolism and IL10 showed significant differential regulation. Surprisingly, clustering often identified more than two modes of differential regulation. In the TGFb signaling pathway, for example, five distinct modes of regulation were found corresponding to differential regulation of different components of the canonical pathway. Thus, skin tissue in SSc patients shows that parts of canonical pathways are a regulated differently in separate subsets of patients. Furthermore, the fit Gibbs distributions identify putative co-regulation within pathways that is not annotated in the standard pathway diagrams.

Conclusion: Canonical gene pathways show complex modes of regulation in SSc skin tissue with different parts of the pathway regulated differently. The mechanisms behind this regulation are unknown, but the present study has established a framework for future pathway-based studies on gene expression in SSc.

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The Melanocortin System: A New and Important Actor on the Scene of Systemic Sclerosis. Grethe N. Andersen[1], Olga Nagaeva[2], Lucia Mincheva-Nilsson[3] and Jarl E.S. Wikberg[4]. [1]Hospital of Vendsyssel/Ålborg University, Hjørring, Denmark, [2]University of Umeå, Umeå, Sweden, [3]University of Umeå, Sweden, [4]Department of Pharmaceutical Pharmacology, Uppsala, Sweden

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrotic destruction of the skin, vascular tree and inner organs. In SSc, the leading edge of the skin lesion is infiltrated by mononuclear cells, causing cytokine network abnormalities with increased levels of tumor necrosis factor alpha (TNFa) and the main inducer of extracellular matrix (ECM) production: transforming growth factor beta (TGFb). Due to evidence of several abnormalities in TGFb signalling, the CAT-192 study, in which patients with diffuse (d)SSc of recent onset, were treated with recombinant antibodies against human TGFb1, was initiated. As the melanocortin system plays a significant role in the regulation of TGFb and TNFa synthesis, we examined the content of messenger (m)RNA for the melanocortin receptor subtypes: MC1, 2, 3 and 5 and for the precursor protein pro-opio-melanocortin (POMC) for their natural agonist ligands (the melanocyte stimulating hormones (MSHs) and adrenocorticotroin (ACTH) in skin biopsies from the leading edge of the skin lesion in a patient with dSSc, before and after treatment with recombinant human anti-TGFb monoclonal antibodies (mAbs) as well as in skin biopsies from 3 healthy controls.

Methods: Skin biopsies, 4 mm in diameter, were achieved from the upper arm and the leading edge of the skin lesion in a recent onset dSSc patient, who participated in the CAT-192 study, before and after treatment with recombinant human anti-TGFb1 mAbs and from 3 healthy controls. The biopsies were minced, RNA extracted and examined for content of TNFa-, TGFb-, MC1-, 2-, 3-, 5- and POMC mRNA by means of quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR).

Results: In the biopsy taken from the leading edge of the skin lesion pre-treatment TNFa and TGFb levels were 4 times higher than in healthy controls, the POMC mRNA levels was similar to that found in controls. The MC1 mRNA level was slightly lower than in controls, while the MC2 and MC3 mRNA levels were immeasurable and the MC5 mRNA level low. In the biopsy taken post anti-TGFb mAbs treatment, TNFa and TGFb levels were normal. The most amazing finding was, however, an enormous rise in MC2 and MC3 mRNA levels, while MC5 mRNA increased 20-fold, POMC mRNA was considerably higher than in the pre-treatment biopsy.

Conclusion: Our results point at the suppression of the melanocortin system in the leading edge of the dSSc skin lesion, including suppressed expression of mRNA for the MC subtypes: 1, 2, 3 and 5 as well as of POMC mRNA. Treatment with anti-TGFb mAbs resulted in an exceptionally large increase in mRNAs for POMC, MC1, 2, 3, 5, probably a rebound effect, as TGFb is known to suppress POMC synthesis.

Melanocortin receptors are Gs-protein coupled and their activation results in a rise in intracellular cAMP, which in turn may inhibit the production of connective tissue growth factor (CTGF), a cytokine mandatory to TGFb stimulated ECM synthesis. Thus we hypothesize that the downregulation of the melanocortin system by TGFb, may further promote ECM synthesis in SSc and that the hyperpigmentation seen in SSc may be due to rebound effects in the melanocortin system in skin lesions of longer standing and decreasing TGFb concentrations.

2327

Identification of a Gene Expression Signature in Limited Cutaneous Systemic Sclerosis That Includes Several Vascular Genetic Factors. Cecilia B. Chighizola[1], Pia Moinzadeh[2], Korsa Khan[3], Tammara A. Wood[4], Pier Luigi Meroni[5], David J. Abraham[6], Michael L. Whitfield[4], Voon Ong[7] and Christopher P. Denton[3]. [1]University Of Milan, Milan, Italy, [2]Royal Free Hospital, Medical School, London, United Kingdom, [3]UCL Medical School, London, United Kingdom, [4]Dartmouth Medical School, Hanover, NH, [5]University of Milan, Milan, Italy, [6]Centre for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom, [7]UCL Medical School, London, England

Background/Purpose: Systemic sclerosis (SSc, scleroderma) has a heterogeneous clinical presentation, unpredictable outcome and incompletely understood pathogenesis. Skin changes are the hallmark of SSc: vascular dysfunction, tissue fibrosis and immune dysregulation are key events.

Gene-expression profiling is a powerful tool not only to distinguish between scleroderma and normal skin, but also to detect different subsets. Moreover, analysis of genome wide mRNA signatures could provide further insights into pathogenesis and help identifying biomarkers to predict pattern of organ involvement and drug response. To complement several published studies have focused mainly on diffuse subset of SSc, we performed gene expression profiling in skin samples from patients with limited cutaneous SSc (lcSSc).

Methods: 4 mm skin punch biopsies were performed in 10 patients with lcSSc and 5 healthy controls. Total RNA was extracted from whole skin biopsy. Gene expression profiling was performed on a 44,000 element DNA oligonucleotide microarrays (Agilent Technologies). Each sample was analyzed in duplicates for a total of 30 microarray hybridizations. Probes missing more than 20% of data were excluded. Data were processed to display the changes in gene expression as the Lowess normalized $\log_2$ of the ratio of the intensity relative to its average. Spots with intensity 1.5 fold over background were selected. Each probe was centred on its median value across all arrays. 3578 genes whose expression varied from median value by 2-fold in at least two experiments were identified and analyzed by heuristic clustering. Wilcoxon test was used to select genes with a significant differential expression between lcSSc and control samples. Correction for multiple testing was applied. Our gene expression findings were validated by qRTPCR on 10 representative genes in independent biological replicate samples.

Results: All samples from affected individuals but one clustered onto one branch in the resulting dendogram. 469 probes with a false discovery rate $<$ 0.1% were selected. Among these, we identified potential pathogenic mediators whose relevance in SSc pathogenesis has already been investigated (Table 1).

In particular, a "vascular signature" emerged across lcSSc samples (in italics). This is consistent with both clinical manifestations and scientific reports, supporting a prominent vascular involvement in lcSSc. See **Table 1** for representative genes that were significantly differentially expressed.

Table 1.

Pathogenic Mediators Mean (SD) for scaled normalised expression of biological replicates with corrected p-value and mean fold change	p-value	Mean (SD) lcSSc (n=10)	Mean (SD) Control (n=5)	Mean fold change lcSSc/control
Pre-B-cell colony enhancing factor 1	0,0022	0,476 (0,809)	−0,982(0,438)	2.5
Cell adhesion molecule with homology to L1CAM	0,0022	0,255 (0,415)	−0,816 (0,369)	2.3
Periostin	0,0022	0,382 (0,570)	−1,448 (0,415)	2.3
Endothelin receptor type B	0,0033	0,136 (0,440)	−1,358 (0,469)	2.2
IL-8	0,012	0,151 (0,324)	−0,690 (0,558)	2.2
Interleukin 1 receptor, type I	0,01	0,273 (0,521)	−0,528 (0,438)	2.5
Intimal thickness-related receptor	0,0142	0,148 (0,506)	−0,754 (0,594)	2.2
Heat shock 105kDa/110kDa protein 1	0,0022	0,467 (0,528)	−0,502 (0,219)	2.9
Membrane metallo-endopeptidase CD10	0,0069	0,256 (0,400)	−0,608 (0,527)	2.3
Cadherin 19, type 2	0,0101	0,015 (0,603)	−1,290 (0,659)	2.0
Integrin, beta 8	0,0232	−0,059 (0,876)	−1,130 (0,873)	1.9
Intracellular signalling pathways				
Zinc finger protein 354A	0,0071	0,172 (0,361)	−0,620 (0,446)	2.3
PTEN	0,02	0,350 (0,516)	−0,456 (0,578)	2.8
Autoantigens				
Centromere protein F, 350/400ka (mitosin)	0,0143	0,344 (0,497)	−0,546 (0,424)	2.6
Sjogren syndrome antigen B (autoantigen La)	0,0197	−0,181 (0.702)	−1,372 (0,626)	1.9
Sjogren syndrome antigen A2 (60kDa)	0,0273	0,007 (0,572)	−0,642 (0,706)	2.0

Conclusion: Gene expression profiling of skin biopsies clearly differentiates lcSSc samples from healthy controls. Consistently with both clinical manifestations and previous scientific reports, we found a proangiogenic profile across lcSSc samples. These studies will inform biomarker discovery and studies of pathogenic mechanisms that may be especially relevant to vascular complications of SSc.

2328

A Novel Automated Longitudinal In Vivo Assessment of Bleomycin Induced Pulmonary Fibrosis in Mice Using In Vivo High Resolution Micro-Computed Tomography. Ellen De Langhe[1], Greetje Vande Velde[1], Jeroen Hostens[2], Frank P. Luyten[1], Ben Nemery[1], Uwe Himmelreich[1], Jeroen Vanoirbeek[1] and Rik Lories[1]. [1]KU Leuven, Leuven, Belgium, [2]Skyscan

Background/Purpose: In vivo high resolution μCT imaging in animal models of lung disease allows longitudinal observations of pathological processes and image-based measurements of functional parameters. Current μCT image based algorithms for fibrosis quantification are characterized by lower spatial resolutions, insufficient correlation to histopathological or physiological data, and are labor intensive.

Methods: Lung fibrosis was induced in 8-week old male C57/Bl6 mice, by intratracheal instillation of 0.05U bleomycin (BLM) or control phosphate buffered saline (PBS). Mice were treated daily with imatinib (50mg/kg/d via daily i.p. injection) or vehicle control (AD). A 'scanning only' group evaluated scan toxicity (all n=6). Freely breathing, isoflurane sedated mice were scanned weekly at 35 μm resolution (SkyScan® in-vivo μCT) with retrospective respiratory gating. 4 weeks after induction, invasive pulmonary function tests were performed (Flexivent® SCIREC). Tracheotomised mice were euthanized and lungs were scanned for pressure-volume loop construction, by externally applying decreasing pressures (30-0 cmH_2O). A fully automated algorithm calculated aerated lung volumes and densities. Lungs were collected for histopathological scoring (Ashcroft score). The hydroxyproline assay quantified total collagen content.

Results: Serial scanning caused no abnormalities. Imatinib attenuated fibrosis by 30%, based on Ashcroft score and lung compliance. Untreated BLM-challenged lungs had significantly lower aerated lung volumes, calculated upon μCT images, reflecting restrictive pulmonary disease. Imatinib-treated BLM-challenged animals had lung volumes intermediate between untreated BLM challenged and the control groups. Calculated lung volumes correlated to Ashcroft score and hydroxyproline content. Constructed pressure-volume loops agree with invasive pulmonary function tests. Plotted mean density histograms discriminate between our 5 experimental groups and show the dynamic progression of fibrosis in the longitudinal setup. The reconstructed 3- and 4D images provide critical information on topographical distribution of fibrosis.

Conclusion: We present a fully automated in vivo μCT fibrosis analysis protocol, resulting in quantitative measurement of pulmonary volumes in the bleomycin induced pulmonary fibrosis model. We show that the resulting volumes correlate with histopathological scores, total collagen contents and invasive pulmonary function tests. We demonstrate that this imaging technique and consecutive automated analysis is suitable for serial imaging of individual animals and is sensitive enough to detect modest treatment effects.

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Gene-Gene Interactions In Interferon Pathway Gene-Mutations In European and American Scleroderma Cohorts. Pravitt R. Gourh[1], Filemon K. Tan[2], Blanca Rueda[3], Frank C. Arnett[2], Shervin Assassi[2], John D. Reveille[2], Timothy RD Radstake[4], Maureen D. Mayes[2], Javier Martin[5] and Sandeep K. Agarwal[2]. [1]UTHSC-Houston Medical School, Houston, TX, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]Facultad de Ciencias de la Salud. Universidad de Granada, Granada, Spain, [4]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [5]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain

Background/Purpose: Tpe-I interferon(IFN), a central mediator of innate immunity, has been shown to be the hallmark peripheral blood gene expression pattern in lupus(SLE) and a similar type-I IFN signature has been noted in systemic sclerosis(SSc). Interferon regulatory factor 5 and 7(*IRF5/IRF7*) and tyrosine kinase 2(TYK2) are important genes involved in this signaling cascade. The purpose of this work was to investigate the association of *IRF5, IRF7, TYK2* polymorphisms with SSc.

Methods: We performed SNP genotyping for *IRF5(rs20024640), IRF7(*rs1061502*), TYK2*(rs2304256) genes using the Taqman Assay in 4 large cohorts comprising of North-American Caucasian, Dutch, Italian and Spanish samples totaling to 2,091 SSc patients and 1,434 race-matched controls. All SSc patients fulfilled ACR criteria or had at least 3 of the 5 CREST features. HWE testing, chi-square, logistic regression(LR) were used for statistical comparisons. Mesoscale assays were used for cytokine detection.

Results: After HWE verification, all 3 SNPs showed association with SSc in US Cohort with recessive pattern in IRF5 and a dominant pattern in IRF7 and TYK2. By LR analysis after controlling for gender and cohorts the association was confirmed in all cohorts{IRF5:P<0.0001,OR(CI)-0.68(0.6–0.8);IRF7:P=0.006,OR(CI)−0.80(0.7–0.9);TYK2: P=0.05,OR(CI)−0.85 (0.7–0.99)}. The association was stronger with anti-centromere subset{IRF5: P=0.0002,OR(CI)−0.59(0.5–0.8);IRF7:P=0.0008,OR(CI)−0.69(0.6–0.9); TYK2:P=0.04,OR(CI)−0.79(0.6–0.9)}.

The data was modeled based on mode of inheritance for the 3 SNPs and LR analysis performed controlling for gender and cohorts and revealed an extremely protective effect for the combination of mutations vs the wildtype{$IRF5^M$/$IRF7^M$,$TYK2^M$ vs $IRF5^{WT}$/$IRF7^{WT}$,$TYK2^{WT}$:P<0.0001; OR(CI)−0.39(0.3–0.6)}.

In the $IRF5^{WT}$/$IRF7^{WT}$,$TYK2^{WT}$group, the SSc patients had increased levels of TNF-α and IL-6 as compared to controls and there was no difference amongst the patients and controls in the $IRF5^M$/$IRF7^M$,$TYK2^M$ group.

Conclusion: Our data confirms the association of *IRF5* SNP with SSc and also demonstrates for the first time the association of IRF7 and TYK2 SNPs with SSc.

We demonstrate a gene-gene interaction in SSc between three non-linked loci- *IRF5, IRF7* and *TYK2*.

The 3 gene-SNPs have a protective effect in SSc patients and the presence of the 3 mutations simultaneously has the most protective effect. This effect is stronger in the anti-centromere subset of SSc patients.

Plasma TNF-α and IL-6 levels were increased in the SSc patients wildtype for the 3 SNPs vs controls, whereas there was no difference in TNF-α and IL-6 levels in the SSc patients having mutations for the 3 SNPs vs controls.

In summary, IRF5,IRF7,TYK2 SNPs have a protective effect in SSc which is stronger when there are polymorphisms on all of the genes as compared to each of them alone. The presence of these 3 polymorphisms simultaneously correspond to a lower level of proinflammatory cytokine production as compared to wildtype.

This suggests an important role of interferon pathway polymorphisms in susceptibility to SSc and the exact role of these interactions and their function in SSc susceptibility needs to be elucidated experimentally.

2330

Human Leukocyte Antigen Alleles in Juvenile Onset Systemic Sclerosis. Anne M. Stevens[1], Maureen D. Mayes[2], John D. Reveille[2], Gretchen R. Henstorf[3] and J. Lee Nelson[4]. [1]University of Washington, Seattle, WA, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]Seattle Children's Research Institute, Seattle, WA, [4]Fred Hutchinson Cancer Rsch, Seattle, WA

Background/Purpose: Systemic sclerosis (SSc) is rare in children and little is known about factors contributing to its pathogenesis in this population.

HLA class II allele associations have been reported for adult onset SSc. We evaluated HLA class II alleles in patients with juvenile onset SSc and families.

Methods: 50 children with juvenile onset systemic sclerosis were studied. HLA genotyping was conducted to high resolution for HLA-DRB1, DQA1 and DQB1. Demographic and clinical characteristics were summarized including race/ethnicity, sex, age at onset, whether disease was diffuse or limited and antibodies to topoisomerase 1 and centromere.

Results: Among the 50 children 41 were Caucasian, 4 African American, 1 Asian, 1 Native American, 2 other and 1 unknown. One child was a triplet. For analysis 40 singleton, Caucasian, juvenile SSc patients were compared to 109 similar healthy children. 85% of patients were female (34/40). The mean age of onset was 10.4 years (range 2.3–15.9). 23 patients had diffuse and 17 limited SSc. 32% had antibodies to topoisomerase 1 (13/40) and 10% to centromere (3/30 tested). HLA-DRB1*03 was present in 52% of diffuse SSc (12/23) compared to 20% of normals (22/109), odds ratio 4.3 p=0.003. DRB1*03 was not increased in limited SSc (29% 5/17). HLA-DRB1*11 was somewhat overrepresented in limited SSc (35% 6/17) compared to normals (19% 21/109), but this was not significant (not increased in diffuse SSc). There was no suggestion of increased HLA-DRB1 compatibility of children and their mothers (66% 23/35 were bi-directionally mismatched).

Conclusion: HLA-DRB1*03 was significantly increased in juvenile onset diffuse SSc in Caucasian patients compared to age similar healthy children. This result is dissimilar to adult Caucasian women where the primary association reported has been with HLA-DRB1*11. HLA-DRB1 sharing was not increased in mother-child pairs.

ACR/ARHP Poster Session C
T-cell Biology and Targets in Autoimmune Disease: Lymphocyte Biology and Targets in Autoimmune Disease
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

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Methylprednisolone Modulates MicroRNA and Gene Expression in Human CD4$^+$ T Cells: A Novel Mechanism of Anti-Inflammatory Action. Trevor E. Davis[1], Katalin Kis-Toth[2], Attila Szanto[3], Laurie C. Miller[4] and George C. Tsokos[5]. [1]Floating Hospital for Children at Tufts Medical Center; Beth Israel Deaconess Medical Center, Boston, MA, [2]Beth Israel Deaconess Medical Center, Boston, MA, [3]Harvard Medical School; Massachusetts General Hospital, Boston, MA, [4]Tufts Medical Center, Boston, MA, [5]Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, MA

Background/Purpose: MicroRNAs (miRNAs) are short RNA species (20–23 nt) that act post-transcriptionally to regulate messenger RNA (mRNA) translation or stability. They influence many biological processes such as immune system development and function. Abnormal levels of miRNAs have been implicated in cancers and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Steroids are "first line" anti-inflammatory medications that act through gene regulation both transcriptionally and post-transcriptionally. In many instances, steroids cause mRNA destabilization, indicating a potential role for miRNAs.

Methods: Naive CD4$^+$ T cells were isolated from peripheral blood of healthy donors using negative selection. Cells were activated by anti-CD3/anti-CD28 antibodies for 24h with or without 10^{-6} M methlyprednisolone treatment. Supernatants were collected for cytokine measurements by ELISA. A portion of cells was used for flow cytometric analysis and the remainder used for RNA or protein isolation. RNAs were simultaneously tested on miRNA and mRNA microarrays using the Wafergen system. Result ant Ct values were converted to relative copy numbers and normalized to housekeeping genes RNU44 (miRNAs) and B2M (mRNAs). These normalized values were compared between the untreated and treated groups. Genes with at least 2-fold expressional changes between groups were selected for further investigation. Potential targets for these selected miRNAs were obtained from the bioinformatic resource Targetscan. The potential targets were cross-referenced with the mRNAs selected from the mRNA array and subjected to further analysis. Individual qPCR assays were used to verify the treatment effects on selected miRNAs and mRNAs.

Results: We identified 12 miRNAs decreased by steroid treatment (miRNA 17, 25, 27b, 101, 133A, 155, 299-5P, 300, 496, 548K, 646, and 1244) with simultaneous increase of 52 predicted mRNA targets (e.g. APAF1, ARID4A, ATRX, BCL-2, BMPR2, BNIP3L, CCNG1 and 2, CD28, DUSP1, MNT, RB1CC1, SOCS1, TOB1). We identified 8 miRNAs increased by steroid treatment (miRNA 98, 181b-1, 514, 543, 590-5P, 758, 1207-5P, 1243) with simultaneous decrease of 20 predicted mRNA targets (e.g. ARHGAP31, BAG4, CASP-3, CCND2, FAS, IL-1A, SARM1, SMAD7, TNF, TNFRSF1B, UHRF1). Other notable mRNAs decreased by steroid treatment, although not targeted by identified miRNAs, were BCL2A1, CCND3, CCNE1, CDC6, CDK10, CDK4, IL12RB2, IL2, IL2RA, IRF1, LTA, MNAT1, NFKB2, RELA, TIRAP, TNFRSF1B, TRAF2, and TRAF4. Notable mRNAs that increased by steroid treatment, though not targeted by identified miRNAs, were ATM, CARD8, CASP-8, MAF, and SMAD3.

Conclusion: Using simultaneous high throughput analyses of both miRNA and mRNA combined with bioinformatic miRNA target prediction, we identified a group of miRNAs altered by methylprednisolone treatment in activated CD4$^+$ T cells with potential regulation of their target genes. These targets have been implicated in T cell activation, proliferation and homeostasis. Based on these findings, methylprednisolone may act via these miRNAs to regulate T cells, a novel mechanism to impart anti-inflammatory effects.

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Deficient Thymic T Lymphopoeisis in Rheumatoid Arthritis Is Not Due to the Lack of CD34+ Lymphoid progenitors. Manuela Rossol[1], Anett Schulz[1], Annika Schatz[2], Undine Meusch[2], Dagmar Quandt[2], Christoph G. Baerwald[3] and Ulf Wagner[3]. [1]Translationszentrum für Regenerative Medizin (TRM), University of Leipzig, Leipzig, Germany, [2]University of Leipzig, Leipzig, Germany, [3]University Hospital, Leipzig, Germany

Background/Purpose: An important role for CD4+ T cells in the pathogenesis of rheumatoid arthritis (RA) is implicated by the HLA-DRB1*04 association of the disease, by the massive T cell infiltration in the rheumatoid synovium, and by the success of T cell directed therapies. Several lines of evidence show, that the T cell compartment of patients with RA is characterized by premature immunosenescence and a disturbed homeostasis. Aim of the study was to analyze if the reduced frequency of naïve CD4+ T cells in the peripheral blood of RA patients is due to a reduced bone marrow output of CD34+ haematopoietic stem cells and lymphoid progenitors.

Methods: Mononuclear cells of the peripheral blood of 28 RA patients (median age 63.1 years) and 28 age-matched healthy controls (median age 63.4 years) were analyzed by flow cytometry. RA patients were all ACPA+ and RF+, and 50% were SE-DR4+.

Results: The frequency of CD34+ haematopoietic stem cells as well as the frequency of lineage-negative CD34+ cells in the peripheral blood of RA patients is not different from healthy controls (0.09% vs. 0.08% and 0.007% vs. 0.006%).

The frequency of the pre-thymic lymphoid progenitor characterized by CD34+/Lin-/CD24-/CD10+ is increased in patients with RA compared to healthy controls (16 cells per 1E07 PBMC vs. 9 cells per 1E07 PBMC, p=0.01). However, the thymic output, characterized by the frequency of recent thymic emmigrants (CD4+/CD45Ra+/CD31+) is decreased in RA patients (32.0% vs. 43.9%, p=0.007).

Conclusion: The frequency of the CD34+/Lin-/CD24-/CD10+ lymphoid progenitor is increased in RA compared to healthy controls, while the thymic output of CD31+ recent thymic emigrants is reduced. We hypothesize, therefore, that insufficient thymic T cell genesis is the underlying cause of the disturbed T cell homeostasis in this disease, and might also contribute to the pathogenesis of the disease.

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Synovial Fluid Vγ9Vδ2 T Cells Activated by Synovial Fibroblasts Induce Their Apoptosis. Anna Bendersky[1], Victoria Marcu[1], Yackov Berkun[2], Itamar Goldstein[1], Maya Gerstein[1], Shay Padeh[1] and Ilan Bank[1]. [1]Sheba Medical Center, Ramat Gan, Israel, [2]Hadassah Hebrew University Medical Center, Jerusalem, Israel

Background/Purpose: Recent data suggest that higher levels and proliferative responses of synovial fluid (SF) Vγ9+ T cells to a metabolite in the mevalonate pathway critical for survival of synovial fibroblasts (synfib), isopentenyl pyrophosphate (IPP), are positive prognostic indicators in juvenile idiopathic arthritis (JIA) (Berkun et al., J. Rheumatol 2011, 38:6, 1123). We designed experiments to define the functional role of SF Vγ9+ T cells in JIA.

Methods: Twenty JIA patients undergoing therapeutic arthrocentesis were studied. Mononuclear cells (MC) were isolated from the SF and PB by ficoll- hypaque density centrifugation. Plastic adherent cells from SF were cultured giving rise to CD90+CD14- synfib cell lines. MC were analyzed by flow cytometry after cell surface membrane staining with fluorescent dye

labeled specific monoclonal antibodies (mAb) to identify T cell subsets. Proliferation was assessed by flow cytometric analysis of 5,6-carboxyfluorescein diacetate succinimidyl ester (CFSE) labeled MC. Apoptosis was measured by annexin V staining of CFSE labeled fibroblasts after 48 hour culture alone, with IPP (2ug/ml) or with zoledronate (4uM). Cytokines were assayed by intracellular immuno-staining of freshly isolated or briefly cultured MC activated with phorbol myristate acetate (PMA) and ionomycin with or without added IPP, followed by flow cytometric analysis after staining of the cells with subset specific mAb.

Results: Equally high percentages (~35%) of PMA+ionomycin activated Vγ9+ T cells in SF and peripheral blood monuclear cells (PBMC) produced TNFα and IFNγ and a few (~1–3%) secreted IL-17. Stimulation with IPP, which is a potent auto-antigen for Vγ9J1.2+ T cells further equally amplified cytokine secretion among the SF and PBMC Vγ9+ T cells. However, only the SF Vγ9+ T cell subset expressed high levels of CD69 *in situ* suggesting its recent activation by synovial auto-antigens. Moreover, 24 hour co-culture of freshly isolated MC, with cultured synfib, but not with skin derived fibroblasts, enhanced CD69 on the SF but not the PB Vγ9+ T cells, which was further potentiated by zoledronate, a farnesyl pyrophosphate synthase inhibitor that increases endogeneous intracellular levels of IPP. Vγ9+ T cell proliferation in response to IPP, which was significantly lower in SF than PBMC cultures, was enhanced by depleting SF CD4+CD25+ FoxP3+ cells (Treg), but, importantly, both SF and PB Vγ9+ T cells proliferating in response to IPP induced apoptosis of co-cultured synfib in the presence of zoledronate or IPP, in a Vγ9+ T cell dose dependent manner.

Conclusion: Synfib induce activation of SF Vγ9+ T cells specifically and serve as auto-antigen (IPP)-presenting cells for cytokine secreting SF Vγ9+ T whose IPP driven proliferation is partly controlled by SF Treg. These activated Vγ9+ T cells induce apoptosis of synfib conditioned to express high levels of the IPP auto-antigen, suggesting they may play a critical role in controlling the proliferation of certain fibroblasts in the synovium.

2334

Defining Pathogenicity of Human Th17 Cells in Rheumatoid Arthritis. Hiroshi Kato[1], Judith Endres[1] and David A. Fox[2]. [1]University of Michigan, Ann Arbor, MI, [2]Univ of Michigan Med Ctr, Ann Arbor, MI

Background/Purpose: Th17 cells, while crucial in host defense, may also play central causative roles in many autoimmune diseases including RA. Although our knowledge concerning murine Th17 cells, especially the mechanisms of their differentiation, has rapidly expanded, the pathogenic functions of human Th17 cells as well as immune-regulatory factors reversing such pathogenicity have not been fully defined. We assessed induction of cell-cell interaction molecules on fibroblast-like synoviocytes (FLS) by human CD4 T cell subsets as well as roles of IL-4 in regulating pathogenic features of human Th17 cells.

Methods: CD4 T cells isolated from healthy adult donors were cultured in RPMI culture media with 10%FCS, 1% Penicillin/Streptomycin, and 2% L-glutamine for 5 days either in the presence of plate bound anti-CD3, soluble anti-CD28, anti-IL-4, and IL-12 to induce Th1 cells, or autologous mature dendritic cells, soluble anti-CD3, anti-IFN-γ/IL-4/TGF-β, IL-1, IL-6, and IL-23 to induce Th17 cells. Th1 or Th17 cells were co-cultured with passage 4–8 FLS for 48 hours with/without neutralization of IFN-γ, IL-17, or both. Alternatively, FLS were treated only with IFN-γ or IL-17 for 48 hours. Expression of MHC-II, CD40, and CD54 on the FLS were assessed by surface staining followed by flow cytometry analysis. In a separate experiment, CD4 T cells were stimulated under Th17 polarizing conditions for 3 rounds interspersed with 2 days rest. After each round of stimulation, a part of Th17 cells was stimulated under Th2 polarizing conditions: plate bound anti-CD3, soluble anti-CD28, anti-IFN-γ, and IL-4. In all the experiments, T cell phenotypes were assessed by measurement of IFN-γ or IL-17 in culture supernatants by ELISA or intracellular staining of IL-17 versus IFN-γ/IL-4 followed by flow cytometry analysis.

Results: FLS significantly up-regulated MHC class II, CD40, and CD54 upon co-culture with Th1 or Th17 cells. Th1 cells, which secreted significantly higher amount of IFN-γ than Th17 cells, were more potent in up-regulating these molecules. During the co-culture of Th17 cells and FLS, neutralization of IFN-γ significantly abrogated FLS expression of MHC class II, CD40, and CD54 while neutralization of IL-17 did not inhibit and in some experiments augmented FLS expression of MHC class II, CD40, and CD54. Treatment with IFN-γ significantly up-regulated FLS expression of MHC class II, CD40, and CD54. Treatment with IL-17 at higher than 10ng/ml, which was comparable to what was secreted by Th17 cells, significantly decreased FLS expression of CD40 and CD54. *In vitro* induced human Th17 cells lost both IFN-γ and IL-17 expression upon exposure to IL-4, even after two rounds of Th17 polarization.

Conclusion: These data suggest that IFN-γ but not IL-17 is more contributory to human Th17 cell pathogenic function in the induction of relevant surface molecules on FLS, and that neutralization of IL-17 might be detrimental depending on the context. Given that IL-4 suppresses human Th17 cell differentiation as well as both IFN-γ and IL-17 synthesis by human Th17 cells, even after multiple rounds of Th17 polarization, IL-4 could serve as a potent immune-regulatory cytokine in Th17-driven autoimmune disease.

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T Cell Receptor Signal Strength Controls Onset and Severity of Arthritis in Antigen (Proteoglycan Epitope)-Specific T Cell Receptor Transgenic Mice. Katalin Olasz[1], Ferenc Boldizsar[1], Katalin Kis-Toth[2], Oktavia Tarjanyi[1], Akos Hegyi[3], Willem van Eden[4], Tibor A. Rauch[3], Katalin Mikecz[3] and Tibor T. Glant[3]. [1]Pecs, Hungary, [2]Boston, MA, [3]Rush University Medical Center, Chicago, IL, [4]Utrecht, Netherlands

Background/Purpose: T cell receptor transgenic (TCR-Tg) mice specific for the most arthritogenic 5/4E8 epitope of the G1 domain of cartilage proteoglycan (PG) were generated and backcrossed into arthritis-prone BALB/c background. Although over 90% of $CD4^+$T cells of all TCR-Tg lines "uniformly" expressed Vβ4 chain, some of the transgenic lines (e.g., TCR-Tg"A") proved to be highly sensitive to, and spontaneously developed, arthritis, while others were less susceptible (e.g., TCR-Tg"B"). The goal of this study was to understand how a single (monoclonal) TCR signaling can control the onset and severity of arthritis, and what level of T cell signaling is required for arthritis onset and severity.

Methods: TCR-TgA, TCR-TgB and wild-type (WT) BALB/c mice were immunized with recombinant human G1 domain on days 0, 21 and 42. Animals were sacrificed (i) before the immunization, (ii) 10 days after the 1st injection, (iii-iv) 4 days before the 2nd and 3rd, and (v-vi) 5 days after the 2nd and 3rd immunizations (n=4 in each group). Serum cytokines and auto-antibodies (Abs), antigen-specific *in vitro* T cell responses were measured. T and B cell markers (including activation, costimulatory, FoxP3, and apoptotic markers) and phosphorylation levels of ZAP-70, ERK1/2 and p38 in spleen and joint-draining lymph node (LN) cells were compared by flow cytometry. The cell surface expression and copy number of Vβ4 and Vα1.1 chains of 5/4E8 epitope-specific TCR were determined.

Results: TCR-TgA mice developed a more severe arthritis earlier than WT or TCR-TgB mice. AutoAbs to mouse G1 domain, APCAs or RFs were significantly higher (3–5-fold differences) in TCR-TgA than in TCR-TgB mice. This more pronounced Ab secretion in TCR-TgA mice was associated with a higher B cell percentage compared to that in TCR-TgB mice during the whole immunization period in the joint draining LNs or the spleen. Among the intracellular and cell surface markers, the $CD4^+$ $ICOS^{High}$ increased continuously in TCR-TgA (and arthritic) mice. However, the $CD4^+CD25^+FoxP3^+$ cell ratio was also significantly higher in TCR-TgA than either WT or TCR-TgB mice indicating that regulatory T cells (Tregs) play a dispensable role in regulating autoimmune processes in this model of RA. In contrast, $CD4^+$ T cells of TCR-TgB mice expressed twice as much TCR and CD3 molecules than the $CD4^+$ T cells in TCR-TgA line, and, upon stimulation, these T cells expressed significantly higher sensitivity to antigen-specific apoptosis. Indeed, when TCR-TgB $CD4^+$ T cells were engaged with the 5/4E8 peptide, significantly higher levels of phosphorylation of the key downstream signaling molecules were detected than in TCR-TgA T cells.

Conclusion: A strong arthritogenic (5/4E8) epitope-specific TCR-initiated signal in PG-TCR-TgA mice led to optimal T-cell activation and generated a "super-arthritic" phenotype. In contrast, an extremely "strong" TCR signal, likely due to higher TCR expression, led to *in vivo* T cell apoptosis and diminished arthritis in TCR-TgB mice. Theoretically, only the "optimal" T cell signaling (even triggered by multiple arthritogenic epitopes) can create the optimal milieu for autoimmunity and RA.

2336

Short Combination Therapy with Anti-CD3 and Anti-TNF Is Associated with Long Term Inhibition of Established Collagen-Induced Arthritis. Fabien Depis[1], Eric Hatterer[1], Céline Lamacchia[2], Cem Gabay[2], Jean-Marc Waldburger[2], Walter Reith[3], Marie Kosco-Vilbois[1] and Yann Dean[1]. [1]Nov Immune S.A., Plan-Les-Ouates, Geneva, Switzerland, [2]University Hospitals of Geneva, Geneva, Switzerland, [3]University of Geneva Medical School, Geneva, Switzerland

Background/Purpose: NovImmune has developed a fully human anti-CD3 monoclonal antibody (mAb), NI-0401, that is in clinical development and for which a subcutaneous formulation is available. In patients, NI-0401 modulates T cell responses and modifies T cell subsets. A plethora of data demonstrates that in addition to components of innate immunity, e.g. TNF, adaptive immunity involving T cells is implicated in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA). In preclinical models of RA, as well as in RA patients, T cell infiltration and high levels of TNF are observed in affected joints. The objective of this study was to determine the effect of anti-CD3 therapy in mouse collagen induced arthritis (CIA), either alone or in combination, with a TNF neutralization strategy.

Methods: Anti-mouse mAbs V1q-Novi and 2C11-Novi were developed to act as surrogate reagents for their therapeutic counterparts Humira (anti-TNF) and NI-0401 (anti-CD3), respectively. CIA was induced in DBA/1 mice. The mAbs were administered intraperitoneally at onset of arthritis as follows: daily injections of 50 micrograms of 2C11-Novi for five consecutive days and a single administration of 100 micrograms of V1q-Novi.

Results: Targeting T cells with a short course of 2C11-Novi did not significantly modify disease severity in arthritic mice. In contrast, the single dose of the neutralizing anti-mouse TNF mAb (V1q-Novi) significantly inhibited disease progression only up to 10 days. Strikingly, the combination of the two mAbs demonstrated a potent synergy with increased duration of action, as assessed by clinical scores, up to 3 weeks beyond that observed with the anti-TNF therapy alone. The frequency and number of pathogenic and regulatory CD4+ T cell subsets in the draining lymph nodes were determined in order to investigate the cellular mechanisms of combination therapy. The results did not demonstrate any enhancement of CD25+Foxp3+ regulatory T cells but a significant reduction in pathogenic T effector cells (Th1 and Th17 specific for type II collagen).

Conclusion: Our data show that a short course therapy with anti-CD3 and anti-TNF antibodies inhibits the progression of established CIA by targeting collagen-specific Th1 and Th17 cells in relevant lymphoid tissues. This combination strategy could be employed in patients with RA using NI-0401 via a convenient subcutaneous administration.

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Antigen-Specific Regulatory Tr1 Lymphocytes As New Cell-Therapy Approach for Immunotherapy in Arthritis. Delphine Martire[1], Julie Quentin[1], Anne-Laure Mausset-Bonnefont[1], Helène Asgnali[2], Nathalie Belmonte[2], Arnaud Foussat[2], Christian Jorgensen[3] and Pascale Louis-Plence[1]. [1]Inserm U844, Montpellier, France, [2]TxCell, Valbonne-Sophia Antipolis, France, [3]CHU Lapeyronie, Montpellier, France

Background/Purpose: Tr1 cells have been characterized as induced T regulatory lymphocytes (Treg) inhibiting inflammation in various chronic inflammatory models. Based on these data, a Phase I/II clinical trial is currently under investigation in Crohn's disease (TxCell). However, the therapeutic potential of these cells has not yet been evaluated in rheumatoid arthritis. In this study, we investigated the therapeutic potential of bovine type II collagen-(bCII) specific Tr1 cells, isolated from TBC mice, in the experimental model of collagen-induced arthritis (CIA).

Methods: Collagen type II specific Tr1 clones were obtained from TCR transgenic mice and expanded in vitro. Selected clones showed in vitro antigen specificity, Tr1 cytokine profile ($IL10^{high}/IL4^{neg}$) and IL10- and TGFb-dependent suppressive activity. Male DBA/1 mice were immunized with bovine type II collagen (bCII) and 10×10^6, 3×10^6, 1×10^6, $0.3\times10^6$of Tr1 cells were injected (i.v) 28 days post-immunization. Hind paws swelling and clinical signs of arthritis were scored, as well as biological parameters such as the level of anti-bCII antibodies in the sera of treated mice and the cytokine profile of bCII specific T cells.

Results: One single injection of 3×10^6 or $1\times10^6$of Tr1 cells at day 28, in ongoing arthritis, significantly inhibits the development of arthritic disease, shown by reduction of disease severity and incidence. In contrast the injection of 0.3×10^6 and 10M of Tr1 cells did not improve the clinical signs of arthritis. The analysis of the bCII specific T cell responses following euthanasia of the mice injected with $3\times10^6$and $1\times10^6$of Tr1 cells revealed a decrease of proliferation of bCII specific T cells and a slight increase of IL-10 secreted by activated splenocytes. The protection of the mice was associated with a decrease of anti bCII specific antibodies in the sera,.

Importantly, these preliminary data indicate that a single injection of Tr1 cells at disease onset could reduce disease severity and incidence in experimental arthritis.

Conclusion: Single dose 3×10^6, $1\times10^6$of Tr1 cell administration showed a reduction of disease incidence and severity in CIA demonstrating the therapeutic potential of Tr1 cells in arthritis. A phase I/II clinical trial is ongoing in Rheumatoid Arthritis patient in France (TxCELL, France).

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Differences in Immune Cell Profile and Related Gene Expression Provide Clues to Susceptibility to Arthritis in Humanized Mice. David Luckey, Behrens Marshall and Veena Taneja. Mayo Clinic, Rochester, MN

Background/Purpose: Predisposition to develop Rheumatoid arthritis (RA) is associated with the presence of certain genetic factors. Genome wide association studies meta analysis has identified genes in the MHC region provide the strongest association. Pathways driven studies confirmed HLA mediated processes involved in susceptibility to RA. HLA-DQ8 haplotypes are associated with susceptibility while DQ6 haplotypes are associated with resistance to develop RA. We have characterized naïve DQ8 and DQ6 humanized mice for expression of various genes and T and B cell subsets. The purpose is a) to evaluate the immune cell profile associated with susceptibility, and b) to determine altered expression of genes of Th1/Th17 network in naïve mice to predict its association with susceptibility/protection.

Methods: We have generated HLA transgenic mice lacking all endogenous class II molecules (AEo) and expressing alleles known to be associated with susceptibility or resistance to arthritis. HLA-DQ8 renders susceptibility to develop collagen-induced arthritis (CIA) upon immunization with type II collagen while DQ6 mice are resistant to CIA. Arthritis in humanized mice mimics human disease in histopathology and antibody profile. Naïve mice were characterized for the presence of various T and B cell subsets by FACS analysis using conjugated antibodies. Further, naïve CD4+CD62L cells were cultured in vitro in various conditions to drive cytokine response to determine if they are programmed to produce proinflammatory cytokines. We next assessed the expression of genes related to Th1 and Th17 network in splenic cells isolated from naïve transgenic mice using quantitative RT-PCR technology

Results: Arthritis resistant and susceptible mice showed differences in presence of subsets of T and B cells. While overall T regulatory cells expressing FoxP3 were similar in both strains, CD8+FoxP3+ cells occurred with increased frequency with a concomitant decreased frequency of CD4+FoxP3+ cells in CIA-resistant mice compared to susceptible strain. Naïve CD4+CD25- CD62L+ cells isolated from DQ8 mice when cultured with various cytokines in vitro produced Th17 cytokines while DQ6 mice produced higher levels of IL-10. B cells expressing CD40 and CD80 were significantly lower in numbers in CIA-resistant compared to susceptible mice. PCR arrays to profile TH1/Th17 network showed that naïve CIA-susceptible mice express gene associated with production of proinflammatory cytokines and chemokines, IL-17, IL-23, IL-13, CCL2 and CCL20 while these genes are under expressed in CIA-resistant mice. Following immunization with type II collagen, CIA-resistant mice produced immune response to the antigen but do not produce proinflammatory cytokines.

Conclusion: The gene expression data in arthritis susceptible and resistant mice may provide an immune profile to predict susceptibility and hence may be useful to generate therapeutic targets for rheumatoid arthritis.

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Investigation of Fibrinogen-Reactive T Cells in the Pathogenesis of Mouse Models of Rheumatoid Arthritis. Kristen N. Cordova[1], Rocky L. Baker[1], Gene Barbour[1], Kathryn Haskins[1] and V. Michael Holers[2]. [1]University of Colorado, AMC, Aurora, CO, [2]Univ of Colorado School of Med, Aurora, CO

Background/Purpose: Citrullinated proteins, derived from the conversion of peptidyl-arginine to peptidyl-citrulline, are present in the joints of rheumatoid arthritis (RA) patients, who also uniquely produce high levels of anti-citrullinated protein antibodies (ACPAs). Citrullinated fibrin(ogen) is abundant in rheumatoid synovial tissue, and ACPA-positive RA patients exhibit circulating immune complexes containing citrullinated fibrinogen,

suggesting that citrullinated fibrinogen is a major target of ACPAs in RA. ACPAs specific for citrullinated fibrinogen have also been shown to also enhance damage in animal models of autoimmune arthritis, and mice deficient in fibrinogen display reduced disease severity in the collagen induced arthritis (CIA) model of RA. Fibrin deposition in the joint is one of the most consistent features of both RA and animal models of RA, and several groups have demonstrated a role for fibrin in the pathogenesis of autoimmune arthritis by using thrombin inhibitors to hinder fibrin polymerization, resulting in disease suppression. T cells are believed to be involved in this process by initiating, controlling and driving antigen specific immune responses in RA.

Previously, we found that mice immunized with human fibrinogen (HF) or citrullinated human fibrinogen (HCF) develop a proliferative response to both HCF and HF present in lymph nodes and spleens. To determine if fibrinogen-reactive T cells are important in the pathogenesis in mouse models of autoimmune arthritis, we studied the phenotype of the T cells after immunization with HCF and isolated T cell lines reactive to HF or HCF.

Methods: DBA1/J mice were immunized with HCF, and then lymph nodes were taken at various time points and either evaluated directly *ex vivo* or cultured *in vitro*. *Ex vivo* T cells were evaluated for the presence of activation markers and cytokine production after antigen stimulation, while T cell lines were cultured long term *in vitro* with antigen and IL-2, and evaluated in the same manner. T cell lines were sorted and cultured based upon the vβ region of their T cell receptor (TCR) in order to obtain a uniform population of cells.

Results: We found by *ex vivo* analysis that, following two immunizations of HCF, mice develop higher levels of CD4 cells with an activated effector phenotype (CD44hi+CD62L-) than CFA-injected controls, and TNFα, IFNγ, and IL-17 are produced specifically by CD4 cells in response to challenge with HCF. Cultured T cell lines produce higher levels of TNFα and IL-17 as well as IL-6 when stimulated with HCF. One antigen-specific sorted line, HCF5 vβ5+, is highly reactive to citrullinated forms of both HF and mouse fibrinogen.

Conclusion: We conclude that fibrinogen-reactive CD4 T cell lines exhibit an inflammatory phenotype that may have an effect in inflammatory autoimmune arthritis. Currently, T cell lines are being evaluated *in vivo* to determine if they affect disease in CIA and in anti-collagen antibody-induced arthritis mouse models.

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Lysophosphatidylcholine Enhances Suppressive Function of Human Naturally Occurring Regulatory T Cells Through TGF-Beta Production. Hitoshi Hasegawa, Jin Lei, Takuya Matsumoto, Sachiko Onishi, Koichiro Suemori and Masaki Yasukawa. Ehime University Graduate School of Medicine, Toon, Japan

Background/Purpose: Regulatory T cells (Treg) play a pivotal role in the maintenance of self-tolerance and immune homeostasis and are shown to exert therapeutic effects on autoimmune diseases. There are at least two subsets of Treg cells, naturally occurring Treg (nTreg) and peripheral induced Treg (iTreg) cells. The identification of molecules controlling Treg differentiation and function is important in understanding host immune responses and application to therapy. Previously, from screening of the libraries of lipids and nuclear receptor ligands, we isolated the fourteen bioactive molecules that enhanced Foxp3 expression and suppressive properties of human Treg cells and reported that peroxisome proliferator-activated receptor agonists together with TGF-beta converted human $CD4^+CD25^-$ T cells into functional $Foxp3^+$ regulatory T cells. In this study, of these, we demonstrated that lysophosphatidylcholine (LPC) enhanced Foxp3 expression and suppressive function of human nTreg cells, and analyzed this mechanism of LPC.

Methods: $CD4^+CD25^+CD127^{-/low}$ cells were isolated from human PBMC as nTreg cells, cultured for 72h in the presence of LPC, and then were examined the expression of Foxp3, suppressive function, and cytokine production. Furthermore, we analyzed the mechanism by which human nTreg cells were increased suppressive function through LPC.

Results: Foxp3 expression and suppressive properties of LPC-treated $CD4^+CD25^+CD127^{-/low}$ (nTreg) cells were increased significantly in comparison with those of the non-treated nTreg cells. This was due to TGF-beta1 production from nTreg cells treated with LPC. LPC enhanced the expression levels of mRNA and protein of latent TGF-beta1 in nTreg cells through its receptor, G2A. This was also confirmed with the human TGF-beta1 promoter assay. Moreover, LPC released and activated latent TGF-beta1 on nTreg cells. On the other hand, LPC did not induce the production of TGF-beta1 from $CD4^+CD25^-CD45RA^+$ T cells and $CD4^+CD25^-CD45RO^+$ T cells, although both cells expressed G2A. In addition, LPC-treated $CD4^+CD25^-CD45RA^+$ T cells did not convert to iTreg cells.

Conclusion: We demonstrated that LPC enhanced Foxp3 expression and suppressive function of human nTreg cells through TGF-beta production. TGF-beta and IL-2 are known to play an important role in the maintenance and function of human nTreg cells. LPC is a highly abundant bioactive lysolipid present at high concentrations in the circulation. Taken together, LPC may also contribute to the maintenance and function of human nTreg cells.

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Multifunctional T Cell Reactivity to Native and Glycosylated Type-II Collagen in Rheumatoid Arthritis. Vivianne Malmström[1], Omri Snir[1], Johan Bäcklund[2], Lars Klareskog[1] and Rikard Holmdahl[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institutet, Stcokholm, Sweden

Background/Purpose: Type II collagen (CII) is a cartilage-specific protein to which a loss of immune tolerance may trigger autoimmune reactions and lead to arthritis. The major T cell epitope on CII, aa259–273, can be presented by several *HLA-DRB1*04* alleles both in its native and posttranslational-glycosylated forms. Here, we aimed to functionally explore and compare CII-autoreactive T cells isolated from blood and synovial fluid of patients with rheumatoid arthritis (RA).

Methods: Peripheral blood and synovial fluid mononuclear cells were obtained from 10 *HLA-DRB1*04* RA patients and stimulated *in vitro* with several variants of the $CII_{259–273}$epitope: *(a)* unmodified, or glycosylated on *(b)* lysine-264, *(c)* lysine-270, or *(d)* both lysine-264 and 270. Activation was assessed by determination of CD154 upregulation on responding T cells followed by intracellular staining for IL-17, IFNg and IL-2 by multicolor flow cytometry.

Results: Multifunctional T cell responses towards all examined variants of the $CII_{259–273}$ peptide could be detected. A comparison between blood and joint-derived T cell function revealed a significant increase of proinflammatory cytokines secreted by synovial T cells, in particular IFNg ($p=0.004$). Studies of longitudinal samples show that T cell responses were sustained over the course of disease, and even included epitope spreading.

Conclusion: Determination of CD154 upregulation in combination with intracellular cytokine staining provides a sensitive approach to study infrequent autoreactive T cells. Inflammatory T cell responses to both glycosylated and non-glycosylated variants of the major CII epitope in the same patients suggests that CII autoreactivity may be more common than previously appreciated.

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Circulating CD4+CD161+ T Cells As Biomarker of Disease Activity in Recently Diagnosed, Non-Treated Rheumatoid Arthritis Patients. Paulina Chalan, Wayel H. Abdulahad, Minke G. Huitema, Bart-Jan Kroesen, Elisabeth Brouwer and Annemieke M.H. Boots. University Medical Center Groningen, Groningen, Netherlands

Background/Purpose: Ample evidence suggests a role for T lymphocytes in the pathogenesis of rheumatoid arthritis (RA). CD161 was shown to confer tissue migratory properties to T cells and may thus contribute to tissue pathology. The role of CD161+ T cells in recently diagnosed RA has not been investigated yet. Our first objective was to provide clues on T-cell subset(s) involved in RA by analyzing frequencies of naïve (T_{Naive}), central memory (T_{CM}), effector memory (T_{EM}), terminally differentiated (T_{TD}) T lymphocytes and by assessing CD161 expression in blood of newly-diagnosed RA patients and paired peripheral blood (PB)- synovial fluid (SF) samples of late-stage RA. Secondly, we assessed the cytokine profile of PB and SF- derived CD4+CD161+ T cells. Thirdly, we investigated in a longitudinal study, the influence of regular methotrexate (MTX) treatment on circulating CD4+CD161+ T cells

Methods: Blood from recently diagnosed, non-treated RA patients (n=30), age-/sex-matched healthy controls (HC, n=27) was stained with fluorochrome-conjugated anti-CD4, CD8, CD45RO, CCR7, CD161 antibodies and analyzed using flow cytometry. 21 patients had a second measurement 3 months after start of MTX treatment. DAS28, ESR, CRP were assessed at baseline and at 3 months (after treatment). T-cell subset composition was also analyzed in paired PB and SF samples from patients with an active disease (n=9). Cytokine (TNF-α, IFN-γ, IL-4, IL-17) and cytolytic granule (Perforin, Granzyme B) expression of PB- and SF- derived lymphocytes was assessed by intracellular staining and flow cytometric analysis

Results: The frequency of CD4+ T_{EM} was found to be significantly decreased while the frequency of CD4+ T_{Naive} was significantly increased in newly-diagnosed RA patients when compared to HC. Of note, the frequency

of CD4+CD161+ T cells, found to contain mostly effector memory cells, was significantly decreased in RA (p=0.04). The percentage and the absolute number of circulating CD4+CD161+ T cells correlated inversely with DAS28 (−0.41, p=0.028 and −0.42, p=0.023, respectively). We observed a significant enrichment of CD4+, but not CD8+ T cells expressing CD161 in SF when compared to PB (p=0.039). SF-derived CD4+CD161+ T cells showed enhanced IFN-γ and reduced IL-17 expression compared to their PB-derived counterparts. After 3 months of MTX treatment, a reduction in disease severity was associated with normalization of circulating CD4+CD161+ T lymphocytes

Conclusion: The frequency of CD4+ $T_{EM}$is significantly decreased while the frequency of CD4+ T_{Naive} is increased in PB of early RA. The decline of circulating CD4+CD161+ T lymphocytes correlated inversely with disease activity. The observed preponderance of CD4+CD161+ T cells in SF compared to PB suggests their influx in the joint. Increased IFN-γ production by SF CD4+CD161+ T cells may contribute to the disease process in RA. Furthermore, the normalisation of circulating CD4+CD161+ T cells following MTX treatment suggests that this subset might qualify as a biomarker of disease activity in RA.

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Circulating Human Collagen II-Reactive T Cell in Early Rheumatoid Arthritis Produce IL17. Anna Laura Fedele[1], Chiara Nicolò[2], Gabriele Di Sante[2], Barbara Tolusso[1], Silvia L. Bosello[1], Elisa Gremese[1], Francesco Ria[2] and Gianfranco Ferraccioli[1]. [1]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [2]Institute of General Pathology, Catholic University of the Sacred Heart, Rome, Italy

Background/Purpose: Joint damage in Rheumatoid Arthritis is likely due to pro-inflammatory T cells specific for collagen and recruited into the synovium, where they are activated and promote acute presentation of the disease. We previously described the T cell repertoire specific for human Collagen II peptide 261–273 (huColl261) in HLA-DR4+ Early Rheumatoid Arthritis (ERA) patients, compared to that of DR4+ healthy subjects and followed it along disease course, showing that T cells specific for this epitope appear during flares of the disease but tend to disappear during remission (Ria et al., Art Res Ther, 2008). Here we report preliminary observations regarding the presence of specific clonotypes recognized by the ability of hColl-specific (HuColl2) T cells to respond to Collagen II peptide and we describe that they seem to secrete IL-17 more than IL-13.

Methods: PBMC obtained from 22 consecutive ERA patients were collected. All patients were typed for HLA-DRB1. 11 patients were DR 4+, 4 were DR1+ one was DR 4,1+. Patients were tested for the presence of HuColl2 peptide response by immunoscope. In 4 ERA patients synovial fluid cells were also examined. PBMC were also purified from 2 ERA patients and one RA patient at his first remission of disease, and stimulated in vitro with huColl261. Sixteen hours later, IL-17 and IL-13 secreting cells were enriched by MACS® secretion assay. The presence of huColl261-specific TCRs was assessed by immunoscope in samples enriched or depleted for each cytokine, and in samples allowed to proliferate for 3 days in response to the peptide antigen.

Results: We examined the usage of two TCR beta chains that we showed to be frequently used in DR4+ ERA patients. Collagen-specific T cells carrying BV11(139b) were used by 6/12 ERA DR4+ subjects, 2/4 DR1+ subjects(that were both also DR15+) and by 2/6 patients negative for both DR4 and DR1. Usage of BV13b (199) appears to be more specific for DR4+ subjects, since we found collagen specific T cells using this TCR-beta chain in 5/10 DR4+ ERA patients versus 1/10 DR4- ERA subjects. T cells obtained from 3 PB samples were tested for their capacity to secrete specific cytokines (IL17 or IL13) in response to stimulation with collagen II. T cells secreting any of the two cytokine represent only a part of the circulating T cell repertoire specific for huColl261, similar to the observation that a minority of the circulating repertoire is actually able to home to the synovium. IL17-secreting cells were detected in all 3 samples, but it appears that T cells from one patient in remission needed additional stimuli that include bacterial derived non antigenic moieties in order to produce IL-17. huColl261-specific IL-13 producing cells were detected only in one of the 2 ERA subjects.

Conclusion: By the immunoscope technique we could dissect the immune response against human collagen in ERA subjects. Results show that some rearrangements of the TCR-beta chain co-segregate with the collagen-specific response restricted by DR4 and/or DR1. The T cell precursors actually driving the proinflammatory response in the synovium by the production of IL-17 appears to represent a limited portion of the entire collagen specific repertoire.

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A Novel Human Autoantigen Induces T and B Cell Responses in Patients with Antibiotic-Refractory Lyme Arthritis. Elise E. Drouin[1], Robert J. Seward[2], Chunxiang Yao[3], Kianoosh Katchar[1], Gail McHugh[1], Klemen Strle[1], Catherine E. Costello[3] and Allen C. Steere[1]. [1]Massachusetts General Hospital and Harvard Medical School, Boston, MA, [2]Massachusetts General Hospital, Harvard Medical School and Boston University School of Medicine, Boston, MA, [3]Boston University School of Medicine, Boston, MA

Background/Purpose: Antibiotic-refractory Lyme arthritis (ARLA), defined as persistent synovitis lasting months to years after spirochetal killing with 2–3 months of oral and IV antibiotic therapy, is hypothesized to result from *B. burgdorferi*-induced autoimmunity in affected joints. Previous attempts to identify autoantigens based on sequence homology with borrelial proteins, proteome microarrays or recombinant antibody probes had been unrevealing. Therefore, we devised an innovative new approach that combines discovery-based proteomics with translational research for the identification of naturally processed, immunogenic HLA-DR-presented autoantigens in synovial tissue.

Methods: Naturally presented HLA-DR peptides were purified from the synovial tissue of individual patients, identified by tandem mass spectrometry, synthesized and tested for autoreactivity using the same patient's PBMC. Peptides shown to have autoreactivity were further evaluated for disease-associated T and B cell autoreactivity using PBMC and sera from a large cohort of patients with antibiotic-refractory Lyme arthritis and from individuals in comparison groups.

Results: Of the 120 non-redundant peptides identified from the synovial tissue of a single patient, only one peptide, which was derived from endothelial cell growth factor (ECGF), was recognized by his PBMC. Testing of PBMC from 44 additional patients with ARLA showed that 21 (48%) also had T cell autoreactivity with 1 or more of 7 T cell epitopes of ECGF, compared with 8 of 29 patients (28%) with antibiotic-responsive arthritis, 3 of 19 (16%) with erythema migrans (EM, an early disease manifestation), and 1 of 18 healthy control subjects (6%), as demonstrated by ELISPOT assay. In addition, as determined by ELISA and Western blotting, 49 of 112 patients (44%) with ARLA had IgG anti-ECGF autoantibodies with titers as high as 1:11,000; most patients with T cell responses also had B cell reactivity with this autoantigen, suggesting these responses were linked. In comparison with ARLA patients, antibody responses to ECGF were found in 11 of 32 patients (34%) with antibiotic-responsive arthritis (P=NS), 2 of 33 (6%) with EM (P<0.001), and 11 of 91 healthy subjects (12%) (P<0.001). ARLA patients with anti-ECGF-antibodies more often had HLA-DRB1*04 or 1501 alleles (alleles previously associated with chronic Lyme arthritis) compared with patients who lacked such autoantibodies. Finally, ECGF was found to be abundant in both synovial fluid and synovial tissue in ARLA patients, demonstrating the presence of the autoantigen at the site of inflammation.

Conclusion: About half of the patients with ARLA had T and B cell reactivity with the human protein ECGF. This is the first autoantigen identified that induces both T and B cell autoreactivity in ARLA patients. Clinical testing for anti-ECGF autoantibodies is a promising biomarker for diagnosis, and is likely to help in treatment decisions, including the use of DMARDs after antibiotic therapy. Furthermore, this innovative, cutting-edge methodology for identifying novel autoantigens is directly applicable to any of the chronic inflammatory arthritides, including rheumatoid arthritis.

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IL-2/IL-2mAb Complex Induced Expansion of Treg Cells and Prolonged Suppression of Collagen Induced Arthritis in Mice by Fortifying IL-2 Signaling Pathways. seon Yeong Lee[1], Hye Jwa Oh[1], Joo-Yeon Jhun[1], Jun Geol Ryu[1], Mi La Cho[1], ji Hyeon Ju[1], Sang Heon Lee[2], Sung Hwan Park[1], Charles D. Surh[3] and Ho Youn Kim[1]. [1]Rhematism Research Center, Seoul, South Korea, [2]Division of Rheumatology, Seoul, South Korea, [3]Department of Immunology

Background/Purpose: To investigated the effect of IL-2/JES6-1(anti-IL-2 mAb) complex on in the control of collagen-induced arthritis (CIA) and to evaluate its impact on the induction/suppression of Treg and Th17.

Methods: Wild type and CIA DBA1/J mice were injected intraperitoneally (i.p.) with IL-2 or IL-2/JES6-1 three times with 2 day intervals. Surface markers of Tregs (CTLA4, GITR, ICAM, CD103, PD1, CD101, GARP and Foxp3) were analyzed by flow cytometry (FACs). After injection of IL-2 or IL-2/JES6-1, the time kinetics of IL-2 signaling

molecules (*phospho*(*p*)-STAT5, *p*-AKT and *p*-p38/MAPK) was examined by FACs and western blot. The concentration of IL-17 and IL-10 were measured by ELISA.

Results: Injection of IL-2/JES6-1 increased the proportion of $Foxp3^+$ Tregs in splenic $CD4^+$ T cells and reached the highest level on Day 4 after injection. Surface expression of CTLA4, GITR and GARP was simultaneously increased on the same day. Activation of *p*-STAT5 was apparent within 3 hours after injection. IL-2 signalings, including *p*-AKT and *p*-p38/MAPK, were also higher in the splenocytes treated with IL-2/JES6-1. The IL-2/JES6-1 suppressed the induction of CIA and the production of IL-17, while increasing the level of IL-10 in the spleen. Repeated injections of IL-2/JES6-1 complex, 3 weeks after primary immunization, prolonged the suppressive effect up two month after first the onset of arthritis.

Conclusion: Injection of IL-2/JES6-1 complex effectively suppressed the inflammatory response. The expansion of Treg (via STAT5) and concomitant increase of IL-2 signaling pathways by IL-2/JES6-1 postulates its potential usage as new therapeutic agent for arthritis

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High Density Lipoproteins Stabilize Antigen Presenting Cell:T Cell Conjugates by Altering the T Cell Receptor Signalling Kinetics. A.L. Gomes[1], J. Delgado-Alves[1] and E.C. Jury[2]. [1]Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisboa, Portugal, [2]University College London, London, United Kingdom

Background/Purpose: Epidemiologic studies in patients with autoimmune disease show a link between lipid metabolism and the immune system. In patients with systemic lupus erythematosus (SLE) a major cause of premature death is not the disease itself but events related to atherosclerosis associated with a shift in the serum cholesterol LDL:HDL ratio. In T lymphocytes, changes in plasma membrane lipid order have been correlated with altered T-cell antigen receptor (TCR) signalling resulting in differential patterns of proliferation and cytokine production. Interestingly, T cells from SLE patients are characterised by altered plasma membrane lipid microdomains and reduced lipid order. Here, we study the effects of HDL on the stability of plasma membrane lipid order and consequently on T lymphocyte signalling activation and proliferation.

Methods: CD4+ T lymphocytes were isolated from healthy donors by negative selection using magnetic beads. Cells were incubated with 350nM HDL for 2, 4, 24, 48 and 72 hours and assessed for plasma membrane lipid order, using the fluorescent probe di-4-ANEPPDHQ, and membrane cholesterol levels using filipin binding. For functional assays, cells were also stimulated with IL-2, anti-CD3 and anti-CD28 antibodies. The effect of HDL on T cell-antigen presenting cell (APC) interaction, TCR-associated intracellular signalling and cell cycling was assessed by flow cytometry using cell tracker markers, phosphoflow antibodies and DAPI, respectively. Cytokine production was assessed in supernatants using Cytokine Bead Array following the manufacturer's protocol.

Results: The results reveal that HDL reduces plasma membrane lipid order in $CD4^+$ T lymphocytes without altering total cholesterol levels. Culture with HDL did not alter the frequency of T cell-APC conjugate formation; however, HDL did increase the stability of T cell-APC conjugate interaction over a time course of 30 minutes. HDL also influenced the kinetics of proximal TCR-associated signalling events by prolonging TCR-zeta and ZAP-70 phosphorylation levels. Downstream signalling events were also affected demonstrated by delayed phosphorylation of ERK and increased NFKB phosphorylation compared to T cells not treated with HDL. The changes in T cell-APC interaction and TCR-mediated signalling were associated with altered T cell function in terms of proliferation shown by an increased frequency of cells in the G2/M phase of cell cycle, increased IL-6 production, and reduced IL-10 and TNF-alpha production compared to untreated control T cells. Thus the results suggest that differential levels of serum HDL could influence the response of T cells during immune activation.

Conclusion: In patients with SLE HDL levels can be severely affected. The consequences of altered serum cholesterol levels are typically associated with endothelial cell damage leading to cardiovascular disease. Here, we show that HDL directly affects TCR signalling and cytokine production in $CD4^+$ T lymphocytes, further supporting a tight link between the lipid metabolism and the immune system. This work was funded by Arthritis Research UK fellowship award (18106) to ECJ and by Fundação Amadeu Dias. ECJ and DAJ share senior authorship.

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The Induction of c-Maf in Th17 Cells and Its Implications in the Development of Memory Th Cells. Kojiro Sato, Fumihiko Miyoshi and Toshihide Mimura. Saitama Medical University, Saitama, Japan

Background/Purpose: Th17 cells are a newly identified Th cell subset that mainly produces IL-17 (IL-17A). They are implicated in the pathogenesis of several inflammatory diseases, including RA. We previously reported that Th17 cells, but not Th1 or Th2 cells, promote the differentiation of osteoclasts, which are responsible for the bone resorption observed in the damaged joints of RA. Next, we wanted to identify the network of transcription factors at work in the course of Th17 differentiation.

Methods: We performed GeneChip transcriptome analysis using time-course mRNA samples from Th cells cultured under Th1, Th2 and Th17 conditions, respectively.

Results: Proto-oncogene Maf (encoding c-Maf) was significantly induced in Th17 cells. Th cells derived from c-Maf transgenic (Tg) mice produced significantly more IL-17 than wild type (WT) Th cells. Interestingly, most of the Tg Th cells had a memory phenotype ($CD62L^{lo}$/$CD44^{hi}$), suggesting that c-Maf might play important roles not only in Th17 differentiation, but also in the induction of memory Th cells. Consistent with this, much more Maf, Il23r and Il17a were expressed in WT memory-like Th cells generated by transferring Th cells into T-cell deficient Rag-2 knockout (KO) mice (utilizing homeostatic expansion) than in naïve Th cells. In order to perform loss-of-function analysis, we tried to generate bone marrow-chimeric mice (Rag-2KO mice with c-Maf deficient hematopoietic cells), as c-Maf knockout mice are embryonically lethal. As expected, when transferred into Rag-2 KO mice, c-Maf deficient Th cells produced less Il23r and Il17a compared with control Th cells, although there was no difference detected by flow cytometry in the expression levels of memory markers ($CD62L^{lo}$/$CD44^{hi}$). We next sorted human naïve, central memory and effector memory Th cells from the peripheral blood and performed transcriptome analysis again, and found that human effector memory Th cells also express Maf at a high level. In fact, it was the second most induced transcription factor in effector memory Th cells.

Conclusion: Although it seems that c-Maf is unnecessary for the expression of surface memory markers, it is indeed important for the expression of Il17a in memory Th cells. c-Maf is induced not only in mouse memory Th cells, but also in human memory Th cells, suggesting the importance of the transcription factor in the memory Th cell differentiation.

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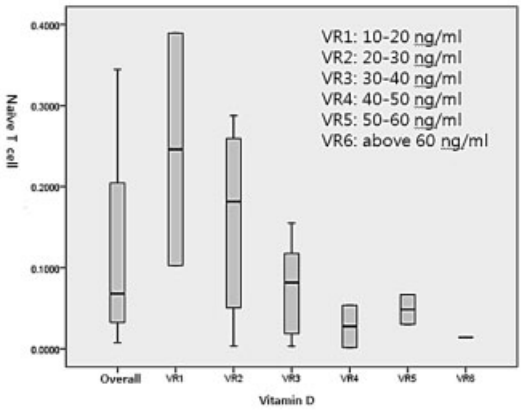
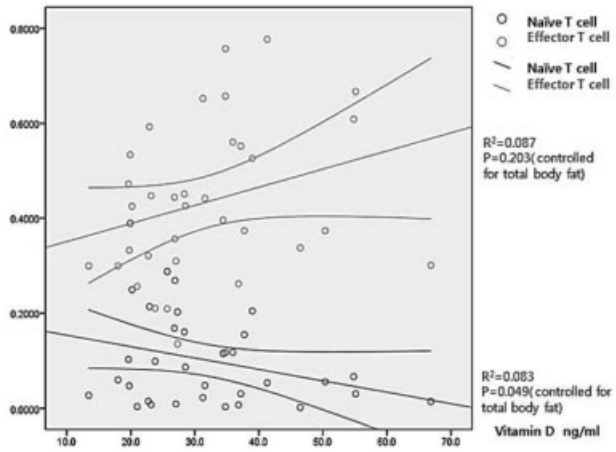
A Novel Role for Vitamin D in Immunosenescence: Is Enough Too Much for Naïve CD8 T Cells? Yong Gil Hwang[1], Fei Chu Lim[1], Qi Wu[1], PingAr Yang[1], Gordon Fisher[2], Gary Hunter[3], Hui-Chen Hsu[1] and John D. Mountz[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, Alabama, USA, [3]Department of Human Studies, University of Alabama at Birmingham, Birmingham, Alabama, USA, [4]University of Albama at Birmingham/Birmingham VA Medical Center, Birmingham, AL

Background/Purpose: Intensive repletion of vitamin D (Vit D) has been advocated for patients with rheumatoid arthritis (RA) and systemic lupus erythematosis (SLE) who have high risk in cardiovascular disease (CVD). However, meta-analyses showed that calcium supplements with or without Vit D was associated with increased risk of CVD. Of note, CD8 T cells have the highest levels of Vit D receptor and senescent CD8 T cells are associated with increased prevalence of CVD and adverse outcomes. This study determined the relationship between Vit D levels and CD8 T-cell status.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 34 healthy female subjects (all >60-yr-old). Naïve, effector, and senescent CD8 T cells were determined based on expression of CD28 and CD95 (Fas). PBMCs were stimulated with phytohemagglutinin (PHA) (10 μg/ml) and [3H]-thymidine incorporation was measured at days 3 (D3 PHA) and 7(D7 PHA). Anti-Fas antibody was added at days 2 and 4 (D7 PHA+anti-Fas) to induce apoptosis. Sera levels of 25-Hydroxy Vit D, IFNγ, IL-1, IL-6, IL-17, and IL-4 were determined by ELISA. Lipid profile and body composition data were measured. Bone density was determined by dual-energy X-ray absorptiometry.

Results: Overall, 19 (56%) participants had hypovitaminosis (equal or less than 30 ng/ml)(23.7± 4.8) and 15 (44%) subjects had higher than 30 ng/ml (42.2 ± 10.3). There was no difference in age(64±4), race, body fat, or lipid profile between the two groups. The low Vit D group had lower maximal oxygen consumption (p=0.019) and lower bone density only in L1 and L2 levels. There was a significantly higher percentage of naïve CD28+CD95- CD8 T cells (13.2% ±11.2, p=0.026) and a lower percentage of effector CD28+CD95+ CD8 T cells (37.8% ±13.5, p=0.018) in the low Vit D group. In contrast, high Vit D group had a lower percentage of naïve CD8s (6.2%± 6.1) but a higher percentage of effector CD8s (50.6% ±16.5). There was no significant difference in CD28-CD95+ senescent CD8 T cells and in D3 PHA and D7 PHA between the two groups. However, subtraction of D7 PHA+anti-Fas from D7 PHA was significantly higher in the low Vit D group (p=0.041). The low Vit D group had lower IL-4 and IL-17 as well as higher IL-1 and IL-6.





Conclusion: High levels of Vit D are correlated with decreased naïve and increased effector CD8 T cells, which are characteristic changes of CD8 compartment associated with ageing. These changes might be related with the anti-apoptotic effects of Vit D. The results indicate that while low levels of Vit D may predispose to development of autoimmune disease, high levels of Vit D may have a role in autoimmune disease progression and amplification, increased risk of CVD.

2349

AKAP79 Expression Is Increased in Systemic Lupus Erythematosus T Cells and Reduces IL2 Production. Gabriel Criado, María Galindo, A. Javier García-González, Jose L. Pablos and María J. Pérez-Lorenzo. Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain

Background/Purpose: Reduced activation of Protein Kinase A (PKA) and IL2 production are characteristic of T cells from SLE patients. AKAP79 is a part of a heterogeneous group of proteins (A-kinase Anchoring Proteins) that associate to and regulate the activity of PKA. In addition to its association to PKA, AKAP79 interacts with Protein Kinase C (PKC) and Calcineurin, key regulators of IL2 production and T cell activation. Therefore, altered expression and/or function of AKAP79 can play a role in the deficient activation of PKA and IL2 production that characterise SLE T cells.

The aims of our work were to quantify the expression of AKAP79 in SLE T cells and analyse its role in T cell activation

Methods: T cells were isolated by negative selection from SLE patients (n= 21) and healthy controls (HC, n= 20). RNA was purified, retrotranscribed to cDNA and levels of AKAP79 and β-actin transcripts were quantified by quantitative real-time PCR using Sybr Green technology. Ten fold dilutions of Jurkat T cell line cDNA were included in each run and standard curves were generated by linear regression using log(Ct) versus log(cell number), and the cell equivalent (CE) number for the test samples was calculated. Data are expressed as the ratio between AKAP79 CE number and β-actin CE number, yielding the relative RNA expression units (REU). AKAP79 and β-actin protein expression was detected in T cell lysates by Western Blot, quantified with Quantity One Software and protein expression units (PEU) were calculated as the ratio between AKAP79 and β-Actin signal. Statistical differences between groups were analysed with non-parametric Mann-Whitney U test using GraphPad Prism software. For functional assays, Jurkat T cells were transduced with dual promoter pRRL-AKAP79/GFP- or control pRRL-GFP-expressing lentiviruses and stimulated with plate-bound anti-CD3 and soluble anti-CD28 antibodies, RNA was isolated and IL2 transcripts quantified by quantitative real-time PCR.

Results: T cells from SLE patients had significantly higher levels of AKAP79 mRNA compared to HC (3.70 +/− 0.77 REU in SLE vs 1.97 +/− 0.27 REU in HC, P= 0.008). Increased expression of AKAP79 in SLE T cells was confirmed at the protein level (0.68 +/− 0.18 PEU in SLE vs 0.37 +/− 0.05 PEU in HC, P= 0.04). Furthermore, levels of AKAP79 protein in SLE T cells positively correlated with SLEDAI (Pearson r=.64, P= 0.004). Analysis of AKAP79 function showed that overexpression of AKAP79 significantly reduced IL-2 expression upon TCR stimulation (20.64 +/− 0.19 REU in pRRL-AKAP79/GFP vs 6.02 +/− 0.06 in pRRL-GFP, P= 0.001).

Conclusion: AKAP79 is overexpressed by T cells in SLE patients and can contribute to the deficient IL2 production characteristic of these cells.

2350

Oxidation Impairs PKCδ Signaling in Lupus. Gabriela Gorelik and Bruce C. Richardson. University of Michigan, Ann Arbor, MI

Background/Purpose: Defective T cell signaling combined with genetic and environmental factors is currently believed to play a key role in the development and establishment of autoimmunity.

Previous work demonstrated that decreased T cell ERK pathway signaling causes a lupus-like disease by decreasing DNA methyltransferase expression, causing hypomethylation and overexpression of methylation-sensitive genes resulting in autoimmunity. Similar results were found in CD4+ T cells from lupus patients. We recently demonstrated that a defective phosphorylation of PKCδ on T^{505} is responsible of the decreased ERK signaling in CD4+ T cells from lupus patients.

Recent reports have implicated oxidative stress in lupus pathogenesis with increased levels of reactive oxygen and nitrogen species. 3-NO2-Tyr proteins are increased in lupus and our preliminary evidence indicates that PKCδ is aberrantly nitrated in lupus T cells making it refractory to Thr phosphorylation and unable to activate the ERK pathway. Further, H_2O_2 is also increased in lupus.

The purpose of this research was to study the modification of PKCδ phosphorylation induced by H_2O_2 and its consequences on T cell ERK pathway signaling.

Methods: CD4+ T cells were purified from normal donors or active lupus patients by Ficol density gradient centrifugation and negative selection with magnetic beads. When indicated, cells were transfected using Amaxa nucleofection technology. The purified cells were treated with H_2O_2 and stimulated with 50 ng/ml phorbol 12-myristate 13-acetate (PMA) where indicated. Signaling protein expression and phosphorylation were quantitated in cellular lysates by immunoblotting.

Results: Purified T cells were incubated with increasing concentrations of H_2O_2 and then phosphorylation of kinases was analyzed by WB. H_2O_2 decreased the levels of p-Thr^{505} PKCδ following PMA stimulation as was observed previously in the presence of peroxynitrite and in lupus T cells. This effect was concentration and time-dependent (p-T^{505} PKCδ/PKCδ: mean ± SEM: 75.4 ± 6.9% decrease, p<0.03 treated vs non-treated, n=4, 5mM, 15 min). H2O2 affected only PKCδ, since PKCα and PKCθ were unaltered. Then, we studied if ERK signaling was impaired by H_2O_2 in T cells similar to lupus T cells where p-T^{505} PKCδ is decreased. Total and p-ERK were quantitated in H_2O_2 treated T cells. PMA stimulated ERK phosphorylation

was decreased after treatment ($p<0.02$). To investigate the mechanism by which H_2O_2 is affecting p-T^{505} PKCδ, T cells were incubated with L-NMMA, a NOS inhibitor, prior to H_2O_2 treatment. PKCδ phosphorylation was partially restored (p-T^{505} PKC δ/PKC δ: 39.5 ± 5.2% $p<0.05$, n=3 and 9.5 ± 1.2% $p<0.05$, n=3 inhibited vs non inhibited) after NOS inhibition. These results suggest that H_2O_2 may inactivate PKCδ through nitration similar to peroxynitrite. Both oxidants reproduced the PKCδ and ERK defect observed in lupus T cells.

Conclusion: These results demonstrate that H_2O_2 induces same modifications on PKCδ phosphorylation as those observed in the presence of peroxynitrite and in lupus T cells. Overall these results indicate that PKC δ may a the link between oxidative stress and the epigenetics modifications that drive to autoimmunity in lupus.

2351

Linker for Activation of T Cells Is Displaced From the Immunological Synapse in Lupus T Cells After T Cell Activation. Nursamaa Abdoel[1], Carmen Bracho[2], Martin A. Rodriguez[1] and Ana M. Blasini[1]. [1]Hospital Universitario de Caracas, Caracas, Venezuela, [2]Instituto Venezolano de Investigaciones Científicas, Miranda, Venezuela

Background/Purpose: Several abnormalities in T cell receptor (TCR)-mediated signaling have been demonstrated in lupus T cells. LAT, a critical protein localized in lipid rafts and intracellular cytoplasmic vesicles, provides docking sites for the assembly of the calcium activation complex and other molecules needed for the coordinated activation of the MAPK signaling pathway. We have shown impaired ERK activation in lupus T cells activated via TCR/CD3 complex. Abnormal assembly of supramolecular activation complexes may impair downstream MAPK activation in lupus T cells. We have previously observed that activation via TCR/CD3 induces a significant decrease in the amount of LAT in total cell lysates from lupus T cells stimulated for 5 minutes compared with healthy control T cells (13.25 ± 2.65 vs. 21.58 ± 2.78; MFI ± SME, p= 0.038, n= 16). This finding was confirmed using confocal microscopy, a method that also revealed delocalization of LAT and GM1 at lipid rafts in SLE T cells stimulated for 5 min versus resting T cells (0.975 ± 0.002 vs. 0.978 ± 0.001; Pearson Rr ± SME, p= 0.008, n= 14). In order to test whether diminished LAT levels induced by activation of SLE T cells could affect the trafficking pattern in and out of the immunological synapse, we examined the behaviour of LAT and two key signaling molecules (PLCγ1 and adaptor Grb2) in artificially in vitro simulated T-cell synapses in SLE patients and healthy controls.

Methods: Highly enriched T cells were adhered to pLL coated slides and activated for 5 and 15 min at 37°C with 4.5 mm superparamagnetic polystyrene beads coated with antibodies against CD3ϵ and CD28. Cells were fixed, permeabilized and stained with antibodies recognizing LAT, Grb2 and PLCγ1. The cell-bead complexes were evaluated by confocal microscopy and densitometries were obtained using ImageJ, 1.44, National Institutes of Health, USA.

Results: Analysis revealed that activation via CD3/CD28 during 15 minutes induced a significant decrease in the amount of LAT at the synapse in lupus T cells in comparisson with resting T cells (24.95 ± 4.48 vs. 31.51 ± 8.68; MFI ± SME, p=0.020, n= 8), a difference not found in healthy control cells. LAT levels out of the synapse were also diminished after activation of lupus T cells (18.39 ± 4.05 vs. 19.25 ± 6.28; MFI ± SME, p=0.022, n=8). PLCγ1 and Grb2 recruited to the synapse remained unchanged upon activation in both SLE and healthy T cells.

Conclusion: We conclude that activation via CD3/CD28 negatively regulates LAT expression both in and out of the synapse in SLE T cells. The mechanistic cues for the downregulation of LAT in response to T cell activation in lupus T cells are currently unclear. The diminished expression of LAT after TCR-CD3 activation may potentially disrupt downstream signaling events and impair activation of the MAPK cascade in human lupus T cells. Supported by FONACIT grants No.S1–200000440 and the program "Fortalecimiento al Postgrado de Desarrollo de Alto Nivel" No. 1220/OC-VE.

2352

Effects of Direct Ras Inhibition on Lupus T Cell Cytokine Secretion. Ioana Moldovan, Leticia Ortloff, Adrian Costinescu, Keith K. Colburn and Lora Green. Loma Linda University, Loma Linda, CA

Background/Purpose: Direct ras inhibition by farnesylthiosalycilate (FTS), has been previously used in MRL/lpr mice, a known mouse model for lupus, and had beneficial effects in decreasing disease activity, suggesting that ras inhibition may represent a novel therapeutic approach for systemic lupus erythematosus. In previous experiments from our group, ras inactivation by FTS was able to markedly decrease the level of CD40Ligand (CD40L), a major player in the immune response, in lupus T cells and did not affect the level of CD40L in T cells from healthy controls, supporting the hypothesis that there is an intrinsic defect in the Ras signaling pathway in lupus.

The purpose of this study was to assess the effects of ras inhibition on cytokine secretion in lupus lymphocytes, in an attempt to further elucidate the molecular mechanisms by which ras blockade could influence lupus activity. We used TCR dependent and independent stimulation protocols and measured the levels of cytokines secreted by lupus lymphocytes versus controls subjected to Ras inhibition with FTS.

Methods: Blood from four healthy donors and five lupus patients was obtained. The lupus patients had moderately active disease (SLEDAI>3). T lymphocytes were separated by negative selection using an enrichment protocol. In each experiment, half of the samples were treated with 25 micromoles FTS for two hours. The samples where then divided equally and exposed for another two hours to a TCR (T cell receptor) independent stimulus (phorbol myristate plus ionomycin), TCR stimulation with anti CD3 plus anti CD28 antibodies, or left unstimulated in the control group. Both T helper (Th)-1 (IL-2, TNFα, and IFNγ) and Th-2 (IL-4, IL-10, IL-6, IL-13) cytokines were measured using a Luminex assay. Statistical differences were assessed using the t-test method.

Results: For T lymphocytes subjected to the TCR-dependent stimulation protocol, treatment with FTS significantly decreased the levels of both Th1 and Th2 related cytokines in lupus cells, and had no significant effects on cytokine secretion from normal subjects. The exception was IL-6, which levels increased, consistent with the cell stimulation. No significant differences between the normal and the lupus cytokine secretion were observed for both the TCR-independent protocol group and the unstimulated group.

Conclusion: Our study suggests that direct ras inhibition by FTS is a potent inhibitor of cytokine secretion in lupus T cells, possibly via TCR signal blockade, and does not affect normal T cells. The only cytokine secretion that was not affected was IL-6, likely controlled through a different signaling pathway. Both this present study and our previous studies on the effects of FTS on CD40L secretion in lupus T lymphocytes support the hypothesis that the ras signaling pathway plays a major role in lupus and that and that a possible abnormality is present in the ras pathway from lupus lymphocytes, which may account for the differences observed. The lack of effect on blood from normal subjects and the efficient decrease in the immune function of T cells further supports a potential therapeutic role of ras inhibition in treating lupus disease.

2353

A Progesterone Receptor Regulates T Helper Cell Type 1 Functions and T Cell-Dependent Antibody Responses In Vivo. Alan Wong, Edward A. Clark and Grant C. Hughes. University of Washington, Seattle, WA

Background/Purpose: Progesterone (Pg) is a reproductive steroid that can suppress inflammation, cellular immunity and antibody production. Under physiologic conditions, Pg signals through two types of receptors: intracellular Pg receptors (iPRs) that are ligand-activated transcription factors, and membrane bound Pg receptors (mPRs) linked to inhibitory G proteins. However, the precise immunoregulatory functions of iPRs and mPRs in immune cells remain unknown. Determining these functions is critical for understanding links between female reproduction and autoimmunity, sexual immune dimorphisms, the immune requirements of pregnancy and the immunomodulatory effects of widely used synthetic forms of Pg. Here, we show that iPRs are natural regulators of T helper cell (Th) type 1 (Th1) functions and T cell-dependent (TD) antibody responses.

Methods: We measured primary TD IgG responses to alum-adsorbed DNP-KLH (or NP-OVA) and primary T cell-independent type 2 (TI-2) responses to DNP-Ficoll in iPR-deficient (iPRKO) and wild type (WT) mice. Spleen CD19+ B cells from naïve mice were compared for their ability to secrete IgG in vitro. Spleen CD4+ T cell (Th cells) were assessed for their ability to secrete Th1-related IFN-gamma or Th2-related IL-4 after CD3/CD28 stimulation, as well as their suppression by Pg. We used quantitative PCR to measure transcription in CD4+ T cells of IFN-gamma, T-bet and Pg receptor genes.

Results: iPRKO mice generated significantly more antigen-specific IgG1 and IgG2a than WT mice after TD immunization; in contrast, TI-2 IgG responses in iPRKO mice were deficient. Regulation of TD responses by iPR did not appear to involve B-cell intrinsic effects, since iPRKO B cells were deficient in their ability to secrete IgG in vitro in response to either T cell-associated signals (anti-CD40, IL-4) or T cell-independent signal (LPS). However, CD4+ T cells from iPRKO mice made significantly more IFN-gamma, but not IL-4, after CD3/CD28 stimulation in vitro compared to WT T cells, even in the absence of Pg. In the presence of Pg, IFN-gamma induction was significantly suppressed in CD4+ T cells in an iPR-dependent manner, as was transcriptional repression of

the IFN-gamma gene (ifng). Compared to WT, iPRKO CD4+ T cells made more IL-4, and showed more proliferation, but only in the presence of Pg.

Conclusion: iPR-mediated signals regulate Th1 functions and TD Ab responses in vivo. This appears to involve regulation of ifng by two mechanisms. First, iPR serves as a ligand-activated transcriptional repressor of activation-induced ifng transcription and IFN-gamma production in CD4+ T cells. Second, iPRKO CD4+ T cells, ex vivo or stimulated in vitro without Pg, showed enhanced levels of activation-induced ifng mRNA or IFN-gamma production, indicating iPR also regulates ifng locus structure. Interestingly, iPR may also be involved in suppressing other pathways of Pg signaling, since without iPR, CD4+ T cells became hypersensitive to proliferative effects of Pg. This latter effect may account for the increased levels of Th2-related IgG1 after TD immunization. The role of PR in other T cell-dependent immune responses is the focus of ongoing research. This work supported by NIH grant AI073739 and a related ARRA supplement.

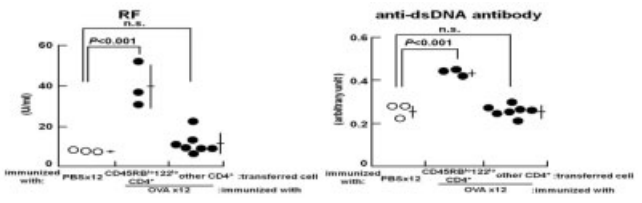
2354

The Autoantibody-Inducing CD4 T Cell*ai*CD4 T cell) Which Induces Systemic Lupus Erytematosus (SLE) Belongs to CD45RB^{lo}122^{lo} Subpopulation. Yumi Miyazaki[1], Ken Tsumiyama[1] and Shunichi Shiozawa[2]. [1]Kobe University Graduate School of Health Science, Kobe, Japan, [2]Kobe University Graduate School of Health Science and Medicine/ The Center for Rheumatic Diseases, Kobe University Hospital, Kobe, Japan

Background/Purpose: We have repeatedly immunized mice normally not prone to autoimmune disease with the same antigen and showed that repeated immunization reproducibly caused systemic autoimmunity, systemic lupus erytematosus (SLE). We show that a novel T cell type which we term an autoantibody-induing CD4 T cell (*ai*CD4 T cell) is generated *via de novo* T cell receptor (TCR) revision at periphery, in spleen. The *ai*CD4 T cell induced varieties of autoantibodies including rheumatoid factor (RF) and anti-Sm and anti-dsDNA antibodies, and also helped final differentiation of CD8 T cell into cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation to induce lupus tissue injuries (Tsumiyama K. *et al.* PLoS ONE 4(12):e8382, 2009). We here tried to assign the CD number on *ai*CD4 T cell, and show that *ai*CD4 T cell belongs to CD45RB^{lo} 122^{lo} population.

Methods: BALB/c mice were repeatedly immunized with ovalbumin (OVA), keyhole limpet hemocyanin (KLH) or staphylococcal enterotoxin B (SEB). RF, anti-Sm and anti-dsDNA antibody were measured using ELISA. To assign CD number on the *ai*CD4 T cell, expression of effector / memory markers including CD45RB, CD27, CD122, PD-1, CD44, CD62L, CD127, CCR7 and Ly6C were studied using splenic CD4 T cell of repeatedly immunized mice. These splenic CD4 T cells were further isolated referring to CD45RB, CD27 and CD122 markers, and fractioned cells were adoptively transferred into naïve recipients. Autoantibodies were measured in sera of recipient mice 2 weeks after transfer.

Results: Upon repeated immunization >12x with OVA, KLH or SEB, varieties of autoantibodies including RF and anti-Sm and anti-dsDNA antibodies were increased ($P<0.01$). We also noted that CD45RB^{lo}, CD27^{lo} and CD122^{hi} CD4 T cells were significantly expanded as compared with control mice upon immunization with either OVA, KLH or SEB ($P<0.001$). We fractioned CD4 T cells by referring CD45RB, CD27 and CD122 markers. We adoptively transferred fractioned CD4 T cells into naïve recipients and tested if RF and anti-dsDNA antibody were increased. This transfer studies showed that RF and anti-dsDNA antibody were significantly increased by the transfer of either CD45RB^{lo} CD4 T cells or CD122^{lo} CD4 T cells. However, the transfer of CD27^{lo} CD4 T cell and CD27^{hi} CD4 T cell both induced the increase of RF and anti-dsDNA antibody. We then transferred CD45RB^{lo} 122^{lo} CD4 T cells into naïve mice to show that both RF and anti-dsDNA antibody were significantly increased ($P<0.001$).



Conclusion: The *ai*CD4 T cell that induces SLE belongs to CD45RB^{lo} 122^{lo} CD4 T subpopulation.

2355

Sex-Specific Effects of Segmented Filamentous Bacteria In the Autoimmune-Prone NOD Mouse Strain—Segregation with Diabetes Protection In Females but Not Males. Martin A. Kriegel[1], Esen Sefik[2], Jonathan A. Hill[2], Hsin-Jung Wu[2], Christophe Benoist[2] and Diane Mathis[2]. [1]Brigham & Women's Hospital/Harvard Medical School, Boston, MA, [2]Harvard Medical School, Boston, MA

Background/Purpose: Segmented filamentous bacteria (SFB) are commensals capable of inducing a robust Th17 population in the small intestinal lamina propria (SI-LP) of the mouse gut. Consequently, SFB can promote IL-17-dependent autoimmune responses, including inflammatory polyarthritis in the K/BxN (KRN/NOD) mouse that resembles rheumatoid arthritis (Wu et al, Immunity 2010). Here, we exploit the incomplete penetrance of SFB colonization of NOD mice in our animal facility to explore its impact on autoimmune diabetes.

Methods: Fecal DNA was isolated from 4–6-wk old NOD mice using bead beating and phenol/chloroform. Realtime PCR was performed with SFB-specific 16S rDNA primers. Insulitis was assessed with H&E staining of pancreata. Lamina propria lymphocytes (LPL) were prepared and analysed using FACS. Intracellular cytokines were detected after ex vivo stimulation with PMA/ionomycin. RNA from sorted LPL was amplified, biotin labeled, purified and hybridized to an Affymetrix chip. Microarray data was analysed with the GenePattern suite.

Results: There was a strong co-segregation of SFB-positivity and diabetes protection in females, but not in males, which remained relatively disease-free regardless of the SFB status.

Cumulative Incidence of Autoimmune Diabetes

SFB Status	Males	Females
SFB-Positive	17.4%	15.8%
SFB-Negative	11.1%	91.3%
p-value	ns	<0.0001

In contrast, insulitis did not depend on SFB colonization suggesting that it may somehow modulate diabetes unfolding. SFB-positive, but not SFB-negative mice had a substantial population of Th17 cells in the SI-LP whereas Th1 and Treg populations were unaffected in the gut, pancreatic or systemic lymphoid tissues. Th17 signature transcripts dominated the very limited SFB-induced molecular changes detected in SI-LP CD4$^+$ T cells.

Conclusion: A single commensal bacterium, and the gut immune system alterations associated with it, can either promote or protect from autoimmunity (i.e. rheumatoid arthritis versus type 1 diabetes) in predisposed mouse models, likely reflecting their variable dependence on different Th subsets. Remarkably, the effects of SFB on autoimmunity in the NOD mouse were gender-specific, adding an entirely novel mechanism to help explain sex differences in autoimmune diseases. These findings should set the basis for a better understanding of strongly female-biased human autoimmune diseases like Sjogren's syndrome or SLE, both of which are also modelled in the autoimmune-prone NOD mouse strain.

2356

Expansions of Interleukin-21-Secreting CD4 $^+$T Helper Cells in Inflammatory Arthritides. Pedro L. Vieira[1], Maria C. Lebre[2], Saïda Aarrass[2], Thomas Newsom-Davis[1], PP. Tak[2] and Gavin R. Screaton[1]. [1]Imperial College London, London, United Kingdom, [2]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting synovial tissue in multiple joints. The inflammatory process in RA is regulated by several cytokines, especially TNF, which is produced not only by macrophages and DCs but also by activated antigen-specific CD4$^+$ T helper (Th) cells. IL-21 is a pleiotropic type 1 cytokine that shares the common cytokine receptor γ-chain, γ(c), with IL-2, IL-4, IL-7, IL-9, and IL-15. IL-21 is most homologous to IL-2. Whereas IL-2 promotes development of regulatory T cells and confers protection from autoimmune disease, IL-21 promotes differentiation of Th17 cells and is implicated in several autoimmune diseases, including type 1 diabetes, systemic lupus erythematosus and rheumatoid arthritis. IL-21, an inflammatory cytokine that belongs to the common γ-chain receptor binding family is secreted by several cell types including Th17 and T follicular helper cells (TFh). An increasing number of inflammatory molecules are being identified that may contribute to

RA pathology. Therefore we investigated the expression of interleukin-17A (IL-17A), IL-21 and IL-22 in RA, psoriatic arthritis (PsA) and undifferentiated arthritis (UA). In addition we dissected the in vitro requirements for the differentiation of human IL-21-secreting $CD4^+$ T helper (Th) cells.

Methods: Expression of surface markers and cytokine production at the single cell level in peripheral blood (PB) and matched synovial fluid (SF) from RA (n=8), PsA (n=4) and UA (n=5) patients, as compared to PB of healthy control subjects (n=25), was evaluated by flow cytometry following polyclonal stimulation ex-vivo. IL-21 concentrations were assessed by ELISA in cell-free SF samples of RA (n=15), PsA (n=14) and UA (n=9) patients and in 6 days supernatants of RA (n=6) and spondyloarthropathy (SpA, n=5) synovial biopsy cultures. Immunohistochemistry analysis were performed on synovial tissues (STs) of healthy donors (HD), RA, PsA, OA, and gout patients and sections were evaluated by digital image analysis.

Results: We observed significant expansions of IL-21-secreting cells, which represented up to 47% of total $CD4^+$ Th cells in SF. While the expression of IL-21 in STs and SF did not differ between the different arthritides, in ST IL-21 was significantly higher in inflammatory arthritis compared to HD. Interestingly, RA synovial biopsies released significantly higher levels of IL-21 compared to SpA. $CD4^+IL\text{-}21^+$ could be detected in RA ST that do not co-localized with IL-17 neither IL-22. Synovial IL-21-secreting cells did not phenotypically fit the TFh cell paradigm in that they did not express CXCR5. In humans, differentiation of naïve $CD4^+$ T cells into IL-21-secreting cells in vitro was preferentially driven by IL-21 and/or IL-6 in the additional presence of transforming growth factor-β.

Conclusion: IL-21 and IL-21 blocking therapy is now being tested in a number of diseases. The results of this study enhance the rationale for a trial of IL-21 blockade in RA where it may provide a useful adjunct in those patients refractory to or unable to tolerate anti-TNF therapy.

2357

Th17 but Not Th22 Cells Display Pathological Behaviour in Rheumatoid Arthritis Synovial Inflammation. Jan Piet van Hamburg, Odilia B.J. Corneth, Sandra M.J. Paulissen, Nadine Davelaar, Patrick S. Asmawidjaja and Erik Lubberts. Erasmus MC, University Medical Center, Rotterdam, Netherlands

Background/Purpose: T cells and their cytokines play a central role in the processes underlying synovial inflammation in rheumatoid arthritis (RA). In particular the IL-17A and IL-22 producing Th17 cells have been shown to be critically involved in the induction and progression of arthritis. Recently a novel Th22 subset was discovered, which was characterized by the expression of IL-22 in the absence of IL-17. However, it remains unclear whether Th22 cells, like Th17 cells, directly contribute to RA synovial inflammation. In this study we examined the potency of Th22 cells to activate synovial fibroblasts. In addition, it was investigated whether IL-22 is critical in Th17-mediated experimental arthritis.

Methods: Th17 (CD4+CD25-CCR6+CCR4+CCR10-) and Th22 (CD4+CD25-CCR6+CCR4+CCR10-) cells were analyzed in peripheral blood of treatment-naïve RA patients in comparison to age and sex matched healthy controls by flow cytometry. Furthermore, synovial fluid of patients with established RA was analysed for the presence of Th17 and Th22 cells. To test the contribution of IL-22 or Th22 in synovial inflammation, co-culture experiments of RA synovial fibroblasts (RASF) with Th22 and Th17 cells were performed. The *in vivo* relevance of IL-22 in synovial inflammation was investigated in a T cell-mediated arthritis model using mice deficient for IL-22.

Results: Both the Th17 and Th22 cell populations were increased in peripheral blood of treatment naïve patients with early RA compared to age and sex matched healthy controls. In addition, Th17 and Th22 cells were present in synovial fluid of patients with early RA. When RASF were co-cultured with Th17 or Th22 cells, in both conditions the neutralisation of IL-22 resulted in an induction of the pro-inflammatory cytokine IL-6. In contrast, IL-22 activation with FICZ (6-formylindolo(3,2-b)carbazole) resulted in a reduction of IL-6. Comparing the RASF co-culture condition of Th17 with Th22, Th17 cells were markedly more potent than Th22 cells in the induction of IL-6, IL-8 and matrix metalloprotease (MMP)-1 and MMP-3. In line with this, mouse Th17 cells lacking IL-22 expression were able to induce IL-6 expression in mouse synovial fibroblasts similar as normal mouse Th17 cells. In addition, no difference in T cell-mediated experimental arthritis severity was found between IL-22 deficient mice compared to wild type mice.

Conclusion: These findings show that both Th17 and Th22 cells are present in patients with RA. However, in contrast to Th17 cells, Th22 cells are less potent activators of RASF activation and IL-22 even appear to have an inhibitory effect on IL-6 production. These data imply that treatment of T cell-mediated inflammatory arthritis should focus on targeting Th17 cells rather than Th22 cells.

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HRES-1/Rab4 Lupus Susceptibility Gene Selectively Regulates Mammalian Target of Rapamycin Complexes 1 and 2 in T Lymphocytes. Tiffany Telarico[1], Gabriella Miklossy[2], David Sabatini[3], David Kwiatkowski[4], Nahum Sonenberg[5] and Andras Perl[2]. [1]SUNY Upstate Medical University, Syracuse, NY, [2]Upstate Medical University, Syracuse, NY, [3]Whitehead Institute for Biomedical Research, Cambridge, MA, [4]Brigham and Women's Hospital, Boston, MA, [5]Goodman Cancer Research Centre, McGill University, Montreal, QC

Background/Purpose: Activation of the mammalian target of rapamycin (mTOR) mediates abnormal activation of lupus T cells via HRES-1/Rab4-regulated endosomes. *In vivo* blockade of mTOR by rapamycin improves disease activity both in lupus-prone mice and patients with SLE. Importantly, mTOR is co-localized to recycling endosomes with HRES-1/Rab4 and Rab5A, small GTPases over-expressed in SLE T cells. Therefore, we examined the role of HRES-1/Rab4 in the activity of mTOR complexes 1 (mTORC1) and 2 (mTORC2) and feedback regulation of the endocytic pathway by mTOR.

Methods: Glutathione-S-transferase (GST) pull down assays were used to identify binding partners of HRES-1/Rab4, GDP-locked dominant-negative HRES-1/$Rab4^{S27N}$, GTP-locked HRES-1/$Rab4^{Q72L}$ and phosphorylation-defective HRES-1/$Rab4^{S204Q}$ in peripheral blood lymphocytes (PBL). Adeno-associated viruses (AAV) expressing HRES-1/Rab4 isoforms in pAAV-IRES-GFP were used to infect PBL. Jurkat cells expressing HRES-1/Rab4 or HRES-1/$Rab4^{S27N}$ were also utilized. Expression and phosphorylation of proteins were measured by western blotting. Regulation of the early endosome by mTOR was studied by Rab4A and Rab5A expression, which regulate endocytic recycling and receptor internalization, respectively, in mouse embryonic fibroblasts (MEFs) deficient in Rictor, mLST8 (a mTORC1 and mTORC2 component), TSC1 and TSC2 (negative regulators of mTORC1), and 4E-BP1 (a mTORC1 substrate). Student's t-test was used to evaluate gene expression changes by western blot.

Results: Using GST pull-down assay, HRES-1/Rab4 showed direct interaction with mLST8, a component shared by mTORC1 and 2. HRES-1/$Rab4^{S27N}$and HRES-1/$Rab4^{S204Q}$ were associated with Raptor (regulator of mTORC1) and Rictor (regulator of mTORC2), respectively. HRES-1/Rab4 over-expression in AAV-transduced PBL and Jurkat cells stimulated mTORC1, as indicated by phosphorylation of S6 kinase (2.0-fold increase in PBL, p=0.015, 1.5-fold increase in Jurkat cells, p=0.02) and 4E-BP1 (1.5-fold increase, p=0.0026 in PBL, 0.76-fold decrease in dominant negative HRES-1/$Rab4^{S27N}$Jurkat cells). HRES-1/Rab4 over-expression reduced Rictor (30% decrease, p=0.002) while HRES-1/$Rab4^{S27N}$ increased Ser473 phosphorylation of Akt, a downstream target of mTORC2 (4.2-fold increase, p=0.049), suggesting that HRES-1/Rab4 inhibits mTORC2 activity. Inactivation of TSC2, which negatively regulates mTORC1, increased Rab4A (1.8-fold increase, p=0.046) and Rab5A expression (2-fold increase, p=0.007). Inactivation of TSC1 increased Rab5A (3.1-fold increase, p=0.009), but had no effect on Rab4A expression. Absence of mTORC1 substrate 4E-BP1 reduced Rab5A expression (0.6-fold, p=0.002). Inactivation of Rictor increased expression of Rab4A (1.3-fold increase, p=0.01) and Rab5A (7.8-fold increase, p=0.03).

Conclusion: HRES-1/Rab4 selectively promotes mTORC1 and represses mTORC2 activity in lymphocytes. Increased mTORC1 activity enhances HRES-1/Rab4 and Rab5A expression, while mTORC2 exerts opposite effects. These results suggest that early endosome traffic regulators operate in a positive feedback cycle with mTORC1 and negative feedback cycle with mTORC2.

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Abatacept (CTLA-4Ig) Treatment Reduces Activation Induced Cell Death (AICD) and Susceptibility of T Cells to Regulatory T Cell Suppression in Patients with Rheumatoid Arthritis (RA). Michael Bonelli[1], Lisa Goeschl[1], Stefan Blueml[1], Anastasiya Hladik[1], Emmi Puujalka[1], Carl-Walter Steiner[1], Josef Smolen[2] and Clemens Scheinecker[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: Abatacept (CTLA-4Ig) inhibits the binding of CD28 to the B7 ligands CD80/CD86 on antigen presenting cells (APC) and thereby effector T cell activation. Besides APC, costimulatory molecules can also be expressed on T cells upon activation. Whether this allows CTLA-4Ig to directly affect distinct T cell subsets, exerting a positive or negative effect, remains unclear.

We therefore performed phenotypic and functional analysis of T cells in RA patients before and after the initiation of CTLA-4Ig therapy.

Methods: Peripheral blood mononuclear cells (PBMC) were collected from RA patients (n=15) before and 2 and 4 weeks after the initiation of CTLA-4Ig therapy. Proportions of naïve and memory $CD4^+$ T cells and $CD4^+CD25^+Foxp3^+$ regulatory T cells (Treg) were determined by flow cytometry (FACS). In addition T cells were analyzed for the expression of marker molecules characteristic for activated T cells and Treg. PBMCs from healthy controls (HC) were pre-incubated with different doses of CTLA-4Ig before T cell receptor (TCR) stimulation and analyzed by FACS. Moreover apoptosis was induced in CTLA-4Ig incubated cells by anti-Fas antibody and DNA fragmentation was measured by TUNEL staining. Finally $CD4^+CD25^+$ Treg were isolated from RA patients by cell sorting and analyzed for their functional capacity. In addition suppression assays were performed with Treg and responder T cells from HC after pre-incubation of individual cell populations with CTLA-4Ig.

Results: Proportions of $CD4^+$ T cells and Treg substantially increased 2 and 4 weeks after the initiation of CTLA-4Ig treatment. No differences were observed for the percentage of memory and naïve $CD4^+$ T cells. Phenotypic analyses revealed a downregulation of activation associated marker molecules and of CD95 on $CD4^+$ T cells and Treg. Likewise, pre-incubation of PBMCs from HC with CTLA-4Ig before stimulation led to a dose dependent downregulation of activation markers on $CD4^+$ cells and Treg. Moreover in vitro analyses of $CD4^+$ T cells and Treg from HC showed a dose dependent decrease in AICD after incubation with CTLA-4Ig. Functional analysis of isolated Treg from RA patients revealed a diminished suppressive capacity of Treg 4 weeks after treatment with CTLA-4Ig. However, only the pre-incuabtion of responder T cells, but not of Treg, from HC resulted in a decreased T cell suppression.

Conclusion: Within our study we were able to demonstrate for the first time a direct effect of CTLA-4Ig on T cells in RA patients, which results in increased proportions of $CD4^+$ and Treg, the downregulation of CD95 and a decrease in AICD. Blockade of costimulatory molecules on T cells by CTLA-4Ig leads to a diminished susceptibility of T cells for Treg suppression which might be counter balanced by increased Treg numbers.

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Do Immune Complexes (ICs) Binding Low Affinity FcγRIIIA/B Bearing $CD4^+$T Cells Contribute to the Autoimmune Pathology? Anil K. Chauhan[1] and Terry L. Moore[2]. [1]Saint Louis University, St. Louis, MO, [2]Saint Louis University, Saint Louis, MO

Background/Purpose: Low affinity Fc receptor, FcγRIIIA/B has not been previously reported on $CD4^+$T cells. A key role for FcγRIIIA/B receptors in B cell responses and other leukocyte functions has been well established. We asked the question whether the ICs binding to $CD4^+$ T cells in SLE patients is mediated via FcγRIIIA/B expression on autoimmune $CD4^+$T cells.

Methods: $CD4^+$T cells from normal subjects and SLE patients were analyzed for ICs binding in flow cytometric analysis. To analyze the nature of the receptors on the T cells, ICs wer binding was investigated using anti-FcγRIIIA/B monoclonal antibody in competitive inhibition assay. The $CD4^+$ T cells directly from SLE patients and the cells from normal were expanded by activating with anti-CD3 and anti-CD28. These cells were then stained using anti-FcγRIIIA/B antibodies and examined by confocal microscopy. The total RNA purified from these cells were then analyzed for the presence of Fc receptor transcripts using two sets of gene specific primer with RT-PCR. The identity of these amplified transcripts were further re-confirmed by DNA sequencing.

Results: We observed that a small population of $CD4^+$T cells in normal population (1 to 4%) demonstrated IC binding. This population expanded to 5 to 12% in the SLE patients (n=17). The $CD4^+$ T cells activated using anti-CD3 and anti-CD28 also demonstrated expansion of the FcγRIIIA/B population. A 50% inhibition of labeled aggregated human gamma-globulin to these cells was observed with anti-FcγRIIIA/B monoclonal antibody. The immunoprecipitates prepared using anti-FcγRIIIA/B showed protein bands of expected molecular size 26 – 29 kDa for low affinity type III receptors. The RT-PCR from total RNA, amplified an appropriate size gene product using two set of different primers specific to *FcγRIIIA/B* gene. The PCR product on further DNA sequence analysis confirmed the expression of the *FcγRIIIA/B* gene in $CD4^+$T cells. These results confirm the presence and the expansion of FcγRIIIA/B^+CD4^+T cells in autoimmune pathology. The ICs show binding to these peripheral $CD4^+$cells expressing FcγRIIIA/B.

Conclusion: The presence of FcγRIIIA/B on $CD4^+$T cells implies a role for ICs in T cell mediated responses observed in SLE pathology. T cell receptor (TCR) complex that mediate downstream signaling during T cell activation, require phosphorylation of ζ-chain. The ζ-chain forms heterodimer with the FcRγ chain. The FcRγ chain is the signaling unit of FcγRIIIA that can replace ζ-chain function in T cells. This implies that the T cells can be activated by signaling proteins that are part of major B cell signaling pathway. Our results point sharing of this pathway by $CD4^+$ T cells during autoimmune pathology. Further investigation of the role for FcγRIIIA/B receptors and ICs in T cell physiology during the disease pathogenesis of SLE is required.

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Leptin Modulates Apoptosis of Autoimmune T Cells in Systemic Lupus Erythematosus. Gil Amarilyo[1], Noriko Iikuni[2], Bevra H. Hahn[3] and Antonio La Cava[4]. [1]UCLA, Los Angeles, CA, [2]UCLA, CA, [3]UCLA David Geffen School of Medicine, Los Angeles, CA, [4]Univ of California Los Angeles, Los Angeles, CA

Background/Purpose: In systemic lupus erythematosus (SLE), the abnormal clearance of dead cells leads to the availability and accumulation of self-antigens that can facilitate the initiation and maintenance of T cell-driven autoimmune responses. Leptin is an adipokine that controls metabolism and pro-inflammatory immune responses, and is significantly increased in patients and mice with SLE. Purpose of this study was to study the influence of leptin on apoptosis in SLE.

Methods: Thymocytes from (NZB x NZW)F1 (BWF1) lupus-prone mice were incubated with dexamethasone (that promotes apoptosis) in the presence or not of leptin and compared with their parental strains (NZB and NZW mice) for the induction of apoptosis (measured by TUNEL assay). Additional controls included thymocytes from non autoimmune mice. The expression of the anti-apoptotic molecule bcl-2 in CD4 T cells was evaluated in parallel by flow cytometry. To study the effects of leptin on apoptosis in autoreactive CD4 T cells, ovalbumin (OVA) T-cell receptor transgenic DO11.10 mice were immunized with OVA and then divided into two groups: one receiving leptin and one serving as control (receiving vehicle). Peripheral OVA-specific autoreactive T cells sorted by tetramer staining were co-stained for BrDU, annexin V and bcl-2. Concomitantly, proliferation and apoptosis of peripheral autoreactive cells in BWF1 lupus mice immunized with two different anti-DNA Ig-derived epitopes and treated or not with leptin was investigated.

Results: Leptin inhibted T cell apoptosis in BWF1 lupus mice as compared to the parental NZB and NZW mice ($P<0.03$ for both) and to the non-autoimmune animals ($P<0.01$). This inhibition of apoptosis by leptin associated with the upregulation of the anti-apoptotic molecule bcl-2 ($P<0.009$), both in thymocytes and in peripheral T cells. Interestingly, administration of leptin facilitated the survival and proliferation of peripheral T cells autoreactive to anti-DNA Ig-derived epitopes in BWF1 lupus mice, as shown in flow cytometry and proliferation assays. Similarly, in OVA-transgenic DO11.10 mice, leptin treatment was associated with inhibition of apoptosis and the induction of bcl-2 in peripheral OVA-specific CD4 T cells, and also with an increased proliferation of the autoreactive T cells.

Conclusion: Leptin facilitates the survival and proliferation of autoreactive T-cells through a leptin-dependent upregulation of bcl-2. This newly described role of leptin in the facilitation of autoreactive T cell activity in SLE may have implications for new targeted therapeutic approaches in the disease.

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Identification of a $CD62L^{hi}CD44^{low}$ T_{FH} Precursor Capable of Developing into An $IL21^{hi}$ $IL17^{hi}$ Mature T_{FH} in Autoimmune BXD2 Mice. Yanna Ding[1], Hui-Chen Hsu[1] and John D. Mountz[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham and Birmingham VAMC, Birmingham, AL

Background/Purpose: Follicular T helper (T_{FH}) cells have been found in some SLE patients and correlated with autoantibodies production and disease severity. We recently identified that autoimmune BXD2 mice demonstrated higher T_H-17 and GCs response and displayed 2.5-fold increased frequency of $CXCR5^+ICOS^+$ T_{FH} in the spleen compare to B6. T_{FH} is now considered as the key effector T cells for antibody formation. However, rational therapy to target T_{FH} by blocking its development is impeded by lack of identification of the phenotype of the T_{FH} precursor CD4 T cells. The aim of this study is to determine the T_{FH} precursor in BXD2 mice.

Methods: Single cell suspensions or isolated CD4 T cells prepared from mouse spleens were subjected to FACS staining with or without culture with IL-21/IL-17. CD4 T cells were used for RNA extraction and Real-time PCR analysis for mRNA levels of T_{FH}-related genes. Frozen spleen sections were subjected for confocal imaging analysis of CD62L, CD44, IL-21, IL-17 and CXCR5 in CD4 T cells.

Results: Compared to CD4 T cells from B6 mice, CD4 T cells in BXD2 mice displayed an expansion of the $CD62^{hi}CD44^{hi}$ effector and $CD62L^{-}CD44^{hi}$ memory phenotype with a concomitant reduction in $CD62L^{hi}CD44^{-}$ and $CD62L^{hi}CD44^{lo}$ naïve CD4 T cells. Interestingly, highest levels of IL-21 was observed in $CD62L^{hi}CD44^{lo}CD4$ T cells whereas highest levels of BCL6, IL-17, CXCR5, were observed in the $CD62^{int}CD44^{hi}$ effector CD4 T cells from BXD2 mice, suggesting that upregulation of IL-21 occurs prior to upregulation of IL-17. Consistent with this, compared to WT BXD2 mice, there was decreased frequency of $IL\text{-}17^{+}$ T_{FH} in BXD2-*Il21*$^{-/-}$ mice. In contrast, increased frequency of $IL\text{-}21^{+}$ T_{FH} was observed in BXD2-*Il17r*$^{-/-}$ mice.

In vitro IL-21 stimulation shifted $CD62L^{hi}CD44^{-}$ naïve CD4 into the $CD62L^{hi}CD44^{lo}$ phenotype and promoted BCL6 and IL17R expression in $CD62L^{hi}CD44^{lo}$ CD4 T cells of BXD2 and BXD2-*Il21*$^{-/-}$ mice. IL21 plus IL17 induced the highest levels of BCL6 in $ICOS^{+}CXCR5^{+}T_{FH}$. Real-time PCR confirmed that IL21 treatment increase mRNA levels of *Bcl6*, *Il21*, *Il17r* and *Il17*.

Confocal imaging analysis showed that $CD62L^{hi}CD44^{lo}$ CD4 located between naïve CD4 T area and GC while $CD62^{hi}CD44^{hi}$ subset located in LZ of a GC where $IL\text{-}17^{+}IL\text{-}21^{+}$ T_{FH} can also be visualized.

Conclusion: Our study suggests that the $CD62L^{hi}CD44^{lo}$ CD4 subset that produces IL-21 is a T_{FH} precursor, and that the $CD62^{hi}CD44^{hi}$ subset that produces CXCR5, IL-17, and IL-21 is the mature T_{FH}. Because the development of spontaneous GC was dramatically diminished in both BXD2-*Il21*$^{-/-}$ and BXD2-*Il17r*$^{-/-}$ mice despite the increased frequency of T_{FH} in BXD2-*Il17r*$^{-/-}$ mice, our results suggest that the formation of spontaneous GC in BXD2 mice requires both IL-17 and IL-21. IL-21 stimulates BCL6, IL-21 and IL-17. IL-17 provides an additional signal to stimulate BCL6 in T_{FH}.

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Effects of Altering Fli1 Levels in Lupus T Cells on Disease Expression and T Cell Function in the MRL/Lpr Mouse Model. Fahmin Basher[1], Marlene Bunni[1], Zainab Amani[1], Xian Zhang[2] and Tamara K. Nowling[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina & Ralph H Johnson VA Medical Center, Charleston, SC

Background/Purpose: The Ets factor Fli1 is implicated as a key modulator of lupus disease expression. Over-expressing Fli1 in healthy mice, results in the development of an autoimmune kidney disease similar to that observed in lupus. Lowering the global levels of Fli1 in two lupus mouse models significantly improved disease and prolonged survival. Lowering the levels of Fli1 in hematopoietic cells in MRL/lpr lupus mice resulted in significantly improved kidney disease. The cell type mediating this protective effect is unknown. We have analyzed the effects of reducing Fli1 levels in lupus T cells on disease expression using an adoptive transfer model and on T cell function in kidney infiltration, proliferation and apoptosis assays.

Methods: T cells were isolated from spleens of MRL/lpr Fli1+/+ and Fli1+/− mice. Fli1+/+ T cells were transferred into MRL/lpr Fli1+/− mice and Fli1+/− T cells were transferred into Fli1+/+ mice. As a control, Fli1+/+ T cells and Fli1+/− T cells were also transferred into Fli1+/+ and Fli1+/− mice, respectively. All donors and recipients were 7 weeks old. Urine and blood were collected at 2, 4, 8 and 12 weeks after transfer. ELISAs were performed to measure proteinuria and serum anti-GBM, anti-dsDNA and Ig levels. Proliferation was measured by CFSE staining and apoptosis by AnnexinV staining following stimulation with PMA and ionomycin. T cell subsets infiltrating the kidney were analyzed by flow cytometry.

Results: Transferring Fli1+/+ T cells into Fli1+/− mice does not significantly increase the urine albumin levels of the Fli1+/− mice but transfer of Fli1+/− T cells into Fli1+/+ mice decreases the levels of urine albumin compared to controls. Similarly, Fli1+/+ mice that received Fli1+/− T cells had significantly decreased serum IgG levels ($p=0.026$) but Fli1+/− mice that received Fli1+/+ T cells did not have a significant increase in IgG levels compared to controls. Additionally, MRL/lpr Fli1+/− mice have significantly fewer numbers of total T cells infiltrating the kidney compared to MRL/lpr Fli1+/+ mice at 14 weeks of age ($p=0.017$). Specifically, MRL/lpr Fli1+/− had both decreased percentages and numbers of CD4+ T cells ($p<0.004$) and activated/memory CD3+ T cells ($p<0.02$). However, no significant differences were observed in proliferation or apoptosis between MRL/lpr Fli1+/+ and Fli1+/− T cells.

Conclusion: These results suggest that reducing Fli1 levels in T cells may have specific effects on autoantibody production. Because transferring Fli1+/− T cells into Fli1+/+ mice resulted in reduced urine albumin and serum IgG levels and transferring of Fli1+/+ into Fli1+/− mice did not significantly increase urine albumin and serum IgG levels, it suggests that T cells with reduced Fli1 levels may be playing a regulatory role to suppress Fli1+/+ pathogenic T cells. In addition, the results of the kidney infiltration analyses suggest Fli1 also may play a role in T cell migration, proliferation, apoptosis and/or differentiation. However, our results indicate Fli1 does not significantly affect proliferation or apoptosis of lupus T cells following mitogenic stimulation. The role of Fli1 on T cell differentiation and regulatory function are currently being explored.

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DNA Methylation Regulates Gene Expression in CD4+CD28- T Cells Through Micrornas. Dipak R. Patel, Anura Hewagama, Gabriela Gorelik, Sushma Yarlagadda, Faith Strickland and Bruce C. Richardson. University of Michigan, Ann Arbor, MI

Background/Purpose: CD4+CD28- T cells are enriched in chronic inflammatory diseases like rheumatoid arthritis and lupus. They are cytotoxic and resistant to apoptosis. Disease severity and atherosclerosis correlate with increasing numbers of these cells.

Compared to CD28+ cells, CD28- CD4 T cells over-express killer immunoglobulin-like receptors (KIRs) and other molecules that may contribute to their pro-inflammatory phenotype. These genes are regulated by DNA methylation- CD4 T cells demethylated in vitro over-express KIRs and other immunostimulatory molecules. This is a result of decreased signaling through the ERK and JNK pathways, which consequently decreases activity of enzymes (DNMTs) responsible for DNA methylation. Changes in DNA methylation also affect microRNA (miRNA) expression, and the role of miRNAs in CD28- T cells is unknown. We studied differences in mi- and mRNAs in CD4+CD28+ and CD4+CD28- T cells. Protein phosphatase 5 (PP5), expressed in CD4+CD28- but not CD4+CD28+ T cells, inhibits both ERK and JNK signaling, so we also hypothesized that overexpressing PP5 in CD4 T cells will induce expression of methylation sensitive genes unique to CD28- T cells.

Methods: PBMCs from healthy donors were stimulated with phytohemagglutinin (PHA). CD4 T cells were then isolated by negative selection and cultured 3 days with IL-2. CD4+CD28+ and CD28- cells were separated by flow cytometry. Over 900 miRNAs were profiled with PCR arrays, and mRNAs analyzed with Affymetrix arrays. Micro- and mRNAs of interest were compared in CD4+CD28+ and CD4+CD28- T cells isolated from lupus patients. CD4 T cells stimulated with PHA from healthy donors were transfected with vectors encoding either GFP or GFP and PP5 (Amaxa). GFP+ cells were analyzed by flow cytometry 3 days after transfection.

Results: Twelve miRNAs were over- or underexpressed > 1.5-fold in CD4+CD28- T cells relative to CD4+CD28+ cells. MicroRNAs 362 and 500* were over-expressed in CD28- T cells generated in vitro and CD28- T cells isolated from SLE patients. These miRNAs were also overexpressed in CD4 T cells demethylated in vitro. CD20 and KIR mRNAs were over-expressed in CD28- T cells from both systems, and these mRNAs are predicted to be regulated by miRNAs that were underexpressed in CD28- T cells. CD20 mRNA was increased in patients with SLEDAI<4, compared to patients with more active disease. Surface expression of KIR protein was increased 4 fold ($p=0.045$) in CD4+ T cells transiently transfected with PP5, compared to cells transfected with a control vector.

Conclusion: MicroRNAs 362 and 500* are increased in CD4+CD28- T cells as well as CD4 T cells demethylated in vitro, indicating they are regulated by DNA methylation. These miRNAs are predicted to interact with proteins regulating DNA methylation (MBD1, DNMT3a) and apoptosis (Fas), and these interactions are being confirmed. CD20 and KIR mRNAs were also increased in CD4+CD28- T cells, and this could contribute to their phenotype. CD20+ CD4 T cells are present in RA, and they are eliminated by rituximab. Overexpressing PP5 increases KIR, supporting the hypothesis that PP5 blocks inhibitory signaling pathways upstream of KIR. PP5's effects on these pathways and other methylation sensitive genes are currently being studied.

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CTLA-4 and TNF-á Promoter –308 A/G Polymorphisms and ANCA-Associated Vasculitis Susceptibility: A Meta-Analysis. Young Ho Lee, Sung Jae Choi, Jong Dae Ji and Gwan Gyu Song. Korea University Medical Center, Seoul, South Korea

Background/Purpose: The aim of this study was to explore whether the cytotoxic T lymphocyte associated antigen-4 (CTLA-4) or tumor necrosis factor-α (TNF-α) polymorphisms contribute to anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) susceptibility.

Methods: The authors conducted a meta-analysis on associations between polymorphisms of the 3′ untranslated region (UTR) microsatellite at exon 3, exon 4 CT60 (A/G), exon 1 +49 (A/G), and promoter −318 (C/T) of CTLA-4, and TNF-α promoter −308 (A/G) and AAV susceptibility as determined using; 1) allelic contrast and 2) homozygote contrast, 3) recessive, and 4) dominant models.

Results: A total of 11 comparisons were considered in this meta-analysis. These studies encompassed 7 CTLA-4 studies and 4 TNF-α studies in 10 European populations and 1 Asian population. The $(AT)_n$ repeat polymorphisms of CTLA-4 were found to be significantly associated with AAV in European populations (OR of 86 vs. xx allele = 0.402, 95% CI = 0.184–0.875, p = 0.022). The one study conducted on this polymorphism in Asians showed no significant association with AAV. Meta-analysis of the 86/86 (recessive effect), 86/86 and 86/xx (dominant effect), and 86/86 vs. xx/xx (homozygote contrast) of the $(AT)_n$ repeat revealed a significant association with AAV in Europeans. Both the *CTLA-4 CT60* and *+49* polymorphisms were found to be significantly associated with AAV in European populations, and allele and genotype-based analyses showed a significant association between the *CTLA-4 CT60* and *+49* polymorphisms with AAV in Europeans (OR of the A allele of CT60 = 0.769, 95% CI = 0.619–0.017, p = 0.035; OR of the T allele of +49 = 1.382, 95% CI = 1.147–1.664, p = 0.001, respectively). Meta-analysis of the *CTLA-4* -318 polymorphism failed to identify any association with AAV. Furthermore, meta-analysis of the AA genotype, the AA and AG genotypes, and the A allele of TNF-α failed to reveal any association with Wegener's granulomatosis (WG).

Conclusion: This meta-analysis demonstrates that the CTLA-4 polymorphisms confer susceptibility to AAV in Europeans. In contrast, no association was found between the TNF-α -308 polymorphism and susceptibility to WG in Europeans.

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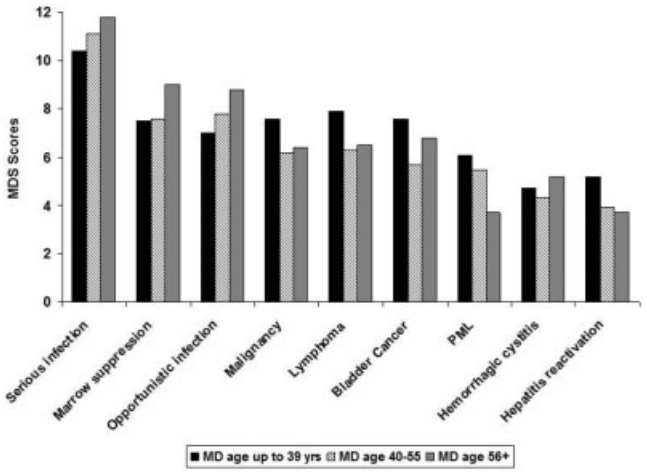
How Do Rheumatologists Choose Between Cyclophosphamide and Rituximab? Raluca Cozmuta[1], Peter A. Merkel[2] and Liana Fraenkel[3]. [1]St. Vincent Medical Center, Bridgeport, CT, [2]Boston University School of Medicine, Boston, MA, [3]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT

Background/Purpose: Recent randomized controlled trials have found that rituximab is as effective as cyclophosphamide at inducing remission in patients with ANCA-associated vasculitis (AAV). As a result, the treatment decisions depend substantially on how rheumatologists perceive differences in the risk profiles associated with both options. The objective of this study was to quantify the influence of specific adverse events (AEs) on rheumatologists' treatment decisions for patients with newly diagnosed AAV.

Methods: We administered a MaxDiff Scaling (MDS) survey to rheumatologists attending the 2010 American College of Rheumatology National Meeting. The survey included 23 AEs associated with either rituximab and/or cyclophosphamide. Participants were given the following instructions: *On the following pages you will be asked to consider (given your knowledge about the severity and probability of each of the adverse events) how much each adverse event influences your decision about which medication to prescribe for a 50 year old post-menopausal woman with newly diagnosed severe ANCA-associated vasculitis. Assume the patient is hospitalized with pulmonary and renal involvement.* The survey asked respondents to choose the most important item from a series of sets (determined by the MDS software) containing different combinations of 4 items from the master list of 23 AEs. We used Hierarchical Bayes modeling to generate the mean relative importance score for each adverse event. We subsequently examined the association between physician characteristics and ratings using multivariate linear regression models.

Results: 118 physicians completed the survey; mean age (SD) = 48 years (10); 68% male; 81% spend the majority of time in clinical practice; 39% work in an academic setting; 46% see between 1 and 5 patients with AAV per year; 22% see between 6 and 10 patients with AAV per year, and 25% see more than 10 patients with AAV per year. Although there was significant viability in rankings, physicians' treatment decisions were most strongly influenced by the risk of infection (see Figure). Older physicians were more strongly influenced by the risks of infection (standardized estimate= 0.29, p=0.004) and less strongly influenced by the risk of cancer (standardized estimate= − 0.25, p=0.02) compared to younger rheumatologists (after adjusting for gender, work setting, and number of patients with AAV seen per year).



Conclusion: Despite the lack of difference in the risks of serious infections in head-to-head clinical trials, risk of serious infection is the most important risk considered by rheumatologists in deciding which treatment to prescribe for AAV. Future studies generating precise risk estimates for both rituximab and cyclophosphamide-based remission-induction regimens will help inform and improve medical decision making for patients with AAV and prescribing physicians.

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Treatment for ANCA-Associated Vasculitis: What Are the Experts Prescribing? Raluca Cozmuta[1], Peter A. Merkel[2] and Liana Fraenkel[3]. [1]St. Vincent Medical Center, Bridgeport, CT, [2]Boston University School of Medicine, Boston, MA, [3]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT

Background/Purpose: Data from randomized controlled trials suggest that cyclophosphamide (CTX) and rituximab (RTX) are equally effective at inducing remission in severe ANCA-associated vasculitis (AAV), and although the types of risks differ, the burden of adverse events appears to be comparable in the short-term. Therefore, until long-term studies are available, decision making depends primarily on expert opinion and/or extrapolation from use of these agents in other conditions. The objective of this study was to examine treatment choices among AAV experts.

Methods: We invited experts (defined as physicians whose practices focus on vasculitis and physicians engaged in research in vasculitis) to complete a web-based survey. Treatment choices were elicited for 3 scenarios [1) newly-diagnosed severe AAV in a treatment-naïve patient without co-morbidities, 2) recurrent severe AAV in a patient without co-morbidities previously treated with oral CTX, 3) recurrent severe AAV in a patient without co-morbidities previously treated with IV CTX] for 4 patient profiles [22 year-old woman, 62 year-old women, 22 year-old man, 62 year-old man]. Differences between groups were examined using multinomial generalized estimating equation analysis.

Results: The survey was successfully delivered to 145 experts; opened by 94 and completed by 50. 77% were male, 49% were rheumatologists, and 39% were nephrologists. 90% were attending physicians and 4% were trainees. 67% reported spending the majority of their time in clinical practice, 31% in clinical research and 2% in basic research. 71% worked in a university hospital setting. 24% were from the US and 61% were from Europe. Preferences for treatment of newly-diagnosed young women (52% with RTX) differed significantly (p<0.001) from those for older men (76% with CTX) and older women (74% with CTX) (see Table). Efficacy, toxicity and cost were all important reasons underling experts' choices for patients with newly diagnosed AAV. Uncertainty

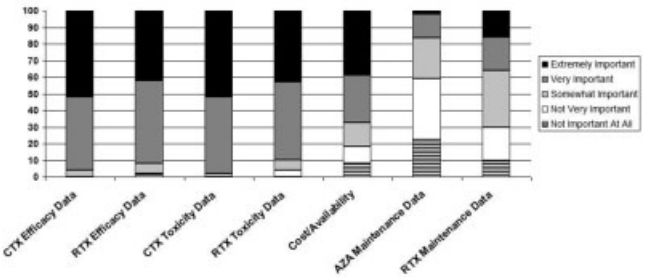
regarding the efficacy of azathioprine and RTX to maintain remission had much less influence (see Figure). 60% or more of respondents preferred RTX for recurrent disease regardless of patients' age or sex.

Table. Treatment Preferences for AAV

	Newly Diagnosed AAV: Treatment Naïve*				Recurrent AAV: Received PO CTX - on AZA			Recurrent AAV: Received IV CTX - on AZA		
	PO CTX	IV CTX	RTX	No Preference	CTX	RTX	No Preference	CTX	RTX	No Preference
Young Woman	2%	30%	56%	12%	2%	92%	6%	5.9%	88.2%	5.9%
Older Woman	10%	64%	10%	16%	17.6%	70.6%	11.8%	19.6%	60.8%	19.6%
Young Man	2%	48%	36%	14%	4%	84%	12%	10%	78%	12%
Older Man	12%	64%	10%	14%	16%	72%	12%	18.4%	61.2%	20.4%

* Treatment preferences for a young woman differ significantly from those of an older woman and older man.

Figure. Importance of Reasons Underlying Treatment Preference



Conclusion: Most vasculitis experts prefer to prescribe RTX for young women with newly-diagnosed AAV and for all patients with recurrent disease who have been previously treated with either oral or IV CTX. In contrast, IV CTX is the preferred treatment among most experts for older patients with new-onset disease. There appears to be less agreement regarding the preferred treatment for newly-diagnosed young men.

2368

Are Patients with ANCA-Associated Vasculitis Entered In Clinical Trials Representative of Patients Followed In Observational Cohorts? Christian Pagnoux[1], Simon Carette[2], Nader A. Khalidi[3], David Cuthberston[4], Paul R. Fortin[5], Gary S. Hoffman[6], Carol A. Langford[7], Paul A. Monach[8], Luc Mouthon[9], Philip Seo[10], Ulrich Specks[11], Steven R. Ytterberg[11], Peter A. Merkel[12], Loic Guillevin[13], French Vasculitis Study Group (FVSG)[14] and The Vcrc[8]. [1]University Health Network, Toronto, Canada, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON, [3]McMaster University, Hamilton, ON, [4]University of South Florida, Tampa, FL, [5]Toronto Western Hospital and University of Toronto, Toronto, ON, [6]Cleveland Clinic Found A50, Cleveland, OH, [7]Cleveland Clinic, Cleveland, OH, [8]Boston University, Boston, MA, [9]Hopital Cochim, Paris, France, [10]Johns Hopkins Vasculitis Center, Baltimore, MD, [11]Mayo Clinic, Rochester, MN, [12]Boston University School of Medicine, Boston, MA, [13]Cochin University Hospital, Paris, France, [14]Paris, France

Background/Purpose: It is not clear whether patients with granulomatosis with polyangiitis (Wegener's; GPA) or microscopic polyangiitis (MPA) entered into therapeutic clinical trials are representative of those followed in observational cohorts.

Methods: We compared the clinical characteristics at diagnosis and subsequent death and/or relapse of patients with systemic/severe GPA or MPA with five-factor score (FFS) ≥1 enrolled in the WEG91 or WEGENT trials to those followed in the FVSG or VCRC observational cohorts (with the same GPA form or MPA severity at diagnosis, and never included in any other therapeutic trial). All patients fulfilled ACR and/or Chapel Hill classification criteria.

Results: Data from 423 patients enrolled in the observational cohorts (167 in the FVSG, 256 in the VCRC) and 220 patients enrolled in the trials (159 WEGENT, 61 WEG91) were available for analysis (Table). Compared to patients in the cohorts, patients in the trials were older, had more frequent and severe renal involvement, and more frequent lung and cardiovascular manifestations at diagnosis. Patients in the trials had a higher mortality, mainly during the first 2 years post-diagnosis, but a lower relapse rate (with a slightly shorter follow-up). We separately analyzed patients with GPA and found similar differences for characteristics at diagnosis, with higher mortality (24% vs 3%; $p<0.001$) and lower relapse rate (50.8% vs 61.5%; $p=0.02$) in the patients in the trials. However, relapse-free survival rates at 5 years post-diagnosis were eventually comparable (38.4% (95% CI, 29.0–47.6) in the FVSG cohort vs. 39.5% (95% CI, 32.5–46.4) in the patients in the trials).

Characteristics	Patients in Observational Cohorts n=423	Patients in Clinical Trials n=220	P value
Diagnosis—n (% of patients with available data)			
Microscopic polyangiitis (MPA)	26 (6.1)	41 (18.6)	***<0.001***
Granulomatosis with polyangiitis (Wegener's; GPA)	397 (93.9)	179 (81.4)	
Age at diagnosis (years ± SD)	46.5 ± 17.3	56.6 ± 13.9	***<0.001***
Sex ratio M/F (n)	218/205	110/110	0.67
Constitutional symptoms (n, (%))	375 (88.9)	194 (91.1)	0.40
Cutaneous manifestations	118 (28.0)	72 (33.8)	0.19
Eye involvement	94 (22.3)	61 (28.6)	0.08
ENT involvement	311 (73.9)	162 (75.0)	0.48
Lung involvement	275 (65.6)	169 (78.2)	***<0.001***
Alveolar hemorrhage	89 (21.5)	59 (27.6)	0.09
Cardiovascular involvement	25 (6.0)	37 (17.5)	***<0.001***
Cardiomyopathy	3 (0.7)	8 (3.8)	0.10
GI manifestations	28 (6.7)	26 (12.3)	***0.02***
Renal involvement	231 (53.7)	174 (80.9)	***<0.001***
Mean creatinine (μmol/l ± SD)	131.4 ± 142	196.0 ± 218	***<0.001***
Mean MDRD-GFR (ml/min/1.73 m^2)	74.4 ± 34.1	56.4 ± 34.3	***<0.001***
Mononeuritis multiplex	81 (19.1)	43 (20.2)	0.94
CNS involvement	14 (3.4)	14 (6.6)	0.11
ANCA status			
Anti-PR3 positive	248 (65.6)	110 (50.0)	0.09
Anti-MPO positive	58 (15.3)	51 (23.2)	***0.01***
Both anti-PR3 and anti-MPO	4 (1.0)	2 (0.9)	0.99
FFS (for patients with MPA only)			
1	24 (92.3)	17 (41.5)	0.23
≥2	2 (7.7)	24 (58.5)	
BVAS	16.7 ± 7.5	22.4 ± 7.5	***<0.001***
Mean follow-up since diagnosis (months ± SD)	72.5 ± 61.7	61.6 ± 44.3	***0.02***
Death	14 (3.3)	49 (22.3)	***<0.001***
Relapse	256 (60.5)	101 (45.9)	***0.01***

Conclusion: Patients enrolled in clinical trials of AAV may differ from those followed in observational cohorts in terms of disease manifestations at diagnosis and mortality and flare rates. These findings may have important implications for interpretation of study results and design of clinical trials.

2369

Optimal Definition for the Duration of Sustained Remission in ANCA-Associated Vasculitis. Gunnar Tomasson[1], Michael Walsh[2], Thomas F. Hiemstra[3], Maarten Boers[4], Peter A. Merkel[1] and EUVAS Investigators[5]. [1]Boston University School of Medicine, Boston, MA, [2]McMaster University, Hamilton, [3]Addenbrookexs Hospital University of Cambridge, Cambridge, United Kingdom, [4]VU University Medical Center, Amsterdam, Netherlands, [5]Cambridge, United Kingdom

Background/Purpose: Outcome measures and end-points in randomized clinical trials (RCTs) in ANCA-associated vasculitis (AAV) were developed by consensus panels of expert investigators. Most RCTs in AAV have been equivalency trials or negative with respect to declaring one treatment strategy significantly superior to the reference strategy. Therefore, outcome measures and end-points currently used remain to be validated with respect to their discriminatory capability between active treatment and placebo. In the IMPROVE trial, azathioprine (AZA) was found superior to mycophenolate mofetil (MMF) for remission maintenance in AAV. Therefore, data from IMPROVE provides an opportunity to explore which elements of currently-used outcome measures and trial end-points are able to discriminate active (effective) treatment from placebo (ineffective or less effective) treatment. *Sustained remission* has been used as end-point for RCTs in AAV and has been arbitrarily defined as a consecutive period of 6 months without evidence of active disease. The objective of this study was to arrive at a definition for *duration* of sustained remission in AAV that best discriminates between more effective treatments vs. less effective treatment in RCTs.

Methods: Subjects were participants in the IMPROVE clinical trial. Remission was defined as score of zero on the Birmingham Vasculitis Activity Score (BVAS). To determine the optimal duration of remission, 36 candidate periods (1 to 36 months long) were tested to arrive at the highest risk ratio (RR) of those subjects who achieved sustained remission between those randomized to AZA vs. MMF.

Results: In the IMPROVE trial, 156 subjects achieved remission and were randomized to AZA (n=76) or MMF (n=80). Median duration of follow-up after remission was achieved was 45.3 months (IQR: 39.1–47.1) and 88% of subjects were followed for at least 24 months. During follow-up, 72 subjects had disease relapse, 30 in the AZA-group and 42 in the MMF-group. The definition of

sustained remission of 6 months resulted in the highest RR (1.6) for achieving sustained remission between the AZA and MMF study groups, and any definition of sustained remission between 4 and 13 months discriminated much better between the two treatment regimens than sustained remission defined outside of this interval (Figure). Remission duration of 3 months or less did not discriminate between AZAand MMF.

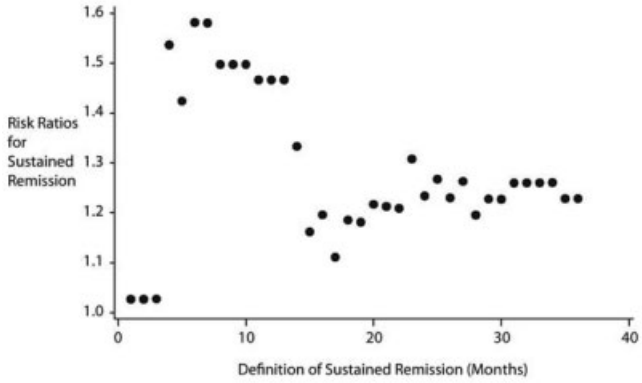


Figure. Risk ratios of achieving sustained remission among subjects randomized to azathioprine vs. mycophenolate mofetil at different definitions for sustained remission in months.

Conclusion: These results suggest that defining sustained remission as a consecutive period of 4 and 13 months is optimal to discriminate between effective treatment and less (non-) effective treatments in AAV. These findings have implications for the design of future trials in AAV.

2370

Neural Correlates of Chronic Fatigue in Granulomatosis with Polyangiitis (GPA; Wegener's)—A Functional Magnetic Resonance Imaging (fMRI) Study. Neil Basu[1], Gareth T. Jones[1], Raashid A. Luqmani[2], Alison D. Murray[1], David M. Reid[1], Gary J. Macfarlane[1] and Gordon D. Waiter[1]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]University of Oxford, Oxford, United Kingdom

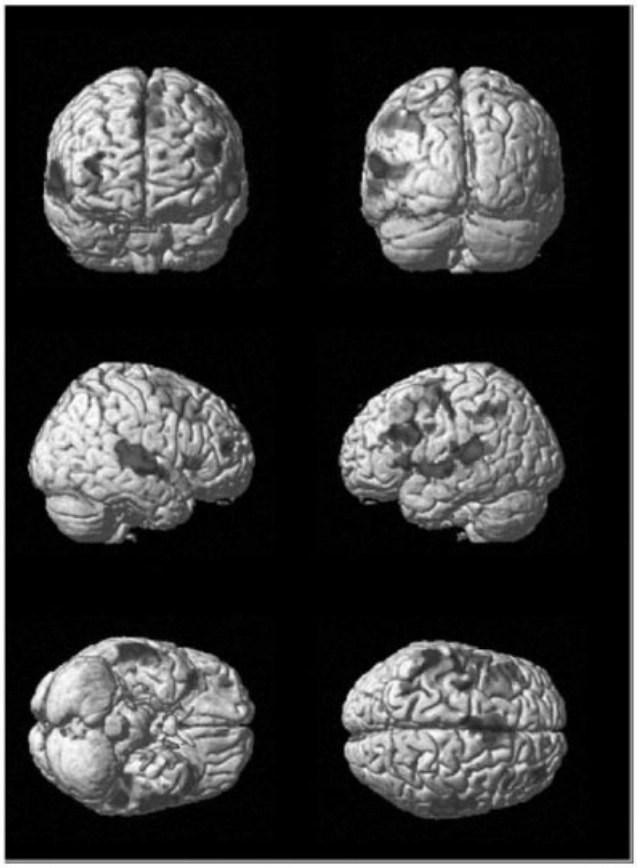
Background/Purpose: Chronic fatigue is a common disabling problem in patients with GPA, even for those in clinical remission. As with other populations, the mechanisms underlying fatigue are poorly understood. Current generic hypothetical models implicate frontostriatal structures of the brain. In order to better understand the mechanisms specific to GPA, we used fMRI to examine the neural correlates of fatigue in patients with clinically inactive disease.

Methods: GPA patients were recruited based on fatigue status; those reporting problems with fatigue for >3 months and scoring >3 on the Chalder Fatigue Scale (CFS) were defined as cases with fatigue (GPA-F), those without fatigue (<3 on the CFS) were defined as cases without fatigue (GPA-NF). All cases were in clinical remission, with a Birmingham Vasculitis Activity Score=0 for >3months. A control group with idiopathic chronic fatigue (CF) was also studied. Controls fulfilled the same fatigue criteria as GPA-F cases and, following medical assessment had no clear clinical explanation for their fatigue.

All subjects completed Hospital Anxiety and Depression Scales (HADS-A, HADS-D). During fMRI, they performed a modified paced auditory serial attention test, a cognitive task validated to induce fatigue.

Functional data was acquired with a 3 Tesla MRI scanner and analysis of the blood oxygen level dependant (BOLD) signal was performed using SPM8. A cluster threshold of $p<.05$, correcting for multiple comparisons was used.

Results: GPA-F (n=12), GPA-NF (n=14) and CF (n=13) groups were not significantly different in terms of age (mean: 58.5, 51.6, 52.2 respectively) and sex (males: 6, 6, 7). As expected, the CFS scores were higher in the fatigued groups (mean 8.5, 1.4, 7.7), but also HADS-A (5.5, 2.6, 4.3) and HADS-D (4.9, 0.9, 3.5). After adjusting for HADS-A and HADS-D, comparison of GPA-F with GPA-NF revealed statistically significantly greater BOLD activation in the left (L) paracentral lobule, L medial frontal gyrus, right (R) thalamus and R lentiform nucleus of the GPA-F group. GPA-F and CF shared many overlapping areas of activation, however, in addition the CF group showed significantly greater activation elsewhere, principally the L precentral gyrus, R superior frontal gyrus and R cingulate gyrus (Figure 1).



Conclusion: 1) Chronically fatigued patients with quiescent GPA activate the basal ganglia, thalamus and frontal lobes of the brain significantly more than a matched population of GPA patients without chronic fatigue. This supports current hypothetical neural models of fatigue processing.

2) FMRI activation patterns of fatigued GPA subjects overlap with those with similarly fatigued controls, however control subjects appear to recruit additional neural regions. This implies an element of condition specificity in neural fatigue processing, which may reflect a difference in the fatigue dimensions experienced by the 2 populations and/or differing aetiological mechanisms.

2371

Mental Health As a Predictor of Disease Flare in Granulomatosis with Polyangiitis (Wegener's Granulomatosis). Morgana L. Davids[1], Huong Do[1], Gunnar Tomasson[2], John C. Davis[3], Gary S. Hoffman[4], W. Joseph McCune[5], Ulrich Specks[6], E. William St Clair[7], John H. Stone[8], Peter A. Merkel[9] and Robert F. Spiera[1]. [1]Hospital for Special Surgery, New York, NY, [2]Boston University School of Medicine, Boston, MA, [3]Genentech Inc, South San Francisco, CA, [4]Cleveland Clinic, Cleveland, OH, [5]University of Michigan, Ann Arbor, MI, [6]Mayo Clinic, Rochester, MN, [7]Duke University Medical Center, Durham, NC, [8]Massachusetts General Hospital, Boston, MA, [9]Boston University, Boston, MA

Background/Purpose: Emotional stress has been anecdotally suspected to contribute to the development of autoimmune disease and trigger disease flares. While several recent reviews suggest that psychological stress plays a role in the pathogenesis of autoimmune disease, no studies have looked at mental health as a risk factor for the onset of flares in patients with granulomatosis with polyangiitis (GPA, Wegener's granulomatosis). The aim of the present study was to investigate the relationship between mental health and disease exacerbations in patients with GPA. The primary hypothesis was that worse mental health was associated with greater likelihood of flare at subsequent visits.

Methods: This was a retrospective analysis of participants in the Wegener's Granulomatosis Etanercept Trial (WGET) who achieved sustained remission (defined as 6 months of continuous remission) during the trial.

Self-reported health was assessed with the Short Form 36 Health Survey (SF-36) at each visit during the trial. The SF-36 includes physical and mental component summary scores (PCS and MCS) which are measured on a scale of 0 to 100, with 100 being the healthiest. Flare status was assessed with the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG). Subjects were considered in remission when their BVAS score was equal to 0. Baseline MCS and PCS were compared for different patient disease stratifications using two-sample t-tests. Data from all visits subsequent to a period of sustained remission were analyzed to assess the relationship between current visit flare status and SF-36 MCS and PCS scores from the preceding visit.

Results: Data from 143 subjects who achieved sustained remission during the WGET were included in the analysis. Baseline MCS and PCS were not significantly different when stratifying patients by disease severity (severe vs. non-severe) or new-onset disease vs. relapsing disease. Baseline MCS and PCS were also similar among patients who remained in remission throughout the trial vs. patients who relapsed. In a multivariable model adjusting for time since enrollment and disease severity, a five-point lower MCS at the preceding visit was associated with a 19% increased likelihood of having a flare at the current visit (OR: 1.19, 95%CI: 1.06–1.33, $p < 0.01$), whereas a five-point lower PCS at a sustained remission visit was only associated with an 8% increased risk of having a flare at the following visit, and this was not significant (OR: 1.08, 95%CI: 0.96–1.21, $p = 0.19$). Analyses using MCS and PCS from two visits prior to the current visit showed no association with current flare status.

Conclusion: Among patients with GPA, a lower MCS at a time of sustained remission predicts an increased likelihood of a disease flare in the immediate future, independent of PCS, whereas a lower PCS at a time of sustained remission is not associated with a flare in the immediate future. This suggests that mental health may be an important independent factor affecting the likelihood of future disease flares in patients with GPA. This association merits further investigation.

2372

Patient-Driven On-Line Survey on Granulomatosis with Polyangiitis. Adam Hall[1], Marta Rode[2], Christian Pagnoux[3] and Elaine Yacyshyn[1]. [1]University of Alberta, Edmonton, AB, [2]None, Jasper, AB, [3]University of Toronto, Toronto, ON

Background/Purpose: Granulomatosis with polyangiitis (Wegener's; GPA) is a rare small-sized vessel vasculitis with a prevalence estimated at 24 to 157 cases/million. These low numbers make it difficult to recruit large numbers of patients for cross-sectional studies. In recent years, along with several patient registry initiatives, internet-based forums and weblogs (blogs) have emerged as a means for patients with rare diseases to connect and share experiences. Recently, one of our patients with GPA posted a link on her blog, requesting GPA patients worldwide to complete a SurveyMonkey® questionnaire on their disease.

Methods: The survey was entirely devised by our GPA patient (M.R.), who put it on-line in November 2010 on her blog (http://weggiesunite.blogspot.com/p/survey-inquiring-weggies-wanna-know.html). The survey targeted patients with GPA, as a self-reported diagnosis, and included 10 questions to anonymously assess country of residence, gender, age at diagnosis, selected comorbidities, presenting symptoms, specialty of the physician who eventually provided the diagnosis, diagnostic delay and initial treatments.

Results: Late June 2011 (after 7.5 months), 369 respondents had completed the survey. Six of them were excluded because of reported associated lupus, inflammatory bowel disease or rheumatoid arthritis. After reviewing the remaining forms for clinical manifestations at diagnosis and initial medications, 345 respondents with consistent evidence for GPA and who filled in >80% of the questionnaire were retained for this analysis. Among them, 61.9% were women and 62.3% were aged between 30 and 60 years at diagnosis. Of the 316 who answered the question where they were living at diagnosis, most of the patients were from North America (74.7%), 16.8% from Europe, and 8.5% from elsewhere (primarily India, New Zealand and Australia).

The main self-reported signs at diagnosis were fatigue (67.8%), sinus issues (67.2%), arthralgias (59.1%), night sweats (41.2%), earache (35.4%), weight loss (35.4%), coughing (32.8%), loss of appetite (31.9%), headaches (30.1%), cutaneous symptoms (30.1%), ocular manifestations (24.9%) or bloody sputum (24.3%). Prior history of allergy was reported by 30.5% of the patients. GPA diagnoses were mostly established by rheumatologists (for 40% of the respondents), but also ENT surgeons, respirologists or nephrologists (for 15.4, 13.0 and 12.2%, respectively). The delay between first symptoms attributed to GPA and diagnosis was 15.1 ± 26.0 months. Only 3 patients reported not having received corticosteroids as part of their initial treatment (cotrimoxazole instead), whereas 61.3% were given cyclophosphamide.

Conclusion: Patient-driven surveys and reported outcome studies represent novel and powerful methods to study rare diseases such as GPA. The high response rate to this original patient-driven online survey strongly supports such initiatives. Even though its design did not allow us to confirm GPA diagnosis, its findings are close to those previously reported on diagnostic delay and initial GPA manifestations.

2373

Rituximab in Relapsing Granulomatosis with Polyangiitis (Wegener's Granulomatosis): a Case Series. Pamela M.K Lutalo, Ian C. Scott, Shirish Sangle and David P. D'Cruz. Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom

Background/Purpose: The relapse rate in ANCA positive granulomatosis with polyangiitis (GPA) vasculitis remains high despite aggressive therapy such as Cyclophosphamide, Methotrexate and Mycophenolate. There is mounting evidence that B cell depletion therapy may have an edge over Cyclophosphamide in managing GPA relapses. We present an observational study in patients with GPA who received B cell depletion therapy.

Methods: 10 patients with severe relapsing ANCA-associated vasculitis were treated with intravenous Rituximab infusions 1 gram on day 1 and day 15 as per protocol between 2006–2010. All patients' disease duration, system involvement and previous immunosuppression was documented. Birmingham Vasculitis Activity Score (BVAS); laboratory markers of disease activity, lymphocyte subsets and ANCA titre were measured at baseline, 1 month, 6 month and 12 month intervals. SPSS-18 was used for statistical analysis.

Results: The mean age = 49 years (33–65 years) and mean disease duration= 9 years. All patients' BVAS scores improved post-Rituximab. Anti-PR3 titres dropped from a median pre-Rituximab PR3= 45 u/ml to a median post-Rituximab PR3= 1 u/ml ($p=0.008$). B-cell depletion was observed in all patients (B-cell count < 5 cells/μL) at 6 months. 2 patients relapsed after 18 months and received further immunosuppressant therapy. The longest documented relapse-free period was 57 months (Table 1).

Details are summarised in table 1.

PATIENT	AGE	GENDER	DISEASE TYPE	DISEASE DURATION (YEARS)	PREVIOUS TREATMENT FAILURES	FEATURES OF CURRENT FLARE	CLINICAL RESPONSE TO RITUXIMAB	ANTI-PR3 TITRES PRE- POST-RITUXIMAB	B CELL LEVELS PRE-/POST-RITUXIMAB	FOLLOW-UP (MONTHS)	NUMBER OF POST-RITUXIMAB RELAPSES
1	55	M	Systemic	10	MTX, AZA, CYC	Lung, sinus peripheral nerves	All features improved	192/1	–/2	4	0
2	37	M	Systemic	2	MMF, CYC	Cresenteric glomerulonephritis	Resolution haematuria, stable GFR	102/2	89/5	9	0
3	53	M	Limited	21	MTX, AZA, MMF, CYC, IVIG	ENT	Improved	0/0	32/5	5	0
4	57	F	Systemic	3	MTX, AZA, MMF, CYC, IVIG	Destructive retro-orbital mass	Improved	6/0	–/1	57	0
5	55	M	Systemic	25	MTX, CYC	Restro-orbital mass with optic nerve compression	Resolution symptoms, reduction mass size	3/1	78/1	34	1
6	65	F	Systemic	6	MTX, AZA, CYC	Headache, retro-orbital mass	Improved	18/0	88/0	18	1
7	38	F	Systemic	5	MTX, AZA, CYC	Retro-orbital mass with optic nerve compression	Improved	46/1	336/1	30	0
8	35	F	Systemic	12	MTX, AZA, CYC	ENT, subglottal stenosis	Improved	43/2	–/1	35	0
9	51	F	Systemic	3	AZA, MMF, CYC	Extra-cranial mass, headache, papilloedema	Improved	5/2	85/0	8	0
10	48	F	Systemic	3	AZA, MMF, CYC	Pulmonary-renal syndrome	Resolution of lung lesions, normal renal function	26/2	39/2	5	0

AZA Azathioprine, CYC Cyclophosphamide, ENT ear, nose, throat GFR Glomerular filtration rate, IVIG intravenous Immunoglobulins, MMF Mycophenolate Mofetil, MTX methotrexate

Conclusion: Our data supports the use of Rituximab therapy in treating GPA relapses and it may provide longer remission in relapsing ANCA associated vasculitis.

2374

B Cell Depletion by Rituximab Severely Reduces Immunoglobulin Levels in Patients with ANCA-Associated Vasculitis Previously Treated with Cyclophosphamide. Jens Thiel, Nora M. Effelsberg, Hans-Hartmut Peter, Reinhard E. Voll, Klaus Warnatz and Nils Venhoff. Dpt. Rheumatology and Centre for Chronic Immunodeficiency, University Hospital Freiburg, Freiburg, Germany

Background/Purpose: In ANCA-associated vasculitides (AAVs) cyclophosphamide (CYC) is part of the standard therapy regimen for severe manifestations. Rituximab (RTX) is effective in the treatment of AAVs. No data on the cumulative effect of a sequential treatment with CYC and rituximab on immunoglobulin levels in AAV are available. Such data are of great interest since both therapies can induce hypogammaglobulinemia

leading to an increased risk of infections worsening the overall outcome. We report a retrospective analysis of the impact of immunosuppressive therapy with CYC and RTX on serum immunoglobulin (Ig) concentrations and peripheral B cells in patients with AAV.

Methods: Ig levels were analyzed in AAV patients either treated with CYC alone or treated with CYC and RTX. The effect of CYC on Ig levels was assessed in study group A (n=26), while the impact of RTX treatment alone was examined in study group B (n=29). In patients previously treated with CYC followed by RTX we compared changes in Ig concentrations prior to CYC to those after RTX treatment (group C; n=15). The median CYC doses were 8.05±0.56 g, 18.76±14.55 and 13.11±13.27 g in groups A, B and C and median RTX doses in group B and C were 1.8±0.8 g and 1.97±1.04 g respectively. The mean prednisone equivalent in patients treated with RTX was 12.35±7.52 mg/day. Statistics: Mann Whitney U Test, if not indicated otherwise.

Results: Mean Ig levels (mg/dL) prior to CYC therapy were normal. Means and standard deviations (SD) for group A are: IgG: 11.84±3.24, IgM: 1.31±0.94, IgA: 2.46±1.19. After CYC treatment IgG, IgM and IgA significantly decreased to 8.6±2.51 (p=<0.001; t-test), 0.88±0.53 (p=0.048), and 1.74±0.6 (p=0.021) respectively. In group B, median IgG levels prior to RTX were 9.74±3.49, IgM levels 0.81±0.45 and IgA levels 2.3±1.15. Over a period of 6 months after treatment, IgG significantly declined to 7.45±2.79 (p=0.001), IgM to 0.52±0.35 (p=0.003) and IgA to 1.69±0.81 (p=0.003). When assessing the effect of RTX therapy following CYC (group C) we observed the strongest decrease of all 3 isotypes: median IgG levels of 12.68±4.29mg/dL prior to CYC decreased to 6.59±1.98mg/dL (p=<0.001) after the dual treatment, IgM of 1.15±0.68 mg/dL to 0.52±0.42 mg/dL (p=0.002), and IgA of 2.65±1.25 mg/dL to 1.56±0.78 mg/dL (p=0.007). Follow-up measurements after RTX treatment did not show an increase in Ig levels within 24 months. RTX led to a complete depletion of B cells (</=2/μl) in all patients within the first 3 months after therapy. Interestingly, in all 7 patients that were available for analysis of peripheral B cell numbers 24 months after last RTX treatment, a persistent B lymphocytopenia with mean a B-cell count of 3.2/μl±1,7 was detected.

Conclusion: In patients with AAV, treatment with CYC leads to a decline in immunoglobulin levels, which is profoundly aggravated by subsequent RTX treatment. Data in our cohort furthermore indicates that B cell repopulation in AAV patients after RTX treatment might be delayed. Hence, Ig concentrations should be assessed after combined treatment with CYC and RTX.

2375

A Cost Effectiveness Analysis of Weekly Complete Blood Count Monitoring for Leukopenia In Patients with Granulomatosis with Polyangiitis (Wegner's) On Cyclophosphamide. Atul A. Khasnis[1], Richard Wilson[2], Gary S. Hoffman[1], Alexandra Villa-Forte[1] and Carol A. Langford[3]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Case Western Reserve University, Cleveland, OH, [3]Cleveland Clinic, Cleveland, OH

Background/Purpose: Daily cyclophosphamide (CYC) is used in the management of patients with severe granulomatosis with polyangiitis (Wegener's) (GPA). Leukopenia is a common toxicity of daily CYC which can be associated with infectious complications; however, no evidence based guidelines exist for white blood count monitoring in these patients. We assessed the cost-effectiveness of weekly compared to monthly complete blood count (CBC) monitoring in patients with severe GPA receiving oral CYC.

Methods: The two CBC monitoring approaches for surveillance of leukopenia and its consequences were compared using a decision analysis model created using TreeAge Pro 2009™. The parameters for prevalence of leukopenia, infections, and outcomes were obtained from an existing registry at the Cleveland Clinic (130 patients) and literature review of studies using daily CYC for management of severe GPA as well as the literature on outcomes in patients with sepsis. Only studies clearly documenting the frequencies of parameters required in the model and the relationship between severe leukopenia and severe infection were included. Parameter values that were unavailable from the published literature were entered by consensus and subjected to wide ranges for sensitivity analyses. Costs were in dollars (2010) and effectiveness as quality-adjusted life-years (QALYs) gained. Analysis was performed from a societal perspective. In addition to a baseline cost effectiveness analysis, we performed univariate sensitivity analyses and probabilistic sensitivity analysis (PSA) to check for robustness of the parameters included in the analysis. Although the base case patient was 45 years old, we analyzed the results over a wide range of patient ages (25–65 years).

Results: The expected utility of weekly CBC monitoring of these patients for leukopenia is 18.74 QALYs versus 18.52 QALYs with monthly CBC. The expected gain is 0.22 QALYs and incurs $489 lower cost per patient. The weekly CBC strategy dominated (was more effective and less expensive than) the monthly CBC strategy. In clinical scenarios generated by the univariate sensitivity analyses where the weekly strategy did not dominate the monthly strategy, it was still more effective but as or more expensive than the monthly CBC strategy. The results were not sensitive to changes in patient age. The acceptability curve generated by PSA also demonstrated dominance of the weekly CBC strategy.

Conclusion: Weekly CBC monitoring appears to be cost-effective for prevention of severe leukopenia and severe infections in patients on daily CYC for GPA. Further prospective studies with systematic data collection regarding frequencies of parameters in the model are required to confirm and validate our findings.

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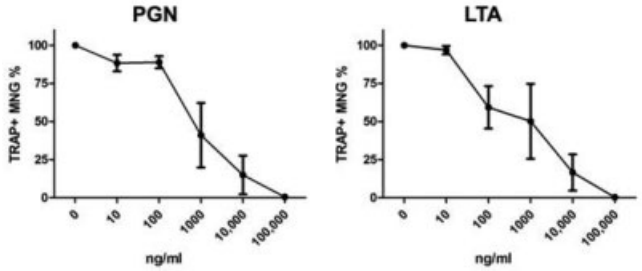
Gram-Positive Bacterial Wall Components Inhibit Formation of Osteoclast-Like Multinucleated Giant Cells: Possible Explanation for Their Scarcity in Sinonasal Inflammation of Granulomatosis with Polyangiitis. Jin Kyun Park. Johns Hopkins University, Baltimore, MD

Background/Purpose: One distinguishing feature of Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, is systemic granulomatous inflammation with multinucleated giant cells (MNG). The phenotype of those MNGs in sinonasal inflammation and their interactions with colonizing bacteria have not been studied to date.

Methods: MNG phenotype was examined by immunohistochemistry in serial paraffin sections of GPA sinus tissue (N=12) using antibodies recognizing the osteoclast (OC)-lineage markers CD68, cathepsin K and using tartrate-resistant-acid-phophatase (TRAP) assay. To examine the influence of the bacteria on MNG formation, monocytes were isolated from peripheral mononuclear cells of three GPA patients and were cultured in 96-well plates in the presence of RANKL, M-CSF and increasing concentrations of bacterial wall component peptidoglycan (PGN) and lipoteichoic acid (LTA). After 9 days, TRAP+ MNGs with 3 nuclei or more per well were counted. Fisher Exact test was performed and $p < 0.05$ was considered significant.

Results: MNGs in GPA sinonasal inflammatory infiltrates expressed TRAP and cathepsin K, specific enzymes of bone-resident osteoclasts. In addition, MNGs expressed CD68, indicating their monocytic lineage. Interestingly, MNGs were less frequently observed in GPA sinus tissues (where Gram-positive bacterial colonization is frequent) as compared to GPA lung tissues (23.1 % vs. 70 %, p=0.04). In the presence of RANKL and M-CSF, monocytes of GPA patients formed on average 229.3 TRAP+ MNG/well ± 74.4 (SEM). MNG formation was inhibited by PGN and LTA in a dose-dependent manner; approximately 50%, 75%, and 100% inhibition were achieved at 1 μg/ml, 10 μg/ml, and 100 μg/ml, respectively (Figure).



Conclusion: The relative rarity of MNG in the sinuses compared to the lungs of GPA patients is striking. The inhibition of MNG formation by Gram-positive bacterial cell wall components may occur preferentially in this sinonasal microenvironment known to be heavily colonized by Gram-positive bacteria in GPA.

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Perspective on Hypoxic Signalling in Granulomatosis with Polyangiitis (Wegener's)—Increased Expression of HIF-1α and Glut-1 in Granulomatous Lesions of the Nasal Cavity. Nina Kesel[1], Antje Müller[2], Dorothee Köhler[1], Martin Laudien[3], Elena Csernok[2], Udo Schumacher[1] and Sebastian Ullrich[1]. [1]University Medical Center Hamburg, Hamburg, Germany, [2]University of Lübeck, Bad Bramstedt, Germany, [3]Christian-Albrechts-University Kiel, Kiel, Germany

Background/Purpose: Hypoxia is a micro-environmental feature in the inflamed tissue. The expression of hypoxia inducible factor 1 α (HIF-1α) and

its major target gene glucose transporter-1 (Glut-1) are markers for hypoxia in human tissues. The aim of this study was to investigate if hypoxia occurs in inflamed nasal mucosa from patients with Granulomatosis with Polyangiitis (GPA) by examining HIF-1α and Glut-1 expression in nasal tissues from patients with GPA and sinusitis, as well as in nasal tissue transplants derived from an immunodeficient mouse model.

Methods: Tissue sections from GPA patients (n=10) with histologic (H&E) features of active inflammation and patients with sinusitis as control (n=10) as well as nasal tissue sections derived from an immunodeficient mouse model were stained immunohistochemically for HIF-1α and Glut-1.

Results: The number of HIF-1α^+ and Glut-1$^+$ cells was found to be significantly higher in GPA compared to sinusitis. The expression of HIF-1α and Glut-1 was in accordance with the severity of inflammation and GPA disease activity.

Conclusion: The localization of hypoxic areas in nasal mucosa from active GPA was identified and an up-regulated expression of two hypoxic signs (HIF-1α and Glut-1) was observed. In addition, HIF-1α and Glut-1 expression were evaluated in an immunodeficient mouse model. According to our data, hypoxia seems to be a prominent feature in granulomatous lesions. Further studies on the pathogenesis of the GPA granuloma need to consider the impact of HIF-1α- and Glut-1-mediated modulation on cell to cell signalling and recruitment of cells into inflamed tissue.

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CT Imaging Characteristics of the Sino-Nasal Tract and Orbits in Granulomatosis with Polyangiitis (Wegener's) and Churg–Strauss Syndrome. A Cross-Sectional Review. Khaldoun Chaabo[1], Shirish Sangle[2], Dhiren Shah[3], Hema Verma[4] and David P. D'Cruz[2]. [1]St Thomas' Hospital, London, SE1 7EH, United Kingdom, [2]Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom, [3]Guy's and St Thomas' Hospitals NHS Foundation Trust, London,SE1 9RT, United Kingdom, [4]Guy's and St Thomas' Hospitals NHS Foundation Trust, London, SE1 9RT, United Kingdom

Background/Purpose: The upper airways are commonly involved in granulomatosis Polyangiitis (GPA) and Churg–Strauss syndrome (CSS), two types of antineutrophil cytoplasmic auto antibodies (ANCA) associated vasculitis. Both disorders are associated with vasculitis and granulomatous formation in the sino-nasal tract leading to chronic rhino-sinusitis. Computed tomography (CT) has been widely accepted as the radiographic modality of choice in the evaluation of rhino-sinusitis especially in delineating the bony structures of the sino-nasal tract. The aim of this cross-sectional study was to evaluate the CT characteristics of the sino-nasal and orbital involvement occurring in GPA and CSS in comparison with the chronic non-vasculitic rhino-sinusitis (NVRS) patients.

Methods: A cross-sectional evaluation of the CT imaging of the sino-nasal tract and orbits was performed in 80 patients in 3 groups. 34 had GPA, 16 CSS, and 30 had NVRS. The scans were randomised and reviewed by one Radiologist blinded to the clinical diagnosis. Sinus mucosal and bony involvement, orbital and naso-septal changes were quantified using Lund-Mackay score (LMS). The results were statistically analyzed using independent binary and continuous statistical tests.

Results: The GPA group consisted of 18 women (53%) and 16 men (47%), the CSS 10 women (62.5%) and 6 men (37.5%) and in the NVRS group 17 women (57%) and 13 men (43%). The median age of the GPA patients was 47 years (28–83), 51 (39–73) for CSS, and 46.5 (27–77) years for NVRS. The mean duration between the time of diagnosis and the time of the CT scan was: 5.9 years in GPA and 2.1 years in CSS.

Twenty eight WG patient (83%) and 8 CSS patients (50%) were positive for ANCA antibodies.

The presence of sinus opacification was observed in 33 WG patients (97%), 15 CSS patients (94%) and all patients with NVRS. The prevalence and severity (LMS) of mucosal thickening was high in the three groups with a higher LMS in the control group (NVRS). The prevalence of sinus bony erosion was 14/34 (41%) in GPA, 1/16 (6%) in CSS and 4/30 (13%) in NVRS. Fisher's exact test revealed statistically significant difference between the prevalence of bony erosions in GPA and controls (P = 0.024), between GPA and CSS (P = 0.019), but not between the CSS and controls (P = 0.65). The prevalence of sinus neo-osteogenesis was 10/34 (29.5%) in GPA, 1/16 (6%) in CSS and 2/30 (6.6%) in NVRS. Fisher's exact test revealed an overall statistically significant difference between the prevalence of neo-osteogenesis in WG and controls (P = 0.026), but not between the GPA and CSS (P = NS), or between the CSS and NVRS (P = NS). Orbital changes involvement were only observed in WG (20.5%) but not in CSS or NVRS (p = 0.005). A naso-septal defect was observed only in WG (20.5%) but not in CSS or NVRS (p = 0.005).

Conclusion: GPA appears to have a distinct radiological phenotype with significant bony erosions, orbital involvement and nasal septal defects which may be used to distinguish GPA from CSS.

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Churg–Strauss Syndrome: Analysis of 58 patients' Relapses and Outcomes. Maxime Samson[1], Camillo Ribi[2], Pascal Cohen[3], Marc Stern[4], Christian Pagnoux[5], Jean-Francois Cordier[6], Luc Mouthon[7] and Loic Guillevin[8]. [1]Hôpital Cochin, University Paris Descartes, Paris, France, [2]Hôpital Universitaire Cantonal de Genève, Geneve, Switzerland, [3]Service de médecine interne, Centre de Références des Vascularites, Université Paris Descartes, APHP, Hôpital Cochin, 75005 Paris, France., Paris, France, [4]Hôpital Foch, Suresnes, France, [5]University of Toronto, Toronto, ON, [6]Division of Pneumology, Hôpital Louis-Pradel, Hospices Civils de Lyon, Lyon 1, Lyon, France, [7]Hopital Cochim, Paris, France, [8]Cochin University Hospital, Paris, France

Background/Purpose: Churg Strauss Syndrome (CSS) is a rare small-sized–vessel vasculitis. Its nonsevere manifestations, as defined by the Five-Factor Score (FFS), respond to corticosteroids (CS) alone. For more severe cases (FFS≥1), combined CS + cyclophosphamide (CYC) is mandatory for disease control, followed by azathioprine (AZA) or methotrexate for maintenance, but relapses remain frequent. This study aimed to describe clinical, biological and immunological characteristics, therapeutic responses and outcomes of CSS patients who suffered ≥1 relapses.

Methods: Relapses and failures occurring during follow-up of 115 CSS patients, stratified according to the 1996 FFS version and enrolled in 2 prospective trials[1,2] between 1995 and 2002, were analyzed. Patients with FFS≥1 (n=43) were assigned to receive 6 or 12 CYC pulses + CS while those with FFS=0 (n=72) received CS alone, with immunosuppressant (IS) adjunction when CS failed. Relapses were defined as the recurrence of ≥1 vasculitis manifestations but excluded an isolated eosinophil rise or asthma exacerbation without eosinophilia. We distinguished between major relapses requiring CS pulses with/without IS, and minor flares treated with dose-intensified CS alone. Failure was defined as the absence of clinical remission with the assigned treatment.

Results: Mean±SD overall follow-up was 69±27.6 months. Among the 115 patients, 58 (50.4%) suffered a relapse (n=51) or failure (n=7). At diagnosis, their mean age was 49.6±13.8 years, mean Birmingham Vasculitis Activity Score 2003 (BVAS) 22.6±7.43, eosinophil count 6.93±5.65 G/L; among the 25 (43.9%) ANCA-positive, 80% had myeloperoxidase specificity. After inclusion, 7 patients suffered primary failures at 3.3±2.1 months, with second-line therapy achieving remission for all, and relapses, minor for 29 (56.9%) patients and major for 22 (43.1%), occurred at 15.75±15.6 months. At relapse, 3 (5.9%) patients were taking CS+IS, 42 (82.4%) CS (mean dose 13.23±12.9 mg/d) alone, 32 (62.7%; CS <10 mg/d) and 9 (17.6%) were not treated; mean BVAS was 7±4.7; eosinophils rose (>0.5 G/L) in 41 (80.4%) and were normal (<0.5 G/L) in 7 (13.7%). CS were reintroduced or increased for 46 (90.2%) patients and IS were prescribed for 20 (39.2%): intravenous CYC for 8, oral CYC for 3 and AZA for 9; 45 (88.24%) achieved remission. Among the 58 patients, 16 (27.6%) entered long-term remission, 37 (63.8%) developed ≥1 new relapse(s) and 5 (8.6%) died. Among the 53 survivors at the last follow-up visit, 4 (7.5%) had stopped CS+IS, 47 (88.7%) were taking CS and 21 (39.6%) an IS: AZA for 16, oral CYC for 2, IVIg for 1 or mycophenolate mofetil for 2. The mean vasculitis damage index was 2.57±1.35, mostly reflecting chronic asthma and peripheral neuropathy.

Conclusion: About half of CSS patients relapse, most often when IS are stopped and CS are <10 mg/d. CS with/without IS were able to obtain second remissions. However, two-thirds of patients suffered further relapses. Five years after diagnosis, almost 90% of patients are still taking CS and about 40% are on IS.

1. Ribi C et al. Arthritis Rheum 2008;58:586–594
2. Cohen P et al. Arthritis Rheum 2007;57:686–693

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IgG4 Immune Response in Churg-Strauss Syndrome. Augusto Vaglio[1], Johanna Strehl[2], Bernhard Manger[2], Federica Maritati[1], Federico Alberici[1], Christian Beyer[2], Juergen Rech[2], Jorg HW Distler[2], Georg Schett[2], Renato Sinico[3] and Jochen Zwerina[2]. [1]University of Parma, Parma, Italy, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]Ospedale San Carlo Borromeo, Milano, Italy

Background/Purpose: Churg-Strauss Syndrome (CSS) is a systemic vasculitis usually occurring in individuals with a history of asthma. TH2 responses are common in allergic diseases and enhance the production of immunoglobulin (Ig)G4 antibodies. We therefore assessed IgG4 immune response in CSS patients.

Methods: We included consecutive patients with CSS (n=34, 22 with active and 12 with quiescent disease), granulomatosis with polyangiitis (GPA, n=18) and healthy controls (n=20). We defined the clinical phenotype of CSS patients and determined serum IgG, IgM, IgA and IgE levels. We further assessed IgG subclass distribution and stained tissue biopsies from CSS patients for local IgG4 production.

Results: Whereas active CSS and GPA patients both showed increased total IgG as compared to healthy controls, CSS (mean±SEM: 272±40 mg/dl) but not GPA (mean 90±17 mg/dl) patients showed significantly increased serum IgG4 levels as compared to healthy controls (mean 35±7 mg/dl; $p<0.001$). Serum IgG4 levels correlated with the number of organ manifestations ($p<0.05$) and with disease severity, as patients with a Five-Factor Score (FFS)≥1 had higher IgG4 levels than patients with a FFS=0 ($p<0.05$). IgG4 levels were normal in CSS patients in remission. Heart involvement and peripheral neuropathy were more frequent in IgG4-high (IgG4>135 mg/dL) CSS patients (p=0.13 and p=0.056, respectively). In three out of the nine available CSS tissue biopsies, intense IgG4-producing plasma cell infiltration were detected.

Conclusion: An increased IgG4 production is found in active CSS; IgG4 levels correlate with disease severity, and may differentiate CSS from other vasculitides such as GPA.

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Airway Inflammation and Systemic Inflammation During Churg-Strauss Syndrome Natural Course: A Multidisciplinary Monocentric Crosse-Sectional Study. Chiara Baldini[1], Sara Grossi[1], Manuela Latorre[2], Pasquale Pepe[1], Valeria Giorgerini[1], Alessandra Della Rossa[1], Federico Dente[2], Silvia Cianchetti[2], Pierluigi Paggiaro[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Pneumology Unit, Italy

Background/Purpose: Asthma is a key feature in Churg-Strauss syndrome (CSS). Nonetheless, the relationship between asthma clinical course and the natural history of the other CSS systemic clinical manifestations over the follow-up have been scarcely investigated. *Primary aim:* to compare asthma activity/severity and systemic disease activity/damage in consecutive patients with a diagnosis of CSS. S*econdary aims*: a) to compare sputum inflammatory markers with blood inflammatory disease biomarkers in order to evaluate the relationship between airway inflammation and systemic inflammation during CSS natural course; b) to compare asthma severity estimated according to clinical and functional findings and airway inflammation as assessed by induced sputum analysis.

Methods: Twenty consecutive patients with a diagnosis of CSS (ACR criteria) were enrolled in this cross-sectional study. Systemic disease manifestations, BVAS and VDI were recorded. All patients were assessed for lung function (Tiffeneau index, FEV1) and bronchial iperreactivity (methacholine challenge test). Asthma severity and control were established according to GINA guidelines and ACT questionnaire. Sputum eosinophil percentages and exhaled nitric oxide (eNO) were measured as markers of airway inflammation. Peripheral blood eosinophiloa, and serum anti-neutrophil cytoplasmic autoantibody (ANCA), eosinophil cationic protein (ECP), IgE, IL2, IL4 and IL5 were also assessed. Chi-square test, t-test and McNemar test were used to assess the primary aim. Pearson correlation coefficient and Welch-ANOVA were employed to investigate secondary aims.

Results: Patients demographic, clinical and laboratory features and data on asthma severity and sputum inflammatory markers are shown in Table 1. Overall, the study results demonstrated that despite the fact that the vast majority of the patients presented a complete systemic remission, the 80% of the patients still showed a moderate/severe persistent chronic asthma. No statistical correlation was found between peripheral eosinophil count and asthma severity. Furthermore, no statistical relationship was obtained between sputum inflammatory markers and blood inflammatory soluble mediators, including ECP. A significant correlation was detected between sputum eosinophil counts and ACT ($r = -0.64$, $P = .014$) and sputum eosinophil counts and GINA control score (p=0.008). No relationship was found between sputum inflammatory markers and FEV1 and FEV1/SVC..

Table 1

Patients n°	20 (9F 11M)		
Age yr (M±SD)	60±14		
Age at diagnosis (M±SD)	51.7±14.5		
Disease duration	8.9±7.7		
Latency asthma-vasculitis	7.3±12.7		
	onset	follow-up	p-value
Eosinophilic count	5004±4240	507±342	<0.0001
Constitutional (%)	90	20	<0.0001
ENT (%)	95	35	<0.0001
Lung Infiltrates (%)	55	5	0.001
Heart (%)	30	10	0.06
PNS (%)	40	40	n.s
Gastrointestinal (%)	15	0	<0.0001
Skin (%)	65	10	<0.0001
BVAS	14±5	3±2	<0.0001
VDI	0	1.6±1	<0.0001

FEV1% predicted (M±SD)(v.n.>80%)			81,45 ± 2.05
FEV1/SVC% (M±SD)(v.n.>88%)			79.2 ± 15.8
SPO2% (median (range))			97 (94-99)
Asthma control	ACT	Well controlled %	14
		Partially controlled %	38.1
		Poorly controlled%	38.1
	GINA guidelines	Well controlled%	19
		Partially controlled %	57.1
		Poorly controlled %	23.8
DLCO (ml/min/mmH) (M±SD)(v.n.>80)			91.48 ± 15
PD20 FEV1 mcg (geometric mean) (v.n.>1000)			341
eNO ppb (median (range)) (v.n.<25 ppb)			39 (8-160)
Sputum eosinophil% (median (range)) (v.n.<3%)			28.21 (0-91.35)

Conclusion: Chronic asthma negatively affects the natural history of CSS. Nonetheless airway inflammation seems to be not correlated to the systemic manifestations of the disease. Sputum inflammatory markers might represent a complementary tool in monitoring asthma in CSS patients as well as blood inflammatory disease biomarkers reflect CSS systemic activity.

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Cell Clonality in Churg-Strauss Syndrome: What Pathogenetic Role? Chiara Baldini[1], Sara Galimberti[2], Pasquale Pepe[1], Sara Grossi[1], Elisabetta Sordi[2], Valeria Giorgerini[1], Alessandra Della Rossa[1] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Hematology Unit, Pisa, Italy

Background/Purpose: A sustained and elevated blood eosinophilic count of unknown origin exceeding 1500 cells/ml and leading to organ infiltration characterises both Churg-Strauss syndrome (CSS) and idiopathic hypereosinophilic syndrome (lHES), leading to overlapping classifications, especially in ANCA negative patients. Important therapeutic implications may derive from the understanding of the pathogenetic pathways underlying these two conditions. This is a monocentric, cross sectional study aimed at assessing the prevalence of TCR g- and d-chain gene rearrangements in consecutive patients with a diagnosis of CSS. *Secondary aims:* a) to compare the prevalence of TCR g- and d-chain gene rearrangements in CSS vs lHES b) to explore any correlation between TCR rearrangements and clinical and laboratory features in patients with CSS and lHES

Methods: Consecutive patients with a diagnosis of CSS (ACR criteria) or lHES (Chusid criteria) were enrolled in the study from January 2010 to April 2011. Salient features prospectively collected in the study were 1) demographic data 2) clinical, immunologic and molecular features at the onset of the disease and 3) during disease evolution. Eosinophil cationic protein (ECP), IL2, IL4 and IL5 were measured as biomarkers of eosinophilic activation. TCR g- and d-chain gene rearrangements was evaluated by fluorescent PCR. Statistical analysis was performed by chi-square test, ANOVA and t-test

Results: Twenty-four patients with a diagnosis of CSS and 19 patients with a diagnosis of lHES were enrolled in the study. Table1 summarises patients demographic, clinical and laboratory data. Nine CSS patients out of 24 showed positive TCR g- and d-chain gene rearrangements with an overall prevalence of 37.5%. Out of them, 2 CSS patients had a confirmed positive serology for ANCA and 3 a histologically proven necrotizing vasculitis. No statistically significant difference was detected in the prevalence of TCR g- and d-chain gene rearrangements in CSS in comparison to lHES (37.5% CSS vs 57.8% lHES, p=0.22). In patients with mild to severe eosinophilia, TCR g- and d-chain gene rearrangements correlated only with the presence of constitutional symptoms.No correlation was found between TCR gene rearrangements and eosinophilic count, IL2, IL4 and IL5.

Table 1.

Clinical manifestations	CSS (24)	HES (19)	p-value
Male/Female	13/24	13/19	0.37
Age (mean ± SD)	58 ± 14	57 ± 16	0.64
Disease duration (mean ± SD)	6.7 ± 5.3	4.2 ± 4.2	0.09
Asthma	24	5	<0.0001
Age asthma at onset (mean ± SD)	41 ± 15	31 ± 20	0.32
Latency between asthma (mean ± SD)	9.7 ± 13	9.8 ± 9.7	0.99
Eosinophilia at onset (mean ± SD)	6060 ± 5110	6494 ± 7191	0.83
Constitutional symptoms	17/24	2/19	0.99
ENT involvement	18/24	6/24	0.005
Kidney involvement	1/24	1/19	0.99
Heart involvement	7/24	3/19	0.47
Purpura	11/24	0/9	0.03
Lung transient infiltrates	13/24	2/9	0.004
Peripheral nervous system	13/24	2/19	0.004
Abdominal pain	8/24	6/19	0.99
Splenomegaly	0/24	2/19	0.18
ANCA-MPO	9/24	0/19	0.01
Vasculitis	16/24	0/19	<0.0001
TCR clonality	9/24	11/19	0.22

Conclusion: This study demonstrated a comparable prevalence of TCR gene rearrangements in CSS and lHES.A cross-talk between eosinophils and clonal T-cells may play a potential role in the pathogenesis of both HES and CSS.

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Cocaine and ANCA Associated Vasculitis-Like Syndromes: A Single Centre Study. Khaldoun Chaabo[1], Shirish Sangle[2] and David P. D'Cruz[3]. [1]St Thomas' Hospital, London, SE1 7EH, United Kingdom, [2]Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom, [3]St Thomas' Hospital, London, United Kingdom

Background/Purpose: Cocaine is a potent vaso-constrictor leading to destructive inflammation and necrosis. We describe the clinical and serological manifestations mimicking ANCA associated vasculitis in chronic cocaine users.

Methods: We describe 6 patients with a history of chronic cocaine abuse, referred to our Vasculitis Clinic at St Thomas' Hospital for possible ANCA associated vasculitis. All patients presented with upper respiratory tract involvement with nasal septal defects and ongoing active sinusitis. Two patients presented as late onset asthma with significant eosinophilia (>10%), arthralgia, and peripheral neuropathy. One had cautaneous vasculitis and another presented with intestinal perforation and hematuria. All patients had imaging of chest and. Two patients had nasal mucosa biopsies. Their BVAS, VDI, inflammatory markers and treatment were documented. All patients received corticosteroids. One patient had intravenous cyclophosphamide and 2 others were maintained on azathioprine and methotrexate orally.

Results: Median age of the patients was 37.8 (28 – 42) years. There were 3 male patients. One woman was Far-Eastern in origin and all others were Caucasian. Median duration of cocaine abuse was 10 (6 –15) years. All had naso-septal defects. Four patients had a Wegener's Granulomatosis (WG) - like syndrome and two had Churg-Strauss syndrome (CSS). All were positive for ANCA antibodies. Two patients with a diagnosis of CSS had positive tests for P-ANCA but were negative for myeloperoxidase (MPO) antibodies. One had histopathological features suggestive of CSS in the nasal mucosal biopsy. All WG-like syndrome patients had positive C-ANCA with positive PR-3 antibodies on ELISA. Patients with WG had destructive changes in the sinuses on CT scans of the upper airways. A sino-nasal biopsy in one patient with WG-like syndrome revealed histopathological features suggestive of WG. None had systemic involvement. All were managed successfully with a combination of oral steroids, methotrexate and co-trimoxazole.

Conclusion: Chronic cocaine abuse may be associated with clinical, serological, histo-pathological and radiological manifestations identical to ANCA associated vasculitis. It may be difficult to distinguish cocaine induced midline granuloma from idiopathic ANCA associated vasculitis. The presence of nasal septal defect should raise the suspicion of cocaine use.

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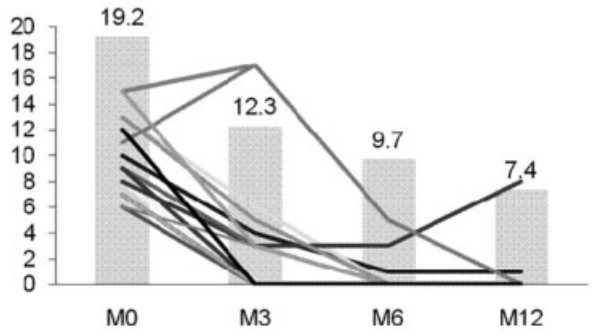
Rituximab Therapy for Systemic Vasculitis Associated with Rheumatoid Arthritis in the AutoImmunity and Rituximab Registry. Xavier Puéchal[1], Jacques-Eric Gottenberg[2], Jean-Marie Berthelot[3], Laure Gossec[4], Olivier Meyer[5], Jacques Morel[6], Daniel Wendling[7], Michel De Bandt[8], Eric Houvenagel[9], Bénédicte Jamard[10], Thierry Lequerré[11], Gauthier Morel[12], Pascal Richette[13], Jérémie Sellam[14], Loic Guillevin[4] and Xavier Mariette for the AutoImmunity and Rituximab Registry[15]. [1]Center for Rare Systemic Autoimmune Diseases, Le Mans General Hospital, Le Mans, France, [2]Strasbourg University Hospital, Strasbourg, France, [3]Nantes University Hospital, Nantes, France, [4]Cochin University Hospital, Paris, France, [5]Bichat University Hospital, Paris, France, [6]Montpellier University Hospital, Montpellier, France, [7]Minjoz University Hospital, Besancon, France, [8]R. Ballanger Hospital, Aulnay Sous Bois, France, [9]St Philibert Hospital, Lomme, France, [10]Toulouse University Hospital, Toulouse, France, [11]Rouen University Hospital, Rouen, France, [12]Valenciennes Hospital, Valenciennes, France, [13]Lariboisière University Hospital, Paris, France, [14]St Antoine University Hospital, Paris, France, [15]Bicêtre University Hospital, Le Kremlin Bicetre, France

Background/Purpose: Rituximab improves articular symptoms in rheumatoid arthritis (RA) and has been recently shown to be an effective induction therapy for ANCA-associated vasculitis. We assessed the efficacy and safety of rituximab in a real-life clinical setting among patients with systemic rheumatoid vasculitis (SRV).

Methods: We analyzed data from the AutoImmunity and Rituximab registry, which includes patients with autoimmune diseases treated with rituximab.

Results: Of the 1,994 RA patients enrolled in the registry, 17 were treated with rituximab for active SRV. At baseline, their mean BVAS/RA was 9.6 with a mean prednisone dosage of 19.2 mg/day. After 6 months of rituximab therapy, twelve (71%) patients achieved complete remission of their vasculitis, four had a partial response, and one died with uncontrolled vasculitis. Mean BVAS/RA was reduced to 0.6 and mean prednisone dosage to 9.7 mg/day. At 12 months, 14 (82%) patients were in sustained complete remission. Severe infection occurred in three patients, corresponding to a 6.4/100 patient-years rate. In the 6 patients who received further rituximab as maintenance therapy, no relapse of vasculitis was observed. However, among the 9 patients who did not, a relapse was observed in 3 patients who were treated with methotrexate alone. Remission was re-established by reintroducing rituximab in two cases.

Figure. Each line shows the progression of the individual BVAS/RA.
Bars show the mean daily dose of prednisone at the different end points of the study.



Conclusion: Complete remission of SRV was achieved in 3/4 of patients receiving rituximab in daily practice, with a significant decrease in prednisone dosage and an acceptable toxicity profile. Rituximab represents a suitable therapeutic option to induce remission in SRV but maintenance therapy seems to be necessary.

2385

Assessment of Disease Activity in Behcet Disease: Comparison of Behcet's Disease Current Activity Form (bdcaf), Behcet's Syndrome Activity Score (bsas) and Routine Assessment of Patient Index Data (rapid) 3 Scores. Sedat Yilmaz[1], Ismail Simsek[1], Muhammet Cinar[1], Hakan Erdem[1], Osman Kose[1], Yusuf Yazici[2] and Salih Pay[3]. [1]Division of Rheumatology, Gulhane School of Medicine, Ankara, Turkey, [2]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY, [3]GATA, Ankara, Turkey

Background/Purpose: Behcet's disease (BD) is a quite heterogeneous clinical syndrome that differs in organ involvement. Furhermore it has a

fluctuating course and there is no spesific laboratory markers in paralel with the disease course. Therefore, it remains to be an important problem for clinicians to define the disease activity in BD. The BDCAF is most commonly used index but a clinical assessor is needed to complete it. As an alternative to BDCAF, a patient-derived assessment tool, Behcet's syndrome activity score (BSAS) has been developed and found to be correlated with the BDCAF in a small number of patients with BD. BSAS consists of 10 questions, which consists of visual analog scales (VAS) for patient's level of discomfort with regards to oral ulcers, genital ulcers, skin lesions, current disease activity along with the number of oral ulcers, genital ulcers, and skin lesions present, and records symptoms attributable to the GIS, vascular, or eye involvement. Routine assessment of patient index data 3 (RAPID3) is a composite index based on 3 multi-dimensional health assessment questionnaire (MDHAQ) components, patient function, pain and patient global assessment. The objective of the present study was to evaluate the BSAS as a new tool for measuring disease activity, as compared to the already established BDCAF, and to use the RAPID3 form as a secondary exploratory index.

Methods: Patients seen consecutively at the Rheumatology Center between May 1 and June 25, 2011 were given the BSAS questionnaire and MDHAQ to complete, and all attending physicians filled the BDCAF. Descriptive statistics, and Pearson correlation coefficients were calculated for each measure.

Results: Fifty-two patients completed all three assessments. The BSAS (range 0–100) mean score was 16.9 (SD 10.7); BDCAF (range 0–12) mean score was 2.6 (SD 1.7); RAPID3 (range 0–30) mean score was 8.9 (SD 5.7), median was 12.5 (IQR 18.5); Physician Global (0–10) mean score was 3.6 (SD 2.1). The correlation between BSAS and BDCAF was moderate (r:0. 491, $p<0.0001$), while BSAS was strongly correlated with RAPID3 (r:0. 65, $p<0.0001$). The correlation between the RAPID3 and BDCAF was found to be poor (r:0.277, $p=0.047$).

Conclusion: We found that the BSAS questionnaire, composed of patient responses only, has a strong, positive correlation with the BDCAF, a questionnaire that is completed by a clinical assessor. An outcome score composed of only patient-derived observations may have the additional advantage of being easier to use in a routine care setting.

2386

The Impact of Positive Pathergy Test on the Performance of Diagnostic Criteria in Behcet's Disease. Fereydoun Davatchi, Bahar Sadeghi Abdollahi, Cheyda Chams-Davatchi, Farhad Shahram, Zahra Ghodsi, Tahereh Faezi, Abdolhadi Nadji, Massoomeh Akhlaghi and Roghieh Larimi. Shariati Hospital-Tehran Univ, Tehran, Iran

Background/Purpose: No diagnostic test exists for Behcet's Disease (BD) except the pathergy test that reveals the pathergy phenomenon of the disease. Positive pathergy test (PPT) is an important criterion of many classification/diagnosis criteria. There are actually 16 sets of diagnosis/classification criteria for BD: Curth (1946), Hewitt (1969), Mason and Barnes (1969), Hewitt Revised (1971), Japan (1972), Hubault and Hamza (1974), O'Duffy (1974), Zhang (1980), Dilsen (1986), Japan Revised (1988), International Study Group (ISG) in 1990, Iran (1993), Classification Tree (1993), Dilsen revised (2000), Korea (2003), and the International Criteria for Behcet's Disease (ICBD) in 2006. The aim of this study was to find, how much PPT accounts in the overall performance of those diagnostic criteria that use PPT as a criterion. We selected 9 of the most renowned of them for this study.

Methods: Patients with BD (6607) were selected as consecutive patients from the Behcet's Disease registry, and 4292 control patients. The diagnosis of BD was made on "Expert Opinion" without taking into account any known criteria. Control patients were those sent to find if they had BD, and the expert opinion was against the diagnosis. The 9 criteria sets were tested in them, once taking into account the PPT, and then without it. The sensitivity, specificity, and accuracy (percent agreement) of them were calculated to find the impact of PPT.

Results: Without PPT, all tested criteria lost some of their sensitivity. The largest lost was for Dilsen, ISG, and revised Dilsen criteria (17.3%, 16.1%, 16.1%). The least was for ICBD, Japan revised, and Classification Tree criteria (6.5%, 7.6%, 7.6%). The largest gain on specificity was for ICBD (3.9%) and the least for Japan and Japan revised criteria (0.1%, 0.1%). The largest lost in accuracy was for ISG, Dilsen revised, and Dilsen criteria (9.5%, 9.5%, 8.6%) and the least for ICBD, Classification Tree, Japan, and Japan revised criteria (3.6%, 4.2%, 4.6%, 4.6%). The best overall accuracy (without PPT) was ICBD, the Classification Tree, and the Japan revised criteria (93.7%, 93%, 86.1%). Details for all tested criteria are shown in Table 1.

Table 1. Performance of different Criteria set with and without pathergy test

		SENSITIVITY			SPECIFICITY			ACCURACY		
	PPT	%	95%CI	Lost%	%	95%CI	Gained%	%	95%CI	Lost%
ISG	Yes	78.0	1.0	16.1	99.0	0.3	0.8	86.3	0.6	9.5
	No	61.9	1.2		99.8	0.1		76.8	0.8	
ICBD	Yes	98.3	0.3	6.6	95.9	0.6	3.9	97.3	0.3	3.6
	No	91.7	0.7		99.8	0.1		93.7	0.5	
JAPAN	Yes	85.0	0.9	7.7	97.7	0.4	0.1	90.0	0.6	4.6
	No	77.3	1.0		97.8	0.4		85.4	0.7	
JAPAN_R	Yes	86.2	0.8	7.6	97.6	0.5	0.1	90.7	0.5	4.6
	No	78.6	1.0		97.7	0.4		86.1	0.6	
DILSEN	Yes	82.0	0.9	17.3	94.7	0.7	5	87.0	0.6	8.6
	No	64.7	1.2		99.7	0.2		78.4	0.8	
DILSEN_R	Yes	79.4	1.0	16.1	98.9	0.3	0.8	87.1	0.6	9.5
	No	63.3	1.2		99.7	0.2		77.6	0.8	
IRAN	Yes	90.7	0.7	13.5	97.0	0.5	0.8	93.2	0.5	7.9
	No	77.2	1.0		97.8	0.4		85.3	0.7	
TREE	Yes	97.2	0.4	7.6	97.3	0.5	0.8	97.2	0.3	4.2
	No	89.6	0.7		98.1	0.4		93.0	0.5	
KOREA	Yes	86.3	0.8	9.9	98.1	0.4	0.7	90.9	0.5	5.6
	No	76.4	1.0		98.8	0.3		85.3	0.7	

Conclusion: ICBD and Classification Tree criteria were the least dependent on PPT to classify patients as having BD. They have also the best sensitivity and the best accuracy without using the PPT, making them the best diagnostic instrument in countries where PPT is rarely encountered (countries far from the Silk Road). They are also the most performing Diagnosis/Classification criteria for countries inside the Silk Road.

2387

A Mucocutaneous Activity Index for Behcet's Disease. Gonca Mumcu[1], Nevsun Inanc[2], Haner Direskeneli[2] and Tülin Ergun[3]. [1]Marmara University-,Faculty of Health Sciences, Department of Health Informatics and Technologies, Istanbul, Turkey, [2]Marmara University School of Medicine, Istanbul, Turkey, [3]Department of Dermatology, Marmara University School of Medicine, Istanbul, Turkey

Background/Purpose: Evaluation of disease activity is fairly difficult in Behçet disease (BD) with different organ manifestations. A "Composite Index" (CI) was previously validated for oral ulcer activity in BD by our group (Mumcu 2009). Although other mucocutaneous symptoms are also common clinical symptoms, no standardized activity index is present to assess all of them together in BD. Therefore, the aim of this study was to develop a disease-specific muco-cutaneous activity index in Behcet's disease.

Methods: One hundred BD patients (F/M:62/38, mean age:37.7±10.8 years) were included in the study. Mucocutaneous index (MI) was composed of genital ulcer activity index (GI), erythema nodosum activity index (EI) and CI. It evaluated both pain scored by visual analogue scale (VAS-pain, 0–100 mm) and functional status coded by Likert-type scale of each involvement during the last month. Score of MI could be between 0 and 30 (0–10 points for each involvement). Internal reliability was evaluated by Cronbach-alpha coefficient in functional disability score, as the same scoring procedure was applied in this multi-item scale. The score was evaluated in patients with both active and inactive disease for content validity. Patients with any mucocutaneous symptom were categorised as active group (n=85), whereas the others were accepted inactive (n=15).

Results: Oral ulcer activity was present in 85% of the patients (n=85) in the study group. The ratios of genital ulcer and erythema nodosum activities were 15% for each involvement (n=15). MI score (5.8±4.8) was higher in active patients (n=85, 6.8±4.6) than inactive ones (n=15, 0±0)($p=0.000$). Similarly, scores of CI, GI and EI were also lower in inactives (0±0) compared to active ones (5.0±2.7, 5.5±3.3 and 5.2±2.3, respectively) for each involvement. Cronbach-alpha coefficients for functional status were 0.9109 for CI, 0.9387 for GI and 0.9572 for EI. Fifteen active patients were examined by both observer 1 (TE) (8.8±2.3) and observer 2 (HD) (9.1±1.3) to evaluate interobserver difference without a significant difference ($p>0.05$). Almost three quarters of active patients (n=74, 74%) were treated with colchicine in BD. The others were using ISs (n=26, 26%). MI score was lower in patients treated with immunosuppressives (3.9±4.9) than colchicine (6.3±4.8) ($p=0.03$).

Conclusion: The validated, new mucocutaneous activity index can be a valuable tool to assess mucocutaneous-specific clinical symptoms and the effects of treatment modalities in BD.

2388

Gender-Specific Differences in Adamantiades-Behçet's Disease Presentation and Their Relationship with *HLA-B5*: An Analysis of 731 Subjects From the German Registry for Adamantiades-Behçet's Disease. Nikolaos G. Bonitsis[1], Liem Binh Luong Nguyen[2], Nestor Papoutsis[1], Andreas Altenburg[1], Ina Kötter[3], Alfred Mahr[2] and Christos C. Zouboulis[1]. [1]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany, [2]Department of Internal Medicine, Hospital Saint-Louis, Paris, France, [3]Department of Internal Medicine II, Rheumatology Division, University Hospital Tübingen, Tübingen, Germany

Background/Purpose: Adamantiades-Behçet's disease (ABD) is a multisystem disorder characterized by highly variable presentations. The factors driving the individual disease expressions are not well known. Gender-specific differences in clinical features, such as increased risk of eye involvement in males, have been proposed. The ABD susceptibility allele *HLA-B5* is tightly associated with male gender and ocular disease, and it could be hypothesized that the effect of gender on ABD expression is to some extent confounded by *HLA-B5* positivity. We undertook a study to investigate the effect of gender on the demographic and clinical features in ABD and to assess whether any differences may account for *HLA-B5* status.

Methods: This study was based on the German Registry of ABD, a national, multicenter registry prospectively collecting demographic, clinical and genetic information for ABD patients since 1990. Age at diagnosis and cumulative clinical variables (oral ulcers, genital ulcers, pathergy reaction and ocular, skin, joint, neurological, heart, pulmonary, and kidney involvement) were compared accordingly to gender and *HLA-B5* status. Statistical analyses used Pearson's chi^2 and Student's t tests.

Results: A total of 731 subjects were evaluated (mean age at diagnosis: 27.8 yr [SD 11.7], 58% males, 40% Germans, 44% Turks). The International Study Group classification criteria were satisfied by 629/728 (86%) subjects overall and by 375/423 (89%) males and 254/305 (83%) females ($P=0.04$). *HLA-B5* was found in 350/603 (58%) and was significantly higher in males (relative risk [RR]: 1.27, 95% CI: 1.09–1.48, $P=0.001$). The age at disease onset did not differ by gender ($P=0.22$). Male gender was associated with a significantly increased prevalence of ocular involvement (RR: 1.21, 95% CI: 1.06–1.38, $P=0.004$), skin involvement (RR: 1.11, 95% CI: 1.02–1.21, $P=0.01$), major vessel involvement (RR: 2.86, 95% CI: 1.89–4.43, $P<0.0001$) and heart involvement (RR: 9.98, 95% CI: 1.41–203.40, $P=0.006$) and a decreased prevalence of genital ulcers (RR: 0.<82, 95% CI: 0.74–0.92, $P<0.0001$) and joint involvement (RR: 0.84, 95% CI: 0.72–0.99, $P=0.03$). Analyses of the clinical characteristics by *HLA-B5* status showed that *HLA-B5* was positively associated with ocular disease (RR: 1.43, 95% CI: 1.22–1.67, $P<0.0001$) and skin involvement (RR: 1.14, 95% CI: 1.04–1.25, $P=0.004$) and negatively associated with gastrointestinal involvement (RR: 0.51, 95% CI: 0.30–0.86, $P=0.008$). The HLA status did not affect the links between male gender and eye and skin involvement, respectively, with RR of 1.10 (95% CI: 0.94–1.32, $P=0.24$) and 1.06 (95 %CI: 0.95–1.19, $P=0.34$) among *HLA-B5* positive patients and 1.15 (95% CI: 0.86–1.55, $P=0.35$) and 1.18 (95% CI: 1.00–1.39, $P=0.05$) among *HLA-B5* negative patients.

Conclusion: This study adds support to gender-specific differences in ABD clinical presentation and to the link between male gender and *HLA-B5* positivity. The fact that *HLA-B5* status did not affect the link between gender and clinical presentation suggests that gender and *HLA-B5* are independent ABD expression modifiers. These findings may provide further insight into the mechanisms underlying the physiopathology of ABD.

2389

Exploration of Male Gender in Heterogeneity of Association Between *HLA-B51/B5* and Behçet's Disease Using Mixture Models. Michael P. LaValley[1], Hailong Cheng[2], Mathilde de Menthon[3] and Alfred Mahr[3]. [1]Boston University School of Public Health, Boston, MA, [2]Sunovion Pharmaceuticals Inc., Marlborough, MA, [3]Hospital Saint-Louis, Paris, France

Background/Purpose: In a previous random effects meta-regression of association between the *HLA-B5* and *HLA-B51* (*HLA-B51/B5*) genotype and Behçet's disease (BD) in case-control studies we found stronger association in studies with greater percentages of male subjects (Male%), and this was the only study factor that explained excess variation (heterogeneity)in association (*Arthritis Rheum* 2009;61:1287–96). To corroborate this result, we use a different association measure and a mixture model analysis that addresses heterogeneity by dividing studies into a small number of fixed effects sub-distributions rather than by use of a non-specific random effect. Study factors are then linked to these sub-distributions.

Method: A systematic literature search and extraction of was conducted as described in previous reports. Unlike previous reports, the arcsine difference (ASD) was used as association measure for *HLA-B51/B5* and case status as it follows a normal distribution more closely than the log odds ratio and has stable variance with sparse data. ASD near 1 indicate much higher prevalence of *HLA-B51/B5* in cases than controls; ASD near 0 indicate equal prevalence. Study level factors were Male%, publication factors, study area, tested allele (*HLA-B5* or *HLA-B51*), classification criteria, clinical manifestations, and ethnic matching of cases and controls. We fit meta-analysis mixture models with 1 to 9 fixed-effects sub-distributions using Bayesian Markov-Chain Monte Carlo with non-informative prior distributions, with the deviance information criterion (DIC) used to choose the number of sub-distributions. Studies were classified to sub-distributions based on posterior probability of membership and study level factors compared between sub-distributions by univariate t- or chi-square tests. Funnel plots of study precision (1/SE^2) by ASD were used to display results.

Results: ASD were calculated for 80 studies with fixed effects combined ASD of 0.39 (95% CI 0.38–0.41) with 68% of the variability in ASD due to heterogeneity. The minimum DIC was obtained with 2 sub-distributions: A) mean ASD 0.32 (95% Posterior Interval 0.10–0.49) and 47% of the studies; B) mean ASD 0.50 (95% Posterior Interval 0.33–0.78). Studies with ASD < 0.41 (dashed line in figure) were assigned to the first sub-distribution. Mean Male% was 56% in sub-distribution 1 and 68% in 2 ($p=0.01$), no other study level factor was significant (all $p>0.1$). Studies with Male% over the median value of 60% (squares in figure) cluster in and near the second sub-distribution.

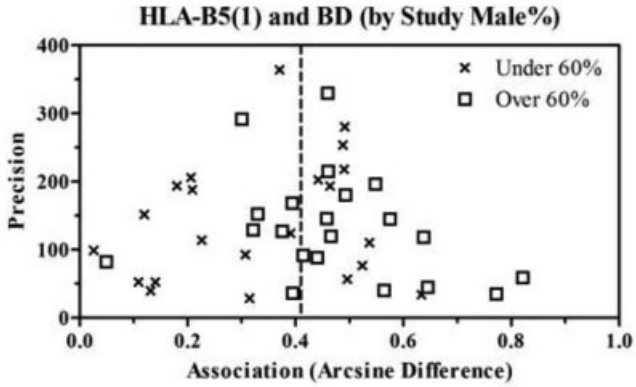


Figure 1. Funnel Plot by Study Male%

Conclusion: This analysis of study-clustering on the outcome corroborates the earlier finding of stronger association between *HLA-B51/B5* genotype and BD in studies with higher percentages of male subjects, providing further evidence of a sex-specific genetic effect in BD. The mechanism underlying the gender-differential effect of *HLA-B51/B5* on BD is unclear.

2390

CC Chemokine Receptor 5 Polymorphism in Behçet's Disease. Fabiola Atzeni[1], Luigi Boiardi[2], Bruno Casali[3], Enrico Farnetti[3], Piercarlo Sarzi-Puttini[1], Nicolo Pipitone[2], Ignazio Olivieri[4], Fabrizio Cantini[5], Fabrizio Salvi[6], Renato La Corte[7], Giovanni Triolo[8], Davide Filippini[9], Giuseppe Paolazzi[10] and Carlo Salvarani[2]. [1]Rheumatology Unit, L. Sacco University Hospital of Milan, Milan, Italy, [2]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [3]Molecular Biology Laboratory, Arcispedale S. Maria Nuova,, Reggio Emilia, Italy, [4]Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy, [5]Stabilimento Ospedaliero Misericordia, Prato, Italy, [6]Dept. of Neurological Sciences, Ospedale Bellaria,, Bologna, Italy, [7]Chair of Rheumatology, University of Ferrara,, Ferrara, Italy, [8]Rheumatology Unit, University of Palermo, Palermo, Italy, [9]Rheumatology Unit, Ospedale Niguarda,, Milan, Italy, [10]Ospedale Santa Chiara, Trento

Background/Purpose: Behçet's disease (BD) is a primary systemic vasculitis characterised by oral and genital ulcerations associated with other clinical manifestations, such as skin lesions, uveitis and thrombosis. The aim of this study was to evaluate potential associations of CC chemokine receptor 5 (CCR5)Δ32 polymorphism with BD and disease expression.

Methods: One hundred and ninety-six consecutive Italian patients satisfying the International Study Group criteria for BD followed up for seven years and 180 healthy controls were genotyped for CCR5Δ32 polymorphism by molecular methods. The patients were grouped on the basis of the presence or absence of clinical manifestations. The diagnoses of deep venous thrombosis (DVT) and

superficial thrombophlebitis (ST) were initially made clinically, and then confirmed by means of ultrasonography or contrast venography.

Results: The distribution of the CCR5Δ32 genotype was not significantly different in the BD patients and healthy controls (p corr = 0.072), but the CCR5Δ32 allele was more frequent in BD than in controls (p corr = 0.004, odds ratio [OR] 3.1, 95% CI 1.5–6.7). Carriers of the CCR5Δ32 allele (Δ 32/ Δ 32 + CCR5/ΔC32] were significantly more frequent in BD patients than in controls (p corr = 0.024, OR 2.37, 95% CI 1.1–5.1).

The CCR5Δ32 polymorphism was found more frequently in the BD patients with ST than in the controls (25.0% vs 5.6%, P=0.009), whereas there was no significant difference between BD patients with and without ST (25.0% vs 10.8%, P=0.07). There was no other significant association between clinical manifestations (including DVT) and the CCR5Δ32 polymorphism in the BD patients.

Conclusion: The CCR5Δ32 polymorphism might be associated with an increased risk of developing BD. Chemokines may have a role in the pathophysiology of BD and in the development of ST.

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Genome-Wide Expression Profiling of CD14+ Monocytes in Behcet's Disease: An Upregulated TGF-b Signaling and N-Methyltransferase Activity. M. Dozmorov[1], F. Ozdemir[2], V. Yilmaz[3], E. Eksioglu-Demiralp[2], J. Wren[1], G. Saruhan-Direskeneli[3], A. Sawalha[1] and H. Direskeneli[4]. [1]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Marmara University, School of Medicine, Department of Immunology, Istanbul, Turkey, [3]Istanbul University, Istanbul Faculty of Medicine, Department of Physiology, Istanbul, Turkey, [4]Marmara University, School of Medicine, Department of Rheumatology, Istanbul, Turkey

Background/Purpose: To obtain a global view of the gene expression profile in CD14+ monocytes of Behcet's Disease (BD), a systemic, inflammatory disorder with unknown etiology.

Methods: Patients with BD (n=3), compared to controls (n= 5) were investigated. Whole-genome microarray profiling was performed with human U133 (Plus 2.0) microarrays on an Affymetrix platform using isolated CD14+ monocyte subset from peripheral blood mononuclear cells. Differentially expressed genes were identified by associative analysis and assessed for gene ontology enrichment (DAVID), affected canonical pathways and networks (Ingenuity Pathway Analysis) and for transcription regulation of the promoters (PAINT).

Results: When genes with at least 3-fold expression difference were selected, 135 unique genes were upregulated, and 36 were downregulated in CD14+ cells in BD. One gene, EZH1, was uniquely overexpressed in BD, with no detectable expression in controls. Out of 135 upregulated genes 87 were phosphoproteins, indicating that proteins coded by those genes are post-translationally modified by the attachment of a phosphate group. Among the upregulated profile, genes related to intracellular organelle lumen (n=27), endocytosis (n=7), enzyme linked receptor protein signaling pathway (n=8) and N-methyltransferase activity (C1orf25, EZH1, MLL, PRDM2 and SETD2) were the most prominent. Canonical pathway analysis showed an upregulated TGF-β Signaling (ACVR1B, BMPR2, PIAS4, SMAD5, SMAD7, SOS1, SOS2 and TGFBR2). Upregulated genes formed a single network highlighting TNFa and interferon-g as major regulators and associated also with several adhesion-related molecules and signal transducer receptors including CD36, ITGB2 and DSC2. When downregulated genes were investigated, 24 molecules out of 36 shared "cell death" ontology, suggesting that CD14+ cells are in proliferation in BD. Some molecules associated with pattern recognition receptors of bacteria and viruses were also downregulated (C5AR1, CLEC7A, IL1B, NLRP3, RIPK2 and TLR4).

Conclusion: Both up- and downregulated genes highlight enhanced proliferation of CD14+ cells in BD. Common hub molecules, mainly interferon-g and TNFa, seem to be activated. Downregulation of molecules related to pattern recognition receptors point to a dysregulated anti-bacterial and viral immunity.

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Parvovirus B19 in Behçet's Disease. Zahra Habibagahi, Mojtaba Habibagahi and Said Mostafa Said Mardani. Shiraz University of Medical Sciences, Shiraz, Iran

Background/Purpose: Behcet is a systemic vasculitis known with repeated oral and genitalia aphthous, ophthalmology, and dermatology manifestations. The etiology of Behcet Disease (BD) is unknown.Viral infections are supposed to have a role in disease pathogenesis. Higher levels of antibodies to herpes simplex and varicella zoster virus antigens have been shown in patients with BD compared to controls. Herpes simplex DNA has been extracted from oral, genitalia and intestinal ulcers of BD patients.

There are varying results that show an association between parvovirus B19 and BD. The quantity of viral DNA in non ulcerated skin rashes was significantly higher than skin ulcers of healthy volunteers, although other investigators could not confirm this relationship. Signs of parvovirus B19 infection has been demonstrated in various autoimmune diseases like vasculitis, rheumatoid arthritis, systemic lupus erythematosus, and reactive arthritis.

The conflicting results of these studies cannot prove the role of parvovirus B19 in BD. Higher prevalence of antivirus antibodies may only be an incidental finding because of the high prevalence of viral infection in population. Persistent viral DNA also may be expected in patients with compromised immunity as a result of delayed in virus clearance.

We aimed to quantify parvovirus B19 DNA in BD patients in comparison to healthy controls by real time PCR and determine the relation of the level of virus DNA with disease severity.

Methods: Fifty five patients with BD (M/F; 0.67, mean age; 37.4 +/− 8.68 years, and mean disease duration of 7 years) were selected according to the International Study Group classification criteria to enroll in study after obtaining consents forms. The study was approved by the ethics committee of Shiraz University of Medical Sciences, Shiraz, Iran.

The patients were selected in a simple random manner and divided into mild, moderate, and severe groups according to disease severity score.

Parvovirus 19 specific quantitative real time PCR with TaqMan technology was used to assess the levels of viral DNA in patients' serum and age/sex matched controls. We also determined the relation between levels of virus DNA and disease severity indexes.

Data analysis was done by SPSS version 16 and using student T test.

Results: The disease was inactive in 8 patients (14.5%) while the disease severity in others was measured as mild in 18 (32.7%), moderate in 16 (29.2%), and severe in 13(23.6%) patients by behcet disease severity score. Among 55 selected patients, only 1 (1.8%) showed detectable virus in her serum. In the control group, 1volunteer (2.4%) had measurable serum B19 virus. No significant difference was found between patients and controls regarding to this finding. Also, the level of B19 DNA in serum was not correlated to the disease severity.

Conclusion: We could not find any relation between BD and parvovirus infection. Disease severity was not affected by the level of virus in patients' serum. Search for parvovirus DNA in tissue samples may be more helpful to show the role of virus infection in BD.

2393

Management and Prognosis of Non-Pulmonary Large Arterial Disease in Behcet's Syndrome: A Reappraisal of 25 Patients From a Single Center. Hasan Tuzun, Emire Seyahi, Caner Arslan, Vedat Hamuryudan, Kazim Besirli and Hasan Yazici. University of Istanbul, Cerrahpasa Medical Faculty, Istanbul, Turkey

Background/Purpose: To assess management and prognosis in a cohort of 25 patients with non-pulmonary arterial aneurysms due to Behcet's (BS) syndrome by formally re-assessing their outcome at the present time.

Methods: We identified 25 (24 M/1F) BS patients with non-pulmonary aneurysms (n= 23) occlusions (n = 2) between 1996 and 2007. All patients fulfilled the International Study Group Criteria for BS. Aneurysms were demonstrated with CT or MRI after first line USG. Standard by-pass procedures were carried out in all patients except in 4 patients with small asymptomatic non-ruptured saccular aneurysms (2 aortic and 2 carotid arteries) which were treated with only medical therapy. For aneurysms located in the aortic bifurcation we preferred aortobiiliac bypasses. For the 6 extremity aneurysms we were able to ligate arteries. For the other 10 extremity aneurysms we used PTFE grafts for bypass procedures. All patients received immunosuppression with cylophosphamide and corticosteroids before the operation and continued in the postoperative period. All patients were examined between January and December 2010, paying special attention for new and anastomotic aneurysms and graft patency.

Results: There was one death and one lost to follow-up. The remaining 23 (92 %) patients were under follow-up after a mean of 7.4 ± 2.9 years following operation. Patients who had ligated arteries complained of mild to moderate claudication. Four (40 %) PTFE grafts occluded without severe complication. Three patients developed relapsing aneurysms elsewhere and 2 other had recurrence at the initial surgical site.

Conclusion: The surgical management of large non-pulmonary arterial complications of BS is quite satisfactory. The prognosis has significantly improved as compared to what we had previously reported, then a 33% mortality at 4 years, from the same center some years ago (1). When the false

aneurysm is in the infrarenal aorta, aortobiiliac bypass is the preferred surgical intervention. Extremity aneurysms can be treated with synthetic graft insertion, but occlusions can be seen. In selected cases ligation can give satisfactory results, however post-operative claudication is common. In some patients with small intact saccular aneurysm surgery may not be necessary. Patients must be prescribed to immunosuppressive therapy with cylophosphamide and corticosteroids before and after the surgical intervention in order to avoid BS activation.

Reference:

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2394

Long-Term Outcome of Arterial Lesions in Behçet's Disease: A Series of 101 Patients. David Saadoun[1], B. Asli[2], Bertrand Wechsler[2], Habib Houman[3], Guillaume Geri[2], Jean-Charles Piette[2], Zahir Amoura[2], Mathieu Resche Rigon[1] and Patrice Cacoub[2]. [1]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]CHU Pitié-Salpêtrière, Paris, France, [3]department of internal medicine hôpital la rabta Tunis Tunisie, France

Background/Purpose: The vasculitis of Behçet's disease (BD) is distinctive because of involvement of both arteries and veins of all sizes. The concept of vasculo-Behçet has been adopted for cases in which vascular manifestations are present and often dominate the clinical features. While venous manifestations are frequent and have been reported in many publications, data regarding arterial lesions in BD are rare and often isolated.

Methods: We reported the main characteristics, treatment and long-term outcome of 101 (12.3%) patients with arterial lesions among a cohort of 820 BD patients. Factors that affect prognosis were assessed by multivariate analysis.

Results: There was 93 (91.2%) male with a median age at diagnosis of BD of 33 [27–41] years. Arterial lesions included aneurysms (47.3%), occlusions (36.5%), stenosis (13.5%) and aortitis (2.7%). Lesions mainly involved aorta (n=25), femoral (n=23) and pulmonary (n=21) arteries. Patients with arterial lesions were more frequently of male gender (91.2% versus 62.4%, respectively, p=0.017) and had higher rate of venous involvement (80.4% versus 29.8%, respectively, p<0.001) compared to those without arterial manifestations. Thirty nine (38.6%) patients achieved a complete remission. In multivariate analysis, the presence of venous involvement [odds ratio (95% CI), 0.29 (0.08–1.11)] and arterial occlusive lesions [0.13 (0.01–1.25)] were negatively associated with complete remission. The use of immunosuppressants [3.38 (0.87–13.23)] was associated with the occurrence of complete remission. The 20-years survival rate was signicantly lower in BD patients with arterial involvement compared to those without arterial lesions (73% vs 89%, p<0.0001, respectively).

Conclusion: In conclusion, the long-term outcome of arterial lesions in BD is poor, especially in case of occlusive lesions and associated venous involvement. The use of immunosuppressants improved the prognosis.

2395

Immunosuppressants Reduce Venous Thrombosis Relapses in Behçet's Disease. anne Claire Desbois[1], Bertrand Wechsler[2], Jean-Charles Piette[3], Du Boutin[1], Zahir Amoura[4], Fabien Koskas[1], Patrice Cacoub[4] and David Saadoun[5]. [1]Department of Internal Medicine and 2Laboratory I3 Immunology, Immunopathology, Immunotherapy, UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [2]Hopital de la Pitie, Paris, France, [3]Paris, [4]CHU Pitié-Salpêtrière, Paris, France, [5]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France

Background/Purpose: Venous disease is more common than arterial involvement and its prevalence may account 14% to 39% of patients with Behçet's disease (BD) according to studies. Venous thrombosis in BD is a severe disorder which may affect many differents sites including inferior vena cava, superior vena cava, pulmonary artery, supra-hepatic vessels and cardiac cavities. Treatment and outcome of venous thrombosis in BD is not well defined.

Methods: Among a cohort of 820 BD patients, 296 patients (36.7%) [73.6% of male and the median (Q1-Q3) age was 30 (24–36) years] fulfilling the international criteria of BD and with venous thrombosis were reported. Factors associated with relapses of thrombosis and mortality were assessed.

Results: There was a total of 582 venous thrombosis events including 555 deep and 27 superficial thrombosis. Main deep thrombosis localizations included limbs (n=323, 55.1%), cerebral veins (n=77, 13.1%), pulmonary embolism (n=57, 9.7%), vena cava (n=63, 10.7%), Budd Chiari syndrome (n=14, 2.4%) and cervical veins (n=13, 2.2%). The mortality rate was 6.4% (19/296) after a median (Q1-Q3) follow up of 4.75 [2–7] years. In univariate analysis, death was associated with male gender (p=0.0088), cardiac involvement (p=0.026) and Budd Chiari syndrome (p=0.004). In multivariate analysis, factors that prevent relapses of venous thrombosis were immunosuppressants [HR 0.27 (0.14–0.52), p<0.001] and corticosteroids [HR 0.62 (0.40–0.97), p= 0.058].

Conclusion: Budd Chiari syndrome is the more severe venous involvement in our series of BD. Immunosuppressants use reduce the relapses of venous thrombosis in BD.

2396

Difference of Manifestations and Treatment Among Behcet's Syndrome Patients in the United States and Japan. Yuri Ohara[1], Mitsumasa Kishimoto[1], Tatsuo Kobayashi[2], Christopher Swearingen[3], M.T. Filopoulos[4], Yasuharu Tokuda[5], Hideto Oshikawa[2], Kazuki Yoshida[2], Masako Utsunomiya[2], Makiko Kimura[2], Masato Okada[1], Kazuo Matsui[2] and Yusuf Yazici[6]. [1]St. Luke's International Hospital, Tokyo, Japan, [2]Kameda Medical Center, Kamogawa City, Japan, [3]University of Arkansas for Medical Sciences, Little Rock, AR, [4]Hospital for Joint Diseases, New York, NY, [5]University of Tsukuba, Ibaraki, Japan, [6]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY

Background/Purpose: Several studies showed regional differences in Behcet's syndrome (BS) presentation. These differences may have consequences in treatment and prognosis. Purpose of our study is to compare BS cohorts from the U.S. and Japan for disease manifestations and treatment histories.

Methods: All BS patients seen in the NYU Hospital for Joint Diseases BS Center in the U.S., St. Luke's International Hospital and Kameda Medical Center in Japan between 2003–2010 were included in the analysis. The diagnosis of BS was made on clinical manifestation and expert opinion. Disease manifestations and treatment histories were reviewed at baseline visits and during follow up.

Results: We included a total 772 patients (the U.S. n=630 and Japanese n=142). Age at onset was significantly older in Japanese patients than the U.S. patients (average 46.85 vs 35.96). Japanese patients were significantly less likely to be female, have genital ulcers or arthritis, and more likely to have epididymitis, pulmonary disease, and HLAB51, B52, and A26 positivity. In addition, significantly more patients had been treated with sulfasalazine/mesalazine in Japan, while significantly more patients in the U.S. received NSAIDs, hydroxychloroquine, thalidomide, first-line immunosuppressants (azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil) and TNF inhibitors (etanercept, infliximab and adalimumab).

Conclusion: There are differences in clinical manifestations in our study. It revealed that the U.S. patients receive more aggressive treatments than in Japanese patients. These regional differences need to be taken into considerations when designing trials, treating patients and developing diagnostic criteria.

2397

Neuro-Behçet′s Disease in Brazil: Higher Incidence in Females and Atypical Manifestations. Livia A. Dutra[1], Celio R. Gonçalves[2], José L. Pedroso[1], Pedro Braga-Neto[1], Alberto A. Gabbai[1], Orlando G. P. Barsottini[1] and Alexandre W. S. de Souza[1]. [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]Universidade de São Paulo, São Paulo, Brazil

Background/Purpose: The type and frequency of systemic and neurologic manifestations of BD (Behçet′s disease) vary with ethnicity. In Brazil, BD occurs as sporadic cases. Here we describe clinical and radiological features of Brazilian patients of mixed ethnicity presenting neurologic manifestations of BD.

Methods: Medical records of 178 BD patients were reviewed from the two largest tertiary hospitals in the city of São Paulo, Brazil, between February 2009 and July 2010. Forty patients (22%) with neuro-Behçet's disease (NBD) were identified. Information about gender, clinical manifestations, cerebral spinal fluid analysis, electromyography, electroencephalogram and brain magnetic resonance imaging was collected.

Results: Among 40 NBD patients, 57.5% were female and parenchimal involvement was observed in 32 (80%). The brain stem was the most affected structure (42%). Neurological complaints were the first manifestations of BD in 7 (17.5%) patients. Other neurologic manifestation observed were: seizures

(27.5%), optic neuropathy (15.0%), isolated aseptic meningitis (15.0%), peripheral neuropathy (7.5%), cerebral venous thrombosis (7.5%) and spinal cord involvement (5.0%). Twenty two patients (55.0%) presented at lease one relapse and aseptic meningitis was the most common relapsing manifestation. No significant difference was found concerning the number of relapses between parenchymal and non-parenchymal groups. Cyclosporin use was not associated with a higher rate of NBD manifestations. A multivariate analysis that included disease duration, white cell count in spinal fluid, cyclosporine use, and immunosuppressive use at onset, age at NBD onset or optic neuritis did not reveal significant associations with relapses in NBD patients.

Conclusion: Brazilian patients with NBD present a different pattern of neurologic involvement when compared to other population groups with a higher prevalence of parenchymal involvement, aseptic meningitis, optic and peripheral neuropathy, and a higher rate of neurologic relapses. Furthermore, the frequency of cerebral venous thrombosis among Brazilian NBD patients is lower than the previously described.

2398

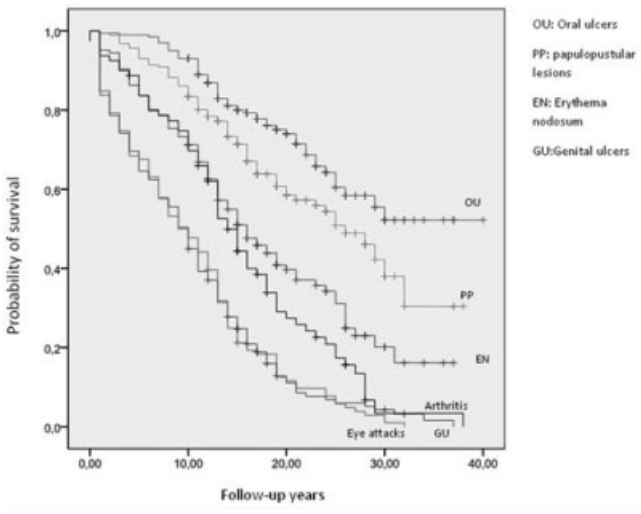
Some Manifestations Disappear Earlier Than Others in Behcet's Syndrome. F. Sevgi Sacli[1], Emire Seyahi[2], Serdal Ugurlu[3], Yilmaz Ozyazgan[2], Cem Mat[2] and Hasan Yazici[2]. [1]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]University of Istanbul, Cerrahpasa Medical Faculty, Istanbul, Turkey, [3]Rheumatology, Istanbul, Turkey

Background/Purpose: In a 20 year outcome study (1), we had observed that the frequency of all mucocutaneous lesions and arthritis decreased in frequency with the passage of time. In this study we investigated whether some manifestations disappeared before other lesions.

Methods: We studied consecutive BS patients who were seen in the dedicated BS outpatient clinic at Cerrahpaþa Medical Faculty in Istanbul between February 2009 and January 2011. Only BS patients whose disease duration and follow-up were 10 years or longer were included in the study. With the help of a questionnaire, patients were asked whether skin mucosa lesions, arthritis and uveitis attacks occurred for the preceding one year. If not, they were asked about the date when the manifestation occurred for the last time. Also a pathergy test was done to those who volunteered.

Results: We studied 202 (114 M, 88 F) patients. The mean age of the patients was 48 ± 8 and the mean disease duration 19 ± 6 years and the mean follow-up 17 ± 6 years. As seen in the Table, the frequency of those with any BS manifestation during the preceding one year including pathergy positivity was decreased significantly at the final visit compared to that found at the initial visit. Kaplan-Meier survival curve showed that, eye attacks were the first to cease followed by genital ulcers, arthritis and skin lesions. The most frequent lesion late during the disease course was oral ulcer, followed by the papulopustular lesions. The probability of continuing to appear still after 30 years of disease onset was 60 % for oral ulcers and 40 % for papulopustular lesions. Men and women showed a similar decreasing trend in all manifestations. A correlation matrix analysis done to see the associations between the last visit manifestations revealed that, the oral ulcers were associated with every lesions while arthritis with papulopustular lesions and eryhthema nodosum.

Figure. Kaplan Meier survival plot for duration of BS manifestations



Conclusion: In BS, some disease manifestations disappear earlier than others. These findings may have important pathogenetic and clinical implications. There has been debate whether the papulopustular skin lesions were, part of BS or whether they were non specific (2). However, the fact that papulopustular lesions continue to appear still late during the follow-up, show us that this lesion is in fact an inherent lesion of BS. Furthermore, the persistence of the well described papulopustular lesions - arthritis association (3), even late during the disease course, might also support the contention that these skin lesions are part of the syndrome rather than chance findings. Finally, since our survey was cross-sectional and retrospective, caution is required in interpretation.

Reference:

1) Kural-Seyahi et al. Medicine (Baltimore) 2003.
2) Jorizzo et al. J Am Acad Dermatol 1995.
3) Diri et al. Ann Rheum Dis. 2001.

2399

Spectrum of Cardiac Lesions in Behçet's Disease. Guillaume Geri[1], Bertrand Wechsler[1], Du Le Thi Huong[1], Richard Isnard[2], Jean-Charles Piette[1], Zahir Amoura[1], Mathieu Resche Rigon[3], Patrice Cacoub[1] and David Saadoun[3]. [1]CHU Pitié-Salpêtrière, Paris, France, [2]Department of Cardiology, CHU Pitié-Salpêtrière, 47–83 Boulevard de l'hôpital, 75651 Paris Cedex 13, Paris, France, Paris, France, [3]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France

Background/Purpose: Behçet's disease (BD) is a multisystemic vasculitis of unknown etiology. Cardiac involvement is rare in BD. Data regarding clinical presentation and outcome of cardiac involvement.in BD are lacking. The aim of this study was to describe the spectrum of cardiac lesions in a large cohort of patients with BD.

Methods: We reported a series of 52 consecutive patients with cardiac involvement fulfilling the international criteria of BD. Multivariate analysis was performed to determine factors associated with complete remission of cardiac involvement in BD.

Results: Among a cohort 807 BD patients, 52 (6.4%) had a cardiac involvement. They were mostly of male gender (86.5%) Mean age at diagnosis was 33.5±16.5 years and cardiac involvement was the first feature of BD in 17 patients (32.7%). Main types of cardiac lesions included pericarditis (n=20; 38.5%), endocardium involvement [mostly aortic insufficiency] (n=14 26.9%), intracardiac thrombosis [right atrium or ventricule] (n=10; 19.2%), myocardial infarction (n=9; 17.3%), endomyocardic fibrosis (n=4, 7.7%) and myocardial aneurysm (n=2, 3.8%). BD patients with cardiac involvement had a higher mortality rate at 5 years compared to those without (16.5% vs 4.2%, p=0.03). Eight patients died after a mean follow up of 3.3±2.7 years [myocardial infarction (n=2), sepsis (n=2), bacterial endocarditis (n=1) and unknown (n=3)]. Large-vessel vasculitis and deep-vein thrombosis occurred more frequently in patients with cardiac involvement than in those without (42.3 vs. 11.1, p<0.0001 and 59.6 vs. 35.8; p<0.005, respectively). Factors associated with complete remission of cardiac involvement were the use of immunosuppressants and colchicin, and oral anticoagulation.

Conclusion: Cardiac lesions involved 6% of our BD patients and are associated with a poor outcome.

2400

Is It Possible to Maintain Remission After Suspension of Infliximab for Sight- and Life-Threatening Involvement in Behcet's Disease? A Proposal of a Tapering Schedule. Rosaria Talarico, Anna d'Ascanio, Laura Bazzichi and Stefano Bombardieri. Rheumatology Unit, Pisa, Italy

Background/Purpose: Behcet's disease (BD) is a systemic vasculitis tipically characterized by recurrent oral and genital ulcers. Ocular and central nervous system (CNS) involvement are worrying complications of the disease and traditional therapies frequently fail to reduce its exacerbations, or to stop its progression. Literature data show growing data reporting effectiveness of TNF-alpha blockers in inducing remission for ocular and CNS involvement in BD. Poor data are available on maintaining remission after suspension of therapy.

The primary aim of this study was to assess the efficacy of Infliximab (IFX) in maintaining remission after suspension of therapy in a cohort of BD patients with severe ocular and CNS involvement. The secondary aim of the study was to quantify the mean number of infusions performed until suspension.

Methods: Among twenty-seven BD patients receiving IFX and prospectively studied, we selected 9 subjects (mean ± SD disease duration: 11±5 yrs) with a minimum period of 12 months of complete remission (defined as the absence of ocular or CNS relapses) according to medical decision. Outcome definition consisted of ophthalmological examination, visual field and/or fluorescein-angiography and/or optical coherence tomography for ocular involvement and neurological examination and magnetic resonance imaging for CNS involvement. After the first 8 infusions, the tapering schedule of suspension was characterized by an administration every 8 weeks for three infusions and then after 10 weeks.

Results: IFX was administered as an intravenous infusion of 5 mg/kg in 4 patients and 3 mg/kg in the others, at time 0, at week 2, 6 and then every 6 weeks; concomitant therapies were: methotrexate in 6 patients, none in 3 and in all low doses of steroids. Indications to start treatment were: ocular involvement in 6 patients (retinal vasculitis and posterior uveitis in all cases) and CNS involvement in 3 (ischemic pons-mesencephalon lesions in 2 subjects and one case of meningoencephalitis with brainstem involvement). At 24 months follow-up after IFX suspension complete disease remission was maintained in all but one cases; one patient who relapsed two months after autonomously withdrawal without any tapering, was successfully promptly retreated and he is still receiving IFX. The mean number of infusions before stopping IFX was 12±3 (min:9, max:15), with a mean period after remission of 14±3 months.

Conclusion: Although further long term follow-up controlled studies are needed to define a standardized duration of infusions, IFX seems to be effective for maintaining remission for ocular and CNS involvement due to BD also after suspension, particularly when gradually tapered. At the moment, we are prospectively validating this tapering schedule in further BD patients with ocular and CNS involvement.

2401

Neurological Involvement in Behcet's Disease: A Worrying Cause of Morbidity and Mortality. Rosaria Talarico, Claudia Ferrari, Anna d'Ascanio and Stefano Bombardieri. Rheumatology Unit, Pisa, Italy

Background/Purpose: Neurological involvement represents a worrying complication of Behcet's disease (BD), constituting an important cause of morbidity and mortality.

The primary aim of the study was to assess the prevalence of neurological involvement in a cohort of patients with BD, who have been followed in the last twenty years in our Institution. The second aim was to evaluate the time interval between BD onset and the onset of neurological involvement. The third aim was to compare the subset of patients with Neuro-BD with the other patients of the cohort.

Methods: One hundred and twenty patients were studied; the males/females, ratio was 1.6:1, with a mean disease duration of 11±5 yrs. Their mean age was 42±7 years (min:18, max:77), while the mean age at disease onset was 25±4 years (min:10, max:58). Prevalence of neurological findings demonstrated by MRI were retrospectively analysed in all patients (pts).

Results: Neurological involvement was observed in 34% (41 patients, 32 males and 9 females; mean age at the onset 25±4 years). The most common presenting symptoms among pts who experienced central nervous system involvement were headache (n=40), behavioural changes (35), hemiparesis (31); pyramidal signs occurred in 15 pts, while sphincter disturbances were observed in 12. The other neurological findings were represented by: meningeal signs (7), optic neuropathy (5), hearing loss (4), seizures (4) and sleepiness: (3). Organic brain involvement, demonstrated by MRI was due to ischemic pons-mesencephalon lesions in 19 pts and to meningoencephalitis with brainstem involvement in the others. Peripheral nervous system involvement was confirmed by electroneuromyographic study in 4 pts, and consisted of peripheral neuropathy prominent in the lower extremities in all cases; we have also observed only 2 cases of endocranial hypertension. Excluding peripheral neuropathy, the onset of CNS involvement was in 2 pts after 1 years of the onset of BD, in 4 cases after 3 years, in 24 after 5 years and in 7 after 10 years. Comparing Neuro-BD with other pts who didn't experience neurological involvement, the only statistical significant difference in the prevalence of the typical features of disease was in the frequency of ocular involvement, that resulted less frequent in BD patients with CNS involvement.

Conclusion: Neuro-BD is more frequent in young males and it never represents a presenting feature of disease. The most frequent time of onset of neurological involvement seems localized after the first 5 years of disease. Since neurological involvement may result in severe functional disability or be a life-threatening disease, a careful follow-up during the first decade after the onset is strongly recommended.

2402

Consensus Statements for Management for Intestinal Behcet's Disease in Japan. Mitsuhiro Takeno[1], Reikou Watanabe[1], Hirotoshi Kikuchi[2], Masakazu Nagahori[3], Kazuyoshi Saito[4], Nagamu Inoue[5], Michiko Kurosawa[6], Yoshiaki Ishigatsubo[1] and Behcet's Disease Reserch Commitee of Japan[7]. [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Teikyo University, Tokyo, Japan, [3]Tokyo Medicai Dental University, Tokyo, Japan, [4]University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, [5]Keio University, Tokyo, Japan, [6]Juntendo University, Tokyo, Japan, [7]Yokohama, Japan

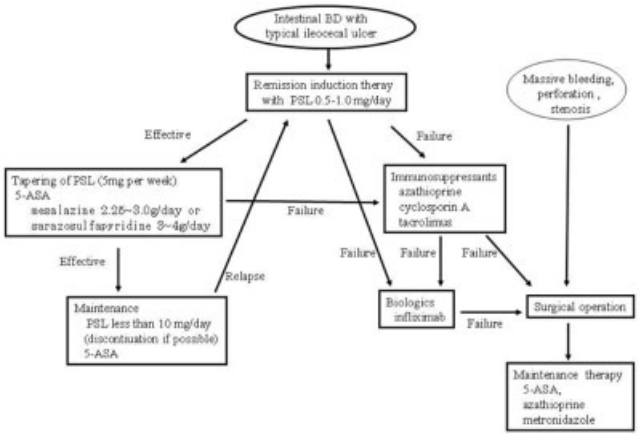
Background/Purpose: Intestinal lesions are found in 10 to 20 % of patients with Behcet's disease (BD) in Japan. It is sometimes hard to differentiate intestinal BD form inflammatory bowel diseases such as Crohn's disease. Moreover, the standard therapy has not been established. Therefore, it is necessary to establish clinical guideline from the diagnosis to the therapy.

Methods: We have previously developed consensus statements for the diagnosis and management of intestinal Behcet's disease using a modified Delphi approach in 2007.

The individual statements were re-evaluated by expert meeting members including 10 gastroenterogists, 4 rheumatologists, one general physician, and one pathologist, based on literatures, a nationwide epidemiological survey of infliximab (IFX) for intestinal BD patients, and individual clinical experience.

Results: The statements consist of diagnosis, assessment of clinical activity, treatment, and supplementary comments. Diagnosis of intestinal BD is made, when round or oval shaped deep ulcers are found in the ileocecal region by endoscopic or radiological examinations in patients who meet the 1987 Japan BD classification Criteria. Other types of intestinal lesions are distinguished from intestinal BD at the present. When patients have typical intestinal ulcer without extraintestinal lesions of BD, they should be carefully monitored. It is necessary to exclude infectious enteritis including tuberculosis, drug-induced enteritis as differential diagnosis. Clinical activity is comprehensively determined by systemic and local findings including endoscopic analysis, and laboratory data.

Recommended pharmacological therapies include corticosteroids, mesalasine, sulfasalazine surazosulfapyridine, and immunosuppressants such as azathioprine. Based on the favorable outcomes of the epidemiological survey, IFX is listed as an option in patients having refractory intestinal lesions to conventional therapies. Surgical operation is considered when massive bleeding, perforation, and stenosis occurred and when pharmacological therapies were insufficient. Algorithm of the therapies is summarized in the following figure.



Conclusions: The consensus statements provide helpful information for physicians who manage patients with intestinal BD.

2403

Measurement of Pain Perception in Children and Adolescents with Musculoskeletal Pain. Melissa Fraga[1], Claudio A. Len[1], Rafael Azevedo[1], Marcelo I. Yoguim[1], Maria Teresa Terreri[2] and Maria Odete E. Hilário[1]. [1]Universidade Federal de São Paulo/UNIFESP, São Paulo, Brazil, [2]Universidade Federal de São Paulo/UNIFESP, Sao Paulo, Brazil

Background/Purpose: The fact that musculoskeletal pain in childhood and adolescence is related to physical, emotional, familiar and cultural factors make both diagnosis and treatment real challenges in pediatric rheumatology. Therefore, the approach must be individual and based in the perception of each patient. Our aim was to measure the individual perception in hypothetical situations related to physical pain, emotional pain (deprivation of the company) and pain related to medical procedures.

Methods: We evaluated pain perception in 150 children and adolescents (8–18 years), that were included in 3 distinct groups: 50 with polyarticular juvenile idiopathic arthritis (JIA), 50 with idiopathic musculoskeletal pain (IMP) and 50 healthy children (without clinical history of chronic or recent acute pain). Pain perception was measured by 3 vignettes that illustrated life situations related to pain: physical trauma (bicycle fall), medical procedure (needle injection) and social isolation; the scores were measured by a 100 mm visual analogical scale (VAS). The evaluation also included 3 questionnaires: CHAQ, PedsQL 4.0) and the Pediatric Pain Coping Inventory (PPCI).

Results: JIA patients presented worse physical ability (measured by the CHAQ) when compared to IMP patients ($p<0{,}0001$). On the other hand, we observed lower scores in the IMP group in all aspects of health related quality of life ($p<0{,}0001$), including the physical domain. Concerning individual perception of pain, children and adolescents with IMP presented higher scores in the 3 pain situations ($p<0{,}0001$). With respect to pain coping, the 5-factor solution of the PPCI (cognitive self-instruction, seek social support, strive to rest and be alone, cognitive refocusing and problem-solving self-efficacy), children with IMP had worse scores in all of them, excluding cognitive self-instruction ($p<0{,}001$).

Conclusion: Our data reinforce the belief that the treatment of musculoskeletal pain should be performed by a multidisciplinary team, not just based on the use of analgesics. The perception has pain is personal and involves physical, emotional and social aspects. We also conclude that a focused education is required for pain coping, once the attitudes taken by children and adolescents in the presence of pain are not always for its control.

2404

Development of a Quality Patient-Health Care Provider Communication Scale Based On Patients' Perspective. Elizabeth G. Salt, Leslie J. Crofford, Jamie L. Studts, Robert W. Lightfoot and Lynne Hall. University of Kentucky, Lexington, KY

Background/Purpose: Effective patient-provider communication is an important component of quality health care for patients with rheumatoid arthritis (RA) (Lempp et al., 2006). Existing measures of patient-provider communication in samples of patients with RA have significant limitations (Berrios-Rivera et al., 2006; Smith et al., 2006). The aims of this study were to: devise a measure of the quality of patient-provider communication based on patients' perspectives; and evaluate the psychometric properties of this measure in a sample of patients with RA in a university clinic setting.

Methods: Items were developed from focus group sessions and individual interviews with 15 patients with RA. The participants described dimensions of quality patient-provider communication. The item pool generated was reviewed by experts in scale development and rheumatology. Final adjustments to the measure were made after six patients with RA provided feedback on item readability and ease of comprehension. A cross-sectional volunteer sample of 150 RA patients was recruited to evaluate the reliability and validity of the measure. A subset of 99 patients completed the measure again two weeks later to evaluate test-retest reliability.

Results: For the 21-item *Patient-Health Care Provider Communication Scale* (PHCPCS), the estimate of internal consistency was.89 using Cronbach's alpha, and the estimate of test-retest reliability over a 2-week time period was moderate ($r=0.52$, $p=0.01$, $n=99$). Two dimensions of the quality of patient-provider communication (*Quality Communication* and *Negative Patient-Health Care Provider Communication)* were identified using principal components analysis. The *Perceived Involvement in Care Scale* (Lerman et al., 1990) was moderately correlated with the PHCPCS ($r=0.34$, $p=0.01$) (Tables 1–2).

Table 1. Principal Components Analysis with Varimax Rotation of the Patient-Health Care Provider Communication Scale with Two Components Rotated ($N = 150$)

Items	I[δ]	II[δ]	Component[a]	
12.	Takes my health concerns seriously		.87	.03
10.	Pays attention to what I say about my health condition.		.85	.14
28.	Feel comfortable with the way my health care provider relays health information to me.‡		.83	.25
13.	Believes the symptoms that I report.‡		.82	−.02
23.	Treats me as she or he would want to be treated.		.81	.06
19.	Treats me with kindness.		.80	.12
24.	Approaches my treatment with a positive attitude.		.80	.15
22.	Explains my health condition in detail.		.77	.18
16.	Is patient.		.75	.17
3.	Answers my questions about my health.		.73	.01
11.	Tries to find the answers to my health problems.		.73	.08
7.	Understands my concerns about my health condition.		.72	.05
20.	Presents me with all of the treatment options.		.72	.13
21.	Is knowledgeable about my health condition.		.70	.05
14.	Is honest with me about my health.		.69	.02
8.	Is concerned about my understanding of my health.		.67	−.02
30.	Am able to make health-related decisions because of the information provided by my health care provider.		.60	−.07
27.	Feel comfortable telling my health care provider about my health concerns.		.59	.14
4.	Asks me questions so that he/she understands my health problems.		.54	.02
9.	Knows about my life outside of my health condition (stressors and joys).*		.45	−.15
25.	Is personable.*		.44	−.04
15.	Is decisive about their recommendations for my health condition.*		.43	.16
1.	Uses words I can understand to explain my health condition.*		.41	.10
2.	Uses written information, models, and pictures to help me understand my health condition.*		.35	−.14
18.	Talks down to me.‡		.21	.83
17.	Has been rude to me.		−.08	.83
6.	Makes me feel that I am bothering him/her with my medical concerns.		.05	.74
5.	Is in a hurry when he or she is seeing me.		.31	.73
29.	Have avoided telling my health care provider about my health because I am afraid of what they will think or say.		.49	.63
26.	Have questions about my health that I have not asked. *		.16	.34

[a] Component I= *Quality Communication*
* Component II= *Negative Patient-Health Care Provider Communication*
Items were deleted from the final scale because wording and lower component loadings.
‡ Items were deleted from the final scale because of inter-item correlations greater than.80.
[δ]↓lumns represent component loadings. Items with component loadings greater than.30 for Components I and II are underlined.

Table 2. Intercorrelations Among the Patient-HCP Communication Scale and Subscales and the Perceived Involvement in Care Scale (PICS) and Subscales[a].

Patient-HCP Communication Scale Total/Subscale	PICS Total Score	PICS Subscale Scores: Doctor Facilitation	Patient Information	Patient Decision-Making
Total Score	.19*	.34***	.08	−.04
Quality Communication	.27**	.38***	.15	.02
Negative Patient-Health Care Provider Communication	−.09	*.05*	−.10	−.14

[a] Sample size varies from 149 to 150 due to missing data.
* $p \leq .05$; ** $p \leq .001$; *** $p \leq .0001$

Conclusion: A measure of the quality of patient-provider communication was developed based on the patient perspective, and the measure demonstrated evidence of reliability and validity in a sample of patients with RA. This measure could assist health care providers in improving RA patient care by increasing our understanding of the effects of the interaction between patient and provider.

2405

"It's Totally Turned Around the Way I Think": The Patient Perspective of Cognitive Behavioural Therapy for Fatigue In Rheumatoid Arthritis. Emma Dures[1], Karen Kitchen[2], Celia Almeida[1], Nicholas Ambler[3], Alena Cliss[1], Alison Hammond[4], Bev Knops[3], Marianne Morris[1], Annette Swinkels[1] and Sarah Hewlett[1]. [1]University of the West of England, Bristol, United Kingdom, [2]University of Bristol, Bristol, United Kingdom, [3]Frenchay Hospital, Bristol, United Kingdom, [4]University of Salford, Salford, United Kingdom

Background/Purpose: RA fatigue is a common, overwhelming symptom caused by interacting clinical and psychosocial factors. Cognitive

behavioural therapy (CBT) addresses links between thoughts, feelings and behaviours and uses cognitive restructuring to help patients make behaviour changes. In a randomised controlled trial, group CBT for RA fatigue reduced fatigue impact and severity and improved perceived coping, mood and quality of life.[1] A nested qualitative study explored the nature of the processes and outcomes of the programme from the patient perspective.

Methods: After the end of each programme, a focus group with participants was run by researchers not involved in programme delivery (10 groups, 38 patients). Transcripts were analysed using a hybrid (inductive & deductive) thematic approach. Initial codes were generated, depicting patterns across the datasets, and combined to form themes. Analysis was by an independent researcher with a subset analysed by a research team member and a patient partner.

Results: 3 overarching themes were identified

"They made us work it out ourselves" (how the programme facilitated change). Patients spontaneously highlighted key elements of CBT as critical, including guided discovery and personal goal-setting ("we own our own plans and they've not been foisted on us"), peer support ("I think we all learnt something from each other") and steering by tutors ("they had to throw the ball into the court for us to pick it and what they have also had to do is stop us going off at a tangent"). Metaphors were memorable ("the picture [assertiveness] sort of stuck in my mind of this little submissive guy in the middle which was me and I thought a lot about that and I'm not like that at all now"). Fatigue itself was a barrier for some ("it was very tiring").

"Taking a different route" (the nature of changes). Cognitive changes included accepting RA fatigue ("you're never going to get back to optimum health because optimum health is actually a myth"). Emotional changes included being less volatile ("I was quite fiery but I've calmed down") and less fearful ("I'm not so scared of it [fatigue] now"). Greater self-efficacy and enhanced problem solving ("you analyse these things and then you can turn them around and make them work differently") led to perceived behaviour change and success ("I am managing my fatigue rather than the fatigue managing my life").

"My life has changed so much it's unbelievable" (benefits beyond fatigue). Patients re-engaged in previously abandoned activities, ("I got my life back again, you know it's nice, I enjoy myself"), with greater social participation ("I have turned outwards rather than inwards"), improved relationships ("how I am with my family, that has brought us quite a lot closer together") and being more active ("I actually feel more confident to try more things now").

Conclusion: Patients highlighted that CBT elements were key to making behaviour change, suggesting information alone would have been insufficient. Despite the focus on fatigue, benefits extended into wider life issues. Further research should examine whether this is due to the far-reaching impact of fatigue on daily life or the application of CB approaches to those issues.

[1] Hewlett et al. Ann Rheum Dis 2011;70:1060–7

2406

Factors Affecting Role Strain In Patients with Newly Diagnosed Rheumatoid Arthritis. Mary-Beth Coty[1], John A. Myers[1], Elizabeth G. Salt[2] and Said K. Abusalem[1]. [1]University of Louisville, Louisville, KY, [2]University of Kentucky, Lexington, KY

Background/Purpose: The purpose of the study was to examine the affect multiple roles, role stress, and key psychosocial variables (self-efficacy, social support) had on role strain in patients with rheumatoid arthritis (RA).

Methods: Eighty men and women newly diagnosed with RA (< 4 years) completed questionnaires that assessed roles stress (role conflict, role overload, and lack of role balance), social support, generalized self-efficacy, and role strain (psychological distress, absence of positive affect or life satisfaction). Descriptive statistics, correlation coefficients, and linear regression models were used during data analysis. Four linear regression models were used to determine if role conflict, role overload, and role balance independently predicted overall role strain, psychological distress, positive affect, and satisfaction with life. Self-efficacy and social support were then tested to determine whether they modified these relationships.

Results: This predominantly Caucasian female sample (73.8%) was educated (70.1% had at least some college), employed (58.8%), married or partnered (77.5%), and in their relationship for an extended time (24.42 years). The mean age and duration of disease was 54.2 years and 24.2 months, respectively. Role balance influenced each outcome ($p<0.001$). Role conflict only affected role strain ($p<0.001$) and no effect was found from role overload. Self-efficacy modified relationships with role strain ($p=0.002$) and life-satisfaction ($p=0.028$). Social support did not modify any relationships.

Conclusion: The findings from this study suggest that the degree of role strain is influenced by perceptions of role stress and feelings of being self-efficacious and less to do with support received from others. Few models exist describing the relationships among multiple role involvement and psychosocial variables that influence psychological well-being in patients with RA. This study makes significant progress towards our understanding of this important health topic

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2407

Integrating An Acceptance-Oriented Cognitive-Behavioural Therapy within Multidisciplinary Rehabilitation for Highly Distressed Patients with Arthritis: A Proof-of-Concept study. Johanna E. Vriezekolk[1], Rinie Geenen[2], Agnes M.M. Eijsbouts[1], Frank H.J. van den Hoogen[1], Hanneke Beenackers[1], Helma Slot[1], Wim G.J.M. van Lankveld[1] and Cornelia H.M. van den Ende[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Utrecht University, Utrecht, Netherlands

Background/Purpose: Targeting psychological distress is not common practice in rehabilitation. This study investigates the potential effectiveness and feasibility of an acceptance-oriented cognitive-behavioural therapy embedded in a multidisciplinary rehabilitation programme for rheumatic patients with high levels of psychological distress and impaired daily functioning despite adequate medical treatment.

Methods: Highly distressed adult patients with inflammatory rheumatic diseases or osteoarthritis referred for multidisciplinary treatment were included in this observational study. High levels of psychological distress was based on established cut-off scores for (sub)clinical levels of depressed mood and anxiety (IRGL). Primary outcome was psychological distress (yes/no). Other outcomes were quality of life (SF-36), acceptance (ICQ), and coping flexibility (COFLEX). Repeated measurements were taken before and after treatment, and at 1 year follow-up. Effect sizes (ES) were calculated. Individual changes were evaluated by the reliable change index (RCI) and clinically significant change (CSC) methodology. Feasibility of the programme was examined through evaluation of screening and admission patterns, attrition rates and patient satisfaction.

Results: Of 141 referrals, 87 (64%) were highly distressed. Thirty-five patients were eligible for treatment and 25 patients (mean age 51 (7.1), 76% female, 48% osteoarthritis) were enrolled in the study. Three out of every four patients who were highly distressed before treatment were not longer distressed after treatment and at 1 year follow-up. Reliable improvement to a well-functioning level for rheumatic patients was observed for almost half of the highly distressed patients. The SF-36 health domains improved to levels showing trivial to small deviations from the norm for rheumatic patients after treatment (mean ES = −0.15) and follow-up (mean ES = −0.17). A large increase of acceptance was found (ES >= 1.41). Attendance rate (> 95%) and patient satisfaction (ranging from 6.8–8.0) were high.

Conclusion: Preliminary evidence for the effectiveness of an acceptance-oriented cognitive-behavioural therapy embedded in a multidisciplinary rehabilitation programme for highly distressed patients with rheumatic diseases was demonstrated.

2408

Family Stress in Childhood of Patients with Fibromyalgia. Robert S. Katz[1], Sharon M. Ferbert[2], Ben J. Small[3] and Susan Shott[1]. [1]Rush University Medical Center, Chicago, IL, [2]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL, [3]Rush University Medical School, Chicago, IL

Background/Purpose: We explored the issue of childhood stress as a possible precipitating factor predisposing to FMS.

Methods: As a part of an Internet survey administered by the volunteer community fibromyalgia organization 763 female respondents with self-described FMS answered questions about various forms of childhood stress. The respondent selected one of the choices from 1 = not to 4 = often. Only women's responses were analyzed to eliminate confounding by gender. *To validate the Internet Survey, an identical rheumatology office questionnaire was administered to 115 FMS patients and 63 control patients with other rheumatic diseases*. The chi-square test of association was used to compare percentages and the Mann-Whitney test was done to compare FMS respondents and controls with respect to age and frequency ratings. A 0.05 significance level was used and all tests were two-sided.

Results: In the Internet survey the mean respondent age was 49.8 ± 11.4 years. FMS respondents had higher frequency ratings than controls for emotional trauma (2.6 ± 1.2 vs. 1.9 ± 1.2, $p < 0.001$), loud arguments between parents (2.3 ± 1.2 vs. 2.0 ± 1.1, $p = 0.005$), verbal abuse (2.3 ± 1.2 vs. 1.8 ± 1.1, $p < 0.001$), feeling neglected (2.2 ± 1.2 vs. 1.8 ± 1.1, $p < 0.001$),excessive parental drinking (2.0 ± 1.3 vs. 1.6 ± 1.0, $p = 0.017$)), physical trauma (2.0 ± 1.1 vs. 1.5 ± 1.0, $p < 0.001$),witnessing domestic violence (1.8 ± 1.1 vs. 1.5 ± 1.0, $p = 0.005$) and sexual abuse (1.6 ± 1.0 vs. 1.4 ± 0.9, $p = 0.040$)). FMS respondents had lower frequency ratings than controls for maternal affection (3.0 ± 1.0 vs. 3.3 ± 1.0, $p = 0.002$) and paternal affection (2.7 ± 1.1 vs. 3.1 ± 1.1, $p < 0.001$).

In the rheumatology office questionnaire the mean age was 48.1± 12.3 years for FMS patients and 50.7 ± 13.6 for control patients ($p = 0.092$). 81.7% of the FMS patients and 61.9% of the control patients were women ($p = 0.004$). FMS patients had worse frequency ratings than control patients for emotional trauma (2.2± 1.3 vs.1.5± 0.9, $p<0.001$), loud arguments between parents (2.2± 1.2 vs. 1.8± 1.0, $p = 0.031$), verbal abuse (1.9± 1.2 vs. 1.5± 0.9, $p = 0.008$), feeling neglected (1.7± 1.1 vs. 1.3± 0.8, $p = 0.013$), physical trauma (1.6± 1.0 vs. 1.3± 0.7, $p = 0.009$), sexual abuse (1.4± 0.9 vs. 1.1± 0.3, $p = 0.002$), and maternal affection (3.3± 0.9 vs. 3.6± 0.8, $p = 0.027$). There was no statistically significant difference between FMS and control patients with respect to witnessing domestic violence (FMS 1.5± 0.9 vs. control 1.4 ±0.8, $p = 1$), how often the mother was in the home (FMS 4.0 ±0.2 vs. controls 4.0 ±0.3, $p = 0.52$), how often the father was in the home (FMS 3.7 ± 0.8 vs. controls 3.8 ± 0.7, $p = 0.43$), paternal affection (3.0 ± 1.0 vs. 3.1 ± 1.0, $p = 0.69$), or excessive parental drinking (1.9± 1.2 vs. 1.7± 1.1, $p = 0.22$).

Conclusion: FMS patients experienced frequent stress during childhood, including more emotional and physical trauma, loud arguments between parents, verbal abuse, more feelings of neglect, more sexual abuse, and less maternal and paternal affection, compared to controls. Stress during childhood may be a major factor predisposing to FMS.

2409

Childhood Social Ostracism in Fibromyalgia. Afton L. Hassett[1], Sharon M. Ferbert[2], Susan Shott[3] and Robert S. Katz[3]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL, [3]Rush University Medical Center, Chicago, IL

Background/Purpose: Multiple investigations related to early life stress in fibromyalgia (FM) have reported high rates of physical, sexual, and emotional abuse**.** Other chronic stressors, however, have rarely been evaluated. Social ostracism during grade school years could produce emotional and physiological consequences. Herein, we present preliminary data that childhood social ostracism could be another early life stressor worth assessing in patients with FM.

Methods: 763 female respondents with self-described FM and 115 denying FM diagnosis (controls) completed an online survey in which questions related to childhood social interactions were queried. Only the women's responses were analyzed to eliminate confounding by gender. Respondents were allowed to endorse more than one option. The online questionnaire was developed by the volunteer organization Advocates for Fibromyalgia Funding, Treatment, Education and Research (AFFTER). Percentages were compared using the chi-square test of association with a 0.05 significance level.

Results: Participants were predominantly married (64.5%) or divorced (14.3%), with a mean age of 49.8 ± 11.4 years. When asked about their childhood, FM respondents were significantly more likely than controls to report having been a loner (31.6% vs. 12.2%, $p < 0.001$), having had no friends (7.1% vs. 0%, $p = 0.003$), having had difficulty making friends (34.7% vs. 17.4%, $p < 0.001$) and keeping friends (16.4% vs. 3.5%, $p < 0.001$). In contrast, 49.8% of FM respondents indicated that most of the children they knew liked them, which is not significantly different from the 47.8% rate for controls. Similarly, the difference between the 30.3% of FM respondents and 35.7% of controls who reported having had many friends was not significant.

Conclusion: A subgroup of FM patients (approximately one third) likely experienced social ostracism during their childhood years. The lack of social support, loneliness and even bullying associated with having few or no friends can have long-term emotional and physiological consequences that could play a role in the manifestation of FM. Approximately one half recalled good social adjustment in childhood and could represent a more resilient subgroup of individuals with FM.

2410

The Role of Pain and Depression in Self-Reported Fatigue/Energy in Systemic Lupus Erythematosus. Feridey N. Carr[1], Perry M. Nicassio[2], Dilrukshie Cooray[3], Ioana Moldovan[4], Emmanuel P. Katsaros[5], Karina D. Torralba[6], Shuntaro Shinada[7], Meenakshi Jolly[8], Mariko L. Ishimori[9], Alisa L. Wilson[9], Daniel J. Wallace[10] and Michael H. Weisman[11]. [1]California School of Professional Psychology at Alliant International University—Los Angeles, Alhambra, CA, [2]UCLA, Los Angeles, CA, [3]Harbor UCLA Medical Center, Torrance, CA, [4]Loma Linda Univ Medical Center, Loma Linda, CA, [5]Loma Linda Univ, Loma Linda, CA, [6]University of Southern California-Los Angeles County Medical Center, Los Angeles, CA, [7]USC Keck School of Medicine, Los Angeles, CA, [8]Rush University Medical Center, Chicago, IL, [9]Cedars Sinai Medical Ctr, Los Angeles, CA, [10]Cedars-Sinai/UCLA, Los Angeles, CA, [11]Cedars Sinai Med Ctr, Los Angeles, CA

Background/Purpose: Fatigue is reported by 50 to 80% of patients (pts) with systemic lupus erythematosus (SLE)[1]. Pain is also a common problem. Studies have shown that levels of depression are higher in pts with SLE [2]. This study examined the contribution of pain and psychological distress to fatigue.

Methods: 125 Caucasian and Hispanic adult pts with SLE were recruited from 4 medical centers in Los Angeles. Demographic data along with measures of disease activity and psychological functioning were collected. The Systemic Lupus Activity Questionnaire (SLAQ) evaluated patient-reported disease activity, while the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) assessed lupus activity. Psychological functioning was evaluated using the Patient Health Questionnaire (PHQ-9) and the Helplessness and Internality Subscales of the Rheumatology Attitudes Index. A subscale of the SF-36, Vitality, measured energy. A visual analogue scale for fatigue (FVAS) and visual analogue scale measuring pain (PVAS) were also utilized.

Results: Two hierarchical regressions were conducted. Ethnicity, age, annual income, and education were also included as variables in the model.

In the first analysis where fatigue was the dependent variable, ethnicity was entered in the first step, followed by age, income and education on step 2, PVAS, SLAQ and SLEDAI at step 3, and psychological factors at step 4. At step 1, ethnicity was significant, R^2 change =.15, $F(1,123) = 21.63$, $p<.001$, be = -.39, $p <.001$, with Caucasians reporting more fatigue. At step 2, no demographic variables were significant. At step 3, PVAS, SLEDAI and SLAQ were significant when entered as a block, R^2 change =.56, $F(3,117) = 77.54$, $p<.001$. However, the contribution of pain independently explained a large amount of variance, be =.73, $p<.001$. At step 4, depression was significant, R^2 change =.03, $F(3,114) = 5.26$, $p<.01$, be =.25, $p<.001$.

In the second analysis, energy was the dependent variable and the sequence was repeated. At step 1, ethnicity was again significant, R^2 change =.14, $F(1,123) = 20.08$, $p<.001$, be =.38, $p<.001$, with Hispanics reporting more energy. At step 2, demographic variables were not significant when entered as a block, R^2 change =.04, $F(3,120) = 2.01$, $p=.117$. However, age was independently significant, be = -.20, $p<.05$. At step 3, PVAS, SLEDAI and SLAQ were significant when entered as a block, R^2 change =.23, $F(3,117) = 15.08$, $p<.001$. Of those variables, only pain uniquely predicted energy, be = -.4, $p<.001$. At step 4, depression was significant, R^2 change =.09, $F(3,114) = 6.72$, $p<.001$, be = -.33, $p<.001$.

Conclusion: Both pain and depression are strong predictors of fatigue. This was confirmed when pain and depression were negatively correlated with energy. As pain often interacts with psychological factors, these results support a need for clinical assessment of pain and depression among pts with SLE.

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2411

Piloting a Patient Health Questionnaire Depression Screening Tool in a Hospital-Based Multi-Disciplinary Lupus Clinic. Su Jin Kim[1], Pretima Persad[2], Monica C. Richey[2], Mavis Seehaus[1], Roberta Horton[1], Kyriakos A. Kirou[2], Doruk Erkan[2] and John Barnhill[3]. [1]Dept. of Social Work Programs - Hospital for Special Surgery, New York, NY, [2]Mary Kirkland Center for Lupus Care—Hospital for Special Surgery, New York, NY, [3]Division of Psychiatry—Hospital for Special Surgery, New York, NY

Background/Purpose: Studies have demonstrated that patients with Systemic Lupus Erythematosus (SLE) exhibit high levels of depression, which can adversely affect adherence to medical treatment and health outcomes. Due to increasing reports of depression from our patients, we

piloted the Patient Health Questionnaire (PHQ-9), a nine item depression screening inventory. Our goal was to more accurately assess depression among our Lupus Clinic population to provide appropriate interventions for mental health services.

Methods: Adult patients seen in our Lupus Clinic completed a self-administered PHQ-9 Depression Screening Tool provided by a Nurse Practitioner. Once scored, all patients were referred to the Social Work Manager (SWM) for an assessment and appropriate referrals. Patients scoring in the *minimal (score 1–9) or moderate (10–19) depression* ranges received a psychosocial assessment (psycho-educational counseling related to depression); they were also provided with a mental health resource sheet with referrals. If open to receiving a referral, patients were given specific mental health agency referrals through 1–800-LIFENET, a mental health referral line. Patients who requested a mental health referral were followed closely by the SWM by telephone to see if an appointment was received. Patients who scored in the *severe (20–27) depression* range and/or exhibited any active suicidal ideations were initially assessed by the SWM and then evaluated that same day by our Psychiatric Liaison.

Results: Fifty patients (mean age: 37 +/− 14 [18–74]) were screened (88% Female; 52% Caucasian, 38% African American, 10% Asian; 48% Hispanic). Forty-eight (96%) were English speakers; 40 (80%) were low income, with Medicaid as their primary insurance. The table shows the distribution and mean age of patients among the different levels of depression based on their PHQ-9 Scores. Twenty patients (40%) were provided with specific mental health referrals as per their requests; 18/20 (90%) that requested referrals reported initiating mental health services and actively attending psychotherapy and/or psychiatry.

Level of Depression	# of Patients (%)	Mean Age +/− SD	Mean PHQ-9 Score +/− SD
None (0)	3 (6)	51.3 +/− 4.6	0
Minimal (1–9)	24 (48)	34.2 +/− 14.8	5.3 +/− 2.2
Moderate (10–19)	19 (38)	36.7 +/− 13.7	13.8 +/− 2.7
Severe (20–27)	4 (8)	48.5 +/− 17.6	22.8 +/− 1.5

Conclusion: This pilot depression screening initiative indicates the potential effectiveness of a self-report screening tool (PHQ-9) in a population of chronically-ill patients with lupus. We found that depression is common in the lupus clinic population and that these patients will not only agree to seek psychiatric treatment but will generally be able to access it. Our results outline the increased need to regularly screen lupus patients for depression as it can impact on their overall disease and quality of life. The PHQ-9 screening tool as well as our triage system may serve as a useful model that can be incorporated into routine lupus patient assessments.

2412

The Challenges of Being a Father with Systemic Sclerosis. Janet L. Poole[1], Donna Haygood[2] and Cindy F. Mendelson[1]. [1]University of New Mexico, Albuquerque, NM, [2]Bernalillo Public Schools, Bernalillo, NM

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune connective tissue disease that affects multiple systems and results in thickening of the skin, vascular insufficiency and fibrotic changes in the muscles, joints and internal organs. SSc is a rare disease primarily affecting women. However, men also have SSc. The mean onset of SSc is between 30–50 years of age which are peak years when men are becoming or being fathers. The role of a father can be impacted in many ways by this chronic illness and its unpredictability. Despite the severity of SSc, little is known about the impact this illness has on parenting especially being a father. Therefore, the purpose of this qualitative study is to describe the impact of scleroderma on the role of a father.

Methods: Ten fathers with scleroderma that had children 18 years of age and younger living with them at least 50% of the time, participated in this study. The mean age of the fathers was 44.80 years; mean disease duration was 3.76 years. Ninety percent were married, 60% worked full time, and the mean number of children was two. Fathers completed demographic questionnaires and were interviewed over the telephone. The interviews consisted of questions regarding the aspects of SSc that interfered with their ability to parent, situations in which SSc interfered with their ability to parent, what would make parenting easier, advice for other fathers, and support that makes being a father easier. The interviews were tape-recorded and transcribed verbatim. Content analysis was used to determine the primary codes and a summary statement generated for each code. Working from the summary statements the data was aggregated into two key themes with a single overarching theme.

Results: The overarching theme, *I'm still Dad* described the feelings of the fathers that scleroderma does not negate the fact or importance of parenting. Daily tasks and daily routines change but the fathering role stays constant. The two key themes that emerged from the findings related to the *emotional impact of the illness* and the *day to day realities of the illness*. The unpredictability and rareness of the illness lead to ongoing feeling of isolation and the fear of the mortality of the illness. The daily activities fathers participated with their children changed related to fatigue, vascular and musculoskeletal physical changes. Even though the men had physical challenges, support systems in place helped them to complete day to day routines.

Conclusion: Being a father with scleroderma has positive and negative influences. The negative effects are the inability of the fathers to participate in all of the physically activities the children enjoyed such as outdoor sports and throwing a ball. Being able to take time to spend quality time with the child was a positive influence of the illness.

ACR/ARHP Poster Session C
ARHP Health Services Research
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

2413

Development of a Care Pathway for Inflammatory Arthritis. Shona P. Lee[1] and David Kane[2]. [1]Adelaide and Meath Hospital Inc National Children's Hospital, Dublin 24, Ireland, [2]Adelaide, Meath hospital Dublin (incorporating the National Children's hospital), Dublin 24, Ireland

Background/Purpose: To develop a care pathway for patients with newly diagnosed inflammatory (IA) arthritis at a Dublin teaching hospital. Routine waiting lists and standard outpatient appointments do not serve the challenge of effective management of IA as per international guidelines.

Methods: A change management approach was adopted for implementation of this project. Following consultation with all of the multidisciplinary team, outpatient review appointments by medical doctors, clinical nurse specialist, physiotherapist and occupational therapist were arranged on a phased basis for the first year of treatment, for patients with a diagnosis of IA. Evidence based care informed the development of this pathway. Outpatient visits occurred monthly for the first 3 months and three monthly thereafter for first year. A health professional clinic was part of this pathway whereby all newly diagnosed patients were seen and assessed by allied health professionals at one visit. Outcome measures were agreed. A process for patient self referral back for triage/ urgent review via a telephone helpline was facilitated. Data was collected on an excel spreadsheet.

Results: The care pathway facilitates timely and appropriate assessment and treatment from all of the multidisciplinary team. Appointments are facilitated at an urgent review clinic when the patient needs it, as opposed to when the old system dictated.

Conclusion: Development of the care pathway facilitates holistic care where education, appropriate treatment, necessary medication changes, psychological support and measurement of outcomes can be made in line with international guidelines regarding optimal treatment of pts with newly diagnosed inflammatory arthritis.

2414

Online Access for Patients to Their Electronic Medical Record: Advantages, Drawbacks and Preconditions According to Care Providers. Rosalie van der Vaart[1], Constance H.C. Drossaert[1], Erik Taal[1] and Mart AF van de Laar[2]. [1]University of Twente, Enschede, Netherlands, [2]Medisch Spectrum Twente & Twente University, Enschede, Netherlands

Background/Purpose: Technology currently makes it possible to provide patients access to their own electronic medical record (EMR) from the hospital. The purpose of the study was to see if professional practice is ready for this possibility, by mapping the vision of rheumatology care providers on (dis)advantages and preconditions of this service.

Methods: 18 semi-structured in-depth interviews with 9 nurses (and nurse practitioners) and 13 rheumatologists were conducted. The main aim of the dialogues was to get insight into the motives that care providers have for the acceptation of the possibility to give patients online access to their medical record. Questions were related to the advantages and disadvantages they perceived, the preconditions that they would set and the content that should (or should not) be available to their patients, according to them.

Results: Overall care providers show a very mixed opinion on this topic. Most did see advantages of giving patients access to their medical record. These include: (1) an increase in patients' knowledge, autonomy and

involvement in treatment, (2) improvements in communication, (3) opportunities for the patient to look back on medical data and to show it to relatives and their GP, (4) an increase in trust and service offered to the patient and (5) increased patient safety through check-ups of the record by the patients. Yet, most care providers also reported a number of disadvantages, including: (1) a risk of causing fear, turmoil or patients drawing wrong conclusions because of problems with interpretation of (lab)data and difficulties with jargon, (2) a higher workload, (3) an overflow of questions by patients about the EMR during consult, which causes time constraints or delay in consults, and (4) it would be unpleasant and undesirable if patients read their notes. Important preconditions of this service are therefore: good security of data, careful considerations on if, when and how data will be presented to patients and presumably a filter on parts of the EMR.

Conclusion: According to care providers, giving patients access to their medical record might be a valuable next step into patient empowerment and patient safety, provided that there is optimal security and careful consideration of the content and presentation of the data.

2415

Anti-Tumor Necrosis Factor Dose Escalation Among Biologic Naïve Rheumatoid Arthritis Patients in Commercial Managed Care Plans in the Two Years Following Therapy Initiation. Machaon Bonafede[1], Kathy M. Fox[2], Kathleen L. Wilson[1] and Shravanthi R. Gandra[3]. [1]Thomson Reuters Healthcare, Cambridge, MA, [2]Strategic Healthcare Solutions, LLC, Monkton, MD, [3]Amgen Inc, Thousand Oaks, CA

Background/Purpose: This study estimates dose escalation patterns over the first and second years of therapy among biologic naïve rheumatoid arthritis (RA) patients initiating tumor necrosis factor inhibitor (anti-TNF) therapy with etanercept (ETN), adalimumab (ADA), or infliximab (INF) using real-world managed care claims data.

Methods: Commercially insured non-elderly adult (age 18–65) RA patients initiating anti-TNF therapy between July 1, 2005 and April 30, 2009 were identified using the MarketScan Commercial Claims and Encounters Database. The new use of ETN, ADA, or INF was the index event. A six month pre-index period was used to describe baseline patient characteristics and to identify new anti-TNF use. Patients were excluded if they had a condition for which an anti-TNF therapy was indicated (other than RA) or contraindicated during the pre-index period, including but not limited to psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, HIV, multiple sclerosis, lupus, or cancer. Patients were included if they remained on therapy for 12 months, without switching or having a therapy gap of greater than 60 days. Dose escalation was evaluated in the subset of patients persistent on index therapy for 12 and 24 months. Doses for ETN, ADA, or INF were calculated based on an average weekly dose (AWD). Dose escalation was defined as having at least one average weekly dose (AWD) that was 15%, 30%, or 50% higher than the initial AWD. For INF, the initial dose was defined as the AWD for the fourth infusion. Differences were evaluated using chi-square tests for proportions.

Results: A total of 2,909 patients met the inclusion criteria (mean age 50 years [SD=10] and 74% female). The patients were geographically dispersed with more patients in the South (44%) than in the North Central (28%), West (17%) or East (11%) regions of the US. The majority of patients (79%) lived in an urban area. Nearly half of the patients (47%) initiated anti-TNF therapy with ETN, 33% initiated with ADA, and 20% initiated with INF. During the pre-index period, the three treatment cohorts had similar Deyo Charlson comorbidity index scores (1.07–1.12) and prevalence of methotrexate use (71%–75%), glucocorticosteroid (57%–61%) use or analgesic use (34%–37%). Patients took an average of 8.6 unique medications during the 6 months prior to initiating anti-TNF therapy. Initial AWD were 48mg for ETN, 21mg for ADA, and 52mg for INF. Dose escalation rates for ETN, ADA, and INF were consistent between treatments across years 1 and 2 (see table).

Table. Proportion and magnitude of dose escalation

	Dose escalation rates over a 12 month period			Dose escalation rates over a 24 month period		
Dose escalation Method	ETN (n = 1322)	ADA (n = 1010)	INF (n = 577)	ETN (n = 514)	ADA (n = 401)	INF (n = 265)
115% higher than initial average weekly dose	4%	13%*	44%*	5%	18%*	59%*
130% higher than initial average weekly dose	3%	12%*	32%*	4%	17%*	43%*
150% higher than initial average weekly dose	1%	11%*	18%*	1%	15%*	28%*

$p<0.001$ compared to ETN

Conclusion: RA patients newly initiating ETN had significantly lower rates of dose escalation compared to patients initiating ADA or INF. This finding was consistent across dose escalation measures in both the first and second year following therapy initiation.

2416

Comparing Costs of Tumor Necrosis Factor Blockers Per Treated Patient for Psoriatic Arthritis Using Real-World Data in US Managed Care. Vernon F. Schabert[1], Shravanthi R. Gandra[2], Crystal Watson[2], Seth Goodman[1], Kathy M. Fox[3], Jason Yeaw[1], Sandra Milev[4] and David J. Harrison[2]. [1]IMS Consulting Group, Alexandria, VA, [2]Amgen Inc, Thousand Oaks, CA, [3]Strategic Healthcare Solutions, LLC, Monkton, MD, [4]IMS Brogan, Ottawa, ON

Background/Purpose: Tumor necrosis factor (TNF)-blockers etanercept (ETN), adalimumab (ADA) and infliximab (INF) are FDA approved for the treatment of psoriatic arthritis (PsA). However, they differ in their method of administration, dosing ranges and dosing frequency. These differences can lead to cost fluctuations that can be captured as cost per treated patient using real world data. This study describes annual costs of ETN, ADA and INF per treated PsA patient using real world data.

Methods: IMS LifeLink™ Health Plan Claims database was used to identify adult patients (≥18y) with ≥1 claim for ETN, ADA or INF between 11/1/2005–3/31/2009 (first claim in study period is index claim); including patients new to TNF blocker treatment (i.e., with no claims for a TNF blocker during the 180 days prior to index claim) and those continuing TNF blocker treatment. Patients had to have ≥360 days continuous plan enrollment following index claim (follow-up) and ≥180 days prior to index claim.

In the 180 days prior to index claim, patients had to have a PsA diagnosis, but were excluded if they had a diagnosis of rheumatoid arthritis, psoriasis, ankylosing spondylitis, Crohn's disease, ulcerative colitis or juvenile idiopathic arthritis. Patients were followed until end of study period (3/31/2010) or plan disenrollment.

Mean monthly dose was computed for patients on therapy; wholesale acquisition costs were applied to mean monthly dose and Medicare Physician Fee Schedule was applied to related drug administrations. Costs from restarting index TNF blocker therapy after discontinuation and costs from switching to a different TNF blocker were attributed to patients' index TNF-blocker therapy.

Results: Overall, 3,738 patients with PsA (2,295 ETN, 864 ADA and 579 INF), were identified. Median age ranged from 46.6–48.2 years, with 42–50% female. The 1-year mean cost per treated patient for all patients was lowest for ETN-$14,163, followed by ADA-$18,418 and INF-$24,276. For biologic-naïve patients, mean cost per treated patient was $13,447 ETN, $17,614 ADA and $23,329 INF. For patients continuing biologic therapy, cost per treated patient was $14,476 ETA, $19,098 ADA and $24,806 for INF.

Conclusion: When comparing cost per treated patient across commonly used TNF blockers with different modes of administration and dosing frequencies, ETN has the lowest cost for PsA patients using actual utilization data from US commercially-insured population.

ACR/ARHP Poster Session C
ARHP Research Methodology
Tuesday, November 8, 2011, 9:00 AM–6:00 PM

2417

Measuring Fear of Progression in Patients with Systemic Sclerosis. Linda Kwakkenbos[1], Frank H.J. van den Hoogen[1], José Custers[2], Judith Prins[3], Madelon C. Vonk[4], Wim G.J.M. van Lankveld[1], Eni S. Becker[2] and Cornelia H.M. van den Ende[1]. [1]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [2]Behavioural Science Institute, Clinical Psychology, Radboud University, Nijmegen, Netherlands, [3]Department of Medical Psychology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [4]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Although concerns about the future are often expressed by patients with systemic sclerosis (SSc)(1), as yet no valid quantitative measure is available to assess the extent to which patients with SSc are troubled by those concerns. The purpose of the present study was to validate the Dutch translation of the Fear of Progression-Questionnaire Short

Form (FoP-Q-SF)(2) for patients with SSc. The FoP-Q-SF was originally developed for the assessment of FoP in breast cancer.

Methods: Measurement properties of the FoP-Q-SF were assessed using a cross-sectional design in which 215 patients with SSc were included. Patients completed the FoP-Q-SF as well as questionnaires on physical and psychological functioning.

Psychometric properties of the FoP-Q-SF were assessed using the COSMIN checklist (3).

Results: In total, 69 men and 146 women completed the questionnaires. Most patients (74.1%) were married or living as married. One-third of the patients were employed at time of the study, and 42 % received higher education. Mean time since onset of non-Raynaud symptoms was 9.2 years (SD=7.9). Mean FoP-Q-SF score in patients with SSc was 30.05 (SD= 8.97). There were no indications of floor- or ceiling effects. Confirmative factor analysis supported the single-factor structure of the questionnaire (χ^2 *(52)=96.84, p<.001, RMSEA =.064, CMIN/DF=1.86*). Cronbach's alpha was.86 for the questionnaire. Most of our a-priori determined hypotheses (13 out of 14, 92.8%, Table 1) were confirmed in the data, supporting the construct validity of the questionnaire.

Table 1. Hypotheses and correlations of variables with Fear of Progression Questionnaire-Short Form

HYPOTHESES	CORRELATION	P	CONFIRMED
Moderate to large positive correlation with:			
Anxiety (IRGL[a])	.59	<.001	Yes
Depressive symptoms (CES-D[b])	.58	<.001	Yes
Active problem-oriented coping (CISS[c])	−.01	.862	No
Moderate to large negative correlation with:			
Social functioning (subscale SF-36)	−.39	<.001	Yes
Role-emotional (subscale SF-36)	−.47	<.001	Yes
Mental health (subscale SF-36)	−.58	<.001	Yes
Small to moderate negative correlation with:			
Physical functioning (subscale SF-36)	−.25	<.001	Yes
Role-physical (subscale SF-36)	−.37	<.001	Yes
Bodily pain (subscale SF-36)	−.34	<.001	Yes
General health (subscale SF-36)	−.42	<.001	Yes
Vitality (subscale SF-36)	−.45	<.001	Yes
Age (years)	−.15	.031	Yes
Control variables (No or small correlation):			
Travel distance to hospital (kilometres)	.09	.185	Yes
Body height (centimetres)	−.15	.032	Yes

a.Impact of Rheumatic Diseases on General Health and Lifestyle
b. *Center for Epidemiologic Studies- Depression*
c.*Coping Inventory Stressful Situations*
a.*Medical Outcomes Trust Short Form–36*

Conclusion: Results of the present study demonstrate that the FoP-Q-SF is a useful and valid instrument for the measurement of fear of disease progression in patients with SSc. This is important since fear of progression is one of the most important stressors in these patients.

References

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2418

Construct Validity of Three PROMIS Instruments in An Arthritis Sample. Kirsten A. Nyrop, Bryce B. Reeve, Robert F. DeVellis, Darren Dewalt, Rebecca J. Cleveland and Leigh F. Callahan. University of North Carolina at Chapel Hill, Chapel Hill, NC

Background/Purpose: This study assesses the construct validity of PROMIS® (Patient-Reported Outcomes Measurement Information System®) measures of Physical Function, Pain and Fatigue, using data from an effectiveness study of the *Walk With Ease (WWE)* program for adults with self-reported arthritis/joint pain. Our approach derives from the Multitrait-Multimethod Matrix (MTMM) developed by Campbell and Fiske (1959) -- the PROMIS measures must demonstrate both convergent (concepts that should be related theoretically are related in reality) and discriminant validity (concepts that should *not* be related theoretically are *not* related in reality).

Methods: At baseline, 415 *WWE* participants completed PROMIS measures via Computerized Adaptive Testing (CAT) -- Physical Function, Depression, Fatigue, Pain Impact, Sleep Disturbance, and Satisfaction with Social Role Participation. Participants also completed self-report measures routinely used to assess arthritis outcomes: Health Assessment Questionnaire (HAQ) and visual analogue scales (VAS) for Arthritis Symptoms (Pain, Fatigue and Stiffness). Physical performance was assessed by measures traditionally used in arthritis trials: chair stands, 360° turns, leg stands, walking speeds, and 2-minute step test. Spearman correlations were analyzed to identify associations among variables.

Results: As hypothesized, PROMIS Physical Function and HAQ were correlated(r=0.67, p<.001), and both instruments correlated moderately well (r≥ 0.30) with most physical performance measures. All other PROMIS measures were not as highly correlated with the physical performance measures, with the exception of PROMIS Pain Impact which also correlated with HAQ (r=0.61, p<.001) (Table 1). As hypothesized, the highest correlations for PROMIS Pain and PROMIS Fatigue were with their respective VAS measures (r =0.59 and 0.65). Other PROMIS measures were not as highly correlated with the VAS measures (Table 2).

Table 1. Spearman Correlations between PROMIS Measures, HAQ and Physical Performance Measures

	HAQ	Chair Std 1	Chair Std 3	Turn Right	Turn Left	Leg Std R	Leg Std L	Normal Walk	Fast Walk	2-min Step
PROMIS Pain	0.61	0.34	0.35	0.30	0.32	0.16	0.15	0.26	0.36	0.28
PROMIS Fatigue	0.48	0.24	0.26	0.15	0.15	0.09	0.08	0.18	0.19	0.17
PROMIS Depress.	0.35	0.15	0.12	0.10	0.10	0.00	0.01	0.14	0.13	0.10
PROMIS Sleep D.	0.21	0.17	0.10	0.02	0.01	0.01	0.05	0.01	0.01	0.06
PROMIS Social R.	0.43	0.25	0.24	0.13	0.12	0.11	0.10	0.18	0.18	0.23
PROMIS PhyFunc	**0.67**	**0.38**	**0.41**	**0.40**	**0.40**	**0.27**	**0.25**	**0.44**	**0.50**	**0.39**
HAQ	1.00	0.43	0.44	0.44	0.45	0.25	0.28	0.51	0.54	0.35

Table 2. Correlations between PROMIS Measures and Self-Reported Arthritis Symptoms (Visual Analogue Scales)

	Pain	Fatigue	Stiffness
PROMIS Pain	**0.59**	0.43	0.53
PROMIS Fatigue	0.37	**0.65**	0.44
PROMIS Depression	0.29	0.43	0.29
PROMIS Sleep Dist.	0.22	0.36	0.28
PROMIS Social Roles	0.30	0.39	0.31
PROMIS Phy. Func.	**0.37**	**0.37**	**0.35**

Conclusion: PROMIS Physical Function's construct validity is suggested by its convergence with HAQ and by comparable correlations with physical performance measures. PROMIS Pain and PROMIS Fatigue construct validity are suggested by correlations with VAS measures for pain and fatigue, respectively—higher than all other PROMIS measures. This evidence supports the use of PROMIS measures for Physical Function, Pain and Fatigue as measures of disability and symptoms in an arthritis sample.

2419

Validity of SenseWear Armband to Estimate Energy Expenditure During Activities of Daily Living In Rheumatoid Arthritis. Marie Tierney[1], Alexander D. Fraser[2] and Norelee M. Kennedy[1]. [1]University of Limerick, Limerick, Ireland, [2]Mid Western Regional Hospital, Limerick, Ireland

Background/Purpose: In Rheumatoid Arthritis (RA), it is thought that the level of physical activity may be reduced due to many factors linked with the disease course. However, there is a lack of quality research in the area to confirm this. One of the methodological flaws in the research conducted to date centres on the use of physical activity outcome measures which are not validated in the RA population. The aim of this study is to assess the accuracy of the SenseWear Armband (SWA) to estimate energy expenditure in people with RA during activities of daily living (ADLs).

Methods: 14 (8 male, 6 female) subjects participated in this study. All had a confirmed diagnosis of RA in conjunction with American College of Rheumatology (ACR) criteria, were on a stable steroidal and disease modifying anti-rheumatic drug regime in previous 3 months, were ambulatory independently or with assistance of one unilateral aid, were over 18 years of age and were not

pregnant. Patients were recruited from the rheumatology outpatients' clinic of the Mid-Western Regional Hospitals, Limerick, Ireland. Each subject wore a SWA on the right upper arm and was fitted with the Oxycon mobile indirect calormetry system with facemask which acted as the criterion measure. Subjects performed a 75 minute standardised routine consisting of lifestyle and housework activities of varying intensities. Statistical analyses was performed using PASW (formally SPSS) version 18.0 for Microsoft Windows. Intraclass correlation coefficient (ICC) 2,1 and Bland and Altman analyses were used to assess the level of agreement between the two measures.

Results: 14 (8 male, 6 female) subjects participated in this study. Mean age±standard deviation and BMI±standard deviation was 64.43±6.80 and 26.9±3.4 respectively. The mean length of disease duration±standard deviation was 12.4±13.2 years. SWA is highly accurate at predicting energy expenditure in subjects with RA (ICC=0.85). Bland and Altman analysis also verifies this finding with SWA having a relatively small mean difference (182.48kJ), a small standard error of the mean difference (41.95 kJ) and 95% confidence intervals which are tightly centred around the mean difference (−273.11→ −91.84) when compared to indirect calorimetry. When the activities were grouped based on their intensity, SWA still accurately estimated the energy expenditure levels at all intensities. Activities of 3–5 METS showed an ICC of 0.76, activities of 2–3 METS showed an ICC of 0.81, while activities of 1–2 METS showed an ICC of 0.73.

Conclusion: This is the first occasion this tool has been validated for use in the Rheumatoid Arthritis population. The accurate findings of this study indicate that SWA can accurately be used as a measure of energy expenditure in individuals with RA during activities of daily living.

2420

mtDNA Haplogroups and Serum Levels of SOD2, Catalase and Gelsolin In the Osteoarthritis Disease. Ignacio Rego-Pérez[1], Mercedes Fernández-Moreno[1], Sonia Pértega[2], Carlos Fernández-López[1], Natividad Oreiro[1] and Francisco J. Blanco[1]. [1]INIBIC-Complejo Hospitalario Universitario A Coruña (CHUAC), La Coruña, Spain, [2]Epidemiology Unit. INIBIC-Complejo Hosp. Univ. A Coruña, La Coruña, Spain

Background/Purpose: To measure the serum levels of Manganese Superoxide dismutase (SOD2), Catalase and Gelsolin in order to evaluate their possible application as hypothetical biomarkers in OA together with the mtDNA haplogroups.

Methods: Serum concentrations of SOD2, Catalase and Gelsolin were measured by enzyme-linked immunosorbent assays (ELISAs) in 150 samples from Hospital Universitario A Coruña (77 healthy controls and 73 OA patients). Knee and hip radiographs from the subjects were classified according to Kellgren and Lawrence (K/L) scoring from Grade 0 to Grade IV. Appropriated statistical approaches were carried out in order to assess the incidence of diagnosis and haplogroups, as well as other clinical variables, such as radiologic grade, gender, age and body mass index (BMI), on serum levels of the described enzymes.

Results: Serum levels of SOD2 were significantly increased in OA patients (36378.36 ± 11161.54) compared with healthy controls (20830.11 ± 30811.08), regardless of gender, age and BMI ($p<0.001$), and the higher the radologic grade, the higher the serum levels of SOD2 ($p<0.001$). Serum concentration of Catalase showed a non significant trend towards higher levels in OA patients (21.88 ± 40.94) compared to healthy controls (14.50 ± 27.68), as well as increased levels in carriers of mtDNA haplogroup J ($p=0.027$). Finally, serum levels of gelsolin, an actin-binding protein related to oxidative stress and inflammation, appeared significantly decreased in OA patients (500999 ± 43888.70) compared to healthy controls (511752.99 ± 49709.35) ($p=0.008$), and significantly increased in carriers of the haplogroup U (520178.68 ± 38409.87) ($p=0.015$).

Conclusion: The results obtained support that local inflammation and, specially, oxidative stress are key processes in the OA disease, and SOD2 appears as a candidate biomarker for prognosis of OA. The influence of the mtDNA haplogroups on serum levels of Catalase and Gelsolin could arise from the described different performance of the OXPHOS system among the mtDNA haplogroups.

2421

The Hospital Anxiety and Depression Scale (HADS) Positive Affect Subscale: A Preliminary Evaluation of Its Utility for the Assessment of Resilience in Fibromyalgia. Afton L. Hassett[1], Chad M. Brummett[2], Jenna Goesling[2], Kevin Rakovitis[2], Daniel J. Clauw[3] and David A. Williams[4]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Michigan Health System, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI, [4]Univ of MI Hlth System-Lobby M, Ann Arbor, MI

Background/Purpose: Resilience factors like positive affect have been found to be even better predictors of outcome than negative factors like depression and anxiety in a number of medical populations. However, increasing interest in measuring positive affect in patients with chronic pain is often tempered by concerns about adding patient burden during assessment. Several widely used instruments commonly chosen to measure constructs like depression and anxiety also have positive affect scales, but few of these have been validated for pain states. The objective of this study was to assess the performance of a positive affect subscale contained within the Hospital Anxiety and Depression Scale (HADS) in a sample of patients with chronic pain.

Methods: 170 patients meeting ACR survey criteria for fibromyalgia (FM) completed the HADS, Positive and Negative Affect Scale (PANAS), Brief Pain Inventory (BPI), and the PROMIS Physical Function Short Form 1 (PROMIS SF1). The HADS is a 14-item self-report instrument with two 7-item subscales (anxiety and depression). The positive subscale consists of six items that assess positive emotions (e.g., I feel cheerful). The HADS positive affect subscale was analyzed for internal consistency with Cronbach's alpha. To evaluate convergent and discriminant validity, correlations between the HADS positive affect subscale score were calculated with similar and dissimilar constructs.

Results: Mean age for the participants was 46.3 (SD13.4) years. Most were female (63.5%). The HADS positive affect subscale had good internal consistency (0.79). Pearson correlations supported the validity of the HADS positive affect subscale as its score was significantly related to the PANAS positive affect scale ($r=0.62$, $p<.001$) and inversely related to the PANAS negative affect scale ($r=-0.52$, $p<.001$). Further, the relationships between the HADS positive affect subscale score and clinically relevant variables were significant including BPI pain severity, BPI pain interference and PROMIS SF1 (Table 1). Compared to the PANAS positive subscale and the HADS depression and anxiety subscales, the HADS positive affect subscale demonstrated similar or stronger relationships with clinically relevant measures (also in Table 1).

Table 1.

	HADS Positive	PANAS Positive	PANAS Negative	HADS Depression	HADS Anxiety
BPI Pain Intensity	−.329*	−.237*	.229*	.319*	.230*
BPI Pain Interference	−.460*	−.366*	.307*	.508*	.203*
PROMIS Physical Function	.476*	.358*	−.332*	−.551*	−.307*

*$p < 0.0001$

Conclusion: The HADS positive affect subscale is a promising measure of resilience in chronic pain patients like those with FM. In many instances, the HADS positive affect subscale had stronger associations with the clinical variables of interest than the other commonly used measures. In the case where the HADS is already in use, there will be no additional patient burden to calculate this measure.

2422

A Bayesian Mixed Treatment Comparison Demonstrates Differences Between Anti-Tumour Necrosis Factor Agents in Rheumatoid Arthritis. Susanne Schmitz[1], Roisin C. Adams[2], Michael Barry[2], Cathal Walsh[3] and Oliver M. FitzGerald[4]. [1]Department of Statistics,Trinity College Dublin, Dublin, Ireland, [2]National Centre for Pharmacoeconomics, Dublin, Ireland, [3]Trinity College Dublin and National Centre for Pharmacoeconomics, Dublin, Ireland, [4]St. Vincent's University Hospital, Dublin, Ireland

Background/Purpose: A number of tumour necrosis factor alpha antagonists (anti-TNF-α) are available to treat rheumatoid arthritis. All of these have demonstrated considerable efficacy in placebo controlled trials, but few head-to-head comparisons exist to date. This work's objective is to estimate the relative efficacy among licensed anti-TNFs in patients who have had an inadequate response to methotrexate. Different outcome measures are used to highlight the advantages of continuous measures in such methodologies.

Methods: A systematic review indentified randomized controlled trials comparing the efficacy of licensed anti-TNF-a agents to placebo at 24 weeks in patients who have had an inadequate response to methotrexate. Relative efficacy was estimated using Bayesian mixed treatment comparison (MTC) models. Three different outcome measures were used; Risk ratios of achieving an ACR20 and ACR50 response and the percentage improvement in HAQ score. 80% credible intervals are presented for risk ratios and HAQ improvement.

Results: 16 published trials were included in the analysis. All anti-TNFs show considerably improved efficacy over placebo. The MTC results also provide evidence of some differences in efficacy of the

anti-TNF-α antagonists. Etanercept appears superior to infliximab and golimumab; certolizumab to infliximab and adalimumab. The ACR results find evidence of certolizumab being more effective than golimumab. For HAQ improvement all anti-TNFs appear superior to infliximab and etanercept shows improved efficacy to adalimumab.

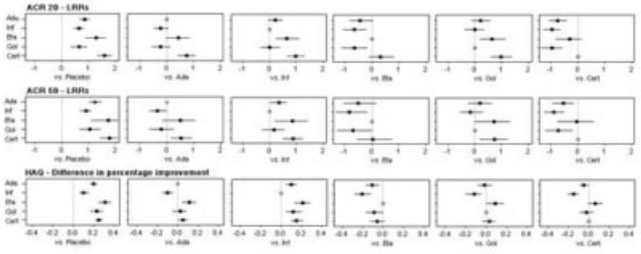

Figure 1. Graph for pair wise log risk ratios (LRRs) for ACR 20 and ACR 50 outcome and estimated HAQ improvement of anti-TNF against placebo and one another. Results are presented at 80% credible intervals.

Conclusion: There are differences in efficacy among the anti-TNF-α antagonists. In a MTC a continuous outcome measure has more strength to detect such differences than a binomial outcome measure, due to its enhanced sensitivity to change.

2423

Development of Quality Indicators for Physical Therapy in Hip and Knee Osteoarthritis. Wilfred FH Peter[1], Ph van der Wees[2], J. Verhoef[3], Z. de Jong[1], L. Vos[1], Wkha Hilberdink[4] and Tpm VlietVlieland[1]. [1]Leids University Medical Center, Leiden, Netherlands, [2]The Royal Dutch Society of Physical Therapy (KNGF) Amsersfoort, CAPHRI Maastricht University, IQ Healthcare, Nijmegen, Netherlands, [3]Hogeschool Leiden, Leiden, Netherlands, [4]Paramedical Center for Rheumatology and Rehabilitation, Groningen, Netherlands

Background/Purpose: In 2010 the revised version of the national Dutch physical therapy practice guideline for hip and knee osteoarthritis (OA) (www.kngfrichtlijnen.nl/654/KNGF_Guidelines_in_English.htm) was published. So far, little is known about its actual use in daily practice. The aim of this study was to develop quality indicators for physical therapy in hip and knee OA according to international criteria.

Methods: The use of quality indicators has been suggested as an appropriate method to estimate adherence to international guidelines (1). Guideline recommendations were rated for their relevance by an expert panel, transformed into indicators and incorporated in a questionnaire called Quality Indicators for Physical therapy in Hip and Knee OA (QIP-HKOA). After pilot testing among 15 PTs an adjusted version was administered to two groups of selected general PTs (n=134) en expert PTs (n=51) to test its discriminative power. In addition, the test-retest reliability of the questionnaire was evaluated in 118 PTs who subscribed to an educational course on the revised guideline who were asked to complete the questionnaire two times with a period of 7 days in between. Finally the internal consistency of the QIP-HKOA was calculated.

Results: The expert panel selected 19 recommendations, which were transformed into a questionnaire, which was slightly adjusted after pilot-testing. Thirteen items concerning treatment (12 items) and the diagnostic process (1 item) showed ceiling effects and/or did not discriminate between general and experts physical therapists and were excluded from the QIP-HKOA. For one of these items, concerning treatment (patient education), the proportion of physical therapists frequently following that item was $< 75\%$ in both groups. Therefore this item was included again. The final QIP-HKOA (containing 7 items) score (range 7–35)was significantly lower in 134 general physical therapists (23.06 SD 4.00) than in 51 expert physical therapists (27.04 SD 4.00) ($p< 0.000$). There was a high correlation (ICC 0.87) between the final QIP-HKOA scores of two time points of 46 physical therapists who completed the questionnaire twice. Cronbachs' alpha was 0.67.

Conclusion: The QIP-HKOA is feasible, valid, has a good test-retest reliability and discriminative power. Internal consistency was questionable. Its value in the measurement of the effectiveness of strategies to implement the guideline needs to be further determined.

Funding: This project is funded by the Royal Dutch Society of Physical Therapy and the Dutch Arthritis Association.

References:

(1) Campbell SM et al, BMJ 2003 Apr 12;326(7393):816–9.

2424

Patient Preference of Disability in Rheumatoid Arthritis. Li Alemo Munters[1], Nina Brodin[2], Elin Löfberg[2], Sara Stråt[2] and Helene Alexanderson[3]. [1]Rheumatology Unit,, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [2]Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Rheumatoid Arthritis (RA) affects the individual on many levels: impairment, activity limitation/ participation restriction and health related quality of life. Patient reported outcomes (PRO:s) have been recommended to be used in RA. The predefined PRO: s have not been as responsive or sensitive to pharmacological or exercise interventions as a patient preference outcome such as the McMaster Toronto Arthritis patient preference disability questionnaire (MACTAR). The aim was to investigate disabilities most important to improve in RA patients in Sweden by using the MACTAR and to compare the self selected disabilities to items in predefined measures for RA. Further aims were to categorize the identified disabilities using the International Classification of Functioning (ICF), to correlate the MACTAR to RA core set measures, and to evaluate test-retest reliability of the MACTAR over one week.

Methods: Forty-five RA patients attending rheumatologists at the Rheumatology Clinic, Danderyd Hospital, Stockholm, Sweden, during a 6 month period were included. They had a median (md) age of 59 years (Q1-Q3) 52–65 and diagnosis duration of md 10 years (4–21). They were assessed regarding disease activity (Disease Activity Score, DAS-28), lower and upper limb function (Timed Stands Test, TST, and Shoulder Function Assessment, SFA), pain (VAS), activity limitation (Health Assessment Questionnaire, HAQ) and Patient Global assessment of well-being (PGA) and patient preference (MACTAR), which was assessed twice within a week.

Results: The most important disabilities to improve were fatigue in relation to social life (n=26), walking (n=21) and sleep (n=19). Fourty-seven percent of the identified disablilities were represented in items of the Comprehensive ICF core-set for RA and 53% in the HAQ. All except one of the identified disabilities were categorized into the ICF activities and participation component. Correlations between the MACTAR were r_s −0.65 to the DAS 28, r_s −0.61 to pain, r_s −0.61 to the PGA, r_s −0.51 to the HAQ, r_s 0.38 to the SFA, and r_s −0.19 to the TST. Test-retest analysis with Weighted Kappa koefficient (K_w) and Intra class correlation coefficient were 0.59 and 0.82 respectively with no systematic differences (sign-test, p=0.22).

Conclusion: The MACTAR identified fatigue in relation to social activities, walking and sleep as the disabilities most important to improve for RA patients in Sweden. Moderate to low correlations were revealed between the MACTAR and RA core set measures. The MACTAR has very good test-retest reliability and could be considered as assessing disabilities important to the patient not covered by recommended RA outcomes.

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Sensitivity to Change of the Bristol Rheumatoid Arthritis Fatigue Scales. Sarah Hewlett[1], Emma Dures[1], John R. Kirwan[2], Fiona Cramp[1], Joanna Nicklin[3], Celia Almeida[1], Kathryn Mitchell[3] and Rosemary Greenwood[2]. [1]University of the West of England, Bristol, United Kingdom, [2]University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom, [3]University of Bristol, Bristol, United Kingdom

Background/Purpose: Fatigue in RA is a major problem and measurement is recommended in clinical trials. The Bristol RA Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ) is a validated 20 item patient reported outcome measure (PROM) (global score 0–70) with 4 subscales: Physical (0–22), Living with fatigue (0–21); Cognitive (0–15) and Emotional (0–12). Three single item numerical rating scales (BRAF NRS) measure fatigue Severity and Effect (0–10) and Coping (10–0).[1,2] This study examined their sensitivity to change.

Methods: RA outpatients given a single high dose of i/m glucocorticoids for clinical reasons, completed PROMs at weeks 0 and 2: BRAF scales, comparator fatigue PROMs [Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), Multi-dimensional Assessment of Fatigue (MAF), Profile of Mood States (POMS), Short Form 36 Health Survey Vitality Subscale (SF-36 VT)], VAS pain and global opinion of disease, and Health Assessment Questionnaire (HAQ).

Results: 42 patients participated: 34 female, mean age 56.7yrs (30–76, SD 12.6yrs), disease duration 10.7yrs (0.05–43, SD 10.7yrs); HAQ 1.875, (0–3, SD 0.65), pain 70.83 (SD 19.9) and global opinion 58.24 (SD 24.93). 15% MAF not scored due to missing data (POMS 9%, SF36 2%, BRAFs 1%). Baseline BRAF fatigue was high: BRAF-MDQ global

43.00/70 (SD 14.51), BRAF-Physical 16.80/22 (3.42), BRAF-Living 11.45/21 (5.60), BRAF-Cognitive 7.90/15 (4.3) and BRAF-Emotion 6.24/12 (3.63); BRAF-NRS Severity 7.15/10 (1.67), Effect 7.04/10 (2.32) and Coping 5.56/10 (low bad) (2.25).

Mean change and effect sizes (change/SD at baseline) show all scales sensitive to change except BRAF-NRS coping (Table 1).

Table 1.

	Mean change	95% confidence interval	P value for paired t test	Effect size
BRAF Global	−7.74	(−12.11, −3.38)	0.001	0.56
BRAF Physical	−2.89	(−4.59, −1.2)	0.001	0.54
BRAF Living	−2.32	(−3.69, −0.95)	0.001	0.53
BRAF Cognition	−1.20	(−2.34, −0.05)	0.041	0.33
BRAF Emotion	−1.34	(−2.34, −0.34)	0.010	0.42
BRAF NRS Sev	−1.25	(−2.07, −0.43)	0.004	0.47
BRAF NRS Effect	−1.25	(−2.09, −0.41)	0.005	0.46
BRAF Cope (Rev)	−0.13	(−1.03, 0.77)	0.771	0.05
SF36 (Rev)	7.68	(0.48, 14.88)	0.037	0.34
FACIT (Rev)	5.57	(2.43, 8.71)	0.001	0.55
POMS	−3.46	(−5.59, −1.32)	0.002	0.53
MAF	−5.34	(−8.65, −2.04)	0.002	0.57
Pain	−20.43	(−27.89, −12.96)	0.001	0.87
Global opinion	−7.93	(−15.81, −0.05)	0.049	0.31

Using a fatigue transition question as an anchor, BRAF-MDQ Global mean change was +3.57 for worse fatigue (SD 5.77, n=7) −2.42 for no change (SD 8.3, n=13) and −15.81 for less fatigue (SD 14.3, n=20); BRAF-NRS Severity was +0.29 (SD 1.38), 0.75 (SD 1.3) and −3.30 (SD 2.27); NRS Effect was +0.71 (SD 1.25), +0.39 (SD 1.9) and −3.0 (SD 2.39).

Conclusion: The BRAF MDQ, NRS Severity and Effect are sensitive to change. The BRAF Coping NRS was not sensitive to change after a pharmacological intervention. Along with the differential effect sizes in the BRAF-MDQ subscales, this supports the theory that fatigue consequences and coping are distinct concepts that require separate PROMs and interventions.

[1]Nicklin et al, AC&R 2010;62:1552–58
[2]Nicklin et al, AC&R 2010;62:1559–68

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Human Amniotic Membrane Stem Cells as an Alternative Cellular Therapy for Articular Cartilage Repair. Emma Muiños[1], Silvia Diaz-Prado[2], Tamara Hermida-Gómez[1], Esther Rendal[1], Isaac M. Fuentes[2], Francisco J. De Toro[1] and Francisco J. Blanco[1]. [1]INIBIC-CHUAC, La Coruña, Spain, [2]INIBIC-CHUAC/University of A Coruña, La Coruña, Spain

Background/Purpose: Amniotic mesenchymal stromal cells (hAMSC) and amniotic epithelial cells (hAEC) are progenitor cells that can be remove from the amniotic membrane. Human amniotic membrane (HAM) has an increasing interest for its use in the field of regenerative medicine. This is due to both cell types are capable to differentiate towards three germinal cell lines. It has large advantages over the others sources of progenitor cells: high availability, large size and no ethical problems regarding with its use. The aim of this study is to determine the useful of the hAMSC and the hAEC on regenerating human joint cartilage in an *in vitro* model.

Methods: HAM was used as support for the culture of hAMSCs or hAECs. Focal injuries in human joint cartilage biopsies were done. Later, a pellet of cells (hAMSCs or hAECs, depending on the repair model developed) was implanted into the focal defects of cartilage. HAM, with the cells grown on it, was placed in direct contact with the cartilage surface to be repaired. These implants were cultured in chondrogenic medium, for 8 weeks. The repair tissues were analyzed by histological and histochemistry techniques considering the *ICRS* macroscopic evaluation of cartilage repair.

Results: Both cell types had good appearance during their cultured on HAM and their transplant onto focal cartilage injuries. hAMSCs and hAECs penetrated into the nearby surface of the chondral defect. The Hematoxylin and Eosin staining displayed that hAMSC or hAECs pellet filled the chondral defect. There was a good integration between the repair tissue and native cartilage. Type II collagen and aggrecan stainings of repair tissue were slightly positive on the extracellular matrix, and positive inside the cytoplasm of the cells. The safranin O staining expressed the presence of proteoglycans. Finally, type I collagen stainings were weak or totally negative (Figure 1). We carried out an *ICRS* macroscopic evaluation of cartilage reparation to compare both kinds of progenitor cells in the *in vitro* model. hAMSCs displayed better degree of defect repair, greatest integration to border zone and, in general, higher repair assessment (Table 1).

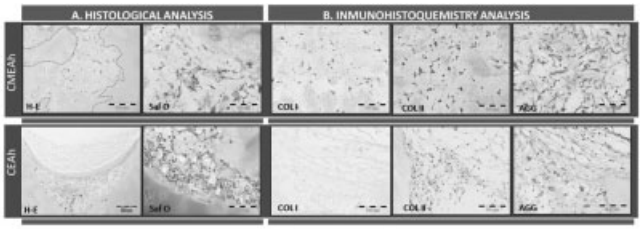

Figure 1: A) Histological and B) inmunohistoquemistry analysis. H-E (hematoxiline-Eosine), Saf O (Safranin O), COL I (Type I Collagen), COL II (Type II Collagen) and AGG (Aggrecan) staining methods.

Table 1. hAMSCs and hEACs means assessment considering the ***ICRS*** **histological visual scale.**

ICRS macroscopic evaluation of cartilage repair	hAMSCs mean	hEACs mean
Degree of defect repair	2.25 (±0.5)	1.5 (±0.58)
Integration to border zone	2.5 (±0.58)	1.75 (±0.96)
Macroscopic appearance	4	4
Overall repair assessment	8.5 (±0.58)	7 (±0.82)
	17.25 (±1.5)	14.25 (±2.06)

Conclusion: We get reduce the area of the defect with quality integration. The morphology of the repair tissue exhibited a fibrocartilaginous appearance and a high cellularity. hAMSCs showed better results *vs.* hAECs considering the *ICRS* macroscopic evaluation of cartilage repair. Support: SERGAS (PS07/84), Cátedra Bioibérica, University of A Coruña and ISC III CIBER BBN CB06-01-0040. FER. Xunta de Galicia.

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JAK2 Mediates the Stimulatory Effects of Transforming Growth Factor beta on Fibroblast Activation and Tissue Fibrosis. Clara Dees[1], Michal Tomcik[2], Katrin Palumbo[1], Alfiya Akhmetshina[3], Angelika Horn[1], Pawel Zerr[1], Oliver Distler[4], Georg Schett[1] and Jorg HW Distler[1]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [3]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [4]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Systemic sclerosis (SSc) is characterized by an uncontrolled activation of fibroblasts resulting in the release of excessive amounts of extracellular matrix components. Janus kinase 2 (JAK2) is a key-regulator of cytokine signaling and mutations in the JAK2 gene have been identified as key-event in the molecular pathogenesis of myeloproliferative diseases. In the present study, we evaluated the role of JAK2 in the pathogenesis of SSc and analyzed the potential of JAK2 inhibition as a novel anti-fibrotic approach.

Methods: Activation of JAK2 was determined by immunohistochemistry for pJAK2. Dermal fibroblasts were stimulated with TGFβ and incubated with the specific JAK2 inhibitor TG 101209 in different concentrations. Fibroblast activation was determined by staining for α-smooth muscle actin (αSMA) and stress fibers. Bleomycin-induced dermal fibrosis and tight-skin 1 (Tsk-1) mice were used to evaluate the anti-fibrotic potential of a specific JAK2 inhibition *in vivo*.

Results: Increased activation of JAK2 with prominent accumulation of pJAK2 particularly in fibroblasts was observed in skin of SSc patients. Of note, the activation of JAK2 persisted in cultured SSc fibroblasts. Inhibition of JAK2 by the selective JAK2 inhibitor TG 101209 or by

siRNA abrogated the activated phenotype of SSc fibroblasts by decreasing the formation of stress fibers by 41 ± 5 %, the expression of αSMA by 41 ± 6 % and the basal mRNA levels of col 1a1 and col 1a2 by 59 ± 4 % and 51 ± 3 % ($p < 0.05$ each). These inhibitory effects in the absence of exogenous stimulation were only observed in SSc fibroblasts, but not in resting healthy dermal fibroblasts. However, stimulation of healthy fibroblasts with TGFβ increased time-dependently the levels of pJAK2. Pre-incubation with TG 101209 abrogated the stimulatory effects of TGFβ on fibroblast activation with decreases in stress fiber formation by 74 ± 12 %, αSMA expression by 84 ± 11 % ($p < 0.05$) and reduced col 1a1 and col 1a2 mRNA levels by 90 ± 21 % and 92 ± 14 % ($p < 0.05$). In addition, the expression of the TGFβ target genes CTGF and PAI-1 was potently reduced. Consistently, inhibition of JAK2 exerted potent anti-fibrotic effects in experimental fibrosis. In the model of bleomycin-induced fibrosis, treatment with TG 101209 decreased dermal thickening by 95 ± 5 % ($p = 0.007$), hydroxyproline content by 76 ± 7 % ($p < 0.001$) and myofibroblast counts completely back to baseline levels ($p = 0.001$). Potent anti-fibrotic effects were also observed in the Tsk-1 model. Application of TG 101209 reduced hypodermal thickening, hydroxyproline content and myofibroblast counts by 82 ± 10 % ($p = 0.002$), 75 ± 25 % ($p = 0.03$) and 99 ± 13 % ($p = 0.01$).

Conclusion: We demonstrate that JAK2 is activated in SSc in a TGFβ-dependent manner and mediates the stimulatory effects of TGFβ on fibroblasts. Inhibition of JAK2 reduced collagen synthesis specifically in SSc fibroblasts, prevented fibroblast activation and exerted potent anti-fibrotic effects in experimental fibrosis. As inhibitors of JAK2 are currently evaluated in clinical trials for myeloproliferative disorders and are well tolerated, our findings might have direct translational implications and stimulate clinical trials with JAK2 inhibitors in SSc patients.

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RNAi Mediated Silencing of the Autoantigen hnRNP-A2 Dcreases Inflammatory Arthritis by Inhibiting Activation of Cells of the Mononuclear Phagocytic System. Sonja Herman[1], Jessy Presumey[2], Juergen Pfatschbacher[1], Wim B. Vandenberg[3], Florence Apparailley[2] and Gunter Steiner[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Hôpital Saint Eloi, Montpellier, France, [3]Radboud University Nijmegen Med Center, Nijmegen, Netherlands

Background/Purpose: HnRNP-A2 belongs to a heterogenous family of nuclear proteins importantly involved in mRNA trafficking, transcriptional and translational processes. Recent evidence let suggest that hnRNPs post-transcriptionally modulate expression of inflammatory mediators such as COX-2, TNF-a, IL-1b and iNOS by affecting mRNA stability and translation. Strong upregulation of hnRNP-A2 at sites of inflammation and the generation of antibodies and autoreactive T-cells against hnRNP-A2 in patients with rheumatoid arthritis (RA) and various arthritis models points towards a potential involvement of this protein in the pathogenesis of inflammatory arthritis.

Methods: Expression of hnRNP-A2 in tissues and cells was analysed by flow cytometry and immunoblotting. In-vitro silencing of hnRNP-A2 was studied in J77.4 cells. Collagen-induced arthritis (CIA) in DBA1 mice and K/BxN serum transfer arthritis in BL/6 mice were used as arthritis models. For silencing of hnRNP-A2 expression, siRNA containing lipoplexes were used, which were injected intravenously once a week. Control animals were treated with unspecifc siRNA/lipoplexes or PBS. Silencing efficiency was analyzed by immunobloting and real-time PCR. Arthritis was measured by an established clinical scoring system, inflammation and bone erosions were analyzed by histomorphometry.

Results: HnRNP-A2 was highly expressed in lymphoid organs such as lymph-nodes, spleen and thymus. Among cells of the immune system monocytes/macrophages showed the strongest expression of hnRNP-A2. Silencing of hnRNP-A2 in a monocytic cell line diminished the proliferative capacity of transfected cells.

Silencing of hnRNP-A2 in vivo revealed a 60%–70% silencing efficiency in lymph nodes and spleen of injected mice. Remarkably, incidence of arthritis in those mice, which were injected with hnRNP-A2 specific siRNA-lipoplexes, was only 20% as compared to 70 and 80%, respectively, in the control groups. Moreover, arthritis scores and weight loss differed significantly from control animals. Histological analysis of paws confirmed that both inflammation and bone erosion were significantly reduced in animals treated with hnRNP-A2 specific siRNA. Serum levels of cytokines typically produced by cells of the mononuclear phagocytic system such as TNF-α, IL-23 and IL-1 were strongly reduced. The effects observed were similar in both arthritis models indicating that hnRNP-A2 is crucially involved in the effector arm of autoimmune arthritis.

Conclusion: In-vivo silencing of hnRNP-A2 largely prevents induction of arthritis development by inhibiting activation of the mononuclear phagocyte system thereby diminishing the inflammatory immune response.

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A Functional *IRF5 V*ariant Predicts Prognosis in Patients with Systemic Sclerosis. Roozbeh Sharif[1], Maureen D. Mayes[1], Filemon K. Tan[1], Olga Gorlova[2], Laura K. Hummers[3], Ami A. Shah[3], Daniel E. Furst[4], Dinesh Khanna[5], Javier Martin[6], Lara Bossini-Castillo[7], Emilio B. Gonzalez[8], Hilda T. Draeger[9], Jun Ying[10], Sandeep K. Agarwal[1], Frank C. Arnett[1], Fredrick M. Wigley[3] and Shervin Assassi[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]University of Texas M.D. Anderson Cancer Center, Houston, TX, [3]Johns Hopkins University, Baltimore, MD, [4]UCLA Medical School, Los Angeles, CA, [5]University of Michigan, Ann Arbor, MI, [6]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [7]Consejo Superior de Investigaciones Científicas (CSIC), Armilla (Granada), Spain, [8]University of Texas Medical Branch, Galveston, TX, [9]Univ of TX Health Sci Ctr, San Antonio, TX, [10]University of Texas M. D. Anderson Cancer Center, Houston, TX

Background/Purpose: The first genome-wide association study (GWAS) in systemic sclerosis (SSc) demonstrated three non-major histocompatibility complex (non-MHC) susceptibility loci in *IRF5*, *STAT4*, and *CD247* regions. Our goal was to investigate the impact of these gene variants on survival and severity of interstitial lung disease (ILD) in SSc. We also examined the effect of the *IRF5* SNPs on its transcript expression in monocytes.

Methods: We examined 1443 Caucasian patients with SSc, enrolled in the GENISOS and Scleroderma Family Registry (n=914 –discovery cohort) and The Johns Hopkins Scleroderma Cohort (n=529-replication cohort). Demographic, clinical, and serologic data were recorded. Forced vital capacity (FVC) % predicted was used as a surrogate for ILD severity. All patients were genotyped by the Illumina Human610-Quad BeadChip. Five SNPs, *IRF5* (rs10488631, rs12537284, rs4728142), *STAT4* (rs3821236), *CD247* (rs2056626) reached genome wide significance in the SSc-GWAS and were examined in the current study. The primary outcome was survival. Cox proportional hazards regression model was used for survival analysis. Then, the correlation of the investigated SNPs with FVC% predicted at enrollment was examined by linear regression. Next, we explored the effect of the three investigated *IRF5* SNPs on transcript expression using gene expression microarrays. The transcript levels of *IRF5* in monocytes were examined conditional on the *IRF5* SNPs in SSc patients and unaffected controls.

Results: Overall, 15.5% of the patients had died over the follow up time of 5.5 years. The *IRF5* rs4728142 minor allele was predictive of longer survival in the discovery cohort (HR: 0.76, 95%CI: 0.60–0.96, $P=0.021$) and in the independent replication cohort(HR: 0.73, 95%CI: 0.54–0.99, $P=0.047$). This SNP was also associated with better survival in the combined cohort (HR: 0.75, 95%CI: 0.62–0.90, p=0.002), which remained significant even after Bonferroni's correction ($p_{corr}=0.01$). Moreover, the impact of this SNP on survival remained significant even after adjustment for age at disease onset, disease type, and autoantibody profile ($p=0.043$). The minor allele frequency of *IRF5* rs4728142 in the combined sample was 49.4%.

Moreover, *IRF5* rs4728142 minor allele correlated with higher FVC% predicted at enrollment ((b: 2.64, CI: 0.43– 4.84, $P=0.019$)), adjusted for disease duration. The other two *IRF5* SNPs, as well as *STAT4* and *CD247* polymorphisms were associated neither with survival nor with ILD severity. Finally, the *IRF5* rs4728142 minor allele was associated with lower *IRF5* transcript expression in patients and controls (p=0.014 and p=0.034, respectively), suggesting that the *IRF5* rs4728142 SNP may be functionally relevant.

Conclusion: This is the first study, linking a non-MHC genetic locus to survival and/or severity of ILD in SSc. A functional SNP in the *IRF5* promoter region (rs4728142), associated with lower *IRF5* transcript levels, was predictive of longer survival and milder ILD in patients with SSc. This finding supports the pivotal role of *IRF5* and related type I interferon pathways in SSc which could lead to identification of novel therapeutic targets and development of prognostic biomarkers.

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Feasibility, Safety and Clinical Effects of a Single Intradermal Administration of Autologous Tolerising Dendritic Cells Exposed to Citrullinated Peptides in Patients with Rheumatoid Arthritis. Ranjeny Thomas, Shayna Street, Nishta Ramnoruth, Helen Pahau, Soi Law, Marion Brunck, Claire Hyde, Brendan O'Sullivan, Christelle Capini, Ai Tran, Jennifer Ng and Sanjoy Paul. Univ of Queensland, Brisbane, Australia

Background/Purpose: Bone marrow-derived dendritic cells modified with the irreversible NF-kappaB inhibitor, Bay11–7082 (Bay-DCs), exposed to arthritogenic antigen, transfer antigen-specific suppression of inflammatory arthritis in mice, through induction of regulatory T cells. We carried out a phase I clinical trial of autologous peripheral blood (PB) Bay-DCs exposed to citrullinated peptide antigens (known as Rheumavax) in HLA-DR shared epitope (SE)+ anti-citrullinated peptide antibody (ACPA)+ rheumatoid arthritis (RA) patients. The aims of this phase I first-in-man study were to demonstrate feasibility and safety of autologous peripheral blood (PB) DC immunotherapy, and to describe its clinical and immune effects.

Methods: Bay-DCs were generated from 250ml PB under good laboratory practice (GLP) conditions after purification of PB mononuclear cells by density sedimentation, and PB monocytes by elutriation, then culture in the presence of RPMI, 10% human serum, 400U/ml GM-CSF and 800U/ml IL-4 and 2.5 uM Bay11–7082 for 60h. During the final 18h, cells were pulsed with a mixture of four citrullinated peptide antigens (cit-vimentin 447–455, cit-fibrinogen beta chain 433–441, cit-fibrinogen alpha chain 717–725, cit-collagen type II 1237–1249). Rheumavax was administered intradermally once to each group of 9 RA patients on usual disease modifying drugs (DMARDs) in 2 progressive vaccine dose levels (total of 18 vaccinated subjects) in an escalating dose regimen. Group 1 received 1 million DCs and group 2 received 5 million DCs on day 1 of study. Open label control group of 11 patients received usual DMARDs. The primary outcomes were 1. clinical, and 2. laboratory measures of safety and 3. citrullinated peptide-specific tolerance; the secondary outcome was clinical response. Patients were evaluated at baseline, monthly for 3 months and finally at 6 months.

Results: We recruited 29 SE+ ACPA+ patients with RA, including 18 females, with mean age 56 (range 38–76), mean disease duration of 5.4 (range 1–10) years, and treated with at least 1 DMARD, to the study. All Bay-DC cultures were sterile. Rheumavax was well-tolerated at both doses and did not provoke local skin reactions, lymphadenopathy, allergic reactions, infections or immediate disease flares. Adverse events were all grade 1 (of 4) severity and included headache (2), and laboratory evidence of anemia (3), lymphopenia (3), leukopenia (3) and elevated alkaline phosphatase (2) or AST (1). DAS scores decreased below 2.5, sometimes for prolonged periods, in 7/9 Rheumavax recipients who commenced the trial with DAS4vCRP>2.5. DAS scores were stable in 7/9 Rheumavax patients who commenced the trial with DAS4vCRP<2.5. Systemic effects of Rheumavax were demonstrated by reductions in CRP, ESR and the homeostatic model of insulin resistance (HOMA-IR). Immune tolerance outcomes will be discussed.

Conclusion: These data demonstrate the feasibility and safety of a single intradermal administration of autologous tolerising dendritic cells exposed to citrullinated peptides in RA patients.

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Genome-Wide Analysis of Imputed Genotypes Identifies Chemokine Receptor-1 *CCR1*) As a Novel Candidate Risk Locus in Behçet's Disease. Yohei Kirino[1], George Bertsias[1], Michael J. Ombrello[1], Duran Ustek[2], Colleen Satorius[1], Julie Le[1], Nobuhisa Mizuki[3], Yoshiaki Ishigatsubo[3], Emire Seyahi[4], F. Sevgi Sacli[4], Ahmet Gul[5], Daniel L. Kastner[1] and Elaine Remmers[1]. [1]National Human Genome Research Institute, National Institute of Health, Bethesda, MD, [2]Istanbul University, Istanbul, Turkey, [3]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [4]University of Istanbul, Cerrahpasa Medical Faculty, Istanbul, Turkey, [5]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

Background/Purpose: Behçet's disease (BD) is a genetically complex disease characterized by recurrent inflammatory attacks affecting the orogenital mucosa, eyes and skin. We have previously performed a genome-wide association study with 311,459 SNPs in 1,215 BD cases and 1,278 healthy controls from Turkey, and have identified independent associations with HLA-B*51, an additional MHC class I locus, *IL10*, and the *IL23R-IL12RB2* locus.

Methods: To identify additional BD susceptibility loci, we carried out whole-genome imputation using as a reference, 96 of the Turkish healthy controls genotyped on Illumina HumanOmni1M-Quad SNP chips. SNPs were excluded for deviation from HWE ($p<5\times10^{-4}$), low call rate (<95%), and low MAF (<5%). Imputation was conducted using MACH v1.0.15 providing 814,474 SNPs for analysis in the 1,215 BD cases and 1,278 healthy controls. Sequenom iPLEX assays were used to validate the imputation results and to fine map the associated region. Two independent replication sets were genotyped for the most significant SNP.

Results: Using a p-value cut-off of 1×10^{-5}, we identified 114 non-HLA gene SNPs suggestive of association with BD. One imputed SNP rs7616215 on chromosome 3, located ~38 kb from the 3' UTR of the chemokine receptor-1 gene (*CCR1*), (odds ratio [OR] 0.71, $p=1.9\times10^{-8}$) exceeded genome-wide significance ($P<5\times10^{-8}$). Fine mapping of the *CCR1* region confirmed the imputation results for rs7616215 and identified 2 additional SNPs in strong LD with rs7616215 that also exceeded genome-wide significance. The association of rs7616215 also replicated using additional Turkish and Japanese BD cases and controls (in a meta-analysis of 2,195 cases and 2,187 controls OR = 0.73, 95% CI 0.66–0.81, $p=1.8\times10^{-10}$). CCR1 belongs to the family of CC-motif chemokine receptors, is expressed on neutrophils, monocytes, and T lymphocytes and binds several chemokine ligands, including CCL5/RANTES, CCL3/MIP-1α, and CCL4/MIP-1β. A role for CCR1 has been characterized in several inflammatory conditions, such as rheumatoid arthritis, multiple sclerosis, and transplantation rejection. ENCODE data indicate that rs7616215 resides in a putative regulatory genomic domain, and analysis of *CCR1* transcripts from the HapMap European (CEU), Chinese (CHB) and Japanese (JPT) subjects showed that the protective minor allele (C) correlated with significantly increased *CCR1* expression ($p<0.03$).

Conclusion: We have identified *CCR1* as a novel risk gene locus in BD, with potential implications in regulation of inflammatory responses in the context of the disease.

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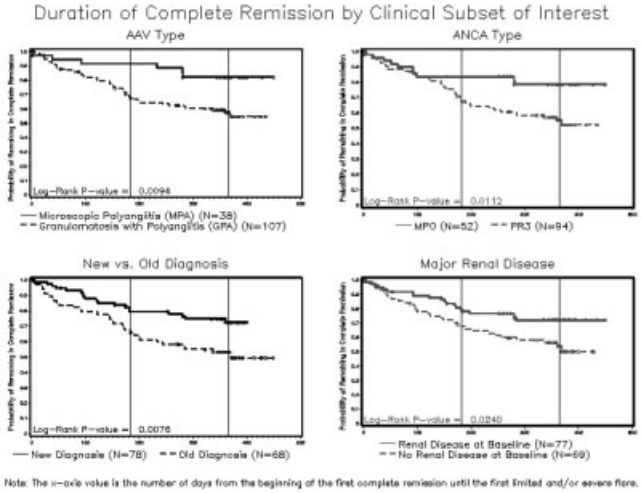
Extended Follow-up of Treatment with Rituximab Versus Cyclophosphamide for Remission-Induction of ANCA-Associated Vasculitis: Which Subsets Are At Greatest Risk for Flare? John H. Stone[1], Peter A. Merkel[2], Philip Seo[3], Robert Spiera[4], Carol A. Langford[5], Gary S. Hoffman[5], Cees GM Kallenberg[6], E. William St. Clair[7], Barri J. Fessler[8], Nadia Tchao[9], Lisa Webber[10], Linna Ding[11], Lourdes P. Sejismundo[12], Kathleen Mieras[13], David Ikle[14], Deborah J. Phippard[9], Brett Jepson[14], Alice Lail[14], Adam Asare[9], Noha Lim[9], Mark Mueller[15], Paul Brunetta[16], Nancy B. Allen[17], Fernando Fervenza[13], Duvuru Geetha[18], Karina Keogh[13], Eugene Y. Kissin[19], Paul A. Monach[19], Tobias Peikert[13], Coen Stegeman[6], Steven R. Ytterberg[13], Ulrich Specks[13] and for the RAVE-ITN Research Group[20]. [1]Massachusetts General Hospital, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Johns Hopkins Vasculitis Center, Baltimore, MD, [4]Hospital for Special Surgery, New York, NY, [5]Cleveland Clinic, Cleveland, OH, [6]University Medical Center Groningen, Groningen, Netherlands, [7]Duke University Medical Center, Durham, [8]Univ of Alabama-Birmingham, Birmingham, AL, [9]Immune Tolerance Network, Bethesda, MD, [10]National Institute of Allergy and Infectious Diseases, [11]NIAID, Bethesda, MD, [12]Johns Hopkins University, Baltimore, MD, [13]Mayo Clinic, Rochester, MN, [14]Rho, Chapel Hill, NC, [15]Food & Drug Administration, Bethesda, MD, [16]Genentech, So San Francisco, CA, [17]Duke University Medical Center, Durham, NC, [18]Johns Hopkins University, York, PA, [19]Boston University, Boston, MA, [20]Bethesda

Background/Purpose: Rituximab (RTX) is non-inferior to cyclophosphamide (CYC) for remission-induction in severe ANCA-associated vasculitis (AAV) [microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener's, GPA)] and superior for patients with relapsing disease. Understanding longer-term outcomes, particularly in certain disease subsets, is essential for optimizing AAV treatment. We evaluated the efficacy of one course of RTX compared to CYC followed by AZA over 18 months (M), with assessments of outcomes according to original treatment assignment, ANCA type, AAV type, renal disease, and relapsing disease at baseline.

Methods: A randomized, double-blind, placebo-controlled trial tested the hypothesis that RTX (375 mg/m^2 iv weekly × 4) was not inferior to CYC (2 mg/kg/d po) for remission-induction at 6 months [*N Engl J Med* 2010]. CYC was replaced by AZA and RTX by placebo between 3–6M if remission was achieved. Patients were followed for a minimum of 18M. Remission was defined as a Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG) of 0, and complete remission by BVAS/WG=0 off prednisone. Remission rates were compared for the following subsets using log-rank tests: new diagnosis vs relapsing disease at baseline; MPO- vs

PR3-ANCA; MPA vs GPA; and presence vs absence of major renal disease at baseline.

Results: Nine centers enrolled 197 patients with severe GPA or MPA (3:1), all positive for either PR3-ANCA or MPO-ANCA (2:1). At entry, 49% of patients had new disease, 52% had major renal disease. Complete remission was achieved and sustained at 6, 12, and 18M by 64%, 47%, and 39% in the RTX arm, vs 53%, 39%, and 33% in the CYC/AZA arm, respectively (P=0.NS). Disease flares in the two treatment arms did not differ in number/severity. No unexpected safety issues were detected. The Figure shows Kaplan-Meier plots for duration of complete remission for pre-specified disease subsets.



Patients at highest risk for flare had relapsing disease at baseline, no major renal disease, PR3-ANCA positivity, or GPA. Relapsing disease and no major renal disease subsets were enriched with PR3-ANCA-positive patients, who overlapped substantially with a diagnosis of GPA. Among RTX-treated patients who achieved complete remission, flares occurred only after the return of detectable levels of B cells.

Conclusion: A single course of RTX is as effective as 18 months of standard therapy (CYC followed by AZA) for remission induction and maintenance in severe AAV. Patients at increased risk for flares are identifiable by ANCA type, AAV type, absence of major renal disease at baseline, and prior flare history. Additional mechanistic studies may define the immunological events surrounding relapses more precisely.

ACR Concurrent Abstract Session
Biology and Pathology of Bone and Joint: Molecular Targets For an Effective Therapy
Tuesday, November 8, 2011, 2:30 PM–4:00 PM

2433

Compromised Expression of the Complement Membrane Inhibitor CD59a Propagates Age-Related Joint Degeneration in Mice. Vishal Paringe[1], Anja C. Bloom[1], Ernest Choy[1], Bryan P. Morgan[1] and Anwen S. Williams[2]. [1]Cardiff University, Cardiff, England, United Kingdom, [2]Cardiff University, Cardiff, United Kingdom

Background/Purpose: The influence of complement-mediated innate immune responses on cartilage and bone homeostasis in the ageing joint have not been studied. Inappropriate complement-mediated cell damage is prevented by membrane regulators such as CD59. Synovial tissue expression of CD59 is altered during inflammatory arthritis; elevated CD59 levels may be necessary to protect joint tissues. Roles of CD59 in maintaining tissue equilibrium and structural architecture within the synovial joint have not been described previously. Since CD59a is the primary regulator of membrane attack complex assembly in mice; we used CD59a-gene-deleted mice ($CD59a^{-/-}$) as tools to unravel the function of CD59a in modulating age-related joint degeneration.

Methods: Hind limbs were collected from C57BL/6J wild type (WT) and $CD59a^{-/-}$ mice at 8-, 20- and 50- weeks of age (6 to 10 mice/group). The Mankin score was used to classify the histopathological severity of osteoarthritic (OA) lesions. Three dimensional radiological image analysis provided objective markers of early degenerative changes at the patellofemoral joint and tibiofemoral joint (TFJ). Sulcus angle, coherence angle, TFJ medial and lateral joint space, femoral subchondral bone thickness, lateral femoral and tibial expansion and osteophytes were measured. Statistical analysis by one-way ANOVA unless specified otherwise. C57BL/6J wild type (WT) and $CD59a^{-/-}$ mice.

Results: Articular cartilage degeneration was detected earlier in $CD59a^{-/-}$ versus WT. In male mice the Mankin score was 0.1 ± 0.1, 4.2 ± 1.4 ($P=0.02$; Mann–Whitney U test) and 7.7 ± 1.8 in $CD59a^{-/-}$ compared with 0.2 ± 0.1, 0.9 ± 0.3 and 7.2 ± 1.6 in WT at 8-, 20- and 50- weeks (all mean±SEM). Lateral subluxation occurred earlier and was of significantly greater magnitude in $CD59a^{-/-}$ than WTs ($P=0.009$; two-way ANOVA). A significant ($P=0.03$) increase in sulcus angle was noted in $CD59a^{-/-}$ mice over time; no such difference was recorded in WTs. Mean coherence angle measured in $CD59a^{-/-}$ at 8-, 20- and 50- weeks was -6.5, $+15.5$ and $+25$ ($P=0.0008$) compared with -2, -7 and $+11$ ($P=0.01$) for WTs indicating significant lateral subluxation of patella with increased age in both strains. TFJ medial and lateral joint space and subchondral bone thickness measurements suggested that bone remodelling was higher in $CD59a^{-/-}$ versus WT at all ages. Osteophytes were clearly visible in $CD59a^{-/-}$ joint specimens across the timecourse but were only observed in WT at 50 weeks. In female mice we observed less articular cartilage pathology than in male mice. However, structural changes indicative of osteoarthritis were consistently more severe in $CD59a^{-/-}$ versus WT mice. Significant joint space narrowing was evident in the medial ($P=0.01$) and lateral ($P=0.01$) compartment of the TFJ in $CD59a^{-/-}$ versus WT (two-way ANOVA). Osteophytes were clearly visible in $CD59a^{-/-}$ joint specimens at 20 and 50 weeks but were only observed in WT mice at 50 weeks.

Conclusion: CD59a deficiency markedly accelerates the progression of age-related joint degeneration in mice. The identification of disease-modifying markers is necessary in order to improve the prediction of disease progression at the individual level and open exciting possibilities for novel treatment options for OA.

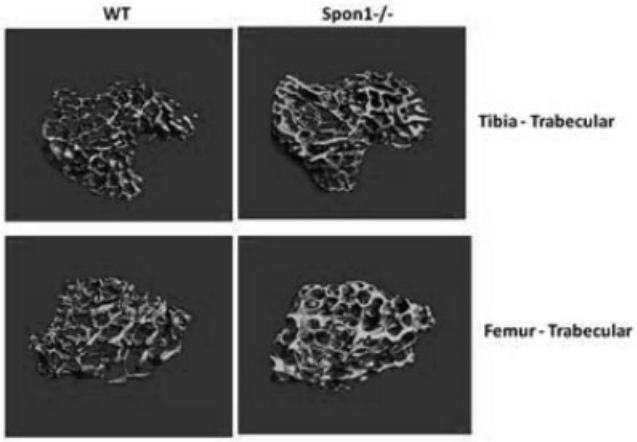
2434

F-Spondin (spondin-1) Null Mice Exhibit Increased Bone Formation. Mukundan Attur[1], Glyn Palmer[1], James Liu[1], Yang Qing[2], Daniel Rifkin[2], Frank Beier[3] and Steven B. Abramson[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]New York University School of Medicine, New York, NY, [3]Schulich School of Medicine and Dentistry, London, ON

Background/Purpose: We have previously reported that F-spondin (spondin-1), a neuroregulatory protein, is upregulated by chondrocytes in osteoarthritis. These studies showed that spondin-1, a member of the TSR (thrombospondin) type I class super family, activated latent TGF-b, which appeared to account for selected *in vitro* effects, including induction of the hypertrophic chondrocyte phenotype. In this study we generated Spon1 knockout mice to investigate in vivo the role of spondin-1 on skeletal maturation.

Methods: Total TGFβ-1 was detected using R &D ELISA kit. MicroCt was performed on the Scanco mCT 35 system on proximal tibia and femurs bone evaluation. Values represent the average of 4 WT and 5 KO mice.

Results: Spondin-1 knockout mice ($Spon1^{-/-}$) were generated by targeted deletion of exon 1 in C57BL/6 mice. Exon 1 deletion was confirmed using Southern blot analysis and PCR using probes specific for wild type (WT) and mutant loci. Spon1−/− null mice were viable and initial macroscopic observations revealed no overt differences in size and body weight compared with WT (mice up to 6 months). Since we previously reported spondin-1 to regulate TGF-b and MMP activities, we measured their levels in adult mutant mice. Relative to WT mice, Spon1 deletion reduced serum levels of total TGFβ-1 (82 ± 20 ng/ml vs. 30 ± 25.0 ng/ml; $p<0.002$) and increased serum total MMP activity (48 ± 15 RFU to 84 ± 18.0 RFU; $p<0.061$). Cultured chondrocytes isolated from the rib cages of 5 day old $Spon1^{-/-}$ mice also produced significantly less TGF-b (30%) compared to WT controls ($p<0.01$). To determine whether Spon1 deletion affected bone phenotype, we performed microCT of tibia and femurs in mutant and WT mice aged 1–6 months. Relative to WT mice, $Spon1^{-/-}$ exhibited increased bone formation at 6 months, evidenced by, a) increased trabecular and cortical bone volume fraction (Bone volume/Total volume: 0.27 ± 0.03 versus 0.15 ± 0.04, $p<0.005$; Fig 1), b) decreased trabecular spacing (0.14 ± 0.02 versus 0.2 ± 0.04, $p<0.03$); and c) increased trabecular number (7.8 ± 1.2, versus 5.0 ± 1.5, $p<0.014$). Interestingly, no significant changes were observed at 1 or 3 months, suggesting that spondin-1 effects are age-dependent.



Conclusion: Our studies indicate that F-spondin or spondin-1, a latent TGF-b activating ECM protein, over-expressed in OA bone and cartilage, regulates bone metabolism in aging male mice. Spon1 $^{-/-}$ male mice exhibit increased trabecular and cortical bone formation. Together these data suggest that a primary function of spondin-1 in skeletal tissue is the regulation of bone mass via latent TGF-b activation. Further studies are in progress regarding the potential of spondin-1 as a drugable target in future therapy of osteoporosis or osteoarthritis.

2435

Synovial Wnt and Wnt-1-Induced Secreted Protein 1 Expression Induce Osteoarthritis-Like Cartilage Damage by Skewing of Transforming Growth Factor-Beta Signaling From Smad 2/3 towards Smad 1/5/8 Phosphorylation. Martijn H. van den Bosch, Arjen B. Blom, Peter L. van Lent, Henk M. van Beuningen, Fons A. van de Loo, Esmeralda N. Blaney Davidson, Peter M. van der Kraan and Wim B. van den Berg. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Although many osteoarthritis (OA) patients show significant synovial involvement, consequences are largely unknown. We found strong up-regulation of canonical Wnts 2b and 16 and Wnt-1-induced secreted protein 1 (WISP1), in knee joints in two experimental murine OA models. Wnt signaling has been implicated in OA incidence and modulation of the β-catenin pathway leads to OA-like changes in cartilage. In addition, TGF-β signaling is critical in cartilage maintenance. TGF-β signals via both ALK5 and ALK1 and downstream via Smad 2/3 and Smad 1/5/8 respectively. In the present study we investigated the potency of canonical Wnts, produced by synovial cells, to induce OA pathology and whether canonical Wnts skew TGF-β signaling from the protective Smad 2/3 pathway to the Smad 1/5/8 pathway, which can induce chondrocyte hypertrophy.

Methods: Western blot analysis was done to detect phosphorylation of Smad 2/3 and Smad 1/5/8. *In vivo* synovial overexpression of genes from the canonical Wnt signaling pathway was achieved by intra-articular injection of adenoviral vectors. Joint pathology was assessed by histology at several time points after injection. Gene expression was analyzed by qPCR after overexpression of Wnt genes in isolated human chondrocytes.

Results: To determine if synovial overexpression of canonical Wnts leads to cartilage damage, adenoviral vectors for Wnts 8a and 16, excluded from targeting chondrocytes because of their size, were injected in murine knee joints. At day 7 a highly significant induction of OA pathology was found at the medial margin of the medial tibial plateau. The incidence was 92% (n=12) for Wnt8a overexpression compared to 17% (N=12) for the control virus and 80% (N=5) for Wnt16 overexpression, but only 20% (N=5) for the control virus. In addition, overexpression of Wnt16 led to significantly increased synovial cellularity, mainly macrophages, and cartilage pathology on the lateral side of the femoral-tibial joint. Because of their relatively small size, Wnts and WISP1 proteins can migrate to the cartilage and possibly alter chondrocyte phenotype. Synovial Wnt8a and Wnt16 overexpression led to β-catenin accumulation in chondrocytes, a tell-tale sign of canonical Wnt signaling, indicating diffusion of Wnts to the cartilage. Moreover, overexpression of canonical Wnts and WISP1 in human chondrocytes led to a significant increase of collagen type I and a significant decrease in type II collagen expression, suggesting a loss of chondrocyte phenotype. Pre-incubation with Wnt3a or WISP alone or Wnt3a + WISP1 together resulted in decreased TGF-β-induced phosphorylation of Smad 2/3, whereas phosphorylation of Smad 1/5/8 was increased. This implies a shift towards dominant TGF-β signaling via the hypertrophy-inducing ALK1 pathway.

Conclusion: Canonical Wnts produced in the synovium may play an important role in OA pathology by inducing β-catenin signaling in the cartilage followed by cartilage damage. Synovial overexpression of canonical Wnts, as is found in experimental OA, may lead to chondrocyte phenotype changes, probably via modulation of the important TGF-β signaling pathway. This underlines that synovial Wnt/WISP1 expression may be a potential target for OA therapy.

2436

Inhibition of Osteoclast Formation by Adenosine A_{2A} Receptor Is Due to Inhibition of NFkB Nuclear Translocation by a PKA-Mediated Mechanism. Aranzazu Mediero[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]New York Univ Medical Center, New York, NY

Background/Purpose: Adenosine, a nucleoside released at sites of injury and hypoxia and which mediates the anti-inflammatory effects of methotrexate, mediates its effects via activation of G-protein-coupled receptors (A_1, A_{2A}, A_{2B}, A_3). Previously we reported that the $A_{2A}R$ agonist CGS21680 inhibited osteoclast differentiation in a dose–dependent manner. We therefore determined which intracellular pathways are involved in $A_{2A}R$-mediated regulation of osteoclast differentiation

Methods: Osteoclast differentiation was studied as the M-CSF/RANKL-stimulated formation of multinucleated TRAP-positive cells from primary murine (C57Bl/6) bone marrow-derived precursors in the presence or absence of CGS21680, ZM241385 (A_{2A} receptor antagonist), activators and inhibitors of PKA/EPAC pathways. Signaling events (PKA/EPAC, MAPK and NFATc1 activation) were studied by Western Blot. A_{2A} Receptor, Cathepsin K and NFATc1 expression were studied by real time RT-PCR. Cytokine expression was assayed by ELISA.

Results: During M-CSF/RANKL-stimulated osteoclast formation the expression of $A_{2A}R$ changed over time, increasing in control and ZM241385 pre-treated cells, an effect which was abrogated in CGS21680-treated cells. Cathepsin K is upregulated in control and ZM241385-treated cells (up to 80 fold, $p<0.001$) but CGS21680 reduces the increase. NFATC1 was upregulated during osteoclast differentiation under all conditions studied. CGS21680 decreased NFkB nuclear translocation in a time-dependent manner, an effect that was abrogated by ZM241385 (88±2% vs 176±12% of control, CGS21680 alone or with ZM241385, respectively, $p<0.001$, n=4), a finding confirmed by direct assay of NFkB transcriptional activity. Western Blot showed PKA activation increased over time in the presence of CGS21680 and this correlated with decreased EPAC activation over the same period of time. CGS21680 increased pERK after 5 and 15min, 1h and 12h (to as much as 119±0.6%, $p<0.001$, n=4), and pre-treatment with ZM241385 reversed this activation. CGS21680 also increased p38MAPK phosphorylation to as much as 110±1% of control, $p<0.5$, n=4), an effect which was abrogated by ZM241385. Finally, CGS21680 activated pJNK over time to as much as 181±2% of control, $p<0.001$, n=4) and ZM241385 partially reversed this effect. A PKA inhibitor (PKI) and/or EPAC activator (8-CPT-cAMP) reversed the effect of CGS21680 on osteoclast differentiation.

Conclusion: Adenosine, acting at $A_{2A}R$, inhibits osteoclast differentiation and regulates bone turnover mainly by the activation of PKA and MAPK, the inhibition of NFkB translocation to the nucleus and decreasing the expression of pro-inflammatory cytokines. Because adenosine mediates the anti-inflammatory effects of methotrexate we speculate that the capacity of methotrexate to inhibit bone erosion in Rheumatoid Arthritis may be mediated by increases in adenosine which inhibit osteoclast formation and function.

2437

MicroRNA-453 Modulates Sonic Hedgehog Gene Expression in Human Chondrocytes by Directly Targeting Its Open Reading Frame. Nahid Akhtar[1] and Tariq M. Haqqi[2]. [1]Case Western Reserve University/Metrohealth Medical Center, Cleveland, OH, [2]Metro Health Medical Center/Case Western Reserve University, Cleveland, OH

Background/Purpose: MicoRNAs (miRNAs) are small endogenous, non-coding RNAs that are important post-transcriptional regulators of gene expression. Sonic Hedgehog (SHH) morphogen is an essential signaling molecule required for numerous processes during development and has recently been implicated in OA pathogenesis. However, regulation of SHH expression in OA remains unclear. Here we studied (a) whether IL-1β-induce

the expression of SHH; and (b) whether miRNAs play a role in regulating expression of SHH in human chondrocytes.

Methods: Chondrocytes were derived by enzymatic digestion of human cartilage from OA patients (OA chondrocytes) undergoing total knee arthroplasty. Chondrocytes were stimulated with IL-1β (5ng/ml) *in vitro* and total RNA was prepared. Expression of SHH and its downstream targets PTCH-1, GLI-1, HHIP, ADAMTS-5 and MMP-13 was quantified by TaqMan Assays. miRGen Targets (http://diana.pcbi.upenn.edu/cgi-bin/miRGen/v3/Targets.cgi) was used to identify miRNAs that potentially target the SHH mRNA and the free energy scores of selected miRNA: mRNA hybrids were determined using RNAHybrid program (http://bibiserv.techfak.uni-bielefeld.de/rnahybrid). miRNAs were purified using the mirVANA system and single stranded cDNA was synthesized with the stem loop-specific primers and the expression of miRNAs was quantified using TaqMan Assays. HEK293 cells were co-transfected with pre-miRNAs, antagomirs and SHH expression plasmid and the protein expression was determined by Western Immunoblotting. Data was analyzed using Origin 6.1 software package and $p<0.05$ was considered significant.

Results: Our results showed that the expression of of SHH was higher in damaged cartilage (stained with India ink, slight or no loss of Safranin O staining) compared to smooth cartilage (no staining with India ink, little or no loss of Safranin O staining) obtained from OA patients at the time of knee arthrthroplasty. The expression of SHH signaling genes and their downstream targets (PTCH-1, GLI-1, and HHIP, MMP-13, ADAMTS-5, COL10A1 and RUNX-2) was also higher in damaged cartilage. A full length search of SHH transcript identified several miRNAs including Hsa-miR-453, Hsa-miR-602 and Hsa-miR-608 with seed matched sites within the coding sequence of SHH mRNA. IL-1β-stimulation (10 ng/ml) resulted in significant up-regulation of SHH mRNA (~11.3-fold at 6h; ~15.5-fold at 12 h) and protein levels in chondrocytes obtained from damaged cartilage. In addition, IL-1β-stimulation also down regulated the expression of Hsa-miR-453 (~4.6-fold at 6h; ~11.6-fold at 12 h), Hsa-miR-602 (~3.9-fold at 6h; ~2.9-fold at 12 h) and Hsa-miR-608 (~3.6-fold at 6h; ~7.5-fold at 12 h) in these chondrocytes. Co-transfection of HEK-293 cells with the SHH expression plasmid and the pre-miR-453 resulted in significant inhibition of SHH mRNA and protein expression, while the transfection of SHH expression plasmid with the antagomirs had no effect on the SHH mRNA and protein expression.

Conclusion: Our findings indicate that miR-453 regulates the expression of SHH in OA chondrocytes by directly targeting its coding sequence. This provides an important and novel perspective for developing therapeutic strategies to treat OA.

2438

The Unfolded Protein Response (UPR) Is Activated by Biomechanical Stress in Normal Cartilage Chondrocytes, but Priming of the UPR Prior to Mechanical Stress Results in Increased Cartilage Catabolism. Matthew R. Husa[1], Freyr Petturson[1], Ron June[1], Shawn Grogan[2], Darryl D'Lima[2], Martin K. Lotz[2], Ru Liu-Bryan[1] and Robert Terkeltaub[1]. [1]UCSD/VAMC, La Jolla, CA, [2]The Scripps Research Institute, La Jolla, CA

Background/Purpose: Mechanical stress can result in either catabolism or anabolism of cartilage matrix by chondrocytes. To investigate the role of mechanical stress in chondrocyte survival and matrix metabolism, we studied the UPR, a fundamental means by which cells successfully resolve stress by controlling protein translation and folding. Three UPR signaling/proteolytic cascades are triggered by dissociation of distinct ER membrane proteins from the chaperone GRP78, which normally dampens the UPR, limits apoptosis, and promotes autophagy. Generation of the UPR-specific transcription factor XBP1s (spliced XBP1) and terminal expression of CHOP are key events. Unsuccessful UPR resolution promotes oxidative stress, inflammation, and apoptosis. Sustained UPR activation (priming) results in increased sensitivity to cell stress. We tested the hypothesis that mechanical stress activates the UPR in chondrocytes, and priming the UPR prior to mechanical stress increases cartilage catabolism.

Methods: Normal bovine knee chondrocytes were placed into 3-D alginate matrix molds and subjected to cyclic compressive forces (maximum compression 22% height, 12% amplitude at 0.5Hz) in a unique biomechanical reactor. Cell death, GAG release and NO production (Griess assay) were measured, and various UPR mediators (GRP78, CHOP) were compared.

Results: Alginate-embedded chondrocytes stimulated with sub-lethal cyclic compressive stress demonstrated rapid increase (over 1–7 days post compression) in GRP78 and CHOP. High-level UPR activation via tunicamycin (UPR activator) prior to mechanical stress induced elevated GAG and NO release beyond that with compression alone ($p<0.05$), although tunicamycin (without injury) had no effect on matrix catabolism.

Conclusion: To our knowledge, this is the first demonstration of UPR activation by mechanical stress in chondrocytes. Moreover, sustained activation of the UPR prior to mechanical stress significantly promotes cartilage matrix catabolism, suggesting that cell stresses known to activate the UPR (inflammatory cytokines, reactive oxygen species, etc) act in concert with mechanical stress to promote catabolic activity in chondrocytes. Thus, UPR dysregulation (or prolonged activation) may be a key event promoting a catabolic phenotype in osteoarthritic chondrocytes. Taken together, these data provide new insights into the regulation of cartilage matrix catabolism, and indicate a primary role of the UPR in OA pathogenesis and chondrocyte mechanotransduction.

ACR Concurrent Abstract Session

Epidemiology and Health Services Research VI: Lupus/Vasculitis

Tuesday, November 8, 2011, 2:30 PM–4:00 PM

2439

Giant Cell Arteritis Is Associated with Incident Coronary Heart Disease-A Population-Based Study. Gunnar Tomasson[1], Johannes Bjornsson[2], Michael P. LaValley[3], Yuqing Zhang[1], Vilmundur Gudnason[4] and Peter A. Merkel[1]. [1]Boston University School of Medicine, Boston, MA, [2]Landspitali University Hospital, Reykjavik, Iceland, [3]Boston University School of Public Health, Boston, MA, [4]The Icelandic Heart Association, Kopavogur

Background/Purpose: There are well-established associations between several systemic inflammatory diseases, including rheumatoid arthritis and systemic lupus erythematosus, with coronary heart disease (CHD). Few studies have described the association between giant cell arteritis (GCA) and CHD. The objective of this study was to determine the association of GCA with CHD in a well-defined population cohort with detailed information on cardiovascular risk factors regardless of exposure status.

Methods: Data from the Reykjavik Study (RS), a population-based prospective study with a primary focus on cardiovascular disease, were used. All persons born in 1907–1935 that were living in Reykjavik, Iceland or in adjacent communities on December 1st 1967 were invited to participate. Subjects came for a study visit in 1967–1996 and information on cardiovascular risk factors, including smoking, blood pressure, diabetes mellitus, body mass index, and serum cholesterol was obtained in a protocolled manner. Temporal artery biopsies (TAbx) were identified for all subjects in the RS in all three pathology laboratories in Iceland during the period 1961–2009. All TAbx were examined in a protocolled fashion by a single pathologist with expertise in vascular pathology. Subjects met exposure criteria for GCA at the date on which a TAbx diagnostic of GCA was obtained. In the RS, there was a continuous surveillance for CHD, defined as myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or sudden cardiac death, until December 31, 2006. Cox proportional hazards regression models were used with GCA status included as a time-varying predictor. Subjects with GCA were considered unexposed until the time they met exposure criteria. Adjustments were done for age, sex, and cardiovascular risk factors.

Results: 19,360 subjects participated in RS, of who 424 subjects were excluded for this study (412 subjects with CHD at baseline and 12 with a TAbx diagnostic of GCA prior to baseline). The 18,936 included subjects had a mean age of 53.5 years (standard deviation (sd): 9.7 years) and 52.2% of subjects were female. TAbx was performed in 678 (3.6%) prior to December 31, 2006 and was diagnostic for GCA in 185 subjects. The 185 subjects with GCA had a mean age at diagnosis of 73.0 years (sd: 6.8, range 55.3–90.0 years) and 129 (69.7%) were females. The median time from study visit to diagnosis of GCA was 18.0 years (inter-quartile range

(IQR): 10.4–24.9). Median follow-up time was 23.7 years (IQR: 15.7–31.3). During follow-up 5,192 (27.4%) of the 18,936 subjects had incident CHD, including 51 (27.6%) of 185 subjects with GCA. Subjects with GCA had increased risk of incident CHD after adjustment for age and sex with HR=1.57 (95% confidence interval (CI): 1.14–2.16). This effect estimate was only minimally attenuated after adjustment for cardiovascular risk factors: HR=1.49 (95% CI: 1.06–2.09).

Conclusion: Compared with the general population, patients with biopsy-proven GCA have an increased risk of incident CHD, even after adjustment for cardiovascular risk factors.

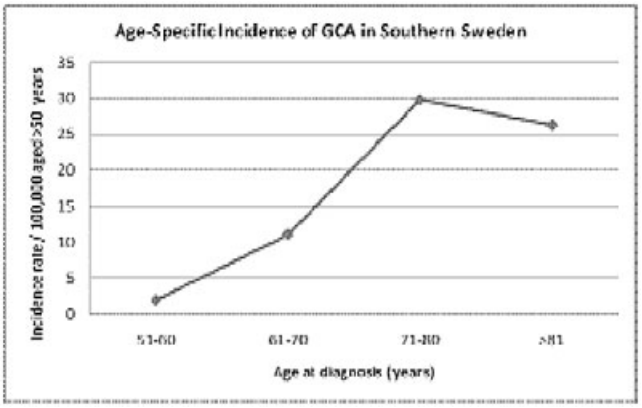
2440

Incidence, Prevalence, and Mortality Rates of Biopsy-Proven Giant Cell Arteritis in Southern Sweden. Aladdin Mohammad[1], Jabbar Mohammad[1], Jan-Åke Nilsson[2], Lennart TH Jacobsson[2], Peter A. Merkel[3] and Carl Turesson[2]. [1]Skåne University Hospital, Lund, Sweden, [2]Skåne University Hospital, Malmö, Sweden, [3]Boston University School of Medicine, Boston, MA

Background/Purpose: To study the epidemiology and survival rates in patients with biopsy-proven giant cell arteritis (GCA) in a well defined population in southern Sweden.

Methods: The study area was the County of Skåne with a total population of 1,243,000 as of December 2010 (36% aged ≥50 years). Patients who underwent temporal artery biopsy (TAB) between 1997 and 2010 and lived in Skåne at time of biopsy were identified using the database at the Departments of Pathology serving the County of Skåne. Only patients with TAB-positive GCA were included in the statistical analysis. Standardized mortality ratios (SMR) were calculated using age- and sex-specific mortality data for the Swedish population as the reference.

Results: A total of 3,510 TABs (2,420 women) were identified. There were 792 patients with TAB-positive GCA (23%). The median age at diagnosis was 76.0 years [Interquartile range (IQR) 69.8–81.1)] for all patients; 75.8 (IQR 69.2–81.2) for men and 76.0 (IQR 70.0–81.1) for women. The annual incidence rate per 100,000 inhabitants aged ≥50 years (total 454,356 inhabitants), was 13.3 (95% CI 12.3–14.2); 7.2 (6.2–8.2) for men and 18.5 (17.0–20.0) for women. The incidence rates increased with older age up to the age of 80, with estimates of 2.0, 11.1, and 29.8 per 100,000 in the age groups 51–60, 61–70, 71–80 years, respectively ($p<0.001$). There was no further increase in the group aged ≥81 years vs. the 71–80 years age group (26.3/100,000), Figure.



As of January, 1, 2011 there were 517 patients (387 women) alive and living within the County of Skåne with a previous TAB positive for GCA. The corresponding point prevalence per 100,000 inhabitants aged ≥50 years was 114 (95% CI 104–124); for men 61 (50–71) and for women 162 (145–178). The median time of follow-up for all patients from diagnosis to March 1, 2011, or death was 60.2 months (IQR 23.8–100.8). Two hundred and fifty-one patients (184 women) died during this follow-up period. For all patients, the absolute survival rate was 92 % at 1 year, 77 % at 5 years and 54 % at 10 years. Mortality during the first 5 years of follow-up was similar to the background population [SMR 1.03 (95 % CI 0.86–1.20)]. The estimated SMR was slightly higher for men: 1.14 (0.82–1.47) as compared to 0.98 (0.78–1.18) for women. With extended follow-up, overall mortality rates among GCA patients remained similar to the expected. In analyses stratified by age, those ≤70 years at diagnosis had a significantly increased mortality [SMR during the first 5 years of follow-up: 1.82 (1.04–2.95)].

Conclusion: The annual incidence rates of GCA in Southern Sweden were comparable with other studies of European populations and increased with age. The prevalence of GCA in Sweden is the highest prevalence for this disease ever reported. Overall, the survival of patients with TAB-positive GCA was similar to that of the general population, but patients diagnosed at age ≤70 years had a significantly increased mortality.

2441

Prevalence and Demographics of Systemic Lupus Erythematosus and Lupus Nephritis Among U.S. Adults with Medicaid Coverage, 2002–2004. Candace H. Feldman[1], Linda T. Hiraki[2], Daniel H. Solomon[1], Tamara Shaykevich[1], Michael A. Fischer[1], Wolfgang C. Winkelmayer[3] and Karen H. Costenbader[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital/ Harvard School of Public Health, Boston, MA, [3]Stanford University School of Medicine, Stanford, CA

Background/Purpose: Past estimates of the prevalence of systemic lupus erythematosus (SLE) in the general U.S. population have ranged from 40 to 150/100,000. Lupus nephritis (LN) occurs in 20–60% of adults with SLE. No information is available on the prevalence and sociodemographics of SLE and LN among adults with Medicaid, the joint federal-state program providing health insurance to low-income individuals. African Americans have higher rates of SLE and LN and are also disproportionately covered by Medicaid. We examined the nationwide prevalence and sociodemographics of SLE and LN among adult Medicaid beneficiaries.

Methods: Individuals aged 18 through 65 with SLE (≥ 2 visits with ICD-9 code 710.0) were identified from the Medicaid Analytic eXtract (MAX), which contains all inpatient and outpatient claims from 49 states and Washington, D.C., 2002–2004. LN was identified from billing codes for ≥ 2 ICD-9 codes for glomerulonephritis, proteinuria and renal failure (PPV 88%; Chibnik et al., 2009). The prevalence of SLE and LN among adults with Medicaid was calculated with 95% confidence intervals among different sociodemographic categories. Crude prevalence ratios were also calculated.

Results: From 18,646,925 adults who were Medicaid beneficiaries between January 1, 2002 and December 31, 2004, we identified 31,018 subjects with SLE (prevalence = 166/100,000). Of these, 93% were female; 38% White, 37% African American, and 12% Hispanic (**Table 1**). The prevalence of SLE was 6 times higher among women than men. African Americans and Native Americans were almost twice as likely to have SLE compared with Whites. The prevalence was highest in the U.S. South for Whites and African Americans, and highest in the U.S. West for Asians and Hispanics. A total of 6,285 (20%) had LN (prevalence = 34/100,000). Women had a 4 times higher prevalence of LN than men. The prevalence of LN was higher among African Americans, Hispanics, Asians and Native Americans than among Whites.

Table 1. Prevalence of SLE and Lupus Nephritis per 100,000 among U.S. Medicaid Beneficiaries aged 18–65 (2002–2004)

	SLE*	Prevalence Ratio	Lupus Nephritis*	Prevalence Ratio
Total	166 (165–168)	-	34 (33–35)	-
Men	37 (35–39)	Referent	11 (10–12)	Referent
Women	220 (218–223)	5.9	43 (42–44)	4.1
Non-Hispanic Whites	130 (127–132)	Referent	19 (18–19)	Referent
African Americans	256 (251–261)	2.0	65 (63–68)	3.5
Asians	107 (99–116)	0.8	33 (29–39)	1.8
Hispanics	134 (130–138)	1.0	29 (27–31)	1.6
Native Americans	239 (225–254)	1.8	56 (49–63)	3.0
Northeast	136 (132–139)	Referent	27 (25–28)	Referent
South	197 (194–201)	1.5	41 (40–43)	1.5
Midwest	155 (151–159)	1.1	34 (32–36)	1.3
West	167 (163–171)	1.2	31 (29–32)	1.1

* Prevalence per 100,000 (95% CI)

Conclusion: From 2002–2004, the prevalence of SLE in the U.S. Medicaid population was 166/100,000 and the prevalence of LN was 34/100,000. We identified considerable sociodemographic variation in the prevalence of SLE and LN. Our estimates are slightly higher than previously reported estimates that were not restricted to Medicaid beneficiaries. Additional studies are needed to determine whether SLE and LN are more common than previously estimated, or whether the low socioeconomic status populations served by Medicaid are at elevated risk.

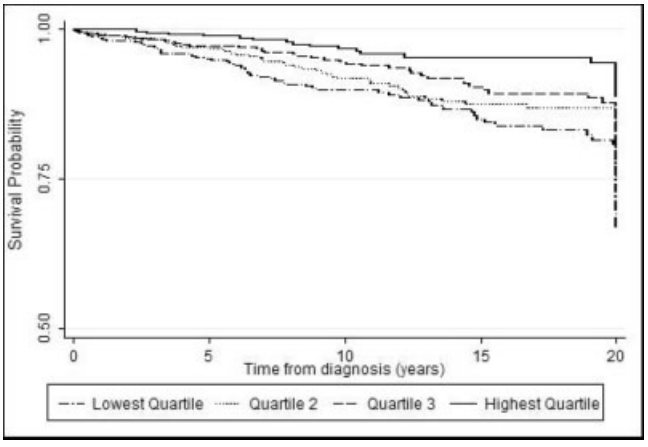
2442

Socioeconomic Status and Survival in Systemic Lupus Erythematosus: Results From the Michigan Lupus Epidemiology and Surveillance (MILES) Program. Sarah M. Barnhart[1], W. Joseph McCune[1], Wendy Marder[1], Patricia C. Cagnoli[1], Emily E. Lewis[1], Peter DeGuire[2], C. Gordon[3], Charles G. Helmick[4], J. Patricia Dhar[5], James C. Leisen[6], Emily C. Somers[1] and MILES Group[7]. [1]University of Michigan, Ann Arbor, MI, [2]MI Dept of Community Health, Lansing, MI, [3]University of Birmingham, Birmingham, United Kingdom, [4]Centers for Disease Control and Prevention, Atlanta, GA, [5]Wayne State University, Detroit, MI, [6]Henry Ford Hospital, Detroit, MI, [7]Ann Arbor, MI

Background/Purpose: Socioeconomic status (SES) has been demonstrated to impact survival among many chronic disease conditions. We performed this analysis to determine if area-based SES was independently associated with survival among systemic lupus erythematosus (SLE) patients from a diverse, population-based setting.

Methods: MILES is a population-based, active SLE surveillance program utilizing multiple sources of case-finding to identify prevalent SLE cases in Washtenaw & Wayne Counties, MI (2002–2005). Detailed record reviews are performed for potential cases meeting eligibility criteria. This analysis used a case definition based on the "gold standard" of rheumatologist investigator judgment ("definite SLE"). Each case was assigned a previously validated area-based SES index score based the sum of standardized scores of 7 census economic indicators (median household income, proportion with income $<$ 200% of fed poverty level, median house value, median monthly rent, mean education level, proportion of college graduates among ages $\geq$ 25 yrs, and proportion of employed persons with a professional occupation) linked to zip code of residence at baseline. Survival was determined by linkage to the MI Vital Statistics Database. Left-truncated Cox proportional hazards modeling was used to evaluate the association between survival and SES. Race, gender, smoking status, age of diagnosis, and number of ACR criteria were included as covariates relevant to survival.

Results: The 1945 cases (mean age at diagnosis 40.4 yrs; 62% African American, 34% White; 90% female) had a median follow-up time of 10.3 yrs since diagnosis. A total of 192 (10%) deaths occurred during follow-up. After adjustment for age at diagnosis, race, sex, smoking status, and total number of ACR criteria, SES was independently associated inversely with survival, both when SES was modeled continuously (HR 0.9, 95% CI 0.9–1.0; p=0.0486) or as quartiles (HRs vs quartile 1: Q2 0.8, Q3 0.7, Q4 0.6; test of trend p=0.0415). The following variables were also associated with reduced survival, after adjustment for all other covariates in the model: black race (white race referent: HR 2.7, 95% CI 1.8–4.2), male sex (HR 1.9, 95% CI 1.3–3.0), "ever" smoker status ("never" referent: HR 1.5, 95% CI 1.1–2.0), and increasing number of ACR criteria (HR=1.1, 95% CI: 1.0–1.2).



Kaplan-Meier survival estimates for SLE by quartile of SES index score

Conclusion: Area-based SES is independently associated inversely with survival in SLE patients from the general population; for each unit decrease in area-based SES score, survival was reduced by 10%. Black race, male sex, smoking, and an increasing number of ACR criteria were independently associated with the reduced survival. Similarly to other chronic disease outcomes, our results add to a growing body of evidence that low SES is associated with reduced survival among SLE patients.

2443

The Natural History and Predictive Factors of Long Term Outcomes in Systemic Lupus Erythematosus. Penny Watson[1], Alan Brennan[1], Helen Birch[2], Hong Fang[3] and Michelle Petri[3]. [1]University of Sheffield, Sheffield, United Kingdom, [2]GlaxoSmithKline, Uxbridge, United Kingdom, [3]Johns Hopkins University School of Medicine, Baltimore, MD

Background/Purpose: Statistical models are often used to extrapolate patient outcomes beyond the clinical trial period for cost-effectiveness analyses. The aim of this study was to develop and test a set of statistical models to describe the natural history of Systemic Lupus Erythematosus (SLE) that can be used in health economic evaluations.

Methods: Longitudinal data from a cohort of 1354 patients with median follow-up of 10 years were included in the analysis. At clinic visits that were scheduled every 3 months, data were collected on SLE Disease Activity Index (SLEDAI), treatment, Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) events, and laboratory tests. Independent statistical models were run to describe the disease. Change in SLEDAI score was estimated as a function of gender, ethnicity and binary variables to indicate renal involvement, increased DNA binding, low complement, haematological involvement or anaemia using a linear random effects model. Average prednisone dose was estimated as a function of SLEDAI score with random effects. Organ damage and mortality were estimated as a function of Adjusted Mean SLEDAI (AMS), cumulative average prednisone dose, indicator variables for organ system involvement, and other risk factors associated with long-term outcomes using parametric survival models. A simulation model combined the separate statistical models to reproduce the cohort to assess the validity of the natural history predictions.

Results: The disease activity model found that previous SLEDAI, age, ethnicity, increased DNA binding, low complement and organ involvement significantly affected future SLEDAI score. In the prednisone model a unit increase in average SLEDAI increased average prednisone dose increased by 0.77mg per day. Risk of mortality, cardiovascular, renal and peripheral vascular damage increased with higher AMS ($p<0.1$). Organ involvement predicted mortality, cardiovascular, renal, neuropsychiatric, pulmonary, gastrointestinal, ocular, and skin damage. Corticosteroids increased the risk of gonadal failure, diabetes, cardiovascular, musculoskeletal, neuropsychiatric, and gastrointestinal damage. The simulation reproduced the baseline characteristics and patient outcomes reported in the cohort. Figure 1 illustrates the proportion of patients who died or reported organ damage in the cohort and simulated cohort.

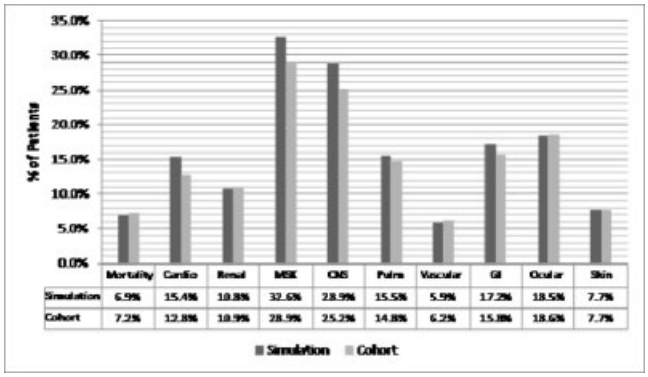


Figure. The proportion of patients who recorded mortality or organ damage at time of withdrawal from cohort or simulation.

Conclusion: The analysis generated a natural history model that could be used to extrapolate patient outcomes beyond a clinical trial and to estimate the long term benefits of reducing disease activity and steroid exposure. This can be used to estimate the effectiveness and cost-effectiveness of new treatments for SLE.

2444

The Georgia Lupus Registry: The Incidence and Prevalence of Systemic Lupus Erythematosus. S. Sam Lim[1], Rana Bayakly[2], C. Gordon[3], Charles G. Helmick[4], Kirk Easley[5], Gaobin Bao[1], Neeta Shenvi[5] and Cristina M. Drenkard[1]. [1]Emory University, Atlanta, GA, [2]Georgia Department of Public Health, Atlanta, GA, [3]University of Birmingham, Birmingham, United Kingdom, [4]Centers for Disease Control and Prevention, Atlanta, GA, [5]Emory University-Rollins School of Public Health, Atlanta, GA

Background/Purpose: US epidemiologic estimates of SLE are outdated and have varied widely due to the use of different case definitions, limited sources for case ascertainment, and small source populations. The Georgia Lupus Registry (GLR) is a population-based registry designed to more accurately estimate the incidence and prevalence of SLE for blacks and whites in the two counties (Fulton and DeKalb) that include Atlanta, Georgia.

Methods: The state HIPAA exemption for surveillance allowed health care providers and facilities to provide access to protected health information without written patient consent. Sources of cases included hospitals (20), rheumatologists (35), nephrologists (10), dermatologists (20), commercial labs, and population databases. Trained abstractors reviewed >8,000 medical records identified as possibly having SLE. Incidence rates (per 100,000 person years) were determined for years 2002–2004 and prevalence rates (per 100,000) for 2002. Definite cases had ≥4 ACR criteria; probable cases had 3 ACR criteria plus a final diagnosis of SLE by a rheumatologist. Rates were age adjusted using the 2000 projected US population. Age adjusted estimates and 95 % confidence intervals were calculated by the direct method using R (routine ageadjust.direct).

Results: Prevalence of SLE (2002)

		Definite		Definite + Probable	
Race/ Sex	Population[1]	Cases (n)	Adjusted Rate (95% CI)	Cases (n)	Adjusted Rate (95% CI)
Total	1552970	1153	72.8 (68.6, 77.3)	1345	85.8 (81.2, 90.5)
Black	765475	889	118.5 (129.4, 127)	1021	138 (129.4, 147.2)
female	408642	806	196.2 (182.6, 210.7)	922	226.6 (211.9, 242.3)
male	356833	83	23.7 (18.5, 31.3)	99	29.2 (23.3, 37.4)
White	720292	251	32.7 (28.8, 37.2)	311	40.7 (36.3, 45.7)
female	352914	222	59 (51.4, 67.5)	276	73.3 (64.9, 82.7)
male	367378	29	7.5 (5, 11.2)	35	9.4 (6.4, 13.5)

Average annual incidence of SLE (2002–2004)

		Definite		Definite + Probable	
Race/Sex	3 year Population[1]	Cases (n)	Adjusted Rate (95% CI)	Cases (n)	Adjusted Rate (95% CI)
Total	4742264	266	5.6 (4.9, 6.3)	332	6.9 (6.1, 7.7)
Black	2321302	196	8.6 (7.4, 9.8)	245	10.7 (9.3, 12)
female	1239819	168	13.4 (11.4, 15.7)	215	17 (14.7, 19.5)
male	1081483	28	3 (1.9, 5.2)	30	3.3 (2, 5.4)
White	2210389	62	2.7 (2, 3.5)	77	3.3 (2.6, 4.2)
female	1082131	53	4.7 (3.5, 6.2)	66	5.8 (4.5, 7.5)
male	1128258	9	0.7 (0.3, 1.5)	11	0.8 (0.4, 1.7)

[1] US Census Bureau 2000, Vintage 2009
13 validated prevalent and 10 incident cases from other racial/ethnic groups were excluded.

Conclusion: The GLR is one of the most comprehensive epidemiologic efforts in SLE in the US and provides updated and more accurate incidence and prevalence rates in a large white and black population. Black women have significantly higher incidence than previously reported. Overall prevalence is also higher and may indicate longer survival and/or more frequent diagnosis. SLE continues to afflict significant numbers of people with a disproportionate burden on black women.

ACR Concurrent Abstract Session
Miscellaneous Rheumatic and Inflammatory Diseases
Tuesday, November 8, 2011, 2:30 PM–4:00 PM

2445

Rilonacept (Interleukin-1 Trap) for Treatment of Colchicine Resistant Familial Mediterranean Fever: A Randomized, Multicenter Double-Blinded, Alternating Treatment Phase II Trial. Philip J. Hashkes[1], Steven J. Spalding[2], Edward H. Giannini[3], Bin Huang[4], Grace Park[5], Karyl S. Barron[6], Michael H. Weisman[7], Noune Pashinian[8], Andreas Reiff[9], Jonathan Samuels[10], Dowain A. Wright[11], Daniel L. Kastner[12] and Daniel J. Lovell[4]. [1]Cleveland Clinic/Shaare Zedek Medical Center, Jerusalem, Israel, [2]Cleveland Clinic, Cleveland, OH, [3]PRCSG-Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]National Institutes of Health/NHGRI, Bethesda, MD, [6]NIAID-NIH, Bethesda, MD, [7]Cedars Sinai Med Ctr, Los Angeles, CA, [8]Glendale, CA, [9]PRSCG, Los Angeles, CA, [10]NYU Hospital for Joint Diseases, New York, NY, [11]Childrens Hospital Central Cal, Madera, CA, [12]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

Background/Purpose: There is no proven treatment alternative for pts with familial Mediterranean fever (FMF) whose disease is resistant to, or do not tolerate colchicine. Since pyrin has an important role in IL-1β regulation we hypothesized that IL-1 inhibition would decrease the number of FMF attacks in these pts. We aim to determine if rilonacept, a fusion protein that binds and neutralizes IL-1, decreases the number of FMF attacks compared to placebo.

Methods: FMF pts ≥4 years of age with at least 1 FMF attack per month despite adequate doses of, or intolerant to colchicine were recruited at 6 U.S. sites. Pts received two 3-month courses of rilonacept (Arm A) at 2.2 mg/kg (max 160 mg) by weekly SC injection and two 3-month courses of placebo (Arm B). Pts were randomized to 1of 4 treatment sequences (ABAB, BABA, ABBA, BAAB). Escape visits were allowed to switch arms (blinding was maintained) for pts with at least 2 attacks within a course. The primary outcome was the difference in the frequency of FMF attacks between rilonacept and placebo courses. Responders were defined as pts with a >40% difference. Data were analyzed by signed rank tests and Bayesian methods.

Result: Fourteen pts were randomized, 8 males and 6 females, mean (±SD) age 24.4±11.8 yrs (range 4.5–47.3; 4 pts <18 yrs), disease duration 17.5±12.6 yrs, with 3.1±2.0 attacks per month at baseline. Eleven pts completed 12 months and 3 discontinued early (1 each due to lack of efficacy, distance from study site and lost to follow-up). Among the 12 pts who completed at least 2 treatment courses, the mean number of attacks per month was 1.0±1.2 on rilonacept vs. 1.8±0.9 on placebo (P=0.027). The risk ratio for attacks (ArmA/ArmB) by Bayesian analysis (consistent for all prior assumptions) was 0.57±0.17 (2.5–97.5 percentile estimates of 0.31–0.98, significant lower rate in Arm A). There were 8 responders; all 4 non-responders were adults. Significant exploratory outcomes include the number of treatment courses without attacks (29% Arm A vs 0% Arm B, P=0.004), courses with >50% decrease in attacks compared to baseline (75% Arm A vs 35% Arm B, P=0.006), the proportion of time pts were treated with Arm A (57.5%) vs Arm B (42.5%, P=0.05) and fibrinogen levels (P=0.04). No significant differences were seen in the proportion of days in attack (Arm A 0.15±0.2 vs Arm B 0.22±0.23, P=0.08), number of escape courses (25% Arm A vs 46% Arm B, P=0.13), patient/parent (P=0.07) and physician global assessment (P=0.14), the modified Armenian Severity Score (P=0.1) and other acute phase reactants. There were significant differences in physical but not psychosocial aspects of quality of life between treatment arms (P=0.01 and 0.64, respectively). The median time to develop 2 attacks was >90 days (not reached by end of course) in Arm A vs 36 days in Arm B (p=0.009). There were 2 respiratory infection SAEs, 1 on rilonacept and 1 on placebo. Injection site reactions were significantly more frequent with rilonacept (P=0.04) but no differences were seen in other adverse events, including infections.

Conclusion: Rilonacept significantly reduces the number of FMF attacks and has an acceptable safety profile. IL-1 inhibition is a treatment option for most colchicine resistant FMF pts and especially children.

2446

Interleukin-1 Beta It Is: High Efficacy of Canakinumab In Schnitzler Syndrome. Heleen D. de Koning, Joost Schalkwijk, Johanna van der Ven-Jongekrijg, Monique Stoffels, Jos W. M. van der Meer and Anna Simon. Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Schnitzler syndrome is a chronic disabling auto-inflammatory disorder, characterized by chronic urticaria, paraproteinemia and systemic inflammation. The effectiveness of the interleukin-1 receptor antagonist (IL-1ra) anakinra in over 40 cases to date implies a crucial pathophysiological role of IL-1, but does not discriminate between IL-1a and IL-1β. The burden of painful daily injections raised the need for longer-acting agents, and in vitro findings hinted at IL-1β as the principal proinflammatory cytokine involved in the pathophysiology. Canakinumab is a monoclonal anti-IL-1β antibody which requires administration only once every 4 to 8 weeks. It is effective in Cryopyrin-Associated Periodic Syndrome (CAPS), a rare hereditary autoinflammatory disorder caused by increased IL-1β activation, which has phenotypical similarities to Schnitzler syndrome. We therefore initiated a trial of canakinumab in Schnitzler syndrome to determine long-term safety and efficacy.

Methods: Upon ethical approval and patients' informed consent, we started an open-label trial (ClinicalTrials.gov NCT01276522) with canakinumab (150 mg subcutaneously once every 4 weeks) in eight patients with Schnitzler syndrome, either classical or variant type, for 6 months. In order to enter the study, the patients would stop their treatment with anakinra and report to us at time of recurrence of symptoms.

Results: The 6 men and 2 women (age 59–75) that were included had suffered from Schnitzler syndrome for 5 to 25 years, and had been asymptomatic on daily anakinra injections for 4 months to 7 years. Within 36 to 96 hours after stopping anakinra, the patients gradually developed general malaise, non-pruritic to burning urticaria, fever and arthralgia, as before initiation of anakinra. Four to six days after discontinuing anakinra, they presented with disseminated urticaria, arthralgia (arthritis in some), strongly elevated serum C-reactive protein (CRP) concentrations and neutrophilic leukocytosis. Upon a single subcutaneous injection of 150 mg canakinumab, their symptoms started to abate within 6–16 hours, and all were asymptomatic after two to seven days. CRP concentration dropped dramatically within the first week and remained low or undetectable. After an initial complete response, one patient quit the study because symptoms returned within four weeks and he did not want an increased dose. The others are still in complete remission. No serious adverse events occurred. The final patient will complete the 6 months study in September 2011 so full data will be available at time of presentation.

Conclusion: Monthly injection with canakinumab is an effective long-acting treatment of Schnitzler syndrome. This observation singles out IL-1β as the key cytokine responsible for inflammation in Schnitzler syndrome, thereby providing a pivotal pathophysiological clue for this enigmatic disorder and corroborating the evidence for its autoinflammatory nature.

2447

Proteasome Disability Syndrome: An Analysis of the Pathogenesis of a New Autoinflammatory Syndrome, Nakajo-Nishimura Syndrome. Hiroaki Ida[1], Kazuhiko Arima[2], Nobuo Kanazawa[3] and Koh-ichiro Yoshiura[2]. [1]Kurume University School of Medicine, Kurume, Japan, [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Wakayama Medical University, Wakayama, Japan

Background/Purpose: Nakajo-Nishimura syndrome (NNS) (MIM 256040) is a new autoinflammatory disorder that segregates in an autosomal recessive fashion and shows inflammatory and wasting symptoms including periodic fever, skin rash, myositis, partial lipodystrophy, contracture of joints and calcification of basal ganglia. The purpose of this study is to detect the responsible gene and to analyze the molecular features in cells from patients with NNS.

Methods: 1) Genomic DNA samples were analyzed with the SNP microarray-based homozygosity mapping following to determine the affected gene by direct sequencing. 2) Proteins from immortalized NNS lymphoblastoid cell lines were separated into fractions by glycerol gradient. Each fraction was assayed for 3 different peptidase activities of the proteasome, chymotrypsin-like, trypsin-like, and caspase-like activities, using the fluorescent peptide substrates. 3) An amount of proteasome subunits and accumulation of ubiquitinated proteins were detected by Western blotting. 4) Immunological staining was performed on skin biopsy sections obtained from NNS patients. 5) Concentrations of 27 different cytokines were determined using a multiplex bead-based enzyme linked immunosorbent assay on a suspension array in serum samples obtained from healthy controls (HC), rheumatoid arthritis (RA) patients, and NNS patients. 6) We investigated activation of the various signal transduction pathways that could be responsible for inflammation using EMSA and Western blotting.

Results: 1) We detected a homozygous mutation in the human *PSMB8* gene that encodes immunoproteasome subunit β5i in patients with NNS. 2) The resultant amino acid substitution (G201V) abolished all three peptidase activities of proteasome and 3) disturbed maturation of the immunoproteasome complex. 4) Accumulation of ubiquitinated proteins was detected in the NNS lymphoblasts and infiltrating cells in the skin lesion of patients with NNS. 5) The productions of inflammatory cytokine (IL-6) and chemokine (IP-10) were seen in greater numbers in sera from NNS patients compared to HC and RA. 6) While no differences in the amount of the NF-kB p65/p50 heterodimer were observed in nuclear extracts from NNS and HC fibroblasts, the amounts of phosphorylated p38 (p-p38) in the nuclear extracts from NNS fibroblasts and peripheral blood leukocytes were seen in larger amounts, irrespective of TNF-α stimulation.

Conclusion: Our findings reveal that a decrease in proteasome activity, which is associated with a novel mutation of the β5i immunoproteasome subunit, causes definitive human autoinflammatory phenotypes in NNS. This fact suggests that the ubiquitin-proteasome pathway might play an important role for inflammation and provides a new insight into the pathogenesis of other persistent inflammatory diseases.

2448

Progressive Multifocal Leukoencephalopathy Associated with Immunosuppressive Therapy in Rheumatic Diseases: Evolving Role of Biologic Therapies. Eamonn S. Molloy[1] and Leonard H. Calabrese[2]. [1]St Vincent's University Hospital, Dublin 4, Ireland, [2]Cleveland Clinic, Cleveland, OH

Background/Purpose: Progressive Multifocal Leukoencephalopathy (PML) is a rare and often fatal opportunistic infection recently associated with several biologic therapies. However, ascribing risk to individual therapies has been problematic. This study examined the aggregate experience of PML reported in association with autoimmune rheumatic diseases (ARD) in the FDA Adverse Event Reporting System (AERS) database.

Methods: A Freedom of Information Act request was submitted for all cases of PML and/or JC virus infection within the FDA AERS database, updated through March 31, 2010. MedWatch forms with identified ARD were selected for further analysis. PML was classified as confirmed or unconfirmed, based on results of cerebrospinal fluid analysis and/or brain biopsy. Relevant data collected included drug treatment and disease association cofactors of PML.

Results: 30 confirmed cases of PML in the setting of ARD were identified (16 SLE, 9 RA, 5 other). Of these, 15 were treated with biologic agents (14 rituximab (RTX), 6 anti-TNF therapy). RTX was the most recent biologic treatment for ARD in all 14 confirmed cases associated with its use; 5 patients were treated with anti-TNF therapy prior to RTX. PML developed after a median of 2 courses of RTX (range 1–4). The median interval between the first and last infusion of RTX and the development of PML was 12 months (range 1–59) and 5 months (range 0–29), respectively. Two RTX-treated patients were receiving no other immunosuppressive therapy at the apparent time of onset of PML; all other biologic-treated patients were also receiving one or more synthetic disease-modifying agents. Three biologic-treated patients (2 RTX, 1 infliximab) were concomitantly receiving CYC at the time of onset of PML; three additional RTX-treated patients had previously received CYC. Two RTX-treated patients had received chemotherapy for malignancy (1 oropharyngeal cancer, 1 MALT lymphoma). No confirmed cases of PML were reported in association with the use of other biologic agents such as tocilizumab, anakinra or abatacept. The remaining 15 confirmed cases of PML among ARD patients were treated with synthetic DMARDs only. 12 of these had received an alkylating agent (10 CYC, 2 chlorambucil), in 9 cases this was ongoing at the time of development of PML. Of the 30 confirmed cases of PML, 13 were treated with azathioprine and 7 with mycophenolate mofetil.

Conclusion: PML is a reported complication of various ARD and associated with both synthetic and biologic immunosuppressive therapies. Definitive attribution of causality is not possible given the small numbers of cases, potential for reporting bias and existence of confounders in many cases. However, the relative paucity of confirmed cases in patients recently treated with anti-TNF therapy, despite their widespread use, suggests that a causal relationship is unlikely. In contrast, there is an increasing, specific signal emerging regarding the association between RTX and the development of PML. Although this is a rare complication, continued vigilance is mandated by the devastating nature of PML, particularly in patients with current or prior exposure to an alkylating agent.

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Pulmonary and Extrapulmonary Recurrence of Sarcoidosis After Lung Transplantation. Fariha Kausar[1], Troy K. Takagishi[1], Rochella A. Ostrowski[2] and Rodney Tehrani[3]. [1]Loyola University Medical Center, Maywood, IL, [2]Loyola Univ Medical Ctr, Maywood, IL, [3]Loyola Univ Medical Center, Maywood, IL

Background/Purpose: Sarcoidosis accounts for 2.8% of lung transplants (LT) in the United States. It has been reported to be the most frequently recurring disease after LT. Although recurrence of pulmonary sarcoidosis has been estimated to be as high as 47% following LT, multiple studies have suggested that outcomes for sarcoidosis patients undergoing LT are equivalent to those of overall transplant patients. A review of literature revealed no studies documenting extra-pulmonary recurrence of sarcoidosis following LT. We predict that pulmonary and

extra-pulmonary recurrence of sarcoidosis after LT is frequent. We hypothesize that survival rates are similar in patients undergoing LT due to sarcoidosis (LT/sarcoidosis) compared to patients undergoing LT due to COPD (LT/COPD).

Methods: We performed an observational and retrospective chart review of all patients with LT/sarcoidosis at a large tertiary care medical center between 1992–2010. We searched for any histologic recurrence of pulmonary sarcoidosis on surveillance lung biopsies done after LT, as documented by the presence of non-caseating granulomas. We also searched for possible extra-pulmonary recurrence of sarcoidosis after LT, by doing extensive chart reviews of patients' follow up visits. We then plotted out survival outcomes of LT/sarcoidosis and compared them to survival outcomes of LT/COPD in the UNOS national registry from 1/1/91 to 12/31/09. COPD was chosen as the control group because it comprises the largest group of patients undergoing LT in the United States.

Results: From 1992–2010, 29 patients underwent LT at a large tertiary care medical center for end-stage pulmonary sarcoidosis. 6/29 (20.6%) patients had pulmonary recurrence of sarcoidosis, documented as non-caseating granulomas on surveillance lung biopsies. This equates to 1 episode of pulmonary recurrence/16.95 patient-years. 5/29 (17.2%) patients had possible extra-pulmonary recurrence of sarcoidosis. This equates to 1 episode of extra-pulmonary recurrence/20.34 patient-years. The Kaplan-Meier survival curves for LT/sarcoidosis and LT/COPD respectively at 30 days was 89.6% and 95.3%, at 1 yr was 89.6% and 83.1%, at 3 yrs was 74% and 65.3%, and at 5 years was 61.7% and 49.8%. Survival rates between the two groups were compared using the Chi-square test and found to be statistically insignificant.

Conclusion: To the best of our knowledge, there is no literature documenting extra-pulmonary recurrence of sarcoidosis after LT. Survival outcomes for LT/sarcoidosis patients have been shown to be equivalent to those of overall transplant patients. We found that both pulmonary and extra-pulmonary recurrence of sarcoidosis is frequent after LT. Pulmonary recurrence was histologic and not necessarily of clinical relevance. We found that survival rates did not differ significantly between the LT/sarcoidosis and LT/COPD groups. In LT/sarcoidosis patients, we found that early mortality is high, a finding also cited by other studies. Although recurrence is frequent, LT remains a feasible option for patients with end-stage pulmonary sarcoidosis.

2450

TNFRSF1A and MFEV Mutations in Idiopathic Recurrent Acute Pericarditis. Guillaume Geri[1], Pierre Hausfater[2], Catherine Dodé[3], Nathalie Costedoat-Chalumeau[1], Zahir Amoura[1], Jean-Charles Piette[1], Damien Sène[1], David Saadoun[4] and Patrice Cacoub[1]. [1]CHU Pitié-Salpêtrière, Paris, France, [2]Department of Emergency, CHU Pitié Salpetriere, 47–83 Boulevard de l'hôpital, 75651 Paris cedex 13 France, Paris, France, [3]Biochemistry and Molecular Genetic, CHU Cochin, rue du Faubourg Saint Jacques, 75014 Paris, France, Paris, France, [4]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France

Background/Purpose: Recurrent acute pericarditis (RAP) is the most common complication of acute pericarditis. The etiological search is often inconclusive and up to 85% of RAP are idiopathic. Serosal membrane inflammation is a common feature of hereditary periodic fever syndromes (HPFS) such as Familial Mediterranean Fever (FMF) and tumour necrosis factor receptor-1 associated periodic syndrome (TRAPS). Genetic biomarkers of HPFS are helpful, i.e. mutations of MFEV for FMF and TNFRSF1A for TRAPS. We aimed at assessing the prevalence of HPFS genetic markers in idiopathic RAP.

Methods: Consecutive patients with idiopathic RAP, defined as > 2 episodes of pericarditis and a negative check-up, from a French tertiary hospital were included. Mutations of MFEV and TNFRSF1A were searched for by amplifying (PCR) genomic DNA and direct sequencing. Epidemiological, clinical and biological features, and therapeutic response were compared in RAP patients presenting with and without HPFS mutations.

Results: 81 patients (mean age at first RAP diagnosis 41.6 ± 18 years; F/M sex ratio 0.44) were included, 45 (55.6%) patients were European and 6 (7.4%) North African. A familial history of pericarditis was noted in one case. The mean number of RAP episodes per patient was 4.0 ± 2.5. An increase of inflammation biomarkers was evidenced in 30/81 (37.0%) patients. RAP was associated with extra-cardiac symptoms in 30 (37.0%) patients, mainly pleural effusion (n=12) and joint involvement (n=8).

A MFEV mutation was evidenced in 6/39 (15.4%) patients, i.e. heterozygous M694V (n=2), heterozygous M694I (n=1) and heterozygous E148Q (n=3). A TNFRSF1A mutation was evidenced in 6/38 (15.8%) patients, i.e. heterozygous R92Q (n=4), heterozygous P46L (n=1) and homozygous R92Q (n=1). None patient had a mutation on both TNFRSF1A and MFEV.

Before colchicine treatment, patients with compared to those without HPFS mutations had a higher number of RAP episodes (4.8 ± 3.5 vs. 4.0 ± 1.7; $p=0.95$). After colchicine treatment, a PAR relapse was evidenced more frequently in patients with compared to those without HPFS mutation [5/12 (41.7%) vs. 4/27 (20%); $p=0.10$].

Conclusion: Patients with "idiopathic" recurrent acute pericarditis showed high prevalence of hereditary periodic fever syndrome genetic mutations. A higher frequency of pericarditis relapse seems to be associated with the presence of such mutations.

ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Predictors and Outcomes
Tuesday, November 8, 2011, 2:30 PM–4:00 PM

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Predictors of Organ Damage Despite Serologic Remission in a Subset of Patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID). Cailin H. Sibley[1], Nicole Plass[1], Carmen Brewer[2], Kelly King[2], Christopher Zalewski[2], H. Jeffrey Kim[2], Rachel Bishop[3], Patrick Kicker[1], Zachary Phillips[1], Joseph G. Dolan[1], Deborah Stone[4], Dawn C. Chapelle Neal[1], Christopher Snyder[1], John Butman[5], Robert Wesley[5] and Raphaela T. Goldbach-Mansky[1]. [1]NIAMS/NIH, Bethesda, MD, [2]NIDCD/NIH, Bethesda, MD, [3]NEI/NIH, Bethesda, MD, [4]NHGRI/NIH, Bethesda, MD, [5]NIH, Bethesda, MD

Background/Purpose: NOMID, caused by mutations in *NLRP3*, results in organ-specific and systemic inflammation with elevated serum inflammatory markers. While patients universally respond to therapy with IL-1 blocking medications, organ damage progresses in a subset of patients.

Methods: 26 patients were treated with anakinra (IL-1 receptor antagonist) for a minimum of 36 months. Clinical and laboratory parameters were measured at scheduled intervals.

Results: Patients frequently relapsed and remitted from inflammatory control with serum remission (CRP$<$0.5 mg/dl) observed in 51.6% of the study visits. At 36 months, 11/25 patients had elevated leukocytes in the CSF ($>$ 5 cells/ml) obtained by lumbar puncture (LP). Of these patients, 7/11 (63.6%) had normal CRP values compared to 8/14 (57.1%) without CSF leukocytosis. Of the patients without leptomeningeal enhancement on MRI, CSF leukocytosis was seen in 12/15 (80%) at baseline and 6/19 (31.8%) at 36 months suggesting that imaging is not as sensitive as LP to detect aseptic meningitis in this cohort. The majority of patient ears (36/44, 81.8%) did not worsen by ASHA criteria over 36 months, while 8/44 ears (18.2%) from 7 patients showed worsening. Patients with worsened ears had a higher mean CRP over the first 36 months of the study at 1.68 compared to 0.89, $p=0.0172$ and inner ear inflammation as manifested by cochlear enhancement on gadolinium-enhanced MRIs was higher for ears that worsened compared to those that did not worsen (0.478 ± 0.104 vs. 1.229 ± 0.284, $p=0.0161$). The mean deviation on automated visual field testing across all patients was stable over the examination period except in two patients where their four eyes worsened by greater than 10% over the treatment period in the absence of clinically detectable intraocular inflammation. In both patients optic nerve thickness was severely decreased at baseline. Mean visual field deviation scores per eye at three years strongly correlated with optic nerve thickness (Pearson correlation = 0.59, $p=0.016$, n = 16).

Conclusion: Control of disease at the serum level is inadequate to prevent further organ damage in some patients with severe NOMID. Low grade CNS

inflammation and progressive hearing loss can occur in some patients even when serum markers are low. Inner ear MRIs are non-invasive tools to monitor cochlear inflammation. Our data suggest that monitoring of inflammatory organ manifestations is necessary to guide treatment decisions and prognostic estimates in NOMID. These data suggest that aggressive dose escalation of IL-1 blocking therapy to control systemic and organ specific inflammation is necessary to prevent progressive organ damage in patients with severe NOMID.

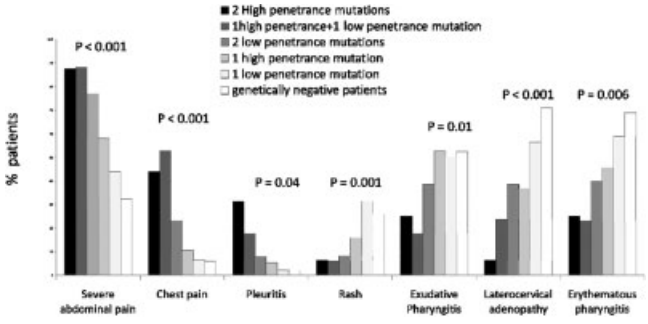
2452

Impact of *MEFV* Mutations in Caucasian Children with Periodic Fevers: Clinical Evidence for a Gain of Function Effect. Silvia Federici[1], Giuseppina Calcagno[2], Martina Finetti[3], Romina Gallizzi[4], Antonella Meini[5], Agata Vitale[2], Francesco Caroli[1], Marco Cattalini[5], Roberta Caorsi[1], Francesco Zulian[6], Alberto Tommasini[7], Antonella Insalaco[8], Maria Pia Sormani[9], Maurizia Baldi[10], Isabella Ceccherini[1], Alberto Martini[3] and Marco Gattorno[1]. [1]G. Gaslini Institute, Genova, Italy, [2]Sezione di Reumatologia Pediatrica, Università di Messina, Messina, Italy, [3]IRCCS G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [4]Sezione di Immunologia e Reumatologia Pediatrica, Università di Messina, Messina, Italy, [5]Dipartimento di Pediatria, University of Brescia, Brescia, Italy, [6]University of Padua, Padova, Italy, [7]Dipartimento di Pediatria, Univerity of Trieste, Trieste, Italy, [8]Divisione di Reumatologia, Ospedale Pediatrico Bambino Gesù, Roma, Italy, [9]Unità di Biostatistica, DISSAL, University of Genoa, Genova, Italy, [10]Ospedale Galliera, Genova, Italy

Background/Purpose: despite FMF is considered an autosomal recessive disease caused by mutations of *MEFV*, one third of patients carry one mutation only. Aim of the present study was to analyze the clinical manifestation associated with periodic fever in a set of Caucasian children with periodic fever to evaluate the actual impact of *MEFV* mutations on the phenotype.

Methods: 113 Caucasian patients carrying *MEFV* mutations (46 with mutations in two alleles, 67 heterozygous) and 205 genetically negative patients for MEFV, TNFSF1A and MEFV (70% with a PFAPA phenotype) were analyzed. The extracellular region of the p55 TNF receptor (from exon 1 to exon 6) of the TNFRSF1A gene, the 10 coding exons (from 2 to 11) of the MVK gene and exons 2, 3, 5 and 10 of the MEFV gene were analyzed by means of denaturing high-performance liquid chromatography (DHPLC) and DNA sequencing. For each patient detailed clinical information about family and personal history, prevalence and frequency (sometimes, often, always) of the clinical manifestations associated with fever episodes had been collected by means of a standardized questionnaire. The following groups were considered: patients with: i) 2 high penetrance mutations (M694V, M694I, M680I), ii) 1 high, 1 low penetrance mutation, iii) 2 low penetrance mutations, iv) 1 high penetrance mutation, v) one low penetrance mutation, vi) genetically negative.

Results: Patients with two *MEFV* mutations displayed higher prevalence of chest pain ($p = 0.001$, Fisher's Exact Test), pleurisy ($p = 0.003$) and severe abdominal pain ($p = 0.002$). In contrast, patients carrying one mutation displayed an higher prevalence of erythematous ($p = 0.01$) and exudative ($p = 0.009$) pharyngitis, enlarged cervical lymph nodes ($p = 0.002$) and skin rash ($p = 0.007$). Moreover, patients with 2 *MEFV* mutations displayed also a later disease onset (mean 47 ± 40 months) and a shorter duration of fever episodes (2.9 ± 1.6 days) in respect to heterozygous patients (mean 30 ± 36.9 months, $p = 0.02$; and 5.1 ± 6.9 days, $p = 0.03$, respectively).The frequency of "FMF-like symptoms" decreases from patients carrying two high penetrance mutations towards patients with a single low penetrance mutation with a opposite behavior for "PFAPA-like symptoms" (Figure).



Conclusion: the present study shows a dosage effect of MEFV mutations not consistent with a pure autosomal recessive disorder. A dominant negative or gain of function effects or variants of still unidentified modifier genes may influence the presence of a FMF phenotype in heterozygous patients.

2453

Development of a Clinical Disease Activity Measure for Juvenile Localized Scleroderma. Suzanne C. Li[1], Kathryn S. Torok[2], Elena Pope[3], Katie G. Stewart[4], Gloria C. Higgins[5], Egla C. Rabinovich[6], Kathleen M. O'Neil[7], Ivan Foeldvari[8], Kathleen A. Haines[1], Heidi Jacobe[9], Marilynn G. Punaro[4], Ronald M. Laxer[10], Themba Nyirenda[1] and Knut M. Wittkowski[11]. [1]Hackensack University Medical Center, Hackensack, NJ, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]Hospital for Sick Children, Toronto, ON, [4]Texas Scottish Rite Hospital, Dallas, TX, [5]Nationwide Childrens Hosp, Columbus, OH, [6]Duke University Medical Center, Durham, NC, [7]Okla Univ Health Science Ctr, Oklahoma City, OK, [8]Hamburger Zentrum Kinder-und Jugendrheumatologie, Hamburg, Germany, [9]UT Southwestern Medical Center at Dallas, Dallas, TX, [10]The Hospital for Sick Children, Toronto, ON, [11]Rockefeller University, NY

Background/Purpose: Juvenile localized scleroderma (jLS), unlike adult disease, frequently involves deeper tissues and other organs. Children are at risk for major morbidity including limb length discrepancy, facial hemiatrophy, and arthropathy. There is a need for validated sensitive assessments to be able to conduct comparative effectiveness studies. We describe our efforts to develop a validated clinical jLS disease activity measure.

Methods: A prospective study of jLS patients was conducted, with active to inactive patients enrolled at 2:1 ratio. Each patient had one lesion (study lesion) examined at 3 study visits by same clinician. Assessed features included change in lesion size, erythema, violaceous color, skin thickness, warmth, distinct margin, skin texture, and atrophy. Lesion temperature was measured with a handheld infrared thermometer, and parents were asked for their global assessment (GA) of their child's disease activity and impact.

Physicians rated disease activity (DA) of study lesion and overall disease, and damage of study lesion and overall disease on visual analog scales (physician global assessment (PGA)). Spearman's rho was calculated between each assessed parameter and PGA using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results: 103 jLS patients were enrolled at 8 pediatric rheumatology centers from 2/2009 to 6/2010. Most patients were Caucasian, female, and had linear scleroderma, either alone or as part of mixed morphea (Table 1).

Table I. Demographics

	All Patients	Active Patients (71)	Inactive Patients (32)
Age (median) at study entry [range]	11.54 yrs [0.33–21.25 yr]	11.00 yrs [0.33–19.67]	12.04 yrs [5.25–21.25 yr]
Age (median) at disease onset [range]	8.0 yrs [0–15.33 yr]	8.0 yrs [0–15.33 yr]	7.0 yrs [2–14 yr]
Disease duration at study onset [range]	2.75 [0.08–15.75 yr]	2.17 [0.08–11.75 yr]	2.92 [1.42–15.75 yr]
Sex	76F: 24 M (76%)	53 F: 15 M (78%)	23 F: 9 M (72%)
jLS Subtype	37 Linear trunk/limb 13 Linear head/PRS 10 Circumscribed deep 4 Circ superficial 6 Generalized Morphea 32 Mixed Morphea	26 Linear trunk/limb 9 Linear head/PRS 7 Circumscribed deep 2 Circ superficial 4 Generalized Morphea 22 Mixed Morphea	11 Linear trunk/limb 4 Linear head/PRS 3 Circumscribed deep 2 Circ superficial 1 Generalized Morphea 10 Mixed Morphea
Ethnicity/race	72 Caucasian 6 Hispanic 3 African Am 4 SE Asian 2 Asians 12 Mixed	51 Caucasian 5 Hispanic 2 African Am 3 SE Asian 2 Asians 5 Mixed	21 Caucasian 1 Hispanic 1 African Am 1 SE Asian 7 Mixed

Interim analysis of 59 patients who completed all 3 study visits showed different patterns of correlation with PGA of DA of study lesion for several parameters, most having fair to moderate level of correlation (Table 2). Some parameters correlated at all, others at only 1 or 2 visits, suggesting some may be time dependent. Dermal and subcutaneous atrophy, dyspigmentation, and stable lesion size correlated with PGA of damage.

Table 2. Correlation between clinical parameters and PGA of DA of study lesion

	Visit 1			Visit 2			Visit 3		
Parameter	Spearman's Rho	Confidence Interval	p value	Spearman's Rho	Confidence Interval	p value	Spearman's Rho	Confidence Interval	p value
Erythema	0.651	0.473, 0.777	<0.0001	0.477	0.215, 0.653	0.0001	0.624	0.438, 0.759	<0.0001
Larger lesion	0.283	0.028, 0.502	0.0298	0.326	0.077, 0.538	0.0112	0.441	0.209, 0.627	0.0004
Stable lesion size	−0.356	−0.561, −0.110	0.0053	−0.297	−0.514, −0.044	0.0219	−0.372	−0.573, −0.128	0.0035
Parental GA of DA	0.486	0.243, 0.671	0.0002	0.369	0.122, 0.573	0.0041	0.457	0.225, 0.640	0.0003
Skin thickness: border	0.301	0.049, 0.517	0.0201	0.297	0.042, 0.516	0.0232			NS
Skin thickness: center			NS	0.356	0.107, 0.562	0.0058	0.493	0.258, 0.666	<0.0001
Abnormal skin texture	0.361	0.115, 0.565	0.0047	0.329	0.080, 0.540	0.0105			NS
New non-study lesion	0.380	0.137, 0.580	0.0028			NS	0.262	0.007, 0.486	0.0444
Violaceous color	0.348	0.101, 0.555	0.0066			NS			NS
Distinct Margin	0.444	0.212, 0.629	0.0004			NS			NS
Lesion warmth			NS			NS	0.516	0.297, 0.683	<0.0001

Conclusion: This is the first multi-center prospective study to evaluate correlation between clinical features and DA in jLS. Interim analysis of 59 patients identified several clinical features correlated with PGA–DA at fair to substantial levels. We have now finished study data collection and will be carrying out multivariate analysis to determine relationships and level of correlation of parameters. We hope to generate a weighted clinical DA measure to enable rigorous evaluation of treatment efficacy. Identifying optimal therapy for jLS will reduce disease and medication-related morbidity, and thereby improve the long-term outcome for these patients.

2454

Defining Clinical Remission and Inactive Disease in Juvenile Systemic Lupus Erythematosus. Rina Mina[1], Laura E. Schanberg[2], Marisa Klein-Gitelman[3], B. Anne Eberhard[4], Gloria Higgins[5], Karen Onel[6], Nora G. Singer[7], Kathleen M. O'Neil[8], Deborah M. Levy[9], Shannen L. Nelson[10], Wajeeha Yousaf[11], Rubén J. Cuttica[12], Lori B. Tucker[13], Michael W. Beresford[14], Graciela Espada[15], Angelo Ravelli[16], Alberto Martini[17], Edward H. Giannini[18] and Hermine Brunner[19]. [1]Cincinnati Children's Med Ctr, Cincinnati, OH, [2]Duke University Medical Center, Durham, NC, [3]Children's Memorial Hospital, Chicago, IL, [4]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [5]PRCSG, Columbus, OH, [6]University of Chicago, Chicago, IL, [7]MetroHealth Medical Center, Cleveland, OH, [8]Okla Univ Health Science Ctr, Oklahoma City, OK, [9]The Hospital for Sick Children, Toronto, ON, [10]Cincinnati Children's Hospital, Cincinnati, OH, [11]University of Cincinnati, [12]Hospital de Pediatría Pedro de Elizalde, Buenos Aires, Argentina, [13]BC Childrens Hospital, Vancouver, BC, [14]Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [15]Childrens Hosp Ricardo Gutierrez, Buenos Aires, Argentina, [16]Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genova, Italy, [17]IRCCS G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [18]PRCSG-Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [19]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background/Purpose: An initial Delphi survey delineated key commonalities for a standard definition of clinical remission and inactive disease in jSLE. However, additional clarifications were required. The aim of this project is to develop a definition of and criteria for clinical remission and inactive disease in jSLE.

Methods: A second international Delphi survey was conducted among pediatric rheumatologists. Consensus was set at 75%. Data from a cohort of jSLE (n=36) patients considered to be in remission by their treating physician were compared to the results of the survey.

Results: There were 311 respondents (response rate: 52%). Consensus was achieved regarding the key definitions under consideration (Table 1). Respondents agreed that with clinical remission: a) there could be at most one mild, non-limiting symptom (i.e. fatigue, joint pains, headaches or myalgia) but no objective physical signs of disease activity; b) the ANA could be persistently abnormal but not the complete blood count, urine sediment, and complement C3; and c) there could be regular use of several systemic medications (Table 1). Majority of the respondents stated that regular use of non-steroidal anti-inflammatory drugs and hydroxychloroquine with clinical remission were permissible. Data from jSLE patients supported the results of the survey.

Table 1. Definition of Clinical Remission and Clinically Inactive Disease in JSLE

		Acceptable Use of Medications for Lupus				
Construct	**Time frame**	**Cortico steroids**	**Immuno suppressives**	**Preventive medications¶**	**Medications to treat SLE damage**	**Consensus**
Clinically Inactive Disease	Time-point	Yes	Yes	Yes	Yes	93% (227/244)
Clinical Remission on Medication	Time-period: ≥ 6 months	Yes	Yes	Yes	Yes	95% (231/244)
Clinical Remission on Preventive Medication	Time-period: ≥ 6 months	No	No	Yes	Yes	95% (224/237)
Clinical Remission Off Medication	Time-period: ≥ 12 months	No	No	No	Yes	83% (200/241)

Legend: Preventive medications include systemic medications that can be used to prevent disease and treat damage such as statins, aspirin, angiotensin converting enzyme (ACE) inhibitors, biphosphonates, vitamin D, and omega-3-fatty acids

Conclusion: Consensus has been reached on the definition of 'Clinical Remission' and 'Clinically Inactive Disease' in jSLE. The results of the Delphi process will be used to guide the data-driven development of provisional criteria of clinical remission and inactive disease in jSLE.

2455

Cancer Risk In Pediatric Systemic Lupus: Updated Analyses. Sasha Bernatsky[1], Rosalind Ramsey-Goldman[2], Earl D. Silverman[3], Ciaran M. Duffy[4], Kiem Oen[5], Alan M. Rosenberg[6], Laura E. Schanberg[7], Kathleen M. O'Neil[8], Emily von Scheven[9], Jeremy Labrecque[1], Elizabeth M. Turnbull[1] and Ann E. Clarke[1]. [1]Research Institute of the McGill Univ. Health Ctre, Montreal, QC, [2]Northwestern University, Chicago, IL, [3]Hospital for Sick Children, Toronto, ON, [4]Children's Hospital of Eastern Ontario, Ottawa, ON, [5]University of Manitoba, Winnipeg, MB, [6]Royal University Hospital, Saskatoon, SK, [7]Duke University Medical Center, Durham, NC, [8]Okla Univ Health Science Ctr, Oklahoma City, OK, [9]UC San Francisco, San Francisco, CA

Background/Purpose: There is increasing interest in the malignancy profile of patients with systemic lupus erythematosus, SLE. Compared to the wealth of data regarding cancer risk in adults with SLE, relatively little is known about cancer risk in pediatric-onset SLE. Our objective was to assess the observed cancer incidence in a large combined clinical cohort of individuals with pediatric-onset SLE, and compare this to the expected incidence, based on general population cancer incidence rates.

Methods: We ascertained cancer incidence within the SLE clinic registries maintained at six North American pediatric rheumatology centers (Duke University Medical Center N=79; University of California-San Francisco N=219; University of Oklahoma N=31; Sick Children's Hospital Toronto N=368; University of Manitoba, Winnipeg N=45; Royal University Hospital, Saskatoon, SK N=34; and Montreal Children's Hospital N=21).Subjects in each clinic registry were linked to regional tumor registries to determine cancer risk over theobservational interval, spanning the calendar years 1974–2009. In-situ cancers were excluded. The person-years of follow-up for each subject were calculated from the date first seen at the rheumatology clinic, and the first of three possible events: death, cancer, or the end of the study interval (December 31, 2009). Pooling the data, we determined the total number of observed cancers occurring over the total person-years of observation. Total number of cancers expected to occur over the observation interval was calculated by multiplying the person-years in the cohort by the geographically matched age, sex, and calendar year-specific cancer rates, and summing over all person-years. The ratio of observed to expected malignancies represents the standardized incidence ratio, SIR.

Results: The study sample was comprised of 797 patients. The proportion of females in the cohort was 79%, and the average age at cohort entry was 13.1 years (SD=3.8); these characteristics were consistent across all six cohorts. Subjects were observed for a total of 5649 patient-years, with an average follow-up of 7.1 years (SD=6.1). Within this observation interval, based on regional age- and sex-appropriate cancer rates, 2.1 invasive cancers would have been expected, however, 9 invasive cancers occurred, for an SIR of 4.29, 95% confidence interval, CI 1.96, 8.14. These events occurred an average of 13.5 years after SLE diagnosis (the most recent being within two months after SLE diagnosis, the latest event being 22.8 years after SLE diagnosis). The cancer cases included two non-Hodgkin lymphoma, NHL, and one leukemia, for a hematologic cancer SIR of 6.7 (95% CI 1.4, 19.5).

Conclusion: These data represent the most up-to-date results from our multi-centre initiative to clarify baseline cancer risk in pediatric-onset SLE. This suggests an increased risk in over-all cancer occurrence in pediatric onset SLE, which may be driven by hematologic cancer risk. Further work is in progress to further assess this issue.

2456

Distinct Functional Activation and Connectivity Patterns for a Visuo-Constructional Task in Childhood-Onset Systemic Lupus Erythematosus and Matched Controls. Marisa Klein-Gitelman[1], Adlin Cedeno[1], Aimee Baker[2], Frank Zelko[1], Dean Beebe[2], Blair Dina[1], Anna Carmela P. Sagcal-Gironella[3], Darren Gitelman[4], Hermine Brunner[2], Mark Difrancesco[2] and Brian Zappia[2]. [1]Children's Memorial Hospital, Chicago, IL, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Cincinnati Children's Hospital, Cincinnati, OH, [4]Northwestern University, Chicago, IL

Background/Purpose: To use functional MRI (fMRI) to characterize brain activation and connectivity differences for a visuo-constructional (VC) task between cSLE patients and matched best-friend controls.

Methods: As part of a broader study protocol, 44 subjects (F:M=36:8; age 10–17 yrs; 59% African-American, 41% Caucasian; 11% Hispanic), 22 with cSLE and 22 controls matched for age, sex, and race performed a square completion task during fMRI. This task exercises visuo-constructional ability (VCA), a domain showing deficits by formal neuropsychological testing in cSLE.

Image data were pre-processed and analyzed for activation in SPM8 (www.fil.ion.ucl.ac.uk/spm) and for functional connectivity using CONN v.12.p (nitrc.org). Image data, acquired at 3 Tesla, consisted of T2*-weighted echo-planar images with TR=3s, 64×64 matrix, 256 mm FOV, and 44 axial 3 mm slices. A high resolution T1-weighted anatomic reference image was acquired for each subject. Average activation was calculated for the cSLE and control groups. Differences in connectivity strength to specific regions of interest between groups were assessed.

Results: Figure 1A shows activation and deactivation patterns for the control group when performing the square completion task. This is compared to the activation patterns for the cSLE group in Figure 1B. Qualitatively, the cSLE group activates more strongly in the ventral visual stream while the control group is stronger in frontal regions including the anterior cingulate (AC). More deactivation is observed in the posterior cingulate (PC) region for controls compared to cSLE.

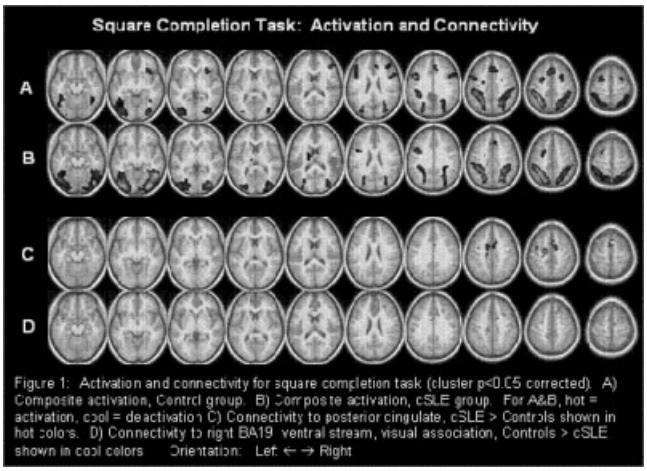


Figure 1: Activation and connectivity for square completion task (cluster p<0.05 corrected). A) Composite activation, Control group. B) Composite activation, cSLE group. For A&B, hot = activation, cool = deactivation C) Connectivity to posterior cingulate, cSLE > Controls shown in hot colors. D) Connectivity to right BA19 ventral stream, visual association, Controls > cSLE shown in cool colors Orientation: Left ← → Right

Led by these trends in activation, differences between subject groups were calculated with regard to voxel-wise functional connectivity to the PC region (Figure 1C) and to the right visual association (rVA) region (Figure 1D). During the square completion task, cSLE subjects maintained a stronger connection between the PC and frontal cortex, particularly the AC, while connectivity between the rVA and the ACC was stronger for the control group.

Conclusion: For a VC task, probing a domain known to show deficits for cSLE, these findings suggest that regions of the brain, such as the PC, that generally need to deactivate when engaged in a challenging task, are not suppressed as much in cSLE compared to controls and that stronger connectivity is maintained between these regions and the frontal lobe. A complementary finding is that connectivity between rVA, part of the ventral visual stream, and the frontal lobe is more robust for the control subjects while cSLE subjects need to activate the ventral stream more strongly to perform the task. Together, these results suggest an imbalance of task-negative and task-positive communication and function in networks pertaining to VCA in cSLE.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Clinical Aspects: Diagnostic and Remission Criteria
Tuesday, November 8, 2011, 2:30 PM–4:00 PM

2457

Patients with a Severe Clinical Disease Course Can Be Identified Using Cluster Analysis – Results From a Canadian National Early Arthritis Cohort. Ye Sun[1], Cindy Lim[2], Gilles Boire[3], Boulos Haraoui[4], Carol A. Hitchon[5], Edward C. Keystone[6], Janet E. Pope[7], J. Carter Thorne[8], Diane S. Ferland[9], Vivian P. Bykerk[10] and CATCH Investigators[11]. [1]Mount Sinai Hospital, Toronto, ON, [2]Mount Sinai Hospital, Toronto, [3]CHUS - Sherbrooke University, Sherbrooke, QC, [4]Institut de Rhumatologie, Montreal, QC, [5]University of Manitoba, Winnipeg, MB, [6]Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Mount Sinai Hospital, Toronto, ON, [7]St. Joseph's Health Care, University of Western Ontario, London, ON, [8]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [9]LaSalle, QC, [10]Brigham & Women's Hospital, Boston, MA, [11]Canada

Background/Purpose: In any patient (pt) with early RA there is significant variability of their disease course. In order to predict treatment response it is important to understand which patients (pts) will fit in any given disease trajectory (traj) based on that pts' baseline (BL) presentation. We aimed to determine if pts clinical disease course fit into distinct clusters as trajectories (trajs) and whether differences in clinical course could be attributed to specific baseline characteristics or to pts medication use.

Methods: We applied a group-based trajectory of modeling approach proposed by Nagin (1) to 185 early RA patients with 2 years of follow up, from a national early inflammatory arthritis observational cohort study, to test the hypothesis that clustering exists.

Results: 5 distinct trajs were identified within this sample of RA pts (Figure). BL variables age, employment status, RF and ESR were identified to be significantly different between the clusters (Table). Pts in traj 1 had low levels of disease activity (DA) and went into remission. In traj 5 pts had very high levels of DA (DAS28 > 7.0) at BL and remained in that state. In traj 2 pts had moderate levels of DA and remained in that state. Two groups of pts emerged presenting initially with high DA but diverged in their course. Although pts in traj 3 and traj 4 had the same DA at BL, pts in traj 3 showed marked improvement and went into remission whereas those in traj 4 had high moderate DA despite more intense treatment than those in traj 3. Overall, pts with a worse clinical disease course needed more intense therapy over time.

Baseline characteristics	1	2	3	4	5	p-value
N = 185	38	38	46	51	12	
Age (years), >50 (%)	27.5	56.5	50	61.6	50	**0.0194**
Gender, Female (%)	77.5	87.2	65.2	74.1	83.3	0.193
Ethnicity, Caucasian (%)	90	82.1	91.3	78.8	58.3	0.0547
Education, > High school (%)	75	69.3	58.7	46.2	58.3	0.0524
Income > $50,000 (%)	65.6	42.3	39	36.4	40	0.1246
Full time employment (%)	80	51.3	58.7	40.4	33.3	**0.0012**
Married/Common Law (%)	67.5	71.8	63	73.1	50	0.5341
Current Smoking (%)	25	10.3	10.9	17.3	16.7	0.3671
RF positivity (%)	55.9	74.2	34.2	45.7	45.5	**0.0161**
Anti-CCP positivity (%)	56.2	63.6	56.2	60	50	0.9601
Erythrocyte Sedimentation Rate (ESR) (mean (SD)	9.24 -8.7	26.4 -18.6	31.1 -25.1	35.3 -22.7	41.3 -23.9	**<0.0001**
Disease Duration months (mean (SD))	7.04 -2.99	6.78 -3.53	5.48 -2.81	6.31 -3.07	6.3 -3.68	0.1622

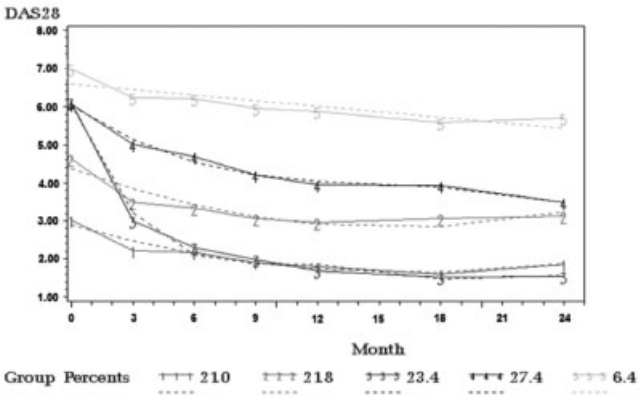


Figure. Patient's clinical course over time clustered into trajectories based in clinical presentation.

Conclusion: Distinct differences in clinical course occurs over 2 years in pts with early RA that can be predictably clustered into a disease trajectory using the methodology of Nagin. This method could enhance predictive modeling of patient outcomes using BL clinical factors in studies of observational RA cohorts and allow better understanding of treatment responses.

References:

1 Nagin D.S. (2005), Group-based modeling of development. Cambridge, Massachusetts, Harvard University Press.

2458

Defining Erosive DISEASE Typical of RA In the LIGHT of the 2010 ACR/EULAR Criteria for Rheumatoid Arthritis–PHASE 1. R. Knevel[1], Désirée van der Heijde[1], Tom W.J. Huizinga[1], Cédric Lukas[2], Bernard G. Combe[2] and Annette H.M. van der Helm-van Mil[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Hopital Lapeyronie, Montpellier, France

Background/Purpose: Last year, the EULAR in collaboration with the ACR derived the 2010 classification criteria for Rheumatoid Arthritis (RA)1. According to these criteria, RA can be classified if patients fulfill 6 out of 10 points or if

patients have 'typical' erosive disease on radiographs. At the publication of the criteria it was agreed that the definition of significant erosive disease should be further investigated1. This study reports the first stage of the results of a EULAR taskforce that aimed to define RA-specific erosiveness.

Methods: Baseline radiographs of hands and feet of early arthritis patients included in the Leiden EAC between 1993 and 2006 (n=980) were studied. It was evaluated which number of erosive joint as well as which location of erosiveness could best identify patients with RA. In this study, RA was defined by the initiation of any DMARD-therapy during the first year of follow-up. MTX therapy was not commonly used before 2000, which makes it a less suitable outcome measure than any DMARD-therapy. Secondly, it was tested which degree of erosiveness could best identify persistent disease after 5-years follow-up. It was aimed to have a high specificity and a low false positive classification.

Results: Data on treatment in the first year and on disease persistency over 5-years was available for respectively 902 and 886 patients. 64% of the patients were female, 37% anti-CCP+ and 42% RF+. For all outcome measures the presence of more than 4 erosive joints resulted in the highest specificity (95–97%) and positive predictive value (94%) (Table I). No difference in joint location was observed for specific joints (MCP/PIP/MTP) or extremities (hands/feet).

Table 1. Test characteristics when the cut-off of erosiveness was set at different number of erosive joints.

			Leiden-EAC						
Outcome	**Erosion-group**	**N (%)***	**Sens**	**Spec**	**PPV**	**NPV**	**LR+**	**LR-**	**AUC**
DMARD	no erosions	395							
(N=902)	≥1 joint	507 (56)	0.72	0.75	0.85	0.57	2.90	0.37	0.74
	≥2 joints	387 (43)	0.57	0.86	0.89	0.50	4.03	0.50	0.72
	≥3 joints	307 (34)	0.46	0.89	0.89	0.45	4.09	0.61	0.67
	≥4 joints	227 (25)	0.35	0.93	0.91	0.42	5.21	0.70	0.64
	> 4 joints	179 (19)	0.28	0.97	0.94	0.40	8.51	0.74	0.62
PERSISTENCY	no erosions	395							
(N=886)	≥1 joint	473 (54)	0.12	0.97	0.93	0.28	4.61	0.90	0.55
	≥2 joints	358 (41)	0.47	0.80	0.89	0.30	2.41	0.65	0.64
	≥3 joints	283 (33)	0.38	0.85	0.90	0.28	2.63	0.72	0.62
	≥4 joints	209 (24)	0.29	0.92	0.92	0.27	3.45	0.78	0.60
	> 4 joints	169 (19)	0.24	0.95	0.94	0.26	4.55	0.81	0.59

Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio
* number and percentage of patients positive in this analysis

Applying this erosion criterion in addition to the recently published ACR/EULAR 2010 criteria1 resulted in 14 patients that were additionally classified as RA compared to applying the ACR/EULAR 2010 criteria without assessing radiographic data. All of these 14 patients had persistent disease over 5 years.

Conclusions: These data indicate that the presence of >4 erosive joints is highly specific for RA. Comparable analyses in an independent cohort of early arthritis patients is required to define RA-specific erosiveness in the light of the 2010 ACR/EULAR criteria.

References:

1. Aletaha, D et al. Arthritis Rheum. 2010;62:2569–81.

2459

The New ACR/EULAR Definition of Remission in Rheumatoid Arthritis: A Comment on the Patient Global Assessment Criterion. Marloes Vermeer[1], Ina H. Kuper[1], Arie E. van der Bijl[2], Hetty Baan[3], Marcel D. Posthumus[4], Herman L.M. Brus[5], Piet L.C.M. van Riel[6] and Mart A.F.J. van de Laar[1]. [1]University of Twente & Medisch Spectrum Twente, Enschede, Netherlands, [2]Isala Klinieken, Zwolle, Netherlands, [3]Ziekenhuisgroep Twente, Almelo, Netherlands, [4]University Medical Center Groningen, Groningen, Netherlands, [5]TweeSteden Ziekenhuis, Tilburg, Netherlands, [6]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands

Background/Purpose: Recently, new definitions of remission in rheumatoid arthritis (RA) for clinical trials have been proposed by the ACR/EULAR committee. According to the Boolean based definition, a patient is in remission when the scores on the following measures are all ≤1: 28 tender joint count (TJC28), 28 swollen joint count (SJC28), C-reactive protein (CRP, mg/dL) and patient global assessment (PGA, 0–10 scale). However, it remains debatable whether or not the PGA criterion represents remission. The hypothesis of this study is that patients in daily clinical practice will frequently score high on the PGA, despite low scores on objective clinical parameters that represent remission. The objective of the present study was to assess the prevalence of ACR/EULAR remission in a cohort of patients with very early RA in daily clinical practice, and to analyze cases in which all remission criteria except for the PGA criterion were fulfilled.

Methods: Data were used from the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort study. In this study, patients with very early RA (symptom duration ≤1 year) were treated according to a treat to target strategy aiming at remission (DAS28<2.6). PGA was assessed using a visual analogue scale (VAS) for arthritis specific global health. In observations where the TJC28, SJC28 and CRP criteria were met but not the PGA criterion, a higher PGA score could be explained by disease activity in joints not included in the 28 joint count (e.g. the feet). To take this into account, more comprehensive joint counts were used. We defined clinical remission as a TJC53≤1, SJC44≤1 and CRP≤1.

Results: This study analyzed 4866 observations of a total of 588 patients. ACR/EULAR remission for all 4 measures was observed in 17.9% (869/4866) of the observations. In 20.8% (1014/4866) of the observations, patients had a high PGA score (>1) despite low tender and swollen joint counts (TJC28≤1, SJC28≤1) and normal CRP (≤1). The distribution of the PGA showed wide ranges beyond the cut point for remission (median (IQR) of 2.5 (1.8–3.9)). When using more comprehensive joint counts, clinical remission (TJC53≤1, SJC44≤1 and CRP≤1) was observed in 1571 of 4866 observations. In half of these observations (787/1571), the new remission definition was not met due to high scores on the PGA.

Conclusion: In a considerable number of cases, high scores on the PGA (>1) were observed, despite a low number of tender and swollen joints and normal CRP. This might lead to misclassification of patients that are clinically in remission, but have high PGA scores due to other reasons. This finding was not explained by disease activity in joints not included in the 28 joint count. Apparently, other factors than these objective clinical parameters influence the PGA. Therefore, caution should be taken when using the new remission definition with regard to the PGA criterion.

2460

Performance of the New ACR/EULAR Remission Criteria Compared to DAS28 Remission in Unselected Real-Life Patients with Rheumatoid Arthritis. Dörte Huscher[1], Katja Thiele[2], Sascha Bischoff[2], Marina Backhaus[3], Martin Aringer[4], Ina Kötter[5] and Angela Zink[1]. [1]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Charité University Medicine, Berlin, Germany, [4]Uniklinikum TU Dresden, Dresden, Germany, [5]Department of Internal Medicine II, Rheumatology Division, Tübingen, Germany

Background/Purpose: The new ACR/EULAR remission criteria comprise two equally applicable definitions: either a boolean definition (number of swollen and tender joints each ≤1, CRP≤1 mg/dl, and patient global assessment ≤1 [NRS 0–10]), or a simplified disease activity index (SDAI) score of ≤ 3.3. Both definitions are more stringent than the established EULAR criterion based on a DAS28<2.6. Even though the criteria have been developed data-driven, it has to be further evaluated how these criteria perform in different cohorts of real-life patients.

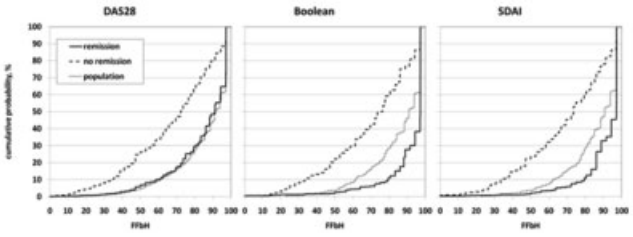
Methods: We used cross-sectional data of 6,864 RA patients, enrolled in the National Database of the German Collaborative Arthritis Centres between 2007 and 2009, for whom all 3 remission criteria could be calculated. Patients seen in more than one year were included only once. The functional status was measured by the Hannover Functional Status Questionnaire (FFbH) in percent of full function (0–100%)[1]. For patients in remission according to one ouf of the three criteria the functional status was compared to data from the age and sex matched general population.

Results: 75% of the patients were female, their mean age was 61.5 years, the median disease duration 9.1 years, and the mean DAS28 3.4. 1,931 patients (28%) were in DAS28 remission, 476 (7%) in boolean and 740 (11%) in SDAI remission.

If patients fulfilled the new, but not the DAS28 criterion, this was mainly due to high ESR (mean ESR 39.0 for patients in boolean but not DAS28 remission, and 39.1 for those in SDAI but not DAS28 remission). If patients fulfilled the DAS28 but not the new criteria, this was due to patient global assessments exceeding 1 (mean patient global for DAS28 remission but not boolean: 3.4, DAS28 remission but not SDAI: 3.6).

Compared to the DAS28 criterion, the new criteria select more stringently patients with low pain (mean 1.0 for boolean and 1.3 for SDAI compared to 2.8 for DAS28 remission), low fatigue (1.1, 1.3 and 2.6, respectively) and good function (92.4%, 91.8% and 84.3% of full function, respectively).

Compared to a population cohort (Fig.1), patients in remission according to the new criteria have a functional status that is even superior to their age and sex matched population counterparts.



Conclusion: The RA new remission criteria stringently select patients who have nearly no functional limitation, pain or fatigue. Since the functional status of these patients is better than expected from the age and sex matched population, a weakness of the new criteria could be that patients with disabling co-morbid conditions cannot reach remission even if their RA is entirely inactive. Other disabling conditions might influence the self-rating, even if patients are asked explicitely to refer to the RA only. More research is needed to better understand the influence of co-morbidity on patients' self assessments and the consequences for the definition of remission.

2461

RAPID3 Remission Vs New ACR Rheumatoid Arthritis Remission Criteria: RAPID3 Has Similar Utility and May Be Used in Everyday Clinical Care. Yusuf Yazici[1], Maria T. Filopoulos[2] and Christopher J. Swearingen[3]. [1]Division of Rheumatology, New York University School of Medicine and NYU Hospital for Joint Diseases, New York, NY, [2]NYU Hospital for Joint Diseases, New York, NY, [3]University of Arkansas for Medical Sciences, Little Rock, AR

Background/Purpose: New remission criteria for RA have been introduced to be more stringent than currently available definitions of remission, by DAS28, CDAI or RAPID3. However there is very little information regarding the feasibility of the new remission criteria in routine clinical care and if it is better than RAPID3 definition of remission, a very simple, patient friendly tool and easily implemented in everyday patient care.

Methods: Arthritis Registry Monitoring Database (ARMD) has been collecting prospective patient data since 2005 in all patients seen in routine care at New York University. Each patient in this setting (with any diagnosis) completes a 2-sided, 1-page MDHAQ (multidimensional health assessment questionnaire) at every visit while waiting to see the physician in the infrastructure of clinical care. The MDHAQ includes scales for physical function, pain, patient global estimate (PATGL), fatigue, and a self-report RADAI painful joint count. Last visits of RA patients seen between between July 2005 and April 2011 were studied. Differences in self-report MDHAQ scores, RAPID3 (routine assessment of patient index data 3; an index of function, pain, and PATGL), and the new ACR remission criteria were analyzed.

Results: 704 RA patients were evaluated (mean age 53.9 (15.4), disease duration 5.5 (7.5) years, 80% female. 116 (16%) were in remission as defined by RAPID3 (≤ 3 of total 30 points) at last visit, while 61 (9%), 190 (27%), and 337 (48%) were in low, moderate and high disease activity respectively. Disease characteristics are given in Table 1, by RAPID3 scores. Similar classification percentage (17%) was seen by the new ACR criteria for remission. Percent agreement between remission by RAPID3 and new ACR criteria was 96% with a very strong agreement beyond chance (kappa = 0.86, $p < 0.001$).

	Remission	Mild	Moderate	Severe	Total
N	116	61	190	337	704
Age (Years)	52.7 (15.6)	53.0 (14.7)	51.8 (15.5)	55.6 (15.3)	53.9 (15.4)
Duration (Years)	4.8 (6.2)	4.7 (6.6)	5.3 (7.3)	6.1 (8.2)	5.5 (7.5)
Female (%)	88 (76%)	49 (80%)	151 (79%)	272 (81%)	560 (80%)
Function [0–10]	0.3 (0.5)	0.9 (0.9)	1.8 (1.3)	4.3 (1.9)	2.7 (2.2)
Pain [0–10]	0.6 (0.6)	1.9 (1.0)	3.7 (1.6)	7.4 (1.8)	4.8 (3.1)
Global [0–10]	0.4 (0.6)	1.8 (0.9)	3.5 (1.5)	7.0 (1.9)	4.5 (3.0)
MD Global [0–10]	1.0 (1.1)	1.7 (1.7)	2.0 (1.6)	3.0 (1.6)	2.3 (1.7)
Swollen [0–28]	0.1 (0.4)	0.5 (1.5)	1.2 (2.7)	2.7 (3.9)	1.7 (3.3)
Tender [0–28]	0.7 (2.0)	1.5 (3.5)	2.7 (3.5)	5.1 (4.9)	3.4 (4.4)
ESR (mm/hr)	17.5 (15.6)	20.9 (17.5)	24.5 (22.4)	31.4 (25.2)	25.3 (22.4)

Conclusion: Remission defined by RAPID3 (≤3/30) performs similarly to the new ACR remission criteria in this patient population and can likely be used in routine care as a target for disease control with similar benefits. The ease of use of RAPID3 compared to the new criteria may make it a good option for busy clinicians.

2462

American College of Rheumatology/European League Against Rheumatism Remission Criteria Achievement in Rheumatoid Arthritis: Data From 32 Countries. Nasim A. Khan[1], Tuulikki Sokka[2] and QUEST-RA[3]. [1]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, [2]Jyvaskyla Central Hosp, Jyväskylä, Finland, [3]Jyväskylä

Background/Purpose: To a) assess the newly proposed American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) rheumatoid arthritis (RA) remission criteria prevalence in a multi-national cohort of RA patients and compare it to remission rates according to previous definitions and b) assess non-RA disease activity related factors that are independently associated with non-achievement of the ACR/EULAR remission.

Methods: This analysis is based upon 8488 patients in the Quantitative Standard Monitoring of Patients with RA (QUEST-RA) database who received usual care from rheumatologists in 32 countries. ACR/EULAR remission criteria was defined by fulfillment of all of the following: tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, patient's global assessment (PTGL) ≤ 1, and Erythrocyte Sedimentation Rate (ESR) < 30 mm/h for women or < 20 mm/h for men. ESR was used due to it's wider availability and measurement uniformity. Remission rates according to Disease Activity Score 28 (DAS28) and ACR, were available for 24 countries from the previous publication. We defined subset of patients in "near-remission" if they met any three of the four ACR/EULAR remission criteria. Multivariable logistic regression (MLR) model that included socio-demographic factors, RA characteristics, psychological distress measure, and comorbidity burden was performed to identify factors associated with non-achievement of the ACR/EULAR remission criteria.

Results: 550 (6.5%) patients met the ACR/EULAR remission criteria. ACR/EULAR definition leads lower remission rates than DAS28 but is quite similar to ACR definitions of remission (Table). 1052 (12.4%) patients met the near-remission criteria. The individual criteria (n, %) that excluded meeting of the ACR/EULAR remission in these patients were: PTGL (719, 68.3%), TJC (99, 9.4%), SJC (101, 9.6%), and ESR (133, 12.6%). DAS28 score [median (Q1-Q3)] for the remission and the near-remission groups were 1.75 (1.36–2.11) and 2.12 (1.71–2.58) respectively; while the corresponding Clinical Disease Activity Index (CDAI) score were 0.9 (0.4–1.8) and 4.10 (2.59–6.47) respectively. Residence in Low GDP country, low education level, longer RA duration, more comorbidites and psychological distress were associated with lower likelihood of achieving remission.

Table. Unadjusted rates of remission according to different remission definitions in the QUEST-RA study by country (DAS28 and ACR remissions from the reference)

	Definition of remission (percentage of patients)		
Country	ACR/EULAR	DAS28	ACR
Serbia*	0	0.0	0.0
Kosovo*	0	1.0	0.0
Egypt*	0.1		
Lithuania*	0.3	1.4	0.3
Russia*	0.6	4.5	2.8
Finland**	12.8	36.6	12.3
Netherlands**	13.6	40.8	16.3
Ireland**	14.2	22.4	14.0
USA**	14.2	36.1	13.8
Greece**	20.3	36.5	21.5
Total (for entire cohort)	6.5	19.6	8.6

*Countries with lowest ACR/EULAR remission rates; **Countries with highest ACR/EULAR remission rates

Conclusion: Prevalence of ACR/EULAR remission was low in this large multinational cohort of RA patients. Several non-disease activity related variables are associated with non-achievement of remission as per the stringent ACR/EULAR definition.

Reference.

1. Arthritis Rheum 2008, 58: 2642–2651.

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Immediate and Delayed Impact of Oral Glucocorticoid Therapy On Risk of Serious Infection In Patients with Rheumatoid Arthritis: A Nested Case-Control Analysis Using a Weighted Cumulative Dose Model. William G. Dixon[1], Michal Abrahamowicz[2], Marie-Eve Beauchamp[2], David W. Ray[3], Sasha Bernatsky[4], Samy Suissa[5] and Marie-Pierre Sylvestre[6]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]McGill University, Montreal, QC, [3]The University of Manchester, Manchester, United Kingdom, [4]McGill UHC/RVH, Montreal, QC, [5]Royal Victoria Hosp, McGill Un, Montreal, [6]University of Montreal, Montreal, QC

Background/Purpose: The association between glucocorticoid (GC) therapy and serious infection in patients with rheumatoid arthritis (RA) is uncertain. It is unclear which treatment regimes increase risk, what degree of risk is conferred, or what happens to risk on stopping therapy. Most published work uses crude models of exposure e.g. current use, ever use or cumulative dose. These ignore variations of dose with time and apply improbable weights to past therapy. The aim of this study was to explore the application of a novel weighted cumulative dose (WCD) model to examine the risk of serious infection in patients with RA treated with GC therapy compared to no GC therapy within a nested case-control analysis from a Canadian administrative database, and to compare the results with conventional approaches.

Methods: A case-control analysis matched 1,851 serious infection cases to up to five controls, selected from 16,207 elderly RA patients using disease modifying anti-rheumatic therapy between 1985–2003 in RAMQ, Quebec, Canada. Serious infections were identified as the first occurrence of a primary hospital discharge diagnosis of infection. Oral GC dosage was derived from dispensed pharmacy records. Ten conventional multivariable conditional logistic regression models, each representing GC exposure differently, were compared to a WCD model where GC exposure was represented as the weighted sum of past doses. Weights were estimated to reflect the relative importance of doses taken at different times in the past. Co-morbidity, disease severity and DMARDs were potential confounders and adjusted for in all analyses.

Results: All ten conventional models found a statistically significant association between GC exposure and risk of hospitalization for infection. However, the goodness of fit varied considerably depending on the way GC exposure was represented, the time window over which it was considered, and whether GC dose was taken into account. The WCD model predicted risks better than conventional models (>25 AIC units difference). Current and recent doses had the highest impact on current risk. However, doses taken up to 2.5 years ago were also associated with increased infection risk. Accepting some residual confounding by indication, a current GC user of 5mg prednisolone had a 33%, 53% or 105% increased risk of serious infection when used continuously for the last 3 months, 6 months or 3 years, respectively, compared to a non-user. The risk associated with 5mg prednisolone taken for the last 3 years was equivalent to that associated with 30mg taken for the last month. Discontinuing a two-year course of 10mg prednisolone six months ago halved the risk of infection compared to ongoing use.

Conclusion: GC therapy is associated with infection risk in older patients with RA. Current and recent doses have the greatest impact on infection risk but doses taken up to 2.5 years ago still affect the risk. Knowing how risk depends on past pattern of GC use can guide prescribing to minimize infection risk.

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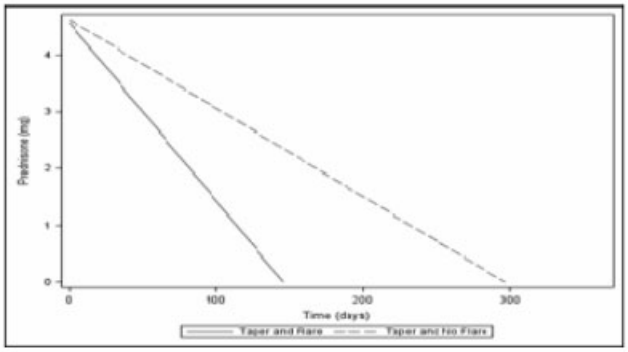
Successful Tapering of Glucocorticoids (GC) in Rheumatoid Arthritis Patients-Results From the Consortium of Rheumatology Researchers of North America Registry. Thasia G. Woodworth[1], Elizabeth Thomas[2], Jeffrey D. Greenberg[3] and Daniel E. Furst[4]. [1]Leading Edge Clinical Research, Stuart, FL, [2]Axio Research, LLC, Seattle, WA, [3]New York University School of Medicine, New York, NY, [4]UCLA, Los Angeles, CA

Background/Purpose: Rheumatoid arthritis (RA) treatment guidelines currently support short-term use of low dose glucocorticoids (GC) when methotrexate (MTX)/DMARDs treatment is initiated. Discontinuation when disease control is achieved is recommended to limit side effects of chronic use (fracture risk, cataracts, ASHD, diabetes). However, the most reliable approach to tapering and discontinuation is not well known. The purpose of this analysis was to identify factors, including RA flares that influence tapering of GC.

Methods: We identified RA patients who achieved stable disease control (CDAI) and stable GC dose over 2 visits (2–7 months apart), with at least 2 subsequent visits, during treatment with DMARDs and GC in the CORRONA RA database. Time to RA flare, operationally defined as an increase in CDAI by >= 1 category or need for additional GC (oral dose increase or intraarticular) from date of established stable disease, was examined in patients who tapered GC versus those who maintained stable doses. Patients who had less than 12 months of follow-up or/and did not flare were censored. Rate of tapering prednisone dose was compared among patients who tapered and experienced flare in the first year compared to those who tapered without flare. Baseline characteristics that might influence flare events and GC tapering were evaluated.

Results: 1076 patients met criteria for analysis, 284 (26.4%) tapering GC (tGC) in year 1 and 792 who remained on stable GC (sGC). CDAI remission/low disease activity was comparable for the tGC group (69.3%) and the sGC group (64.8%). More than half of patients in each group were receiving at least 5 mg/d prednisone, and ~70% were receiving MTX, with more than 60% receiving at least one additional DMARD or/and biologic. Compared to sGC patients, those in the tGC group had fewer flares over time: hazard ratio, 0.697 (95% CI 0.602–0.806, p=<0.001). Of 284 tGC patients, 145 did not flare in the first year. Patients without flare decreased dose at a significantly slower rate, 0.47 mg/month versus 0.95 mg/month (p<0.0001), as shown in graph. Baseline factors associated with successful tapering included use of a biologic (p=0.027) and/or MTX (p=0.042), and possibly baseline CDAI (p=0.061).



GC tapering rates in tGC patients not flaring (dotted line) vs flaring (solid line)

Conclusion: Successful tapering without flare was associated with incremental decreases in GC that were about half those associated with flare. Patients with good baseline disease control receiving MTX and/or a biologic appear less likely to flare. Stable GC did not appear to prevent flare.

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Preliminary Results of a Multicentre Randomised Controlled Trial of Etanercept and Methotrexate to Induce Remission in Patients with Newly Diagnosed Inflammatory Arthritis. Edith Villeneuve[1], Jackie L. Nam[2], Elizabeth Hensor[3], Richard J. Wakefield[4], Philip G. Conaghan[5], Mike J. Green[6], Andrew K. Gough[7], Mark Quinn[8], Richard J. Reece[9], Sally R. Cox[10] and Paul Emery[11]. [1]Leeds Institute of Molecular Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, QC, [2]NIHR Leeds Musculoskeletal Biomedical Research Unit, LIMM, University of Leeds., Leeds, United Kingdom, [3]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [4]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals, Leeds, United Kingdom, [5]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [6]York Teaching Hospital NHS Foundation Trust, Harrogate, United Kingdom, [7]Harrogate District Hospital, Harrogate, United Kingdom, [8]The York Hospital, York Teaching Hospital NHS Foundation Trust, York, United Kingdom, [9]University of Birmingham, Birmingham, United Kingdom, [10]SA Pathology / Flinders Medical Centre, Adelaide, Australia, [11]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom

Background/Purpose: Treatment of early rheumatoid arthritis (RA) with methotrexate (MTX) and etanercept (ETN) achieves high rates of remission.(1) Treating patients with inflammatory arthritis (IA) at an early stage

may provide a window of opportunity for further improvement. The objective of this study was to compare the efficacy of 12 months of methotrexate (MTX) monotherapy (mono) vs. MTX plus etanercept (ETN) combination (combo) therapy in achieving clinical remission defined as no tender or swollen joints (NTSJ), and DAS28(CRP) remission in patients with new IA.

Methods: 18 month study; inclusion criteria: DMARD-naïve, clinical synovitis in ≥1 joint, <3month duration, and positive for RF, ACPA or shared epitope. Patients were randomised to receive MTX up to 25mg/ wk plus placebo (PBO) or MTX (same titration) plus ETN 50mg/ wk for 12 months, followed by MTX monotherapy for both groups. If patients achieved sustained clinical remission(NTSJ [RAI+SJC=0] for >26 weeks), the ETN/PBO injections were stopped prior to 12 months. If patients had NTSJ >12 weeks after stopping ETN, MTX was weaned. Additional DMARDs were allowed after 12 months if there was ongoing disease activity. The primary outcome was NTSJ at week 52. Remission (NTSJ and DAS28(CRP) remission) and LDAS28 for the first 52 weeks are reported here. Pearson's chi-square was used to compare the groups. Holm-corrected threshold for 5% significance was set to $p<0.006$ for secondary outcomes.

Results: 110 patients were enrolled; 55 in each group. Mean age 48.6 years, 76% female, median symptom duration 7.0 months, mean baseline DAS28 4.22. 53% were RF+ve and 77% ACPA+ve. NTSJ at wk 2 was 11% vs. 2%, $p=0.051$ and at 26 weeks 16% vs. 24%, $p=0.340$ in the combo and the MTX mono groups respectively. NTSJ at wk 52 was achieved in 31% of the combo and 29% of the MTX mono group ($p=0.835$). At wk 2, the proportion of patients achieving DAS28 remission and LDAS28 was significantly greater in the combo than in the mono group (38% vs. 9%, $p<0.001$ and 53% vs. 26%, $p=0.003$). At wk 26 and wk 52 a high proportion of patients in both groups were in DAS28 remission and LDAS28 [wk 26 (DAS28 remission 67% vs. 49%, $p=0.053$; LDAS28 82% vs. 62%, $p=0.020$), wk 52 (DAS28 remission 67% vs. 64%, $p=0.688$; LDAS28 82% vs. 73%, $p=0.255$)]. Nine patients (8.2%) withdrew due to lack of efficacy and 5 (4.5%) due to toxicity.

Conclusion: In this group of patients with newly diagnosed inflammatory arthritis, rapid clinical responses were demonstrated with MTX+ETN combination therapy. High proportions achieved DAS 28 remission and low disease activity with approximately one third of patients demonstrating no clinical synovitis at one year. A particularly good response was also seen in this study with MTX monotherapy with similar results to the combination therapy group seen at one year. Predictors of response will be examined.

1. Emery P, Kvien TK, Combe B, Foehl J, Robertson D, Pedersen R, et al. Very early (< 4 months) treatment with combination etanercept (ETN) and methotrexate (MTX) produces significantly better remission rates: results from the COMET study. Ann Rheum Dis 2010;69(Suppl3):57.

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Subsequent Therapy of Patients with Biologic Response Modifiers or Disease-Modifying Antirheumatic Drugs After Coccidioidomycosis.
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Background/Purpose: Coccidioidomycosis (cocci, Valley fever) is a fungal infection endemic to the Southwestern United States, affecting approximately 150,000 people annually. While most are subclinical pulmonary infections, patients on biologic response modifiers (BRMs), including tumor necrosis factor (TNF) antagonists, are at higher risk of developing severe or disseminated disease. There are currently no guidelines regarding BRM or disease-modifying antirheumatic drug (DMARD) therapy or duration of antifungal therapy following cocci.

Methods: A retrospective chart review identified patients who developed cocci while on DMARDs or BRMs. Patients were seen at least once in a University-affiliated or Veterans Administration outpatient rheumatology clinic in Tucson, Arizona between 2007–2009. Charts were reviewed up to June 1, 2011. Review emphasized the mode of diagnosis, clinical manifestations, antifungal therapy and duration, and management of BRM/DMARDs after the diagnosis was made.

Results: We identified 44 patients with cocci during treatment with a BRM and/or DMARD. Rheumatologic treatment was BRM alone (11), DMARD alone (8), or combination therapy (25). Cocci manifestations were asymptomatic positive serologies (6), pulmonary cocci (29), or disseminated disease (9). After the diagnosis of cocci, patients had no change in immunosuppressive therapy (10), all BRM and DMARDs stopped (26), or BRM stopped but DMARD therapy continued (8). All but 3 patients had antifungal therapy initiated for 3 months or longer.

Follow-up data were available for 38 patients. BRM and/or DMARD therapy was continued or resumed in 33 and none have had dissemination or complications from cocci. Sixteen also continued on antifungal therapy. Four patients were not treated with BRM/DMARD due to remission of their rheumatic disease; 1 patient was not treated with BRM/DMARD due to dissemination. The most common reasons for continuing antifungal therapy were persistent positive serologies and disseminated cocci. The most common reason for stopping antifungal therapy was negative cocci serology. Follow-up for patients who stopped antifungals or were never treated is 3 to 96 months (median 30 mos).

Conclusion: Treating with a BRM and/or DMARD after cocci infection appears to be safe in some patients based on our small series. Several patients with negative serologies and resolution of infection resumed BRM/DMARD without concomitant antifungal therapy. Some patients with disseminated disease or persistently positive serologies continued on antifungal therapy when a BRM/DMARD was restarted. Larger studies with longer follow up are indicated to further characterize the relationship between BRM/DMARD therapy and this endemic fungal infection.

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Red Blood Cell Folate Polyglutamates Are An Important Determinant of RA Disease Activity In Patients On Methotrexate – Implications for Folic Acid Supplementation.
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Background/Purpose: Methotrexate (MTX) produces anti-arthritic effects at least in part through folate depletion. Patients receiving MTX are given supplemental folic acid which is thought to reduce MTX adverse effects with minimal effects on efficacy. There is conflicting evidence between United States (US) and New Zealand (NZ) cohorts as to whether elevated red blood cells (RBC) MTX polyglutamate (MTXGlu) concentrations are associated with lower disease activity in RA. However, data from both cohorts suggest that RBC folate polyglutamate (FPGs) may be an important determinant of disease activity. The aim of this study was determine the contribution of RBC $MTXGlu_n$ and RBC FPGs to disease activity in patients with RA from NZ and the USA.

Methods: Data from 428 patients receiving MTX monotherapy (256 patients from the US and 172 patients from NZ) were combined. Cohorts were compared and multivariate logistic regression analysis was undertaken to determine the relationships between RBC $MTXGlu_n$, RBC FPG and RA disease activity (DAS28>5.1).

Results: The mean age of the combined cohorts was 62.4years (18–90.8yrs), 73.6% were female, 61 (14%) were receiving weekly SC MTX and the remainder oral MTX. The majority of patients (386, 90%) were receiving supplemental folic acid (5mg/week in NZ and 1mg/day in US). In comparison to the US cohort, patients in the NZ cohort received higher MTX dose (15.8 vs. 14.0mg/wk; $p<0.001$) and fewer patients were receiving steroids (31.4% vs. 48%; $p<0.001$). DAS28 was significantly lower in the NZ cohort than the US cohort (2.97 vs. 3.8; $p<0.001$). This improved disease control was commensurate with higher long-chain RBC $MTXGlu_3$ (45 ± 1.6 vs. 40 ± 1.5; $p=0.02$) and lower RBC FPGs concentrations (518 ± 22 vs. 1111 ± 32 nmol/l; $p<0.001$) in the NZ cohort than the US cohort. Multivariate logistic regression analysis allowing for age, MTX dose, route of MTX administration, use of steroids, and country revealed that a DAS28>5.1 was associated with lower long-chain $MTXGlu_n$ concentrations ($MTXGlu_3$: $p=0.021$; $MTXGlu_{3-5}$ $p=0.02$) but higher RBC FPGs ($p=0.01$). There was a significant positive correlation between RBC FPGs and DAS28 ($r^2=0.1$, $p<0.001$). For patients with RBC folate ≥1000nmol/L significantly fewer patients had DAS28>5.1 when $MTXGlu_3$ concentrations were ≥20nmol/l compared to <20nmol/L ($p=0.04$) (Table 1).

Table 1. Number (%) of patients with DAS28>5.1 by long chain $MTXGlu_3$ and FPG concentrations

	RBC folate polyglutamates	
$MTXGlu_3$	Low (<1000nmol/l)	High (≥1000nmol/l)
Low (<20nmol/l)	3/44 (6.8%)	8/21 (38%)
High (≥20nmol/l)	10/172 (5.8%)	14/99 (14.4%)

Conclusion: In RA patients on methotrexate, disease activity is dependent on both long-chain MTXGlu and RBC folate concentrations. However, the RBC folate concentration appears to be the more important determinant. Because higher supplemental folic acid doses as well as dietary fortification in the US result in higher RBC folate concentrations in the US than in NZ, further studies will be important to determine the most appropriate regimen for folic acid supplementation in patients on MTX.

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Discontinuation of Adalimumab Without Functional and Structural Progress After Attaining Remission in Patients with Rheumatoid Arthritis. Yoshiya Tanaka[1], Shintaro Hirata[1], Shunsuke Fukuyo[1], Masao Nawata[2], Satoshi Kubo[1], Kunihiro Yamaoka[2] and Kazuyoshi Saito[1]. [1]University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, [2]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Background/Purpose: Biologics targeting TNF has revolutionized the treatment of RA, enabling high clinical remission rate and producing emerging endpoint of treatment, which has made us approach to biologic-free remission. Discontinuation of TNF inhibitors after acquisition of remission is an important issue from the viewpoints of safety and economy. However, reports on this topic are only from BeSt study and TNF20 study in early RA. We have reported that infliximab could be discontinued after attaining low disease activity by the RRR study. All of which were treated with infliximab. Recent finding in OPTIMA study using adalimumab is also done for early RA. The present study was undertaken to seek the possibility of discontinuing adalimumab therapy after acquiring clinical remission of RA and to evaluate progression of articular destruction during infliximab discontinuation.

Methods: The study included patients with any disease duration, but excluded patients who had received steroids at dosages greater than 5mg/day. After obtaining DAS28<2.6 for more than 24 weeks, adalimumab was discontinued. The primary endpoint was DAS28<3.2 at 6 months after the discontinuation. Modified total Sharp score (mTSS) was checked at registration and 1 year after the discontinuation. The second endpoint is DAS28, SDAI, mTSS and HAQ at 1 year after the discontinuation.

Results: Among 156 RA patients treated with adalimumab and MTX, 40 patients discontinued adalimumab because DAS28<2.6 was kept for more than 24 weeks. The average of age was 58, mean disease duration was 93 months and mean duration treated with adalimumab was 62 weeks. The disease duration was significantly shorter in patients who could discontinue adalimumab than those who kept the therapy. Thirty and 16 patients were estimated at 6 months and 1 year, respectively after the discontinuation of adalimumab. Twenty two cases (73%), 17 cases (57%) and 21 cases (79%) reached DAS28<3.2 low disease activity, DAS28<2.6 remission and SDAI<3.3 remission for 6 months after discontinuation of adalimumab, respectively, indicating the study is satisfied with the primary endpoint. DAS28 at study entry affected the primary endpoint and cut-off point affecting the study achievement was 1.9, suggesting "deep remission" is required for the discontinuation. Of 16 patients estimated at year 1 after the discontinuation, 10 (63%), 11 (69%) and 14 (88%) reached DAS remission, SDAI remission and HAQ remission, respectively. Radiographic estimation could be done in 17 patients. The ΔmTSS from the discontinuation to year 1 was −0.2 and 1.9, and the ratio of structural remission for 1 year was 100% and 71%, in 10 patients who kept remission for 1 year and 7 patients who flared within 1 year after the discontinuation, respectively.

Conclusion: Although it is a limited study, after reduction of disease activity to clinical remission in patients with RA by adalimumab, most patients, especially reaching "deep remission", could successfully remain clinical remission without adalimumab for 6 months or 1 year and without radiologic and functional progression of articular destruction. Thus, tight control targeting remission by ADA potentiates biologic-free remission without functional progress.

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Efficacy and Safety of Abatacept Over 12 Months in Patients with Lupus Nephritis: Results From a Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase II/III Study. Richard Furie[1], Kathy Nicholls[2], Tien-Tsai Cheng[3], Frederic Houssiau[4], Ruben Burgos-Vargas[5], Shun-Le Chen[6], Richard Aranda[7], Stephanie Meadows-Shropshire[8], Michael Kinaszczuk[8] and Joan T. Merrill[9]. [1]North Shore-Long Island Jewish Health System, Lake Success, NY, [2]Royal Melbourne Hospital, Victoria, Australia, [3]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, [4]Cliniques Universitaires Saint-Luc, Brussels, Belgium, [5]Hospital General de Mexico, Mexico City, Mexico, [6]Joint Molecular Rheumatology Laboratory of Institute of Health Sciences and Shanghai Ren Ji Hospital, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences and Shanghai Jiao Tong University School of Medicine, Shanghai, China, [7]Bristol-Myers Squibb [at time of study], Princeton, NJ, [8]Bristol-Myers Squibb, Princeton, NJ, [9]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Abatacept (ABA), a selective T-cell costimulation modulator approved for rheumatoid arthritis, is being evaluated for lupus. Preclinical data in murine lupus and Phase II data in systemic lupus erythematosus (SLE) pts with arthritis, serositis or discoid lesions[1] supported the development of ABA in lupus nephritis (LN).

Methods: This was a 12-mth Phase II/III double-blind study in pts with active ISN/RPS Class III or IV LN, requiring: urinary protein/creatinine ratio (UPCR) ≥0.44 mg/mg (50 mg/mmoL); active urinary sediment (>5 red blood cells [RBC]/high power field [hpf] or >8 white blood cells/hpf or cylindruria); and renal biopsy within 3 mths (if biopsy 3–12 mths, abnormal C3, C4 or anti-dsDNA also required). All pts received mycophenolate mofetil (MMF; target dose 1.5–3.0 g/day dependent on race) and up to 60 mg/day prednisone or equivalent (with response-guided taper after 28 days). Pts were randomized to placebo (PBO) or IV ABA (either 3 mths of ABA 30 mg/kg followed by 9 mths of 10 mg/kg [30/10], or 12 mths of 10 mg/kg [10/10]). The primary efficacy endpoint was time to Complete Renal Response (CRR: GFR within 10% of pre-flare/screening value; UPCR <0.26 mg/mg [30 mg/mmol]; inactive urinary sediment) confirmed at 30 days after the first response, compared using a Cox proportional hazards model. Secondary endpoints included time to Renal Improvement (RI) and Mth 12 rates of CRR and RI (RI: ≥50% UPCR reduction, GFR ≥50% improved if screening 15–59, otherwise ≥90% of screening; no active sediment). Exploratory endpoints included 1) Patient Response (PR: UPCR <0.5 mg/mg [56.5 mg/mmol] or ≥50% UPCR improvement to <1.0 mg/mg [113 mg/mmol] if baseline ≤3.0 mg/mg [339 mg/mmol] or to 3.0 mg/mg if baseline >3.0; RBCs within reference range (<5–8/hpf) or ≥50% reduction; serum creatinine normal or ≤25% above baseline) and 2) Renal Response (RR: serum creatinine ≤25% above baseline; ≥50% UPCR improvement to <1.0 mg/mg if baseline ≤3.0 or to <3.0 mg/mg if baseline >3.0). Safety was assessed.

Results: Of 298 treated pts, 228 (76.5%) completed Mth 12 (78.0, 74.7, and 76.8% in PBO, ABA 10/10, and ABA 30/10). Time to CRR did not differ between groups (p=0.549 and 0.422) for ABA 10/10 and 30/10 vs PBO) nor did time to RI. Efficacy at Mth 12 is shown (Table). A subset analysis of 122 nephrotic pts (baseline UPCR >3.0 mg/mg) found ~20–30% greater reduction in UPCR in pts randomized to ABA vs PBO from Mth 6, maintained to Mth 12. Safety is reported (Table). Cause of death appeared to be underlying disease for 5 pts and infection for 7.

	Placebo N=100	10/10 N=99	30/10 N=99
CRR at Month 12, % (95% CI)	3.0 (0.6, 8.5)	3.0 (0.6, 8.6)	5.1 (0.7, 9.4)
Estimate of difference vs placebo (95% CI)	NA	0.0 (−4.6, 4.7)	2.4 (−2.4, 7.2)
RI at Month 12, %	55.0	52.5	55.6
Hazard ratio estimate (95% CI)	NA	1.0 (0.69, 1.48)	1.1 (0.76, 1.61)
PR at Month 12, % (95% CI)	34.0 (24.7, 43.3)	30.3 (21.3, 39.4)	38.4 (28.8, 48.0)
Odds ratio (95% CI)	NA	0.88 (0.49, 1.59)	1.21 (0.68, 2.13)
RR at Month 12, % (95% CI)			
Estimate of difference vs placebo	33.0 (23.8, 42.2) NA	39.4 (29.8, 49.0) 6.2 (−7.1, 19.0)	45.5 (35.6, 35.3) 12.6 (−1.1, 26.2)
Deaths, n (%)	7 (7.0)	2 (2.0)	5 (5.1)
SAEs, n (%)	31 (31.0)	28 (28.3)	33 (33.3)
Serious infections, n (%)	17 (17.0)	18 (18.2)	23 (23.2)
Most common:*	3 (3.0)	4 (4.0)	4 (4.0)
Pneumonia	0	6 (6.1)	3 (3.0)
Herpes zoster	2 (2.0)	1 (1.0)	5 (5.1)
Gastroenteritis	2 (2.0)	2 (2.0)	0
Urinary tract infection			

*Reported in more than one pt in either abatacept group

Conclusion: ABA, MMF and steroids exhibited a safety profile similar to MMF and steroids in pts with LN. Pre-specified efficacy endpoints did not demonstrate a benefit at 12 mths for ABA vs PBO. Among nephrotic pts, an exploratory analysis showed improvement in proteinuria with ABA, suggesting that additional exploration may be warranted to investigate potential biologic activity in this subset.

[1]Merrill JT et al. *A&R* 2010;**62**:3077–87

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Active Immunization Against IFNα with IFN-Kinoid in SLE Patients Is Safe, Immunogenic and Induces Down-Regulation of IFN-Mediated Genes. Frédéric. A. Houssiau[1], Raskov Rashkov[2], Eric Hachulla[3], Estibaliz Lazaro[4], Christian Jorgensen[5], François Spertini[6], Xavier Mariette[7], Géraldine Grouard-Vogel[8], Bernard Fanget[8], Olivier Dhellin[8], Bernard Lauwerys[1] and Pierre Vandepapelière[8]. [1]Université catholique de Louvain, Brussels, Belgium, [2]MHAT Sveti Ivan Rilski, Sofia, Bulgaria, [3]Internal Medicine, Lille CEDEX, France, [4]Hôpital Haut-Lévêque, Pessac, France, [5]Hospital Lapeyronie, Montpellier, France, [6]CHU Vaudois, Lausanne, Switzerland, [7]Université Paris-Sud, Le Kremlin Bicetre, France, [8]NEOVACS SA, Paris, France

Background/Purpose: Interferon alpha (IFNα) is associated with the severity and disease activity of SLE. Active immunization against IFNα induces polyclonal antibodies against all IFNα subtypes *in vivo* and prevents severe renal lupus disease in NZW/NZB SLE-prone mice. We evaluate IFNα-Kinoid in a first clinical study in SLE patients.

Methods: IFNα-Kinoid (IFNα-K, Neovacs SA, Paris, France) is an immunotherapeutic agent composed of recombinant human IFNα conjugated to KLH as a carrier protein, inactivated and adjuvanted with ISA-51 emulsion.

Twenty-eight patients with mild to moderate, seropositive lupus (SLEDAI 4–10) were enrolled in a double-blind, placebo-controlled, phase 1–2, dose escalation study to evaluate the safety and the immunogenicity of four doses of IFNα-K (30, 60, 120 or 240 mg) administered intramuscularly on Days 0, 7 and 28 with an optional fourth dose on Day 84. Safety evaluation included recording of adverse events and monitoring of haematological and biochemical parameters. Immune responses were measured through titration of anti-IFNα and anti-KLH antibodies, and cellular lymphoproliferation assays. Clinical response was assessed by evaluation of BILAG, SLEDAI, PGA, SRI and titration of serum auto-antibodies, and of IFNα regulated chemokines. PBMC were harvested at several time-points and transcriptomic studies were performed on total RNA using Genechip HGU133 Plus 2.0 arrays.

Results: The safety profile is very favourable. Few minor and transient local and systemic reactions have been observed following immunization. Only minor and transient infections were reported. Two lupus flares were reported as related serious adverse events, one in the active group in a patient who had spontaneously stopped glucocorticoid therapy after the first IFNα-K dose, the other in the placebo group. A dose-related anti-IFNα antibody response was measured in all immunized patients. Antibodies peak after the last dose and decline afterwards.

Transcriptomic studies performed on baseline PBMC samples indicated that the patients cluster into two groups, characterized by the presence or absence of an IFNa signature. Patients with a positive signature have significantly higher dsDNA Ab titers and significantly lower C3 and C4 levels. In the patients with a baseline IFN signature, follow-up transcriptomic studies, performed as early as 38 days after the first IFNα-K injection, showed a significant down-regulation of the expression of IFN-induced genes in the IFNα-K group as compared to the placebo recipients, and, more generally, of SLE over-expressed genes as a whole.

Conclusion: This is the first study to show positive immune and pharmacodynamic results with active immunotherapy against Interferon-α in the treatment of Systemic Lupus Erythematosus. These results are promising and further studies are planned in order to expand upon these observations.

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Omega-3 in Systemic Lupus Erythematosus: A Double-Blind, Placebo-Controlled Randomized Clinical Trial In Systemic Lupus Erythematosus. Kayode J. Bello[1], Hong Fang[1], Laurence S. Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland, Baltimore, MD

Background/Purpose: Potential health benefits of Omega-3 fatty acids have been reported in cancer, depression, immune and inflammatory processes, and especially in the cardiovascular system (dyslipidemia and cardiac function). In a previous clinical trial, Omega-3 was reported to reduce disease activity in SLE. We performed a clinical trial to examine the effect of Omega-3 on disease activity, endothelial function, inflammatory markers and lipids in SLE patients.

Methods: A randomized, double-blind, placebo controlled clinical trial of Omega-3 polyunsaturated fatty acids was performed. 85 SLE patients (mean age 47.18, 55.29% Caucasian, 37.65% African-American, 94.11% female) were randomly assigned to two treatment groups of either 3 gram Omega 3 (Lovaza, GSK) or placebo for twelve weeks. Disease activity was measured using the physician global assessment (PGA) and SELENA-SLEDAI score. Endothelial function was measured using flow mediated dilation (FMD) calculated from high resolution B-mode ultrasound of brachial artery diameter in response to vasoactive stimuli. Blood samples were drawn for inflammatory markers (s-ICAM-1, s-VCAM-1, IL-6) and lipids profile at baseline and 12-week follow up visits.

Results: Omega 3 had no benefit for disease activity in SLE or for flow mediated dilation (FMD). There was no significant reduction in inflammatory markers. Total cholesterol and LDL cholesterol significantly increased in the Omega 3 group.

Table 1. Association between Omega 3 and various factors in patients with SLE

	Mean Change in Omega 3 Group (SD) (n=42)	Mean Change in Placebo Group (SD) (n=43)	P-value*
s-ICAM-1	−1.61 (40.27)	−5.56 (48.74)	0.2456
s-VCAM-1	−17.52 (101.65)	26.57 (135.98)	0.0918
IL-6	−1.95 (11.16)	−27.60 (186.37)	0.2447
Cholesterol	3.36 (27.24)	−6.48 (22.95)	0.0228
Triglycerides	−43.45 (71.71)	−29.48 (61.81)	0.7041
HDL	2.55 (8.49)	−2.21 (11.87)	0.0929
LDL	3.11 (21.99)	−1.87 (18.29)	0.0266
PGA	0.07 (0.54)	0.21 (0.44)	0.2914
SLEDAI	−0.17 (1.87)	0.51 (2.18)	0.1122

* Based on ANCOVA model using baseline values as a covariate

Table 2. Differences (post-treatment – pre-treatment) in mean percent diameter changes (SD) of flow-mediated dilation among those treated with Omega-3 or Placebo

Period	Variable	Omega-3	Placebo	P-value[1]
Post-Pre differences	Baseline	0.00 (0.04)	0.00 (0.05)	.99
	30 second % change	−0.60 (7.80)	−0.89 (0.83)	.87
	60 second % change	−2.36 (10.01)	−2.73 (8.72)	.86
	90 second % change	−3.96 (11.73)	−2.76 (9.68)	.62

[1] Based on a two-sample t-test.

Conclusion: In this trial, Omega 3 did not affect disease activity, improve endothelial function nor reduce inflammatory markers in SLE. Longer trials might be required if there are delayed clinical effects. However, there was evidence that Omega 3 may increase LDL cholesterol, which would reduce enthusiasm for its long term use in SLE.

2472

Effect of Belimumab Treatment on Renal Outcomes: Results From Phase 3 Belimumab Clinical Trials in Patients with Systemic Lupus Erythematosus. M.A. Dooley[1], F. Houssiau[2], C. Aranow[3], D.P. D'Cruz[4], Anca D. Askanase[5], D. Roth[6], Z.J. Zhong[7], W. Freimuth[7], E.M. Ginzler[8] and BLISS-52/-76 Study Groups[9]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Université catholique de Louvain, Brussels, Belgium, [3]Feinstein Institute for Medical Research, Manhasset, NY, [4]St. Thomas' Hospital, London, United Kingdom, [5]NYU School of Medicine, New York, NY, [6]GlaxoSmithKline, King of Prussia, PA, [7]Human Genome Sciences, Inc., Rockville, MD, [8]SUNY-Downstate Medical Center, Brooklyn, NY, [9]Multicenter

Background/Purpose: To evaluate the effect of belimumab on renal parameters in two phase 3 trials including patients with active systemic lupus erythematosus (SLE) without acute lupus nephritis.

Methods: Autoantibody-positive (antinuclear antibody ≥1:80 or anti-double-stranded DNA [anti-dsDNA] ≥30 IU/mL) SLE patients (N = 1684) with Safety of Estrogen in Lupus Erythematosus National

Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score ≥6 were randomly assigned to belimumab 1 or 10 mg/kg, or placebo, plus standard therapy, for 52 wk (BLISS-52; NCT00424476) or 76 wk (BLISS-76; NCT00410384). The studies were not designed to assess treatment effects on renal outcomes, and patients with severe active lupus nephritis were excluded. Renal parameters collected included renal flares, renal remission, proteinuria, renal items from SELENA-SLEDAI and BILAG, as well as anti-dsDNA and complement (C3/C4) levels. Pooled data are reported through wk 52.

Results: At baseline, 16.4%, 16.1%, and 15.1% of patients treated with placebo, and belimumab 1 and 10 mg/kg, respectively, had renal involvement by SELENA-SLEDAI; 10.5%, 11.1%, and 10.3% had BILAG A or B renal domain scores; and 5.7%, 5.9%, and 6.0% had proteinuria ≥2 g/24 h. Over 52 wk, belimumab-treated patients had numerically lower rates of renal flare, higher rates of renal remission, and shorter time to 1st renal remission vs those treated with standard therapy alone (table). In patients with baseline proteinuria >0.5 g/24 h, the median % reduction in proteinuria at wk 52 was numerically greater in the belimumab groups. More belimumab plus standard therapy patients had renal improvement by both SELENA-SLEDAI and BILAG (10 mg/kg only) measures at wk 52 vs standard therapy alone. More patients receiving belimumab plus standard therapy converted from anti-dsDNA–positive at baseline to negative, and had normalized low baseline C3/C4 levels at wk 52 vs standard therapy alone. In patients with low C3/C4 and anti-dsDNA–positivity at baseline, the difference in wk-52 SELENA-SLEDAI renal improvement between belimumab plus standard therapy and standard therapy alone was more pronounced than in the overall population.

Renal Involvement at Baseline and Outcomes at Wk 52: Pooled Data	Standard Therapy Plus Placebo (n = 562)	Belimumab 1 mg/kg (n = 559)	Belimumab 10 mg/kg (n = 563)
SELENA-SLEDAI renal involvement at baseline (any of hematuria, proteinuria, pyuria, urinary casts), n (%)	92 (16.4)	90 (16.1)	85 (15.1)
BILAG renal domain A or B score at baseline, n (%)	59 (10.5)	62 (11.1)	58 (10.3)
Renal flare over 52 wk, n (%)[a]	16 (2.8)	14 (2.5)	8 (1.4)
Renal remission over 52 wk in patients with baseline proteinuria ≥1 g/24 h, (%)[b]	n = 44/75 58.7	n = 44/67 65.7	n = 55/78 70.5
Median time to first renal remission, d (min, max)	167 (27, 364)	139 (26, 343)	140 (26, 337)
Median % change in proteinuria from baseline at wk 52[c]	n = 116 −27.5	n = 110 −48.3	n = 112 −39.1
Any SELENA-SLEDAI renal improvement at wk 52, %[d,e]	n = 41/92 44.6	n = 46/90 51.1	n = 46/85 54.1
SELENA-SLEDAI proteinuria item improvement, %[f,g]	n = 33/79 41.8	n = 37/78 47.4	n = 31/69 44.9
Any SELENA-SLEDAI renal improvement in low C/anti-dsDNA+ subgroup at wk 52, %[e,h]	n = 21/62 33.9	n = 25/60 41.7	n = 30/60 50.0
Proteinuria item improvement in lowC/anti-dsDNA+ subgroup at wk 52, %[g,h]	n = 16/53 30.2	n = 21/54 38.9	n = 23/53 43.4
BILAG renal improvement at wk 52, %[e,i]	n = 11/22 50.0	n = 10/24 41.7	n = 14/22 63.6
Anti-dsDNA conversion from positive (≥30 IU/mL) at baseline to negative at wk 52, % [j]	n = 19/280 6.8	n = 47/314 15.0+	n = 50/313 16.0#
Low baseline C3 conversion to normal/high (≥90 mg/dL) level at wk 52, %[k]	n = 30/176 17.0	n = 51/193 26.4*	n = 77/202 38.1#
Low baseline C4 conversion to normal/high (≥16 mg/dL) level at wk 52, %[k]	n = 40/218 18.3	n = 86/246 35.0#	n = 115/259 44.4#

*p <0.05; +p <0.01; #p <0.001; otherwise, p = not significant.
[a] Renal flare defined as per Alarcón-Segovia D, Tumlin JA, Furie RA, et al. *Arthritis Rheum.* 48;442–54, 2003; [b]renal remission defined as erythrocyte count <10 cells/hpf, absence of cellular casts, and proteinuria <1 g/24 h equivalent without doubling serum creatinine level; [c]in patients with baseline proteinuria >0.5 g/24 h; [d] in patients with renal involvement at baseline; [e]p values not reported because studies were not designed to examine belimumab's treatment effect on individual organ domains and sample sizes are small; [f]in patients with renal item involvement at baseline; [g]proteinuria decrease of >0.5 g/24 h equivalent or decrease to ≤0.5 g/24 h equivalent; [h]in patients with positive anti-dsDNA (≥30 IU/mL), low C (C3 <90 mg/dL; C4 <16 mg/dL) and renal organ (or specific item) involvement at baseline; [i]in patients scored as having active renal disease at baseline by the principal investigator; improvement defined as step down from baseline BILAG A or B score to B, C, or D at wk 52; [j]in patients with positive anti-dsDNA at baseline; [k]in patients with low C at baseline. C, complement.

Conclusion: These data from a small subgroup of patients with renal involvement at baseline suggest that belimumab may have beneficial effects on renal outcomes in SLE and support initiation of a randomized trial to evaluate belimumab treatment for lupus nephritis.

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Allogeneic Mesenchymal Stem Cells Transplantation in Severe and Refractory Systemic Lupus Erythematosus-Four Years Follow up. Lingyun Sun, Dandan Wang, Huayong Zhang, Xia Li and Xuebing Feng. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: To assess the long-term efficacy and safety of allogenic bone marrow or umbilical cord derived mesenchymal stem cells transplantation (MSCT) for patients with severe and treatment-refractory systemic lupus erythematosus (SLE). ClinicalTrials.gov Identifier: NCT00698191.

Methods: A single-arm trial involved 87 SLE patients, aged from 12 to 56 years old, that were either refractory to standard treatment or with life-threatening visceral involvement. Disease duration was 37.5 months (range, 2 to 264 months). 51 of 87 patients were each given a total of 0.6~2.4gm of CYC intravenously. The other 36 patients received no CYC due to poor physical conditions at baseline. Twenty-three patients were infused once with bone marrow (BM) derived MSCs, 46 patients received once umbilical cord (UC) derived MSCs, while the other 18 patients were transplanted multiple MSCs, due to disease relapse or unsatisfactorily controlling. Allogeneic BM or UC MSCs were administered 1.0×10^6/kg of body weight intravenously once time. The clinical manifestations and laboratory parameters were compared pre- and post-MSCT, with a mean follow-up of 27 months (range, 12 to 48 months). Adverse event was monitored all the time during and post-MSCT.

Results: During the 4 years follow up, the overall rate of survival was 94% (82/87). Five patients died 5, 6, 6, 10 and 18 months post-MSCT respectively, due to uncontrolled infection or disease relapses. Disease-free survival (SLE Disease Activity Index, SLEDAI less than 3 and prednisone dose less than 10mg per day) was 28% at 1 year (23/83), 31% at 2 years (12/39), 42% at 3 years (5/12) and 50% at 4 years (3/6). Rates of relapse (SLEDAI increased at least by 3 and an increase in prednisone or immunosuppressive drug) were 12% (10/83) at 1 year, 18% (7/39) at 2 years, 17% (2/12) at 3 years and 17% (1/6) at 4 years. The overall rate of relapse was 23% (20/87). Significant improvements in SLEDAI score, serum albumin and complement C3 were examined at 1, 2, 3, and 4 years post transplantation. Renal function assessed by 24-hour proteinuria improved 1, 2, 3 and 4 years after MSCT. For those with abnormal levels of serum creatinine and urea nitrogen at baseline, these indexes improved significantly 1 and 2 years after MSCT. Glomerular filtration rate (GFR) was detected for 25 patients before MSCT and then yearly after transplantation, significant improvement was found for 11 patients (56.6 ± 22.8ml/min before MSCT, 78.0 ± 28.1ml/min at 1 year, 91.8 ± 21.3ml/min at 2 years, both $p<0.01$), no change in 12 patients (65.2 ± 27.7ml/min before MSCT, 63.5 ± 30.1ml/min at 1 year, 60.5 ± 32.6ml/min at 2 years), and deterioration in 2 patients (from 78.0 ± 8.5ml/min before MSCT to 30.0 ± 7.1 at 2 years), who also had disease relapses 28 and 24 months after MSCT respectively. During 4 years follow up, no transplantation-related adverse event was observed for all the patients. For 93% (76/82) patients, dose of glucocorticoid was tapered to less than 10mg per day, and dose of immunosuppressant was tapered to maintenance level for 60% (49/82) patients at the last follow up.

Conclusion: Allogeneic MSCs transplantation is a safe and effective therapeutic option for severe and refractory SLE patients.

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Abatacept for Lupus Nephritis: Alternative Outcome Measures Support Opposing Interpretations of Data From a Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase II/III Study. David Wofsy[1], Stephanie Meadows Shropshire[2], Jan L. Hillson[3] and Betty Diamond[4]. [1]VA Medical Center, San Francisco, CA, [2]Bristol-Myers Squibb, Richmond, VA, [3]ZymoGenetics Inc., Seattle, WA, [4]Feinstein Institute Med Rsch, Manhasset, NY

Background/Purpose: Recent trials of novel therapies for lupus nephritis (LN) have used varying primary endpoints, but there is no consensus about which may be most sensitive to change or most representative of clinical status. We compared the performance of two different outcome measures when applied to the same data set from a double-blind, controlled phase II/III study of abatacept (ABA) in patients with LN (trial IM101075- efficacy and safety reported in a separate abstract).

Methods: In IM101075, 300 subjects were randomized 1:1:1 to one of: 3 mos ABA 30 mg/kg and 9 mos of 10 mg/kg [30/10]; 12 mos ABA10 mg/kg [10/10]; or placebo, administered IV in combination with MMF (target dose 1.5–3.0 gm/d) and corticosteroids (prednisone 60 mg/d or equivalent with response-guided taper.) We compared two outcome measures (OM) that have been accepted by

the FDA for use in trials of ABA for LN. OM1, from IM101075, is the proportion of subjects with complete response (CR) at Study Day 337 and 365, defined as eGFR within 10% of pre-treatment value, urine prot:creat ratio (UPCR) <30 mg/mmol, and normal urine sediment. In contrast, OM2 as defined in the ongoing ACCESS study (NCT00774852) is the proportion of subjects who reach CR,defined as serum creatinine either normal or ≤125% of baseline, UPCR <0.5 g/g, and prednisone dose ≤10 mg/d at Study Day 365; urine sediment is not a component of OM2. In 24 subjects from IM101075, renal disease was too mild at entry (UPCR <1 g/g) to apply the OM2 criteria; therefore, these subjects were excluded from the analysis of OM2.

Results: The analysis of OM1 in study IM101075 showed few CRs overall and no difference among the groups (Table). In contrast, OM2 yielded a much higher CR rate and significant differences among groups. The results with OM2 were most striking in patients who were nephrotic at baseline (UPCR >339 mg/mmol).

	Control	ABA 10/10	ABA 30/10
OM1 at Day 337 and 365 (all treated patients), n/N (%)	3/100 (3.0%)	3/99 (3.0%)	5/99 (5.1%) 2.4
Estimate of difference vs. Control (95% CI)		0.0 (−4.6, 4.7)	(−2.4, 7.2)
OM2 at Day 365 (patients with UPCR >1 at entry), n/N (%)	19/90	32/92 (34.8%)	27/92 (29.3%)
Estimate of difference vs. Control (95% CI)	(21.1%)	13.7 (0.6, 26.4)	8.2 (−4.4, 20.7)
OM2 at Day 365 (subjects nephrotic at baseline), n/N (%)	2/45 (4.4%)	9/38 (23.7%)	9/39 (23.1%)
Estimate of difference vs. Control (95% CI)		19.2 (4.4, 35.8)	18.6 (4.0, 35.0)

n=number of subjects with CR, N=number of subjects in the analysis

Conclusion: These findings demonstrate the importance of the choice of outcome measure for LN trials, and they strongly suggest that OM2 is more sensitive to differences between groups. The ability of either measure to predict long-term outcome remains to be determined. These findings have implications for the interpretation of the IM101075 study from which the data were drawn, supporting further evaluation of the efficacy ABA+MMF in patients with LN.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis II: Genetics
Tuesday, November 8, 2011, 2:30 PM–4:00 PM

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A Large-Scale, Multi-Racial Replication Study Identifies Novel Systemic Lupus Erythematosus Susceptibility Loci At *IRF8*, *TMEM39A,* and *IKZF3/ZPBP2.* Christopher J. Lessard[1], Indra Adrianto[1], John A. Ice[1], Jennifer A. Kelly[1], He Li[1], Graham B. Wiley[1], Astrid Rasmussen[1], Marta E. Alarcon-Riquelme[2], Juan-Manuel Anaya[3], Sang-Cheol Bae[4], Elizabeth E. Brown for PROFILE[5], Chaim O. Jacob[6], Judith A. James[7], Javier Martin[8], Timothy B. Niewold[9], Bernardo Pons-Estel[10], Betty P. Tsao[11], Timothy J. Vyse[12], John B. Harley[13], Edward Wakeland[14], Kenneth M. Kaufman[15], Courtney Montgomery[1], Carl D. Langefeld[16], Patrick M. Gaffney[17] and Kathy L. Moser[17]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [3]Universidad del Rosario-Corporacion para Investigaciones Biologicas, Bogota, Colombia, [4]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [7]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [8]Instituto de Parasitologia y Biomedicina Lopez-Neyra (CSIC), Granada, Spain, [9]University of Chicago, Chicago, IL, [10]Rosario, Argentina, [11]UCLA School of Medicine, Los Angeles, CA, [12]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [13]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [14]Univ of Texas SW Med Ctr, Dallas, TX, [15]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation and US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [16]Wake Forest University Health Sciences, Winston-Salem, NC, [17]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, heterogeneous autoimmune disorder characterized by inflammation, loss of tolerance to self-antigens, and dysregulated interferon responses. In this study, we sought to replicate loci with suggestive association with SLE from a previously published genome-wide association scan.

Methods: Genotyping was performed using Illumina iSelect technology. Stringent quality control measures were applied for Hardy- Weinberg proportions, missing genotypes, and excess missingness between cases and controls. In addition, genetic outliers were determined using principal component (PC) analysis. Only SNPs with minor allele frequencies >1% were considered. After quality control filtering, 3562 SLE cases and 3491 controls of European ancestry (EA), 1527 cases and 1811 controls of African-American (AA) descent, and 1265 cases and 1260 controls of Asian (AS) origin were included in the replication analysis. SNP-SLE association was tested using logistic regression under an additive genetic model in PLINK while adjusting for the first three PCs and gender. Meta-analysis was performed using METAL.

Results: Three regions exceeded genome-wide significance (GWS) after the trans-racial replication study. One region that replicated in EA, AA, and AS subjects was located at 11q24.1 outside the 3′UTR region of interferon regulatory factor 8 (*IRF8*; $P_{meta} = 2.34 \times 10E\text{-}9$). Approximately 300 additional SNPs were genotyped in the region of *IRF8*. Two risk haplotypes were observed within the EA subjects ($P = 3.85 \times 10E\text{-}7$ and $P = 7.99 \times 10E\text{-}10$). Logistic regression conditioning on the most significant SNP in each haplotype indicated that these effects were independent. The other two loci included a coding SNP in *TMEM39A* (transmembrane protein 39A; $P_{meta} = 8.62 \times 10E\text{-}9$), and an intra-genic SNP at 17q21 between the genes *IKZF3/ZBP2* in a shared promoter region ($P_{meta} = 3.48 \times 10E\text{-}9$). All three regions have been implicated in other autoimmune diseases. In addition, 13 other loci were replicated in EA but did not exceed GWS with $5 \times 10E\text{-}8 < P < 9.99 \times 10E\text{-}5$ (*CFHR1, CADM2, LOC730109/IL12a, LPP, LOC63920, SLU7, ADATMTSL1, C10orf64, SEN3, OR8D4, FAM19A2, STXBP6,* and *TMCO5*).

Conclusion: *IRF8* is a transcription factor involved in the regulation of the interferon pathway, which has been widely reported to be dysregulated in SLE and other autoimmune diseases. No biologically relevant data has been published for *TMEM39A*. Association with *IRF8* and *TMEM39A* has been previously reported with multiple sclerosis (MS). *IKZF3* is an important transcription factor regulating B lymphocyte proliferation and differentiation. Multiple other autoimmune diseases have identified association with this interval, including Crohn's disease, ulcerative colitis, primary biliary cirrhosis, and rheumatoid arthritis. Thus, this study identified 3 novel SLE risk loci exceeding GWS and replicated 13 additional loci suggestive of association.

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Identification of Novel Genetic Susceptibility Loci In African-American Lupus Patients Using a Candidate Gene Association Study. Elena Sanchez[1], Mary E. Comeau[2], Barry I. Freedman[2], Jennifer A. Kelly[1], Kenneth Kaufman[3], Carl D. Langefeld[2], Elizabeth E. Brown for PROFILE[4], J.T. Merrill[1], Betty P. Tsao[T0], Diane L. Kamen[11], Gary S. Gilkeson[12], Judith A. James[13], Tomothy J. Vyse[14], Patrick M. Gaffney[15], Chaim O. Jacob[16], Timothy B. Niewold[17], Bruce C. Richardson[18], John B. Harley[19], Marta E. Alarcon-Riquelme[20] and Amr H. Sawalha[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Wake Forest University Health Sciences, Winston-Salem, NC, [3]Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [4]University of Alabama at Birmingham, Birmingham, AL, [10]UCLA School of Medicine, Los Angeles, CA, [11]Medical University of SC, Charleston, SC, [12]Division of Rheumatologyand Immunology, Medical University of South Carolina, Charleston, SC, [13]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [14]King's College London, Guy's Hospital, London, United Kingdom, [15]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [16]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [17]University of Chicago, Chicago, IL, [18]University of Michigan, Ann Arbor, MI, [19]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [20]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK

Background/Purpose: Candidate gene and genome-wide association studies have identified several disease susceptibility loci in lupus patients.These studies have been largely performed in European-derived and Asian lupus patients. In this study, we examine if some of these same susceptibility loci increase lupus risk in African-American individuals.

Methods: Single nucleotide polymorphisms tagging 15 independent lupus susceptibility loci were genotyped in a set of 1,724 lupus patients and 2,024 normal healthy controls of African-American descent. The loci examined included: PTPN22, FCGR2A, TNFSF4, STAT4, CTLA4, PDCD1, PXK, BANK1, MSH5(HLA region) CFB (HLA region), C8orf13-BLK region, MBL2, KIAA1542, ITGAM, and MECP2/IRAK1.

Results: We provide the first evidence for genetic association between lupus and five lupus susceptibility loci in African-American lupus patients (C8orf13-BLK, BANK1,TNFSF4, KIAA1542 and CTLA4; P values= $8.0 \times 10–6$, $1.9 \times 10–5$, $5.7 \times 10–5$,0.00099, 0.0045, respectively). Further, we confirm the genetic association between lupus and five additional lupus susceptibility loci (ITGAM, MSH5, CFB, STAT4, and FCGR2A; P values= $7.5 \times 10–11$, $5.2 \times 10–8$, $8.7 \times 10–7$, 0.0058, and 0.0070, respectively), and provide evidence for a genome-wide significance for the association between ITGAM and MSH5 (HLA region) for the first time in African-American lupus patients.

Conclusion: These findings provide evidence for novel genetic susceptibility loci for lupus in African-Americans and demonstrate that the majority of lupus susceptibility loci examined confer lupus risk across multiple ethnicities.

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Risk Alleles of SLE Associated IL10 SNPs Conferred Differential Binding to Transcription Factors. Daisuke Sakurai[1], Jian Zhao[1], Yun Deng[1], Kenneth Kaufman[2], Jennifer A. Kelly[3], Robert P. Kimberly on behalf of PROFILE investigators[4], Marta E. Alarcón-Riquelme on behalf of the BIOLUPUS and GENLES networ[5], John B. Harley[6], Sang-Cheol Bae[7], Chaim O. Jacob[8], Timothy J. Vyse[9], Timothy B. Niewold[10], Patrick M. Gaffney[11], Kathy L. Moser[11], Judith A. James[12], Gary S. Gilkeson[13], Diane L. Kamen[14], Carl D. Langefeld[15], Deh-Ming Chang[16], Yeong Wook Song[17], Chack-Yung Yu[18], Jennifer M. Grossman[19], Rita M. Cantor[20], Bevra H. Hahn[19] and Betty P. Tsao[1]. [1]David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [2]Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [5]Oklahoma Medical Research Foundation; Center for Genomics and Oncological Research, Oklahoma City; Granada, Spain, OK, [6]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [7]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [8]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, [9]Divisions of Genetics and Molecular Medicine and Immunology, King's College London, London, United Kingdom, [10]University of Chicago, Chicago, IL, [11]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [12]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK, [13]Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC, [14]Medical University of SC, Charleston, SC, [15]Wake Forest University Health Sciences, Winston-Salem, NC, [16]National Defense Medical Center, Taipei, [17]Seoul National University College of Medicine, Seoul, South Korea, [18]7Center for Molecular and Human Genetics, The Research Institute at Nationwide Children's Hospital and The Ohio State University, Columbus, OH, [19]UCLA David Geffen School of Medicine, Los Angeles, CA, [20]University of California Los Angeles, Los Angeles, CA

Background/Purpose: Interleukin-10 (IL-10) is produced at high levels by B cells and monocytes of SLE patients and promotes B cell hyperactivity and autoantibody production in these individuals. In a trans-ancestral study, we assessed 16,003 case-control samples to fine map of the *IL10* locus and to evaluate SLE-associated SNPs for potential functions.

Methods: Eight tag SNPs selected from HapMap CEU dataset to cover the *IL10* locus and 347 ancestry informative markers (AIMs) were genotyped on a customized Illumina array. Samples used in association tests included European Americans (EA), African Americans and Gullahs (AA&Gullah), Asians (AS) and Hispanic and Native Americans (Hisp&NA). AIMs were used to estimate global ancestry for each subject and eliminate genetic outliers. We performed Chi-square test to compare the allelic difference between cases and controls, likelihood ratio test to distinguish independent signals from associated SNPs. K562 nuclear extracts were used in electrophoresis mobility shift assay (EMSA) to assess whether SLE-associated *IL10* SNPs might function in IL-10 regulation.

Results: In EA, six SNPs that defined a 6-kb haplotype block were significantly associated with SLE, exhibiting the strongest signal at rs3024505 ($P=2.25\times10^{-8}$, OR=1.29, 18.2% in 3980 cases vs. 14.7% in 3546 controls). Association signals of the other 5 SNPs were eliminated after conditioning on rs3024505, suggesting rs3024505 alone could explain the association of *IL10* with SLE in EA. In non-European ancestries, the SLE-associated allele of rs3024505 present at lower allele frequencies consistently exhibited higher frequencies in cases than controls (AA&Gullah: 4.5% in 1680 cases vs. 3.9% in 1935 controls, AS: 3.1% in 1272 cases vs. 2.7% in 1270 controls, Hisp&NA: 9.0% in 1580 cases vs. 8.3% in 812 controls) but was not significantly associated with SLE. rs3024505 located at 1kb down-stream of 3′UTR was in complete linkage disequilibrium (LD) with rs3122605 (10kb up-stream of 5′UTR), rs3024493 (intron 3) and rs3024495 (intron 4). EMSA results in Figure 1 revealed no binding activity to nuclear extracts using DNA fragments containing rs3024505 or rs3024493, but preferential binding activity in the risk allele of rs3122605 and rs3024495 compared to its respective non-risk allele. These results were consistent with bioinformatic predictions that the risk allele of rs3122605 and rs3024495 conferred differential binding to lymphoid transcription factors MZF1 and CP2/ZID, respectively.

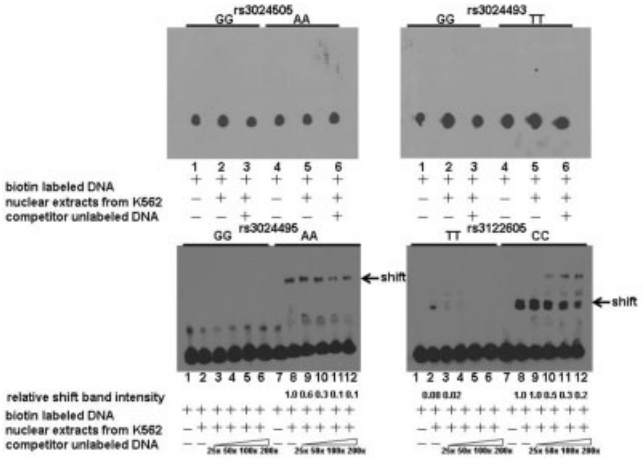


Figure 1. Transition of G to A at rs3024495 and T to C at rs3122605 alters specific binding to nuclear extracts. EMSA analysis of DNA fragment containing rs3024505, rs3024493, rs3024495 or rs3122605 was performed. Competition analysis using increasing concentration of unlabeled oligonucleotide competitor demonstrates the presence of the specific protein-DNA complexes in risk allele of rs3024495 and rs3122605, but not of rs3024505 or rs3024493. Results are one of the three experiments using three separate preparations of myeloblastoma K562 cell line extracts.

Conclusion: Our trans-ancestral mapping localized the association of *IL10* with SLE to rs3024505 in European ancestry, which was in complete LD with rs3122605 and rs3024495 located in the 5′ upstream region and intron 4, respectively. Preferential binding to transcription factors by the risk allele of rs3122605 and rs3024495 might regulate expression of *IL10* transcripts, predisposing to SLE.

2478

Determination of the Contribution of An *IRF5*-SLE Risk Haplotype to *IRF5* expression and Alternative Splicing Using Next-Generation Sequencing. Rivka Stone[1], Peicheng Du[2], Di Feng[1], Lars Ronnblom[3], Maija-Leena Eloranta[4], Robert Donnelly[1] and Betsy Barnes[1]. [1]University of Medicine and Dentistry of New Jersey, Newark, NJ, [2]New Jersey Medical School, Newark, NJ, [3]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden, [4]Section of Rheumatology, Uppsala University, Uppsala, Sweden

Background/Purpose: The transcription factor interferon regulatory factor 5 (*IRF5*) exists as multiple alternatively spliced 1.6-kb transcripts with unique cell type-specific expression. Polymorphisms in the *IRF5* gene have been shown to confer either risk for or protection from the development of systemic lupus erythematosus (SLE), possibly by contributing to aberrant alternative splicing and dysregulated IRF5 expression in patients with SLE. We have recently demonstrated that IRF5 expression and alternative splicing are significantly elevated in SLE patients and expression was associated with an *IRF5* SLE risk haplotype. The aim of this study was to unambiguously determine whether an *IRF5* SLE haplotype defines the profile of *IRF5* transcripts expressed, thus controlling the global function of IRF5 in SLE.

Methods: Standard molecular cloning techniques were used to isolate novel *IRF5* transcripts from purified peripheral blood mononuclear cells (PBMC) and monocytes of genotyped SLE patients and healthy donors. Next-generation sequencing technologies were used to construct comprehensive *IRF5* expression profiles in same samples. Using an array of open-source next-generation sequencing analysis software tools, *IRF5* transcripts were

quantified within and across samples and novel splice sites were identified by *de novo* junction discovery.

Results: Molecular cloning from purified PBMC and monocytes of genotyped SLE patients and healthy donors provided support that SLE patients have enhanced alternative splicing of *IRF5*. By this method, we identified 14 new differentially spliced *IRF5* transcripts in donor immune cells; 9 of which were specific to SLE. Using the ABI SOLiD 3 Plus system, we obtained at least 2×10^6 50-bp reads per sample, providing an unprecedented coverage depth of *IRF5* greater than 3,000-fold (equivalent to ~27,000 clones). Results from next-generation sequencing correlated well with results from cloning yielding identical abundance rankings for the variants. These data provide significant support that a distinct profile of *IRF5* transcripts is expressed in SLE patients as compared to healthy donors. Additionally, data support that the *IRF5* SLE haplotype defines *IRF5* transcript expression in SLE patients.

Conclusion: This study provides the first formal proof that an *IRF5*-SLE risk haplotype defines the profile of *IRF5* transcripts expressed in immune cells of SLE patients and healthy donors. We posit this newly defined workflow of next-generation sequencing as an alternative to traditional molecular cloning, whereby differentially spliced transcripts of a single gene can be rapidly enriched, identified, and quantified in donor RNA samples.

2479

Lupus Nephritis Susceptibility Markers in *PDGRFA-GSX2, SLC5A11, ID4, and HAS2-SNTB1* Regions Identified From a Meta-Analysis of Genome Wide Association Studies of Women with Systemic Lupus Erythematosus. Sharon A. Chung[1], Elizabeth E. Brown[2], Adrienne H. Williams[3], Tushar Bhangale[4], Paula S. Ramos[3], Julie T. Ziegler[3], Barry I. Freedman[3], Robert P. Kimberly[2], Timothy J. Vyse[5], Peter K. Gregersen[6], Chaim O. Jacob[7], Marta E. Alarcon-Riquelme[8], Betty P. Tsao[9], John B. Harley[10], Timothy W. Behrens[4], M. Petri[11], M. Ilyas Kamboh[12], F. Yesim Demirci[12], Susan Manzi[13], Lindsey A. Criswell[1], Kathy L. Moser[14], Patrick M. Gaffney[14], Robert R. Graham[4] and Carl D. Langefeld[3]. [1]University of California, San Francisco, San Francisco, CA, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Wake Forest School of Medicine, Winston-Salem, NC, [4]Genentech, Inc., South San Francisco, CA, [5]King's College London, London, United Kingdom, [6]Feinstein Institute for Medical Research, Manhasset, NY, [7]University of Southern California, Los Angeles, CA, [8]Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK, [9]University of California, Los Angeles, Los Angeles, CA, [10]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [11]Johns Hopkins University School of Medicine, Baltimore, MD, [12]University of Pittsburgh, Pittsburgh, PA, [13]Allegheny Singer Research Institute, Pittsburgh, PA, [14]Oklahoma Medical Research Foundation, Oklahoma City, OK

Background/Purpose: Lupus nephritis (LN) is a clinical manifestation of systemic lupus erythematosus (SLE) resulting from glomerular immune complex deposition and inflammation. LN demonstrates familial aggregation and accounts for significant morbidity and mortality. To facilitate the identification of SLE patients at highest risk for developing LN, we conducted a meta-analysis of three independent genome-wide association studies of SLE.

Methods: Through genotyping and imputation, over 2.5 million markers were assessed among 2,001 women with SLE of European descent. SLE cases were considered to have LN if they fulfilled the American College of Rheumatology renal criterion for SLE or had a renal biopsy consistent with LN. Logistic regression adjusting for admixture was computed to test for association between each genetic marker and LN (N=588 LN cases and N=1423 SLE cases without nephritis).

Results: The strongest evidence for association was observed outside the major histocompatibility complex (MHC) including markers localized to 4q11-q13 (*PDGFRA-GSX2*; OR 3.41; 95% CI 2.1–5.54; $P=2.7\times10^{-7}$), 16p12 (*SLC5A11*; OR 2.85; 95% CI 1.93–4.22; $P=3.0\times10^{-7}$), 6p22 (*ID4*; OR 0.57; 95% CI 0.46–0.7; $P=4.3\times10^{-7}$) and 8q24.12 (*HAS2-SNTB1;* OR 3.15; 95% CI 1.97–5.03*;* $P=6.2\times10^{-7}$). Both *HLA-DR2* and *HLA-DR3*, two well established SLE susceptibility loci, showed evidence of association with LN as assessed by their proxies rs9271366 (OR=1.37; 95% CI 1.09–1.71; P=0.037) and rs2187668 (OR 1.47; 95% CI 1.22–1.77; $P=6.0\times10^{-5}$), respectively. Within the MHC, a marker in the Class I region, rs9263871 (*C6orf15-HCG22*), had the strongest evidence of association with LN independent of *HLA-DR2* and *HLA-DR3* (OR 1.7; 95% CI 1.35–2.13; $P=5.0\times10^{-6}$).

Conclusion: This study is the first genome-wide investigation of LN, and provides promising evidence for non-MHC markers involved in the development of LN given SLE.

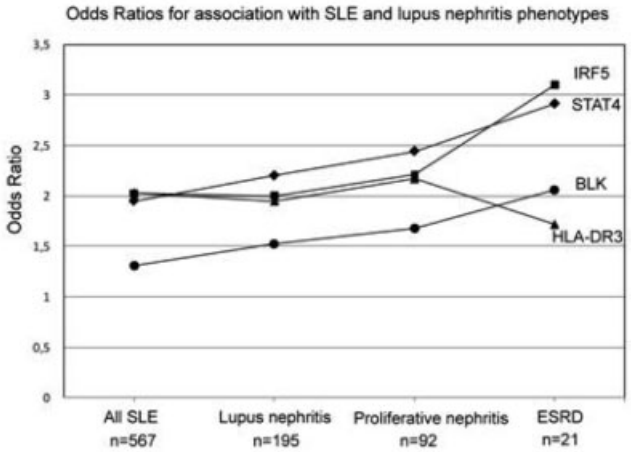
2480

Association of *STAT4, IRF5* and *BLK* Polymorphisms with Severity and Outcome in Lupus Nephritis. Karin G. Eriksson[1], Agneta Zickert[2], Johanna K. Sandling[3], Andreas Jönsen[4], Elisabet Svenungsson[2], Lars Rönnblom[1], Timothy W. Behrens[5], Robert R. Graham[5], Ward Ortmann[5], Ann-Christine Syvänen[3], Iva Gunnarsson[2] and Gunnel Nordmark[6]. [1]Section of Rheumatology, Uppsala University, Uppsala, Sweden, [2]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [3]Molecular Medicine, Uppsala University, Uppsala, Sweden, [4]Section of Rheumatology, Lund University, Lund, Sweden, [5]Genentech Inc, South San Francisco, CA, [6]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden

Background/Purpose: Lupus nephritis (LN) is a cause of significant morbidity and mortality and occurs in 15–50 % of patients with SLE. Proliferative nephritis is considered the most severe form. Approximately 10 % of LN patients develop end stage renal disease (ESRD). Several susceptibility genes for SLE have been identified where an association with LN has been shown for single nucleotide polymorphisms (SNPs) in *STAT4* and *ITGAM* (1–3). In a previous study, Swedish patients with SLE and controls were genotyped on a custom 12K SNP chip (Illumina Infinium II) (4). The aim of this investigation was to analyze the genetic data from our previous study (4) for association with LN, in particular proliferative nephritis and renal outcome.

Methods: A total of 567 Swedish Caucasian patients with SLE and 512 matched controls were included. All patients fulfilled the ACR criteria for SLE and 195 (34.4 %) had a history of LN. Renal biopsies were available from 153 patients where 92 (60.1 %) had a proliferative nephritis, WHO class III or IV. During follow-up (median 14 years, range 0–46), 11.1 % reached ESRD. Case-control analyses were performed for patients with LN, proliferative nephritis and ESRD, respectively. The allele frequencies in cases and controls were compared with Fisher's exact test and the results compared with analysis of all SLE patients versus controls.

Results: We detected strong signals of association between SNPs rs11889341 in *STAT4* (OR 2.2, 95% CI 1.7–2.8), rs2070197 in *IRF5* (OR 2.0, 95% CI 1.5–2.7) and rs3135394 as a marker for *HLA-DR3* (OR 1.95, 95% CI 1.4–2.6), in the analysis of LN patients versus controls (all $p < 0.0001$). In addition, six genes showed an association with LN with OR 1.5–2.2, $p < 0.001$ (*PMS2, TNIP1, CARD11, ITGAM, BLK* and *IRAK1*). When analyzing only the patients with proliferative nephritis versus controls the OR for association increased for *STAT4, IRF5* and *BLK* to 2.4, 2.2 and 1.7 respectively (all $p < 0.01$). For patients in ESRD the OR for *STAT4, IRF5* and *BLK* increased further to 2.9, 3.1 and 2.1 whereas the OR for association with the *HLA-DR3* marker was decreased to 1.7. The association between the risk alleles in *IRF5, STAT4* and *BLK* and LN phenotypes was stronger than the association to SLE per se.



Conclusion: Risk alleles in *STAT4, IRF5* and *BLK* are associated with an increased risk for LN. The association with the severe form, proliferative nephritis, was particularly strong and the risk of developing ESRD was even more striking. On the contrary, the *HLA-DR3* marker did not display a strong association with LN. We conclude that variations in genes in immunological pathways predispose to LN severity and renal outcome.

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2481

Effect of Warfarin On Survival In Scleroderma-Associated and Idiopathic Pulmonary Arterial Hypertension. A Bayesian Approach to Evaluating Treatment In Uncommon Disease. Sindhu R. Johnson[1], John T. Granton[2], George A. Tomlinson[2], Haddas Grosbein[3], Thaolan Le[4], Peter Lee[5], M. Elizabeth Seary[3], Gillian A. Hawker[6] and Brian M. Feldman[3]. [1]Toronto Western Hospital, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]The Hospital for Sick Children, Toronto, ON, [4]University Health Network Pulmonary Hypertension Programme, Toronto, ON, [5]Mt. Sinai Hospital, Toronto, ON, [6]Women's College Hospital, Toronto, ON

Background/Purpose: Warfarin is recommended in scleroderma-associated pulmonary arterial hypertension (SScPAH) and idiopathic PAH (IPAH) to improve survival. There is no evidence to support this recommendation in SScPAH and the evidence in IPAH is conflicting. We evaluated the ability of warfarin to improve survival using 2 large SScPAH and IPAH cohorts.

Methods: The effect of warfarin on all-cause mortality was evaluated. Bayesian propensity scores (PS) were used to adjust for baseline differences between patients exposed and not exposed to warfarin, and assemble a matched cohort. Bayesian Cox proportional hazards models were constructed using informative priors based on international PAH expert elicitation.

Results: Review of 1,138 charts identified 275 SScPAH (n=78 (28%) treated with warfarin), and 155 IPAH patients (n=91 (59%) treated with warfarin). Baseline differences in PAH severity and PAH medications between treated and untreated patients were resolved using PS matching. In the matched cohort of 98 SScPAH patients (n=49 treated with warfarin), the posterior median Hazard Ratio (HR) was 1.06 (95%CrI 0.70,1.63). In the matched cohort of 66 IPAH patients (n=33 treated with warfarin), the posterior median HR was 1.07 (95%CrI 0.57,1.98). The probability that warfarin improves median survival by 6-months or more is 23.5% in SScPAH and 27.7% in IPAH. Conversely, there is a greater than 70% probability that warfarin provides no significant benefit or is harmful.

Conclusion: There is a low probability that warfarin improves survival in SScPAH and IPAH. Given the availability of other PAH therapies with demonstrable benefits, there appears to be little role for warfarin in improving survival for these patients.

2482

Diffusion of Carbon Monoxide Predicts Survival in Systemic Sclerosis Patients with Pulmonary Hypertension and Interstitial Lung Disease. Benjamin E. Schreiber[1], Chris Valerio[1], Greg Keir[2], Clive Handler[1], Athol U. Wells[2], Christopher P. Denton[3] and John G. Coghlan[1]. [1]Royal Free Hospital, London, London, United Kingdom, [2]Royal Brompton Hospital, United Kingdom, [3]UCL Medical School, London, United Kingdom

Background/Purpose: Predictors of survival in systemic sclerosis patients with concurrent interstitial lung disease and pulmonary hypertension are poorly understood.

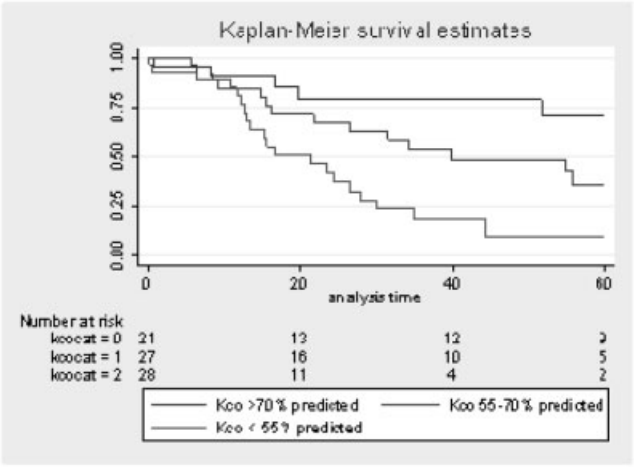
Methods: Retrospective analysis of a large regional single centre cohort of patients with systemic sclerosis associated pulmonary hypertension. Inclusion criteria were a diagnosis of systemic sclerosis, precapillary pulmonary hypertension as defined by mean pulmonary artery pressure (mPAP) >= 25 mmHg and pulmonary capillary wedge pressure (PCWP) <= 15 mmHg, and FVC < 70% predicted and presence of significant lung fibrosis on CT.

Results: 76 patients were identified. Mean age was 54.9 years. 51 (67%) female. 34 (44.7%) were classified to diffuse subset. Mean haemodynamics were: mPAP 37.3, PVR 554.6 dynes.s.cm-5. Mean survival was 34.3 months (95% CI 23.4–55.7).

The following variables did not predict survival on univariable analysis: age (p=0.09), gender (p=0.59), right atrial pressure (0.47). heart rate (0.36), cardiac output (0.29), cardiac index (0.76), mean pulmonary artery pressure (p=1.00), pulmonary vascular resistance (p=0.08), oxygen saturation (p=0.41), mixed venous saturation (p=0.23), systolic blood pressure (p=0.37), diastolic blood pressure (p=0.10), six minute walking distance (p=0.10, n=47), NTproBNP (p=0.98, n=27), FVC % predicted (p=0.72), anti-centromere antibody status (p=0.31), anti-topoisomerase-1 antibody status (p=0.12).

Significant variables on univariate analysis were functional class (p=0.007), Dlco % predicted (p=0.03), FVC/DLCO (p=0.006) and Kco % predicted (p<0.0005, n=76). On multiple variable Cox analysis with these four variables, Kco % predicted is the only significant predictor (p=0.017).

Kco % predicted has tertiles at 54.2 and 69.6. Kco % predicted was grouped into tertiles: <55%, 55–70%, >70%. The hazard ratio associated with dropping by one category is 2.4 (95% CI 1.5–3.7).



The survival differs in three groups (p=0.0002 by log-rank). 1, 3 and 5 year survival by group is given below:

	1 yr survival	3 yr survival	5 yr survival
Kco > 70% predicted	90.3% (67–98)	78.9% (53–92)	71.0% (43–87)
Kco 55–70% predicted	84.4% (63–94)	53.4% (32–71)	36.0% (16–57)
Kco < 55% predicted	80.4% (59–91)	18.5% (6–37)	9.2% (2–25)

Conclusion: Patients with systemic sclerosis, interstitial lung disease and pulmonary hypertension have a poor survival. We found that no demographic and haemodynamic variables predicted survival in this patient cohort.

On multiple variable models the only significant independent predictor of survival was Kco % predicted, which is the calculated diffusion of carbon monoxide adjusted for alveolar volume. KCO may reflect the extent of impairment of parenchymal dysfunction by combining both interstitial and vascular components of the disease process. Kco % predicted is a powerful predictor of outcome in this patient group.

2483

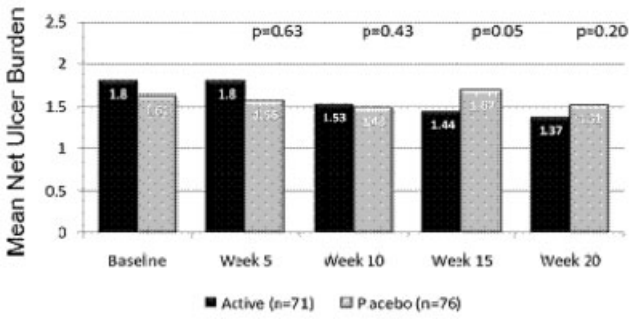
Digital Ischemic Ulcers in Scleroderma Treated with Oral Treprostinil Diethanolamine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. James R. Seibold[1], Fredrick M. Wigley[2], Elena Schiopu[3], Christopher D. Denton[4], Richard M. Silver[5], Virginia D. Steen[6], Thomas A. Medsger Jr.[7], Maureen D. Mayes[8], Soumya Chatterjee[9], Lorinda Chung[10], Mary Ellen Csuka[11], Dinesh Khanna[3], Tracy M. Frech[12], Jerry A. Molitor[13], Naomi F. Rothfield[14], Ariane L. Herrick[15], Robert W. Simms[16], Janet E. Pope[17], Kristan D. Rollins[18], Carl Arneson[18], Michael Wade[18] and on behalf of DISTOL Investigators[19]. [1]Scleroderma Research Consultants LLC, Avon, CT, [2]Johns Hopkins University, Baltimore, MD, [3]University of Michigan, Ann Arbor, MI, [4]Royal Free Hospital, Medical School, London, England, [5]MUSC, Charleston, SC, [6]Georgetown Univ Medical Center, Washington, DC, [7]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [8]University of Texas Health Science Center at Houston, Houston, TX, [9]Cleveland Clinic, Cleveland, OH, [10]Stanford Univ Medical Center, Palo Alto, CA, [11]Medical College of Wisconsin, Milwaukee, WI, [12]University of Utah School of Medicine, SLC, UT, [13]Univ of MN MMC108, Minneapolis, MN, [14]University of Connecticut, Farmington, CT, [15]School of Translational Medicine, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [16]Boston University School Medical, Boston, MA, [17]St. Joseph's Health Care, University of Western Ontario, London, ON, [18]United Therapeutics Corp, Research Triangle Park, NC, [19]DISTOL Investigator Centers

Background/Purpose: Prostacyclins are effective vasodilators for vascular features of systemic sclerosis (SSc, scleroderma) but systemic delivery requires the cumbersome logistics of intravenous infusion. Treprostinil diethanolamine (TDE) is an innovative salt form of the

prostacyclin analog treprostinil for oral delivery as a sustained-release (SR) osmotic tablet for twice-daily dosing. The objective of this study was to evaluate the safety and efficacy of TDE SR for digital ulcers (DU) in patients with SSc.

Methods: This was a randomized (1:1), placebo-controlled, parallel group, multicenter study of TDE in adult patients with SSc and presence of at least one DU meeting protocol definition as "active" at Baseline. Known PAH or bosentan therapy were excluded. Study drug was titrated to maximum-tolerated dose (up to 16 mg bid), with assessments at Weeks 5, 10, 15 and 20. The primary endpoint was change in net ulcer burden at Week 20. Secondary endpoints included patient DU pain, physician and patient global assessment and patient Raynaud symptoms by visual analogue scale (VAS), healing of cardinal ulcer, prevention of new ulcers, and measures of hand function and quality of life.

Results: 148 subjects (109 F/ 38M), mean age of 48.8 years and mean SSc disease duration of 10.5 years were enrolled in 27 centers. 64% of subjects had limited cutaneous SSc. Results for net ulcer burden were as follows:



Improvement ($p<0.05$) occurred in several secondary endpoints, including physician global DU VAS, SHAQ-DI (Scleroderma Health Assessment Questionnaire-Disability Index) components related to hand function, dyspnea VAS, and patient impression of change in overall ulcer status and of Raynaud symptoms. While there were no differences in outcome in subjects classified clinically as either limited or diffuse SSc, exploratory analyses of individuals who were anti-centromere antibody negative demonstrated a reduction in placebo-corrected mean net ulcer burden of −1.01 ($P=0.01$) at Week 20. Discontinuation due to adverse events occurred in 13% on TDE vs 8% on placebo with 82% and 86% completing the study, respectively.

Conclusion: Administration of TDE SR to patients with DU did not result in a statistically significant reduction in net ulcer burden compared to placebo. A variety of secondary endpoints suggested utility for Raynaud symptoms. Critical tissue ischemia in SSc may involve factors other than afferent vasomotor perfusion. Future studies of healing will benefit from refinements in both outcomes assessments and identification and stratification of subjects.

2484

Microvascular Damage and Cardiac Fibrosis Detected by Heart MRI are a Hallmark of Systemic Sclerosis Heart Involvement. Tatiana Sofia Rodriguez-Reyna, Martha Morelos-Guzman, Pablo Hernandez-Reyes, Jaime Morales-Blanhir, Karla Montero-Duarte, Cynthia Martinez-Reyes, Carlos Reyes-Utrera and Jorge Vazquez-Lamadrid. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

Background/Purpose: Heart involvement has been described in 37–80% of systemic sclerosis (SSc) patients; prevalence rates vary depending on the diagnostic method and the type of patients included in the studies. Our aims were to determine the prevalence of heart involvement (fibrosis and microvascular damage) in a cohort of SSc patients without cardiovascular risk factors (diabetes, hypertension, dyslipidemia), to describe the patterns of heart involvement using cardiac MRI and coronary angiotomography, and to correlate these data with disease subsets, target organ involvement and laboratory parameters.

Methods: We included patients from our SSc cohort. They underwent clinical evaluation, EKG, CPK, CPK-MB, ultrasensitive-CRP, ESR, SSc-specific autoantibodies (anti-Topoisomerase I, anticentromere, anti-U1 RNP, anti-PMScl, anti-Pol III, anti-Ku), antiphospholipid antibodies (anticardiolipins, anti-β-2 glicoprotein 1, lupus anticoagulant), coronary angiotomography, and cardiac MRI (SSFP sequences to evaluate fibrosis, and adenosine challenge for semiquantitative perfusion analysis with signal intensity curves using echoplanar TIGRE images). Statistical analysis was performed using SSPS v.15; Chi^2 was used to analyze ordinal variables and Student′s t test to analyze numerical variables.

Results: We included 62 SSc patients (29 with diffuse cutaneous SSc (dcSSc): 47%, and 33 with limited cutaneous SSc (lcSSc): 53%); 60 of them were female; the mean time of evolution was 9.7 years; the mean LVEF was 59.4%; 79% showed subendocardic perfusion defects; 45% showed myocardial fibrosis (17.8% with patchy distribution, 35.7% in bands, 10.7% subendocardic, 28.5% with mixed patterns and 7.1% transmural), with higher prevalence in dcSSc than in lcSSc (58.6% vs 33.3%; $p=0.04$); the percentage of myocardium affected by fibrosis was significantly higher in dcSSc (6.7%) than in lcSSc (1.6%; $p=0.02$). Cardiac fibrosis was more prevalent in basal anteroseptal (27%) and inferoseptal (12.9%) segments, as well as in the middle segments of the anteroseptal wall (19.4% and 12.9% in segments 8 and 7, respectively). Ninety three percent of coronary angiotomographies were normal (mean Ca score 2.9); 28.8% of patients had abnormal EKGs (39.3% of dcSSc vs 19.3% of lcSSc, p=NS). Cardiac fibrosis was associated with lower LVEF (55.8 vs 66.5%, $p<0.0009$) and inversely associated with vascular involvement (86.7 vs 100%, $p=0.03$). Microvascular damage was associated with higher CRP (1.28 vs 0.22; $p=0.001$) and positive anti β2 glycoprotein 1 (aβ2GP) IgG antibody ($p=0.001$). There was no association of cardiac fibrosis or microvascular damage with abnormal calcium score nor atherosclerosis.

Conclusion: Patients with systemic sclerosis show preserved systolic function, high frequency of cardiac fibrosis and subendocardic concentric perfusion defects, related to microvascular damage. Cardiac fibrosis is more frequent in basal and middle segments of the left ventricle. These abnormalities are not caused by coronary artery disease. Cardiac MRI is a sensitive, noninvasive, useful method to detect heart involvement in SSc. Elevated CRP and positive anti-aβ2GP IgG antibodies may help to identify patients at risk for SSc heart involvement.

2485

Development and Internal Validation of a Two-Year Mortality Risk Prediction Rule in Early Diffuse Systemic Sclerosis Patients. Robyn T. Domsic[1], Mary Lucas[1], Stephen R. Wisniewski[2], C. Kent Kwoh[3], Michael J. Fine[3] and Thomas A. Medsger[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Univ of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, PA

Background/Purpose: Knowledge of mortality risk and associated predictors is important in SSc clinical trial design to risk stratify patients, but there is no validated short term mortality model in early diffuse cutaneous systemic sclerosis (dcSSc). The objective of this study was to derive and validate a two year mortality model in early dcSSc patients.

Methods: We used a large prospectively enrolled medical center SSc databank to identify an inception cohort of adult early dcSSc patients seen for an initial visit between 1980 and 2007. Patients were considered to have early dcSSc if their first visit occurred less than two years after the first symptom attributable to scleroderma, with skin thickening documented as proximal to the elbows or knees. Due to the small number of non-Caucasian patients, the analysis was limited to Caucasians. Vital status was determined using the Social Security Death Index. The population was randomly divided into derivation (two-thirds) and validation (one-third) cohorts. Predefined candidate predictor variables at the first visit (demographic, history, physical exam, lab values, organ system involvement and organ severity using the Medsger severity scale) were placed into a stepwise multivariable logistic regression model. Regression diagnostics were performed and area under the curve was calculated to assess discrimination in the derivation and validation cohorts.

Results: 791 early dcSSc patients were identified, of whom 424 had all objective testing required to assess severity of internal organ involvement at the first visit. The mean age was 50.3 ± 13.6 years and 75% female. The median duration of disease at first visit of 0.91 years (IQR 0.66, 1.33), and the mean modified Rodnan skin thickness score was 25.0 ± 11.7. There were no significant differences between the 424 and the 367 without the complete objective testing on these parameters. The final derivation cohort included 260, and the validation cohort 127 patients.

At two years, 74 of the 424 (19%) had died. Significant independent predictors of two-year mortality were older age, male gender, increased

skin thickness progression rate, severity of GI, cardiac and skeletal muscle disease, and degree of anemia (Table 1). The area under the curve (AUC) in the derivation cohort was 0.86 (95% CI 0.80–0.91), and when the model was applied to the validation cohort the AUC = 0.81 (95% CI 0.74–0.90).

Table 1. Multivariate model of two-year mortality in early diffuse systemic sclerosis patients

	Odds Ratio	95% Confidence Interval (CI)	p-value
Age at First Visit (years):			
<35	0.50	0.11–2.19	0.02
35–44	0.44	0.14–1.54	
45–54	1.00	–	
55–64	2.02	0.75–5.47	
>65	2.94	1.01–6.93	
Skin Thickness Progression Rate:			
Slow	–	–	0.04
Intermediate	1.04	0.38–2.80	
Rapid	2.74	1.08–6.93	
Medsger Gastrointestinal Severity:			
None	–	–	0.006
Mild	1.54		0.64–3.71
Moderate/severe	5.14	1.88–14.05	
Medsger Muscle Severity: None	–	–	0.006
Mild	1.56	0.65–3.73	
Moderate/severe	5.67	1.64–19.60	
Medsger Cardiac Severity: None	–	–	0.04
Mild	0.10	0.01–0.90	
Moderate	1.70	0.63–4.60	
Severe	2.15	0.56–8.27	
Hemoglobin level: >12 mg/dL	–	–	.005
10–12 mg/dL	4.41	1.79–10.87	
<10 mg/dL	2.55	0.90–7.15	

Conclusion: We have developed a multivariable model with high accuracy for identifying early dcSSc patients at risk for short term mortality. Based on the area under the receiver operating curve, we were able to internally validate this model in a randomly selected early dcSSc patient population. This model may be used to risk stratify patients for clinical trials and to provide prognostic information for patients and their treating physicians.

2486

Race and Mortality Risk in Scleroderma. Allan C. Gelber, Rebecca L. Manno, Adrianne Woods, Ami A. Shah, Francesco Boin, Laura K. Hummers and Fredrick M. Wigley. Johns Hopkins University, Baltimore, MD

Background/Purpose: Experience suggests that African Americans express autoimmune disease differently than other racial groups. In the context of systemic sclerosis (scleroderma), we sought to determine whether race was related to mortality risk in a large observational cohort study.

Methods: Between January 1, 1990 and December 31, 2009, a total of 2394 patients with scleroderma were evaluated at a single university medical center. Among this group, 329 African American and 1415 Caucasian patients were prospectively followed. Cumulative incidence of mortality was estimated using Kaplan-Meier analysis. In addition, the independent risk of mortality associated with race was estimated using Cox proportional hazards analysis, with adjustment for age at disease onset, gender, scleroderma disease subtype and Scl-70 serologic status.

Results: Among the cohort of 1744 patients with follow-up visits to the scleroderma center, there were 1445 (83%) women and 299 (17%) men, among whom 1060 (61%) manifested the limited and 684 (39%) the diffuse cutaneous subtype of disease. Mean age (+SD) at disease onset was 46 (+14) years. During a median follow-up period of 4 years, 700 [159 African American; 541 Caucasian] patients died. Overall, cumulative mortality at 1, 3, 5 and 10 years of follow-up was 8, 22, 32 and 54%, respectively. At 5 years of follow-up, cumulative mortality was 35% among the African American compared to 31% among the Caucasian patients [logrank p = 0.0595). The relative risk of mortality, in unadjusted and adjusted analyses, associated with African American compared to Caucasian race, was as follows:

Model confidence interval	Relative Risk	95%
Unadjusted	1.2	1.0–1.4
Age-adjusted	1.4	1.2–1.7
Age, gender, disease subtype-adjusted	1.3	1.1–1.6
Age, gender, disease subtype, Scl-70-adjusted	1.6	1.2–2.1

Moreover, in stratified age-adjusted analyses, African Americans were at greater risk for mortality in both the Scl-70 seropositive [RR1.7; 95%CI 1.0 – 2.9] and seronegative [RR 1.6; 95%CI 1.2 – 2.2] strata.

Conclusion: In a large biracial cohort assembled over a 20 year period at a single referral center, overall mortality at 10 years of follow-up was approximately 54%. African Americans experienced a 60% increase in mortality relative to Caucasians, after taking age at disease onset, gender, cutaneous disease subtype and Scl-70 serologic status into account. These findings imply that race is modestly related to disease severity and mortality risk in scleroderma.

ACR Concurrent Abstract Session
ACR Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment
Tuesday, November 8, 2011, 2:30 PM–4:00 PM

2486A

Efficacy and Safety of Adalimumab in Patients with Non-Radiographic Axial Spondyloarthritis – Results From a Phase 3 Study. Joachim Sieper[1], Désirée van der Heijde[2], Maxime Dougados[3], Philip J. Mease[4], L. Steven Brown[5] and Aileen Pangan[5]. [1]Charité Universitätsmedizin, Berlin, Germany, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Paris-Descartes University, Cochin Hospital, Paris, France, [4]Seattle Rheumatology Associate, Seattle, WA, [5]Abbott Laboratories, Abbott Park, IL

Background/Purpose: Adalimumab (ADA) is indicated for treatment of ankylosing spondylitis (AS) and was also effective in a pilot study of patients (pts) with non-radiographic axial spondyloarthritis (axSpA).1 ABILITY 1, the first pivotal trial to use the ASAS axSpA criteria, was designed to evaluate the efficacy and safety of ADA in axSpA pts without radiographic sacroiliitis.[2]

Methods: ABILITY 1 is an ongoing multi-country, phase 3 study. Eligible pts fulfilled the ASAS axSpA criteria but not modified NY criteria for AS, had BASDAI ≥ 4 cm, total back pain VAS ≥ 40 mm, and inadequate response/intolerance/contraindication for NSAIDs. Pts were randomized 1:1 to ADA (40 mg every other wk) or placebo (PBO) for 12 wks followed by a 92-wk open-label extension. Primary endpoint was ASAS40 response at wk 12. Subgroup analyses were performed to evaluate the impact of the following baseline conditions on the primary endpoint: sex, race, age, weight, CRP, HLA-B27, sacroiliitis by MRI, history of IBD or uveitis, and concomitant DMARD or NSAID use. Logistic model was performed to assess treatment and subgroup interaction, with significant interaction defined as Pvalue £0.10.

Results: Of the 192 randomized pts, 7 pts (4 ADA, 3 PBO) were excluded from efficacy analyses due to investigator noncompliance, leaving 91 randomized to ADA and 94 to PBO. Baseline demographics/disease characteristics were comparable between ADA and PBO groups (% or mean): females (52/57), age (38/38 yrs), symptom duration (10/10 yrs), duration since diagnosis (3/3 yrs), BASDAI (6.4/6.5), elevated CRP (32/39) and history of HLA-B27 positivity (79/71). Positive MRI fulfilling the imaging arm of the ASAS criteria was present in 51% of ADA and 46% of PBO pts. Baseline BASDAI was comparable regardless of which arm of the ASAS criteria pts fulfilled (MRI/HLA-B27): 6.4 (+/–), 6.2 (+/+) and 6.6 (–/+). A significantly higher percentage of ADA pts achieved the primary endpoint and other clinical and imaging outcomes compared to PBO (Table). The only significant interaction terms in the subgroup analyses for wk 12 ASAS40 were for the age and CRP subgroups (Table). Response rates were similar between MRI positive and negative pts. During the double-blind period, safety analyses for all 192 randomized pts revealed comparable results for ADA and PBO (%): AEs (57.9/58.8), serious AEs (3.2/1.0), and infectious AEs (29.5/28.9); there were no serious infections, TB, malignancies, or demyelinating disease.

Table. Week 12 Efficacy Outcomes*

	ADA N=91	PBO N=94	*P* value[a]
Primary endpoint:			
ASAS40, %	36.3	14.9	<0.001
Other efficacy endpoints:			
ASAS20, %	51.6	30.9	0.004
ASAS 5/6, %	30.8	6.4	<0.001
ASAS partial remission, %	16.5	5.3	0.014
BASDAI 50, %	35.2	14.9	0.001
ASDAS inactive disease state, %	24.2	4.3	< 0.001
Mean change in CRP, mg/L†	– 4.3	– 0.3	<0.001
Mean change in SI joint SPARCC score ‡	– 3.2	– 0.6	0.003
Mean change in spine SPARCC score ‡	– 1.8	– 0.2	0.001
ASAS40 response by subgroup: %	**ADA N=91**	**PBO N=94**	**Interaction *P* value[b]**
Sacroiliitis on baseline MRI			
Positive	34.8	16.3	0.649
Negative	37.8	13.7	
HLA-B27			
Positive	40.8	15.6	0.342
Negative	18.8	13.6	
Age,			
<40	46.4	13.5	0.051[c]
≥40	20.0	16.7	
CRP,			
Normal	27.4	17.5	0.027
Abnormal	55.2	10.8	

* non-responder imputation except where stated; † LOCF; ‡ Observed data (N ADA/PBO): SPARCC SI joint (84/84), SPARCC spine (85/83). [a]compares ADA to PBO, [b]logistic regression model interaction term, [c]age ≥40yrs combined for logistic regression analysis.

Conclusion: Adalimumab significantly improved the signs and symptoms of pts with active non-radiographic axSpA. Pts <40 yrs or with elevated baseline CRP were more likely to achieve ASAS40 with ADA, consistent with a previously published report.1 ABILITY 1 results suggest a favorable benefit-risk profile for ADA as treatment for non-radiographic axSpA pts.

References:
1. Haibel H, et al. Arthritis Rheum 2008;58:1981. 2. Rudwaleit M, et al. Ann Rheum Dis 2009;68:777

2486B

Non-Steroidal Anti-Inflammatory Drugs Reduce Radiographic Spinal Progression in Patients with Ankylosing Spondylitis but Not in Non-Radiographic Axial Spondyloarthritis. Denis Poddubnyy[1], Hildrun Haibel[2], Joachim Listing[3], Elisabeth Märker-Hermann[4], Henning Zeidler[5], Jürgen Braun[6], Martin Rudwaleit[7] and Joachim Sieper[2]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Charité – Campus Benjamin Franklin, Berlin, Germany, [3]German Rheumatism Research Centre, Berlin, Germany, [4]Dr. Horst Schmidt Kliniken, Wiesbaden, Germany, [5]Medizinische Hochschule, Hannover, Germany, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]Ev. Krankenhaus Hagen-Haspe, Hagen, Germany

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are clinically effective and considered as a first line therapy in patients with axial spondyloarthritis (SpA) including ankylosing spondylitis (AS). At the same time NSAIDs might work not only as symptom-modifying drugs, but might also have disease-modifying activities retarding radiographic spinal progression and syndesmophyte growth in AS [1]. However, this earlier report [1] has not been confirmed until now. Furthermore, the influence of NSAIDs on radiographic progression has not been investigated so far in non-radiographic axial SpA (nrSpA). The objective of the study was to investigate the effect of NSAIDs intake on the radiographic spinal progression in patients with AS and nrSpA.

Methods: 164 patients with axial SpA (88 with AS and duration of symptoms <10 years; 76 with nrSpA and duration of symptoms <5 years) from the German Spondyloarthritis Inception Cohort (GESPIC) [2] have been selected for this analysis based on availability of spinal radiographs at baseline and after 2 years of follow-up and of the data on NSAIDs intake during this period of time. None of the patients included in this analysis received anti-TNF therapy. Radiographs of the cervical and lumbar spine were centrally collected, digitized, and subsequently scored according to the mSASSS independently by two trained readers, who were blinded for time point and all clinical data. Data on NSAIDs intake were collected at baseline and every 6 months thereafter during 2 years of follow-up. An index of the NSAIDs intake [3], as recommended by ASAS, counting both dose and duration of drug intake (range 0–100) was calculated. High NSAIDs intake was defined as a mean NSAID intake index over 2 years of ≥ 50, low NSAIDs intake—as a mean NSAID intake index <50.

Results: Patients with AS and high NSAIDs intake (n=24 or 27%), in comparison to patients with low NSAIDs intake (n=64 or 73%), had a significantly lower rate of radiographic spinal progression as assessed by the change of mSASSS score over 2 years (0.02±1.38 vs. 0.96±2.78 mSASSS units, respectively, p=0.039), and numerically lower rates of patients with progression by ≥ 2 mSASSS units (8.3% vs 21.9%) and with new syndesmophyte formation (4.2% vs 15.6%) over 2 years. After adjustment for other factors potentially associated with radiographic spinal progression in this cohort (baseline syndesmophyte, elevated acute phase reactants and smoking status) the high NSAIDs intake showed significant association with reduced radiographic spinal progression (OR=0.23, 95%CI 0.55–0.98 for the mSASSS progression by ≥ 2 units, p=0.047). In nrSpA, no significant differences regarding radiographic progression between subgroups with high (n=19 or 25%) and low NSAIDs intake (n= 57 or 75%) was found.

Conclusion: A high NSAIDs intake over 2 years is associated with lower radiographic progression in patients with AS. The lack of influence of NSAIDs intake on radiographic progression in nrSpA might be related to the relatively low baseline structural damage of the spine in this group.

References:
1. Wanders A, et al. Arthritis Rheum 2005;52:1756–65. 2. Rudwaleit M, et al. Arthritis Rheum. 2009;60:717–27. 3. Dougados M, et al. Ann Rheum Dis 2011;70: 249–51.

2486C

Gender Related Differences in Severity of Psoriatic Arthritis. Lihi Eder[1], Arane Thavaneswaran[1], Vinod Chandran[2] and Dafna D. Gladman[1]. [1]Toronto Western Hospital, University of Toronto, Toronto, ON, [2]Toronto Western Hospital and University of Toronto, Toronto, ON

Background/Purpose: It has been shown that males (M) with ankylosing spondylitis tend to suffer from more severe spinal disease while females (F) are more likely to have peripheral joint involvement. Gender related differences have not been thoroughly explored in Psoriatic Arthritis (PsA). We aimed to investigate whether there are gender differences in clinical and radiographic joint damage among patients with PsA.

Methods: A cross-sectional analysis was performed among patients who have been followed in a large PsA clinic from 2006 to 2011. Patients were followed according to a standard protocol. Demographic, clinical and radiographic data were retrieved from the clinic database. The number of clinically damaged joints (68 assessed joints) was defined as the presence of limitation of range of movement of >20% not related to the presence of joint effusion, presence of joint deformity, subluxation, loosening, or ankylosis. Axial involvement was defined by radiological evidence of either bilateral at least grade 2 sacroiliitis or unilateral grade 3 or 4 sacroiliitis. Radiographic damage to 42 joints was assessed according to a modification of the Steinbrocker method. Radiographic joint damage scores were grouped into four ordered categories: 0, 1–10, 11–30, >30. The association between gender and the following outcome variables: radiographic joint damage, clinical joint damage and axial involvement were assessed through multivariate regression analyses after adjustment for age, duration of PsA, smoking and level of education.

Results: 636 PsA patients were included in the study (F: 41.8%, M: 58.2%). There were no differences in the mean age (F: 52.2±13.9, M: 52.4±13 years) or age at diagnosis of PsA (F: 36.6±13.7, M: 37.3±12.6 years) across the genders. The age at diagnosis of psoriasis was lower in females (F: 26.5±15.2, M: 29.4±13.7years, p=0.01). While the frequency of HLA-B*27 was similar across genders (M: 16.7% F: 15.1%

p=0.61), males had more frequent axial involvement (M: 42.9% F: 31% p=0.0003). Active joint count was higher in females compared to males (F: 5.4±8.9 M: 3.9±7.2 p=0.03), however, swollen joint count was similar across the genders (F:0.6±1.5 M:0.6±1.9 p=0.76). In a multivariate negative binomial regression analysis male gender was associated with higher clinically damaged joint count (estimate 0.25 p=0.04). In addition, radiographic peripheral joint damage was worst among males. Although unadjusted modified Steinbrocker scores were similar in males and females (F: 21.2±35 M: 22.4±18.9 p=0.65), in multivariate analysis males were more likely to be in a higher radiographic damaged joint category than females (OR 1.56, 95% Confidence interval (CI) 1.1–2.1, p=0.006). Finally, multivariate logistic regression analysis showed that male gender was associated with axial involvement (OR 2.1, 95% CI 1.4–3.1, p=0.0002).

Conclusion: Among patients with PsA, men tend to accumulate more peripheral and axial joint damage compared to women. It is unclear whether these findings are secondary to differences in occupational physical activity, hormonal changes or other factors.

2486D

Interleukin-17A Blockade with Secukinumab Reduces Spinal Inflammation in Patients with Ankylosing Spondylitis As Early As Week 6, As Detected by Magnetic Resonance Imaging. Xenofon Baraliakos[1], J. Braun[1], D. D. Laurent[2], D. Baeten[3], D. van der Heijde[4], J. Sieper[5], P. Emery[6], I. McInnes[7], J. van Laar[8], R. Landewe[9], P. Wordsworth[10], J. Wollenhaupt[11], H. Kellner[12], A. M. Wright[13], S. Gsteiger[13] and W. Hueber[2]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Novartis Institutes for BioMedical Research, Basel, Switzerland, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Charite Campus Benjamin Franklin, Berlin, Germany, [6]University of Leeds, Leeds, United Kingdom, [7]University of Glasgow, Glasgow, United Kingdom, [8]Newcastle University, Newcastle upon Tyne, United Kingdom, [9]Maastricht University Medical Center, Maastricht, Netherlands, [10]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [11]Eilbeck Hospital, Hamburg, Germany, [12]Centre for Inflammatory Joint Diseases, Munich, Germany, [13]Novartis Pharma AG, Basel, Switzerland

Background/Purpose: Magnetic resonance imaging (MRI) is considered gold standard for assessment of spinal inflammation in ankylosing spondylitis (AS). So far, TNF blockers are the only treatment that demonstrated significant reductions of spinal inflammation in AS. In a recent trial, inhibition of IL-17A by secukinumab (AIN457) resulted in significant improvement of clinical signs and symptoms of AS[(1)]. We determined whether clinical effects observed after 2 infusions (10mg/kg i.v.) of secukinumab coincide with reductions of bone marrow edema seen on MRI.

Methods: Patients with active AS (n=30) who fulfilled the 1984 modified New York criteria were enrolled in a 28-week double blind, placebo controlled study. Patients were randomized 4:1 to receive secukinumab 2×10 mg/kg or placebo, given 3 weeks apart. The primary endpoint of the clinical trial was the proportion of patients achieving Assessment of SpondyloArthritis international Society (ASAS) 20 response at week 6. Sagittal MR images of the spine were performed including T1- and short tau inversion recovery (STIR) sequences at baseline, week 6 and week 28. Images were analyzed by an independent reader, who was blinded to treatment allocation and chronology of images, using the "Berlin modification" of the AS spinal MRI (ASspiMRI-a[(2)]) scoring system. Wilcoxon signed-rank test was used for the evaluation of changes between baseline and follow-up in each treatment arm.

Results: 27 patients (22 secukinumab; 5 on placebo) had evaluable MR images at baseline. Few patients (at week 6: 2 secukinumab; 3 placebo; at week 28: 6 secukinumab, 1 placebo) missed follow-up MRIs, mostly due to early discontinuation. MRI scores at baseline and changes at week 6 and week 28 are shown in Table 1. MRI score improvements were seen as early as week 6 and sustained up to week 28. Early improvements at week 6 were especially noted in patients with higher baseline scores (*Figure1, arrows*). Only minor changes were seen in patients on placebo (*Figure1, closed circles*).

Table 1. MRI scores at baseline, week 6 and week 28/end of study

	Secukinumab 2x10mg/kg			Placebo		
	Baseline	Week 6	Week 28*	Baseline	Week 6	Week 28
Number of patients	22	22	16	5	3	5
ASAS20 responders (n)	-	14	6	-	1	1
Mean Berlin score ± SD	9.2 ± 8.9	6.7 ± 6.6	5.7 ± 6.2	20.6 ± 20.2	21.0 ± 24.6	19.0 ± 19.3
P-value (vs. baseline)	-	0.10	0.16	-	0.50	0.25

* Data from 6 patients who discontinued prior to week 28 (lack of response) were not analyzed.

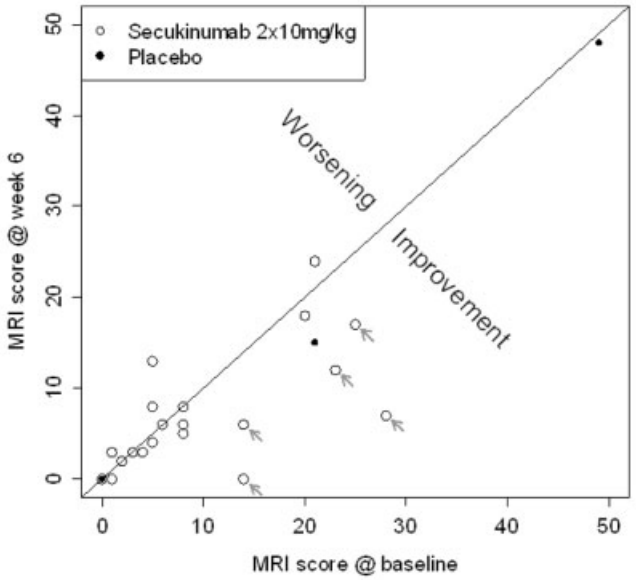


Figure 1. Changes of MRI scores from baseline to week 6

Conclusion: This exploratory study in patients with active AS suggests that after treatment with only 2 infusions of secukinumab substantial reductions of spinal inflammation as detected by MRI occurred. MRI changes were seen as early as 6 weeks after start of treatment, and were maintained up to week 28. Results are consonant with MRI findings obtained in previous AS trials with TNF blockers. Our results provide support that secukinumab may be a potential treatment for patients with active AS.

(1) Baeten D et al, EULAR 2011, OP0174; (2) Braun J et al, Arthritis Rheum 2003

2486E

Radiographic Scoring Instruments Have High Specificity for Detecting Change in Axial Psoriatic Arthritis. Vinod Chandran[1], Ali Ibrahim[2], Arane Thavaneswaran[3], Lihi Eder[3], Philip Helliwell[4], Richard J. Cook[5] and Dafna D. Gladman[3]. [1]Toronto Western Hospital and University of Toronto, Toronto, ON, [2]Queen's University, Kingston, ON, [3]Toronto Western Hospital, University of Toronto, Toronto, ON, [4]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [5]University of Waterloo, Waterloo, ON

Background/Purpose: Axial inflammatory arthritis is an important manifestation of psoriatic arthritis (PsA). Various instruments may be used to quantify radiographic spinal damage in axial PsA (AxPsA) including the Bath Ankylosing Spondylitis (AS) Radiology Index- spine (BASRI-spine), the modified Stoke AS spinal score (mSASSS), the Radiographic AS spinal score (RASSS) and the PsA Spondylitis Radiology Index (PASRI). We recently showed that these systems have good reliability in AxPsA. However, sensitivity to change is still not known. We aimed to determine the sensitivity to change of available scoring methods in AxPsA.

Methods: Spinal radiographs of 105 patients diagnosed with AxPsA (grade 2 or greater sacroiliitis and inflammatory back pain and/or restricted spinal mobility) were retrieved for 2 time points at least 2 years apart, and subsequently anonymized to name and order of examination. All radiographs were scored by three rheumatologists using a standard form, which allows calculation of BASRI-spine, mSASSS, RASSS and PASRI, along with features (such as osteoarthritis, DISH) that may be associated with PsA or complicate scoring. An independent expert reader determined whether there was radiographic progression from an overall impression after reading the radiographs with knowledge of chronologic order. This assessment was considered to represent 'true' change (gold standard). Descriptive statistics,

paired t-tests and logistic regression were used to determine whether the instruments accurately captured radiographic worsening.

Results: The 105 patients (71 males, mean age 52 years, mean PsA duration 16 years) had on average 8 actively inflamed joints, 1.6 swollen joints, 15 clinically damaged joints. The mean BASRI-spine, mSASSS, RASSS and PASRI scores at the time of first X-ray was were 3.4, 3.4, 3.6 and 8.5, respectively. The mean duration between the two sets of radiographs was 3.5 years. BASRI-spine (p= 0.02), mSASSS (p = 0.02) and PASRI (p= 0.01) showed statistically significant difference in mean scores between the two time points. The proportion of patients with worsening scores using the instruments was: PASRI 32%, BASRI-spine 29%, mSASSS 25%, RASSS 23%. 25 of the 105 (24%) patients showed progression as determined by the gold standard. The sensitivity (95% CI) and specificity (95% CI) for any increase in score to detect true change was as follows: BASRI-spine 0.48 (0.28,0.68), 0.78 (0.67,0.86); mSASSS 0.52 (0.32,0.72), 0.84 (0.73, 0.91); RASSS 0.44 (0.25,0.65), 0.84 (0.73,0.91); PASRI 0.52 (0.32, 0.72), 0.74 (0.63,0.83). Logistic regression analyses adjusted for age at first X-ray, presence of osteoarthritis and DISH showed that an increase in score was associated with the following odds ratios (95% CI) for 'true' change: BASRI-spine 3.0 (1.15,7.82), mSASSS 5.27 (1.92,14.48), RASSS 3.70 (1.32,10.36) and PASRI 3.06 (1.18,7.95).

Conclusion: 24% of patients with AxPsA show worsening of radiographic damage over 3.5 years. Available scoring systems for quantifying radiographic AxPsA have moderate sensitivity but high specificity to detect 'true' change. All measures performed equally well in detecting change.

2486F

Nail Disease in Psoriasis Is Associated with Sonographically Determined Systemic Subclinical Enthesopathy. Zoe R. Ash[1], Ilaria Tinazzi[2], Concepcion Castillo-Gallego[3], Chung Kwok[4], Caroline Wilson[5], Mark Goodfield[5], Paolo Gisondi[6], Ai Lyn Tan[1], Helena Marzo-Ortega[1], Richard J. Wakefield[7], Paul Emery[8], Sibel Aydin[9] and Dennis McGonagle[10]. [1]University of Leeds, Leeds, United Kingdom, [2]University of Verona, Verona, Italy, [3]Hospital Universitario La Paz, Madrid, Spain, [4]Leeds Teaching Hospitals, Leeds, United Kingdom, [5]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [6]University of Veronia, Verona, Italy, [7]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals, Leeds, United Kingdom, [8]Leeds Institute of Molecular Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK, Leeds, United Kingdom, [9]Goztepe Training and Research Hospital, Istanbul, Turkey, [10]University of Leeds and Leeds Teaching Hospitals, Leeds, United Kingdom

Background/Purpose: Psoriasis is associated with subclinical enthesopathy and psoriatic nail disease predicts psoriatic arthritis development. Based on previous observations that the nail is directly anchored in the entheses around the distal interphalangeal joint, this study tested the hypothesis that nail disease in psoriasis was more strongly associated with systemic subclinical enthesopathy than psoriasis without nail disease.

Methods: Forty six patients with psoriasis (without arthritis) were evaluated for the presence of nail disease. Thirty-one of the forty-six psoriasis cases had clinical nail disease. Twenty-one sex and age matched healthy controls (HC) were also recruited. A total of 804 entheses were scanned including the upper and lower limbs entheses by an ultrasonographer blinded to clinical details.

Results: Patients with psoriasis had higher enthesitis scores than HC [med (range): 21 (0–65) vs. 11 (3–39), p=0.005]. The enthesitis scores of psoriasis patients with nail disease [23 (0–65)] were higher than both patients without nail disease [15 (5–26), p=0.02] and HC [11 (3–39), p=0.003]. Sonographically determined inflammation scores of the entheses in patients with nail disease [13 (0–34)] were higher than in patients without nail disease [8 (2–15), p=0.02] and HC [5 (0–19), p<0.001]. Modified NAPSI (nail psoriasis severity index) scores on all nails were correlated to both inflammation (r^2 =0.45, p=0.005) and chronicity entheseal US scores (r^2 =0.35, p=0.04). The duration of psoriasis also tended to correlate with entheseal inflammation (r^2 =0.29; p=0.05) whereas no link between PASI and US scores was evident.

Conclusion: These findings confirm that systemic subclinical enthesopathy is common in psoriasis and shows a specific link with contemporaneous nail disease thus offering a novel microanatomical basis for the predictive value of nail psoriasis for PsA evolution.

2487

Determinants of Depressive Symptoms in Patients with Systemic Sclerosis, Including Fear of Progression and Appearance Self Esteem. Linda Kwakkenbos[1], Wim G.J.M. van Lankveld[1], Madelon C. Vonk[2], Eni S. Becker[3], Frank H.J. van den Hoogen[1] and Cornelia H.M. van den Ende[1]. [1]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [2]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Behavioural Science Institute, Clinical Psychology, Radboud University, Nijmegen, Netherlands

Background/Purpose: As a consequence of Systemic Sclerosis (SSc), patients report high levels of depressive symptoms. So far, potential determinants of these depressive symptoms are not comprehensively studied. Therefore, it is not clear which factors should be targeted in treating depressed SSc patients. This study was conducted to determine which disease-related and psychological factors, including fear of progression and appearance self esteem, are associated with depressive symptoms, independently of sociodemographic factors.

Methods: In total, 215 patients with SSc completed questionnaires on sociodemographics, physical functioning, pain, fatigue, psychosocial characteristics and depressive symptoms (CES-D). In addition, disease characteristics were collected by the attending rheumatologist. Hierarchical linear regression analysis was conducted to assess associations with depressive symptoms.

Results: Sample characteristics are displayed in Table 1. Mean CES-D score was 12.9 (SD 9.7) and the prevalence of patients scoring >= 16 in our sample was 32.1%. The prevalence of probable depression (CES-D>=19) was 25.1%. Besides pain and fatigue, neither sociodemographic factors, nor physician assessed disease characteristics and physical limitations were important determinants of depressive symptoms (Table 2). Significant determinants were mostly in the psychological domain, with lower satisfaction with social support, emotion-focused coping, helplessness, and higher fear of progression as independent determinants of depressive symptoms (total R^2=.65).

Table 1. Patient demographic and disease characteristics

Number of patients (% female)	215 (67.9%)
Mean age in years	56.4 (SD = 12.0, range 17.9–86.7)
Time since onset first Non-Raynaud symptom	9.2 (SD = 7.9, range 0.2–51.8)
Higher education (>12 yrs)	87 (41.2%)
Currently employed	70 (32.6%)
Married/ cohabitating	162 (75.4%)
Patients with limited SSc	158 (74.9%)
Mean mRSS	6.4 (SD = 5.9, range 0–37)
ANA positive	196 (91.2%)
ACA positive	54 (25.1%)
Anti-TOPO positive	57 (26.6%)
Anti-RNP positive	14 (6.5%)

mRSS, modified Rodnan Skin Score; ANA, antinuclear antibody; ACA, anticentromere antibody; anti-TOPO, antitopomerase antibody; anti-RNP, antiribonuclear protein antibodies

Table 2. Hierarchical regression analysis of demographics, disease status and psychological variables predicting depressive symptoms (CES-D, range 0–60).

	Variable	B[a]	[95% CI]	P	Beta[a]	Total R^2
1) Demographics	Age	−.04	[−.12, .05]	.371	−.05	
	Sex	−.86	[−3.00, 1.28]	.427	−.04	.03
2) Socioeconomic status	Higher education	−.37	[−2.42, 1.69]	.725	−.02	
	Married/Cohabitating	−2.0	[−4.41, .43]	.106	−.09	.07
3) Disease characteristics	Limited disease	−.04	[−2.38, 2.31]	.975	.00	
	Disease duration	.02	[-.10, .14]	.738	.02	
	mRSS	.08	[-.10, .26]	.409	.05	.09
4) Physical functioning	HAQ score	−1.16	[−2.95, .62]	.200	−.09	
	Pain	.05	[.00, .09]	.054	.11	
	Fatigue	.23	[.13, .33]	<.001	.31	.44
5) Psychosocial factors	Social support	−.03	[−.12, −.01]	.014	−.14	
	Helplessness	.39	[.04, .75]	.030	.17	
	Acceptance	.06	[−.26, .37]	.693	.03	
	Problem-focused coping	−.03	[−.12, .07]	.618	−.03	
	Emotion-focused coping	.18	[.08, .28]	<.001	.23	
	Avoidance coping	.06	[−.05, .16]	.298	.06	
	Appearance self esteem	−.23	[−.49, .03]	.083	−.10	
	Fear of progression	.20	[.05, .34]	.007	.18	.65

[a]Final model

Conclusion: A routine psychological assessment is recommended for patients with SSc, since assessment of physical functioning without systematically taking psychological factors into account might not be sufficient to identify patients at risk for depressive symptoms. For the development and trialling of psychological interventions, fear of progression could be an important target.

2488

Lifestyle Intervention for Health-Related Quality of Life in Overweight and Obese Patients with Systemic Lupus Erythematosus: A Pilot Study. Carol M. Greco[1], Amy D. Rickman[1], Nehal Shah[1], Anne E. Mishler[1], Nicole L. Wilson[2], John M. Jakicic[1], Susan Manzi[3] and Amy H. Kao[3]. [1]University of Pittsburgh, Pittsburgh, PA, [2]W Penn Allegheny Health System, Pittsburgh, PA, [3]Allegheny Singer Research Institute, Pittsburgh, PA

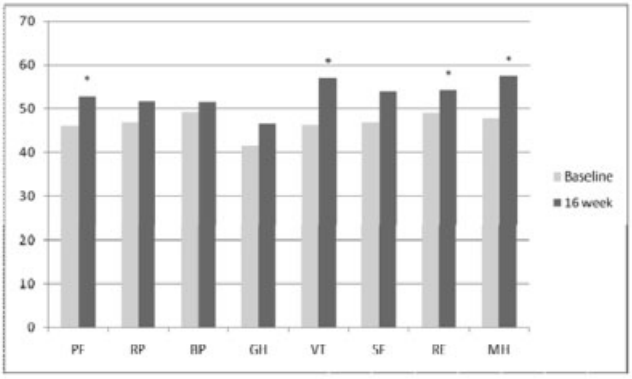
Background/Purpose: Many patients with systemic lupus erythematosus (SLE) are sedentary and have poor health-related quality of life (i.e. fatigue, pain, depressive symptoms). Few studies have evaluated the effects of a lifestyle intervention in patients with SLE. The purpose of this pilot study was to investigate the feasibility and effects of a 16-week lifestyle intervention on weight loss and health-related quality of life in SLE patients who are overweight or obese.

Methods: The lifestyle intervention program included a reduced calorie diet (1200/1500 kcal/d) and progressively increased physical activity from 100 to 300 min/wk by week 16. Participants met weekly as a group, completed food journals daily and engaged in a home exercise program. Measures included weight, Eating Behavior Inventory (EBI), Fatigue Severity scale (FSS), SF36 Health Survey v2, pain visual analog scale (VAS), and the Center for Epidemiologic Depression Scale (CES-D). Wilcoxon signed-rank tests were used to determine significant differences between baseline and 16 week self-report assessments.

Results: Participants were 15 women with SLE (mean age=39.7±10.4yrs, 53% Caucasian, mean body mass index =30.8±3.7 kg/m^2). Nine participants completed the study and provided baseline and 16-week assessments (60% completion rate). At baseline, 88% of study completers had clinically significant depressive symptoms as defined by CES-D >/=16, and the majority (67%) had significant fatigue as defined by FSS >/=36. Mean percentage weight change was −9.8±2.8% and mean weight lost was 8.2±2.0 kg. All 9 participants improved their healthy eating behavior assessed by EBI (change, +19, interquartile range [IQR]: 8 to 25, p=0.008). Significant improvements were seen in fatigue assessed by FSS (−7, IQR: −18 to 0, p=0.05) and SF36 Vitality Scale (+6.24, IQR: 3.1 to 18.6, p=0.009). Pain VAS improved (−11, IQR:−11 to −2, p=0.01) but not SF36 Bodily Pain scale (+4.2, IQR: 5.1 to 0, p=0.152). SF36 physical function improved as well (+4.2, IQR: 2.1 to 8.4, p=0.02). For mental health, depressive symptoms by CES-D (median: −4.5, IQR: −6.5 to −4, p=0.02), SF 36 Mental Health (+8.4, IQR: 2.8 to 14.1, p=0.008) and Role Emotional (+3.9, IQR: 0 to 3.9, p=0.03) all improved. Significant correlations were observed between changes in weight and fatigue (FSS: r=0.73, p=0.02; SF36 Vitality: r= 0.73, p= 0.03).

Conclusion: These results demonstrate that a lifestyle program focusing on weight loss and increased physical activity can lead to significant improvements in health-related quality of life, including mental health and fatigue in overweight/obese SLE patients. Research with a larger sample, a control group, a longer-term follow-up and strategies to improve retention will be important to determine how a lifestyle program may further impact the lives of SLE patients.

SF36v2 T-scores at Baseline and 16 weeks



* P< 0.05

2489

Sexual Activity and Impairment Among Women with Systemic Sclerosis. Brooke Levis[1], Marie Hudson[1], Ruby Knafo[1], Murray Baron[2], Warren Nielson[3], Marilyn Hill[3] and Brett D. Thombs[1]. [1]McGill University, Montreal, QC, [2]Jewish General Hospital, Montreal, QC, [3]Univ of Western Ontario, London, ON

Background/Purpose: Systemic Sclerosis (SSc), or scleroderma, is a chronic, multi-system, connective tissue disorder with a number of physical and psychological consequences that might be expected to affect sexual functioning among women, including fatigue, depression, distressing changes in appearance, Raynaud's phenomenon, skin tightening and discomfort, vaginal tightness and dryness, thickening of the skin around the lips, finger ulcers and calcium deposits that are painful to the touch, gastrointestinal symptoms, joint pain and muscular weakness. Existing studies of sexual functioning among women with SSc have concluded that rates of sexual dysfunction are high, but have been limited by the use of single, unvalidated items to assess dysfunction and problems; by not explicitly distinguishing between sexual inactivity and sexual dysfunction; by small sample sizes; by investigating only a limited amount of etiological factors, or by not including multivariate assessments. The objectives of this study were to assess (1) the rates of sexual activity and impairment in a large sample of female SSc patients, (2) clinical correlates of sexual activity/impairment, and (3) common sources of pain during and after sex.

Methods: Cross-sectional, multi-center study of female SSc patients from the Canadian Scleroderma Research Group Registry. Patients underwent medical examinations and clinical histories and were asked whether they had engaged in sexual activities with their partner in the past 4 weeks. Sexually inactive patients indicated reasons for inactivity. Sexually active patients completed a 9-item version of the Female Sexual Function Index (FSFI) and items related to problems that may be linked to sexual dysfunction in SSc. Multivariate logistic regressions were done to assess independent predictors of activity/inactivity and sexual dysfunction.

Results: 238 of 559 patients (43%), including 226 of the 412 patients currently in relationships (55%), reported having engaged in sexual activities with a partner in the past 4 weeks. Independent predictors ($p<0.05$) of sexual activity were younger age, fewer GI symptoms and less severe Raynaud's symptoms. Among the 165 sexually active patients with complete data for all variables, 102 (62%) scored below the FSFI cut-off of 22.5, indicating impaired sexual function, which was independently associated with older age, higher skin scores and more severe breathing problems. Ratings of pain both during and after sex were substantially higher for all 10 variables reflecting potential sources of pain among those impaired in comparison to those not impaired. Both during and after sexual activity, women with sexual impairment were significantly more likely to report at least one source of pain ($p<0.001$). Among individual sources of pain, after controlling for multiple comparisons, they were significantly more likely to report vaginal pain ($p<0.001$).

Conclusion: Rates of sexual impairment are high among women with SSc compared to rates reported in the general population. Research is needed to develop interventions to address impaired sexual function in women with SSc.

2490

The Relationship Between Cognitive Function and Physical Function in Persons with Rheumatoid Arthritis. So Young Shin, Laura J. Julian, Margaret I. Wallhagen and Patricia P. Katz. University of California San Francisco, San Francisco, CA

Background/Purpose: Population-based studies have found that cognitive impairment contributes to declines in daily function, yet no study has examined this relationship in persons with rheumatoid arthritis (RA). We addressed this gap by examining the association of cognitive impairment with functional limitations and disability in persons with RA.

Methods: Individuals with RA participating in a longitudinal cohort study who resided in the San Francisco Bay Area visited the clinical research center for a study visit that included a range of physical, psychosocial, and biological metrics. Cognitive function was assessed using a battery of 12 standardized neuropsychological measures yielding 16 indices covering a range of cognitive domains. On each test, subjects were classified as 'impaired' if they performed 1 *SD* below age-based population norms. The total cognitive impairment score was calculated by summing the transformed scores, ranging from 0 (no impairment) to 16 (worst impairment). Functional limitations were assessed with both performance-based (Short Physical Performance Battery [SPPB]; lower scores = worse function) and self-reported (Health Assessment Questionnaire [HAQ];

higher scores = worse function) measures. Disability was measured with the Valued Life Activities (VLA; higher scores = worse function) scale. Multiple regression analyses, controlling for gender, race, educational level, marital status, income, duration of RA, severity of RA, C-reactive protein (CRP), and depression were conducted to identify whether cognitive impairment independently predicted physical function difficulties.

Results: One hundred forty four subjects with a mean (±*SD*) age of 57.7 (±11.1) years were included. Sixty percent were female, 76% were white, and 10% had met criteria for major depressive disorder. Mean educational level was 15.1 (±2.3) years and duration of RA was 19.3 (±11.1) years. Mean total cognitive impairment score was 2.6 (±2.4), and ranged from 0–11. The proportion of persons who were classified as cognitively impaired on each test ranged from 9% (semantic fluency test) to 28% (non-verbal fluency test). The proportion of persons cognitively impaired on four or more tests was 29%. After controlling for gender, race, educational level, marital status, income, duration of RA, severity of RA, CRP, and depression, the total cognitive impairment score was significantly associated with greater functional limitations (SPPB: β = -.27, p =.008; HAQ: β =.27, p =.001) but not with disability (VLA: β =.12, p =.120).

Conclusion: Cognitive impairment was significantly associated with increased functional limitations in persons with RA. The findings of this study suggest that consideration of cognitive impairment may be warranted to improve functional status in persons with RA. None.

2491

Cognitive Impairment in Persons with Rheumatoid Arthritis. So Young Shin, Patricia P. Katz, Margaret I. Wallhagen and Laura J. Julian. University of California San Francisco, San Francisco, CA

Background/Purpose: For persons with chronic diseases such as rheumatoid arthritis (RA), intact cognitive function is crucial for performing main daily activities and adhering to self-management regimens. Persons with impaired cognitive function have decreased functional independence, reduced quality of life, and increased risk of mortality. Although several mechanisms may influence cognitive function in RA, it has not been well-studied in this population. This study explored the prevalence and possible predictors of cognitive impairment in persons with RA.

Methods: Individuals with RA participating in a longitudinal cohort study who resided in the San Francisco Bay Area visited the clinical research center for a study visit that included a range of physical, psychosocial, and biological metrics. Cognitive function was assessed using a battery of 12 standardized neuropsychological measures yielding 16 indices covering a range of cognitive domains. Subjects were classified as 'impaired' if they performed 1 *SD* below age-based population norms on at least 4 of 16 indices. Logistic regression analyses were conducted to identify which of the following were significant predictors of cognitive impairment: gender, race/ethnicity, income, education, disease duration, disease severity measured by the Rheumatoid Arthritis Disease Activity Index, C-reactive protein (CRP), steroid use, depression, and cardiovascular risk factors (self-reported presence of hypertension, diabetes, stroke, current smoking, or obesity [from body mass index]).

Results: One hundred subjects with a mean (±*SD*) age of 58.5 (±10.4) years were included. Eighty three percent were female, 83% were white, and 7% had met criteria for major depressive disorder. Mean educational level was 15.2 (±2.2) years and duration of RA was 21.1 (±11.6) years. The proportion of persons who were classified as cognitively impaired on each test ranged from 8% (visuo-spatial test) to 31% (non-verbal fluency test). Mean total cognitive impairment score was 2.5 (±2.2), and ranged from 0–10. The proportion of persons who were classified as cognitively impaired was 30%. Race, education, duration of RA, and cardiovascular risk factors independently predicted cognitive impairment controlling for income, severity of RA, CRP, steroid use, and depression. Individuals with cognitive impairment were more likely to be nonwhites (OR = 5.81, 95% CI: 1.16–29.05), and had less education (OR = 1.35, 95% CI: 1.05–1.75), lower disease duration (OR = 1.05, 95% CI: 1.01–1.10), and increased cardiovascular risk factors (OR = 3.36, 95% CI: 1.04–10.80).

Conclusion: About one third of RA patients were cognitively impaired. Nonwhites, persons with less education, shorter duration of RA, and one or more cardiovascular risk factors were more likely to have cognitive impairment in this cohort. These findings suggest that the burden of cognitive impairment in RA is significant, and future studies identifying specific etiological contributors to cognitive impairment are warranted.

2492

Accounts of Chronic Pain and Emotional Distress in Children and Youth with Juvenile Idiopathic Arthritis or Chronic Pain: Qualitative Analysis of Interviews to Assess Content Validity of the Patient Reported Outcome Measurement Information System. C. Jeffrey Jacobson[1], Jennifer Farrell[2], Susmita Kashikar-Zuck[2], Emily Verkamp[2], Michael Seid[3] and Esi Morgan DeWitt[2]. [1]University of Cincinnati, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Cincinnati Children's Hospital Medical Center, Cincinnati

Background/Purpose: Chronic pain in children and adolescents is associated with functional impairment, increased distress, and reduced quality of life. Assessment of the pain experience is heavily dependent on child and youth self-reports of pain intensity, pain quality and emotional distress. However, knowledge about how children and adolescents understand and talk about their pain and distress and how this may vary across diagnosis, gender, or age or developmental stage is limited. Little research has examined the thematic, semantic and linguistic content of child accounts of pain and distress across these groups The objective of the current study was to qualitatively evaluate the content validity of the NIH Patient Reported Outcomes Measurement Information System (PROMIS, nihpromis.org) pediatric measures for self-reported health outcomes from the perspective of children and youth with juvenile idiopathic arthritis (JIA) or chronic pain syndromes. The eight PROMIS pediatric measures include a Pediatric Pain Interference Scale as well as emotional distress scales.

Methods: Trained interviewers conducted semi-structured individual interviews with children and youth ages 8 to 18 years old with either JIA or a non-inflammatory chronic pain syndrome). Each interview covered 2 to 4 of the health concepts underlying the 8 PROMIS pediatric domains: Anxiety, Anger, Depressive Symptoms, Fatigue, Pain Interference, Peer Relationships, Physical Function (Upper Extremity, and Mobility). For each domain, interviews elicited the subjective meaning of the construct and using both open-ended and structured probes. Participants also completed PROMIS Short Forms which were scored. Audio-recorded interviews were transcribed verbatim and entered into a qualitative text management software program (NVIVO8) to facilitate analysis. Transcript content was evaluated in relation to 1) the item-conceptual content of the 8 PROMIS domains 2) possible age-related differences in comprehension and reporting of the domains and 3) possible diagnosis-related differences in expression and reporting of the domains.

Results: 31 youth (16 JIA, 15 chronic pain) were interviewed, mean age 13.7 years (range 8–18), 80.6% female. We found age- and gender-related differences in child-reported understandings, expression, and articulation of the domains of anger, anxiety, depression and pain interference. Children younger than 14 years typically had difficulty defining one affective-distress domain without referring to another. Female participants were more verbally expressive than males. Differences based upon diagnosis were also explored to see whether there was any evidence of medical socialization in these illness groups.

Conclusion: These findings suggest need for a rigorous developmental approach to pediatric patient reported outcome measure development. Experience and expression of health constructs differed based upon developmental status, and possibly in part due to medical socialization.

ACR Concurrent Abstract Session
B-cell Biology and Targets in Autoimmune Disease
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

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Effective Anti-CD20 Therapy for Arthritis Is Associated with B-Cell Depletion in Efferent Lymph Nodes and Increased Lymph and Cellular Flow in Lymphatic Vessels From Arthritic Joints. Jie Li, Christopher T. Ritchlin, Ignacio Sanz, Andrea Bottaro, Ronald Wood, Lianping Xing and Edward M. Schwarz. University of Rochester School of Medicine and Dentistry, Rochester, NY

Background/Purpose: B cell depletion therapy (BCDT) is an effective intervention for some RA patients. However, the mechanisms that underlie the reduction of synovitis and decline in macrophage numbers remain unknown. Contrast enhanced (CE) MRI and near infrared (NIR) imaging of indocyanine green (ICG) of TNF-Tg mice has demonstrated that arthritic progression from the ankle to the knee is initially prevented by increased lymphatic drainage to "expanding" lymph nodes (LN), which significantly increase in size due to the accumulation of non-activated polyclonal CD23+/

CD21hi B cells (B-in). Subsequently, knee flare occurs following a sudden decrease in lymphatic flow, and LN collapse due to B-in translocation from the follicles into the sinus space, resulting in "clogging" of the lymphatic vessels. Here we tested the hypothesis that BCDT ameliorates TNF-induced knee arthritic flare by removal of B-in from the LN, which leads to increased flow and inflammatory cell egress through lymphatics in arthritic joints.

Methods: TNF-Tg mice with expanding or collapsed popliteal LN (PLN) were identified by CE-MRI and their knee synovial volume was quantified. Mice with collapsed PLN were treated with anti-CD20 (n=8; 16 knees) (10mg/kg/i.v. every 2 weeks) or placebo (n=4; 8 knees) for 6 weeks, with continuous CE-MRI every 2 weeks. Lymphatic flow was quantified by NIR-ICG. In vivo imaging of macrophages, B cells and T cells in lymphatic vessels draining the leg was performed by co-injection of fluorescently labeled dextran and antibodies against CD11b, IgM or CD3 into the footpad 2hr prior to direct immuno-fluorescent microscopy (IFM) of the surgically exposed vessels.

Results: NIR-ICG imaging demonstrated that collapsed PLN displayed decreased lymphatic draining vs. expanding in ICG clearance rate (43.8±17.6% vs.86.3±3.4%, p=0.018) and lymphatic pulsing frequency (0 vs. 1.4±0.03 pulse/minute). IFM showed a significant increase in the number of CD11b+ cells in lymphatic vessels afferent to collapsed vs. expanding PLN (No./mm vessel: 26.6±1.6 vs. 5.8±5.5, p=0.0007). Anti-CD20 treatment significantly decreased knee synovial volume (4.55±2.39mm^3 vs. 8.98±4.16mm^3 in placebo, p=0.02) at 6-weeks, and synovitis progression (p=0.0003) vs. the placebo group, which demonstrated a significant (p=0.0001) 0.81mm^3/week increase in synovitis. Anti-CD20 also increased ICG clearance rate vs. placebo (90.4±8.5% vs. 69.3±21.7%, p=0.03). The increased lymphatic flow was associated with a decrease in CD11b+ cells in lymphatic vessel (No./mm vessel: 1.8±0.4); a finding equivalent to that in vessels afferent to expanding PLN.

Conclusion: These results indicate that some arthritic flares are associated with B cell translocation into the lymphatic sinuses of LN, which "clogs" draining lymph from the joint. BCDT could clear these B-in cells and restore lymphatic draining function, leading to reduced tissue damage by removing CD11b+ inflammatory cells and other catalytic factors from affected joints. Thus restoration of lymphatic function is a novel mechanism of action for BCDT in treatment of RA.

2494

A Whole-Blood Transcriptomic Signature Predicts Clinical Response to Rituximab in Rheumatoid Arthritis. Jeremie Sellam[1], Sandrine Marion-Thore[2], F. Dumont[2], Franck Letourneur[3], Stephanie Rouanet[4], Yassine Taoufik[5], Jean Sibilia[6], Jacques G. Tebib[7], Xavier Le Loët[8], Bernard G. Combe[9], Maxime Dougados[10], Xavier Mariette[11] and Gilles Chiocchia[3]. [1]Hopital Saint-Antoine, Pierre et Marie Curie University Paris 6, AP-HP, 75012, France, [2]INSERM U1016, Institut Cochin, Paris Descartes University, Paris, France, [3]Institut Cochin, 75014 Paris, France, [4]Roche, Neuilly sur Seine, France, [5]Hopital Bicetre, Université Paris Sud, AP-HP, France, [6]Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, Strasbourg, France, [7]Centre Hosp Lyon Sud, Pierre Benite, France, [8]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, [9]Hopital Lapeyronie, Montpellier, France, [10]Paris-Descartes University, Paris, France, [11]Université Paris-Sud, Le Kremlin Bicetre, France

Background/Purpose: The first aim of this study was to investigate transcriptomic profile of peripheral blood sample from rheumatoid arthritis (RA) patients before rituximab (RTX) to identify gene expression profile predictive of clinical response. The second aim was to analyze the transcriptomic profile of the same patients at week 24 (W24) after RTX.

Methods: 224 RA patients refractory or contra-indicated to anti-TNF were treated with RTX 1 g day 1 and 15 in an open label trial (SMART study) and clinical response was assessed at W24 using EULAR response. Two groups of patients were set up: non responders (NR, 29%) and responders (R, 71%), the later including both moderate (49%) and good responders (22%). This transcriptomic study involves 69 patients randomly selected among the 224 encompassing 24 NR and 45 R. RNA was extracted from peripheral blood sample and then amplified. Gene expression profiling was performed using Affymetrix Human gene 1ST array which covered the whole genome. Results were analyzed using both linear method LIMMA and ANOVA.

Results: Before RTX, differential gene expression between R versus NR at week 24 showed that 203 genes were significantly differentially deregulated. This set of genes allowed a good classification of 82% of the patients according to their response status. This first gene expression signature was then reduced to 62 genes by using Pearson correlation and allowed to correctly classify 90% of the patients into groups R and NR. The molecular signature consisted in genes regulating (a) inflammatory response including upregulation of interleukin 33 (IL-33), a member of the IL-1 family and of IRAK1, mediating the pleiotropic effect of IL-1 and downregulation of genes related to interferon (INF) response such as IFIH1, TRIM22, and DHX58, (b) cell to cell interaction: EMR4P and E-selectin playing a role in leukocyte trafficking were significantly higher in R and (c) cellular development including ZHX3, a transcriptional repressor downregulated in R. At W24 post-treatment, genes involved in B cell development and B cell functions were strongly down regulated in both groups, as expected after RTX. Differences in the regulation of B cell pathways were found between groups in term of quantity, and surprisingly, the NR group exhibited a larger number of down regulated B-cell related genes with more down-regulation of the immunoglobulin genes.

Conclusion: A pre-treatment molecular signature predicts the response to RTX in 90% of RA patients. This molecular signature involves upregulation of IL-33 and downregulation of IFN pathway. The comparison between pre and post-treatment signature revealed an unexpected stronger down-regulation of B cell genes in NR compared to R patients.

2495

A Humanized Monoclonal Antibody Against a Surface Ligand of Mononuclear Cells Suppress Autoimmune Inflammatory Diseases by Upregulation of IL-10 Secretion. Yaakov Naparstek, Rina Ulmansky, Galia Katzavian, Ronit Meyuhas, Alon Hershko, Eli Moallem, Shira Yair and Dorit Landstein. Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Background/Purpose: We have previously shown that resistance to Adjuvant Arthritis (AA) is due to the presence of anti-heat shock protein (HSP) antibodies, directed at peptide 6, a 16 amino-acid surface epitope, that cross reacts with a mononuclear cell surface ligand. In this work we have studied the effect of a humanized monoclonal antibody against peptide 6 on various models of autoimmune arthritis and colitis and the mechanism of their anti-inflammatory effect.

Methods: We have recently developed a humanized anti-peptide 6 antibody that cross reacts with a surface ligand of human mononuclear cells. Incubation of this antibody with murine and human mononuclear cells induced the secretion of IL-10.

Results: The antibodies bound to a cross reacting epitope of adenyl cyclase associated protein (CAP1) in human monocytes and induced upregulation of IL-10 mRNA, by upregulation of transcription factors that bind the IL-10 promoter, resulting in the induction of IL-10 secretion. Suppression of CAP1 expression by specific siRNA reduced the binding of the protective antibodies to the cells. Treatment of mice and rats with collagen induced arthritis, adjuvant arthritis and TNBS colitis with this antibody induced upregulation of serum IL-10 and suppression of disease. The level of anti peptide 6 antibodies in the serum of patients with rheumatoid arthritis was significantly lower than in healthy controls.

Conclusion: We conclude that HSP contains protective B-cell epitopes exposed on its surface, and that natural and acquired resistance to autoimmune arthritis is associated with the ability to develop an antibody response to these epitopes. These antibodies cross react with a monocyte surface receptor and modulate cytokine production. Lower levels of anti peptide 6 antibodies in patients with RA suggest that they play a role in protection against human autoimmune diseases as well. The monoclonal humanized anti-peptide 6 antibody may serve as a new therapeutic tool for suppression of human arthritis and inflammatory bowl diseases by skewing the immune system selectively towards an anti-inflammatory response.

2496

B Cells Enhance the Type I Interferon Production by Plasmacytoid Dendritic Cells Via CD31. Lars Rönnblom[1], Olof Berggren[1], Gert Weber[2], Niklas Hagberg[1] and Maija-Leena Eloranta[1]. [1]Section of Rheumatology, Uppsala University, Uppsala, Sweden, [2]Structural Biochemistry, Free University of Berlin, Berlin, Germany

Background/Purpose: The type I interferon (IFN) system and B lymphocytes are activated in lupus and several other autoimmune rheumatic diseases. The main producer of IFN-α is the plasmacytoid dendritic cell (PDC), and the produced IFN can stimulate B cells and promote autoantibody production. However, the role of B cells on the PDC function has not been examined before. We therefore investigated the regulatory effect of B cells on the type I IFN response by PDC after stimulation with immune complexes (IC), virus and CpG-DNA. We further studied whether the PDC and B cell cross-talk was mediated by soluble factors or by cell-cell contact.

Methods: PDC and B cells were isolated from peripheral blood mononuclear cells from healthy blood donors. PDC alone or in co-cultures with B cells were stimulated with purified U1 snRNP and IgG from SLE patients (RNA-IC), herpes simplex virus (HSV) or the CpG containing oligonucleotide ODN2216. Supernatants from stimulated B cell cultures were collected after 20h and investigated for their stimulatory effect on the IFN-α production. The co-culture supernatants were analyzed for IFN-α, and several other cytokines. The cells were stained by monoclonal antibodies and analyzed by flow cytometry for intracellular IFN-α, as well as PDC and B cell associated cell surface molecules (BDCA-2, CD20, CD31 and CD38). Neutralizing antibodies to CD31 were used to investigate the PDC and B cell interactions.

Results: B cells enhanced the IFN-α production by PDC 3 to 15 fold (1000–8000 U IFN-α/ml) with all IFN inducers. B cells more strongly enhanced the PDC response when stimulated with HSV compared to RNA-IC and ODN2216 ($p=0.0001$ and $p=0.019$, respectively). PDC and B cells formed cell aggregates when IFN inducers were present in the co-cultures. Supernatants from ODN2216-stimulated B cells markedly promoted the IFN-α production by PDC, while supernatants from RNA-IC-stimulated B cells were poor IFN-α enhancers. Anti-CD31 antibody inhibited the IFN-α production induced by RNA-IC in co-cultures of PDC and B cells (~80% reduction), but not in co-cultures stimulated with ODN2216. Pre-incubation of PDC or B cells with anti-CD31 antibodies before co-culturing the cells with RNA-IC, reduced the IFN-α production to the same extent as when anti-CD31 antibodies were added directly to the co-cultures. PDC were responsible for the IFN-α production in the co-cultures. The PDC produced higher amounts of IFN-α per cell when stimulated by RNA-IC compared to ODN2216, while the latter induced higher frequency of IFN-α producing PDC. All IFN-α producing PDC showed high expression of CD31.

Conclusion: Our findings reveal an important interaction between the innate and adaptive immune system with B cells promoting the PDC function and increasing the type I IFN response to several different IFN-α inducers, including IC containing nucleic acids. B cells enhance the IFN-α production by PDC both via cell-cell contact and soluble factors depending on the stimuli. Since B cells are activated by type I IFN, this PDC-B-cell cross-talk may be of fundamental importance in the etiopathogenesis of SLE, and contribute to the observed IFN signature and chronic immune activation in SLE and other systemic rheumatic diseases.

2497

The Critical Role of Protein Kinase C Beta in Lupus Development in Lupus Mice. Luojing Chen. University of Rochester, Rochester, NY

Background/Purpose: B cells play a central role in lupus and targeting B cells for the treatment of lupus is an area of great interest. Protein kinase C beta (PKCbeta) is important for mature B cell survival by mediating BCR and BAFF signaling. However, the function of PKCbeta in the survival of lupus B cells and the development of the disease has not been investigated.

Methods: Using congenic mouse models bearing the disease loci: Sle1 or Sle1Sle3, we generated PKCbeta deficient mice (Sle1.PKCbeta−/− and Sle1Sle3.PKCbeta−/− mice).

Results: the deficiency in PKCbeta abrogated all lupus associated phenotypes such as high levels of autoantibodies in serum and proteinuria and the appearance of Ig deposition in kidneys. Compared with Sle congenic lupus mice, PKCbeta deficient mice have a remarkable decrease in spleen size and greatly reduced activated CD4 T cells and B cells, CD4/CD8 T cell ratio, and CD138 plasma cells, of which are all typically high in lupus mice. In addition, PKCbeta deficient lupus mice showed a severe decrease in peritoneal B1 cells and have an impaired immune response to both T-cell dependent and independent antigens. Furthermore, we found that mouse lupus B cells, as well as a prototype of human autoreactive B cells (9G4+), display enhanced sensitivity to PKCbeta inhibition. The absence of PKCbeta impairs anti-IgM mediated proliferation and survival responses in lupus B cells, at least in part due to down-regulation of the NF-kB pathway. More importantly, the lack of detection of kidney lesions from the PKCbeta deficient lupus mice indicates the critical role of PKCbeta in lupus development.

Conclusion: Our results suggest that PKCbeta may represent a potentially specific therapeutic target for lupus treatment.

2498

Effect of Intravenous Cyclophosphamide Treatment on B Cells in SLE Nephritis. Chungwen Wei[1], John Jung[1], Valentin Marian[1], Donna F. Hardwick[2], Gema Souto-Adeva[3], Youqun Huang[1], Bridget Neary[1], Gabor G. Illei[3] and Iñaki Sanz[1]. [1]University of Rochester, Rochester, NY, [2]NIH MSC 1616, Bethesda, MD, [3]NIDCR/ NIH #10 1N110, Bethesda, MD

Background/Purpose: Intravenous pulse cyclophosphamide (IVCY) has been shown to effectively induce remission and improve long-term outcome in patients with proliferative lupus nephritis. Despite its effectiveness, the mechanism of its efficacy is still not clear. Nonetheless, orally administered cyclophosphamide has been shown to suppress B cell proliferation and differentiation *in vitro*. However, the depth of IVCY-induced B cell depletion and its potentially differential impact on specific B cell subsets remains to be formally investigated. This study investigates the effects of IVCY on B cell profiles as a first step towards understanding its mechanism of action and identifying biomarkers of favorable response.

Methods: SLE patients treated with IVCY for active SLE were recruited either before initiation of treatment or during treatment (n=12). PBMCs were analyzed by two 12-color flow panels designed to recognize all major B cell subsets and to in-depth subset either memory or transitional B cell compartments. These panels share seven anchor markers (live/dead, CD3, CD19, IgD, CD27, CD38 and CD24) and include CD21, B220, CD95, CXCR3 in the memory panel and MTG, CD10, IgM, CD23 in the transitional panel. The resulting B cell profiles from the cross-sectional and longitudinal analyses of these patients were compared to those generated from a group of healthy subjects (n=9).

Results: In all, we analyzed 26 samples from 12 patients treated with IVCY. Of those, 22 represented longitudinal samples from 8 patients and 4 represented unique samples. Of which, 5 were baseline samples (pre-CY) and the other 21 were collected at different time points during the treatment (post-CY). The pre-CY group had a higher level of B cells than the healthy control group ($p<0.01$), while the post-CY group exhibited a severe B cell lymphopenia compared to both HC and pre-CY groups ($p<0.001$). Levels of $CD21^-$ and $CD95^+$ activated B cells in both IgD^-CD27^+ and IgD^-CD27^- switched memory subsets were elevated in the pre-CY group compared to the HC group ($p<0.01$). After treatment, there was a decrease in the IgD^+CD27^- population (which consists of both naïve and transitional B cells) and a concomitant increase in the switched memory cells. Despite the amelioration of clinical symptoms, the post-CY group still exhibited a memory dominant B cell profile. Of the 5 patients with a baseline, 4 responded well to the treatment. The mean SLEDAI went down from 18.5 to 4, and all achieved remission of proteinuria. Serum creatinine levels were also decreased by as much as 50%. Prior to IVCY treatment, the vast majority of B cells from these patients were bound *in vivo* by the VH4–34 encoded $9G4^+$ autoantibody. Strikingly, 9G4 painting was completely abolished from these responders after treatment.

Conclusion: In contrast with Rituximab, patients treated with IVCY with a favorable clinical response are characterized by the persistence of a dominant population of memory cells and lack of naïve/transitional dominance during reconstitution phases. Detailed B cell profiling in SLE patients treated with CY may provide significant insights into the pathogenic role of different B cell compartments and identify biomarkers of disease response and possibly of long-term remission.

ACR Concurrent Abstract Session
Cytokines, Mediators, and Gene Regulation II
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

2499

IL-27 Receptor Signaling Is Critical for B Cell Differentiation in Collagen Induced Arthritis. Odilia B.J. Corneth[1], Anne-Marie Mus[2], Patrick S. Asmawidjaja[2], Rudi W. Hendriks[2] and Erik Lubberts[2]. [1]Erasmus MC, University Medical Center, Rotterdam, Rotterdam, Netherlands, [2]Erasmus MC, University Medical Center, Rotterdam, Netherlands

Background/Purpose: Th17 cells play a critical role in the autoimmune mouse model for rheumatoid arthritis, collagen induced arthritis (CIA). IL-27 receptor (IL-27R) signaling induces Th1 differentiation and IL-10 production and inhibits Th17 differentiation. In addition, IL-27R signaling is linked to B cell proliferation and IgG2a class switch recombination. In experimental autoimmune encephalomyelitis (EAE), an autoimmune mouse model for multiple sclerosis, IL-27R knock-out mice showed higher proliferation of draining lymph nodes with more production of IL-17, IL-6 and TNFα. We therefore hypothesized that CIA would be enhanced in IL-27R knock-out mice compared to wild type controls. The purpose of this study is to investigate the role of IL-27R signaling in CIA.

Methods: IL-27R knock-out mice and wild type controls were immunized with chicken collagen type II and complete Freunds Adjuvant (CFA), and boosted again 21 days later. Mice were euthanized 10, 36, 45 and 63 days

after immunization and B and T cell subsets in spleen, lymph nodes and joints were analyzed using flow cytometry. Furthermore, auto-antibodies were determined in serum using ELISA and immunohistochemic analysis of the spleen and histological analysis of the joints was performed. For antigen induced arthritis, mice were immunized with methylated bovine serum albumin (mBSA) in CFA and a local injection of mBSA in the knee joint was given one week later.

Results: Interestingly, both the incidence of CIA and the arthritis score were significantly lower in IL-27R knock-out mice compared to wild type controls. In addition, synovial inflammation was markedly decreased in IL-27R knock-out mice. Although the proportion of Th17 cells was increased in IL-27R knock-out mice, the total number of CD4+ T cells was significantly lower. To assess whether Th17 cells were pathogenic we made use of the Th17 mediated antigen induced arthritis (AIA) model. Inflammation of the knee joints in IL-27R knock-out mice in AIA was comparable to wild type controls, showing that the pathogenicity of these cells is normal. As B cells also play a significant role in CIA, we then analyzed B cells by flow cytometry. The total number of B cells was lower in IL-27R knock-out mice. Also, IL-27R knock-out mice hardly develop germinal center B cells, which we confirmed by immunohistochemistry. In line with this, we found that collagen specific IgG antibody levels were lower in these mice suggesting a critical role for IL-27R signaling in further differentiation of mature B cells.

Conclusion: Our data show a critical role of the IL-27 receptor signaling in the development of CIA. IL-27R deficient mice have a higher proportion of Th17 cells with normal pathogenic function but reduced numbers of CD4+ T cells en B cells. In addition, the development of germinal center B cells was significantly impaired. These data suggest that IL-27 receptor signaling is involved in both T en B cell development and function and that the lack of germinal center B cells in the IL-27R deficient mice is most critical for the reduced expression of CIA.

2500

Interleukin-27 Receptor-Deficient Mice Develop Exacerbated Inflammatory Arthritis Associated with Heightened T- and B- Cell Responses. Gareth W. Jones[1], Anwen S. Williams[1], Mari A. Nowell[1], Brendan J. Jenkins[2] and Simon A. Jones[3]. [1]School of Medicine, Cardiff University, Cardiff, Wales, United Kingdom, [2]Monash Institute of Medical Research, Monash University, Melbourne, Australia, [3]Cardiff University, Cardiff, United Kingdom

Background/Purpose: Cytokine control of the adaptive immune response is a central process in the development of inflammatory diseases. T helper cells that produce interleukin-17 (IL-17; Th17 cells) have recently been identified as a distinct T cell subset implicated in a number of autoimmune diseases including rheumatoid arthritis (RA). As such, targeting of the inflammatory pathways that promote Th17 cell responses are currently of interest for developing new therapies to treat RA. The interleukin (IL)-6 family of cytokines share the ubiquitously expressed glycoprotein 130 (gp130) receptor for activation of intracellular signaling pathways and members of this family, most notably IL-6 and IL-27, have emerged as key regulators of the Th17 cell response. Through differential activation of signaling transducers and activators of transcription (STAT)1 and STAT3, IL-6 and IL-27 have opposing outcomes on the generation of Th17 cells. IL-6/STAT3 signaling promotes the differentiation of Th17 cells from naïve T helper cells while IL-27 *via* STAT1 counteracts this IL-6-driven process. Accordingly, IL-6 receptor-deficient (IL-6R$^{-/-}$) mice are protected from inflammatory arthritis, display no T cell infiltrates in the synovium and have an impaired Th17 cell response. Studies in IL-27R$^{-/-}$ mice have highlighted an anti-inflammatory role for IL-27 in inflammatory diseases. However, the mechanisms linking IL-27 to arthritis progression remain unclear.

Methods: Experimental inflammatory arthritis was induced in wild type (WT) mice and IL-27R$^{-/-}$ mice. Disease severity was assessed through measurement of joint swelling, histological analysis of joint sections and x-ray. Flow cytometry, immunohistochemical and immunological assays were used to monitor the peripheral immune response and the cellular response within the synovium. To support *in vivo* studies, *in vitro* approaches investigated T helper cell responses to IL-27.

Results: IL-27R$^{-/-}$ mice developed exacerbated inflammatory arthritis, displaying increased synovial infiltrates and bone erosions compared to WT mice. IL-27R$^{-/-}$ mice also displayed increased peripheral Th17 cell responses and higher serum IL-17 levels. Surprisingly, these mice also had heightened B cell responses associated with an increase in antigen specific serum IgG levels. Immunohistochemical analysis of synovial infiltrates revealed increased activation of STAT3 was associated with disease exacerbation, further confirming a damaging role for local STAT3 activation in arthritis progression.

Conclusion: Experimental inflammatory arthritis provides a valuable model for understanding the role of cytokines in inflammation-induced disease pathology. In this regard, IL-27R$^{-/-}$ mice develop exacerbated joint disease, demonstrating a protective role for IL-27 in inflammatory arthritis. This anti-inflammatory effect of IL-27 is attributed to regulation of T- and B-cell responses and modulation of STAT1/3 activation. Excessive activation of STAT3 within the joint contributes to inflammation-induced joint pathology and modulating the STAT1/3 axis may provide a potential therapeutic approach. In this regard, targeting of the IL-27 signaling pathway is currently being explored.

2501

IL-22 Restrains the Progression to Severe Arthritis. Sujata Sarkar, Xiaoqun Zhou and Swaroopa Bommireddy. University of Arizona, Tucson, AZ

Background/Purpose: IL-22 belongs to the IL-10 family of cytokines and may be produced by T cells, NK cells or LTi cells. IL-22 is pathogenic in psoriasis and protective in inflammatory bowel disease and hepatitis. IL-22 knock-out mice have a reduced incidence of arthritis, however role of IL-22 during various phases of arthritis and its effector function in arthritis remains to be elucidated. This study was undertaken to evaluate the role of IL-22 and the underlying mechanism of action during effector phase of arthritis.

Methods: 8–10 week old DBA mice were immunized with collagen and CFA (complete Freund's adjuvant) to induce arthritis. Spleen, draining inguinal lymph nodes and paws were collected from naïve mice, mice 2 weeks following immunization and from mice with arthritis for analysis of expression of IL-22 and IL-22 receptor by real time PCR. To analyze the effector function of IL-22, splenocytes from various phases of arthritis or single cell suspension of arthritic paws were restimulated with collagen, anti-CD3 or H37Ra in the presence or absence of IL-22. IL-17, IFN-g, TNFa, IL-10, IL-1b, IL-1a and IL-6 were measured in culture supernatants by ELISA. For studies evaluating the in vivo function of IL-22, recombinant IL-22 or HBSS was administered, ip, every day, from days 23–35 following immunization with collagen and CFA (days 23–35 covers the period prior to the onset of arthritis and into the effector phase). Mice were scored for clinical arthritis every other day. At the conclusion of the exp around day 35, paws, spleen, draining lymph nodes, and serum were collected for various assays. Paws were analyzed for synovial inflammation, bone and cartilage damage by histopathology. Single cell suspension of spleen and draining inguinal lymph nodes were restimulated with collagen, anti-CD3 or H37Ra for analysis of IL-17, IFN-g, and IL-10 responses. For some experiments neutralizing anti-IL-10 antibody was administered in conjunction with recombinant IL-22.

Results: IL-22 is upregulated in lymphoid organs during arthritis and in arthritic paws. Further, IL-22 production could be induced in splenocytes from arthritic mice following re-stimulation in an antigen specific fashion with collagen. In-vitro studies showed that exogenous IL-22 induced IL-17, IL-6 and IL-10 in splenocytes during the effector phase of arthritis. Although IL-22 induced IL-17, IL-6 in vitro, in vivo administration of IL-22 was associated with a significant delay in progression of severity of arthritis. Splenocytes from mice receiving recombinant IL-22 showed an increased IL-10 production, without a significant increase in IL-17 or IFN-g. Administration of neutralizing anti IL-10 antibody in conjunction with recombinant IL-22 reversed the protective effect of IL-22 in arthritis.

Conclusion: While, IL-22 induces proinflammatory (IL-17, IL-6) as well as anti inflammatory cytokines (IL-10) in vitro, in vivo administration of IL-22 is associated with significant reduction in progression to severe arthritis in an IL-10 dependent manner. These findings are suggestive of a protective role of systemic IL-22 around the onset of arthritis.

2502

Interferon-γ and Toll-Like Receptor 9 Collaborate to Cause Both Leukopenia and Anemia In a Murine Model of Macrophage Activation Syndrome by Two Distinct Mechanisms. Katharine Slade[1], Scott Canna[1], Portia Kreiger[2] and Edward M. Behrens[1]. [1]Childrens Hospital of Philadelphia, Philadelphia, PA, [2]A.I. DuPont Hospital for Children, Wilmington, DE

Background/Purpose: Macrophage Activation Syndrome (MAS) is a deadly complication of multiple pediatric rheumatologic conditions. One of the most striking features of MAS is the profound cytopenias that occur during the disease. Using our recently described murine model of Toll-like Receptor 9 (TLR9) induced MAS, we dissected the mechanisms by which Interferon-g (IFNγ) and TLR9 induce both leukopenia and anemia.

Methods: Mice were repeatedly injected i.p. with 50 μg of the TLR9 agonist CpG1826 as previously described to induce MAS. To explore the role of IFNγ, IFN$\gamma-/-$ mice were repeatedly injected with PBS, CpG, recombinant murine IFNγ (10 μg), or both CpG and IFNγ. To determine the cellular effectors of the IFNγ response we made use of mice deficient in the IFNγ receptor (IFNγR$-/-$). Bone marrow chimeric mice were made by exposing mice to sub-lethal gamma irradiation (900 rads) followed by bone marrow transplantation. Wild type mice were reconstituted with 1×10^6 cells from either wild type control mice or IFNγR$-/-$ mice. Chimeric experiments with the converse combinations were also performed.

Results: IFNγ and CpG were both required to induce leukopenia and anemia, injection of either of these stimuli singly did not induce a cytopenia. In contrast, IFNγ was necessary and sufficient to induce the MAS hepatitis, while CpG was not necessary for this feature of the disease. Wild type mice reconstituted with IFNγR$-/-$ marrow did not develop the CpG induced leukopenia compared to mice reconstituted with IFNγR$+/+$ marrow, suggesting the IFNγ responsive effectors cells mediating leukopenia are radiosensitive marrow cells. Interestingly, mice reconstituted with IFNγR$-/-$ marrow had as severe an anemia as mice with wild type marrow, suggesting a distinct IFNγ mediated mechanism for anemia that requires a radioresistant cell. As with leukopenia, IFNγ induced MAS hepatitis was at least partially mediated by a radiosensitive marrow cell. Hypercytokinemia was largely unaffected by the absence of IFNγR in the marrow in that serum IL-6, IL-10, and IL-12 levels remained similar between groups. IFNγ levels were higher in mice reconstituted with IFNγR$-/-$ marrow, likely due the the lack of negative feedback from the receptor.

Conclusion: In a murine model of TLR9 induced MAS, both IFNγ and TLR9 are required to induce leukopenia and anemia. This suggests that blockade of either of these pathways may be sufficient for treatment of MAS associated cytopenia in autoinflammatory settings. In contrast, IFNγ was more important for MAS induced hepatitis, and therefore is a more attractive target for this complication. Since different cellular effectors are responsible for these different mechanisms, cell targeted therapies would need to be chosen rationally based upon MAS symptomatology, as opposed to a "one size fits all" approach. Future studies are being directed at definitively identifying which cell types are involved in each of these processes.

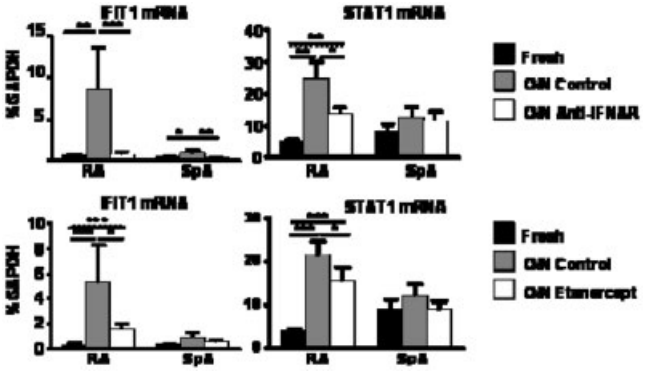
2503

Opposing Regulation of IFN Response Genes and *STAT1* in Rheumatoid Arthritis Synovial Fluid Macrophages by TNFá and the Synovial Fluid Microenvironment. Rachael A. Gordon, Galina Grigoriev, George D. Kalliolias and Lionel B. Ivashkiv. Hospital for Special Surgery, New York, NY

Background/Purpose: Increased expression of IFN-g-inducible genes in rheumatoid arthritis (RA) synovial tissues and macrophages (Mf) has been verified in several studies. IFN-g-inducible genes enhance antigen presentation and inflammatory cytokine production and thus a synovial IFN-g response likely contributes to RA pathogenesis. Most of these IFN-g-inducible genes are targets of the transcription factor STAT1. STAT1 is activated by, and mediates the effects of, several cytokines, particularly IFN-g, type I IFNs (IFNa/b), IL-6, IL-10 and IL-27. Because IFN-g is expressed at vanishingly low concentrations in RA synovium, and RA synovial Mf responses to IL-6, IL-10 and IL-27 are attenuated, type I IFNs emerge as potential activators of synovial STAT1 in RA. Recently we have shown that long term TNFa exposure initiates an IFNb-mediated autocrine loop in blood-derived Mf; here we test whether TNFa also could contribute to an IFN response in RA synovial Mf, and thus to the 'IFN signature' observed in RA.

Methods: Synovial fluid (SF) Mf obtained from 24 patients with RA and 18 patients with spondyloarthopathies (SpA) were cultured ex vivo for 12h in the presence or absence of IFNa/b blockade (anti-IFNAR) or etanercept. Expression of IFN-inducible genes was measured by qPCR. The Friedman test followed by post-hoc analysis with the Wilcoxon matched-pairs signed rank test was used for statistical analysis. (*=$p<0.05$, **=$p<0.01$, ***=$p<0.001$).

Results: Expression of IFN-inducible genes (*IFIT1*, *MX1, CXCL9, CXCL10* and *STAT1*) was increased on ex vivo culture of RA macrophages and was down-regulated by blockade of endogenous IFNa/b or TNFa (**Figure** and data not shown). Inclusion of SF in the cultures suppressed expression of these IFN response genes (not shown). RA SF inhibited also the induction of TNFa induced expression of *IFIT1* and *STAT1* by 91% and 82% respectively in blood-derived Mf from healthy donors (not shown, n=23, $p<0.0001$).



Conclusion: A STAT1/IFN-signature apparent in RA SF Mf increased on ex vivo culture and was dependent on autocrine TNFa, which activated type I IFN signaling. RA SFs suppressed the TNF-mediated IFN signature in RA synovial Mf, and also suppressed induction of IFN responses by exogenous TNFa in control Mf. Our findings implicate TNFa as a major inducer of the RA synovial IFN response and suggest that the expression of IFN response genes in RA synovium is regulated by interplay between TNFa and opposing homeostatic factors expressed in the synovial microenvironment.

2504

Plasmacytoid Dendritic Cells in Human Lupus Bone Marrow Are Primed for Interferon Alpha Production. Sarah Nevarez, Arumugam Palanichamy, Alfred Rabinovich, Jennifer Barnard, Jamie Biear, Ben Panepento, Chungwen Wei, Christopher Ritchlin, James Kobie, Iñaki Sanz and Jennifer H. Anolik. University of Rochester, Rochester, NY

Background/Purpose: Inappropriate activation of type I interferon (IFN) plays a key role in the pathogenesis of systemic lupus erythematosus (SLE). We have previously reported an IFN signature in SLE bone marrow (BM). However, the etiology and impact of IFN activation in the BM remains unclear. Here we examined the homeostatic balance between immune cells in the BM microenvironment and the differential capacity of plasmacytoid dendritic cells to produce IFN.

Methods: BM aspirates were obtained from SLE patients and age matched healthy controls (HC) (n=10). B cell, T cell and dendritic cell (DC) subsets from BM and paired peripheral blood (PBL) were analyzed by multiparameter flow cytometry for defined subset and effector molecules (B cell markers: CD19, CD27, IgD, MTG, CD24, CD38, IgM, CD10, CD23, 9G4, CXCR3, B220, CD95, CD21, CD24; T cell: CD3, CD4, CD45RA (memory), CCR7 (central memory), CXCR5 and ICOS (T follicular helper), CXCR3 (Th1), CCR4 (Th2), CD25 and FoxP3 (Treg), HLADR4; DC: CD11c, CD123, CCR7, CD40, CXCR3, HLADR, CCR5. PBMCs were stimulated with CpG 2216 or CpG 2006 for 2h at 37C, followed by protein transport inhibition (Brefeldin A) for 2h and staining for surface Lin1, CD304, CD123 and intracellular IFNa.

Results: CpG induced type I IFN production in pDCs in a dose dependent fashion. A higher proportion of BM pDCs produced IFNa compared to paired PB (%pDCs + for IFN: 5.2+1.5 vs. 0.9+0.5, 5ug/mL CpG 2006). Notably, significantly more pDCs from lupus BM produced IFNa compared to normal BM (71.9% vs. 5.2%). This was despite the fact that DC fractions in SLE BM and PB were lower than age matched controls (mDC in BM: 7.3+1.6 vs. 15.2+2.4%, p=0.03; pDC in BM: 0.50+0.11 vs. 0.95+0.28%, p=0.19). Phenotypic differences were observed in SLE pDCs with higher CXCR3 expression (p=0.05). The differences between T cell subsets in PB vs. BM in both SLE and HC were striking with significantly lower fractions of CD4+ T cells (e.g. 30.6+4.9 vs. 10.7+5.4% in SLE), Th1 cells (e.g 58.4+2.7 vs. 12.4+6.5% of memory T cells in HC), and Tregs (e.g. 2.0+0.4 vs. 0.6+0.2 in SLE) in BM (p=0.009–0.05) and altered Treg phenotype (high HLADR, CCR4 in BM). There were significantly lower CD4+ T cells and higher Tregs in SLE BM and PB. As expected BM samples had higher fractions of precursor B cell populations compared to paired PB (p=0.0001 for CD10+ B cells). BM naïve and transitional B cells had much lower expression of CD23 compared to PB in both SLE and HC (p=0.02–0.006). Notably, mature B cells in SLE BM were very abnormal compared to HC with an expansion of CD27-IgD- memory (p=0.008) and activated, effector memory B cell populations (e.g on the switched memory for SLE vs. HC CD95+% 42.2+18.3 vs. 20.7+6.2, p=0.05 and CD21-% 30.5+13.6 vs. 10.9+2.5, p=0.008).

Conclusion: These results suggest that the bone marrow is an important but previously unrecognized target organ in SLE. Circulating immune complexes and apoptotic fragments in SLE BM may serve as ligands for toll like receptors on pDCs, and along with disturbances in the T cell and DC compartment, contribute to aberrant IFN production. IFN production in the BM impacts B cell development and may contribute to an activated B cell compartment.

ACR Concurrent Abstract Session
Epidemiology and Health Services Research II: Osteoarthritis
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

2505

Racial/Ethnic Differences in Physical Activity Among Participants in the Osteoarthritis Initiative (OAI). Jing Song[1], Marc Hochberg[2], Rowland W. Chang[3], Larry Manheim[1], Jungwha Lee[3], Pamela A. Semanik[4], Leena Sharma[3] and Dorothy D. Dunlop[1]. [1]Northwestern Univ Med School, Chicago, IL, [2]University of Maryland School of Medicine, Baltimore, MD, [3]Northwestern University, Chicago, IL, [4]Rehabilitation Institute of Chicago, Chicago, IL

Background/Purpose: Physical activity offers important health benefits to adults, including those with lower limb osteoarthritis (OA). This study examined whether there are racial/ethnic differences in objectively measured physical activity among people with or at risk for OA of the knee.

Methods: Physical activity was measured using accelerometers at the 48-month clinic visit in 1897 OAI participants (1085 with radiographic knee osteoarthritis (RKOA) in at least one knee and 812 participants without RKOA in both knees at baseline). Time spent in moderate-to-vigorous (MV) intensity activities was calculated to assess if participants met U.S. Department of Health and Human Services (DHHS) physical activity guidelines for arthritis populations (≥150 MV minutes/week in bouts lasting 10 or more minutes). Racial/ethnic differences in meeting guidelines were examined by bivariate and multivariate logistic regression models adjusting for socio-demographic factors (age, gender, income, education) and health factors (comorbidity, depressive symptoms, overweight/obesity, presence and severity of knee pain).

Results: Only 11.0% of these participants met the recommended physical activity guideline: 8.4% and 14.3% of the RKOA and the non-RKOA groups respectively. Overall African Americans compared to Whites were substantially less likely to meet the physical activity guidelines after adjusting for socio-demographics (odds ratio [OR] = 0.21, confidence interval [CI] = [0.08, 0.58]). After adjusting for health factors and presence of RKOA, racial/ethnic differences were attenuated but remained significant (OR=0.33, CI = [0.12, 0.87]). These differences held separately within the RKOA and no RKOA groups. After adjusting for all risk factors, racial/ethnic differences remained significant in the RKOA group (OR=0.30, CI = [0.10, 0.88]) and were substantial but not significant in the no RKOA group (OR = 0.34, CI = [0.09, 1.36]). Differences in overweight/obesity and pain were independent, strong, and significant contributors to the observed racial/ethnic differences in the combined sample and subgroups.

DHHS physical activity guideline attainment by race/ethnicity: percentages of adults with and without baseline radiographic knee OA (RKOA) after adjustment for age, gender, education, income*

Race/Ethnicity	Sample Size	Meeting DHHS Physical Activity Guidelines/ Active (≥150 MV bout mins/week)
Overall (n=1897)		
	n	% [95% CI]
African American	290	5.3 [1.9, 13.7]
White	1607	16.7 [11.8, 21.3]
Participants with Baseline RKOA (n=1085)		
	n	% [95% CI]
African American	166	3.1 [1.0, 9.0]
White	919	16.0 [11.8, 21.3]
Participants without Baseline RKOA (n=812)		
African American	124	8.1 [1.8, 29.4]
White	688	26.0 [19.2, 34.3]

* 4+ valid days of accelerometer monitoring; reference group are men aged 49–64 with 13+ education years and >$50k income.

Conclusion: Despite benefits from physical activity, attainment of physical activity guidelines among persons with or at risk of radiographic knee OA was low, especially for African Americans. Specific intervention in the African Americans community targeting overweight/obesity and pain may reduce future racial/ethnic differences in physical activity guideline attainment.

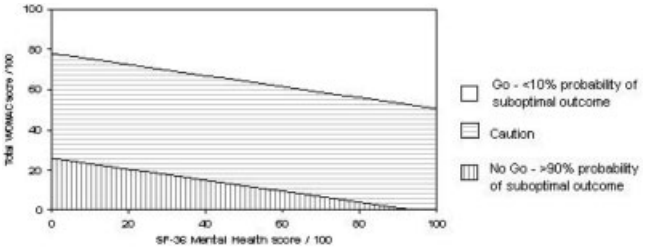
2506

Tool for Patient Selection to Optimize Patient-Reported Outcomes Following Total Joint Arthroplasty. Gillian A. Hawker[1], Ruth Croxford[2], A. M. Davis[3], Sheila Dunn[1], Joy G. Elkayam[1], Melissa R. French[1], M. A. Gignac[4], Susan B. Jaglal[5] and Joanna Sale[5]. [1]Women's College Hospital, Toronto, ON, [2]Institute for Clinical and Evaluative Science, Toronto, [3]Health Care and Outcomes Research, Toronto Western Research Institute; Departments of Rehabilitation Science and Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, [4]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [5]University of Toronto, Toronto, ON

Background/Purpose: When medical management of hip or knee arthritis fails, total joint arthroplasty (TJA) is recommended. On average, TJA outcomes are good to excellent, but significant variability has been observed. We previously identified predictors of suboptimal TJA outcome, defined as insufficient improvement in arthritis pain and disability. The aim of this study was to use these data to develop a tool for use at point of care to help select patients for TJA.

Methods: The initial model was based on analyses of data from a population cohort with hip/knee arthritis in which annual interviews, from 1996 to 2008, were linked with health administrative databases to examine receipt of primary, elective TJA. Suboptimal outcome was defined as a pre-post change in WOMAC summary score < Minimal Important Difference (MID) proposed Wyrich et al (MID = 0.5 SD change of the mean difference in scores). Pre- and post-surgery WOMAC scores were those obtained at the interview prior to the index TJA date, and closest in date to the end of the post-operative period (i.e. 6 months post surgery), respectively. Predictors of suboptimal outcome were modeled using logistic regression; Akaike's Information Criterion was used to determine the size of the best predictive model, and then all possible subset regression was used to identify the final model of the selected size. Using the final multivariable model predicting suboptimal outcome, graphs were created to depict likelihood of suboptimal outcome based on the four final predictor variables: WOMAC summary score (higher scores worse); SF-36 mental health score (higher scores better); OA versus inflammatory arthritis (IA); and presence of other troublesome hips/knees.

Results: Of 166 cohort members who received a primary, elective TJA following their baseline interview and completed a post-TJA assessment, 48.7% met criterion for sub-optimal outcome (reduction in WOMAC score of < 9/100 points). Four graphs were created: OA *with* and *without* other troublesome hips/knees (78.9% and 13.9%, respectively) and IA *with* and *without* other troublesome hips/knees (6.0% and 1.2%, respectively). Figure 1 shows the results for the largest group, those with OA and at least one other troublesome hip/knee. For individuals with IA, the "go" region was smaller and the "no go" region was larger, while the reverse was true for those with no other troublesome hips/knees ("go" region larger and "no go" region smaller). Results using alternative definitions for suboptimal outcome were similar.



Conclusion: Individuals with little pain and disability pre-surgery are likely to experience a suboptimal outcome; conversely, individuals with extreme pain and disability are likely to obtain a meaningful improvement in pain and/or function. Between the two extremes, patient mental health contributes to pain and disability in predicting the likelihood of a suboptimal outcome.

2507

The Association Between Lifelong Joint Force From Physical Activity, Local Joint Factors and Knee Osteoarthritis. Charles R. Ratzlaff[1], Mieke Koehoorn[1], Jolanda Cibere[2] and Jacek A. Kopec[3]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Ctr of CA, Vancouver, BC, [3]Arthritis Research Centre of Canada, Vancouver, BC

Background/Purpose: To examine the association between lifelong knee joint force, local joint factors and knee osteoarthritis (OA).

Methods: Design: Prevalence study, cross-sectional design; retrospective report of physical activity (PA)

Setting: Canada-wide population, Internet study

Source population: Canadian Association of Retired Persons

Outcome: Knee OA (self reported medically diagnosed PLUS pain, aching and stiffness most days)

Exposures

Lifetime Physical Activity: Data on sport, occupation and household activities from age 20–50 was self-reported via a validated online survey. For each specific activity type (e.g., each sport, occupation) detailed questions were asked regarding frequency, duration and intensity. Activities were further deconstructed by time spent in major body movement type (e.g., walk, run, squat).

Knee joint force from lifetime PA was estimated as the product of bodyweight (kg), typical knee force for specific activity type (% bodyweight) and time in specific activities (hours), and reported in kg-hours. Mean values for 5-year intervals over a person's lifetime, averaged over all subjects, were calculated. This variable was then categorized into quintiles based on the overall distribution in the sample.

Alignment. Self-reported standing presence of bow legs, knock-knees or neutral, using novel line diagrams.

Coordination. Coordination sub-scale of the Physical Self-Description Questionnaire (1), a self-administered validated, reliable instrument.

Joint hypermobility syndrome. The validated Hypermobility Questionnaire (2) was used to assess for the presence of joint hypermobility syndrome (JHS).

Other variables. Age, gender, BMI, previous knee joint injury

Analysis: Multiple logistic regression models were constructed separately for men and women to examine if levels of lifetime knee force were associated with a risk of knee OA, adjusting for age, injury, BMI, alignment, coordination and JHS.

Results: The 4,269 subjects had a mean age of 61.5 years, mean BMI of 27.5 and 63% were female. The highest quintile of mean lifetime knee force was a risk factor for development of knee OA in males (OR 2.03; 95% CI 1.08, 3.80) and females (1.67; 95% CI 1.11, 2.49). The highest levels of lifetime knee force from occupational activity in men and household activity in women were associated with a 2–3 fold increase in knee OA. In the final adjusted model, previous knee injury, obesity and malalignment (women) were also associated with prevalent knee OA. Higher coordination was protective. JHS was not a risk.

Conclusion: Lifelong knee force was generally safe for the knee, supporting the promotion of exercise as a major public health initiative. However, high levels of occupational force in men and household force in women were risk factors. This is the first report of a validated lifetime PA questionnaire that converted PA data to joint loading units, and used it to quantify the biomechanical effects and dose-response of PA on knee health, and the first report of an aspect of neuromuscular control (coordination) protecting against knee OA.

1. Marsh HW et al.J **Sport** Exerc Psychol. 1994;16:270–305.
2. Hakim AJ, Grahame R. Int J Clin Pract. 2003 Apr;57(3):163–6.

2508

Incidence of Knee Symptoms and Radiographic and Symptomatic Knee Osteoarthritis in African Americans and Caucasians: The Johnston County Osteoarthritis Project. Barbara T. Do[1], Louise Murphy[1], Charles G. Helmick[1], Yiling J. Cheng[1], Kamil E. Barbour[1] and Joanne M. Jordan[2]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]UNC Thurston Arthritis Center, Chapel Hill, NC

Background/Purpose: Estimate the population-based incidence of 5 knee osteoarthritis (kOA)-related outcomes.

Methods: We analyzed baseline (1991–1997) and first follow up (1999–2005) data from Johnston County Osteoarthritis Project participants (n=1,590; aged > 45 years). The 5 outcomes were: 1) knee symptoms (pain, aching, and/or stiffness on most days); 2 & 3) radiographic and severe radiographic kOA (Kellgren-Lawrence [K-L] radiographic grades >2 and >3, respectively); 4) symptomatic kOA (K-L grade >2 and knee symptoms in radiographically affected knee); and 5) severe symptomatic kOA (K-L grade >2 and severe knee pain in radiographically affected knee). For each outcome, overall and stratified (age; sex; race; highest education attainment; body mass index [BMI] at age 18 and at baseline; and history of knee injury in affected knee) incidence rates were estimated among those who did not have the outcome at baseline.

Results: Overall incidence rates (people per 100 person-years) were 7.1 for knee symptoms, 3.1 for radiographic kOA, 2.6 for symptomatic kOA, 1.8 for severe radiographic kOA, and 0.5 for severe symptomatic kOA. In the stratified analyses, incidence of almost all outcomes rose with increasing age, clinically measured baseline BMI, self-reported BMI at age 18, and decreasing levels of education. The most consistent differences in absolute and relative incidence across all outcomes were for lowest and highest baseline BMI category (e.g., for symptomatic kOA, 1.6 among those with BMI < 25 (under/normal weight) and 4.5 among BMI ≥ 35 (obese class II). Last, for all outcomes, incidence was generally a quarter to a third higher among African Americans than Caucasians.

Conclusion: In this sample of ≥45 year olds, 0.5 to 7% developed at least one of the kOA-related outcomes each year. Age, BMI at both 18 and at baseline were the strongest predictors of symptomatic, severe symptomatic, and severe radiographic kOA incidence. More widespread intervention efforts (self-management education, physical activity, weight management, joint injury prevention) may reduce the onset and impact of these outcomes.

2509

Sick Leave and Disability Pension Among Patients with Knee Osteoarthritis. Jenny Hubertsson[1], Ingemar F. Petersson[1], Carina A. Thorstensson[2] and Martin Englund[3]. [1]Musculoskeletal Sciences, Dept of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [2]Spenshult Hospital for, Oskarstrom, Sweden, [3]Lund University, Lund, Sweden

Background/Purpose: To investigate the burden of sick leave and disability pension in patients with knee osteoarthritis (OA) and to compare these figures with the general population using prospectively ascertained cohort data.

Methods: Using the Skåne Health Care Register we identified all subjects seeking health care in primary, secondary, or in hospital care, registered with the diagnosis of OA of the knee (ICD-10 code M17) at least once during the period of 1998–2009, aged 16–64 years and resident in the Skåne County (population 1.2 million) during 2009. Using subjects' unique personal identification number, we then linked year 2009 social insurance data administered by the Swedish Social Insurance Agency. First, we calculated the share of knee OA patients who during 2009 had received either sickness benefit or disability pension payment and estimated the increase in risk compared to the general population in Skåne County aged 16 to 64 years (n=789 366) standardised for age. We also calculated the mean number of days with sickness benefit or disability pension. Second we estimated the proportion of the total number of sick leave and disability pension days attributable to knee OA or associated comorbidities in knee OA patients. To do this we calculated the total amount of days generated by knee OA patients and subtracted the total amount of days expected for this group (assuming the same rate as in the general population standardized for age and sex). We then divided the remaining share with the total amount of days for the county to calculate the proportion of days specific to knee OA patients.

Results: We identified 15 345 persons (49.6% women) who had been diagnosed with knee OA during the last 12 years and were at working age and resident in Skåne during 2009. They had a mean (SD) age of 55 (8.2) years for women and 53 (9.2) years for men. Compared to the general population the risk for having had one or more episodes of sick leave was 1.82 (95% CI 1.73–1.91) for women and 2.03 (95% CI 1.92–2.14) for men and the risk for disability pension was 1.54 (95% CI 1.48–1.60) for women and 1.36 (95% CI 1.28–1.43) for men. During 2009, the mean (SD) numbers of sick days (including days of sick leave and of disability pension) per knee OA patient and year was 114 (155) days for women and 63 (124) days for men. Of all sick leave and disability pension in the entire population, 2.0% of days were estimated to be attributable to knee OA or its associated comorbidity (3.1% for sick leave and 1.7% for disability pension).

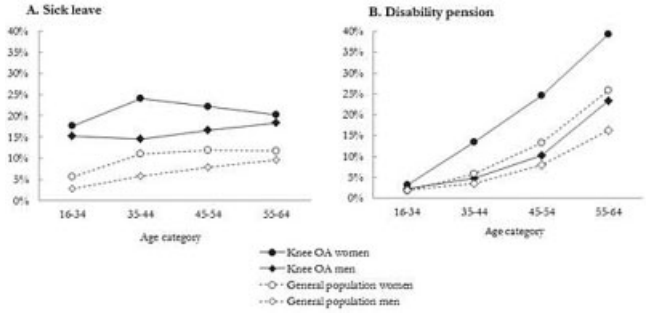


Figure 1. Proportion who had received sick leave or disability pension sometime during 2009.

Conclusion: Patients with knee OA have an almost two-fold increased risk for sick leave and about 40–50% increased risk for disability pension compared to the general population. Further, in the Swedish population about 2% of the total amount of sick days in the society is attributable to knee OA or associated comorbidity in knee OA patients.

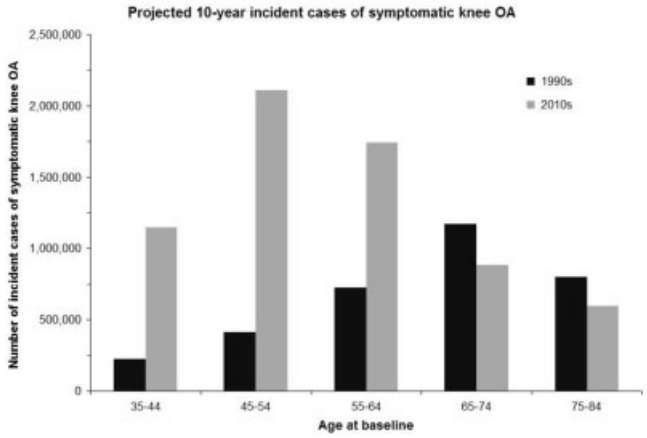
2510

Projecting the Future Public Health Impact of the Trend Toward Earlier Onset of Knee Osteoarthritis in the Past 20 Years. Sara A. Burbine, Alexander M. Weinstein, William M. Reichmann, Benjamin N. Rome, Jamie E. Collins, Jeffrey N. Katz and Elena Losina. Brigham and Women's Hospital, Boston, MA

Background/Purpose: Symptomatic knee osteoarthritis (OA) affects about 7% of Americans over the age of 45. Obesity and knee injuries have become more prevalent in recent years, which may contribute to increasing incidence of symptomatic knee OA, particularly in younger age groups. Temporal trends in the age of symptomatic knee OA onset and the resulting public health impact have yet to be studied.

Methods: We used the OAPol Model, a validated computer simulation model of the natural history of knee OA, to estimate the age-stratified 10-year incidence of symptomatic physician-diagnosed knee OA during two distinct time periods (the 1990s vs. the 2010s). Symptomatic knee OA incidence data for the 1990s were derived from published literature. Data for the 2010s were derived from the National Health Interview Survey 2007–08. We followed a simulated cohort from age 25 to death to track the onset of symptomatic knee OA. We coupled model output and CDC population estimates from each time period to project the number of incident cases of knee OA in the US population over each 10-year period. We compared ages of OA onset and 10-year cumulative incidence of knee OA for the two time periods.

Results: The mean age of physician-diagnosed knee OA onset fell from 72 ± 12 years (mean ± standard deviation) in the 1990s to 56 ± 18 years in the 2010s. Americans ages 35–84 in the early 2010s were expected to incur 6,475,642 incident cases of symptomatic knee OA over the next decade, with those ages 45–64 accounting for 59% of these cases (Figure). Among Americans who were ages 45–54 at the beginning of the 1990s, an estimated 412,214 incident cases of knee OA were expected over the subsequent 10 years, resulting in a 10-year cumulative incidence of 1.5%. Among people in the same baseline age group in the 2010s, 2,108,881 incident cases of symptomatic knee OA are expected over the next 10 years, a cumulative incidence of 4.8%. The projected number of 10-year incident cases among those ages 65–74 at baseline decreased slightly between the 1990s (1,169,615 cases) and the 2010s (882,997 cases).



Conclusion: Since the early 1990s, the age of onset of physician-diagnosed symptomatic knee OA has shifted dramatically, occurring on average 16 years earlier in life. This trend may reflect temporal changes in the prevalence of OA risk factors, as well as thresholds for patient care-seeking and physician diagnosis of OA. If the current OA incidence trend continues, nearly 6.5 million Americans between the ages of 35 and 84 will be diagnosed with symptomatic knee OA in the next 10 years, with those ages 45–64 accounting for more than half of these incident cases. A resulting spike in the utilization of healthcare, specifically total knee replacements, could have a dramatic economic impact and place additional burden on the healthcare system.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Clinical Aspects: Predictors of Outcome
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

2511

Clinical Disease Activity and Acute Phase Reactant (APR) Levels Are Discordant Among Patients with Active Rheumatoid Arthritis (RA) and Contribute Separately to Predicting Outcome At 1 Year. Jonathan Kay[1], Susan P. Messing[2], Joel M. Kremer[3], Jeffrey D. Greenberg[4] and Daniel E. Furst[5]. [1]University of Massachusetts Medical School, Worcester, MA, [2]University of Rochester School of Medicine and Dentistry, Rochester, NY, [3]Albany Medical College and The Center for Rheumatology, Albany, NY, [4]New York University School of Medicine, New York, NY, [5]UCLA Medical School, Los Angeles, CA

Background/Purpose: Clinical trials of new treatments for RA typically require subjects to have an elevated APR, in addition to swollen and tender joints. However, many pts in clinical practice fail to meet these entry criteria. Despite having elevated individual components of the CDAI, such as tender and swollen joint counts and pt and MD global assessment, some pts with active RA may have normal ESR and/or CRP levels. Thus, clinical disease activity and APR levels can be discordant.

To address the **hypothesis** that clinical measures and APR each contribute separately to predicting the outcome of RA pts at 1 year, we assessed the relationship between CDAI and APR elevation in a large US registry of RA pts by comparing baseline characteristics and 1 year clinical outcomes of pts with active RA, grouped by baseline APR levels.

Methods: Using CORRONA data through 1/8/10, eligible pts had CDAI >2.8 (not in remission) and values for ESR and CRP. APR levels were considered elevated if ESR >28 mm/hr or CRP >1.5 mg/dL. Baseline was entry into the database, not necessarily a new drug start. The 1 year follow-up visit (365 ± 60 days) used was that with complete data available for mHAQ and components of CDAI. Comparisons were assessed subsequent to linear modeling using generalized estimating equations.

Results: Among 27,526 RA pts in the CORRONA database, 7804 with active RA (CDAI >2.8) met criteria for sample inclusion. Of these, 53% had neither elevated ESR nor CRP. Among the remaining pts, 16% had elevated ESR but not CRP, 15% had elevated CRP but not ESR, and 16% had elevated ESR and CRP levels. 1304 patients were evaluated at 1 year.

At baseline, pts with active RA but no elevation of either APR had significantly lower mHAQ and CDAI than pts in any other group ($p<0.006$). Also, pts with both APR elevated had higher mHAQ and CDAI than the other three groups ($p<0.003$). The groups with elevation of only one APR (ESR or CRP) were similar to each other, had higher mHAQ and CDAI then than those with no elevation of either APR ($p<0.006$) and had lower mHAQ and CDAI than those with both APRs elevated ($p<0.003$). Individual components of the CDAI followed the same trends (see Table).

Baseline characteristic	CDAI >2.8, ESR ≤28, CRP ≤1.5 (Group 1) (n=757)	CDAI >2.8, ESR >28, CRP ≤1.5 (Group 2) (n=195)	CDAI >2.8, ESR ≤28, CRP >1.5 (Group 3) (n=171)	CDAI >2.8, ESR >28, CRP >1.5 (Group 4) (n=181)
Age	59.28 ± 13.05	65.62 ± 12.83	59.35 ± 14.02	62.19 ± 13.80
Duration of RA (years)	11.49 ± 10.31	12.63 ± 9.70	12.59 ± 10.39	14.03 ± 11.85
1-year follow-up duration (days)	361.20 ± 32.19	358.44 ± 31.23	359.04 ± 32.66	361.13 ± 31.86
mHAQ	0.34 ± 0.39*	0.48 ± 0.49	0.45 ± 0.46	0.64 ± 0.58**
CDAI	13.40 ± 10.03*	16.77 ± 10.81	16.19 ± 12.54	20.84 ± 13.94**
Tender joints	3.69 ± 5.04*	5.07 ± 5.14	5.04 ± 6.40	6.33 ± 7.04†
Swollen joints	4.54 ± 5.12	5.29 ± 5.27	5.05 ± 5.54	6.73 ± 5.84†
Pt global assessment	34.15 ± 24.56*	38.32 ± 24.92	34.81 ± 25.01	44.85 ± 28.46†
MD global assessment	19.77 ± 15.83*	25.78 ± 18.08	26.26 ± 21.10	32.94 ± 21.17**

Values are mean ± SD. *$p<0.006$ for Group 1 vs. Groups 2, 3, & 4. ** $p<0.006$ or †$p<0.05$ for Group 4 vs. Groups 1, 2, & 3. Differences between Groups 2 & 3, other than age, were not statistically significant.

At the 1 year follow-up visit, mean mHAQ decreased by 0.10 ± 0.45 among the pts with elevation of both APR but increased by 0.05 ± 0.34, 0.06 ± 0.35, and 0.02 ± 0.32 in Groups 1, 2, & 3, respectively ($p<0.004$). The decrease in mean CDAI also was greatest among the pts with active RA and both APR elevated (−6.24 ± 15.04) and was significantly larger than in each of the other groups ($p<0.002$).

Conclusion: In a large US registry, over half of active RA pts do not have elevated ESR or CRP levels and APR levels are discordant in 31%. The magnitude of both clinical and functional improvement at 1 year correlates with the number of APR elevated at baseline.

2512

Discordance Between Patients and Physicians in Assessments of Global Disease Activity in Rheumatoid Arthritis: Agreeing to Disagree. Thomas V. Jones[1], Wenzhi Li[1], Andrew S. Koenig[1] and Michelle Stewart[2]. [1]Pfizer Inc., Collegeville, PA, [2]Pfizer Inc., Groton, CT

Background/Purpose: Physicians and patients often disagree when assessing disease severity.[1–4] Disagreements may indicate a focus on different aspects of the disease or differing perceptions of improvement. Understanding differing objectives for treatment may guide efforts to improve patient care. The purpose of this analysis is to examine differences between physicians' and patients' assessments of disease activity in RA and possible explanations for these differences.

Methods: Patients with moderate RA despite stable doses of oral MTX received open-label etanercept 50 mg weekly plus MTX for 36 weeks. Patients and physicians completed the global assessment of disease activity measure, a 0–10 fixed integer response visual analogue scale (VAS) rating patients' arthritis activity over the proceeding 2–3 days, with higher scores indicating more severe activity. The difference between each pair of patients' and physicians' scores were categorized as follows: positive discordance (patient global–physician global ≥2), negative discordance (physician global – patient global ≥2) or concordance (absolute difference between the 2 disease activity scores <2). The correlations (Pearson's r) with demographic characteristics and clinical variables were explored (concordance was combined with negative discordance for analysis). Stepwise logistic regression was used to determine significant predictors of discordance.

Results: Of the 834 RA patients (female 83%, Caucasian 74%, mean age 48y; disease duration 7y, mean baseline DAS28=4.4) the majority were concordant with physicians (72.7%) followed by positive discordance (24.7%) and negative discordance (2.6%) at week 36. Baseline morning stiffness, and week 36 HAQ, DAS28, morning stiffness, pain (BPI), and fatigue (FACIT-F), and change from baseline in CRP, ESR, HAQ, DAS28, BPI, and FACIT-F were significantly associated with discordance. At week 36, mean DAS28 for the positive discordant group was 2.8 (SD 1.1) compared to 3.1 (SD 1.3) for the negative discordant group and 2.2 (SD 0.9) for the concordant group (Table). Discordance was associated with patients' pain (OR 1.3, CI 1.14–1.56) and general health VAS (OR 1.1, CI 1.06–1.10). Among the 443 patients who achieved 0–1 SJC, 0–1 TJC, and CRP≤1 at week 36, positive discordance was still evident (20.8%) whereas negative discordance was lower (1.8%).

Table. Comparisons among concordant and discordant pairs based on patients' and physicians' global assessment of disease activity.

Variable	Concordant N=556	Positive Discordance N=189	Negative Discordance N=20	ANOVA F Statistic
Change in CRP	7.0 (17.0)	−3.4 (14.7)	0.9 (11.0)	0.006
Change in ESR	−11.1 (12.6)	−7.6 (11.2)	−3.6 (11.9)	0.0002
HAQ	0.5 (0.5)	0.9 (0.6)	0.7 (0.6)	<.0001
Change in HAQ	−0.7 (0.54)	−0.3 (0.6)	−0.5 (0.5)	<.0001
DAS28	2.2 (0.9)	2.8 (1.1)	3.1 (1.3)	<.0001
Change in DAS28	−2.2 (0.9)	−1.6 (1.0)	−1.4 (1.3)	<.0001
Patient General Health Assessment VAS	1.47 (1.16)	4.48 (1.79)	1.6 (1.27)	<.0001
Morning stiffness; min (SD)	38.6 (165.6)	77.9 (163.9)	62.7 (135.9)	0.0195
Morning stiffness, baseline; min (SD)	158.5 (313.5)	226.6 (383.6)	230.1 (445.2)	0.0485
BPI	1.07 (1.31)	3.21 (2.19)	1.89 (1.52)	<.0001
Change in BPI	−2.64 (2.05)	−1.46 (2.38)	−2.04 (2.4)	<.0001
FACIT-F	43.14 (7.99)	35.65 (9.47)	38.85 (9.38)	<.0001
Change in FACIT-F	9.42 (8.79)	4.9 (9.43)	9 (10.89)	<.0001

All values are mean values (SD) at week 36 unless otherwise indicated. "Change in" denotes change from baseline at week 36.

Conclusion: Over one quarter (27.3%) of patients were discordant with physicians (positively or negatively) regarding the rating of their disease activity. In most cases, discordance occurred due to higher severity ratings by patients (positive discordance). Substantial discordance remained when patients had minimal swollen and tender joint counts and a low CRP value. Further investigation may facilitate better alignment between outcome measures and treatment targets and aid efforts to improve disease management.

2513

Development of a Matrix Risk Model to Predict Rapid Radiographic Progression in Early Rheumatoid Arthritis. Results From a Randomized Trial Population. Saedis Saevarsdottir[1], Kristina Forslind[2], Kristina Albertsson[1], Hamed Rezaei[1], Arvid Engström[1], Pierre Geborek[3], Ingemar F. Petersson[3], Sofia Ernestam[4], Johan Bratt[4] and Ronald F. van Vollenhoven[1]. [1]The Karolinska Institute, Stockholm, Sweden, [2]Helsingborgs Lasarett and Lund University, Lund, Sweden, [3]Lund University, Lund, Sweden, [4]Karolinska University Hospital, Stockholm, Sweden

Background/Purpose: Some patients with early rheumatoid arthritis (RA) show rapid radiographic progression (RRP). It has been suggested that a combination of baseline predictors could be used as a "matrix" to help clinicians identify subpopulations with increased risk of RRP[1–3], in order to choose initial therapy in a rational manner. The objective of this study was to validate previously published matrix models and develop an optimized matrix model for prediction of rapid radiographic progression (RRP) in patients with early RA.

Methods: Data from the SWEFOT-trial population were used[4]. In this trial, all patients were started on MTX 20 mg/week. Patients who achieved low disease activity after 3–4 months continued on MTX, while the other patients were randomized to add either sulfasalazine and hydroxychloroquine or infliximab. Hand and foot X-rays were obtained at baseline and after 1 and 2 years, and scored by the Sharp-van der Heijde (SvdH) method. RRP was defined as an increase in total SvdH of ≥5 after 1 year[1–3]. Potential baseline predictors of RRP were selected from multivariate analyses and previous studies, and combined in 3-parameter matrices, considering clinical feasibility and ease of use.

Results: Data where analyzed for 273 patients and this subgroup was representative of the study population. Of these, 65 patients had RRP. A matrix risk model including the following: C-reactive protein (CRP<10 vs. 10–35 vs. >35 mg/L), baseline erosions (yes/no) and current cigarette smoking (yes/no) differentiated best between RA patients with and without an increased risk of RRP. A step-up gradient was observed, where 63% of patients carrying all 3 predictors had RRP after 1 year vs. 12% with none (figure). The risk ratio for highest vs. lowest risk was 5.88 (95% CI 2.36–14.62). The previously published matrices[1–3] did not differentiate well between patients with and without RRP in this patient population.

Conclusion: This matrix, based on a trial that reflects standard care, identifies subpopulations of RA patients at high risk for RRP and, being based on easily accessible and objective variables, could be useful to clinicians for making appropriate treatment decisions. Validation of the matrix model in other populations is needed.

[1]Vastesaeger N, et al. Rheumatology, 2009;48:1114–1121.
[2]Visser K, et al. Ann Rheum Dis, 2010;69:1333–1337.
[3]Durnez A, et al. Ann Rheum Dis, 2010 Dec 21 (epub ahead of print).
[4]Van Vollenhoven R F. et al. Lancet, 2009;374:459–466.

2514

Derivation and Validation of An Infection Risk Score to Predict the Risk of Serious Infections for Rheumatoid Arthritis Patients. Jeffrey R. Curtis[1], Fenglong Xie[2], Paul M. Muntner[2], Lang Chen[2], Shuo Yang, Kenneth G. Saag[1] and Elizabeth S. Delzell[2]. [1]Univ of Alabama-Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL

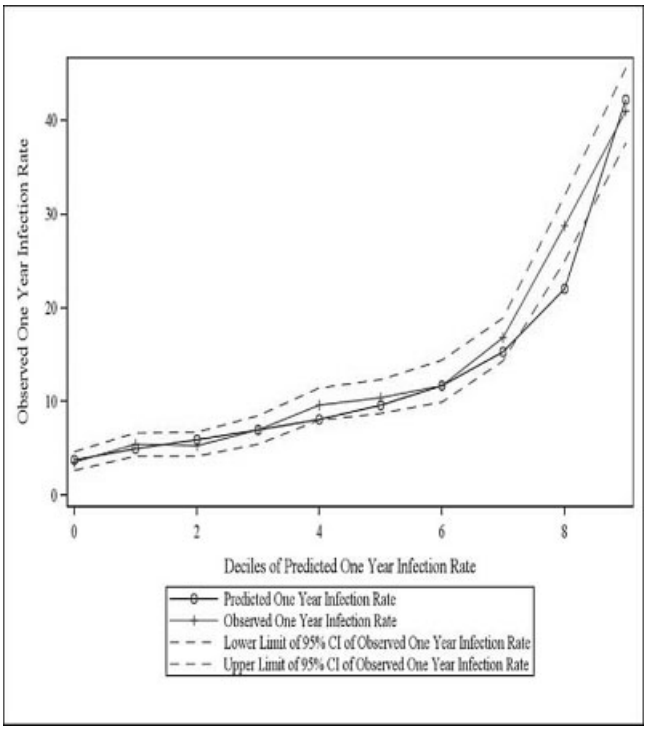
Background/Purpose: Infections remain important in characterizing the safety profile of therapies for rheumatoid arthritis (RA) therapies. There are currently no tools to predict the risk of infection for individual RA patients. Our objective was to derive and validate an infection risk score to predict the 1 year risk for serious infections among RA patients starting new biologics.

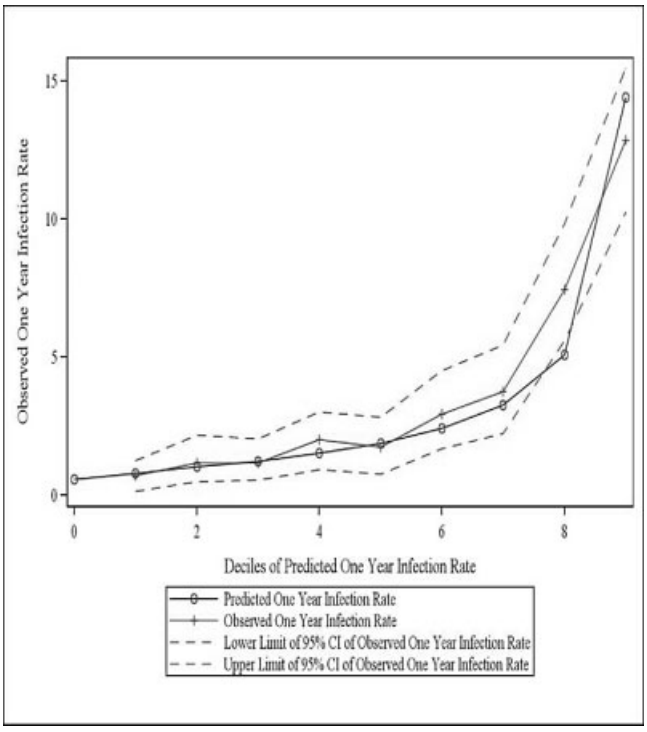
Methods: Using 2 administrative databases that included RA patients with commercial insurance or Medicare/Medicaid, we derived a dataset-specific infection score. The commercially insured database included individuals age < 65, and Medicare enrollees age >= 65. Observation time began when patients initiated methotrexate, leflunomide, or sulfasalazine/ hydroxychloroquine added to MTX. The outcome of the infection score was hospitalized infection in the subsequent one year, estimated using Cox models. We included in the score factors related to infection based upon content knowledge, prior literature, and strength of the association with the infection outcome.

Calibration and discrimination were assessed by plotting observed versus predicted risk in deciles. Validation was conducted by comparing predicted versus observed risk in 200 bootstrap samples, also used for 95% confidence intervals for observed risk. Dataset-specific weights for infection risk factors were computed and compared descriptively.

Results: Among 23594 (14702 Medicare/Medicaid, 8892 commercially-insured) new users of MTX, LEF, or SSZ/HCQ, we identified 1765 hospitalized

infections in the subsequent year. The infection score identified 25 and 13 factors significantly associated with serious infections in Medicare and commercially-insured RA patients; 10 of these factors were in-common. Weights for most risk factors in the two datasets differed modestly. Discrimination of the infection score was good (not shown); there was high agreement between predicted and observed infection risk (figure 1-Medicare, figure 2-commercially insured).





Conclusion: The one-year risk for serious infections can be accurately predicted at a patient level. This novel infection score can be used to control for infection-related confounding in future safety analyses where outcome data are sparse. It may also inform patient-physician communication, assist in risk stratification, and guide use of therapeutics for arthritis.

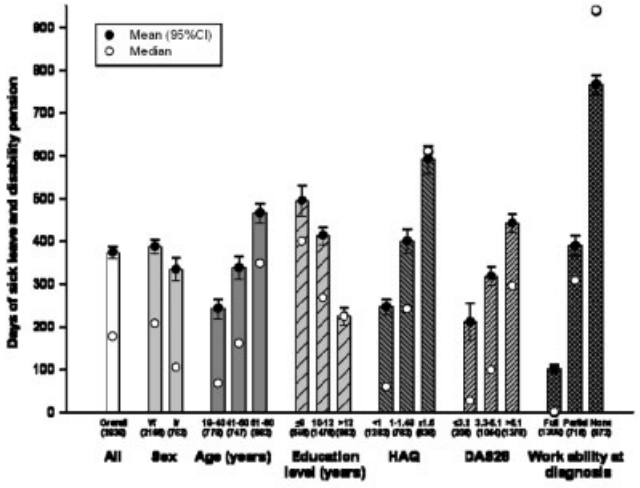
2515

Predictors of Work Disability During the First 3 Years After Diagnosis in a National Rheumatoid Arthritis Inception Cohort. Tor Olofsson[1], Ingemar F. Petersson[2], Jonas Eriksson[3], Martin Englund[4], Julia F. Simard[3], Pierre Geborek[1], Lennart TH Jacobsson[5], Johan Askling[3] and Martin Neovius[3]. [1]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund University, Lund, Sweden, [2]Musculoskeletal Sciences, Dept of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [3]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Stockholm, Sweden, [4]Lund University, Lund, Sweden, [5]Section of Rheumatology, Malmo, Sweden

Background/Purpose: To estimate predictors of sick leave and disability pension during the 3y period after diagnosis with early RA 1999–2007 in Sweden.

Methods: Individuals aged 19–59y diagnosed with early RA were identified in the Swedish Rheumatology Quality Register (1999–2007; n=3029; mean age 47y; 73% women). Baseline predictors of cumulative days of sick leave and disability pension during the 3y period after RA diagnosis were calculated using linear regression, retrieving days of sick leave and disability pension from the National Social Insurance Agency register covering all inhabitants in Sweden. Due to effect modification by baseline work ability, multivariable analyses were stratified into 3 categories: full=0 days of sick leave and disability pension the month before diagnosis; partial=1–29 days and none=30 days.

Results: In unadjusted analysis, there were large differences between categories of each predictor regarding cumulative days of sick leave and disability pension during the 3 years following RA diagnosis (Figure). In adjusted multivariable analysis, baseline levels of HAQ, DAS28, VAS global, VAS pain and tender joint count as well as age, education level and unemployment status were significant predictors of cumulative days during the 3y period, when stratifying for baseline work ability. Generally, the largest regression coefficients were seen for the subgroup with partial work ability at baseline and the smallest for the group with full work ability. A one-unit higher HAQ score was associated with 49 additional days off work ($p<0.001$) if having full work ability at baseline, 134 days ($p<0.001$) if having partial work ability and 112 days ($p<0.001$) if having no work ability. The corresponding coefficients for a one-unit higher DAS28 at baseline were 18 ($p<0.001$), 47 ($p<0.001$) and 30 days ($p=0.006$). A 10-year higher age at diagnosis was associated with 20 additional days off work ($p<0.001$) if having full work ability at baseline, 83 days ($p<0.001$) if having partial work ability and 77 days ($p<0.001$) if having no work ability. For education level (comparing ≤9 to >12 years) the corresponding coefficients were 79 ($p<0.001$), 159 ($p<0.001$) and 86 days ($p=0.03$).



Cumulative days of sick leave and disability pension during the first 3 years after RA diagnosis given as mean and as median and stratified for selected baseline variables (unadjusted).

Conclusion: The baseline level of work ability was strongly associated with total days of sick leave and disability pension during the 3y period after RA diagnosis. Taking this into account, modifiable disease variables such as HAQ and DAS28, as well as age and education level, were also significant predictors. The results indicate that interventions have the largest effect in the patient group with partial work ability at diagnosis.

2516

Do Rheumatoid Arthritis Patients Meeting American College of Rheumatology/European League Against Rheumatism Remission Have Improved Functional Ability, Quality of Life and Work Productivity Compared to Those with Low Disease Activity? Aarat M. Patel[1], Christine L. Amity[2], Lynne M. Frydrych[2], Derek Sippel[2], Donald Jones[2], Danielle Goudeau[2], Heather Eng[3], David Kyle[3], Melissa Saul[3], Daniel Hal Solomon[4], Stephen R. Wisniewski[3], Larry W. Moreland[5] and Marc C. Levesque[2]. [1]Univ of Pittsburgh Med Ctr / Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]Univ of Pittsburgh, Pittsburgh, PA, [4]Brigham & Womens Hospital, Boston, MA, [5]University of Pittsburgh, Pittsburgh, PA

Background/Purpose: RA patients meeting the new ACR/EULAR definition of remission should have better clinical outcomes than those with low disease activity. Therefore, we compared functional ability, HRQOL, work impairment and medication use between those meeting new ACR/EULAR remission and those in low disease activity or other defined states of remission.

Methods: Subjects were from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry (n=721). We analyzed self-administered patient questionnaires (routine assessment of patient index-3 (RAPID3), short form-12 (SF12), work productivity and activity impairment (WPAI)), physician exam data (DAS28 and CDAI) from a single RACER visit. Subjects were grouped according to whether they met ACR/EULAR remission, DAS28 and CDAI remission, low, moderate and high disease activity. Demographics, questionnaire data and medication use were compared between those who did not fulfill the new remission criteria but did fulfill other remission and low disease activity states using Mann Whitney-U and Pearson Chi-Square tests.

Results: ACR/EULAR remission was achieved by 17.6% of the cohort. Age, sex, race and disease duration were similar between disease activity groups. The mean SF-12 physical and mental component scores (PCS / MCS) for subjects in ACR/EULAR remission were similar to healthy, comparably aged subjects. Subjects in CDAI remission (n=109) also met ACR/EULAR remission and had comparable SF-12, WPAI and RAPID3 scores (data not shown). In contrast, not all subjects in DAS28 remission (n=274) also met the ACR/EULAR definition of remission (n=127). Subjects in DAS28 remission but not ACR/EULAR remission (n=147) and subjects in DAS28 and CDAI low disease activity had worse SF12, WPAI and RAPID3 scores (**Table 1**). The use of DMARDs and/or biologics was similar between the remission and low disease activity groups. However, the ACR/EULAR and CDAI remission groups used significantly less narcotics and corticosteroids than subjects in DAS remission and all other disease activity groups ($p<0.0001$).

Table 1. Comparison of different remission and low disease activity definitions to the ACR/EULAR definition of remission and their effect on work productivity and health assessment (n = 721)

	ACR/EULAR Remission (n = 127)	DAS28 Remission (n = 147)	*P*	DAS28 Low Disease Activity (n = 125)	*P*	CDAI Low Disease Activity (n = 246)	*P*
SF12 PCS	45.8 ± 9.4	38.4 ± 9.1	<0.0001	34.4 ± 8.9	<0.0001	36.76 ± 9.3	<0.0001
MCS	52.4 ± 8.1	48.8 ± 10.0	0.005	47.0 ± 9.4	<0.0001	48.0 ± 9.9	<0.0001
WPAI (%) Activity Imp.	13.7 ± 20.7	29.4 ± 26.3	<0.0001	42.6 ± 24.2	<0.0001	35.1 ± 26.6	<0.0001
Time mixed	0.6 ± 3.2	9.6 ± 23.7	0.01	2.7 ± 11.4	0.143	5.9 ± 17.8	0.011
Imp. Working	9.4 ± 18.5	20.0 ± 21.9	<0.0001	29.3 ± 25.2	<0.0001	24.5 ± 22.8	<0.0001
Overall Imp.	10.1 ± 18.7	25.8 ± 29.4	<0.0001	31.5 ± 26.6	<0.0001	28.0 ± 26.8	<0.0001
RAPID5	1.0 ± 1.0	1.9 ± 1.7	<0.0001	3.4 ± 1.8	<0.0001	3.0 ± 1.8	<0.0001

* Remission definitions were individually applied to all subjects and those fulfilling ACR/EULAR remission are removed from other categories so some subjects are not represented in multiple groups. **Those in CDAI remission fulfilled ACR/EULAR remission so comparisons were not made.
RACER = Rheumatoid Arthritis Comparative Effectiveness Research ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; DAS28 = disease activity score 28-joint count; CDAI = clinical disease activity index; SF12 = short form-12; PCS = physical component score; MCS = mental component score; WPAI = Work Productivity and Activity Impairment; RAPID3 = Routine Assessment of Patient Index Data-3

Conclusion: RA subjects in ACR/EULAR remission had a quality of life similar to healthy comparably aged subjects suggesting that the new ACR/EULAR remission criteria represent a true state of remission. The DAS28 definition of remission is not comparable since RA subjects in ACR/EULAR remission had better RAPID3, SF12 and WPAI scores. ACR/EULAR remission was associated with improved functional ability, HRQOL and work productivity compared to DAS28 and CDAI low disease activity. Medication data suggests that for subjects not in remission, achieving remission will require more optimal and/or greater use of combinations of immunosuppressive therapies. Our future goal is to determine the cost-effectiveness and the risk:benefit of more aggressive treatment approaches for patients not yet in remission and to study remission longitudinally.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Human Etiology and Pathogenesis II: Pathogenesis of Rheumatoid Arthritis—What's New?
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

2517

Unique DNA Methylome Signature in Rheumatoid Arthritis (RA). Kazuhisa Nakano[1], John Whitaker[2], Wei Wang[3], David L. Boyle[2] and Gary S. Firestein[2]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]UCSD School of Medicine, La Jolla, CA, [3]UCSD, La Jolla, CA

Background/Purpose: Genome wide association studies have identified novel DNA polymorphisms associated with increased risk and severity of RA. However, even genetically identical twins have only a 12–15% concordance rate of RA. Epigenetics defines non-DNA encoding influences that could contribute to disease susceptibility and severity. DNA methylation of CpG motifs is one mechanism that can silence or activate genes. While the methylation of individual genes has been explored in RA, no systematic analyses have been performed. Therefore, we performed an unbiased genome-wide evaluation of DNA methylation loci in fibroblast-like synoviocytes (FLS) isolated from the site of disease in RA.

Methods: Genomic DNA was isolated from fifth passage 6 female RA and 5 female control (osteoarthritis) FLS lines and evaluated using the Illumina HumanMethylation450 chip. Cluster analysis of data was performed and corrected using Benjamini-Hochberg adjustment for multiple comparisons ($p<0.05$ considered significant). Pathway analysis was determined using the Kyoto Encyclopedia of Genes and Genomes (KEGG).

Results: 476,311 CpG loci out of 485,512 were technically adequate for analysis after excluding loci with high background or absent signal. Cluster analysis surprisingly showed that FLS completely segregated into RA and control based solely on DNA methylation patterns, with nearly 2000 loci from 1200 genes being differentially methylated in RA. Permutation analysis confirmed the specificity and statistical significance of clustering. Hypomethylated loci were identified in key genes and promoter regions relevant to RA, such as *CHI3L1* (gp39), *CASP1* (caspase 1), *STAT3, MAP3K5,* and *MEFV* (pyrin), and *WISP3*. Hypermethylation was observed in several loci related to RA, including *TGFBR2* and *FOXO1*. Hypomethylation was associated with increased gene expression with some genes, such as the joint specific antigen *CHI3L1*. In addition, grouped analysis of differentially methylated loci showed that over 200 genes have multiple CpGs that are significantly hyper or hypomethylated. For example, *COL1A1* (type I collagen) has 41 loci, of which 4 are signficantly hypomethylated in RA FLS with an enrichment of 79-fold compared to OA FLS ($P<10^{-6}$). Enrichment for MEFV (pyrin) hypomethylation is nearly 200-fold ($P<10^{-6}$). Of interest, 4 of 16 loci in the TNF promoter are hypermethylated in RA (relative enrichment=451; $P<10^{-9}$), suggesting that epigenetic control of TNF is aberrant in RA. Pathway analysis showed that hypomethylation was significantly increased in multiple pathways, including focal adhesion, cell adhesion, leukocyte transendothelial migration, adipokine signaling and extracellular matrix interactions.

Conclusion: The first genome wide unbiased evaluation of DNA methylation shows that RA FLS bear a striking pattern of DNA methylation distinct from control FLS that involves key genes involved in immune response, cell trafficking and inflammation. DNA methylation of critical genes and regulatory pathways in primary synoviocytes is a novel method to determine non-DNA encoding contributions to RA and identify new therapeutic targets.

2518

A Distinctive Oral Microbiome Characterizes Periodontitis in Patients with Early Rheumatoid Arthritis. Jose U. Scher*[1], Carles Ubeda*[2], Walter Bretz[3], Michael H. Pillinger[1], Yvonne Buischi[3], Pamela B. Rosenthal[4], Soumya M. Reddy[1], Jonathan Samuels[1], Peter M. Izmirly[4], Gary E. Solomon[1], Mukundan Attur[1], Michele Equinda[2], Nicholas Socci[2], Agnes Viale[2], Gerald Weissmann[4], Dan R. Littman[4], Eric G. Pamer[2] and Steven B. Abramson[1]. [1]NYU Hospital for Joint Diseases, New York, NY, [2]Memorial Sloan-Kettering Cancer Center, The Lucille Castori Center for Microbes, Inflammation and Cancer, New York, NY, [3]NYU College of Dentistry, New York, NY, [4]NYU School of Medicine, New York, NY

Background/Purpose: To profile the subgingival oral microbiota abundance and diversity in patients with new-onset, never-treated rheumatoid arthritis (NORA), in comparison with chronic-established RA (CERA), and healthy individuals.

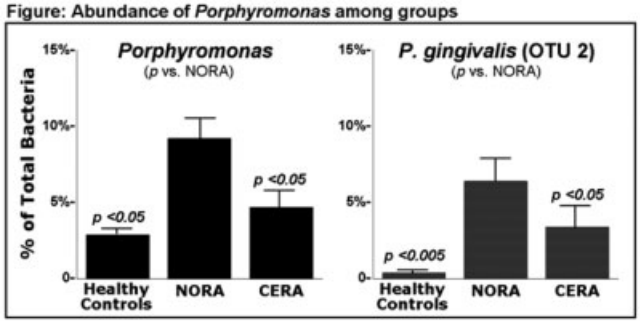
Methods: Periodontal status, clinical activity and sociodemographic factors were determined in patients with NORA (n=25), CERA (n=27), and healthy subjects (n=14). All RA patients enrolled in the study were ACPA positive. Dental examinations and biofilm acquisitions were performed by three calibrated and qualified periodontists in the NYU Rheumatoid Arthritis Periodontal Disease (RAPD) clinic. Massively parallel-454 pyrosequencing technologies were used to compare the composition of microbial communities in subgingival biofilms and establish correlations between presence/abundance of bacteria and disease phenotypes.

Results: The severe forms of periodontal disease were found in 75% percent of NORA patients, higher than that observed in CERA (57%), and healthy controls (8%) (p <0.01, all RA vs healthy controls; see Table). The oral microbiome of RA patients was equally dense and diverse compared to controls. However, the microbiome of patients with NORA was distinct, characterized by several bacterial families and genera that are more prevalent and abundant than observed in CERA), or healthy controls. Specifically, red-complex bacteria, the most virulent periodontopathic organisms, are overabundant in NORA, and decrease in better-controlled, treated RA (CERA). A single species-level operational taxonomic unit (OTU) belonging to the genus *Porphyromonas* and homologous to *P. gingivalis* is significantly more prevalent and abundant in NORA patients than in CERA or healthy subjects (p<0.05) (Figure).

Table. Prevalence and severity of periodontal disease in healthy individuals and patients with NORA or CERA

		Severity of Periodontal Disease			
Group	**Healthy Gums**	**Gingivitis**	**Slight**	**Moderate**	**Severe**
Healthy controls (n=14)	**62%**	15%	0	15%	8%
NORA (n=25)	0	4%	4%	17%	**75%**
CERA (n=27)	0	10%	10%	23%	**57%**
***p* value (ANOVA)**	$p<0.01$	NS	NS	NS	***p* <0.001**

Figure: Abundance of *Porphyromonas* among groups



Conclusion: Moderate to severe periodontal disease is present in over 90% of patients with new onset RA. Our data indicate that the oral microbiome of these drug-naïve, ACPA + NORA patients is distinct at disease onset, characterized by the overabundance of a single and virulent *Porphyromonas* species. These studies suggest that the further identification and characterization of a particular *Porphyromonas* species may explain the reported link between RA and periodontal disease.

2519

MiR-196a Is An Important Regulator of Synovial Fibroblasts In the Pathogenesis of Rheumatoid Arthritis. Maria Filkova[1], Michelle Trenkmann[1], Joanna Stanczyk[1], Mojca Frank[1], Christoph Kolling[2], Lars C. Huber[3], Beat A. Michel[1], Renate E. Gay[1], Ladislav Senolt[4], Steffen Gay[1] and Astrid Jüngel[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland, [3]Clinic and Policlinic for Internal Medicine, University Hospital Zurich, Switzerland, Zurich, Switzerland, [4]Institute of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Background/Purpose: Based on the comprehensive analysis of the expression of 260 miRs in RA synovial fibroblasts (SF) versus osteoarthritis (OA) SF, we found miR-196a to be one of the most downregulated miRs in RA. The dysregulation of miR-196a has been observed in disease conditions such as cancer showing oncogenic or tumor suppressive roles in a cell- or tissue specific fashion.

Objectives: To analyze the expression, regulation and the functional role of the miR-196a in RA as well as to investigate its contribution to the aggressive behavior of RASF.

Methods: TaqMan Low Density Array was performed to analyze the expression of 260 miRs in primary cell cultures of RASF and OASF (n=3 each). Expression of miR-196a was analyzed in additional RASF (n=10), OASF (n=9), RA (n=6) and OA (n=4) synovial tissues by TaqMan RealTime-PCR by single assays. Chromatin immunoprecipitation (ChIP) was used to analyze histone methylation (H3K4me3, H3K27me3) and acetylation (H3-Ac) within both promoters MIR-196A1 and MIR-196A2 in RASF (n=13) and OASF (n=11). Measurement of potential target genes by TaqMan RealTime-PCR and functional experiments (MTT, scratch assay, AnnexinV FACS) were performed following Lipofectamine transfection with pre-miR-196a (25nM) or miR-196a inhibitor (100nM) after 48h.

Results: Expression of miR-196a is significantly lower in RASF (dCt 6.94±1.78) than in OASF (dCt 3.89±0.21, p<0.0001) as well as in RA synovial tissues (dCt 8.42±0.9) compared with OA (dCt 5.14±0.71, p=0.01). Expression of miR-196a was not affected by proinflammatory cytokines (TNFα or IL-1β), TLR ligands (LPS), 1% hypoxia or 5'AZA mediated DNA demethylation. ChIP of MIR-196A2 promoter revealed significantly higher methylation of repressive H3K27me3 in RASF than in OASF (ratio to H3: 0.99±0.39 vs. 0.03±0.00, p=0.005), lower methylation of activating H3K4me3 (ratio to H3: 0.10±0.03 vs. 0.47±0.14, p=0.002) and hypoacetylation of H3 (ratio to H3: 0.18±0.06 vs. 0.63±0.15, p=0.008) in RASF compared to OASF. Expression of miR-196a (dCt) correlated significantly with these histone modifications (H3K27me3: r=0.93, p<0.0001, H3K4me3: r=−0.68, p=0.01, H3-Ac: r=−0.72, p=0.006). Predicted miR-196a targets HOXC8, HOXA9, RASSF3, HMGA2 and ANXA1 were down/upregulated after transfection with pre-miR/miR inhibitor (n=4). Pre-miR-196a reduced cell proliferation by 27.5% and migration by 41.5%, while miR-196a inhibitor enhanced both proliferation by 81.9% and migration by 231% (n=4). Apoptosis of RASF was induced by pre-miR-196a by 54.1% while it was reduced by miR-196a inhibitor by 52.3% (n=3).

Conclusion: The data demonstrate that low expression of miR-196a in both RA synovial tissue and in isolated synovial fibroblasts contributes to the aggressive and invasive phenotype of RASF. Moreover, functional assays confirmed that miR-196a contributes to the characteristic behavior of these cells by regulating proliferation, migration and apoptosis. Therefore, miR-196a epigenetically regulated by histone methylation and acetylation appears to function as an important contributor to the pathogenesis of RA.

Acknowledgement: This work was supported by IAR-EPALINGES, FP7 Masterswitch, and ARTICULUM fellowship.

2520

Epigenome Analysis Reveals TBX-5 As a Novel Transcription Factor Involved in the Activation of Rheumatoid Arthritis Synovial Fibroblasts. Emmanuel Karouzakis[1], Michelle Trenkmann[1], Caroline Ospelt[1], Christoph Kolling[2], Renate E. Gay[1], Beat A. Michel[1], Steffen Gay[1] and Michel Neidhart[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Schultess Clinic, Zurich, Switzerland

Background/Purpose: Changes in DNA methylation and histone marks have been associated with diseases such as cancer, rheumatoid arthritis (RA) and systemic lupus erythematosus. Previously, we reported global genomic hypomethylation in RA synovial fibroblasts (RASF). Now, we searched for specific genes that are differentially methylated in RASF in comparison to osteoarthritis synovial fibroblasts (OASF).

Methods: Genomic DNA from OASF and RASF was isolated; 40 μg genomic DNA was used to perform seven methylation immunoprecipitation (MeDIP) reactions per patient; 1 μg of total input and methylated immunoprecipitated DNA was labelled with Cy3 /Cy5 dyes and hybridizised to a human promoter array (NimbleGen, Roche). Differentially methylated genes were confirmed with individual MeDIP reactions, combined bisulphite restriction digestion (COBRA) and bisulphite sequencing. The expression of related transcripts was determined by quantitative SYBR PCR and protein analysis was performed by Western blot and immunohistochemistry. Changes in histone marks, namely H3 K4 trimethylation and H3 K27 trimethylation were analysed by chromatin immunoprecipitation (ChIP).

Results: The promoter array analysis revealed 30 gene promoters which were hypomethylated in RASF. The TBX5 gene was significantly more methylated in the promoter and transcriptional initiation site of OASF than RASF, as shown by MeDIP assay (Promoter: OASF 16±4.5 and RASF 0.60±0.15 fold enrichment, p<0.03, n=4; transcriptional initiation site: OASF 17±2.9 and RASF 5±3.5 fold enrichment, p<0.04, n=6). The MeDiP results were confirmed by individual COBRA assays and bisulphite sequencing of the TBX5 promoter. TBX5 transcripts were significantly more expressed in RASF than OASF (RASF dCt: 16.0 ± 0.6; OASF dCt: 19±0.3, p<0.005, n=8). Overall, we found a 13-fold increase of TBX5 mRNA in

RASF compared to OASF. In addition, Western blot showed that the TBX5 protein was expressed in RASF, but not in OASF. Immunohistochemistry of synovial tissues confirmed that TXB5 is expressed in RA (n=6), but not in OA (n=6). The expression of TBX5 was nuclear and mostly localised in the synovial lining of RA tissues. Furthermore, in the TBX5 locus, ChIP revealed that RASF had more H3 K4 trimethylation– associated with an open chromatin -, than OASF (RASF H3 K4 trimethylation: 0.67±0.06 ratio to histone 3; OASF H3 K4 trimethylation: 0.02±0.005 ratio to histone 3, $p<0.01$ n = 4–5). On the other hand, OASF were found to have enrichment for H3 K27 trimethylation – associated with a closed chromatin -, when compared to RASF (OASF 0.25±0.09; RASF 0.02±0.001, $p<0.01$ n = 4–5). Previously, it was shown that TBX5 regulates genes such as cadherins, CDKN2A and gelsolin in the area of heart development and cancer.

Conclusion: Promoter specific DNA hypomethylation and an open chromatin are responsible for the intrinsically up-regulated TBX5 expression in RASF. TBX5 may be a novel regulator of cell junctions (cadherins), proliferation (CDKN2A) and extracellular matrix (gelsolin) and thereby associated with the chronically activated phenotype of RASF.

2521

9G4 Expression on Antibodies to Citrullinated Residues in Patients with Early Inflammatory Arthritis and Established Rheumatoid Arthritis. Rita A. Moura[1], Inmaculada de la Torre[2], Maria J. Leandro[3], Jonathan CW Edwards[3] and Geraldine Cambridge[4]. [1]Rheumatology Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal, Lisbon, Portugal, [2]Gregorio Marañón Hospital, Madrid, Spain, [3]UCL, London, United Kingdom, [4]University College London, London, United Kingdom

Background/Purpose: The rat monoclonal antibody 9G4 recognises immunoglobulin products of the human V4–34 germ-line heavy chain gene. Antibodies encoded by V4–34 are inherently autoreactive against red blood cells. 9G4+ autoantibodies to other targets (eg DNA) have also been described in autoimmune disease. In normal controls (NC), up to 10% of newly generated naïve B cells are 9G4+ but expression on circulating immunoglobulins is low. This is because although 9G4+B cells are present in lymphoid organs from NC they are excluded from germinal center (GC) reactions. Tonsils from patients with lupus, but not from patients with RA, however contain class switched 9G4+ memory B cells, suggesting a defect in pre-GC censoring in lupus, but not Rheumatoid arthritis (RA) patients. Preliminary studies in our laboratory showed increased numbers of circulating 9G4+ plasmablasts in patients with active RA. the aim of this study therefore was to determine whether these plasmablasts could be associated with any autoantibodiy species.

Methods: Patient groups were 27 patients with established RA and 46 with polyarthritis of less than 6 weeks duration of whom 23/46 were subsequently diagnosed with RA (ERA Group), and 23/46 with other arthridites (Early Non-RA group; ENRA). Serum was collected on first clinic visit. Total IgG and IgM anti-CCP2 antibodies and 9G4 expression on anti-CCP antibodies were measured by ELISA (Eurodiagnostica). Positive values in 9G4 analyses were defined as > than 3 SD above mean of 9G4 depleted serum controls. 9G4 was also measured on anti-tetanus toxoid (TT) and Pneumococcocal capsular polysaccharide (PCP) antibodies by ELISA (Binding Site, UK).

Results: 23/27 RA patients were positive for anti-CCP; 18 had both IgM and IgG CCP. 1 patient had only IgM- and 3, IgG-CCP only. Eight of the 27 patients (30%) with established RA had detectable 9G4+ anti-CCP and all were positive for both IgM and IgG anti-CCP. Levels of 9G4 expression correlated more closely with titer of IgM rather than IgG-CCP (Spearman; r2=0.65 cf 0.27). In the ERA group, 15/23 had anti-CCP, 10 had both IgM and IgG anti-CCP, 4 patients had only IgM and 1 only IgG anti-CCP. 4/23 patients (17%) with early RA had 9G4+anti-CCP. All 4 patients had both IgM and IgG anti-CCP. In ENRA patients, only 1 patient with polyarticular gout had 9G4+ anti-CCP antibodies, albeit at low titer and had only IgM anti-CCP. There was no expression of 9G4 on anti-TT or PCP antibodies.

Conclusion: This is the first description of the use of the V4–34 heavy chain gene by autoantibodies to citrullinated peptides. 9G4 expression was largely confined to CCP antibodies from patients with RA. Further, it was present on anti-CCP early after disease onset, and only very weakly expressed on 1 sample from a non-RA patient. Usage of V4–34 by anti-CCP antibodies also increased with increasing titer, particularly in IgM-CCP. It may therefore be possible that expansion of CCP-specific B cell clones may not be due to a breakdown in GC censoring but to a robust expansion of un-switched B cell clones, possibly including or analogous to those in the splenic marginal zone.

2522

Heightened Immune Response to Autocitrullinated *Porphyromonas Gingivalis* Peptidylarginine Deiminase Is a Potential Mechanism for Breaching Immunologic Tolerance in Rheumatoid Arthritis. Anne-Marie Quirke[1], Natalia Wegner[1], Bart Hamilton[2], Peter J. Charles[3], Muslima Chowdhury[1], Elena B. Lugli[1], Jan Potempa[4], Geoffrey M. Thiele[5], Ted R. Mikuls[6] and Patrick Venables[7]. [1]Imperial College London, London, United Kingdom, [2]University of Nebraska Medical Centre and Omaha VA Medical Center, Omaha, [3]Charing Cross Hospital, London, United Kingdom, [4]Jagiellonian University, Krakow, Poland, [5]Univ of Nebraska Med Ctr, Omaha, NE, [6]Omaha VA and University of Nebraska, Omaha, NE, [7]Kennedy Institute, London, United Kingdom

Background/Purpose: *Porphyromonas gingivalis*, a major periodontal pathogen, has been implicated in the pathogenesis of rheumatoid arthritis (RA). It is the only known prokaryote to possess a bacterial peptidylarginine deiminase (PPAD), which in combination with *P.gingivalis* specific proteases, the arginine gingipains (Rgp), citrullinates peptides from both α-enolase and fibrinogen. Because both PPAD and Rgp are of potential importance in disease pathogenesis, we have examined the immune response to both bacterial enzymes in a cohort of patients with RA compared to normal controls, in addition to individuals with periodontitis as a positive control for active *P. gingivalis* infection.

Methods: We cloned GST-His tagged PPAD in a pET-49b(+) vector and expressed it in the protease-deficient BL21 strain of *Escherichia coli*. The enzyme activity was measured using a colorimetric PAD activity assay that detects formation of the ureido group of citrulline, using BAEE as synthetic substrate. Gingipain (RgpB-His) was cloned and expressed using previously published methods. ELISAs using PPAD and Rgp were developed and tested in serum from normal controls (n=80), PD (n=44) and RA (n=82). Reactivity of each serum was calculated as units per ml (AU/ml) using a standard curve on each ELISA plate. The Mann-Whitney U test was used to calculate p-values for mean differences between the sera groups for each peptide. To control for the specificity of the ELISA, 12 RA sera, 10 normal controls and 10 PD sera were examined by both immunoblotting and ELISA.

Results: Recombinant PPAD migrated as a full-length polypeptide with a molecular weight of approximately 68KD. It was a potent citrullinating enzyme using both the BAEE assay and when incubated with fibrinogen peptides as substrates. Immunoblotting with the anti-modified citrulline kit demonstrated that it was autocitrullinated. IgG anti-PPAD antibodies were significantly higher in the RA sera (mean 182.4 AU/ml), than what was found in both the PD sera (mean 96.4AU/ml; $p<0.01$) and the healthy control sera (mean 99.2AU/ml $p<0.05$). The anti-Rgp response was significantly higher in the PD sera (mean 533.8AU/ml) than what was found in both the RA sera (mean 257.6AU/ml, $p<0.001$) and the healthy control sera (mean 299.3AU/ml, $p<0.01$). The specificity of the anti-PPAD and anti-Rgp ELISAs was demonstrated by comparison of 10 healthy controls, 10 PD sera and 12 RA sera with immunoblotting. The results of immunoblotting correlated with those from ELISA both for PPAD ($p<0.05$) and for Rgp ($p<0.001$). In the healthy control sera, 6 patients reacted with PPAD and 4 also with Rgp, indicating that infection with *P. gingivalis* defined by immunoblotting is ubiquitous in the healthy population (~60%).

Conclusion: The anti-PPAD response was significantly elevated in RA patients compared to PD patients and controls, while the anti-Rgp response was higher in PD patients and in normal controls compared to those with RA. The anti-PPAD antibodies in RA could be part of a cross-reactive ACPA response, but more importantly, it could also indicate that PPAD itself could be a mechanism for breaching immunological tolerance to citrullinated antigens.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Further Insights Into Efficacy and Safety of Tumour Necrosis Factor Inhibitors
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

2523

RA, Anti-TNF Therapy, and Risk of Malignant Melanoma-a Nationwide Population-Based Study From Sweden. Pauline Raaschou[1], Julia F. Simard[2], Martin Neovius[2], Marie Holmqvist[2], Jonas Eriksson[2], Johan Askling[2] and the ARTIS studygroup[3]. [1]Clinical Pharmacology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet

Background/Purpose: States of immune suppression, such as post-transplant therapy, have recently emerged as a possible risk factor not only for

non-melanoma skin cancer but also for malignant melanoma (Vajdic CM et al, JAMA 2006). An increased risk of melanoma associated with anti-TNF therapy has been reported (Wolfe F et al, Arthritis Rheum. 2007; Askling J. EULAR Conference Abstract 2009). We aimed to investigate the risk of malignant melanoma in patients with RA compared to the general population, and to investigate whether anti-TNF treatment influences melanoma risk in RA.

Methods: A nationwide and population-based cohort of patients with RA were identified using data from the Swedish outpatient register from 2001 through 2009 (n=56,336). Patients starting anti-TNF therapy were identified through linkage to the Swedish Biologics Register ARTIS and to the national Prescribed Drug Register (n=8,453) To each RA patient, 5 general population comparators were matched for sex, year of birth and county of residence. Occurrence of first-ever invasive malignant melanoma, as well as occurrence of first-ever cancer, irrespective of type (all-site), was assessed through linkage to the national Swedish Cancer Register. Relative risks (RRs) for malignant melanoma and all-site cancer were calculated using Cox regression with age as time-scale and anti-TNF therapy treated as a time-dependent variable, adjusted for selected co-morbidities. RRs were assessed overall and by time since start of anti-TNF therapy.

Results: Based on 135 incident melanomas during 253,572 person-years of follow-up among biologics-naïve patients with RA vs. 718 melanomas during 1,460,120 person-years of follow-up in the general population comparator, the RR for malignant melanoma in biologics-naïve patients with RA was 1.1 (95% CI 0.9–1.3). Based on 32 incident malignant melanomas during 44,858 person-years of follow-up from start of anti-TNF therapy, compared to biologics-naïve RA patients, the RR was 1.8 (95% CI 1.2–2.7). Based on 418 incident all site cancers during 42,418 person-years of follow-up among the anti-TNF exposed, the RR was 1.0 (0.9–1.1) compared to biologics-naïve RA patients (Table). Sensitivity analyses also including in situ melanomas resulted in a relative risk of 1.5 (95% CI 1.1–2.1).

Table. Relative risks adjusted for age, sex and co-morbidities (95% confidence intervals) and number of cases among patients treated with anti-TNF, comparing Swedish patients with RA treated with anti-TNF (n=8,453) to biologics-naïve patients with RA (n=47,883).

	Anti-TNF-exposed vs. Biologics-naïve RA	Time since first anti-TNF treatment start		
	Overall	< 1 year	1–2 years	≥2 years
Melanoma				
Relative risk (95%CI), Cases	1.8 (1.2–2.7), 32	1.5 (0.6–4.1), 4	2.9 (1.4–5.9), 8	1.7 (1.0–2.7), 20
All-Site Cancer				
Relative risk (95%CI), Cases	1.0 (0.9–1.1), 418	1.0 (0.8–1.3), 74	0.9 (0.7–1.2), 63	1.1 (1.0–1.3), 281

Conclusion: In the absence of anti-TNF therapies, RA patients are not at elevated risk of malignant melanoma. Patients selected for and treated with anti-TNF have a higher risk of malignant melanoma than biologics-naïve RA patients.

2524

Opportunistic Infections in Patients Exposed to Anti-Tumour Necrosis Factor Therapy: Results From the British Society for Rheumatology Biologics Register. James B. Galloway[1], Audrey SL Low[1], Louise K. Mercer[1], William G. Dixon[1], Andrew Ustianowski[2], Mark Lunt[1], Kath D. Watson[1], British Society for Rheumatology Biologics Register (BSRBR) control centre consortium[3], Kimme L. Hyrich[1], Deborah PM Symmons[1] and. on behalf of the BSRBR[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]British Society for Rheumatology, London, United Kingdom

Background/Purpose: Anti TNF therapy is associated with an increase in the risk of infections. There are biological reasons to expect that certain infections might be disproportionately increased, especially those where the cellular immune system is crucial to defence. The British Society for Rheumatology Biologics Register (BSRBR) is an ideal setting to establish the risk and pattern of these opportunistic infections (OI).

Methods: The BSRBR was established in 2001 to evaluate the safety of anti-TNF therapies etanercept (ETN), infliximab (INF) and adalimumab (ADA) in people with RA. The anti-TNF treated cohort was recruited alongside a comparator group with active disease (DAS28 >4.2) treated with non-biologic disease modifying anti-rheumatic drugs (nbDMARD). Patients were recruited between 01/10/2001 and 30/06/2008 and followed up prospectively by consultant and patient questionnaires until first OI, 06/31/2010 or death, whichever came first. Tuberculosis was excluded from this analysis as we have reported on this previously. The BSBBR drew up a list of OI at its outset. Rates were compared using Cox proportional hazards. A propensity model was used to adjust for confounders.

Results: 11,864 anti-TNF and 3,666 nbDMARD patients were included (Table). The reported opportunistic infections are shown in the table. The absolute rates of infections were low in both cohorts (anti-TNF 0.8/1000 person years follow up (pyrs); DMARD 0.3/1000 pyrs). The fully adjusted hazard ratio for OI in the anti-TNF cohort was increased at 1.5 (0.3, 7.8). The highest frequency of OI was observed in the INF cohort (incidence: ETN 0.5/1000, INF 1.6/1000, ADA 0.7/1000). The hazard ratio for OI in the INF cohort was significantly higher when compared to either ETN or ADA.

Table. Baseline characteristics and incidence of infections.

	DMARD	All anti-TNF	ETN	INF	ADA
Subjects, n	3,666	11,864	4,136	3,472	4,256
Mean age, years (SD)	60 (12)	56 (12)	56 (12)	56 (12)	57 (12)
Female gender, (%)	2648 (72)	9038 (76)	3190 (77)	2624 (76)	3224 (76)
Disease Duration: years, median (IQR)	6 (1–15)	11 (6–19)	12 (6–19)	12 (6–19)	10 (5–18)
Baseline steroid use: n (%)	834 (23)	5243 (44)	1977 (48)	1609 (46)	1657 (39)
DAS28, mean (SD)	5.1 (1.3)	6.6 (1.0)	6.6 (1.0)	6.6 (1.0)	6.5 (1.0)
Exposure (pyrs)	12,592	45700	23026	13476	17211
All opportunistic infections: n	4	37	9	18	10
Incidence rate/1000 pyrs (95% confidence interval)	0.32 (0.08, 0.81)	0.81 (0.57, 1.12)	0.45 (0.21, 0.86)	1.59 (0.94, 2.51)	0.69 (0.33, 1.27)
Hazard ratio: (95%CI)	Ref	2.77 (0.99, 7.79)	1.68 (0.51, 5.46)	5.14 (1.74, 15.22)	2.23 (0.70, 7.10)
Age & gender adjusted hazard ratio: (95% CI)	Ref	3.30 (1.16, 9.36)	2.03 (0.62, 6.68)	6.02 (2.02, 17.96)	2.61 (0.81, 8.40)
Fully adjusted hazard ratio: (95% CI)*	Ref	1.51 (0.30, 7.75)	0.72 (0.12, 4.40)	3.27 (0.64, 16.60)	1.22 (0.23, 6.37)
			Ref	4.51 (1.86, 10.94)	1.68 (0.65, 4.32)
			0.60 (0.23, 1.53)	2.69 (1.11, 6.54)	Ref
Invasive fungal infection: n	1	3	0	3	0
Legionellosis: n	0	6	0	2	4
Listeriosis: n	1	8	2	4	2
Multidermatomal shingles: n	0	8	3	3	2
Pneumocystis pneumonia: n	1	6	1	3	2
Invasive salmonellosis: n	1	6	3	3	0

*Adjusted for baseline confounders: age, gender, disability, disease activity score, disease duration, steroid use, smoking, chronic lung disease, diabetes and year of entry into the study.

Conclusion: The absolute rate of OI was non-significantly higher in anti-TNF exposed patients. The INF cohort accounted for 44% these cases. Although we have attempted to address the issue of confounding by indication with our propensity model, unmeasured confounding may still exist. While there are limitations to the methodology, this pattern of risk has also been reported by other registries. The replication of this finding in the UK cohort adds weight to the evidence that INF may carry a greater risk of opportunistic infection than other ETN or ADA. It is important to acknowledge that the absolute risk of opportunistic infection was very low.

2525

The Risk of Solid Cancer in Patients Receiving Anti-Tumour Necrosis Factor Therapy for Rheumatoid Arthritis for up to 5 Years: Results From the British Society for Rheumatology Biologics Register. Louise K. Mercer[1], James B. Galloway[1], Audrey SL Low[1], Kath D. Watson[1], Mark Lunt[1], William G. Dixon[1], British Society for Rheumatology Biologics Register (BSRBR) control centre consortium[1], Deborah PM Symmons[1], Kimme L. Hyrich[1] and On behalf of the BSRBR[2]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]British Society for Rheumatology, London, United Kingdom

Background/Purpose: The use of TNF inhibitors in the management of rheumatoid arthritis (RA) has been coupled with concerns about tumorigenesis. Meta-analysis of patient-level data from randomised controlled trials (RCT) has not found an increased risk of solid cancer. The short duration and strict exclusion criteria of RCTs means latent events such as cancer may be missed. The aim of this study was to determine whether anti-TNF influences the risk of cancer when used in routine UK clinical practice.

Methods: The analysis was conducted in the British Society for Rheumatology Biologics Register (BSRBR), a national cohort study. Patients with RA starting treatment with the TNF inhibitors etanercept (ETA), infliximab (INF) or adalimumab (ADA) and a biologic-naïve comparison cohort exposed to non-biologic therapy (DMARD) were recruited between 2001–2009. The first six months of follow up for each subject was excluded from the analysis. Subjects were followed for 5 years, until 31/12/2009 or death, whichever came first. Subjects with a history of solid cancer prior to registration identified by record linkage with the UK cancer registry (NHS-IC) were excluded. Incident cancers were identified in 3 ways; lifelong flagging with NHS-IC; 6 monthly patient and physician questionnaires for 3 years and annual physician questionnaires thereafter. Only the

first solid cancer per subject (excluding non-melanoma skin cancer), confirmed by histology or NHS-IC, was analysed. Cancers occurring after stopping anti-TNF were attributed to the most recent anti-TNF. The rates of solid cancer in the anti-TNF and DMARD cohorts were compared using multivariate Cox proportional hazards models adjusted using inverse probability of treatment weighting (IPTW) for age, gender, comorbidity, disease duration, use of NSAIDs, smoking and registration year. Site specific analyses were performed for sites with ≥10 cancers in each cohort: colorectal, lung/bronchus and female breast.

Results: 386 solid cancers were confirmed: 91 in 3543 DMARD patients and 295 in 11719 anti-TNF patients (84 v 63 per 10000 patient-years (pyrs)) (Table). After adjusting for IPTW there was no difference in risk of solid cancer between the 2 cohorts (hazard ratio (HR) for anti-TNF 0.88 (0.65, 1.17)). The IPTW adjusted HR for ETA was 0.94 (0.68, 1.29), INF 0.87 (0.61, 1.25) and ADA 0.81 (0.57, 1.14). There was no significant difference in risk of colorectal, lung/bronchus or female breast cancer for anti-TNF compared to DMARD. The risk did not vary with duration of follow up.

Table.

	DMARD N=3543	Anti-TNF N=11719	Etanercept N=4072	Infliximab N=3429	Adalimumab N=4218
Follow-up (pyrs)	10828	46361	19672	11572	15116
Age: Mean (SD)	60 (12)	56 (12)	56 (12)	56 (12)	56 (12)
Gender: N(%) female	2552 (72)	8915 (76)	3135 (77)	2586 (75)	3194 (76)
Solid cancer: N	91	295	134	71	90
Solid: Rate per 10000 pyrs	84 (68, 103)	63 (57, 71)	68 (57, 81)	61 (48, 77)	60 (48, 73)
Solid: Unadjusted HR	Referent	0.73 (0.58, 0.93)	0.77 (0.59, 1.01)	0.72 (0.53, 0.98)	0.69 (0.51, 0.92)
Solid: Age and gender adjusted HR	Referent	0.94 (0.74, 1.20)	1.03 (0.78, 1.35)	0.91 (0.66, 1.24)	0.87 (0.65, 1.17)
Solid: IPTW adjusted HR	Referent	0.88 (0.65, 1.17)	0.94 (0.68, 1.29)	0.87 (0.61, 1.25)	0.81 (0.57, 1.14)
Colorectal: N	10	21			
Colorectal: Rate per 10000 pyrs	9 (4, 17)	5 (3, 7)			
Colorectal: IPTW adjusted HR	Referent	1.21 (0.54, 2.70)			
Lung: N	22	72			
Lung: Rate per 10000 pyrs	20 (13, 31)	16 (12, 20)			
Lung: IPTW adjusted HR	Referent	0.89 (0.46, 1.74)			
Female breast: N	14	58			
Female breast: Rate per 10000 pyrs	7 (3, 11)	6 (4, 7)			
Female breast: IPTW adjusted HR	Referent	0.99 (0.51, 1.92)			

Conclusion: In patients without prior solid cancer no increase in solid cancer risk was seen in this UK national cohort of RA patients treated with TNF inhibitors when followed for up to 5 years. Further follow up is warranted to further assess site specific risk and allow for longer latency.

2526

Safety of Infliximab Therapy in Rheumatoid Arthritis Patients with Pre-Existing Hepatitis B Virus Infection. Xuewu Zhang[1], Xia Liu[2], Yuan An[1], Ying Ning[1] and Zhanguo Li[1]. [1]Peking University People's Hospital, Beijing, China, [2]China-Japan Friendship Hospital, Beijing, China

Background/Purpose: To evaluate the safety of treatment with tumor necrosis factor-α (TNF-α) monoclonal antibody (Infliximab) in patients with rheumatoid arthritis(RA) who had normal liver function and pre-existent HBV infection.

Methods: In this multicenter study, all 41 cases met the ACR 1987 revised criteria for RA, including 7 men and 34 women, with average age of 46.2±2.72 years old and average disease course of 11.40±5.72 years. Upon enrollment, patients were assessed for HBsAg, anti-HBC, anti-HbsAb, anti-HBeAb. All patients were HBsAg(−); four of them were only anti-HBC (+); fifteen were anti-HBsAb (+), anti-HBeAb (+) and anti-HBc (+); six were anti-HBsAb (+) and anti-HBeAb (+); forteen were anti-HBsAb(+) and anti-HBc(+), two were anti-HBeAb (+) and anti-HBc (+). 40 patients had normal ALT and AST, and one patient with positive anti-HBc showed elevated ALT before administration of infliximab (60U/L). All patients received intravenous Infliximab therapy with dose of 3 mg/kg at week 0, 2, 6, 14 and 22 respectively after testing liver enzyme, Creatinine, T-bilirubin, leukocyte and platelet. All the above five parameters and HBsAg were reexamined at week 26.

Results: 40 out of 41 patients have their ALT, AST, T-bilirubin, Creatinine, leukocyte and platelet within normal range, with no significant difference between HBV positive and HBV negative groups. As for the patients with elevated ALT and AST levels after infliximab infusion, there was no statistically significant difference between previously HBV infected patients and patients without history of HBV infection. All patients reexamined for HBsAg at week 26 showed negative results.

Conclusion: In RA patients with pre-existing HBV infections, liver function abnormality were not observed during the Infliximab administration, as long as HBsAg was negative with normal liver function at baseline.

2527

Functional MRI (FMRI) Is Much Faster In Detecting Rapid Symptom Control by Certolizumab-Pegol In Patients with Rheumatoid Arthritis Than the Conventional MRI. Juergen Rech[1], Stephanie Finzel[1], Silke Kreitz[1], Matthias Englbrecht[1], Arnd Doerfler[1], Marc Saake[1], Andreas Hess[1] and Georg Schett[2]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: To define rapid effects of tumor necrosis factor (TNF) blockade in the central nervous system (CNS) of patients with rheumatoid arthritis (RA) and to compare that with peripheral effects. We hypothesized that CNS effects precede the clinical response much earlier in patients with RA and therefore performed non-invasive functional Magnetic Resonance Imaging (fMRI) to detect changes of neuronal activity by Blood-oxygen-Level Dependent (BOLD) in the brain (1).

Methods: Ten RA patients with a DAS28 score over 3.2 failing on at least one conventional DMARD were included. All patients started with 400 mg certolizumab treatment at 400mg on days 0, 14 and 28. DAS28 and HAQ scores were performed on days 0, 3, 7 and 28 as well as fMRI scans of the brain using a 3 Tesla scanner (Siemens) with a 8 channel phased array head coil. fMRI signals were retrieved during standardized compression of MCP joints and during finger tapping (control procedure). Also MRI scan of the index hand was performed on day 0 and 28 in five of these patients.

Results: BOLD signal volume and intensitiy in the CNS elicited by joint compression significantly decreased by 38% as early as 3 days after exposure to TNF blockade. This affected the thalamic and somatosensory cortical brain regions involved in nociception as well as the limbic system. No decrease in the clinical parameters (baseline-DAS28 5.4±0,86, baseline-HAQ 1,0±1,32; day 3-DAS28: 4,99±0,63 day 3-HAQ: 0,97±1,6) were observed at this early time point. In contrast, neuronal activity elicited by finger tapping did not decrease after 3 days. BOLD signal volume and intensitiy elicited by joint compression further decreased 28 days after initiation of TNF- blockade when clinical improvement was seen (DAS28 4.3 ± 1.78), but still detectable synovitis was present in 4 out of 5 patients.

Conclusion: TNF blockade elicits a change in neuronal activity in the CNS within days preceding its anti-inflammatory effect. These findings substantiate anecdotal clinical observations of immediate subjective improvement of the patients' condition after exposure to TNF blockade and suggest that immediate changes in neuronal activity precede the resolution of inflammation in arthritis much earlier than peripheral response.

2528

Etanercept Induces a Decrease in Left Ventricular Mass in Patients with Rheumatoid Arthritis. Claire Daien[1], Pierre Fesler[1], Vincent Daien[2], Guilhem du Cailar[1], Anne-Marie Dupuy[1], Jean-Paul Cristol[1], Jean Ribstein[1], Bernard G. Combe[1] and Jacques Morel[1]. [1]Hopital Lapeyronie, Montpellier, France, [2]Hopital Gui de Chauliac, Montpellier, France

Background/Purpose: Mortality in patients with rheumatoid arthritis (RA) is higher than in the general population, which is mainly due to premature cardiovascular disease. RA is associated with increased cardiac mass (left ventricular [LV] hypertrophy) which is a strong marker of cardiovascular morbidity and mortality. Experimental studies suggest that tumour-necrosis factor alpha (TNFa) may induce LV hypertrophy. Vessels abnormalities has also been identified in RA. Aim: To assess the influence of TNF inhibitors or synthetic drug-modifying anti-rheumatic drugs (sDMARD) on LV morphology, macrocirculation (arterial stiffness) and microcirculation (retinal arterial diameter) in RA patients.

Methods: Thirty-eight female patients with active RA were included and allocated to sDMARD (n=17; methotrexate, sulfasalazine, leflunomide) or etanercept (ETN) (n=21), according to current guidelines. Exclusion criteria were diabetes, obesity, previous cardiovascular events, cardiopathy, uncontrolled hypertension, alcohol abuse and renal disease. Clinical and biological monitoring, echocardiography, pulse wave velocity and retinal arterial caliber were performed at inclusion, after 3 and 6 months of etanercept or sDMARD therapy. All cardiovascular determinations of LV mass were performed on an offline station by the same operator who was blind of treatment assigment. Linear regression analysis and paired t test were used.

Results: (mean ± SEM) In sDMARD allocated subjects, age was 50 ± 4 yrs and RA duration was 1.7 ± 0.5 yrs. At baseline, DAS28 was 4.2 ± 0.3, LV mass index was 84 ± 7 g/m2 and LV hypertrophy (LV mass>110 g/m2) was present in 20% of subjects. In ETN allocated subjects, age was 56 ± 3 yrs and RA duration was 9.5 ± 2 yrs. At baseline, DAS28 was 4.8 ± 1.1, LV mass index was

96 ± 4 g/m^2 and LV hypertrophy was present in 25% of subjects. In group of patients on sDMARD, change in LV mass index was not significant after 3 months or 6 months (−1.4 ± 3.4 g/m^2; p=0.70 and −2.68 ± 3.23; p=0.43 respectively); whereas in patients on ETN, LV mass index decreased by −5.31 ± 1.7 g at 3 months (p=0.007) and by −13.99 ± 2.23 g/m^2 at 6 months (p<0.001). At 6 months, LV hypertrophy was present in 18% of patients on sDMARD (mean LV mass index: 88 ± 8 g/m^2) whereas in the ETN group, all patients had normal LV mass (mean LV mass index: 82 ± 3 g/m^2). Pulse wave velocity and retinal arterial diameter were not modified in either group.

Conclusion: In this longitudinal prospective comparative study conducted in RA, etanercept induced a significant decrease of LV mass whereas sDMARD did not influence cardiac remodeling. Macro and microcirculation was not modified by treatment. Those results suggest that TNF may be a main factor of LV hypertrophy. This could partly explain the previously reported benefit of TNFi on cardiovascular morbi-mortality in RA.

ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment III
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

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Autoantibodies Against CD74 and Class II-Associated Invariant Chain Peptide (CLIP) in Spondyloarthritis. Niklas T. Baerlecken[1], Georg H. Stummvoll[2], Reinhold E. Schmidt[3] and Torsten Witte[4]. [1]MD, Hannover, Germany, [2]Medical University of Vienna, Vienna, Austria, [3]Hannover Medical School, Hannover, Germany, [4]Hannover Medical School, Hanover, Germany

Background/Purpose: Spondyloarthritis (SpA) is a relatively common inflammatory disorder with a frequency of 1–2% in the European population. Establishing the diagnosis however may be difficult, since abnormalities in conventional X-ray develop with a latency of several years and so far only HLA-B27 has been established as a laboratory marker of the disorders.

The goal of our study therefore was to identify new autoantibodies as markers of SpA.

Methods: As a screening procedure, we used protein array technology for detection of possible new autoantigens in ankylosing spondylitis (AS). Sera of patients with AS without peripheral manifestation (n = 5) and other diseases (n = 45), were studied. In the second step, the results of the protein macroarray were confirmed by ELISA using commercially available recombinant antigens (Abnova, Taiwan and abcam, United Kingdom) and new synthetic derived peptides (Biomatik, Canada). The sera for the ELISA were obtained from SpA patients visiting the rheumatological outpatients and inpatients clinics of the Medical Universities in Hannover and in Vienna, from 40 patients with rheumatoid arthritis (RA) and 40 with psoriatic arthritis (PsA) without peripheral involvement and from 100 blood donors.

All donors provided informed consent for the study which was approved by our local ethical committee (project number 4928).

We correlated the presence of autoantibodies with the disease duration, HLA-B27, BASDAI and therapy in a subset of the spondyloarthritis patients.

Results: Using the protein array, we detected IgG antibodies against CD74 in 4/5 SpA sera, but only in 1/45 controls. In order to develop an ELISA, we used a peptide which includes the MHC class II-associated invariant chain peptide (CLIP) within the CD74. We could detect IgG- and/or IgA-antibodies against CLIP in 59/128 (46%) of all the sera obtained from patients (treated and untreated patients combined) with SpA. The presence of IgG antibodies against CLIP was 45% and of IgA antibodies against CLIP was 25%. In the subset of patients with AS, 22/31 (73%) had IgG and 11/31 (35%) had IgA autoantibodies and 25/31 (81%) had IgG and/or IgA autoantibodies.

The prevalence of IgG antibodies against CLIP was 9/11 (82%) in SpA patients whose sera were obtained within 1 year after the diagnosis was established, In addition, 8/9 (88%) SpA patients with an active MRI proven sacroiliitis had IgG autoantibodies against CLIP.

In the further control groups, the prevalence of IgG autoantibodies against CLIP was 5/40 (12,5%) in PsA (without axial manifestation), 8/40 (20%) in RA and 3/50 (6%) in *blood donors* and of IgA autoantibodies 3/40 (7,5%) in PsA and 5/40 (12,5%) in RA and 2/50 (4%) in *blood donors* and of IgA and/or IgG autoantibodies 5/40 (12,5%) in PsA and 9/40 (22,5%) in RA and 5/50 (10%) in *blood donors*.

Conclusion: Antibodies against CD74 and CLIP are biomarkers associated with SpA. Considering their specifity and sensitivity of up to 88 % in active SpA, they may be an useful addition to our diagnostic tools for SpA in the future, in particular in the early disease stage.

2530

Incidence of Spondyloarthropathy In Patients with Crohn's Disease: A Population-Based Study. Raina Shivashankar, Edward V. Loftus Jr., William J. Tremaine, Tim Bongartz, W. Scott Harmsen, Alan R. Zinsmeister and Eric L. Matteson. Mayo Clinic, Rochester, MN

Background/Purpose: Spondyloarthropathy (SpA) is an important extraintestinal manifestation of inflammatory bowel disease (IBD), although the frequency is uncertain. We aimed to assess the cumulative incidence and clinical spectrum of SpA in patients with Crohn's disease (CD) in a population-based study.

Methods: The medical records of a population-based cohort of Olmsted County, MN residents diagnosed with CD from 1970 through 2004 were reviewed. Patients were followed longitudinally until moving from Olmsted County, death, or December 31, 2010. We recorded data on musculoskeletal symptoms and disease, and we used the European Spondyloarthropathy Study Group and New York criteria to identify patients with SpA. The cumulative incidence of SpA subsequent to CD diagnosis was estimated using the Kaplan-Meier method.

Results: The cohort included 309 patients with CD, of which 50.2% were women, and the median age at diagnosis of CD was 30.1 years (range 8–91). Prior to CD diagnosis, the prevalence of spondyloarthropathy was 1.3% (95% confidence interval [CI], 0.4%–3.3%). The cumulative incidence of a diagnosis of spondyloarthropathy after an established diagnosis of CD was 2.6% (95% CI, 0.7%–4.5%) at 10 years, 6.2% (2.5%–9.9%) at 20 years, and 10% (3.3%–16.2%) at 30 years. The 10-year cumulative incidence of ankylosing spondylitis was 0 while both the 20-year and 30-year cumulative incidences were 1.4% (95% CI, 0–3.3%). Sacroiliitis, oligoarthritis and polyarthritis were observed in 1.6%, 2.9% and 1.9% of patients in the post-CD diagnosis period, respectively.

Conclusion: We have for the first time defined the actual cumulative incidence of SpA in CD using complete medical record information in a population-based cohort. The cumulative incidence of all forms of SpA increased to about one in 10 patients by 30 years from CD diagnosis, and features of SpA generally occurred within the first 10 years after CD diagnosis. Our results emphasize the importance of maintaining a high level of suspicion for SpA when following patients with Crohn's disease.

2531

How Does Disease Duration Modify the Association of Radiographic Damage with Ankylosing Spondylitis Metrology? Roozbeh Sharif[1], Pooja N. Patel[2], Shervin Assassi[3], Lianne S. Gensler[4], Laura A. Diekman[5], Thomas J. Learch[6], Michael H. Weisman[7], Michael M. Ward[8] and John D. Reveille[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]University of Texas, Houston, Houston, TX, [3]Univ of Texas Health Science, Houston, TX, [4]UCSF, San Francisco, CA, [5]UT Health Science Center, Houston, TX, [6]Cedars-Sinai, Los Angeles, CA, [7]Cedars Sinai Med Ctr, Los Angeles, CA, [8]NIAMS/NIH, Bethesda, MD

Background/Purpose: Previous studies have indicated that radiographic damage is associated with measurements of spinal mobility in patients with ankylosing spondylitis (AS). In the current study, we investigated the correlation of radiographic damage with spinal mobility and examined the impact of gender, disease duration, and anti-tumor necrosis factor (TNF) treatment on this association.

Methods: Study population were participants in the **P**rospective **S**tudy of **O**utcomes in **A**nkylosing **S**pondylitis (PSOAS), a multi-ethnic, multi-center cohort of AS patients in the United States. The study investigators performed the following measurements (AS-Metrology): cervical rotation and flexion, occiput to wall distance, chest expansion, modified Schober, lateral spinal flexion, and hip internal/external rotation. One radiologist (TJL) read all cervical, pelvic, and spinal radiographs. Bath AS Radiologic Index-spinal (BASRI-s) was calculated. We used linear regression to examine the association of AS-Metrology and BASRI-s. We considered the possibility that certain factors might modify this association and examined the interaction term of disease duration, gender, and anti-TNF treatment with BASRI-s in regard to its association with AS-Metrology.

Results: We included 436 patients in the analysis: 70% male, 77% Caucasian, and 85% HLA-B27 positive. Median age and disease duration was 42.3 and 16.3 years, respectively. The BASRI score was associated with all AS-Metrology components ($p<0.001$) except hip external rotation ($p=0.223$). The analysis of potential effect modifier indicated presence of a significant interaction between disease duration and BASRI in regard to its association with AS Metrology ($p<0.05$), while gender and anti-TNF treatment were not effect modifiers. Therefore, we categorized the patient into three groups based on disease duration at enrollment: less than 10, 10 to 20; and more than 20 years and conducted

subgroup analysis. Patients with 10 to 20 years of symptoms demonstrated the highest correlation coefficient between BASRI and AS-Metrology (Table-1). Some of AS-Metrology variables were not normally distributed. Although, analysis of log transformed variable did not make any difference in outcome.

Table 1. Subgroup analysis of correlation between BASRI and AS metrology according to disease duration

	BASRI-s*					
Clinical measurements	**Disease duration** ≤ 10 years (n=126)**		**Disease duration 10–20 years (n=95)**		**Disease duration ≥ 20 years (n=114)**	
	***R*†**	***p-value***	***R***	***p-value***	***R***	***p-value***
Cervical rotation	−0.35	**<0.001**	−0.66	**<0.001**	−0.44	**<0.001**
Cervical flexion	−0.22	**0.011**	−0.68	**<0.001**	−0.58	**<0.001**
Occiput to wall	0.55	**<0.001**	0.70	**<0.001**	0.52	**<0.001**
Chest expansion	−0.30	**0.001**	−0.45	**<0.001**	−0.36	**<0.001**
modified Schober	−0.46	**<0.001**	−0.69	**<0.001**	−0.47	**<0.001**
Lateral spinal flexion	−0.48	**<0.001**	−0.72	**<0.001**	−0.43	**<0.001**
Hip external rotation	0.14	0.113	−0.23	**0.011**	−0.13	0.175
Hip internal rotation	0.05	0.577	−0.30	**0.003**	−0.14	0.128

** BASRI-s: Bath Ankylosing Spondylitis Radiology Index-spinal;*
*** Disease duration calculated from the onset of symptom until enrollment in PSOAS cohort; †R: Correlation coefficient.*

Conclusion: AS-Metrology is associated with BASRI. This correlation peaks 10 to 20 years after the onset of symptoms and is weaker in earlier and later stages of disease.

2532

Selection of Patients with Ankylosing Spondylitis for TNF-Inhibitor Therapy: Comparing Responses in Patients Selected by BASDAI & ASDAS. Karen Minde Fagerli[1], Elisabeth Lie[2], D.M.F.M. van der Heijde[3], Marte S. Heiberg[1], Synnøve Kalstad[4], Erik Rødevand[5], Cecillie Kaufmann[6], Knut Mikkelsen[7] and Tore K. Kvien[2]. [1]Diakonhjemmet hospital, Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Leiden University Medical Center, Leiden, Netherlands, [4]University Hospital in Northern Norway, Tromsø, Norway, [5]St. Olavs Hospital, Trondheim, Norway, [6]Vestre Viken, Drammen, Norway, [7]Lillehammer Hosp for Rheumatic Diseases, Lillehammer, Norway

Background/Purpose: BASDAI is the most commonly used measure to assess disease activity in ankylosing spondylitis (AS), and has been widely used as cut-off for eligibility for TNF-inhibitor (TNFi) therapy. ASDAS has been developed as a composite disease activity score for AS, and cut-off values for disease activity states have been published (Inactive disease <1.3, moderate disease activity 1.3–2.1, high disease activity 2.1–3.5 and very high disease activity > 3.5). High disease activity has been suggested as a suitable cut-off for eligibility for TNFi therapy, but whether this is a better cut-off than BASDAI ≥ 4 has not been widely explored.

Objectives: Compare 3-month responses to TNFi in patients selected by BASDAI or ASDAS alone, both or by neither measure.

Methods: The data is from the NOR-DMARD register where adult patients with inflammatory arthropathies starting a new DMARD treatment are included and followed longitudinally. For these analyses we included all patients with AS who had attended their 3 month follow-up after starting a TNFi, and had complete baseline data for calculating BASDAI and ASDAS. Response measures selected were ASDAS responses, BASDAI50 and ASAS responses, change in BASFI and % of patients with ASDAS inactive disease.

Results: 465 patients were included. The majority of patients were eligible both by ASDAS and BASDAI cut-offs (N=342). 47 patients were not eligible by either. Very few patients were eligible by BASDAI only (N=6), but 70 patients were eligible by ASDAS only. Baseline characteristics are shown in table 1.

Table 1.

		BASDAI < 4 (n=117)		BASDAI ≥ 4 (n=348)	
	Overall N=465	**ASDAS < 2.1 N=47**	**ASDAS ≥ 2.1 N=70**	**ASDAS < 2.1 N=6**	**ASDAS ≥ 2.1 N=342**
Age	43.1 (11.3)	41.3 (10.5)	42.6 (10.9)	47.6 (12.2)	43.3 (11.4)
Sex (% male)	68.1	74.5	81.4	83.3	64.2
Disease duration	11.8 (11.2)	11.2 (10.1)	12.8 (11.9)	13.0 (13.9)	11.6 (11.2)
HLA B27 pos. (%)	89.9	94.4	96.7	83.3	88.1
CRP(median (IQR))	8 (5–20)	3 (1–5)	17 (6–26)	1 (1–2)	9 (5–20.25)
ASDAS	3.48 (1.03)	1.59 (0.40)	2.84 (0.51)	1.94 (0.12)	3.77 (0.83)
ASDAS I.D.* (%)	1.7	17.0	NA	0	NA
BASDAI	3.34 (2.35)	2.12 (1.00)	3.07 (0.77)	4.75 (0.51)	6.44 (1.33)
BASFI	4.44 (2.31)	2.05 (1.92)	2.98 (19.2)	3.96 (2.51)	5.08 (2.07)

*ASDAS inactive disease

Percentages of responses in each group are shown in table 2. Patients who were eligible by both measures had the greatest response by all criteria, except achieving ASDAS inactive disease which is expected due to the higher baseline ASDAS. Patients eligible only by ASDAS have comparable ASDAS clinically important improvement and BASDAI 50 responses to those who are eligible by both measures, and had reasonable responses also using other outcome measures. The group fulfilling only BASDAI criteria is too small to make general assumptions, but responses are poor. Responses are also poor in patients fulfilling neither criteria.

Table 2.

		BASDAI < 4		BASDAI ≥ 4	
	Overall N=394–453	**ASDAS < 2.1 N=44**	**ASDAS ≥ 2.1 N=63–68**	**ASDAS < 2.1 N=5**	**ASDAS ≥ 2.1 N=285–334**
ASDAS M.I*	26.7	0	14.3	0	34
ASDAS C.I.I**	52.4	6.8	58.7	0	58.9
BASDAI 50	42.2	29.5	42.6	40	43.8
ASDAS I.D.***	25.9	50	38.1	0	20
ASAS 20	50.6	11.4	45.6	0	57.5
ASAS 40	36.1	2.3	27.9	0	42.8
Δ BASFI (SD)	−1.40 (1.92)	−0.15 (1.19)	−0.76 (1.22)	−0.81 (1.40)	−1.72 (2.03)

*ASDAS major improvement **ASDAS clinically important improvement ***ASDAS inactive disease

Conclusion: Very few patients who were eligible for TNFi therapy by BASDAI criteria were not also selected by ASDAS criteria. Using ASDAS increased the number of patients eligible for TNFi therapy. Patients who fulfill both BASDAI and ASDAS criteria had the best responses using a set of response measures, but additional patients identified by ASDAS had reasonable responses to TNFi.

2533

Obesity and the Risk of Psoriatic Arthritis in the General Population. Yanyan Zhu[1], Hyon K. Choi[1], Yuqing Zhang[1], Lindsay Wall-Burns[2], Alexis Ogdie[3], Joel Gelfand[4] and Thorvardur Love[5]. [1]Boston University School of Medicine, Boston, MA, [2]Arthritis Research Centre of Canada, Vancouver, BC, [3]University of Pennsylvania, Philadelphia, PA, [4]University of Pennsylvania., Philadelphia, PA, [5]Landspitali University Hospital, Reykjavík, Iceland

Background/Purpose: Psoriatic arthritis (PsA) is a progressive and often destructive joint disease associated with psoriasis (Ps). Although PsA represents a lifelong burden for affected patients, its risk factors are poorly understood. Excess weight has been shown to increase the risk of Ps; however, its impact on the risk of PsA remains unclear. To address this issue, we examined the association between adiposity and the risk of incident PsA among Ps patients from the general population.

Methods: We conducted a cohort study using data from The Health Improvement Network (THIN), an electronic medical records database of the UK general population, collected between 1995 and 2010. Our primary study population consisted of individuals with physician-diagnosed Ps who were aged ≥20 years, had ≥2 years of enrollment in the general practice before entering the study cohort, and did not have a history of PsA. (Validity of the THIN code for Ps has been documented with a positive predictive value (PPV) of 90%.) Our end-points were incident cases of physician-diagnosed PsA. Our exposure of interest was the first body mass index (BMI) measured after Ps diagnosis, which we categorized into 4 levels: <25, 25–29.9, 30–34.9 and ≥35 kg/m^2. Individuals were followed from the time of first BMI measurement after Ps diagnosis until PsA incidence, death, discontinuation of enrollment, or the end of study period, whichever came first. We used Cox proportional hazard model to estimate the hazard ratios (HRs) of PsA after adjusting for potential confounders (i.e. age, sex, and histories of trauma, smoking, and alcohol consumption prior to BMI measurement). In our secondary analysis, we investigated the same association in the entire population, regardless of Ps status.

Results: Among 75,395 individuals with Ps (43% male, mean follow-up of 5 years, and mean age of 52 years), 976 developed PsA. The overall PsA incidence rate was 26.5 cases per 10,000 person-years. The PsA incidence rates increased with increasing BMIs. Compared to individuals with BMIs <25 kg/m^2, the adjusted hazard ratios (HR) were 1.09, 1.22, and 1.48 for BMIs of 25–29.9, 30–34.9, and ≥35 kg/m^2, respectively (p for trend <0.001, **Table**). In our secondary analysis among all individuals, regardless of psoriasis (~2 million), the corresponding multivariate HRs tended to be stronger (1.0, 1.17, 1.58, 1.97; p for trend <0.001); further adjustment of the history of psoriasis in this secondary analysis modestly attenuated the association (1.0, 1.12, 1.46, 1.75; p for trend <0.001).

BMI and the Risk of Incident PsA Among Ps Patents

BMI (kg/m^2)	Number of Incident PsA	Incidence Rate (cases/10,000 person-years)	Adjusted HR (95% CI)
<25	**300**	**23.09**	**1.0 (Reference)**
25–29.9	**341**	**25.37**	1.09 (0.93, 1.28)
30–34.9	**197**	**29.33**	**1.22 (1.02, 1.47)**
≥35	**138**	**38.04**	**1.48 (1.21, 1.82)**
P for Trend	**–**	**<0.001**	**<0.001**

Conclusion: This general population study provides the first large-scale epidemiologic evidence that higher obesity among Ps patients contributes to an increased risk of incident PsA. These findings add substantially to the importance of weight reduction among Ps patients, who often suffer from the metabolic syndrome and obesity.

2534

Frequency and Duration of Drug-Free Remission After One Year of Treatment with Etanercept Vs. Sulfasalazine in Early Axial Spondyloarthritis – 2 Year Data of the ESTHER Trial. In-Ho Song[1], Kay-Geert Hermann[2], Hildrun Haibel[1], Christian Althoff[2], Denis Poddubnyy[1], Joachim Listing[3], Anja Weiβ[3], Bruce Freundlich[4], Martin Rudwaleit[5] and Joachim Sieper[1]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Charite Medical School, Berlin, Germany, [3]German Rheumatism Research Centre, Berlin, Germany, [4]University of Pennsylvania, Philadelphia, PA, [5]Ev. Krankenhaus Hagen-Haspe, Hagen, Germany

Background/Purpose: In patients with early axial spondyloarthritis (SpA) with a disease duration of < 5 years and with active inflammation on magnetic resonance imaging (MRI) in the spine and/or sacroiliac joints (SIJ) on baseline who were treated with etanercept (ETA, n= 40) vs. sulfasalazine (SSZ, n= 36) for 48 weeks [1] to assess: a) the frequency and duration of drug-free remission and b) the efficacy of ETA after flare, and c) long-term response of ETA during year 2 in already ETA-treated patients (ETA treatment in year 1 and year 2).

Methods: At week 48, patients who reached study remission (defined as reaching ASAS remission and being free of active inflammation on whole-body-MRI in the spine and sacroiliac joints) were followed every 6 weeks without active treatment. In case of a flare (defined as a BASDAI increase of 2 points compared to week 48) all patients were (re-)treated with ETA for another year up to week 108. Patients who were in study remission at week 48 and who did not flare were excluded from the study at the end of year 2 (permanent drug-free remission). All patients who were not in study remission at week 48 were treated with ETA in year 2.

Results: Study remission at week 48 was reached significantly more often by ETA- compared to SSZ-treated patients (13/40= 33% vs. 4/36= 11%, p= 0.03). Among patients reaching study remission (n= 17) 70% belonged to the non-radiographic axial SpA group and 30% to the AS group. 23% (9/40) of the ETA-group flared after a mean of 24.4 weeks and 8% (3/36) of the SSZ-group flared after 39.6 weeks (no significant difference for time to flare between both groups).Thus, 8% (3/40) of ETA-treated patients vs. 3% (1/36) of SSZ-treated patients reached drug-free remission. After initiation of ETA during year 2, flare-patients (n= 9) showed a significant (p< 0.001) response to ETA-treatment (table 1): 56% of flare-patients reached ASAS remission and 44% study remission as well as ASDAS inactive disease at week 108.

Formerly ETA-treated patients (n= 22) who did not reach study remission at week 48 showed a good sustained clinical and MRI response at week 108 (50% ASAS remission; 5 additional patients reached ASAS remission at week 108 who were not in remission at week 48; table 1).

Table 1.

Parameter (mean and standard deviation)	Study time point	Remission-Flare Group ETA year 1-ETA year 2 (n= 9)	Remission-Flare Group SSZ year 1-ETA year 2 (n= 3)	Non-Remission-Group ETA year 1-ETA year 2 (n= 22)	Non-Remission-Group SSZ year 1-ETA year 2 (n= 26)
BASDAI	Baseline	5.7 (1.8)	5.9 (1.6)	5.4 (1.1)	5.9 (1.2)
BASDAI	Week 48	1.1 (0.6)	2.0 (1.0)	2.6 (1.7)	4.7 (2.3)
BASDAI	Flare time point	5.0 (1.5)	4.5 (0.4)	Not applicable	Not applicable
BASDAI	Week 108	1.5 (1.4)	1.7 (1.6)	2.7 (2.3)	3.2 (2.6)
MRI SIJ	Baseline	12.0 (6.4)	3.2 (3.9)	8.6 (7.3)	6.5 (5.8)
MRI SIJ	Week 48	1.1 (1.4)	0 (0)	2.4 (3.3)	2.7 (3.2)
MRI SIJ	Week 108	0.4 (0.5)	0 (0)	2.9 (3.7)	1.6 (2.0)
MRI Spine	Baseline	0.2 (0.7)	0.7 (1.2)	3.4 (5.6)	1.3 (2.5)
MRI Spine	Week 48	0 (0)	0 (0)	1.3 (1.9)	1.0 (1.9)
MRI Spine	Week 108	0 (0)	0.3 (0.6)	1.0 (1.7)	0.7 (1.6)
ASAS remission, % (n)	Week 108	56% (5/9)	67% (2/3)	50% (11/22)	23.1% (6/26)
MRI remission, % (n)	Week 108	56% (5/9)	67% (2/3)	13.6% (3/22)	26.1% (6/23)
Study remission, % (n)	Week 108	44% (4/9)	33% (1/3)	14% (3/22)	8% (2/26)
ASDAS inactive disease (<1.3)	Week 108	44% (4/9)	66.7% (2/3)	38.1% (8/21)	28.0% (7/25)

Conclusion: After one year of treatment with ETA 33% of patients with early axial SpA reached study remission, however 23% flared within 24 weeks while only 8% stayed in drug-free remission. Patients treated with ETA for 2 years showed continuously low disease activity with further improvement in a subgroup of patients.

[1] Song I.-H. et al. 2011. Ann Rheum Dis. 2011 Apr;70(4):590–6.

ACR Concurrent Abstract Session
Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics I
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

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Transforming Growth Factor Beta Mediated Activation of Canonical Wnt Signaling Is Crucial for the Development of Fibrosis In Systemic Sclerosis. Alfiya Akhmetshina[1], Katrin Palumbo[2], Christina Bergmann[2], Paulius Venalis[2], Clara Dees[2], Pawel Zerr[2], Angelika Horn[2], Christian Beyer[3], Jochen Zwerina[2], Ormond A. MacDougald[4], Oliver Distler[5], Georg Schett[2] and Jorg HW Distler[2]. [1]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]Department of Pediatrics, University of Erlangen-Nuremberg, Erlangen, Germany, [5]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Wnt signaling profoundly affects developmental processes and plays an important role for tissue homeostasis. Aberrant activation of the canonical Wnt pathway has been implicated in a variety of different diseases. To avoid uncontrolled activation, Wnt signaling is tightly controlled by negative regulators such as dickkopf-1 (Dkk-1). Here, we investigated the interaction between TGFβ dependent pathways and canonical Wnt signaling as a novel molecular mechanism in SSc.

Methods: Canonical Wnt signaling was modulated in vivo using Wnt10b- and Dickkopf (Dkk)-1 transgenic mice. The role of Wnt signaling was investigated in the mouse model of bleomycin-induced dermal fibrosis, in tight-skin-1 (Tsk-1) mice and in mice overexpressing constitutively active TGFβ receptor type I.

Results: Canonical Wnt signaling is activated in SSc and in experimental fibrosis with nuclear accumulation of β-catenin and increased expression of the target gene axin-2. We demonstrate that the activation of canonical Wnt signaling in SSc is mediated by TGFβ. TGFβ decreases the mRNA and protein levels of Dkk-1, a potent inhibitor of Wnt signaling, in a p38 dependent, Smad-independent manner by more than 80%. Indeed, the expression of Dkk-1 is almost undetectable in the skin of SSc patients and in different models of experimental models of fibrosis. Stimulation with TGF-β or overexpression of constitutively active TGFβ receptor type I potently activated canonical Wnt signaling in vitro and in vivo with nuclear accumulation of β-catenin, increased TOP-reporter activity and induction of axin-2. In contrast, inhibition of TGFβ-signaling in experimental models of fibrosis by SD-208, a selective inhibitor of TGFβ receptor kinase activity, almost completely prevented the activation of canonical Wnt-signaling, highlighting the key-role of TGFβ for the activation of Wnt signaling in fibrosis. We also show that the activation of Wnt signaling directly contributes to the profibrotic effects of TGFβ. Canonical Wnt signaling stimulates the release of collagen in vitro and induces massive fibrosis in vivo. Recombinant Dkk-1 strongly reduced the stimulatory effects of TGFβ on cultured fibroblasts and decreased the TGFβ-induced upregulation of collagen, αSMA and stress fibers by up to 75%. Moreover, transgenic overexpression of Dkk-1 amelio-

rates fibrosis in mice induced by adenoviral transfection of constitutively active TGF receptor type I with reduction of dermal thickening, myofibroblast counts and hydroxyproline content by 75 ± 7%, 85 ± 5% and 80 ± 11% respectively ($p < 0.02$ for all). Overexpression of Dkk-1 also exerted potent anti-fibrotic effects in bleomycin induced dermal fibrosis and in Tsk-1 mice.

Conclusion: Canonical Wnt pathway is activated in SSc and potently stimulates fibroblast activation and tissue fibrosis. TGFβ activates canonical Wnt signaling in SSc by decreasing the expression of the Wnt inhibitor Dkk-1. Overexpression of Dkk-1 potently reduces the pro-fibrotic effects of TGFβ and prevents fibrosis in different experimental models, demonstrating that the interaction of the canonical Wnt pathway and TGF-β plays a key role in the pathogenesis of fibrotic diseases.

2536

Anti-Fibrotic Effects of Microrna-145 in Systemic Sclerosis Via a Multi-Step Regulation of TGF-Beta/CTGF Signaling. Serena Vettori[1], Matthias Brock[1], Naoki Iwamoto[1], Britta Maurer[1], Astrid Jungel[1], Renate E. Gay[1], Maurizio Calcagni[2], Gabriele Valentini[3], Jorg HW Distler[4], Steffen Gay[1] and Oliver Distler[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Division of Plastic Surgery and Hand Surgery, Zurich University Hospital, Zurich, Switzerland, [3]Rheumatology Unit, Second University of Napoli, Napoli, Italy, [4]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

Background/Purpose: Since hyperactivity of TGF-β/CTGF signaling is a leading cause of tissue fibrosis, we explored the expression and function of microRNAs (miR) regulating the TGF-β/CTGF pathway in systemic sclerosis (SSc).

Methods: Pooled SSc and healthy control (HC) fibroblasts (n=3) were used to screen the expression of 377 miRs by low-density array. Basal miR-145 and pri-miR-145 expression was analyzed in individual SSc ($n = 12$) and HC ($n = 6$) dermis and fibroblasts. Expression of miR-145 targets, COL1A1 and COL3A1 was analyzed under over-expression or silencing of miR-145 by pre/anti-miR-145 in SSc and HC fibroblasts, respectively, at both RNA and protein level by Real time PCR and Western blotting. A luciferase-based reporter gene system (pmirGLO vector) containing the 3′UTR of TGFBR2, was used to examine the direct interaction with miR-145.

Results: The low-density array displayed 26 down-regulated and 5 up-regulated miRs in SSc fibroblasts. Among these, miR-145 was analyzed further and confirmed to be down-regulated in both SSc dermis and fibroblasts by 45 and 51% respectively ($p < 0.001$). Similar results were obtained for the non-functional primary transcript, pri-miR-145, suggesting a regulation on the transcriptional level rather than post-transcriptional modifications. No significant difference in the expression of miR-145 was found between SSc fibroblasts and untreated controls exposed to hypoxia or pro-fibrotic cytokines (TGF-β, PDGF-B, and VEGF-A). However, down-regulation of miR-145 in SSc was mediated by epigenetic modifications, as inhibition of DNA methyltransferases by 5aza-C increased miR-145 levels by 25% in SSc fibroblasts. In silico analysis predicted multiple molecules of the TGF-β pathway as miR-145 targets including TGFB2, TGFB3, TGFBR2, SMAD3 as well as CTGF. Transfection of SSc fibroblasts with pre-miR-145 confirmed this analysis by decreasing TGFBR2 ($p < 0.001$), SMAD3 ($p < 0.01$) and CTGF ($p < 0.001$) mRNA by 53 to 66%. COL1A1 and COL3A1 mRNA were also reduced to a similar extent ($p < 0.01$). Consistent results were obtained at the protein level for TGF-βRII, Smad3 and collagen types I and III ($p < 0.05$). In addition, active Smad3 (P-Smad3) was also reduced ($p < 0.001$). Transfection of HC fibroblasts with anti-miR-145 further confirmed these findings by mimicking the SSc expression profile with increased expression of TGF-β signalling molecules at the mRNA level. Co-transfection of HEK293 cells with pmirGLO-TGFBR2 3′UTR construct and pre-miR145 reduced the luciferase gene activity by 34% ($p < 0.05$) suggesting a direct regulation by miR-145.

Conclusion: Our findings provide the first evidence for anti-fibrotic effects of miR-145 via direct post-transcriptional repression of TGF-β signaling (TGFBR2 and SMAD3) and CTGF. Our data indicate that the down-regulation of miR-145 in SSc appears independent from major pro-fibrotic stimuli, and thus targeting these stimuli in therapeutic approaches would not correct the effects of miR-145. Because miR-145 was consistently down-regulated in SSc, elevation of miR-145 could be an appropriate approach to treat SSc.

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TLR4 Activation Enhances Fibrotic Responses Induced by TGF-β: A Mechanism for Maintaining and Amplifying Fibrosis in Scleroderma. Swati Bhattacharyya[1], Kathleen Kelly[2], Denisa S. Melichian[2], Kohtaro Ooka[3], Carol A. Feghali-Bostwick[4], Robert A. Lafyatis[5], Timothy RD Radstake[6] and John Varga[1]. [1]Northwestern Univ Med School, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Northwestern University, [4]University of Pittsburgh, Pittsburgh, PA, [5]E5 Arthritis Ctr-BUSM, Boston, MA, [6]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background/Purpose: Fibrosis in scleroderma involves early inflammation and TGF-β production production, followed by sustained fibroblast activation and myofibroblast differentiation. Recent studies indicate a potential role for TLR4-mediated innate immune signaling, triggered by endogenous damage associated molecular patterns generated through tissue injury, in fibroblast activation. We sought to investigate the role and mechanism of TLR4-mediated fibroblast activation in fibrosis.

Methods: The expression of TLR4 and endogenous TLR4 ligands were investigated in scleroderma biopsies, and in a mouse model of fibrosis. The profibrotic effects of the TLR4 ligand LPS and constitutively active TLR4 were examined in skin fibroblasts. The role of TLR4 in fibrosis in vivo was investigated using C3H/HeJ mice with mutated TLR4.

Results: TLR4 was significantly elevated in scleroderma skin and lung biopsies. TLR4 expression was also markedly up-regulated in a bleomycin-induced mouse model of scleroderma. Overexpression of constitutively active TLR4 in fibroblasts dramatically enhanced sensitivity to TGF-β-induced collagen stimulation and myofibroblast differentiation. Similar effects were triggered by the TLR4 ligand LPS. These stimulatory responses were abrogated by specific pharmacological inhibitors of intracellular and extracellular domain of TLR4. Moreover, TLR4-null mouse skin fibroblasts were resistant to TLR4 ligand-mediated synergistic induction of TGF-β responses. TLR4 stimulation resulted in activation of canonical Smad signaling with increased cellular pSmad2/3 level and Smad-dependent transcriptional activity. The levels of the TGF-β pseudoreceptor BAMBI were significantly down-regulated by LPS via a TLR4-mediated pathway. Moreover, all the isotypes of the anti-fibrotic microRNA 29 were suppressed in a time-dependent (or dose dependent) manner with LPS treatment. In this model of scleroderma, TLR4 mutant C3H/HeJ mice showed increased early inflammation, but attenuation of skin and lung fibrosis.

Conclusion: Activation of the TLR4 signaling pathway induces profibrotic responses in normal fibroblasts, and sensitizes these cells to TGF-β. TLR4 signaling appears to be implicated in skin and lung fibrosis in scleroderma. These results lead us to propose a novel model for fibrogenesis in which TLR4 activation by damage-associated endogeous TLR4 ligands contributes to the progression of fibrosis.

2538

Tribbles Homolog 3 Mediates Transforming Growth Factor Beta Driven Dermal Fibrosis In Systemic Sclerosis. Michal Tomcik[1], Katrin Palumbo[2], Jérôme Avouac[3], Angelika Horn[2], Aisa Khodzhigorova[2], Pawel Zerr[2], Clara Dees[2], Alfiya Akhmetshina[4], Christian Beyer[5], Radim Becvar[1], Ladislav Senolt[6], Oliver Distler[7], Georg Schett[2] and Jorg HW Distler[2]. [1]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [4]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [5]University of Erlangen-Nuremberg, Erlangen, Germany, [6]Institute of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [7]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Tribbles Homolog 3 (TRB-3), is a member of a family of pseudokinases called Tribbles which regulate activation of a number of intracellular signaling pathways with roles extending from mitosis and cell activation to apoptosis and modulation of gene expression. The aim of this study was to investigate the role of TRB-3 in the pathologic activation of fibroblasts in systemic sclerosis (SSc).

Methods: Activation of TRB-3 in the skin and dermal fibroblasts was determined by real-time PCR, immunohistochemistry and immunofluores-

cence. Collagen synthesis of human dermal fibroblasts was quantified by real-time PCR and SirCol collagen assay. The expression of TRB3 was inhibited in cultured fibroblasts and in murine models of fibrosis with siRNA. The mouse models of bleomycin-induced dermal fibrosis and dermal fibrosis induced by attenuated adenovirus overexpressing a constitutively active TGF-β receptor I were used to investigate the role of TRB3 in fibrosis.

Results: Increased expression of TRB-3 was detected in the upper layer of the dermis of SSc patients. The overexpression of TRB-3 persisted in cultured SSc fibroblasts (4.1$\pm$0.4-fold increase, $p<0.001$). A similar increase in TRB-3 expression was observed in the skin samples from both murine models of experimental dermal fibrosis, both on mRNA and protein level. The upregulation of TRB3 was mediated by TGF-β. Stimulation of cultured fibroblasts with TGF-β increased expression of TRB-3 protein by 4.5$\pm$0.2-fold ($p<0.001$). Knockdown of TRB-3 by siRNA abrogated the stimulatory effects of TGF-β on fibroblasts and completely prevented the stimulatory effects of TGF-β on the release of collagen and the formation of stress fibers. Moreover, mice lacking TRB-3 were protected from experimental fibrosis. In the model of bleomycin-induced dermal fibrosis, siRNA mediated knockdown of TRB-3 decreased dermal thickening by 50$\pm$1% ($p<0.05$), the hydroxyproline content by 76$\pm$5% ($p<0.01$) and the myofibroblast counts by 86$\pm$10% ($p<0.05$). In the model of dermal fibrosis induced by adenoviral overexpression of constitutively active TGF-β receptor I, knockdown of TRB-3 decreased dermal thickening by 91$\pm$6% ($p<0.05$), completely prevented the accumulation of hydroxyproline ($p<0.01$) and decreased the myofibroblast counts by 82$\pm$7% ($p<0.05$). Consistent with the crucial role of TRB-3 for TGF-β signaling in vitro, knockdown of TRB-3 abrogated the nuclear accumulation of phosphorylated Smad-3 and prevented the induction of TGF-β target genes such as Smad-7 and CTGF in both mouse models.

Conclusion: We demonstrate for the first time a key-role of TRB-3 in fibroblast activation and tissue fibrosis in SSc. TRB-3 is upregulated in SSc and in experimental fibrosis in a TGF-β dependent manner. TRB-3 is essential for the pro-fibrotic effects of TGF-β and targeting of TRB-3 completely prevents the stimulatory effect of TGF-β on cultured fibroblasts. Moreover, knockdown of TRB-3 protected from experimental dermal fibrosis in different mouse models. Considering the potent anti-fibrotic effects observed in this study, TRB-3 might be a promising candidate for molecular targeted therapies of SSc.

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Inhibition of Glycogen Synthase Kinase 3β Induces Dermal Fibrosis by Activation of the Canonical Wnt Pathway. Christina Bergmann[1], Alfiya Akhmetshina[2], Clara Dees[1], Katrin Palumbo[1], Pawel Zerr[1], Christian Beyer[3], Jochen Zwerina[1], Oliver Distler[4], Georg Schett[1] and Jorg HW Distler[1]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Wnt signaling plays a critical role in embryogenesis and in adult tissue homeostasis. The abnormal activation of Wnt signaling is associated with a wide range of diseases and might also play a role in SSc. Glykogen Synthase Kinase 3β (GSK-3) is a crucial regulator of the canonical Wnt signaling. In the absence of Wnt proteins, GSK-3 promotes the phosphorylation and subsequent degradation of β-catenin. Thus, the aberrant activation of the canonical Wnt pathway is prevented. However, in the presence of Wnt, GSK-3 becomes inactive and β-catenin is not degraded but stimulates the transcription of Wnt target genes. The aim of the present study was to define the role of GSK-3 as a central regulator of canonical Wnt signaling for fibroblast activation and in experimental models of SSc.

Methods: We used siRNA and two specific inhibitors, SB216763 and AR-A014418, to inhibit GSK-3 in cultured fibroblasts and in mice. The activation of the canonical Wnt signaling was analyzed by determining the levels of nuclear β-catenin and by measuring the mRNA levels of the Wnt target gene Axin2. The effects of GSK-3 on the release of collagen were evaluated in human dermal fibroblasts, in the mouse model of bleomycin induced dermal fibrosis and in the tight-skin-1 (tsk-1) mice. To investigate whether inhibition of GSK-3 alone is sufficient to induce fibrosis, SB216763 was applied to mice without additional profibrotic stimuli.

Results: Targeting GSK-3 potently activated the canonical Wnt pathway in fibroblasts *in vitro* and *in vivo* with a prominent accumulation of nuclear β-catenin and induction of Axin2. Incubation with inhibitors of GSK-3 dose-dependently upregulated the expression of col1a1 from cultured fibroblasts by up to 2.6 fold ($p<0.05$) and increased the release of collagen protein. Similar results were also obtained upon knockdown of GSK-3 with siRNA. The increased release of collagen was completely abolished by siRNA mediated knockdown of β-catenin suggesting that the pro-fibrotic effects of inhibition of GSK-3 are mediated by the canonical Wnt pathway. In vivo, inactivation of GSK-3 exacerbated bleomycin induced dermal fibrosis with increased dermal thickening by 84$\pm$15%($p<0.05$) compared to bleomycin treatment alone. Inactivation of GSK-3 also aggravated the tsk-1 phenotype. Moreover, inhibition of GSK-3 was sufficient to induce progressive dermal fibrosis in mice with increases in dermal thickening by up to 65$\pm$9% within 8 weeks ($p<0.05$).

Conclusion: We demonstrated that GSK-3 is a crucial regulator of the canonical Wnt pathway in dermal fibroblasts. Inhibition of GSK-3 stimulates the release of collagen from dermal fibroblasts in a β-catenin dependant manner and aggravates experimental fibrosis in different mouse models. Of note, inhibition of GSK-3 alone was sufficient to induce dermal fibrosis. These results highlight the key-role of canonical Wnt signaling in fibrosis and underline the importance of proper control of the canonical Wnt pathway.

2540

The Nuclear Receptor CAR Mediates the Pro-Fibrotic Effects of TGF-β and Contributes to the Development of Experimental Dermal Fibrosis. Jerome Avouac[1], Michal Tomcik[2], Katrin Palumbo[1], Pawel Zerr[1], Clara Dees[1], Alfiya Akhmetshina[1], Christian Beyer[1], Oliver Distler[3], Georg Schett[1], Yannick Allanore[4] and Jorg HW Distler[1]. [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Institute of Rheumatology, Department of Clinical and Experimental Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [3]University Hospital Zurich, Zurich, Switzerland, [4]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France

Background/Purpose: Tissue fibrosis caused by pathological activation of fibroblasts is a major hallmark of systemic sclerosis (SSc). The constitutive androstane receptor (CAR), a member of the nuclear receptor superfamily, is involved in shear and xenobiotic stress. CAR regulates target genes involved in drug metabolism, such as cytochrome P450 family members. CAR activation has also recently been shown to exacerbate hepatic fibrosis. We aim in the present study to investigate whether CAR might contribute to the pathologic activation of fibroblasts in SSc and to the development of experimental dermal fibrosis.

Methods: Expression of CAR was determined in human skin by immunohistochemistry and in fibroblasts by real time PCR and western blots. SSc and healthy dermal fibroblasts were stimulated with TGFβ and incubated with CITCO, a potent and selective agonist for the human CAR. Collagen release from fibroblasts was evaluated by mRNA levels of col1a1 and col1a2 and by the SirCol collagen assay. Col1a2 transcriptional activity was assessed by transfection assays performed with a luciferase reporter construct under control of the -772-bp to +58-bp col1a2 promoter. The synthetic agonist of mouse CAR TCPOBOP was used to evaluate the profibrotic potential of CAR *in vivo* in the mouse model of bleomycin induced dermal fibrosis or in the model of dermal fibrosis induced by local injections of replication deficient adenoviruses overexpressing a constitutively active TGF-β receptor I.

Results: Upregulation of CAR was detected in the skin and dermal fibroblasts of SSc patients. Stimulation of healthy fibroblasts with TGFβ increased the expression of CAR mRNA by 93$\pm$11% and protein by 81$\pm$14% ($p<0.05$ for both). Treatment of healthy or SSc fibroblasts with CITCO significantly increased the stimulatory effects of TGF-β on collagen synthesis. CITCO also amplified the stimulatory effects of TGF-β on col1a2 transcriptional activity by up to 41$\pm$5% ($p=0.03$). Consistently, activation of CAR with TCPOBOP exerted potent profibrotic effects in different models of experimental fibrosis. In the mouse model of bleomycin-induced fibrosis, activation of CAR increased dermal thickening by 35$\pm$1% ($p<0.05$). In addition, the collagen content and the number of myofibroblasts were significantly increased (respectively 42$\pm$3% and 69$\pm$11%, $p<0.05$). In the TGFβRI model, activation of CAR also exerted potent profibrotic effects and increased dermal thickening, collagen content and myofibroblast counts by 51$\pm$5%, 46$\pm$7% and 42$\pm$3%, respectively ($p<0.05$).

Conclusion: We demonstrate that CAR is activated in a TGFβ dependent manner in SSc and mediates the effects of TGF-β on collagen synthesis. In addition, activation of CAR contributed to the development of dermal fibrosis in different mouse models of SSc. Thus, CAR might be a promising new molecular target for the treatment of SSc and other fibrotic processes.

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Does Medication Adherence Itself Confer Fracture Protection? An Investigation of the Healthy Adherer Effect In Observational Data. Jeffery R. Curtis[1], Jeff Lange[2], Huifeng Yun[1] and Elizabeth S. Delzell[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Proctor and Gambel

Background/Purpose: Prior studies have shown a relationship between bisphosphonate (BP) adherence and reduced fractures. One potential concern about the interpretation of this association is the healthy adherer effect, a phenomenon whereby patients who adhere to medications are systematically different than those who do not. The extent to which fracture-adherence analyses might be confounded by the healthy adherer effect in real-world settings is unclear.

Objectives: To quantify the association between high adherence with different medications and fracture risk.

Methods: Using MedstatMarketScan from 2000 to 2008, we identified 125,000 women with a new clinical fracture at the hip, spine, humerus, or wrist. We defined three mutually-exclusive cohorts of patients who initiated within 6 months post-fracture: 1) oral BPs; 2) selective serotonin reuptake inhibitors (SSRI), or 3) ace inhibitor, angiotensin receptor blocker, or calcium channel blocker (ACE/ARB/CCB). These medications were chosen for their expected favorable, unfavorable, and neutral effect on fracture risk. Adherence (medication possession ratio [MPR]) was assessed after 1 year of new use, updated every 90 days. Follow-up time for new fractures began after the MPR measurement and extended up to 4 years. Patients were categorized as highly adherent (MPR>=80%) vs. less adherent (MPR<50%). Cox proportional hazards models evaluated the association between high (vs. low) adherence within each medication group and fracture.

Results: We identified a BP cohort (11,712 patients, mean age=75), SSRI cohort (5,570 patients, mean age=76), and ACE/ARB/CCB cohort (5,731 patients, mean age=77) who initiated these therapies <=6 months after fracture. For these 3 cohorts, 46%, 43%, and 53%, respectively, had MPR >=80% at 12 months.

Crude hazard ratios for hip and non-vertebral fractures (Table) showed that high adherence (vs. lower adherence) with BPs decreased fracture risk; high adherence with SSRIs increased hip fracture risk, and high adherence with ACE/ARB/CCBs was neutral toward fracture risk.

Table. Relationship between High (vs. Lower) Adherence to Bisphosphonates, SSRIs, and ACEI/ARB/CCBs

	Bisphosphonates		SSRIs		ACEI/ARB/CCB	
Fracture Type	N, rate per 100py	HR (95% CI)	N, rate per 100py	HR (95% CI)	N, rate per 100py	HR (95% CI)
Hip, adherent	48, 0.5	0.56	47, 1.4	1.42	288, 1.2	1.15
Hip, non-adherent	84, 1.0	0.39–0.80	40, 1.0	0.93–2.17	187, 1.0	0.74–1.77
Nonvertebral, adherent	495, 5.6	0.76	226, 6.7	1.01	54, 6.3	1.05
Nonvertebral, non-adherent	635, 7.3	0.68–0.86	271, 6.6	0.85–1.20	32, 6.0	0.87–1.26

Conclusion: In this observational analysis of women enrolled in a commercial health plan, we did not find evidence of a healthy adherer effect that suggested that medication adherence itself conferred fracture benefit. Based upon this result, observational analyses evaluating the association between osteoporosis medication adherence and fracture risk appear to not be meaningfully confounded by the healthy adherer effect.

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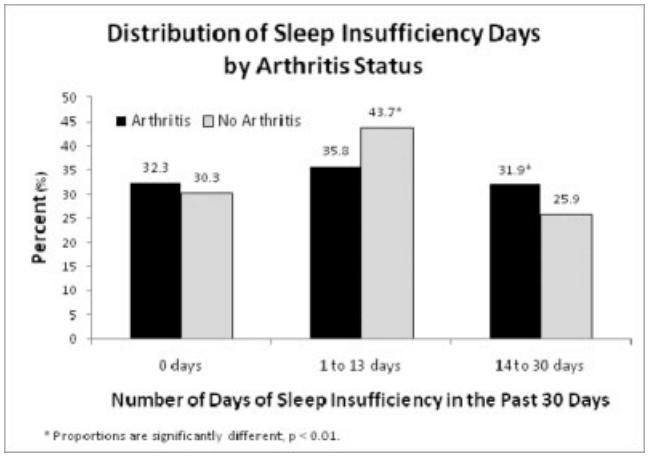
Physical Activity and Frequent Sleep Insufficiency Among US Adults with Arthritis. Jennifer M. Hootman[1], Dianna Carroll[2], Lela McKnight-Eily[2] and Kelli D. Allen[3]. [1]Centers for Disease Control and Prevention, Kennesaw, GA, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]Duke and Durham VA Medical Center, Durham, NC

Background/Purpose: Sleep problems occur in 30–80% of adults with arthritis. Physical activity may be a non-pharmaceutical approach to improving sleep. The purpose of this study was to assess the prevalence of sleep insufficiency and its association with physical activity (PA) level among adults with self-reported doctor-diagnosed arthritis (ARTH).

Methods: Using the 2009 Behavioral Risk Factor Surveillance System (BRFSS, n=424,592; n=153,914 with ARTH) we calculated moderate-intensity-equivalent minutes/week (2*vigorous min/wk + moderate min/wk) of self-reported PA for each respondent. Three PA levels were defined as: Active (ACT) (≥150 min/wk), insufficiently active (INSUF) (>10 – 149 min/wk), and inactive (INACT) (no PA for at least 10 min/wk). Frequent sleep insufficiency (FSI) was defined as reporting not getting enough sleep or rest for 14 or more days in the past 30. Weighted prevalence estimates (%) and 95% confidence intervals (CI) were calculated accounting for the complex sample design. Multivariable logistic regression models (adjusted odds ratios, AOR) were used to assess the association between PA level (INACT = referent) and FSI among adults with ARTH.

Results: Among adults with arthritis, 32% reported 0 days, 36% 1–13 days, and 32% 14+ days (adults without arthritis 30%, 44%, and 26% respectively). [FIGURE] The prevalence of FSI was significantly higher (p<0.0001) among adults with ARTH (31.9%, CI 31.5–32.4) compared to adults without ARTH (25.9%, CI 25.6–26.3). Among adults with arthritis, FSI prevalence decreased as PA level increased (39.4% INACT, 31.1% INSUF, 29.9% ACT, p<0.0001). Compared to INACT, INSUF (crude OR=0.71, CI 0.67–0.75) and ACT (crude OR=0.75, CI 0.71–0.80) PA levels were associated with lower odds of FSI. These adjusted associations remained statistically significant (INSUF AOR=0.89, CI 0.84–0.95; ACT AOR=0.83, CI 0.77–0.89) after adjustment for demographic variables (age, sex, race/ethnicity, education), health status variables (body mass index, self-rated health, arthritis-attributable activity limitation, joint pain) and co-morbid conditions (diabetes, hypertension, heart disease, asthma, frequent mental distress).



Conclusion: 1 in 3 adults with ARTH report FSI. Adults with ARTH meeting ACT levels of PA were 17% less likely to report FSI than INACT, suggesting physical activity may be a promising strategy to decrease FSI in this population. These findings need to be verified in prospective studies.

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Severe Foot Pain, but Not Milder Foot Pain, Is Linked to Falls in Older Men and Women: The Framingham Study. Alyssa B. Dufour[1], Virginia A. Casey[2], Thomas J. Hagedorn[2], Jody L. Riskowski[2] and Marian T. Hannan[3]. [1]Hebrew SeniorLife & Boston Univ, Boston, MA, [2]Hebrew SeniorLife, Boston, MA, [3]Hebrew SeniorLife & Harvard Med Sch, Boston, MA

Background/Purpose: Studies suggest that chronic pain is a risk factor for falls, but less is known about the effects of site-specific pain on the risk of falls. As foot pain is common and potentially affects physical function, the purpose of this study was to examine the association between severity of foot pain and falls in older adults.

Methods: Between 2002 and 2008, a validated examination was used to collect information on foot pain in Framingham Study Offspring cohort and Original cohort members. 2372 subjects who had information on foot pain and falls were included in this analysis. Foot pain (y/n) was queried: "on most days, do you have pain, aching or stiffness in either foot?" Foot pain severity was recorded as: no foot pain (referent), mild pain, moderate pain or severe pain. Subjects were asked if they had accidentally fallen

and hit the floor or ground in the past year (y/n). If a fall had occurred, the number of times they had fallen in the past year was queried. If 2 or more falls were reported, the participant was categorized as a recurrent faller (y/n). Information on falls was obtained from the Framingham exam within 1 year of the foot examination. For those missing falls information within 1 year, data from the most recent, previous or subsequent exam was used. Age (years) and body mass index (BMI, kg/m^2; categorized <25, 25–30, 30–35, 35+) were also collected. Logistic regression was used to calculate odds ratios and 95% confidence intervals for the association between falls (y/n) or recurrent falls (y/n) and foot pain (y/n or severity), adjusting for age, BMI categories, and cohort origin (Framingham offspring and original cohort).

Results: In the 2372 participants (1042 men; 1330 women), mean age was 68 yrs (± SD of 11) and mean BMI was 28 kg/m^2 (± SD of 5). Of the 522 participants reporting foot pain, 16% reported severe pain, 44% reported moderate pain and 40% reported mild pain. 20% of subjects reported falling in the past year, with 6% of fallers reporting recurrent falls. Foot pain (yes/no) was not associated with falls (y/n) or with recurrent falls, but foot pain severity revealed significant associations (Table). Severe foot pain vs. no pain was associated with a 2-fold increased risk of falls (p=.02) and 3-fold increased risk of recurrent falls (p=.001), even after adjustment for covariates. Moderate vs. no foot pain showed an increased risk of both falls and recurrent falls, although not statistically significant, with odds ratios of 1.3 (p=.18) and 1.5 (p=.14), respectively. Subjects reporting mild foot pain had no reported difference in falls from those with no foot pain.

Table. Odds ratios and 95% confidence intervals for the association between foot pain and falls, adjusting for age, BMI and cohort.

	n (%)	Fallen in past year	Recurrent faller (2+)
Foot pain (y/n)	522 (22)	1.11 (0.87, 1.42)	1.42 (0.97, 2.10)
Severity			
No foot pain	1850 (78)	1.0	1.0
Mild foot pain	208 (9)	0.88 (0.60, 1.30)	0.81 (0.40, 1.63)
Moderate foot pain	234 (10)	1.25 (0.90, 1.74)	1.48 (0.88, 2.47)
Severe foot pain	80 (3)	1.78 (1.09, 2.93)	2.94 (1.53, 5.68)

Conclusion: Foot pain alone does not contribute to falls in older people, but severe foot pain increases the odds of falling. Older men and women with foot pain should seek medical treatment early on, in order to prevent the foot pain from progressing and potentially to prevent a fall. Future work will examine foot pain and interventions upon new occurrence of falls.

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A Prospective Study of Alcohol Consumption and Risk of Rheumatoid Arthritis. Bing LU[1], Daniel H. Solomon[1], Karen H. Costenbader[2] and Elizabeth W. Karlson[2]. [1]Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background/Purpose: Several case-control studies suggested that moderate alcohol consumption may reduce risk for RA. However, early symptoms of RA may change alcohol intake and assessing alcohol after RA onset may thus over-estimate the effect of alcohol exposure. No published studies have assessed the association between repeated assessment of alcohol consumption over many years and future RA risk in the setting of a large prospective cohort study.

Methods: The Nurses' Health Study (NHS) was started in 1976, enrolled 121,700 registered female nurses aged 30–55 years from 11 US states, Lifestyle and environmental exposures and outcomes are collected through biennial questionnaires. Alcohol consumption was assessed on the food frequency questionnaire (FFQ) that was completed every 4 years, from 1980 through 2006. Among the 95,516 women who completed the FFQ at baseline, women who reported prevalent RA or other connective tissue disease were excluded and the diagnosis of incident RA through 2006 was confirmed using the connective tissue disease screening questionnaire and medical record review for the American College of Rheumatology criteria. We assessed the exposure variable using cumulative average alcohol consumption. We excluded the most recent record of alcohol intake and calculated the cumulative average alcohol including all other alcohol measures prior to RA onset. We categorized alcohol consumption into 5 groups (none, <5g/d, 5–9 g/d, 10–19 g/d, ≥20g/d). The estimated alcohol content of each alcohol beverage was 13.2 g per bottle or can of beer, 10.8 g per glass of wine, and 15.1 g per standard drink of liquor. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HR), after adjusting for age, smoking, body mass index, menopausal status, hormone use, parity and breastfeeding.

Results: 718 incident cases of RA developed during 2,340,730 person-years of follow-up. The incidence rates of RA were 31, 30, 26, 33 and 34 /100,000 person-years across increasing levels of cumulative alcohol consumption (Table). After adjusting for other potential confounding factors, women who drank <5 grams alcohol per day had a 20% reduced risk of developing RA compared to women who did not drink any (P=0.022) (Table). Among women who drank 5–10 grams alcohol per day, the risk was reduced by 37% (p=0.001). Higher levels of alcohol consumption (≥20 grams per day) were not protective against the development of RA.

Table. Alcohol consumption and risk of RA

Alcohol (gram/day)	No. Cases/ Person-Yrs	Crude Incidence*	HR (95% CI)†	P
None	152/484365	31	1.00	
<5	323/1064692	**30**	0.80(0.66,0.97)	**0.022**
5–9	86/324905	**26**	0.63(0.48,0.83)	**0.001**
10–19	98/293966	33	0.89(0.68,1.15)	0.360
≥20	59/172802	34	0.85(0.62,1.15)	0.288

* Per 100,000 person-years.
† Adjusted for age, smoking, BMI, menopausal status, hormone use, parity and breastfeeding.

Conclusion: In this long-term prospective cohort study of women, with alcohol intake data collected many years prior to the onset of RA, evidence of a protective association between low levels (1–9 grams per day) of alcohol intake and risk of developing RA was found. Higher levels of alcohol intake were not protective. Future studies are needed to confirm and investigate the mechanism of this effect.

2545

Baseline Co-Morbidities Predict Risk of Infection in An Inception Cohort of Rheumatoid Arthritis Patients Receiving Anti-Tumor Necrosis Factor Therapy. Joanne Homik[1], Nguen Xuan Thanh[2], Arto Ohinmaa[1], Cheryl CM Barnabe[3], Liam Martin[3], Susan G. Barr[3] and Walter P. Maksymowych[1]. [1]University of Alberta, Edmonton, AB, [2]Institute of Health Economics, Edmonton, AB, [3]University of Calgary, Calgary, AB

Background/Purpose: To evaluate the frequency of serious infections in Rheumatoid Arthritis (RA) patients treated with anti-Tumor Necrosis Factor (anti-TNF) therapy, associated costs and predictors of developing a serious infection

Methods: RA patients treated with anti-TNF therapy between January 2004 and March 2009 were followed prospectively in our biologics program to assess treatment efficacy and adverse events. Clinical and self-reported data were linked with provincial health care administrative databases. Infections were identified by using ICD 9 and 10 diagnosis codes and categorized as serious if there was an associated hospitalization. We used multivariate Cox-regression to assess independent predictors of the risk of infection and multivariate linear regression to assess independent predictors of infection-related costs.

Results: The cohort consists of 1,086 patients (70% female, mean age of 54 years) with a mean follow-up time of 2.3 years. Seventy percent of patients (n=764) reported an infection during follow-up, while 4% (n=42) suffered a serious infection, for an incidence density rate of 1.67 per 100 patient years of follow up. The most common infections in decreasing order of frequency were bronchitis, cellulitis, sinusitis, cystitis and upper respiratory infections. Compared to patients who remained on their first anti-TNF agent(n=731), patients who switched to another anti-TNF (n=212), patients on DMARD alone (n=75), and patients switched from DMARD to anti-TNF therapy (n=68) had similar Hazard Ratios (HR) (p>0.05) for both any and serious infections. In the cohort of patients on their first anti-TNF agent, the specific agent used did not predict risk of infection. Pre-existing lung disease (HR=1.99, p=0.001), underlying anemia (HR=3.31, p=0.030) and diabetes (HR=1.57, p=0.034) were associated with increased infection risk, while male sex was protective (HR 0.81, p=0.039). There was a trend for greater risk of infection in those patients with a higher

baseline DAS score (HR=3.89, p=0.072), and reduced risk in patients with university level education (HR=0.36, p=0.066).In linear regression, costs were significantly associated with higher baseline HAQ score (p<0.001), longer disease duration (p=0.005) and for those patients who required a switch between anti-TNF agents for inefficacy or adverse events (p=0.043).

Conclusion: Certain pre-existing co-morbidities, such as lung disease, diabetes, and underlying anemia significantly increased the risk of infection. The incidence density rate of serious infections was low (1.67 serious infections per 100 patient years), especially in patients who remained on their first anti-TNF agent (1.35 per 100 patient years) and is lower than reported in other cohorts. The risk of any or serious infection did not differ significantly between specific anti-TNF agents. Healthcare costs due to infections were associated with higher baseline HAQ score, longer disease duration at baseline and switching between anti-TNF agents.

2546

Giant Cell Arteritis Is Associated with An Increase in Both All-Cause and Cardiovascular Mortality. Gunnar Tomasson[1], Johannes Bjornsson[2], Michael P. LaValley[3], Yuqing Zhang[1], Vilmundur Gudnason[4] and Peter A. Merkel[1]. [1]Boston University School of Medicine, Boston, MA, [2]Landspitali University Hospital, Reykjavik, Iceland, [3]Boston University School of Public Health, Boston, MA, [4]The Icelandic Heart Association, Kopavogur

Background/Purpose: Although patients with giant cell arteritis (GCA) have a well-documented risk of involvement of vital arteries and exposure to high doses of glucocorticoids, most epidemiologic studies have found no association of GCA with increased mortality. The objective of this study was to determine the association of GCA with all-cause mortality and cardiovascular mortality (CVM) in a well-defined population cohort with detailed information on cardiovascular risk factors.

Methods: Data from the Reykjavik Study (RS), a population-based, prospective cohort study with a primary focus on cardiovascular disease, were used. All persons born in 1907–1935 that were living in Reykjavik, Iceland or in adjacent communities on December 1, 1967 were invited to participate. Subjects came for a study visit in 1967–1996 and information on cardiovascular risk factors: smoking habits, blood pressure, diabetes, body mass index, and serum cholesterol was obtained in a protocolled manner. Temporal artery biopsies (TAbx) were identified for all subjects in the RS in all three pathology laboratories in Iceland during the period 1961–2009. All TAbx were re-examined in a protocolled and blinded fashion by a single pathologist with expertise in vascular pathology. Subjects met exposure criteria for GCA at the date on which a TAbx diagnostic of GCA was obtained. In the RS, there was continuous surveillance for vital status and CVM, defined as death from cardiovascular disease according to death certificates, until December 31, 2008. Cox proportional hazards regression models with GCA status included as a time-varying predictor were used; subjects with GCA were considered unexposed until the time they met exposure criteria. Adjustments were done for age and sex with additional adjustment for cardiovascular risk factors in the analysis of CVM.

Results: 19,360 subjects participated in RS, of whom TAbx was performed in 731 subjects (3.8%) prior to December 31, 2008. TAbx was diagnostic for GCA in 206 subjects. The 12 subjects who had a TAbx diagnostic of GCA prior to their RS study visit were excluded from this analysis. Therefore, 19,348 subjects were included: mean age 53.5 years (sd): 9.7); 51.9% female. The 194 subjects with GCA had a mean age at diagnosis of 73.2 years (sd: 6.9, range 55.3–90.0) and 70.7% were female. The median time from study visit to diagnosis of GCA was 19.0 years (inter-quartile range (IQR): 13.3–24.1). Median follow-up time was 26.1 years (IQR: 18.4–33.6). During the follow-up time, 11,392 of 19,348(58.9%) subjects died, including 111 out of 194 (57.2%) with GCA. Subjects with GCA had an increased risk of mortality after adjustment for age and sex with HR = 1.46 (95% CI: 1.21–1.74). During the follow-up time, 5,000 of 19,348(25.8%) subjects died from cardiovascular disease, including 54 of 194 (27.8%) with GCA. Subjects with GCA had an increased risk of CVM, HR=1.59 (95% CI: 1.22–2.08). This effect estimate was not attenuated after adjustment for cardiovascular risk factors: HR=1.55 (95% CI: 1.18–2.04).

Conclusion: Compared with the general population, patients with biopsy-proven GCA have a shortened life span, and increased mortality from cardiovascular disease after adjustment for traditional cardiovascular risk factors.

ACR REF Special Session

ACR REF Edmond L. Dubois, MD, Memorial Lectureship: "Interfering" with Vascular Health: How Innate Immunity Promotes Premature Organ Damage in Systemic Lupus Erythematosus

Tuesday, November 8, 2011, 4:30 PM–6:00 PM

2547

Type I Interferons Modulate Vascular Function and Repair, Thrombosis and Plaque Progression In Murine Models of Lupus and Atherosclerosis. Mariana J. Kaplan. University of Michigan Rheumatology, Ann Arbor, MI

Background/Purpose: SLE patients develop premature atherosclerosis not explained by the Framingham paradigm. Subclinical cardiovascular disease (CVD) in SLE is characterized by endothelial dysfunction, an imbalance of vascular damage and endothelial repair, a prothrombotic milieu and atherosclerotic plaque. Evidence from in vitro studies indicates that type I Interferons (IFNs) play a prominent role in increased CV risk in SLE. We now examined in vivo evidence for a role of type I IFNs in endothelial dysfunction, aberrant vascular repair, thrombosis and atherosclerosis in murine models of lupus and atherosclerosis.

Methods: Lupus prone NZM2328 mice (NZM) and atherosclerosis-prone ApoE knockout mice (ApoE−/−) were compared to mice lacking type I IFN receptor (INZM and ApoEIFNR−/−, respectively) in their endothelial vasodilatory function, neoangiogenesis on a matrigel assay, time to clot after carotid photochemical injury and atherosclerotic plaque development. Similar experiments were performed when NZM and ApoE−/− received an IFN-α-containing adenovirus (IFN-AD) or control-AD. Lipids and proinflammatory HDL (piHDL) were quantified.

Results: Loss of type I IFN signaling improves aortic endothelial-dependent vasorelaxation, leads to increases in endothelial progenitor cell (EPC) numbers and function and improves in vivo neoangiogenesis in lupus-prone mice, independent of disease activity. Further, acute exposure to IFN-α decreases endothelial function and repair in lupus-prone and non-lupus prone mice. ApoEIFNR−/− display decreased atherosclerotic burden, while acute administration of IFN-α to ApoE$^{-/-}$ and NZM mice promotes a prothrombotic milieu. Furthermore, Type I IFNs alter lipid levels and piHDL, promoting a proatherogenic environment.

Conclusion: Type I IFNs play a key role in endothelial dysfunction, impaired vascular repair, atherothrombosis and aberrant lipid profiles in murine SLE. These results support a prominent role for type I IFN responses in accelerated atherosclerotic disease and acute coronary events in SLE patients and, potentially, in the general population.

2548

TLR7 Overexpression Drives Autoantigen-Mediated Expansion of Transitional and Follicular B Cells Independently of Type I IFN Signals. Natalia V. Giltiay. Department of Immunology, University of Washington, Seattle, WA

Background/Purpose: Loss of B cell tolerance plays a key role in the development of systemic lupus erythematosus (SLE). Toll-like receptor 7 (TLR7) is an intracellular TLR, specialized in the recognition of ssRNA and is highly expressed by plasmacytoid dendritic cells (pDC) and by B cells. Recent studies suggest that dual engagement of the B-cell receptor (BCR) and TLR7 by endogenous RNA and/or RNA-associated proteins promotes the activation of autoreactive B cells and drives the production of pathogenic anti-RNA Abs. Mice that overexpress TLR7 (TLR7Tg mice) develop SLE-like disease, characterized by increased numbers of myeloid cells and B cells, production of anti-nuclear autoantibodies and increased type I interferon (IFN). The main goal of our study was to define how TLR7 expression affected peripheral B cell development and to reveal the sites were self-reactive B cells are activated by RNA-associated antigens.

Methods: TLR7.1Tg mice were crossed to IRFNaRI-KO or to RNaseTg mice. Analysis of splenic B cell subsets was performed by multicolor flow cytometry. Cell proliferation was quantified by intracellular BrdU staining. Cell apoptosis was measured by Annexin V staining. Mixed bone marrow chimeras (BMC) were generated using allotype marked bone marrow cells.

Results: Young (8–10 week-old) TLR7Tg mice demonstrated significant abnormalities in B cell maturation: both transitional T1 and T2 B cells were increased by 1.5–2 fold; follicular (Fo) B cells by 3–4 fold, whereas the numbers of MZ B cells decreased with age. In vivo BrdU

labeling revealed that 15.4±8 % of the TLR7.Tg transitional B cells (compared to 1.2 ±0.8 in WT) were actively proliferating. TLR7 Tg mice also had increased numbers of apoptotic transitional B cells compared to WT mice suggesting both increased activation as well as negative selection at this B cell checkpoint. In BMC experiments, the persistent activation in T1 cells and their maturation towards Fo B cells in TLR7 Tg but not WT derived B cells indicated that B cell abnormalities were cell intrinsic. When TLR7Tg were crossed to RNaseTg mice, the number of T1 B cells was reduced 2-fold suggesting that RNA-associated antigens drive the expansion of these cells. TLR7 Tg mice that could not respond to type 1 IFN, demonstrated a partial reversion of the splenomegaly and myeloid cell expansion, but no significant effect on the expansion of T1, Fo or CD138+ B cells. In contrast, IFNaRI deficiency resulted in restoration of the MZ B cell population in TLR7Tg mice.

Conclusion: Increased expression of TLR7 causes proliferation and death of early transitional B cells with the net consequence of a B cell intrinsic, type 1 IFN independent, expansion of the transitional and follicular populations. Type 1 IFN does however regulate the MZ B cell population either by promoting egress of this B cell subset into the follicles or by influencing survival. Since overexpression of RNase significantly reduced the numbers of T1 B cells in TLR7Tg mice, it appears that RNA-associated antigens drive their expansion. These results therefore help to define the maturational stages at which activation of TLR7 in peripheral B cells impact B cell fate and also the role of autoantigen and IFN in this process.

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2549

Dual Regulation of IRF4 Function in T- and B-Cells Is Required for the Coordination of T-B Interactions and the Prevention of Systemic Autoimmunity. Alessandra Pernis. Hospital for Special Surgery, New York, NY

Background/Purpose: Effective humoral responses to protein antigens require the precise execution of carefully timed differentiation programs in both T and B cell compartments. Disturbances in this process underlie the pathogenesis of many autoimmune disorders including Systemic Lupus Erythematosus (SLE). Interferon Regulatory Factor 4 (IRF4) is induced upon the activation of T and B cells and serves critical functions in both T and B cells. In $CD4^+$ T helper cells, IRF4 plays an essential role in the regulation of IL-21 production while in B cells it controls class switch recombination and plasma cell differentiation. IRF4 function in T helper cells can be restricted by its interaction with a negative regulator termed Def6, a molecule that shares a high degree of homology with only one other protein, SWAP-70. While naïve T helper cells only express Def6, B cells express both Def6 and SWAP-70. Here we investigated the effects of the lack of both Def6 and SWAP-70 on immune responses.

Methods: Mice deficient in Def6 (on a C57/BL6 background) were crossed with mice deficient in SWAP-70 (also on a C57/BL6 background) to generate mice doubly deficient in Def6 and SWAP-70 (DKO mice). An extensive analysis of young and aged DKO mice was then performed. This analysis included an evaluation of the composition of lymphoid organs by flow cytometry and immunohistochemistry, an assessment of the ability of DKO mice to respond to T-dependent antigens and a thorough investigation of the presence of autoimmune features including the production of autoantibodies and the development of glomerulonephritis.

Results: We found that, on a C57BL/6 background, the absence of both DEF6 and SWAP-70 leads to the spontaneous development of age-related lymphoproliferation, autoantibody production, and glomerulonephritis. Similarly to human SLE, the disease preferentially affected the female gender. The lupus-like disease observed in the DKO mice is marked by the simultaneous deregulation of IL-21 production by T helper cells and increased IL-21 responsiveness by B cells. In the presence of aberrant IL-21 production by DEF6-deficient T cells, the absence of both DEF6 and SWAP-70 in B cells results in exaggerated AID expression, GC formation, and plasma cell differentiation. The B cell abnormalities in these mice are associated with an enhanced ability of IRF4 to access the regulatory regions controlling the expression of AID and Blimp-1. Interestingly, we show that DEF6 and SWAP-70 are differentially employed at distinct stages of B cell differentiation to selectively control the ability of IRF4 to drive the expression of specific target genes.

Conclusion: These studies suggest that DEF6 and SWAP-70 are two structurally and functionally related components of a complex molecular network aimed at ensuring the proper coordination of T and B cell interactions and at preventing the development of systemic autoimmunity.

2550

BAFF/APRIL Inhibition Induces Negative Selection of Naïve Autoreactive B Cells but Does Not Prevent Positive Selection of Autoreactive B Cells in the Germinal Center. Anne Davidson. Feinstein Institute for Medical Research, Manhasset, NY

Background/Purpose: Our goal was to use the anti-DNA heavy chain site directed transgenic glD42 model to analyze the checkpoints for autoreactive B cell selection in autoimmune NZB/W mice. Regulation of transgenic B cells in non-autoimmune glD42 mice is achieved by clonal deletion at the pre-B to immature B cell stage, clonal anergy and receptor editing. Autoreactive hybridomas obtained following LPS stimulation of spleen cells from these mice use a diverse light chain repertoire and have a low affinity for DNA. When the same transgene is introduced into NZB/W mice, tolerance to DNA is broken and high affinity IgG anti-DNA antibodies appear in the serum with age. Whereas the naïve repertoire in NZB/W glD42 heavy chain mice is heavily skewed towards expression of glD42/Vk4–55, a combination that confers only low affinity autoreactivity, nearly all spontaneous IgG anti-DNA antibody producing hybridomas from use the original D42 light chain Vk16–104 (VkRF) that confers high affinity anti-DNA activity.

Methods: B cell subsets from transgenic mice were characterized by flow cytometry and the Vk repertoire of each subset was analyzed by single cell PCR. Expression of the glD42 heavy chain and the VkRF light chain was quantified in B cell subset cell pellets using real-time PCR. Light chains of interest were cotransfected with the glD42 heavy chain into 293 cells and the autospecificity of the resultant antibody determined by ELISA.

Results: Using single cell PCR we first showed that the generation of glD42/Vk4–55 and glD42/VkRF/Jk5 expressing B cells occurs in the bone marrow. There was positive selection of cells expressing light chains that conferred low affinity autoreactivity (including Vk4–55) into the naïve repertoire and counter-selection of these light chains in the germinal centers. In contrast, despite robust negative selection of glD42/VkRF/Jk5 expressing B cells in the bone marrow and transitional B cell stages, positive selection and expansion of rare autoreactive B cells expressing glD42/VkRF/Jk5 occurred in the germinal centers. Several other light chains with high affinity autoreactivity were also selected into the germinal centers. We then determined the effect of limiting BAFF using a 50:50 bone marrow chimera system in which competition from non-autoreactive B cells was provided. Competition significantly inhibited selection of glD42 expressing B cells into the naïve B cell repertoire such that only 4% of follicular B cells used the transgene; selection of naïve transgenic B cells was further inhibited by BAFF/APRIL blockade using TACI-Ig. TACI-Ig did not however inhibit selection of high affinity autoreactive B cells into the class switched repertoire which was still dominated by glD42/VkRF/Jk5 and the mice developed high serum titers of autoantibodies with only a 2 week delay.

Conclusion: These findings in sum show that despite a significant effect of BAFF inhibition on the survival of naïve autoreactive B cells, a major breach in B cell tolerance in NZB/W mice is at the germinal center checkpoint and this is not altered by BAFF/APRIL inhibition. These findings help explain why BAFF inhibition only modestly decreases titers of IgG autoantibodies in lupus mice or SLE patients.

2551

CD4+ Cells Generated with TGF-β and All-Trans Retinoic Acid From Naïve CD4+ Cells Isolated From Lupus Mice Suppress Lupus in Mice. Song G. Zheng. USC Keck School of Medicine, Los Angeles, CA

Background/Purpose: Substantial evidence exists that TGF-β can convert conventional T cells isolated from normal mouse T cells to become Foxp3+ regulatory T cells. However, it is unclear whether TGF-β also converts T cells from lupus-prone mice to become Treg cells once these mice have developed lupus. Recent studies have demonstrated that all-trans retinoic acid (atRA), an active Vitamin A derivative can promote Tregs and inhibit Th17 cell production. We hypothesize that atRA will enhance the development of TGF-β induced Foxp3+ CD4regs

in mice with fully established lupus and enable them to have protective effects *in vivo.*

Methods: Naïve CD4+ cells isolated from NZB/W F1 young mice (<8 weeks) that typically expressed proteinuria (>24 weeks) were stimulated with anti-CD3/CD28 beads and IL-2 (control cells), + TGF-β (Treg cells), + atRA and TGF-β (atRA+TGF-β induced Treg) for 4–5 days. Surface and intracellular staining for CTLA-4, CD62L, CD103, CD122, GITR, TGF-β, CCR9 and $\alpha_4\beta_7$ was examined by flow cytometry. Suppressive activity *in vitro* was examined by adding various ratios of iTreg subsets to responder T cells labeled with CFSE and/or B cells from young or old mice. The cells were stimulated with anti-CD3 antibody in the presence of antigen-presenting cells (APC) isolated from young or old mice. The T cell proliferation was judged by the dilution of CFSE and antibody production by ELISA. *In vivo* protective activity was tested by transferring 5×10^6 various conditioned iTregs to young (8 week-old) or old (24 week-old) NZB/W F1 mice. IgG and anti-DNA in sera was analyzed with ELISA. Proteinuria and survival were monitored. Renal histopathology and IgG deposition were also assessed with H&E and immunoflorence staining.

Results: We found that TGF-β induced >50% naïve CD4+ cells from young mice to become CD25+ Foxp3+ cells that developed strong suppressive activity *in vitro* and *in vivo*. Although these effects were significantly diminished in old mice, the addition of atRA to TGF-β restored Foxp3 expression by CD4+ cells and suppression of T cell proliferation and antibody production that comparable of young mice. These cells also suppressed the expression of CD69, CD80 and CD86, and the IgG production of B cells *in vitro*. These cells suppressed T and B cell responses from young and old mice equivalently. Unlike Tcon, or Tregs induced with TGF-β, a single transfer of 5×10^6 atRA+TGF-β induced Tregs from old mice to young or old B/W F1 mice markedly prevented increased IgG production, decreased anti-dsDNA autoantibodies, suppressed proteinuria and prolonged survival of these mice.

Conclusion: The combination of atRA and TGF-β is able to induce naïve CD4+ cells from mice with lupus nephritis to become CD4+Foxp3+ Treg cells that can prevent the onset of lupus and ameliorate established lupus. Thus, although endogenous Tregs in mice with active lupus fail to prevent progression of disease, syngeneic Tregs induced ex-vivo with the appropriate epigenetic agent have the potential to be used as an adoptive immunotherapy to control autoimmunity.

2552

The Constant Region Contributes to the Antigenic Specificity and Potential Pathogenicity of Anti-DNA Antibodies. Chaim Putterman. Albert Einstein College of Medicine, Bronx, NY

Background/Purpose: Anti-double stranded (ds) DNA antibodies play a key role in the pathogenesis of lupus nephritis. High affinity for DNA and cross-reactivity with particular renal antigens are among the factors associated with enhanced renal pathogenicity. In addition, certain IgG subclasses are particularly enriched in immunoglobulin eluates from kidneys with active lupus nephritis, suggesting that antibody isotype is another important feature determining the outcome of antibody binding to renal antigens. Although classically the variable region was believed to be the sole determinant of antigenic specificity, more recent studies have shown that isotype switching leads to altered binding of a protective antibody. Our hypothesis was that antibody isotype may affect the renal pathogenicity of anti-DNA antibodies, by influencing antigen binding.

Methods: The parent PL9–11 clone is an IgG3 anti-DNA antibody isolated from a MRL/+ mouse (1). To obtain IgG1, IgG2b and IgG2a forms of the original PL9–11 antibody that would share identical variable regions, the PL9–11 (IgG3) hybridoma clone was isotype switched in vitro by stimulation with IL-4 and TGF-β for 7 days, followed by soft-agar cloning and sib selection. The PL9–11 (IgM) variant was generated by cloning the PL9–11 variable region into an IgM expression vector, followed by transfection of the construct into a mutant cell line expressing only the light chain of the original PL9–11 hybridoma. The affinity and specificity of the PL9–11 antibody panel (IgM, IgG3, IgG1, IgG2a, IgG2b) were analyzed using ELISA, surface plasmon resonance (SPR), and cross-inhibition studies. Specificity for renal antigens was studied by binding to mesangial cells, isolated glomeruli, and glomerular proteome arrays. Finally, renal deposition and pathogenicity was assayed by analyzing kidneys of SCID mice injected intraperitoneally with each member of the PL9–11 antibody panel. Antibody concentrations were carefully normalized by ELISA and Western blotting.

Results: By ELISA, we found that PL9–11 and its isotype switched variants had differential binding to single stranded (ss)DNA, dsDNA, chromatin and mesangial cells in order of IgG3>IgG2a>IgG1>IgG2b>IgM. This order of relative affinities of the different IgG isotypes for dsDNA was confirmed in a competition ELISA. In contrast, in binding to Matrigel, laminin, and collagen IV the IgG2a isotype actually had the highest affinity, followed by IgG3>IgG1>IgG2b>IgM. In concert with ELISA assays, assessing antibody specificity in glomerular proteome arrays also revealed significant differences between the members of the PL9–11 panel in binding to multiple antigens. Analysis of SPR and renal histopathology following injection is pending.

Conclusion: Our data suggest that the constant region plays an important role in the affinity and specificity of anti-dsDNA antibodies, and that IgG2a and IgG3 isotypes may be more nephritogenic due to higher potential for binding to multiple glomerular and nuclear antigens.

Reference: 1) Losman, M. J., Fasy, T. M., Novick, K. E., and Monestier, M. Relationships among antinuclear antibodies from autoimmune MRL mice reacting with histone H2A-H2B dimers and DNA. *Int. Immunol.* 5: 513–523, 1993.

ARHP Concurrent Abstract Session
ARHP Research Methodology
Tuesday, November 8, 2011, 4:30 PM–6:00 PM

2553

Developmental Trajectories of WOMAC Knee Pain and Their Predictors Over 3 Years Among Subjects of Osteoarthritis Initiative. Bin Zhang[1], Uyen Sa D. Nguyen[2], Jingbo Niu[2] and Yuqing Zhang[2]. [1]Boston Univ School of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA

Background/Purpose: Pain from knee osteoarthritis (OA) is one of the most common reasons for seeking medical care. Little is known, however, about patterns of change in knee pain over time or the predictors of these pain trajectories. Identifying clusters of individuals with similar pain trajectories over time and the predictors associated with these trajectories will improve our understanding of the etiology of pain so that we can target appropriate intervention to specific groups of subjects whose knee pain are likely to worsen.

Methods: Knee pain severity was assessed at baseline and annually over three years using WOMAC pain questionnaires (0–20 scale) among the participants of the Osteoarthritis Initiative. We used group-based trajectory models, an application of the finite mixture modeling for time-based data, to identify distinctive trajectories of knees that follow similar patterns of pain over time. SAS macro *Proc Traj* was used to carry out the analyses and Bayes information criterion (BIC) was used to select the best model to balance model fitting and complexities. We then compared the baseline risk profiles among different trajectory groups using either $\chi 2$ test or one way ANOVA.

Results: Among 8802 subjects included in this analysis (58% women, mean age: 62, 17% of African Americas, mean BMI: 28.6 kg/m^2, mean WOAMC pain score: 2.3), we identified 8 distinctive trajectories of knee pain severity over 3 years (Figure, Table 1) based on BIC. Overall, the majority (89.5%, Groups 1, 2, 3, 6 and 8) of the individuals' knee pain did not change significantly over 3 years. About 3.3% of knees' pain severity (Groups 4 and 7) improved by > 90%, whereas 7.3% of knees' pain severity worsened (Group 5) by about 15% over 3-year period. Risk profiles were significantly different among the 8 groups. Compared with those who had higher baseline WOMAC pain score (Groups 4–8) subjects with lower scores (Groups 1–3) had fewer women and African Americans, lower prevalence of obesity, depression, and less moderate to severe ROA (Table 1). Of the three groups that had similar baseline WOMAC pain scores but had distinctive WOMAC trajectories (Groups 4, 6, 7), subjects in Group 6 had more African Americans, higher prevalence of obesity, major depressive symptom, and moderate and severe ROA(KL≥3) at baseline. Furthermore, fewer subjects in Group 6 had TKR than those in Group 4 and 7.

Fig. 1: Total WOMAC Knee Pain Trajectory Over Time

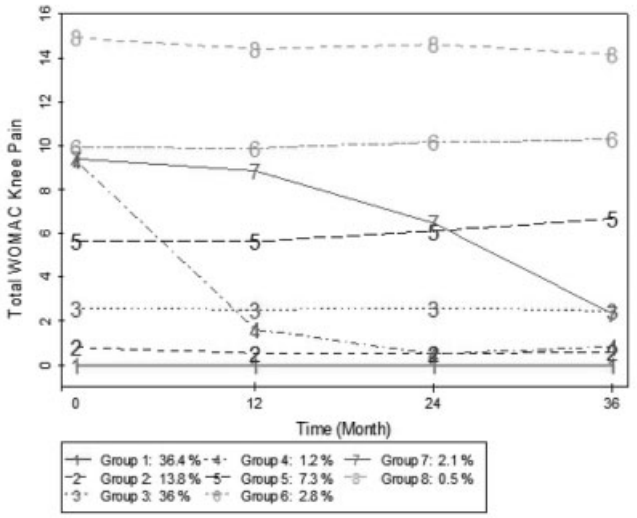


Table 1: Baseline Characteristics of Patient by WOMAC pain trajectory group

Baseline Variables	Group Membership							
	Low Baseline Pain			High Baseline Pain				
	1	2	3	4	5	6	7	8
N	2155	2541	2730	90	864	280	108	34
WOMAC Pain	0	1.0	2.7	10.2	5.9	10.1	10.2	15.3
Age	62	61	61	62	61	59	62	55
Female(%)	52	58	59	60	65	69	71	76
Race(AA %)	9	12	17	34	28	53	40	68
BMI≥30 (%)	26	32	40	48	51	61	55	62
Major Depression Symptom(%CES-D >21)	1.4	2.9	3.6	6.7	7.5	16.5	7.7	40
TKR (%)	0.6	1.1	2.4	6.7	5.0	4.3	18	0
K/L≥3 (%)	14	25	41	40	49	57	53	33

Conclusion: Our study demonstrated the different trajectory patterns of WOAMC pain among subjects with knee OA or at high risk of getting knee OA. The risk profiles for these distinctive trajectories are also different. Future studies should assess whether intervening on modifiable risk factors may change the trajectory of pain severity.

2554

Proteomic Identification of A Panel of Novel Osteoarthritis Biomarkers In Serum and Cartilage. Patricia Fernández-Puente[1], Jesús Mateos[1], Carolina Fernández-Costa[1], Valentina Calamia[1], Cristina Ruiz-Romero[1], Carlos Fernández-López[2], Natividad Oreiro[2] and Francisco J. Blanco[3]. [1]Osteoarticular and Aging Res. Lab. Proteomic Unit-Associated Node to Proteored. INIBIC-CHUAC, La Coruña, Spain, [2]Osteoarticular and Aging Res. Lab. Rheumatology INIBIC-CHUAC, La Coruña, Spain, [3]Osteoarticular and Aging Res. Lab. Proteomic Unit-Associated Node to Proteored/ Lab. Rheumatology Division INIBIC-CHUAC, La Coruña, Spain

Background/Purpose: Osteoarthritis (OA) is a degenerative joint disease that is characterized by cartilage destruction and bone changes, occasionally accompanied by synovial inflammation. A major objective for OA research is the conceptualization and development of early diagnostic strategies. The discovery of protein biomarker panels for early diagnosis, therapeutic purposes and management of several diseases is an area of interest in medicine. In the present work, we have quantitatively screened differential proteins in sera and cartilage from patients suffering OA at diverse stages. To attain this objective, a quantitative proteomics approach has been followed, which is based on peptide differential labelling with iTRAQ reagents and subsequent multidimensional LC-MS/MS analysis.

Methods: 150 serum samples were obtained from OA patients at different stages of the disease (grade II, grade IV and control donors). Cartilage samples were obtained from OA patients undergoing joint replacement and normal donors without history of joint disease. Proteins were extracted with Urea 6M, 2% SDS using a mixer mill. Proteins were quantified, digested with trypsin and differentially labelled with iTRAQ isobaric tags. The peptide mixture was separated by two-dimensional LC coupled to MALDI-TOF/TOF mass spectrometry. Identification and relative quantification of the proteins were performed using ProteinPilot 3.0 software.

Results: The proteomic approach enabled the identification of 349 different proteins in serum. 171 of them could be quantified by the calculation of their iTRAQ ratios, and three sets of proteins were found to be altered with statistical significance ($p<0.05$) in OA samples when compared to healthy controls: a group of 7 proteins were altered (either increased or decreased) specifically in early OA, whereas 14 were modulated only in advanced OA and 7 were modified in both stages. Although some of these proteins, such Cartilage Oligomeric Matrix Protein (COMP), have a previously reported putative biomarker value for OA, most of them are novel biomarker candidates of the disease. 263 proteins were identified in cartilage samples and 59 of them were differential in OA patients compared to control with a significative p-value. Identification and quantification of some of these proteins both in serum and cartilage from OA patients indicate their potential biomarker value for the pathology. The alteration of some proteins was detected in both types of samples. This was the case of cartilage oligomeric matrix protein, lumican, complement factor D or thrombospondin-1, which were all found to be increased in OA, whereas the cytoplasmic actin was decreased. Finally, a number of other proteins were identified as altered either in cartilage (thus increasing our knowledge of OA pathogenesis) or in serum (which have also potential biomarker value).

Conclusion: In summary, we have identified for the first time a panel of novel OA protein biomarkers present in serum and cartilage from human patients by a proteomic approach. The specificity and selectivity of these candidates should be verified in order to develop new molecular diagnosis or prognosis tests for OA.

2555

Development of the United Kingdom Evaluation of Daily Activities Questionnaire in Rheumatoid Arthritis using Rasch Analysis. Alison Hammond[1], Alan Tennant[2], Sarah Tyson[1], Ulla Nordenskiold[3] and Rachel Gill[1]. [1]University of Salford, Manchester, United Kingdom, [2]University of Leeds, Leeds, United Kingdom, [3]Sahlgrenska Univ Hospital, Goteborg, Sweden

Background/Purpose: The Evaluation of Daily Activity Questionnaire (EDAQ) is a patient reported measure of activity/activity limitations in Rheumatoid Arthritis (RA) (Nordenskiold et al 1996). The UK version includes 138 items in 14 activity of daily living and participation domains (Eating/Drinking; Personal Care; Dressing; Bathing; Cooking; Moving Indoors; House Cleaning; Laundry; Moving and Transfers; Communication; Moving Outdoors; Gardening/Household Maintenance; Caring; and Hobbies/ Leisure/ Social Activities). Each domain is split into two sections: one (A) which scores without aids, alternate methods or help; and another (B) which scores items with aids or alternate methods. All items are scored on a 0–3 scale (no difficulty to unable to do). Our aim was to identify if the UK-EDAQ fits the Rasch model in an RA cohort.

Methods: Participants were recruited from Rheumatology clinics. Data from each domain were assessed for initial unidimensionality by a Confirmatory Factor Analysis (CFA). Each domain was analysed separately for sections A and B (where section B overrides section A when applicable). A Root Mean Square Error of Approximation (RMSEA) of 0.10 and below (mediocre fit) was considered adequate as prepepartion for Rasch analysis. Rasch analysis involved testing stochastic ordering (fit); local independence (response dependency and unidimensionality) and properties of invariance across groups (gender, age and employment status: differential item functioning (DIF). RUMM2030 software was used.

Results: 383 people with RA participated: 286 women and 97 men; average age 60.38 (SD 11.18) years; RA duration 13.2 years SD 10.72; 118 (31%) were employed. Average pain (10 point VAS) = 4.99 (SD 2.59) and fatigue 5.61 (SD 2.53). CFA of the 14 domain sections (A&B) indicated unidimensionality after adjustment for local dependency (correlated errors) within each domain. All domains achieved RMSEA < 0.10. All domains satisfied Rasch model expectations after adjustments (by the use of testlets) for local dependency (Chi-square $p>0.05$). Virtually all items had ordered thresholds, and where this was not the case, the disordering was often marginal. Differential Item Functioning (DIF) by age, gender and employment status was also largely absent, with a few notable exceptions. For example, in the domain 'gardening and household maintenance' the item 'climbing ladders' showed significant DIF by age, with older people showing greater problems with this at any given level of the trait (ANOVA $p<0.05$).

Most domains showed a Person Separation Index reliability (PSI) consistent with individual use, even after adjustment for local dependency (PSI range 0.75–0.94). Where values were lower, this was largely a consequence of skewed data and the presence of a substantive floor effect which affects the PSI; whereas classical alpha values remained high. All domains supported strict unidimensionality.

Conclusion: Analysis of the UK- EDAQ support a 14 domain, two component structure (self care and mobility) where each domain, and both components, (independently for sections A and B) satisfy Rasch model requirements after adjustment for local dependency.

2556

Internet Versus Mailed Administration of the Health Assessment Questionnaire Disability Index. Bonnie Bruce[1] and James F. Fries[2]. [1]Stanford Dept of Medicine, Palo Alto, CA, [2]Stanford Univ Medical Center, Palo Alto, CA

Background/Purpose: The Health Assessment Questionnaire Disability Index (HAQ) is a validated paper/pencil patient reported outcome (PRO) instrument for assessing physical function in rheumatology using conventional administration modes. However, it is unknown whether internet administration would be equivalent to paper/pencil administration. We conducted a cross sectional study to compare the HAQ's response rates, item completion rates, and instrument scores between mailed and internet administration.

Methods: Participants with rheumatoid arthritis (RA) and osteoarthritis (OA) were drawn from four longitudinal cohorts. They were classified as Internet-Adept or Not-Adept based on internet experience and comfort. We allocated participants to three study arms (n=126 each) controlling for diagnosis and cohort membership: Adept participants were randomly assigned to complete the HAQ online (Arm 1) or by mail (Arm 2). Not-Adept participants completed the HAQ by mail (Arm 3). Both instruments were similarly formatted, contained a one-week timeframe, the same 20 items, four response options, and were scored 0–100 (100=worst functioning). Data were analyzed using chi-square tests of proportions, means±standard deviation, analysis of variance, and regression analyses controlling for age, gender, and education.

Results: Participants were White (94%), female (65%), had 16 education years ($p>0.05$), and averaged 72 years old. The Not-Adept participants (Arm 3) were older than their Adept (Arms 1 and 2) counterparts ($p<0.001$). There were no differences in response rates (>90%, all study arms) or number of missing items by administration mode ($p>0.05$). Unadjusted HAQ scores were statistically different among study arms ($p<0.001$), increasing with age. Age-adjusted scores were similar among modes and study arms ($p>0.05$).

Conclusion: The HAQ may be administered to RA and OA participants over the internet or by mail with confidence of equivalent results after consideration of age effects. These data provide reassurance that mail, internet, or mixed modes for PROs may each provide valid data after adjustment when necessary. Use of mixed modes with data pooling is likely to be used increasingly in the future, as they can increase study efficiency. These data suggest that valid data pools may result. We suggest, however, that studies report separate analyses by mode to control for inadvertent bias.

2557

Using A Novel Approach to Estimate Effects of Depression On Changes In Knee Pain Severity In Osteoarthritis Initiative. Ke Wang[1], Bin Zhang[2], David T. Felson[3] and Yuqing Zhang[3]. [1]Boston University, Boston, MA, [2]Boston Univ School of Medicine, Boston, MA, [3]Boston University School of Medicine, Boston, MA

Background/Purpose: In rheumatic studies some outcomes (eg. knee pain severity) are repeatedly measured in multiple joints using an ordinal scale. Since these outcomes can fluctuate over time, it is of great interest to identify risk factors that contribute to their fluctuations. Commonly used logistic or linear regressions which can analyze unidirectional change cannot work on this type of outcomes. Other methods such as multistate transition models extended from the Cox proportional hazard model require relatively precise time-to-event measurements, and thus are not suitable for large prospective community-based studies (such as OAI) with small numbers of visits over lengthy time intervals (eg. annual visits). Moreover, since outcomes are joint-specific, within-person correlations need to be accounted for.

We propose a multistate transition model that can appropriately estimate effects of risk factors on changes in an ordinal outcome during infrequent visits, accounting for within-person correlations. We apply the method to investigate depression's effect on fluctuation of knee pain severity.

Methods: Knee pain data are from OAI's four annual visits. The outcome is the time-varying knee-specific WOMAC pain score categorized into 3 levels: no pain (all grades=0), mild (max grade=1 or 2), and severe (max grade=3 or 4). A multistate Markov-chain transition model was used to estimate effects of covariates on transitions (change in levels) of the outcome. A first-order Markov property is assumed for the yearly-spaced observations. A transition happens if pain status changes over two consecutive visits. The predictor is depression status (CES-D score ≥ 16 vs. < 16) at each previous visit. Effect estimates are obtained for all possible transitions accounting for between-knee correlations using the robust covariance estimator and adjusting for age, sex, BMI, and race. Simulations were also carried out to compare results with and without accounting for correlations (results not shown).

Results: 9592 knees are included (mean age 61±9, BMI 29±5, 58% female, 18% black). As shown in Table, subjects with depression are more likely to have knee pain worsening, especially for a rapid progression from no pain to severe pain within one year: The odd is 1.4 times higher for progression from no pain to mild pain, 1.4 times higher for progression from mild to severe pain, and 3.3 times higher for progression from no pain to severe pain than those without depression. On the other hand, subjects with depression are less likely to have knee pain improvement, especially from severe pain to no pain.

Table: Effect of depression (CES-D ≥ 16) on changes in WOMAC pain:

	Previous \ Current	OR [95% CI]		
		No Pain	Mild	Severe
WOMAC Pain	No Pain	1.0 [Reference][1]	1.4 [1.1, 1.7]	3.3 [2.1, 5.1]
	Mild	0.7 [0.6, 0.9]	1.0 [Reference]	1.4 [1.1, 1.8]
	Severe	0.4 [0.2, 0.7]	0.6 [0.5, 0.9]	1.0 [Reference]

[1]A knee is in the reference group at a visit if pain severity does not change compared to the previous visit

Conclusion: We show that our multistate Markov-chain transition model is an appropriate method to analyze changes in a correlated longitudinal ordinal outcome. Results indicate persons with depression are more likely to have knee pain worsening and less likely to have pain improvement than those without depression.

2558

Relationship Between Accelerometer-Based Measures of Physical Activity and the Yale Physical Activity Survey in Adults with Arthritis. Pamela A. Semanik[1], Jungwha Lee[2], Larry Manheim[3], Loretta DiPietro[4], Dorothy D. Dunlop[3] and Rowland W. Chang[2]. [1]Rehabilitation Institute Chicago, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Northwestern Univ Med School, Chicago, IL, [4]George Washington University School of Public Health and Health Services, Washington, DC

Background/Purpose: A reliable, valid self-report measure of physical activity that has clinical applicability would be a valuable addition to providers' resources. This study evaluated the correlation between the Yale Physical Activity Survey (YPAS) indices scores and objective accelerometer measures of time spent in light, moderate-to-vigorous intensity physical activities (MVPA), and MVPA in bouts lasting at least 10 minutes.

Methods: This cross-sectional study analyzed baseline data from 171 persons with rheumatoid arthritis (RA) and 139 persons with osteoarthritis (OA) enrolled in a randomized clinical trial of a physical activity promotion intervention. Persons fulfilling the 1988 ACR criteria for RA and persons with symptomatic, radiologic knee OA (Kellgren-Lawrence Class > 2) wore an accelerometer for 7 days, then responded to the YPAS questionnaire, and questions regarding demographics (age, gender, and race) and health factors [BMI, disease status (HAQ/WOMAC), comorbidities, pain and function]. Spearman Correlation coefficients were estimated between each YPAS index score [Total Time Index (TTI), Energy Expenditure Index (EEI) and Activity Dimensions Summary Index (ADSI)] and accelerometer measures.

Results: Participants were primarily female (RA: 82%, OA: 58%), White (RA: 76%, OA: 58%), older (mean for RA: 55 years, OA: 63 years), and overweight (mean BMI RA: 28, OA: 31); some participants reported

co-morbidities that may have affected mobility (RA: 28%, OA: 24%), pain (mean HAQ pain for RA: 3.4 out of 0[best]-10[worst], mean WOMAC pain for OA: 5.6 out of 0[best]-20[worst]) and functional limitations (mean HAQ function for RA: 0.7 out of 0[best]-3[worst], WOMAC function for OA: 17.5 out of 0[best]-88[worst]). Mean disease duration was 13.5 years (SD= 10) for RA, and 11 years (SD=11) for OA. In the RA participants, the YPAS summary index having the strongest correlation with objective accelerometer measures was the ADSI, which was significantly correlated with Average Daily Minutes of Bouted Moderate/Vigorous Activity ($r = 0.51$), Average Daily Accelerometer Counts ($r = 0.45$), and Average Daily Minutes of Moderate/Vigorous Activity ($r = 0.43$). In OA participants, the YPAS ADSI was also significantly correlated with Average Daily Minutes of Bouted Moderate/Vigorous Activity ($r = 0.36$), Average Daily Minutes of Moderate/Vigorous Activity ($r = 0.31$), and Average Daily Counts ($r = 0.24$).

Conclusion: For both RA and OA groups, the YPAS ADSI, which is fast to both administer and score, had the strongest significant correlations with objectively measured physical activity, which supports the ADSI's use as a tool for clinical applications and in rheumatology research.

2559

Sexual Problems and Sexual Perception in Patients with Ankylosing Spondylitis. Anne Proven[1], Kari H. Berg[2], Elsa Almas[3], Espen E. Benestad[4] and Glenn Haugeberg[5]. [1]MD, Baerum, Norway, [2]MA, Kristiansand.S, Norway, [3]MA, Kristiansand, Norway, [4]MD, Kristiansand, Norway, [5]MD, PhD, Kristiansand.S, Norway

Background/Purpose: Ankylosing spondylitis (AS) is a chronic, systemic inflammatory rheumatic disease which most frequently affects the axial skeleton, but may also affect peripheral joints, tendons and internal organs. This disease which begins in the second or third decade may give rise to significant loss of function and impaired quality of life. Despite the importance of sexuality as part of quality of life, only a few studies have explored this important issue in AS patients. We therefore wanted to explore sexuality in patients with AS in regard to how satisfied they are with their sexual life and whether the patients think their sexuality is influenced by the disease.

Methods: This is a prospective, cross sectional study were patients with established AS seen in the outpatient clinic in three hospitals in the southern and eastern part of Norway, were asked to participate. A broad specter of demographic, clinical data, quality of life data, also including a general questionnaire on sexuality, was collected.

Results: At the end of 2008 105 patients had been included. The patient cohort contained of 66.7% men and 96.1% were HLA-B27 positive. The mean (SD) values for age was 46.2 (14.9) years and disease duration 15.5 (10.6) years. 23.8% patients were current users of biologics and 42.9% were current users of NSAIDs. Mean (SD) values was 3.3 (2.0) for BASDAI, 2.9 (2.2) for BASFI, 3.8 (2.4) for BAS-G, 2.6 (2.0) for BASMI and 0.58 (0.50) for HAQ. For ESR and CRP the mean values were 14.1 (14.5) mm/hr and 9.0 (11.2) mg/l, respectively.

On the sexuality scores 60.4% patients reported sex and sexuality important/very important to be satisfied with their daily life. 31.7% reported sexuality less important and only 7.6% thought sexuality was not important. 48.5% were satisfied/very satisfied with their sexual life while 29.3% were neither satisfied nor dissatisfied and 22.3% were dissatisfied. 49.5% reported to have had problems with their sexuality, however only 13% of the 105 patients had been seeking help to solve the problems. 32.4% of the patients thought their sexual problems were related to their disease, 11.4% in very high degree and 21% in some degree. The main causes of sexual problems from the disease were tiredness in 31.4%, stiffness in 30.5% and pain in 31.4%.

Conclusion: In this study of 105 patients with AS, as many as 49,5% reported to have had sexual problems, and 32,4% thought their sexual problems were related to their AS. The main causes of sexual problems were tiredness, stiffness and pain. We think the number of patients reporting sexual problems was high in this group since disease activity scores and health activity scores in this group was only modest high. More studies are needed to illuminate how sexual life is influenced by AS.

2559A

The Effect of Physician Communication on Treatment Adherence in Patients with Rheumatoid Arthritis. Maria F. Marengo[1], Richard L. Street Jr.[2], Sofia De Achaval[3], Hong Zhang[1], Marsha Richardson[4] and Maria E. Suarez-Almazor[5]. [1]UT MD Anderson Cancer Center, Houston, TX, [2]Texas A&M University, College Station, TX, [3]U.T. MD Anderson Cancer Center, Houston, TX, [4]UT MD Anderson, Houston, TX, [5]University of Texas. M.D Anderson Cancer Center, Houston, TX

Background/Purpose: Treatment adherence could be influenced by many factors. The physician-patient relationship is crucial in medical care. The objective of our study was to evaluate the effect of physician communication on treatment adherence in patients with Rheumatoid arthritis (RA).

Methods: This study was part of a 2– year prospective cohort of 201 patients with RA from 2 publicly-funded county hospitals. Patients' visits were audio typed at baseline and at 3 months. Information included: review of discussions on prescribed drugs, who initiated discussions (physician or patients), and physicians 'affective tone as determined by independent raters, who were graduate students in communication sciences, and followed structured protocol while listening to the audios. Affective tone was rated in the following categories: 'irritated', 'anxious', 'dominant', 'interested', 'friendly 'and 'empathetic'. Each category was scored from 1 to 5, were 1 was the absence of the tone quality, and 5 the highest possible value. The Compliance Questionnaire Rheumatology (CQR) was used to assess patients' adherence to prescribed drugs (score 0–100, where 100 is the most compliance).

Results: 74.6% were female, 52.7% Hispanic, 25% White and 21.4% African-American; mean age was 51y (±11.4), disease duration 7.5y (±5), CQR 70.3(±10.3). On baseline visit the scores of affective tone of interaction were ≤2 for irritated and anxious in 90%, 73%, respectively; and ≥4 for dominant, interested, friendliness or empathetic in 72%, 76%, 69%, and 54%, respectively. Discussions about drugs compliance was initiated by the doctor in 88% of cases. At 3 months there was a significant relationship between increased adherence to prescribed drugs and baseline physician empathetic tone ($r=0.3$, $p=<0.01$). An increased in irritated and anxious tone had association with decreased adherence at 3 months ($r=-0.17$, $p=0.05$ and $r=-0.19$, $p=0.02$). No association was observed with dominant ($r= 0.13$, $p=0.12$), interested ($r=0.12$, $p=0.17$), or friendly ($r=0.11$, $p=0.19$) affective tones.

Conclusion: Physician's communication style had an effect on subsequent patient adherence to prescribed drugs. Empathy and less irritated and anxious tone were associated with adherence in patients with RA.

2559B

Supervised Physical Exercise Improves Endothelial Function and Endothelial Progenitor Cells in Patients with Systemic Lupus Erythematosus. Edgard T. Reis Neto[1], Aline E. Silva[1], Carlos M. C. Monteiro[2], Erika L. Naka[2], Patricia Semedo[2], Neusa P. Silva[1] and Emilia I. Sato[1]. [1]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Escola Paulista de Medicina - Universidade Federal de São Paulo, São Paulo, Brazil

Background/Purpose: Cardiovascular disease (CVD) is an important cause of morbidity and mortality in systemic lupus erythematosus (SLE) and disturbances in endothelial function (EF) are implicated in its pathogenesis. EF also depends on endothelial progenitor cells (EPCs) that enhance angiogenesis, promote vascular repair and have potential as a marker of CVD. SLE patients have endothelial dysfunction and fewer EPCs than healthy controls. A previous study from our group demonstrated that supervised physical exercise (SPE) improved EF in SLE patients. Objective: To evaluate the effect of SPE in EPCs and in vascular endothelial growth factor (VEGF) in SLE patients.

Methods: Prospective, controlled, nonrandomized study in which women with SLE (18–45 years-old) were allocated according to availability to participate in the exercise group (EG) or control group (CG). Intervention: SPE was performed three times a week for 16 consecutive weeks and consisted of 10 minutes of initial warm-up/stretching, 40 minutes of walking at heart rate corresponding to the ventilatory anaerobic threshold, and 10 minutes of cooling down. Patients were evaluated at baseline (T0) and after 16 weeks (T16): high-resolution ultrasound of brachial artery in resting conditions, after reactive hyperaemia (flow-mediated dilation-FMD) and after oral glyceryl trinitrate (GTMD) was performed to assess endothelial function; EPCs were evaluated by flow cytometry using anti-CD34 (FITC), anti-CD133 (PE) and anti-KDR (APC); and VEGF was assessed by ELISA (R&D Systems, Minneapolis, USA).

Results: Four hundred and nine SLE patients were invited to participate, 186 manifested interest, but 110 were excluded due to exclusion criteria, 53 patients dropped out due to personal reasons and 21 were included. Nineteen patients completed the evaluations (mean age 33.4±8.7 years and mean disease duration of 102.6±80.7 months). Twelve patients were assigned in the EG and seven in the CG. Both groups were comparable and homogeneous regarding demographic variables and cardiovascular traditional risk factors. In the EG, we observed a significant increase in FMD (8.3±7.2% *vs* 16.4±8.9%, $p=0.011$) without changes in the CG (3.7±4.5% *vs* 5.6±4.6%, $p=0.526$). In the EG, we also found a significant improvement in exercise tolerance (11.8±2.1min *vs* 13.3±2.1min, $p=0.02$), maximum speed (7.5±1km/h *vs* 8.3±1.1km/h, $p=0.049$) and threshold speed (5.5±0.6km/h *vs* 5.9±0.6km/h, $p=0.011$). EPCs were analyzed in 10 patients of the EG and in seven of the CG. After 16 weeks we observed a significant increase in the number of CD34/CD133/KDR positive cells in the EG (0.38±0.37 vs. 1.57±1.38, $p=0.005$) without difference in the CG (0.62±0.83 vs. 0.82±0.58, $p=0.176$). There was no significant difference in VEGF levels in both groups comparing T0 and T16.

Conclusion: Despite the small number of patients, this is the first study demonstrating that physical exercise can improve endothelial function and EPCs number in SLE patients. The increment in the EPCs may be one of the mechanisms associated with endothelial function improvement after an exercise program. Physical exercise can be a useful strategy to prevent CVD morbidity and mortality in SLE patients.

2559C

Sexual Problems and Sexual Perception in Patients with Ankylosing Spondylitis. Anne Proven[1], Kari H. Berg[2], Elsa Almas[3], Espen E. Benestad[4] and Glenn Haugeberg[5]. [1]MD, Baerum, Norway, [2]MA, Kristiansand.S, Norway, [3]MA, Kristiansand, Norway, [4]MD, Kristiansand, Norway, [5]MD, PhD, Kristiansand.S, Norway

Background/Purpose: Ankylosing spondylitis (AS) is a chronic, systemic inflammatory rheumatic disease which most frequently affects the axial skeleton, but may also affect peripheral joints, tendons and internal organs. This disease which begins in the second or third decade may give rise to significant loss of function and impaired quality of life. Despite the importance of sexuality as part of quality of life, only a few studies have explored this important issue in AS patients. We therefore wanted to explore sexuality in patients with AS in regard to how satisfied they are with their sexual life and whether the patients think their sexuality is influenced by the disease.

Methods: This is a prospective, cross sectional study were patients with established AS seen in the outpatient clinic in three hospitals in the southern and eastern part of Norway, were asked to participate. A broad specter of demographic, clinical data, quality of life data, also including a general questionnaire on sexuality, was collected.

Results: At the end of 2008 105 patients had been included. The patient cohort contained of 66.7% men and 96.1% were HLA-B27 positive. The mean (SD) values for age was 46.2 (14.9) years and disease duration 15.5 (10.6) years. 23.8% patients were current users of biologics and 42.9% were current users of NSAIDs. Mean (SD) values was 3.3 (2.0) for BASDAI, 2.9 (2.2) for BASFI, 3.8 (2.4) for BAS-G, 2.6 (2.0) for BASMI and 0.58 (0.50) for HAQ. For ESR and CRP the mean values were 14.1 (14.5) mm/hr and 9.0 (11.2) mg/l, respectively.

On the sexuality scores 60.4% patients reported sex and sexuality important/very important to be satisfied with their daily life. 31.7% reported sexuality less important and only 7.6% thought sexuality was not important. 48.5% were satisfied/very satisfied with their sexual life while 29.3% were neither satisfied nor dissatisfied and 22.3% were dissatisfied. 49.5% reported to have had problems with their sexuality, however only 13% of the 105 patients had been seeking help to solve the problems. 32.4% of the patients thought their sexual problems were related to their disease, 11.4% in very high degree and 21% in some degree. The main causes of sexual problems from the disease were tiredness in 31.4%, stiffness in 30.5% and pain in 31.4%.

Conclusion: In this study of 105 patients with AS, as many as 49,5% reported to have had sexual problems, and 32,4% thought their sexual problems were related to their AS. The main causes of sexual problems were tiredness, stiffness and pain. We think the number of patients reporting sexual problems was high in this group since disease activity scores and health activity scores in this group was only modest high. More studies are needed to illuminate how sexual life is influenced by AS.

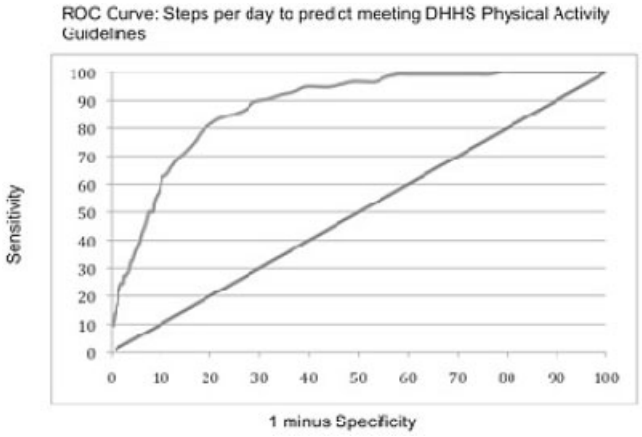
2560

Is 10,000 Steps Enough to Meet Physical Activity Guidelines?: The Multicenter Osteoarthritis Study. Daniel K. White[1], David T. Felson[1], Yuqing Zhang[2], K. Douglas Gross[3], Jingbo Niu[1], Zhaolong Shen[4], Michael C. Nevitt[5], C.E. Lewis[6], James Torner[7] and Tuhina Neogi[4]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University Clinical Edpidemiology Reserach and Training Unit, Boston, MA, [3]MGH Institute of Health Professions, Boston, MA, [4]Boston University, Boston, MA, [5]University of California-San Francisco, San Francisco, CA, [6]University of Alabama, Birmingham City, AL, [7]University of Iowa, Iowa City, Iowa City, IA

Background/Purpose: The Department of Health and Human Services (DHHS) recommends all adults perform 150 minutes of moderate intensity exercise per week in 10 continuous minute bouts in order to achieve Physical Activity Guidelines. Given the popularity of using pedometers to quantify physical activity, a goal of taking at least 10,000 steps per day is frequently set as a benchmark for an 'active' level of activity. However, it is not known if taking 10,000 steps can act as a reasonable goal to approximate meeting Physical Activity Guidelines. Understanding this association is relevant for people with knee osteoarthritis (OA) who are often sedentary but benefit from supervised walking programs to reduce knee pain and improve function. Thus, we examined the ability of the 10,000 steps per day goal to predict meeting the DHHS Physical Activity Guidelines within the Multicenter Osteoarthritis Study (MOST).

Methods: MOST is an NIH funded longitudinal study of people who have or are at high risk for knee OA. Subjects at the 60 month visit wore an accelerometer-enabled pedometer (Stepwatch) to record steps taken over 7 days. Using Stepwatch data, we defined meeting the DHHS Physical Activity Guidelines as walking 150 minutes at a moderate intensity (i.e. a step frequency of at least 100 steps per minute) in at least 10 continuous minute bouts. We also calculated the proportion of subjects who had at least 10,000 steps per day, inclusive of all intensities. We calculated the sensitivity, specificity, and positive predictive value (PPV) of using the 10,000 steps per day goal to identify those who met Physical Activity Guidelines. We also generated a receiver operating characteristic (ROC) curve to determine how well step counts per day in general discriminated meeting Physical Activity Guidelines.

Results: Of the 1380 subjects who had 7 days of monitoring (Age 67 $\pm$ 8 yrs, BMI 31 $\pm$ 6 kg/m^2, female 60%, 9130 $\pm$ 3451 steps/day) 36% walked at least 10,000 steps per day, while only 6% met Physical Activity Guidelines. The sensitivity and specificity of the 10,000 steps per day goal to identify those meeting Physical Activity Guidelines was 88% and 72%, respectively. Of those walking at least 10,000 steps, 15.5% met Physical Activity Guidelines (PPV =15.5%). Overall the area under the curve from the ROC curve was 0.87 which suggests a moderate ability of steps per day to distinguish those meeting Physical Activity Guidelines. See Figure.



Conclusion: The 10,000 steps per day goal did not have sufficient predictive ability due to the low prevalence of meeting Physical Activity Guidelines within this study population. From a broader perspective, further research is needed to understand if health outcomes are optimized from steps per day irrespective of intensity, or solely by intensity of activity.

ARHP Concurrent Abstract Session
ARHP Clinical Practice/Patient Care II
Wednesday, November 9, 2011, 7:30 AM–8:30 AM

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Does Informing Patients about the Link Between Dental Hygiene and Rheumatoid Arthritis Encourage Better Dental Care? Patricia J. Cornell[1], Selwyn Richards[2] and Sarah Westlake[2]. [1]Poole Hospital, Poole Dorset, United Kingdom, [2]Poole Hospital NHS Foundation Trust, Poole, United Kingdom

Background/Purpose: Recent evidence has shown that people with rheumatoid arthritis (RA) have a higher incidence of periodontal disease and that the extent and severity of both the periodontal disease and RA are linked. Furthermore periodontal therapy has been shown to have a beneficial effect on the severity of the RA. Moderate to severe periodontitis may also be a risk factor in the development of RA in non-smokers. One of the most important factors in oral care is access to dental health practitioners. In the UK it is well reported in the media about lack of

access to dental care. We decided to audit the access to dental care in a sample of our patient cohort with inflammatory arthritis. A patient dental care leaflet was produced highlighting the importance of dental care which was distributed to all our inflammatory arthritis patients. We then re-audited a sample of patients to determine if there had been any change in behaviour or access to dental care.

Methods: The first audit took place in 2009. All adult patients attending for rheumatology follow-up during a one month period were given an approved questionnaire to complete. Questionnaires were anonymous and included questions on access to both NHS and Private dental care. During 2010 a Trust approved patient leaflet about the importance of dental care was devised and given to all patients with inflammatory arthritis who attended the hospital rheumatology department. Six months later a second questionnaire was given to all adult patients attending for rheumatology follow-up during a one month period. This second questionnaire included questions on the dental care leaflet along with access to dental care.

Results: Demographics for both audits were similar. In the second audit 139 (95%) patients admitted to receiving the leaflet on dental care. All patients agreed or strongly agreed that the leaflet was easy to understand. Only 10 patients thought the leaflet contained no new information. 74 patients thought the leaflet applied to them and 125 patients thought the leaflet was helpful. Despite this very little change in behaviour was seen although 8 patients admitted that hey could not afford the dentist.

Results from audits of dental health questionnaire

	2009 n = 158			2010 n = 146		
	Yes	No	No anser	Yes	No	No answer
Annual review with dentist	126 (80%)	19 (12%)	13	123 (84%)	18 (12%)	5
Annual review with hygienist	55 (35%)	103 (65%)	0	59 (40%)	87 (60%)	0
NHS dentist	81 (51%)	52 (32%)	25	95 (65%)	34 (23%)	17
Admitted to smoking	19 (12%)	139 (88%)	0	19 (13%)	127 (87%)	0
Offered help to stop smoking	19	NA	NA	19	NA	NA
Have a dry mouth	44 (28%)	109 (69%)	5	43 (29%)	102 (70%)	1
Practitioner aware of dry mouth	14 (31%)	28 (64%)	2	16 (37%)	24 (55%)	3
Use an electric toothbrush	64 (40%)	89 (56%)	5	63 (43%)	83 (57%)	0

Conclusion: Dental care has become increasingly important in the light of new evidence linking severity of RA disease with both smoking and poor periodontal health. In our department a patient education leaflet led to minimal change in behaviour, with a slight increase in the amount of people accessing dental care and a moderate increase in access to NHS instead of private dentistry but no increase in the use of electric toothbrushes. Increasing the awareness of the potential link between poor oral hygiene and RA may have a useful impact on disease severity, however future studies need to concentrate on barriers to changing behaviour which may be due to cost or fear of dentists.

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The Clinical Utility of Using Both the WOMAC and the MDHAQ Questionnaires in An Outpatient Osteoarthritis Clinic. Caroline Jones[1], Laurence A. Rubin[2] and Lesley Bainbridge[3]. [1]St Michael's Hospital, Toronto, ON, [2]St. Michael Hospital, Toronto, ON, [3]University of British Columbia, Vancouver, BC

Background/Purpose: A multidisciplinary osteoarthritis clinic (OA clinic) was established at St. Michael's Hospital to address the needs of an aging population with significant arthritis but not yet ready for joint replacement surgery. The goals of the clinic are to facilitate patient care that allows the patient to decrease pain, improve function and enhance quality of life. In order to objectively measure the patients' pain and function the use of a validated health questionnaire is necessary. Currently, the clinic utilizes two patient questionnaires: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Multidimensional Health Assessment Questionnaire (MDHAQ).

Objectives: The purpose of this study was to examine the clinical utility of adopting both questionnaires into this clinical setting. The research question is what is the correlation between the MDHAQ and the WOMAC in an osteoarthritis patient population?

Methods: Retrospective chart review was conducted of patients who attended the OA clinic between August 2009 and January 2010. There were a total of 73 patients included in this study. The results of the MDHAQ and the WOMAC were correlated and the Pearson correlation coefficient was obtained.

Results: The following table depicts the results of the data collection depicting the maximum, minimum and average score.

Average Score on each measure

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
WOMAC	73	47.76	20.42	3487	9	88
MDHAQ-P	73	6.15	2.78	449	0.5	10
MDHAQ-FN	73	0.88	0.48	64.6	0	1.9
MDHAQ-S	73	13.40	26.82	978	0	180
MDHAQ-G	73	5.18	2.82	378.4	0	10
MDHAQ-FT	73	5.22	3.23	381	0	10

The WOMAC scores were correlated with each of the MDHAQ scores using the SASS system. The results are:

The WOMAC and the MDHAQ pain correlation was O.71

The WOMAC and the MDHAQ function correlation was 0.707

The WOMAC and the MDHAQ global health correlation was 0.68

The WOMAC and the MDHAQ fatigue correlation was 0.711.

The stiffness score did not correlate to the WOMAC score.

Conclusion: The MDHAQ and the WOMAC have a positive correlation. The WOMAC provided a single score with no maximum or minimal values but it is only applicable to patients with hip and knee arthritis. The MDHAQ provides separate scores and is applicable to patients with all types of arthritis but it did demonstrate maximum and minimum values in a number of areas. The questionnaires are easy to complete and score making the information available for use at the time of the patients' appointment. The results of this pilot study support the use of both questionnaires in an outpatient osteoarthritis clinic.

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Work Disability Is Related to the Presence of Arthritis, Not to a Specific Diagnosis. Hernan Maldonado Ficco[1], Rodolfo Perez Alamino[1], Fernando Dal Pra[1], Veronica Lencina[1], Luciana Casalla[2], Mariana Benegas[2], Oscar Rillo[2], Alberto Berman[3], Ana Lucía Barbaglia[3], Veronica Bellomio[4], Francisco Caeiro[5], Josefina Marcos[6], Juan Carlos Marcos[6], Antonio Catalan Pellet[7], Rodrigo Garcia Salinas[7], Sergio Paira[8], Federico Ceccato[8], Enrique Soriano[9], Zaida Bendran[9], Gabriela Salvatierra[10] and Gustavo Citera[1]. [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Hospital Tornu, Buenos Aires, Argentina, [3]Hospital Padilla, Tucuman, Argentina, [4]Consultorio, Tucuman, Argentina, [5]Hospital Privado de Cordoba, Cordoba, Argentina, [6]Hospital San Martin, La Plata, Argentina, [7]Hospital Rivadiavia, Buenos Aires, Argentina, [8]Hospital Jose Maria Cullen, Santa Fe, Argentina, [9]Hospital Italiano, Buenos Aires, Argentina, [10]Centro de enfermedades Reumaticas, Santiago Del Estero, Argentina

Background/Purpose: to evaluate work disability and its main associated factors in patients with early arthritis.

Methods: CONAART (Argentine Consortium for Early Arthritis) is the first early arthritis cohort in Argentina. Patients with at least one or more swollen joints and less than 2 years of symptoms duration were followed up prospectively in 13 rheumatology centers. Social, demographic, familiar, clinical and laboratory data were recollected. At first year and every year X-rays of hands and feet were performed and working status and pharmaco-economic data were evaluated. Work status (employed, unemployed, retired) and type of work were assessed by direct interview using a predesigned questionnaire. Patients retired due to age were excluded from final analysis. Categorical variables were compared using chi square and Fisher test and continue variables using student T test and ANOVA. Variables associated to work disability were analyzed by multiple logistic regression analysis.

Results: 848 patients were included, RA (ACR 87′ Criteria) = 483 (57%), UA= 365 (43%), 694 (81.8%) were women, median age was 46 years (IQR:35–55.7) and median symptoms duration 7 months (IQR:3–12). Demographic data and disease duration were comparable between both groups. Patients with RA had significantly higher disease activity,

worse functional capacity and quality of life, and more severe radiological damage (SENS score) compared to UA patients. Rheumatoid factor positivity was higher in RA vs UA (84.6% vs 34.1% p=0,001). However work disability (unemployed patients) was comparable between groups (RA=21% vs UA=18.6% p=NS). In both groups unemployed patients had higher DAS28, worse HAQ values and less years of formal education (p value <0,005 in all comparisons). Radiological damage was greater in unemployed patients but this difference did not reach statistical significance. In multivariate analysis, disease activity was the main variable associated with unemployment in both groups. No association was found with type of job or physical demand required for it.

Conclusion: Disease activity, but not radiological damage was the main cause of work disability in this cohort of patients with early arthritis, independently of the final diagnosis.

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Psychiatric Disorders in Fibromyalgia Patients, Results Patient Survey. Robert S. Katz[1], Sharon M. Ferbert[2], Alexandra Small[3], Susan Shott[1] and Patricia Kuenzi[1]. [1]Rush University Medical Center, Chicago, IL, [2]Advocates for Funding Fibromyalgia Treatment, Education and Research(AFFTER), Libertyville, IL, [3]University of Illinois Medical School

Background/Purpose: We investigated the extent to which people with fibromyalgia (FMS) have also been diagnosed with psychiatric disorders.

Methods: 115 FMS patients and 63 control patients with other rheumatic diseases answered a rheumatology office questionnaire that contained questions about psychiatric disorders, including anxiety, depression, bipolar disorder, post-traumatic stress disorder, obsessive-compulsive disorder, attention deficit disorder, and alcoholism. The chi-square test of association and Fisher's exact test were used to compare percentages, and the Mann-Whitney test was done to compare FMS and control patients with respect to age. A 0.05 significance level was used and all tests were two-sided.

Results: 81.7% of the FMS patients and 61.9% of the control patients were women ($p = 0.004$). The mean age was 48.1 ± 12.3 years for FMS patients and 50.7 ± 13.6 for control patients ($p = 0.092$). FMS patients were significantly more likely than the control group to report a diagnosis or symptoms of anxiety (66.4% vs. 27.0%, $p < 0.001$), depression (64.2% vs. 28.6%, $p < 0.001$), bipolar disorder (10.4% vs. 0%, $p = 0.006$), post-traumatic stress disorder (15.6% vs. 4.8%, $p = 0.034$), obsessive-compulsive disorder (19.4% vs. 7.9%, $p = 0.045$), and attention deficit disorder (38.1% vs. 6.3%, $p < 0.001$). There was no statistically significant difference between FMS and control patients with respect to the percentage reporting a diagnosis or symptoms of alcoholism (1.9% vs. 3.2%, $p = 0.64$).

Conclusion: These results indicate that FMS patients report concomitant psychiatric diagnoses more frequently than controls, including anxiety, depression, post-traumatic stress disorder, obsessive-compulsive disorder, and attention deficit disorder. The presence of these psychiatric conditions can add to the difficulty of treating FMS.

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Evaluation of ^{13}c-Acetate Plus Lactulose Breath Test, a New Examination to Measure Intestinal Absorption in Patients with Systemic Sclerosis. Tatsuhiro Yamamoto, Yoshihisa Urita, Kaichi Kaneko, Nahoko Tanaka, Yoshie Kusunoki, Kenji Takagi, Shinichi Kawai and Hirahito Endo. Toho University School of Medicine, Tokyo, Japan

Background/Purpose: To determine the quantitative analysis of the severity of the gastrointestinal (GI) involvements and GI predictive score in patients with systemic sclerosis(SSc), we measured the ^{13}C-fatty acid absorption-breath test and lactulose pulse ^{13}C-acetate breath test. Breath tests using fatty acids and acetate with a stable isotope (^{13}C) were carried out on patients with SSc in order to detect malabsorption, hypoperistalsis and bacterial overgrowth. We compared the outcome and a predictive score calculated by the absorption data and analyzed the therapeutic approach.

Methods: ^{13}C-labeled fatty acid absorption breath test and ^{13}C-acetate plus lactulose test were measured in 35 patients with SSc and 20 healthy subjects. ^{13}C-labeled mixed fatty acids 200mg or ^{13}C-acetate 100mg plus lactulose 12g were given orally. $^{13}CO_2$ and H_2 contents in the expired air were analyzed by a mass spectrometer and by a breath analyzer, respectively. Using breath test data, fatty acid absorption were calculated by cumulative ^{13}C excretion for 8 hours and ^{13}C-acetate 100mg plus lactulose breath test were calculated by 3 hours. We measured the therapeutic effects using these breath tests quantitatively in GI involvements of SSc. Intestinal predictive score calculated by each data of ^{13}C-acetate absorption 3h cumulative recovery rate, ^{13}C-labeled fatty acid absorption 8hours cumulative rate, bacterial overgrowth rate and clinical bowel symptom score.

Results: ^{13}C-labeled fatty acid absorption breath test: ^{13}C cumulative excretion for 8 hours in patients with SSc was significantly lower than that of normal subjects. (32 SSc: 12±6%, 20 normal:21±4%, $P<0.05$). ^{13}C cumulative excretion rate in 4 SSc patients with parenteral hyperalimentation showed markedly low data (mean 3.4±2.6%). Lactulose plus ^{13}C-acetate breath test: ^{13}C cumulative excretion rate of 3 hours of ^{13}C-acetate absorption of SSc patients were lower than control. AUC-Cmax, ^{13}C-acetate absorption index of SSc patients were significantly lower than that of normal control (21 SSc 4.8±2.3%, 20 normal 5.4±1.8 %, $P<0.05$). Tmax as the time of peak $^{13}CO_2$ excretion of SSc patients was delayed than control (SSc 55.5±16.6, Control 43.9±10.4 min). After treatment by prokinetic drugs and antibiotics ^{13}C cumulative excretion rate increased 2.88% from 1.88% in a SSc patient with severe GI involvements Breath hydrogen (H_2) levels reflects intestinal bacterial overgrowth. H_2 excretion continued over 20ppm for 120 min after lactulose administration by small intestine bacterial overgrowth. After antibiotics administration H_2 concentration decreased. Predictive score correlated with seriousness of GI involvements. We can suppose connection with treatment plan determination and outcome of GI involvements with SSc.

Conclusion: Severe intestinal involvements loss quality of life in patients with SSc. ^{13}C-fatty acid and lactulose plus ^{13}C-acetate breath test is a simple and non invasive intestinal absorption examination and a use tool for the quantitative evaluation of GI involvements in patients with SSc. GI predictive score calculated by these examinations might be tool for determination of therapeutic approach to severe GI involvements of patients with SSc.

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The Association Between Cardio-Respiratory Fitness and Traditional Cardiovascular Risk Factors in Rheumatoid Arthritis Patients. Jennifer K. Cooney[1], Yasmeen Ahmad[2], Jonathan Moore[1], Andrew Lemmey[1], Jeremy Jones[1], Peter Maddison[1] and Jeanette Thom[1]. [1]School of Sport, Health and Exercise Sciences, Bangor University, George Building, Bangor, Gwynedd, LL57 2PZ, UK., Bangor, United Kingdom, [2]The Department of Rheumatology, Betsi Cadwaladr University Health Board (West), Llandudno, LL30 1LB, UK, Bangor, United Kingdom

Background/Purpose: RA is associated with increased mortality from cardiovascular disease (CVD). Traditional CVD risk factors do not fully explain this increased incidence. RA patients are typically known to have poor cardio-respiratory fitness (CRF), a known CVD risk factor. However their CVD risk factor profile needs further investigation. Thus the aim was to assess RA patients' CRF using a simple tool and to determine whether poor CRF correlated with traditional CVD risk factors.

Methods: 100 RA patients (69 female, 31 male) attending rheumatology clinics were recruited. CRF was measured using the Siconolfi Step Test. Patients were allocated into three groups based on their performance in the step test (i.e. unable to do the test, 'poor' fitness and 'better' fitness). RA activity/severity, traditional CVD risk factors, Framingham 10 year CVD risk and anthropometric characteristics were assessed.

Results: RA patients had well controlled disease (table 1). Some CVD risk factors were mildly elevated but 32% and 28% of patients were taking medication for hypertension and hyperlipidemia respectively. Their Framingham Risk Score was moderate at 16%. Because patients' range of CRF was poor, expected correlations with CVD risk factors were not observed. Despite no difference in disease duration 'unable' patients rated their arthritis as worse, more painful and disabling. Their Framingham Risk was also significantly higher than 'better fitness' patients. 'Unable' patients were also fatter, had bigger waists and were classed as obese (BMI >30).

Table 1. RA characteristics, P<0.05; # 1 vs 2; * 1 vs 3; ^ 2 vs 3

RA factors	Total Group	1. Unable (n=35)	2. Poor (n = 33)	3. Better (n = 32)
Age	59.6 ± 10.2	62.2 ± 8.4*	64.2 ± 7.2^	52.0 ± 10.6
Disease duration	10.4 ± 9.1	11.0 ± 10.5	11.4 ± 9.3	8.7 ± 7.2
DAS28 CRP	2.8 ± 1.4	3.0 ± 1.1	2.6 ± 1.1	2.6 ± 1.2
Global health (0–100)	32 ± 24	46 ± 24#*	23 ± 21	25 ± 19
Pain (0–100)	23 ± 28	35 ± 31*	17 ± 26	16 ± 20
HAQ	.87 ± .76	1.46 ± .68#*	.63 ± .52	.55 ± .74
CRF				
Step test	22 ± 6		18 ± 4	26 ± 5
CVD risk factors				
SBP	140 ± 20	141 ± 21	146 ± 20^	132 ± 19
DBP	81 ± 12	79 ± 11	85 ± 11^	76 ± 12
TC	5.2 ± 1.1	5.2 ± 1.3	5.5 ± 1.0	5.3 ± 1.2
TG	1.5 ± .7	1.7 ± .7#	1.3 ± .6	1.4 ± .7
LDL	3.1 ± 1.0	2.9 ± 1.0	3.1 ± .9	2.3 ± 1.0
HDL	1.5 ± .5	1.4 ± .4	1.7 ± .5	1.5 ± .4
Framingham risk (%)	16 ± 10	20 ± 11#*	16 ± 8	11 ± 9
Anthropometry				
BMI	28 ± 6	31 ± 7*	27 ± 5	25 ± 4
Body fat %	38 ± 15	42 ± 18#*	37 ± 13	33 ± 11
Waist hip ratio	.90 ± .07	.93 ± .07*	.89 ± .07	.88 ± .06

Conclusion: The step test has emerged as a very useful tool, highlighting that RA patients have poor CRF and identifying those at greatest risk of developing CVD in the future. 'Unable' patients and those who perform poorly require medical intervention. This investigation has shown that screening for traditional risk factors may not be enough as the extent of their CVD risk is somewhat masked. Early detection of CVD risk using a tool like the step test could significantly reduce the CVD mortality in RA.

ACR Concurrent Abstract Session
Cytokines, Mediators, and Gene Regulation III
Wednesday, November 9, 2011, 9:00 AM–10:30 AM

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Immune Suppression and Injury Tolerance in Fibrotic Liver Are Mediated by Induced Regulatory T Cells Which Safeguard Fibroplasias From Clearance. Ming Feng[1], Yuan-Ping Han[1] and Song G. Zheng[2]. [1]University of Southern California, Los Angeles, CA, [2]USC Keck School of Medicine, Los Angeles, CA

Background/Purpose: Upon acute injury, hepatic stellate cells (HSCs) are mobilized to lead wound healing through a chain of reactions, from expression of matrix metalloproteinases (MMPs), to activation of latent transforming growth factor-beta (TGF-β), and releasing of active retinoic acids (atRA). On the other hand, TGF-β and atRA together can generate and promote Foxp3+ regulatory T cells (Tregs) from naïve T cells. In chronic injury or infection, HSCs are transformed into myofibroblasts and the liver becomes immune suppression and injury tolerance. In a recent report we showed that many MMP genes in myofibroblatic HSCs are permanently silenced through epigenetic suppression to favor ECM accumulation. Here, we uncover that the fibrotic liver maintains in immune suppression and injury tolerance, as marked by impaired inflammation, accumulation of regulatory T cells (Tregs), which protect fibroplasias from clearance.

Methods: Male mice (C57/BL6) mice with 8–10 weeks old were used. Hepatic fibrosis was induced by intraperitoneal injection with Thioacetamide (TAA) at 160mg/kg body weight for 8 weeks or saline as control. The frequency of hepatic Tregs was examined by flow cytomety and immunofluorescence. Tregs were depleted by the administration of anti-CD25 antibody (PC61) i.p. at 3 days before TAA challenge. 100 ml liposome-encapsulated clodronate (Cl2MDP) was injected intravenously at 24 hours before TAA challenge to deplete kupffer cells. 3 days after TAA challenge, mice were sacrificed and MMPs in liver tissues were tested by Zympgraph. Fibrolysis was evaluated by sirusis staining. The data are expressed as means ± SD. Values were regarded as statistic difference for P<0.05.

Results: We found that CD4+Foxp3+ regulatory T cells accumulated in fibrotic liver and suppressed inflammatory responses evoked by hepatic toxin. The depletion of Tregs by anti-CD25 antibody restored immune response and MMP expression in the fibrotic liver, and promoted fibrosis resolution. However, if depletion of kupffer cells at the same time, hepatic MMPs were reduced and clearance of fibroplasias was inhibited. Co-staining MMPs, F4/480 and desmin for immunofluorescence indicated that in fibrotic liver MMPs were produced by kupffer cells, while in normal liver hepatic stellate cells (HSCs) were the main source of MMPs. Liver fibrosis still can be developed in NOD/SCID mice where adaptive immunity is absent in chronic liver injury, but the fibrosis is resolved promptly. Transfusion of injury-type Tregs into NOD/SCID mice was unable to induce fibrosis, but instead, generated immune suppression and impaired fibrosis resolution.

Conclusion: The immune suppression and injury tolerance in fibrotic liver are mainly mediated by peripheral induced Tregs that safeguard fibroplasias from clearance. It is, therefore, that the control of induced Tregs development and function could be preventive and therapeutic in liver fibrosis in the chronic stage of liver injury and inflammation.

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Activation of c-Jun N-Terminal Kinase and Extracellular Signal-Regulated Kinase Predicts Damage in Systemic Lupus Erythematosus. Mirit Amit-Vazina[1], Yair Molad[2], Eliyahu Yona[3], Lily Amram[3], Olga Bloch[4] and Micha J. Rapoport[4]. [1]Rheumatology Service, Assaf Harofeh Medical Center and Sackler School of Medicine, Tel-Aviv University, Israel, Zerifin, Israel, [2]Rheumatology Unit, Beilinson Hospital, Rabin Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, Petah Tikva, Israel, [3]Internal Medicine Division, Day Care Unit, Assaf Harofeh Medical Center and Sackler School of Medicine, Tel-Aviv University, Israel, Zerifin, Israel, [4]Diabetes and Immunology Research Laboratory, Assaf Harofeh Medical Center and Sackler School of Medicine, Tel-Aviv University, Israel, Zerifin, Israel

Background/Purpose: Aberrant signaling along the p21ras/MAP kinase pathway has been demonstrated in systemic lupus erythematosus (SLE). We have previously reported that the activity of c-Jun N-terminal Kinase (JNK) and Extracellular Signal-Regulated Kinase (ERK) is associated with disease activity in SLE patients. The objective of the present study is to determine whether JNK and ERK activation predicts subsequent permanent end organ damage in a cohort of SLE patients.

Methods: Blood samples of 42 SLE patients were prospectively collected during four consecutive visits. Expression of total ERK and JNK kinases and their active forms (pERK and pJNK) was determined by western blot in whole protein lysates of peripheral blood mononuclear cells. Four years later the permanent damage attributed to SLE was assessed using the SLICC-ACR damage index (SLICC-DI). Correlations between SLICC-DI scores and mean and maximal expression of total ERK and JNK kinases and of pERK and pJNK were assessed by Spearman correlation test. Stepwise regression analysis was used to assess the most significant contributions to SLICC-DI.

Results: Demographic and clinical data of 36 SLE patients who were available for long term follow-up and determination of SLICC-ACR are demonstrated in the table. During follow-up period one female patient died of congestive heart failure complicated by sepsis at the age of 51 after 19 years of disease.

	Mean ± SD	Median
Age (years)	48.25 ± 11.8	49.5
Females (%)	32 (89)	
Disease Duration (years)	16.9 ± 4.3	16
Follow-up Duration Since Last Visit (years)	4.02 ± 0.68	4.25
SLICC-DI	1.9 ± 1.8	2

Mean values of JNK, pJNK and pERK but not ERK obtained during the initial follow-up period correlated positively with SLICC-DI values obtained after long term follow-up (r =0.32, 0.35 and 0.38 respectively, p<0.05 for all). Maximal values of JNK, pJNK and pERK also correlated with SLICC-DI (r=0.45, 0.35 and 0.36 respectively, p<0.01 for JNK and p<0.05 for pJNK and pERK).

On stepwise regression analysis using square root transformation of SLICC-DI values and excluding SLE disease activity index (SLEDAI) maximal value of JNK and mean value of pERK were most significantly associated with SLICC-DI.

	Max JNK	R	RSQ
Step 1	Mean pERK	0.51	0.28
Step 2	0.62	0.38	

Conclusion: The results of this long-term follow-up study indicate that increased expression of JNK as well as activated forms of JNK and ERK is associated with permanent end-organ damage and can serve as predictors of damage in SLE patients.

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Novel Regulation of TNF-α-Induced-IL-18 Bioactivity in Rheumatoid Arthritis Synovial Fibroblasts by Reducing Caspase-1 Via JAK2 Inhibition. Hubert Marotte[1], Tatiana Fedorova[1], Adam J. Pinney[1], Benjamin Lewis[1] and Alisa E. Koch[2]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]Veteran's Administration and Unversity of Michigan, Ann Arbor, MI

Background/Purpose: Rheumatoid arthritis (RA) is the most common inflammatory chronic joint disorder. Interleukin-1 (IL-1) family members play a key part in the pathogenesis of RA. Among the IL-1 cytokine family members, IL-18 is a proinflammatory cytokine, which modulates Th1 development and induces angiogenesis. We previously described regulation of TNF-α-induced-IL-18 bioactivity by blocking the ERK pathway. Here, we focused on modulation of TNF-α-induced-IL-18 bioactivity by reduction of caspase-1 expression.

Methods: Caspase-1 expression in RA synovial fibroblasts treated with TNF-α was assessed by qRT-PCR and Western blot. The critical pathways for TNF-α-induced caspase-1 expression were determined by using chemical inhibitors: pyrrolidine dithiocarbamate (PDTC; a nuclear factor kappa-light-chain-enhancer of activated B cells [NFκB] inhibitor; 200μM), MAPK inhibitors (ERK1/2, PD98059; p38, SB202190; or JNK2, SP600125; 10μM), or AG-490 (a Jak2 inhibitor; 10 μM) followed by TNF-α stimulation. Caspase-1 expression was determined by qRT-PCR and Western blot. Immunofluorescence (IF) staining was performed to check IL-18 production induced by TNF-α with or without preinhibition of ERK1/2 or JAK2 by using antibody recognized immature and mature IL-18. IL-18 functional activity was assessed using an IL-18 bioactivity assay using KG-1 cells and culture supernatants.

Results: TNF-α induced RA synovial fibroblast caspase-1 expression at the mRNA and protein levels in a time-dependant manner ($P < 0.05$; $n \geq 6$ patients). Blocking the Jak2 pathway reduced TNF-α-induced-caspase-1 expression at the transcriptional and protein level by approximately 60% and 40%, respectively ($P < 0.05$; $n \geq 4$). Blocking NFκB, ERK1/2, JNK or p38 pathways had no effect on TNF-α-induced-caspase-1 mRNA expression. We then confirmed by IF that TNF-α-induced IL-18 and investigated roles of ERK1/2 and JAK2 pathways. Blocking the ERK1/2 pathway dramatically decreased IL-18 expression induced by TNF-α. However, when blocking the JAK2 pathway, TNF-α induced intracytoplasmic granular IL-18 expression, suggesting a defect of caspase-1. Finally, blocking the Jak2 pathway, we observed a reduction of IL-18 bioactivity by 52% in RA synovial fibroblasts.

Conclusion: These results show a unique way to block TNF-α-induced-IL-18 bioactivity by blocking capase-1. These data provide a novel role for the Jak2 pathway in RA patients and emphasize the use of Jak inhibitors as a new therapeutic option in the management of RA.

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STAT3 Phosphorylation of Circulating Leukocytes Correlates with Disease Activity in Early Untreated Rheumatoid Arthritis. Krista Kuuliala[1], Antti Kuuliala[1], Saara Aittomäki[1], Suvi Oksanen[1], Sanna Siitonen[2], Hannu Kautiainen[3], Marjatta Leirisalo-Repo[2] and Heikki Repo[1]. [1]Haartman Institute, Helsinki, Finland, [2]Helsinki University Central Hospital, Helsinki, Finland, [3]Central Finland Central Hospital, Jyväskylä, Finland

Background/Purpose: Signal transducer and activator of transcription (STAT) 3 is an important transcription factor in the regulation of inflammation. Experimental models suggest a role for STAT3 in the pathogenesis of RA [1, 2]. We aimed to evaluate STAT3 activation in peripheral blood leukocytes in early untreated RA in relation to disease activity.

Methods: Blood samples were obtained from 31 patients diagnosed with early RA who had not received prior DMARDs or corticosteroids. The mean age of the patients was 47 years (SD 14), median duration of symptoms 8 months (interquartile range 3–24 months), 81% were women, 81% rheumatoid factor positive, and 84% anti-CCP positive. Disease activity was evaluated by calculating the DAS28 score (available in 29 patients). The levels of activated STAT3 in leukocyte subsets (CD14+, CD3+CD4+, CD3+CD8+, CD19+) were determined by flow cytometry following lysis of erythrocytes, fixation and permeabilization of leukocytes, and incubation with phospho-specific (pY705) anti-STAT3 monoclonal antibody (as described in [3]). The proportion of pSTAT3 positive cells was determined using an electronic gate set to include <5% of positively fluorescing cells from a healthy control subject. Correlation coefficients were calculated by Spearman method.

Results: The proportion of pSTAT3 positive CD4+ cells was increased compared to controls in 18/31 patients (58%), CD8+ in 12/31 (39%), CD19+ in 8/31 (26%), and CD14+ in 17/31 (55%). DAS28 correlated with the proportion of pSTAT3+ CD4+ cells (Table), as well as the ratio of CD4+/CD14+ cells and CD4+/CD19+ cells (Table, Figure).

Table. Correlation of DAS28 with the proportion of pSTAT3 positive leukocyte subsets.

Cells	r	p
CD3+CD4+	0.37	0.047
CD14+	−0.06	0.74
CD19+	−0.30	0.11
CD3+CD4+ toCD14+	0.41	0.028
CD+CD4+to CD19+	0.44	0.017
CD14+ to CD19+	0.08	0.69

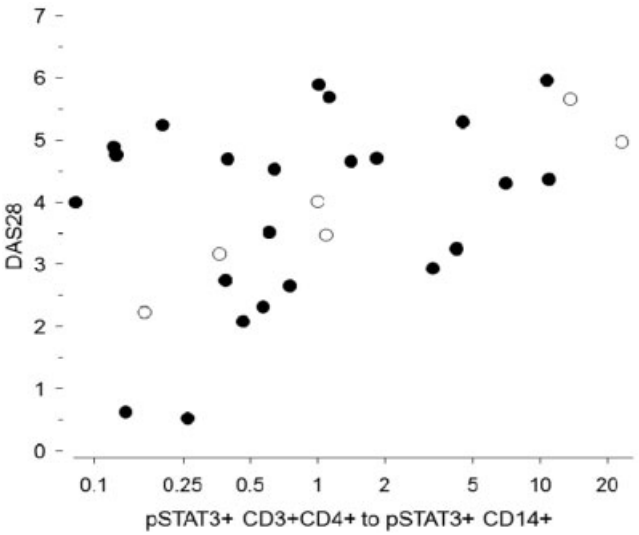

Figure. Correlation of DAS28 with the proportion of pSTAT3+ CD3+CD4+ to pSTAT3+ CD14+ cells. Filled in symbols denote anti-CCP positive and blank symbols denote anti-CCP negative patients.

Conclusion: STAT3 is constitutively activated in circulating leukocytes in early RA. The proportion of pSTAT3+ CD4+ cells correlates with disease activity evaluated by DAS28. Circulating lymphocyte STAT3 activation is not a unique feature of RA since it has also been reported in primary Sjögren's syndrome [4] as well as in acute pancreatitis with severe systemic inflammation [3]. Our results emphasize the heterogeneous involvement of immune inflammatory cells and may provide a novel strategy for personalized medicine in the treatment of early RA.

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2571

What Keeps An Autoantibody-Positive Healthy Individual Healthy? Lauren L. Ritterhouse[1], Holden T. Maecker[2], Hongwu Du[3], C. Garrison Fathman[4], Joan T. Merrill[1], Joel Guthridge[1] and Judith A. James[5]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University School of Medicine, Stanford, CA, [3]Stanford University School of Medicine, Stanford, CA, [4]Stanford Univ Medical Center, Stanford, CA, [5]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: Antinuclear antibodies can be detected in up to 25% of the population, however only 5–7% of the United States is affected by an autoimmune disease. Therefore, a significant number of individuals are capable of mitigating the presence of autoantibodies and avoiding the development of clinical disease. The objective of this study was to investigate features of autoantibody-positive (aAb+) healthy individuals' immune systems and to examine the role that cytokines might play in maintaining immune equilibrium in ANA-positive individuals without autoimmune disease.

Methods: A cohort of 790 individuals was screened by multiplex, bead based assays for autoantibodies against: dsDNA, Chromatin, Ribosomal P, SS-A/Ro, SS-B/La, Sm, Sm/RNP, RNP, SCL-70, Jo-1, and Centromere B. The levels of 52 cytokines were measured in the sera from aAb+ individuals, as well as from matched aAb- controls and SLE patients, using multiplex bead-based assays and ELISAs. Hierarchical clustering was performed with the cytokine data on all individuals and Kruskal-Wallis tests with Dunn's multiple comparisons were used to compare cytokine levels as well as a false discovery rate. Immune cell phenotyping and phospho-flow cytometry was performed on peripheral blood mononuclear cells from a subset of aAb+ and aAb- healthy individuals. Unpaired t-tests and Mann Whitney tests were performed as appropriate.

Results: Of the screened individuals, 57 individuals were positive for at least one autoantibody specificity (7.2%), with 33.3% being Native American, 57.9% European American, 8.8% African American, and 89.5% female. European American aAb+ healthy individuals (n=31) and matched aAb- healthy controls and SLE patients were selected for further analysis. While aAb+ healthy individuals displayed some similar cytokine patterns to SLE patients, they also displayed a suppressed cytokine profile that included decreased T-cell cytokines [IFNγ ($p<0.05$), IL-5 ($p<0.05$), IL-17F ($p<0.01$)], decreased B lymphocyte stimulator levels ($p<0.05$), and increased interleukin-1 receptor antagonist levels ($p<0.001$). An increased percentage of IgD+CD27+ B cells was also found in aAb+ healthy individuals ($p=0.005$). While B cells from aAb+ healthy individuals showed significantly increased pSTAT1 and pSTAT5 in response to IFNγ stimulation ($p=0.004$ and $p=0.005$), decreased pSTAT1 was seen in B cells in response to IL-2, IL-6, IL-7, IL-10, and IL-21 stimulation ($p=0.011$, $p=0.009$, $p=0.005$, $p=0.036$, and $p=0.019$, respectively). CD4+ T cells from aAb+ healthy individuals showed dramatically decreased pSTAT1 and pSTAT3 in response to IL-2 stimulation ($p=0.004$ and $p<0.001$). IFNα stimulation significantly increased pSTAT1 and pSTAT3 in monocytes from aAb+ healthy individuals ($p=0.023$ and $p=0.016$), while IFNγ stimulation significantly increased pSTAT3 ($p=0.005$).

Conclusion: Although aAb+ healthy individuals exhibit features of inflammation and loss of immune tolerance, they are capable of suppressing these responses by regulatory mechanisms likely no longer functional in patients with autoimmune disease.

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Aminopeptidase N/CD13 Localization and Chemotaxis in Rheumatoid Arthritis *In Vivo* and *In Vitro*. Rachel Morgan[1], Nilofar Behbahani-Nejad[1], Judith Endres[1] and David A. Fox[2]. [1]University of Michigan, Ann Arbor, MI, [2]Univ of Michigan Med Ctr, Ann Arbor, MI

Background/Purpose: Aminopeptidase N (CD13, EC 3.4.11.2) is a metalloproteinase expressed on the cell surface of fibroblast like synoviocytes (FLS) that has also been found in soluble form in serum and synovial fluid. We have shown that CD13 is higher in amount and activity in RA synovial fluids compared to OA. It has been suggested but not proven that CD13 can act as a chemokine for T cells in RA. The goal of this study was to determine whether FLS contribute to the CD13 in synovial fluid, and if CD13 could play a role in bringing T cells to the RA joint.

Methods: FLS were cultured in serum free media (Peprogrow) either alone, with cytokines, or with protease inhibitors. Cytokine activated T cells (Tck) were generated using IL-6, TNFα, and IL-2. The antibody 591.1D7.34, developed by our laboratory and another anti-CD13 mAb, WM15, were used to create a novel sandwich ELISA for CD13. CD13 enzymatic activity was measured in parallel by cleavage of L-leucine-7-amido-4-methyl coumarin hydrochloride (L-leu-AMC) to release the fluorescent molecule AMC. T cell chemotaxis was measured using an under agarose system. MMP14 or control siRNA was transfected into FLS and the FLS were grown up in 20% serum media and switched to serum free conditions for 6 hours prior to harvesting. GFP siRNA was used to determine success of transfection. Exosomes were isolated by centrifugation at 110,000 xg from synovial fluid, RA FLS culture supernatant or serum. Following centrifugation over an Optiprep density gradient, exosomes were obtained at 1.110–1.163 gm/ml density.

Results: Recombinant human CD13 was strongly chemotactic for cytokine activated T cells (Tck) over a range of concentrations with peak effect at 200ng/ml CD13 (3.85 chemotactic index, $p=0.0031$). Soluble CD13 was found in supernatants of FLS by ELISA (45.72±10.28 ng/ml) and enzymatic assay (497.96±167.27 nmoles of substrate cleaved per hour per ml). Among various protease inhibitors added to FLS cultures only GM6001 (a metalloprotease inhibitor) prevented release of CD13 into culture supernatants. Knockdown of MMP14 decreased FLS shedding of CD13 protein into the supernatant, as measured both by ELISA and enzymatic assay. We also found CD13 on exosomes in serum (19.16±0.64ng/ml), synovial fluid (66.55±4.68 ng/ml), and FLS culture supernatants (44.28±2.54ng/ml). In addition, the proinflammatory cytokines IFNγ, TNFα, and IL-17 all upregulated expression of CD13 mRNA by FLS, but with distinct kinetics of protein upregulation and compartmentalization induced by each cytokine.

Conclusion: CD13 is shed from the cell surface of FLS into culture supernatants and is found in synovial fluid. This process is mediated by one or more metalloproteases, including MMP14. CD13 is upregulated by proinflammatory cytokines that are commonly found in the RA joint. The combination of upregulation and shedding from FLS contributes to the high levels of CD13 in RA synovial fluid. CD13 induces chemotaxis of Tck, T cells that are similar to those found in the RA joint, at concentrations of CD13 detected *in vivo* in humans. Together this data demonstrates that CD13 could play an important role as a T cell chemoattractant, in a positive feedback loop that contributes to RA synovitis.

ACR Concurrent Abstract Session
Epidemiology and Health Services Research III: Rheumatoid Arthritis
Wednesday, November 9, 2011, 9:00 AM–10:30 AM

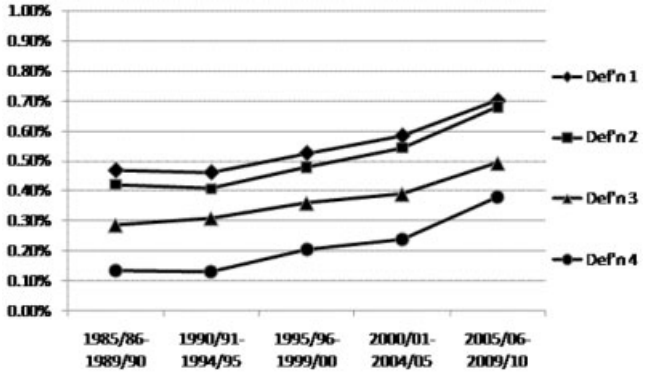
2573

Administrative Definitions of Rheumatoid Arthritis: Rising Prevalence Regardless of Definition Used. Christine A. Peschken[1], Carol A. Hitchon[2], Hui Chen[2], Allan Garland[2], Hani S. El-Gabalawy[2], Charles N. Bernstein[2] and Ruth Ann Marrie[2]. [1]Univ of Manitoba, Winnipeg, MB, [2]University of Manitoba, Winnipeg, MB

Background/Purpose: Recent studies suggest temporal changes in the incidence and prevalence of rheumatoid arthritis (RA), but are inconclusive. Administrative healthcare databases provide large comprehensive longitudinal datasets, but their accuracy for identifying RA must be established, given their use for billing purposes and the diagnostic uncertainty inherent in the disease.

Methods: In a stable population of over 900,000 adults, we used hospital and physician claims from a large administrative database to compare the effect of different case definitions on the 5-year period prevalence of RA from 1985 to 2010. For each 5 year interval, the mid-year population was used as the denominator. For physician claims, we identified RA using The 'International classification of diseases' (ICD)-9 code 714. For hospital claims we identified RA using the ICD-9 code 714 from 1985 to 2004, and the ICD-10 codes M05 & M06 from 2004 onward. Four case definitions were used: 1. ≥2 RA claims ≥2 months apart from any physician; 2. ≥2 RA claims ≥2 months apart from any physician, but excluded if there was a subsequent claim for another inflammatory arthritis or if not confirmed when seen by a rheumatologist; 3. ≥5 claims ever for RA by any physician or hospitalization if registered in the database at least 2 years; or ≥3 claims if registered in the database for < 2 years; 4. ≥2 RA claims ≥2 months apart from a rheumatologist.

Results: The prevalence rate for RA ranged from 0.14% to 0.47% in 1985–1990, and rose steadily to .38%-.70% in 2005–2010, depending on the case definition of RA (Figure 1).



Conclusion: Irrespective of the definition used, we found a steady rise in the prevalence of RA over the 25 year period, similar to the rise in prevalence recently described in Olmsted County. This may reflect true increased incidence, or improved ascertainment due to increasing awareness of RA among physicians, particularly with respect to early diagnosis of RA. Improved ascertainment is supported by the slightly steeper increase in the rate of patients followed by rheumatologists (definition 4) as rheumatology manpower in the region doubled

between 2000 and 2010. This study also demonstrates that only a small proportion of RA patients are followed by rheumatologists (Def'n 4), with most receiving no or episodic rheumatology care. Further attempts at determining diagnostic accuracy and disease outcomes in this 'gap' population using linkages with clinical and prescription databases are underway.

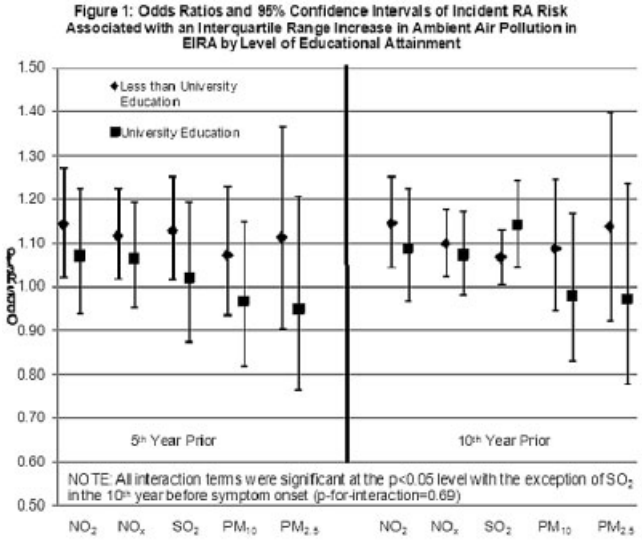
2574

The Association of Ambient Air Pollution Exposures and Risk of Rheumatoid Arthritis: Results From the Swedish EIRA Case-Control Study and the US Nurses' Health Prospective Cohort Study. Jaime E. Hart[1], Henrik Källberg[2], Francine Laden[3], Karen H. Costenbader[1], Marie Holmqvist[2], Lars Klareskog[2], Lars Alfredsson[4] and Elizabeth W. Karlson[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Karolinska Institutet, Stockholm, Sweden, [3]Harvard School of Public Health, Boston, MA, [4]Institute of Environmental Medicine, Unit of Cardiovascular Epidemiology, Karolinska Institutet, Stockholm, Sweden

Background/Purpose: Environmental factors play an important role in the development of rheumatoid arthritis (RA), and airway exposures to environmental agents are postulated to be of special importance. We examined whether long-term exposures to ambient air pollution were associated with risk of RA in the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) Study and in the US Nurses' Health Study (NHS).

Methods: We studied 1,330 incident RA cases and 2,235 controls from EIRA and 91,203 members of the NHS, among whom 762 had developed RA. Exposures to particulate matter (PM_{10}, $PM_{2.5}$) and gaseous pollutants (SO_2, NO_2, and NO_x, in EIRA only) were predicted for all residential addresses. We examined the association of an interquartile range increase in each air pollutant with the risk of RA, and risks of seropositive (rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA)) RA phenotypes, using multivariable logistic regression for EIRA and Cox proportional hazards models for NHS. Models in EIRA were adjusted for age, gender, smoking status, and educational attainment. Models in NHS were adjusted for age, race, reproductive factors, hormone use, physical activity, body mass index, smoking status and pack-years, and individual and area level measures of socioeconomic status. As the relevant etiological time period of exposure is unknown, we examined pollution in various years before RA onset.

Results: In both studies there was no evidence for an increased risk of RA with PM_{10} or $PM_{2.5}$ in any exposure window or with any pollutant in the year of onset, and in some cases modest inverse associations were observed. In EIRA, elevated risks with increases in SO_2, NO_2, and NO_x in the 10^{th} and 20^{th} years prior to RA symptom onset were observed, particularly in models restricted to RF+ and ACPA+ phenotypes. For each interquartile range increase (2 $\mu g/m^3$ for SO_2, 7 $\mu g/m^3$ for NO_2, and 8 $\mu g/m^3$ for NO_x) in exposure in the 10^{th} year prior to onset, the fully-adjusted odds ratios for ACPA+ RA (95% confidence intervals (CI)) were 1.07 (1.01–1.13), 1.11 (1.01–1.21) and 1.07 (1.00–1.14) for SO_2, NO_2, and NO_x respectively. Results were strongest in individuals with less than a university education (Figure 1). In the NHS, only exposures to SO_2 were associated with modest increases in total RA risk (fully adjusted hazard ratio (95%CI) for an interquartile range (16 $\mu g/m^3$) increase in SO_2 10 years prior to onset 1.05 (0.92–1.19)).



Conclusion: In EIRA, we observed elevations in the odds of developing RA and seropositive RA in individuals with higher levels of gaseous air pollution exposures, particularly SO_2. These risks were strongest in those with less than a university education. In NHS, we observed modest elevations only with increasing exposures to SO_2. To the best of our knowledge, this is the first study to examine the effects of air pollution on risk of RA.

2575

The Performance of Matrix-Based Risk Models for Rapid Radiographic Progression in An Observational Cohort of Established Rheumatoid Arthritis Patients. Siri Lillegraven[1], Femke H.M. Prince[2], Nancy A. Shadick[2], Espen A. Haavardsholm[3], Michelle A. Frits[2], Christine K. Iannaccone[2], Tore K. Kvien[3], Michael E. Weinblatt[2] and Daniel H. Solomon[2]. [1]Brigham and Women's Hospital/Diakonhjemmet Hospital, Boston/Oslo, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Diakonhjemmet Hospital, Oslo, Norway

Background/Purpose: Matrix-based clinical risk prediction models have been proposed as a tool to forecast rapid radiographic progression (RRP, defined as ≥ 5 units change in Sharp score/year) in rheumatoid arthritis (RA). The three current models are based on data from clinical trials in early RA, and each model includes 4 of the following variables: treatment, joint erosions, serological status, swollen joint count, CRP and smoking. These models allow calculation of the predicted probabilities for RRP, similar to the use of the Framingham risk score. We tested the performance of the three risk models in an observational cohort with established RA.

Methods: Subjects in BRASS, an observational RA cohort with treatment according to clinical practice, were analyzed. 478 individuals had hand radiographs scored by the Sharp method at baseline and 2 years. All received disease modifying anti-rheumatic drugs (DMARDs) according to typical clinical practice. The three matrix-based risk models assessed were: A) the ASPIRE model[1], B) the BeSt model[2] and C) a model from the second year of the SWEFOT trial[3]. As the models suggest, we calculated separate risk scores for patients using synthetic DMARDs vs. biologics. Patients were classified as having RRP (cases) or not (non-cases) and allocated to the correct matrix cell for each model, with a corresponding predicted risk of RRP. The mean predicted probability for cases and non-cases, the net reclassification improvement (NRI) with continuous outcome, integrated discrimination improvement (IDI) and area under the receiver operating curve (AUC) were calculated for each model.

Results: The median (IQR) age for the 478 patients was 59 (50, 66) years, disease duration 12 (4, 23) years, swollen joint count 6 (2, 13) and tender joint count 7 (1, 4). 84% were female and 86% had presence of erosions at baseline. The percentage of patients with RRP was 12% (32 of 271) in the synthetic DMARD group and 10% (21 of 207) in the biologic DMARD group (either as monotherapy or in combination with synthetic DMARDs). Model statistics summarized in the table indicated that Model B fit our data best, but none of the models separated cases and non-cases well in this cohort.

	Discrimination				*Classification*	
	Model A	Model B	Model C		*Model A vs. model B*	Model B vs. Model C
Mean predicted probability cases/non-cases	9.8/9.1	29.6/20.2	22.3/20.2	**IDI * ‡**	8.7	−7.3
AUC	0.631	0.716	0.617	**NRI with continuous outcome * #**	42	−32.8

* For both NRI and IDI a positive number indicates better performance of the comparator model (mentioned last in the column heading)
‡ IDI compares the difference in mean predicted probability between cases and non-cases for two models
# NRI compares the ability of two models to correctly classify cases and non-cases

Conclusion: Matrix risk models developed in randomized clinical trials of patients with early RA had limited value in this observational cohort of RA patients with established disease. Limitations of this study include lack of feet radiographs, which might have led to fewer patients being classified as RRP, and potential confounding by treatment indication. The value of matrix risk models for RRP might be greater in early RA; larger cohorts may allow for better development and testing of such models. Furthermore, it may be necessary to develop separate risk models for RRP in established disease.

References:

[1] Vastesaeger et al, Rheumatology 2009
[2] Visser et al, ARD 2010[3] Engström et al, EULAR 2011 (abstract)

2576

Are Biologics Cost-Effective? Analysis Based on Real-Life Rheumatoid Arthritis Patients. Hawre Jalal[1], Kaleb Michaud[2], Hyon K. Choi[3], Young Hee Rho[3] and Karen Kuntz[1]. [1]University of Minnesota, Minneapolis, MN, [2]National Data Bank for Rheumatic Diseases & University of Nebraska Medical Center, Omaha, NE, [3]Boston University School of Medicine, Boston, MA

Background/Purpose: Previous cost-effectiveness analyses (CEAs) of biologics for rheumatoid arthritis (RA) based on randomized controlled trials (RCTs) have been limited by short time horizon, failure to properly incorporate adverse events (AE) and discontinuation rates, and poor generalizability to real-world effectiveness. The cost-effectiveness of biologics in real-life RA patients has not been adequately explored. Our objective was to conduct CEAs of several commonly adopted treatment strategies involving sequential use of biologics based on an observational study.

Methods: We developed a Markov simulation model to estimate quality-adjusted life years (QALYs) and costs associated with several treatment strategies for RA patients over the lifespan. We evaluated strategies based on different sequences of 5 biologics (etanercept, infliximab, adalimumab, abatacept, and rituximab) compared to conventional non-biologic DMARDs. We modeled the discontinuation rate of each biologic as well as the reason (i.e. serious AE, cost of medication, or ineffectiveness). Those who discontinued because of ineffectiveness were allowed to transition to the next biologic in the sequence based on the probability of switching biologics in an observational study (the National Data Bank [NDB]). Those who discontinued because of the other reasons switched to nonbiologics. Markov health states were defined by Health Assessment Questionnaire (HAQ) scores and the types of medication the patients received. Transition probabilities, effectiveness measures (i.e., HAQ score improvements), AE rates, quality of life weights, and discontinuation rates were estimated from the NDB. Direct and indirect costs (2009 US dollars) were obtained from the literature. Both costs and effectiveness are discounted by 3% annually.

Results: Biologics were generally more effective than nonbiologics. The most cost-effective sequence of biologics was Etanercept -> Infliximab -> Adalimumab (EIA), with an incremental lifetime effectiveness of 0.1 QALYs compared to nonbiologics. The EIA strategy had an incremental lifetime cost of about $150,000 yielding an incremental cost-effectiveness ratio (ICER) >$1M/QALY, which is well above willingness to pay (WTP) thresholds considered acceptable. In a sensitivity analysis, we increased the HAQ improvement from rates reported in the NDB to those typically reported in trials (Table). Biologic strategies became cost-effective at WTP thresholds of $200K/QALY. However, this ICER is still higher than those reported in RCT-based CEAs.

Table. Cost-Effectiveness of Sequential Biologic Use (EIA) According to Assumptions

Sensitivity Analysis Assumptions	Cost ($)	Incremental Cost ($)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER ($/QALY)
Primary Model	192,905	149,421	13.53	0.10	1,485,800
A	169,738	126,017	14.29	0.75	166,600
A + B	169,183	125,656	14.03	0.57	216,900
A + C	162,520	119,448	13.85	0.74	160,100
A + D	149,189	108,050	12.74	0.54	199,600

A = HAQ progression rates are equivalent to those in RCTs of biologics.
B = There is additional mortality due to serious adverse events.
C = Study population's HAQ ranges between 1.1 and 2.0.
D = Study population's HAQ ranges between 2.1 and 3.0.

Conclusion: We used real-life observational data to model sequences of biologic use, discontinuation rates, and AEs. Using these observational data, we were unable to observe the cost-effectiveness reported by RCT-based CEA. The primary reasons for this discrepancy relate to a lower incremental effectiveness of biologics in real-life compared to RCTs.

2577

Statins and Risk of Acute Myocardial Infarction in Patients with RheumatoidArthritis: A Population-Based Study. Mary De Vera[1], Diane Lacaille[1], Michal Abrahamowicz[2], Jacek A. Kopec[1] and Hyon K. Choi[3]. [1]Arthritis Research Centre of Canada, Vancouver, BC, [2]McGill UHC/RVH, Montreal, QC, [3]Boston University School of Medicine, Boston, MA

Background/Purpose: Given their lipid lowering and anti-inflammatory properties, statins are postulated to have dual cardioprotective and anti-inflammatory benefits in rheumatoid arthritis (RA), a chronic arthritis associated with systemic inflammation and significant cardiovascular disease comorbidity. Our objective was to quantify the impact of statin initiation on risk of acute myocardial infarction (AMI) in a population-based cohort of RA patients.

Methods: We conducted a longitudinal study of statin initiators and non-initiators in a population-based cohort of RA patients followed from May 1996 to March 2006 using data from the British Columbia Ministry of Health. Utilization data for all provincially funded health services, including physician visits and hospitalizations, were obtained for all cohort members. We also obtained complete information on all prescription medications dispensed by pharmacists from January 1996 onwards, as well as mortality data from vital statistics, including date and cause of death. Non-fatal and fatal AMI outcomes were ascertained using hospitalization and Vital Statistics data. We applied propensity score methods to adjust for differences between statin initiators and non-initiators, and used Cox's proportional hazards models to evaluate the association between statin initiation and risk of AMI.

Results: During 15,271 person-years of follow-up in the propensity-score matched cohort of 3,104 statin initiators and 3,104 non-initiators, we identified 261 AMI events (incidence rates, 1.5 and 2.1 per 100 person-years in initiators and non-initiators, respectively). After adjusting for confounding by indication, the hazard ratio (HR) for AMI for statin initiators compared to non-initiators was 0.69 (95% CI, 0.54–0.90). Additional adjustments including the propensity score (HR, 0.68; 95% CI, 0.53–0.88) or unbalanced covariates (HR, 0.68; 95% CI, 0.52–0.88) did not materially change results.

Conclusion: These population-based data indicate that statin use among RA patients is associated with a 31% lower risk of AMI. Findings provide evidence for a postulated cardioprotective role of statins in patients with RA.

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Quality of Care for Common Comorbidities Among Patients with Rheumatoid Arthritis: An Analysis of HEDIS Data. Gabriela Schmajuk[1], Laura Trupin[2], Chris Tonner[3], Amal N. Trivedi[4], Edward Yelin[3] and Jinoos Yazdany[5]. [1]University of California - San Francisco, San Francisco, CA, [2]UC San Francisco, San Francisco, CA, [3]UCSF, San Francisco, CA, [4]Brown University, Providence, RI, [5]University of California San Francisco, San Francisco, CA

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk for cardiovascular disease and osteoporosis compared to the general population. We compared the performance on HEDIS (Health Plan Employer Data and Information Set) quality measures assessing care for comorbidities common in RA (hypertension, diabetes, hypercholesterolemia, and osteoporosis) among individuals with RA compared to the general (non-RA) population.

Methods: We analyzed individual-level HEDIS data for 8,946,881 persons at least 65 years old enrolled in Medicare managed care plans during 2009. Demographic and socioeconomic characteristics were identified through the Medicare beneficiary summary file; ZIP-code-based socioeconomic status was calculated using the Agency for Healthcare Research and Quality's socioeconomic status (SES) index score. Based on the HEDIS RA measure denominator, we identified patients who carried a diagnosis of RA. We calculated performance on 4 HEDIS measures in eligible patients from the RA and non-RA subsets. We used multiple logistic regression to estimate the effect of having RA on measure performance after adjusting for sociodemographic characteristics (sex, age, race, personal income, and ZIP-code-based SES). As a sensitivity analysis, we restricted the RA subset to patients who received a DMARD in order to increase the specificity of RA diagnoses.

Results: The non-RA population (n = 8,867,530) was 58% female, 82% white, and had a mean age of 75.0 years (SD 7.3). Patients in the RA subset (n = 79,351) were 76% female, 82% white, and had a mean age of 75.2 years (SD 6.7). Seventy two percent of RA patients received a DMARD in 2009. Performance on 4 HEDIS measures ranged from 33 to 62% in RA patients and 21–59% in non-RA patients (see Table). With and without adjustment, RA patients were at least as likely to fulfill each measure compared with non-RA patients. A sensitivity analysis comparing HEDIS performance for RA patients who received DMARDs to non-RA patients yielded similar results (data not shown).

HEDIS measure*	Non-RA population Eligible N	Non-RA population Measure performance (%)	RA population Eligible N	RA population Measure performance (%)	Unadjusted OR (RA vs. non-RA)	Adjusted OR† (RA vs. non-RA)
Blood pressure < 140/90 mm Hg in enrollees with hypertension	141,969	59.4	1,598	61.6	1.08 (0.97, 1.19)	1.12 (1.01, 1.24)
Hemoglobin A1C < 8% for enrollees with diabetes	251,344	40.3	2,305	40.9	1.02 (0.94, 1.11)	1.03 (0.95, 1.12)
LDL-C level less than 100 mg/dL for enrollees after a coronary event	162,519	44.5	1,820	43.7	0.97 (0.88, 1.06)	1.04 (0.95, 1.15)
BMD testing and osteoporosis treatment for female enrollees after fracture	109,010	21.3	1,924	33.1	1.82 (1.65, 2.00)	1.76 (1.60, 1.94)

* Technical specifications provided by National Committee for Quality Assurance
† Compared to non-RA performance, adjusted for age, sex, race, personal income, and ZIP-code-based SES.

Conclusion: In this national sample of patients with RA in Medicare managed care plans, management of common comorbid conditions needs improvement. With the exception of osteoporosis testing and treatment, clinical performance on chronic disease quality measures was similar for patients with and without RA.

ACR Concurrent Abstract Session
Metabolic and Crystal Arthropathies II: Concurrent Session on the Anti-Gout Medications - Dosing, Adverse Effects, and Economic Burden
Wednesday, November 9, 2011, 9:00 AM–10:30 AM

2579

Starting Dose, but Not Maximum Maintenance Dose, Is a Risk Factor for Allopurinol Hypersensitivity Syndrome: A Proposed Nomogram for Safe *Starting* Dosing of Allopurinol. Lisa K. Stamp[1], William Taylor[2], Peter B. B. Jones[3], Jo L. Dockerty[4], Jill Drake[5], Christopher Frampton[1] and Nicola Dalbeth[6]. [1]University of Otago, Christchurch, New Zealand, [2]University of Otago, Wellington, New Zealand, [3]Waikato Clinical School, Waikato Hospital, Hamilton, New Zealand, [4]Dunedin Hospital, Dunedin, New Zealand, [5]Christchurch Hospital, Christchurch, New Zealand, [6]University of Auckland, Auckland, New Zealand

Background/Purpose: Allopurinol is the most commonly used urate lowering therapy in gout. Allopurinol hypersensitivity syndrome (AHS) is a rare but potentially fatal adverse event. Risk factors include female sex, age, renal impairment, diuretic use, recent commencement of allopurinol therapy and in some ethnic groups HLA-B*5801. The relationship between allopurinol dose and AHS is controversial. Dosing guidelines based on CrCL have been proposed based on the recognition that doses ≥300mg/d may be associated with AHS, particularly in patients with renal impairment. However, the relationship between allopurinol starting dose and AHS is unknown. The aim of this study was to determine the relationship between allopurinol dosing and AHS.

Methods: A retrospective case-control study of gout patients who developed AHS between January 1998 and September 2010 was undertaken. For each case three controls with gout receiving allopurinol who did not develop AHS were identified. Controls were matched on gender, diuretic use at the time of commencing allopurinol, age ± 10 years, and eGFR. Analysis compared starting dose and maximally achieved dose between cases and controls.

Results: Fifty-four AHS cases and 157 controls were identified. Multivariate analysis allowing for matching between cases and controls, showed that the presence of tophi was associated with a reduced risk of AHS (OR=0.29, 95%CI 0.01 – 0.83; p<0.021). Compared with New Zealand Europeans there was a decreased risk of AHS in patients of Maori and Pacific Island descent (OR=0.24, p=0.02) and an increased risk of AHS in those of Chinese descent (OR=70.8, p=0.005). There was an increase in risk of AHS as the starting dose of allopurinol corrected for CrCL increased. For the highest quintile of starting dose/CrCL, the odds ratio was 23.2 (p<0.01) (Figure 1a). There was no significant difference in the means of the maximum doses of allopurinol ever achieved between cases and controls (Figure 1b). No risk relationship was observed between AHS and maximum dose. Using ROC analysis, starting allopurinol at a dose ≥1.5mg allopurinol/CrCL (mg/ml/min) was associated with 90% sensitivity and 37.5% specificity for AHS.

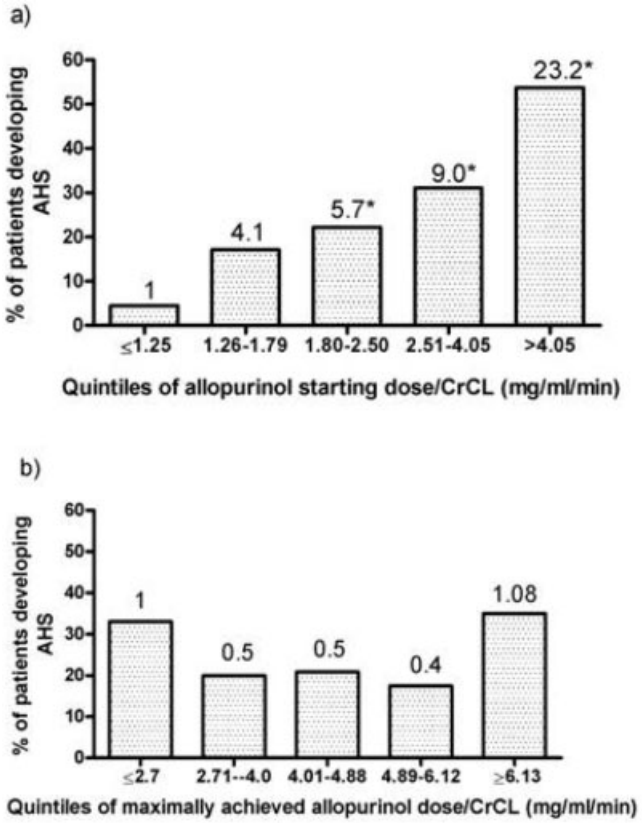


Figure 1. a) The percentage of patients developing AHS in each quintile of starting allopurinol dose/CrCL and the odds ratio for each quintile (*p<0.05). b) The percentage of patients developing AHS in each quintile of maximally achieved allopurinol dose/CrCL and the odds ratio for each quintile.

Conclusion: Starting allopurinol at a dose of 1.5mg/CrCL may greatly reduce the risk of AHS. These data provide information required for a new dosing nomogram, based on a starting dose of 1.5mg/CrCL. Progressive up-titration of dose to achieve the target serum urate is not associated with an increased risk of AHS. Further large prospective clinical trials of such a dosing strategy are required.

2580

Severe Cutaneous Reactions Requiring Hospitalization in Allopurinol Initiators. Seo Young Kim[1], Craig Newcomb[2], David Margolis[2], Jason Roy[2] and Sean Hennessy[2]. [1]Brigham & Women's Hospital, Boston, MA, [2]University of Pennsylvania, Philadelphia, PA

Background/Purpose: Allopurinol, an effective urate-lowering drug, is primarily prescribed for patients with gout. Although rare but potentially life-threatening cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been associated with use of allopurinol, population-based data on incidence and mortality of such reactions is scarce.

Methods: We conducted a large-scale cohort study using the Medicaid claims data (1999–2005) from 5 states with Medicare claims for dual-eligibles. Adults who had at least 180 days of Medicaid eligibility and at least one medical claim present before the first prescription of allopurinol were identified. Subjects with malignancy were excluded. Primary outcome was hospitalization for severe cutaneous reactions identified by the principal discharge diagnosis code 695.1 for erythema multiforme and related conditions, such as SJS and TEN, after initiation of allopurinol. Cumulative incidence rate (IR) and in-hospital mortality was estimated among new users of allopurinol. Age-standardized IR among non-allopurinol users was also estimated for a comparison. Multivariable Cox regression model was used to

compare the risk between the high-dose (≥ 300mg/day) and low-dose allopurinol group after adjustment for potential confounders.

Results: There were a total of 90,358 allopurinol initiators with a mean age of 65.5 (SD 15.6) years. During a follow-up period of 65,625 person-years, 45 were hospitalized with severe cutaneous reactions. Crude IR was 0.69 (95 %CI 0.50–0.92) per 1,000 person-years. All 45 cases occurred within the first 365 days and 41 (91.1%) within the first 180 days (Table 1). Twelve (26.7%) patients died during the hospitalization. Age-standardized IR in non-allopurinol users was 0.03 (95% CI 0.02–0.04) per 1,000 person-years. Age-adjusted rate ratio was 22.98 (95% CI 16.76–30.77) in allopurinol initiators. In our multivariable analysis adjusting for age, comorbidities and recent use of any diuretic, HR was 1.57 (95% CI 0.87–2.84) for the high-dose allopurinol users.

Table 1. Incidence rates (IR) of hospitalization for severe cutaneous reactions in allopurinol initiators

	Number of events	IR (95% CI) per 1,000 person-years
First 365 days	45	0.69 (0.50–0.92)
First 180 days	41	1.51 (1.08–2.05)
First 30 days	20	2.77 (1.69–4.28)

Conclusion: Severe cutaneous reactions in allopurinol initiators were found to be rare but often fatal and occurred mostly in the first 180 days of treatment. Compared to non-allopurinol users, risk of severe cutaneous reactions was 23 times greater in allopurinol initiators. Despite our large study size, we had little precision in estimating the risk relative to different dosage of allopurinol and various exposures to other drugs including specific diuretics.

2581

Colchicine Dosing Guidelines for Gout Patients with Varying Degrees of Renal Impairment Based on Pharmacokinetic Data. Suman Wason, Robert D. Faulkner and Matthew W. Davis. URL Pharma, Philadelphia, PA

Background/Purpose: Dosing of colchicine (Col) in gout patients with renal impairment is currently based on empirical data. This study obtained single-dose pharmacokinetic (PK) data in healthy subjects and subjects with varying degrees of renal impairment to allow predictions of Col steady state concentrations following 1.2mg/day Col given as 0.6 mg twice daily (the currently recommended dose of colchicine for gout flare prophylaxis). Based on these findings, dosing recommendations are made for renally impaired patients who require gout flare prophylaxis to achieve desired Col concentrations (i.e. ~2 ng/mL).

Methods: In this open-label, parallel-group study, 8 subjects in each group were randomized, based on Creatinine Clearance (CrCl), to receive a single dose of oral Col 0.6 mg as follows:

Healthy normal (CrCl> 90 mL/min), mild decrease renal function (CrCl >50 – 90 mL/min), moderate decrease renal function (CrCl >30 – 50 mL/min), severe decrease renal function (CrCl >15 – 30 mL/min), and end-stage renal disease (ESRD) (on and off dialysis, separated by 14 days) CrCl not determined.

Results: Col PK parameters were similar for subjects with normal renal function, subjects with mild renal impairment, and ESRD patients on and off dialysis. However, in subjects with moderate and severe renal impairment, Col clearance was reduced, resulting in higher AUC (approximately 2-fold increase) and Cmax (up to 1.5-fold increase). The single-dose data were then used to predict steady state (10 days) concentrations of Col following the recommended colchicine 0.6 mg twice daily regimen. With twice-daily dosing to steady state, Col concentrations in normal subjects, those with mild decrease, and those in ESRD averaged ~2 ng/mL. These concentrations were greatly exceeded in patients with moderate and severe renal impairment (Col concentrations ~5–6 ng/mL), suggesting that these groups require dosage adjustment.

Metabolites

Despite the reduced clearance of Col in renally impaired subjects, there was no difference in accumulation of metabolites in patients with moderate and severe renal impairment compared to the other groups.

ESRD and dialysis

On the day of dialysis, subjects were given Col 0.6 mg and dialyzed for 3–4 hrs beginning at one-hour post-dose. While on dialysis, the concentrations were generally lower by approximately 0.5 ng/mL.

Conclusion: Based on these data, for the prophylaxis of gout flares, no dosing adjustments are needed for patients with normal renal function or mild impairment (CrCl >50 mL/min) or ESRD on or off hemodialysis. For patients with moderate and severe renal failure (CrCl <50 mL/min), it is recommended that Col dose be reduced 50% (i.e. for those patients requiring 0.6 mg twice daily, the dose should be decreased to 0.6 mg once a day, and for those requiring 0.6 mg once a day, the dose should be decreased to 0.3 mg per day).

2582

Characterization and Management of Infusion Reactions in Refractory Chronic Gout (RCG) Treated with Pegloticase (PGL). Herbert Baraf[1], Robert A. Yood[2], John S. Sundy[3], Faith D. Ottery[4], Zeb D. Horowitz[5] and Michael A. Becker[6]. [1]Arthritis & Rheumatism Assoc, Wheaton, MD, [2]Fallon Clinic, Worcester, MA, [3]Duke University Medical Center, Durham, NC, [4]Savient, East Brunswick, NJ, [5]Celgene Corporation, Basking Ridge, NJ, [6]University of Chicago Medical Center, Chicago, IL

Background/Purpose: PGL is a pegylated mammalian recombinant uricase approved for treatment of pts with RCG, defined by hyperuricemia, progressive gout with signs/ symptoms reflecting inadequate urate control and refractoriness or contraindication to xanthine oxidase inhibitors.

Methods: 212 pts with RCG were treated with PGL 8 mg (q2wks or q4wks) or placebo (PBO) in 2 replicate 6-month blinded randomized controlled trials (RCTs). IR was defined as an adverse event (AE) occurring during or within 2 hrs of infusion. Safety was assessed by AE reports and lab tests. Pts received IR prophylaxis (fexofenadine 60 mg the night before infusion and again with acetaminophen1000 mg in AM, with hydrocortisone 200 mg i.v. just before each infusion). Flare prophylaxis (colchicine, NSAIDs or both) was used throughout the trial. Analysis of IRs by serum urate (SUA) is based on a post hoc analysis, increased risk of IR if SUA levels returned to >6 mg/dL after initial reduction. RCT completers could enroll in an open label extension (OLE) trial with PGL treatment for up to an additional 2.5 years.

Results: Of 212 pts enrolled, 157 completed the RCTs and 151/157 entered the OLE (149 on PGL, 2 observed). The most common AEs reported were gout flares and IRs. Flares were common at baseline, with initial increase and then decrease (Months 4–6) in pts with SUA <6 mg/dL and continued decrease in the OLE. The 169 pts randomized to PGL had 115 IRs in 3391 infusions (RCT+OLE). For the 43 PBO pts, 39 entered the OLE and had 85 IRs (4 on PBO, 81 on PGL) in 1296 infusions. Most IRs occurred after loss of PGL response (SUA >6 mg/dL): 105/115 IRs (91%) in the RCTs and 232/265 IRs (88%) in the OLE. The most common symptoms reported during IRs included chest pain or discomfort, back pain, flushing, nausea ± vomiting, erythema, muscle spasms, abdominal complaints, dyspnea, headache, hyperhidrosis, blood pressure changes (increase or decrease), urticaria, and pruritus; intensity varied from mild to severe. All IRs resolved with supportive measures that included slowing or stopping the infusion and/or 1 or more interventions that included: antihistamines, fluids, corticosteroids, analgesics. One pt received epinephrine for wheezing. No patient required intubation and no deaths resulted from an IR.

Conclusion: These findings suggest that the occurrence of infusion reactions during pegloticase therapy can be significantly abated by routine pre-infusion serum urate measurement and discontinuation of pegloticase therapy with loss of response, i.e., return of SUA to >6 mg/dL after initial reduction. This combination of loss of efficacy and increased risk of IRs adversely alters the benefit/risk ratio of pegloticase therapy and mandates that treatment should be discontinued, particularly if 2 consecutive pre-infusion urate values >6 mg/dL are observed.

IR rates per 100 infusions

	SUA < 6mg/dL	SUA >6mg/dL
RCT	0.5	4.8
OLE	0.8	5.5

2583

Economc Burden of Gout Patients Treated with Urate Lowering Therapy. Anna Forsythe[1] and Hyon K. Choi[2]. [1]Savient Pharmaceuticals, Inc., East Brunswick, NJ, [2]Boston University School of Medicine, Boston, MA

Background/Purpose: Gout is an inflammatory arthritis associated with substantial morbidity by causing tremendous pain and suffering. While gout could lead to increased resource utilization and associated medical costs[1], the

relevant data are limited. We evaluated the burden of illness, resource utilization and costs among adult gout patients treated with a xanthine oxidase inhibitors (XOI, allopurinol or febuxostat) in US managed care health plans.

Methods: We estimated the annual resource utilization and direct costs using IMS LifeLink™ Health Plan Claims Database. The study population consisted of individuals aged ≥18 years with a gout diagnosis (ICD-9-CM: 274.xx) and a XOI claim from 10/1/2008 to 9/30/2009 with the date of the first therapy as the index date. Subjects also needed to continue health plan enrollment for ≥6 months prior to and ≥12 months after the index date and to be covered by Medicare Risk if aged ≥65 years. We defined a gout flare as a gout diagnosis code followed by a claim for NSAIDs, colchicines, corticosteroids, ACTH, or intra-articular aspiration or injection within 7 days, or a diagnosis for joint pain (ICD-9-CM: 719.4) followed by a claim for colchicine within 7 days. Using Chi square tests, we compared patients: (1) with tophi and ≥3 flares vs. without tophi or flares (=controls); (2) with tophi and ≥6 flares vs. controls; and (3) with febuxostat use vs. with allopurinol use. The health plan's allowed amount was used as a proxy for medical costs.

Results: We identified 24,503 XOI-treated gout patients (mean age = 54 years old and 87% male). Comorbidities were similar between those with tophi and ≥3 flares (N=116) and controls (N=15,165). Those with tophi and ≥6 flares (N=21) had a higher rate of hypertension and dyslipidemia than controls ($p<0.05$). Febuxostat users (N=354) had a higher rate of pre-index chronic kidney disease than allopurinol pts (N=24,149, $p<0.001$). Patients with tophi and ≥3 flares had significantly more physician office visits (mean: 17.8 vs. 9.0), laboratory services (mean: 23.6 vs. 12.3), and ancillary services (mean: 23.8 vs. 12.2) than controls (all *p-values* <0.001). Febuxostat patients had more physician office visits (mean: 11.8 vs. 9.7 $p<0.001$) and laboratory services (mean: 16.6 vs. 13.2, $p<0.001$) vs. allopurinol patients. Febuxostat patients used colchicines (53.1%) more often than allopurinol patients (32.2%, $p<0.001$). Total 12-month post-index costs averaged $21,059 among patientswith tophi and ≥3 flares vs. $10,657 ($p<0.001$) in controls. Patients with tophi and and ≥6 flares (N=21) had even higher resource utilization and total healthcare costs of $32,178 (p<0.01) than controls. Febuxostat patients incurred $3,471 higher total outpatient and inpatient medical costs vs. patients on allopurinol.

Conclusion: Our findings indicate that annual resource utilization and costs are substantial among those with tophi and frequent flares. As anticipated, patients with tophi and flares incurred considerably greater costs than those without these features. The economic burden associated with these features should be considered in determining cost-effectiveness of gout management.

Reference:
Wu EQ, et al. 2011

2584

Arhalofenate, a Potential Novel Treatment for Hyperuricemia, with or without Metabolic Co-Morbidities, in Patients with Gout: Meta-Analysis of Urate Lowering in Four Phase 2 Studies in Type 2 Diabetes. Gopal C. Saha, David B. Karpf, Yun-Jung Choi and Brian K. Roberts. Metabolex, Inc., Hayward, CA

Background/Purpose: Hyperuricemia, the cardinal underlying feature of gout, is attributable to under-excretion of uric acid by the kidneys in about 90% of patients. In addition, the majority of gout patients have metabolic co-morbidities such as insulin resistance (pre-diabetes or type 2 diabetes) and hypertriglyceridemia. Many gout patients also have impairment in renal function. Arhalofenate is a novel oral agent that has completed a total of eight phase 1 and four phase 2 studies in healthy volunteers and patients with type 2 diabetes. In phase 1, oral once daily dosing of arhalofenate up to 1000 mg for 10 days demonstrated excellent PK with a half-life of approximately 60 hours. Recent *in vitro* studies have demonstrated that arhalofenate is a uricosuric agent that inhibits the URAT-1 transporter. This abstract reports the effect of arhalofenate on serum urate, as well as glucose and triglyceride levels, from the phase 2 clinical studies conducted to date.

Methods: During development as an insulin sensitizer for type 2 diabetes, a total of four global, randomized, double-blind, controlled phase 2 studies (totaling 955 patients) were conducted to evaluate the safety, PK, and efficacy of once daily oral administration of arhalofenate. Serum urate was measured prospectively, in blinded fashion, using a standard uricase method. A meta-analysis of serum urate results for all compliant patients (detectable study drug in serum) in the phase 2 studies was completed.

Results: In phase 2 studies, administration of arhalofenate at doses of 200, 400, and 600 mg for as long as 24 weeks resulted in significant reductions in fasting glucose (5–20%), HbA1c (0.2–0.6%), and triglycerides (5–20%). Additionally, arhalofenate demonstrated clinically meaningful and statistically significant dose-dependent reductions from baseline in serum urate (mean baseline ~5.0 mg/dL) of 13%, 22%, and 29% for the arhalofenate 200 mg (n=125), 400 mg (n=174), and 600 mg (n=159) groups, respectively, compared to placebo (n=252; p<0.0001 for all dose groups). Patients with mild to moderate renal impairment and those taking aspirin or diuretics experienced comparable reductions in serum urate. Of those patients with a baseline serum urate ≥6.0 mg/dL (mean 6.8–7.1 mg/dL), arhalofenate at doses of 200 mg (n=29), 400 mg (n=37), and 600 mg (n=35) resulted in 48%, 78%, and 83% of patients achieving a serum urate target of <6.0 mg/dL at the end of the study compared to 25% in the placebo group (n=61). Overall, daily treatment with arhalofenate for up to 24 weeks was found to be safe and well tolerated, with no effects on urine pH and no cases of urolithiasis.

Conclusion: Arhalofenate is a novel, oral uricosuric agent which has shown significant and dose-dependent reductions in serum urate and other metabolic parameters in several studies conducted to date in healthy volunteers and patients with type 2 diabetes. Arhalofenate is a potential therapy for treatment of chronic hyperuricemia, with or without metabolic co-morbidities, in patients with gout. Phase 2 proof-of-concept studies in monotherapy, and as add-on to XO-inhibitors, have been initiated in the target population of gout patients with hyperuricemia.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Clinical Aspects: Risk of Cardiovascular Disease
Wednesday, November 9, 2011, 9:00 AM–10:30 AM

2585

Risk of Cardiovascular Disease in Rheumatoid Arthritis Is Independent of Disease Duration and the Level of Disease Activity. Elke.E.A. Arts[1], Jaap Fransen[1], Alfons den Broeder[2], Calin Popa[1] and Piet L.C.M. Van Riel[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Sint Maartenskliniek, Nijmegen, Netherlands

Background/Purpose: Chronic inflammation may act as an independent risk factor for cardiovascular disease (CVD) in rheumatoid arthritis (RA). However, the level of inflammation apparently does not contribute to the risk of CVD in RA patients. Probably, disease duration is more important than the level of inflammation. Indeed, EULAR recommendations for cardiovascular risk management in RA do identify RA disease duration of >10 years as CV risk factor. Hence the objective of this study was to investigate the relationship between duration of inflammation and risk of CVD in RA patients, corrected for the level of inflammation.

Methods: All RA patients with a follow-up time of ≥ 6 months in the Nijmegen early RA cohort without a cardiovascular history were included in this study. The time-averaged DAS28 was calculated for each patient. The effect of disease duration on the risk of developing the first cardiovascular event was estimated by means of Kaplan-Meier survival analysis and Cox proportional hazards regression, including time-averaged DAS28, age and gender as covariates. The incidence of CVD within the first 10 years of the disease was compared with the incidence thereafter, using Kaplan-Meier survival curves and Log-rank testing.

Results: There were 855 patients with 6388 patient years included. Their mean age was 54 years, 66% was female and 76% RF positive, mean baseline DAS28 was 5.0. Ninety-one CV events, including myocardial infarction (MI), cerebrovascular accident (CVA) and heart failure were recorded during follow up. The course of hazards over time (not shown) did not indicate a change in the risk of CVD over disease duration (exposition time), which is also reflected by the absence of a deflection in the survival curves (fig.1a). The CV risk is significantly lower, only in the group of patients with very low DAS28 (<2.9) over time, versus the other groups ($p=0.038$). The survival distributions did not differ between a disease duration of <10 years or >10 years (Log-rank test: $p=0.365$) (fig. 1b).

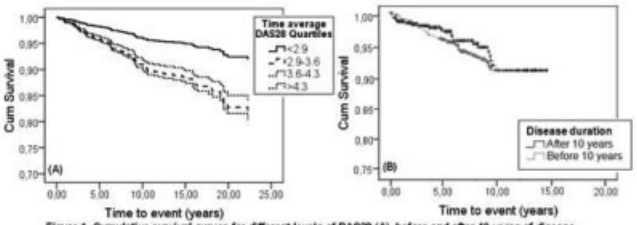


Figure 1. Cumulative survival curves for different levels of DAS28 (A), before and after 10 years of disease duration (B).

Conclusion: The duration of RA, i.e. the length of time a patient is exposed to inflammation, does not appear to further aggravate the risk of CVD over time. Particularly, the risk of CVD in RA patients was not increased after 10 years of disease duration compared to the first 10 years. The level of disease activity did not influence the risk of CVD, unless disease activity was kept at a very low level.

2586

The Effect of Body Mass Index On the Outcomes of Rheumatoid Arthritis. Frederick Wolfe[1] and Kaleb Michaud[2]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]National Data Bank for Rheumatic Diseases and University of Nebraska, Omaha, NE

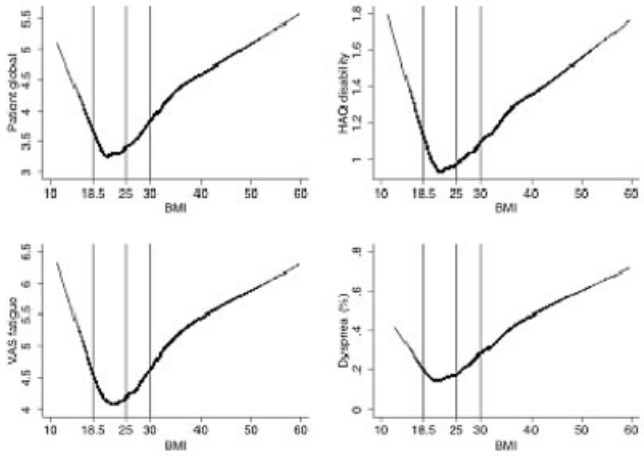
Background/Purpose: Body Mass Index (BMI) has a seemingly paradoxical effect on mortality in rheumatoid arthritis (RA), with the highest risk occurring in those with are underweight UW) (BMI 18.5 kg/m2) and a decreased risk in those who are overweight (OV) (BMI 25.0–29.9 kg/m2) or obese (OB) (BMI ≥30.0 kg/m2) compared with those with normal BMI (NW) (BMI 18.5–24.9 kg/m2). We explored the mechanism for this paradox and the role BMI plays in comorbidity and functional and quality of life outcomes.

Methods: We assessed 24, 549 RA patients for up to 12 years using a semiannual questionnaire. Mortality data were obtained from the U.S. National Death Index. Hazard ratios were estimated with time varying Cox regression.

Results: At a mean age of 61.8 years (71.8% female), 65% were OW or OB. The overall hazard ratio for mortality indicated an increased mortality risk in UW and a protective effect for OW and OB (Table 1). BMI had a U shaped relation to age, with BMI increasing through age 50 and falling thereafter. We identified an interaction between age and BMI on the risk of mortality: under age 50, OB increased mortality risk by 61%, but over age 50 mortality in OW and OB was reduced by 29–37% (Table 1). Regardless of BMI category, a 5-unit increase in BMI was associated with 26.2% (22.7, 29.8) increase in diabetes and a 34.7% (32.3, 37.3) increase in hypertension.

There was a U-shaped relation between all patient-reported clinical outcomes and BMI category. Four representative variables are shown in Figure 1. The "best" BMI for clinical outcomes, regardless of gender was 22–23. Compared with NW, the increase in annual total medical costs was UW $1151, OW $752, OB $3380.

	%	H.R. (95% CI)	H.R. (95% CI)	H.R. (95% CI)
Age Group	All	All	[2]50Years	>50Years
Underweight	2.1	2.13 (1.87, 2.44)	2.62 (1.11, 6.21)	2.46 (2.15, 2.81)
Normal weight	32.9	1.0	1.0	1.0
Overweight	32.1	0.81 (0.75, 0.88)	0.97 (0.60, 1.57)	0.71 (0.66, 0.77)
Obese	33.0	0.94 (0.86, 1.02)	1.61 (1.06, 2.44)	0.63 (0.58, 0.69)



Conclusion: Increased BMI leads to diabetes and hypertension, which are important predictors of mortality in RA. However, increased BMI itself is protective for mortality, except in patients less than 50 years of age. Overweight is not a direct risk factor for mortality, but influences clinical status and overall health. UW, OW and OB contribute to the severity of clinical measures and to increased costs.

2587

Inflammatory Burden Predicts Plaque Formation of Carotid Artery in Rheumatoid Arthritis. Churl Hyun Im, Na Ri Kim, Jong Wan Kang, Ji Hun Kim, Gi Bum Bae, Eon Jeong Nam and Young Mo Kang. Kyungpook National University Hospital, Daegu, South Korea

Background/Purpose: Rheumatoid arthritis (RA) patients have an increased risk of atherosclerosis and cardiovascular (CV) diseases compared with normal population. The chronic exposure to inflammatory mediators has been thought to underlie accelerated atherosclerosis in RA, as well as traditional CV risk factors. The aim of this study was to evaluate the role of inflammatory burden in the formation of carotid plaques in RA patients.

Methods: We performed carotid artery ultrasound to measure the carotid intima-media thickness (IMT) and plaques in 407 consecutive patients with RA and 209 age and sex matched controls. Clinical and laboratory variables relevant to RA activity were obtained. To assess inflammatory burden during the course of disease, the area under curve (AUC) of ESR over time was calculated in 194 female patients with regular follow up for longer than 5 years.

Results: The study population included 329 females and 78 males RA patients. Frequency of carotid plaque and mean IMT were significantly increased in RA group compared with normal controls (plaque 36.1% vs. 24.9%, $P = 0.005$; mean IMT 0.80 ± 0.17 vs. 0.72 ± 0.14 mm, $P < 0.001$). The frequency of CV diseases in RA patients was 5.7% (14 coronary heart diseases and 10 cerebrovascular diseases). Presence of CV diseases in RA patients was associated with carotid plaque ($P = 0.001$), but not with mean IMT. Among the traditional cardiovascular risk factors and RA related variables, fasting blood sugar (FBS), fibrinogen, Korean version of modified Health Assessment Questionnaire, tender and swollen joint counts (TJC and SJC), DAS28, ESR, CRP, and rheumatoid factor (RF) seropositivity were significantly associated with the presence of plaque after the adjustment with age and gender. After multivariate analysis, the factors found to be significantly associated with plaque were older age ($P < 0.001$), male ($P = 0.001$), FBS ($P = 0.033$), TJC ($P = 0.001$), ESR ($P = 0.002$), and RF positivity ($P = 0.008$). In the second step analysis of 194 patients with ESR-AUC calculation, factors significantly associated with the presence of plaque were older age ($P < 0.001$), higher blood pressure ($P = 0.038$), TJC ($P = 0.028$), and ESR-AUC ($P = 0.024$) in multiple logistic regression analysis. ESR-AUC was significantly correlated with plaque number ($r = 0.203$, $P = 0.002$), but not with mean IMT ($r = 0.057$, $P = 0.216$).

Conclusion: Our findings indicate that inflammatory burden increases the risk of carotid plaque formation in RA.

2588

NT-Pro-BNP Levels Are Associated with Increased All Cause and Cardiovascular Mortality in Early Inflammatory Polyarthritis Independent of Disease Severity and Autoantibody Status—Results From the Norfolk Arthritis Register (NOAR). Hoda Mirjafari[1], Suzanne Verstappen[1], Manjari Lahiri[1], Paul Welsh[2], Diane K. Bunn[3], Tarnya Marshall[3], Mark Lunt[1], Naveed Sattar[2], Deborah P. M. Symmons[1] and Ian N. Bruce[1]. [1]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [2]University of Glasgow, Glasgow, United Kingdom, [3]Norfolk and Norwich University Hospitals Trust, Norwich, United Kingdom

Background/Purpose: Patients with inflammatory polyarthritis (IP) experience excess cardiovascular disease (CVD) morbidity and mortality. NT-pro-BNP is a marker for left ventricular stress and is associated with incident CVD in the general population. The purpose of this study was to examine the relationship between NT-pro-BNP and all cause and CVD mortality in patients with early IP and to examine whether any association found was independent of IP disease parameters.

Methods: Patients with early IP (≥2 joints swollen for ≥4 weeks) over 16 years old were recruited to the Norfolk Arthritis Register (NOAR) from January 2000 to Jan 2009. Only subjects with ≤24 months symptom duration were included in this study. Patients completed a Health Assessment Questionnaire (HAQ) and were examined. A blood sample was taken at recruit-

ment to evaluate their C-reactive protein for IP disease activity score ($DAS28_{CRP}$), NT-pro-BNP, rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) status. Patients were considered seropositive if they had either RF or ACPA. Patients were followed up until March 2010. For patients who died, the cause and date of death was provided by the Office for National Statistics. Cox proportional hazards regression models were used to assess the association of NT-pro-BNP with the risk of death from all causes and from CVD. The analysis was adjusted for age, gender, DAS28 and HAQ. We carried out further analysis restricted to subjects with i) seronegative IP and ii) no prior CVD.

Results: Of 961 IP subjects in whom NT-pro-BNP levels were available 617 (64%) were female. 211 (22%) smoked and 163 (17%) had prior CVD. Patients had a median (IQR) follow up of 5.5 (3.7–7.7) years. Median (IQR) NT-pro-BNP and symptom duration at recruitment was 74 (38–153) pg/ml and 5.9 (3.2–10.5) months respectively. After 5526 patient years (pyrs) follow up 93 IP subjects died and in 32 the underlying cause of death was CVD. The mortality rate for CVD was 5.8 per 1000 pyrs (95% CI 5.6–5.9). Each 100 pg/ml increase in NT-pro-BNP level was associated with a 10% increased overall mortality risk and an 11% increased risk of CVD mortality after age and gender adjustment (HR (95% CI); 1.10 (1.06, 1.14) and 1.11 (1.05, 1.17)). These associations remained after adjustment for DAS28 and HAQ score (HR (95% CI); 1.13 (1.05, 2.98), 1.12 (1.04, 1.20)). Restriction of the analysis to subjects with seronegative IP and no prior CVD did not alter the association found (HR (95% CI); 1.08 (1.01, 1.15) and 1.10 (1.00, 1.21)).

Conclusion: Higher NT-pro-BNP levels were associated with death from all causes and from CVD in IP patients, independently of disease activity, prior CVD and autoantibody status. This raises the possibility of utilizing NT-pro-BNP as part of a screening strategy to identify IP patients at increased CVD risk. Studies are needed to investigate why these patients have apparently increased cardiac stress.

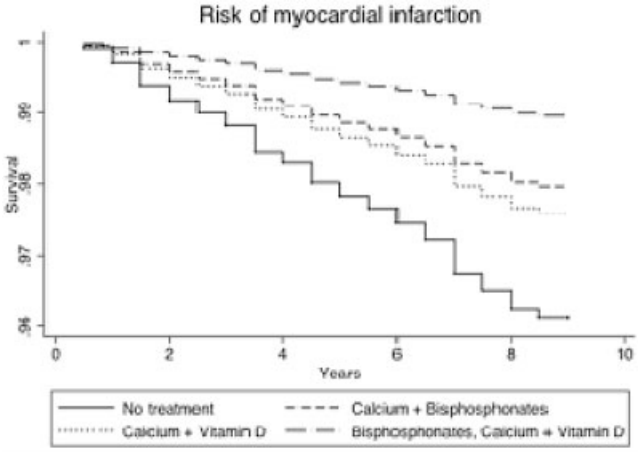
2589

Reduction in the Risk of Myocardial Infarction in Bisphosphonate and Calcium/Vitamin D Treated Rheumatoid Arthritis and Lupus Patients: A Longitudinal Cohort Study. Frederick Wolfe[1], Marcy B. Bolster[2], Cathleen Colon-Emeric[3], Christopher M. O'Connor[4], Kaleb Michaud[5] and Kenneth W. Lyles[4]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Medical Univ of South Carolina, Charleston, SC, [3]Duke University Medical Center and the Durham VA GRECC, Durham, NC, [4]Duke University School of Medicine, Durham, NC, [5]National Data Bank for Rheumatic Diseases, University of Nebraska, Omaha, NE

Background/Purpose: Recent studies have shown a reduction in mortality among patients treated with bisphosphonates. It has been suggested this may be the result of reduction in cardiovascular deaths. In addition, calcium therapy has been linked to cardiovascular risk. Bisphosphonates, calcium and Vitamin D are commonly used in rheumatic disorders such as rheumatoid arthritis and lupus for prevention and treatment of osteoporosis. As the risk of myocardial infarction is increased in rheumatoid arthritis and lupus patients, we evaluated a cohort of these rheumatic disease patients to assess the risk of osteoporosis treatment, including bisphosphonates, on myocardial infarction.

Methods: We studied 155,750 semiannual observations from 23,228 rheumatic disease patients from 2002 through 2010 (93% rheumatoid arthritis, 7% lupus) to determine the effect of bisphosphonate therapy on the risk of myocardial infarction. We used longitudinal population averaged logistic models and Cox regression analyses adjusted for demographic, economic, and cardiovascular risk factors.

Results: Over the course of the study, 26.4% of patients used bisphosphonates (alendronate 16.3%, risedronate 6.8%, ibandronate 3.1%, other bisphosphonates <0.2%). Age, sex, education, smoking, diabetes, hypertension, prednisone, and the use of statins predicted myocardial infarction, statins because of confounding by indication. Patients using bisphosphonates had more severe rheumatoid arthritis and lupus, with reduced functional status and increased prednisone and opioid use, among other measures. Bisphosphonate use was protective for myocardial infarction, odds ratio 0.75 (95% CI 0.58, 0.98), as was calcium and vitamin D (OR 0.57 (95% CI 0.42, 0.77). When calcium/vitamin D and bisphosphonates were analyzed as a group, the 3-drug combination resulted in an OR of 0.38 (95% CI 0.22, 0.66). Calcium and vitamin D alone was also associated with protective effect (OR 0.61 (95% CI 0.43, 0.87)). We also evaluated the effect of bisphosphonate use separately in patients just beginning bisphosphonate therapy, considering observations on therapy compared with those off therapy (Figure 1). The hazard ratio for the 3-drug use was 0.26 (95% CI 0.14, 0.51) in newly beginning patients. Calcium and bisphosphonates without vitamin D was also a significant predictor.



Conclusion: Myocardial infarction was reduced among rheumatic disease patients using bisphosphonate therapy after adjustment for known cardiovascular risk factors and for risk of prescription. Concomitant vitamin D use is associated with a further reduction in myocardial infarction. The data are consistent with studies that have shown reduced mortality risk in bisphosphonate users, and suggest that a randomized clinical trial may be indicated.

2590

Getting to the Heart of the Matter: The Need for More Aggressive Management of Cardiovascular Risk Factors in Rheumatoid Arthritis. Shailey S. Desai[1], James D. Myles[2] and Mariana J. Kaplan[1]. [1]University of Michigan Rheumatology, Ann Arbor, MI, [2]Michigan Institute for Clinical and Health Research, University of Michigan, Ann Arbor, MI

Background/Purpose: In patients with rheumatoid arthritis (RA), the leading cause of mortality is accelerated cardiovascular (CV) disease with a risk similar to that of type 2 diabetes mellitus (DM). Increased CV risk in RA patients is considered secondary to RA-specific mechanisms and to traditional cardiovascular risk factors (CRFs), i.e. smoking, obesity, BP, HDL, LDL, triglycerides, and fasting blood glucose. We hypothesize that CRFs are not as frequently managed in patients with RA as compared to DM or to the general population (GP). The aims of this study were to determine how often CRFs are identified and managed by: 1) rheumatologists and primary care physicians (PCPs) in RA patients; 2) PCPs in patients with RA as compared to DM and the GP.

Methods: We conducted a retrospective cohort study comparing age/gender/ethnicity-matched patients from three groups: RA, DM, and GP (without RA or DM). Patients were seen by a PCP and RA patients were also seen by a rheumatologist at a tertiary care referral center between June 2007-April 2011. Electronic patient records were reviewed during a continuous 12-month period to assess if CRFs were identified and managed. Identification was defined as documenting the CRF at any visit. Management was defined as documenting a plan to address the CRF. Kruskal-Walis test was used for continuous and chi-square test was used for categorical outcomes without accounting for matching. Subgroup analysis assessed how frequently CRF management occurred in patients with abnormal values.

Results: Each group had 251 patients with a mean age of 49 ± 10 years (81% females; 81% Caucasian). BMI and systolic BP were significantly higher in the DM as compared to RA and GP groups. LDL was significantly lower in the DM (99.5 ± 37.1 mg/dl; $p<0.001$) as compared to RA and GP groups (113.7 ± 32.4 mg/dl, 111.4 ± 29.1 mg/dl respectively). PCPs identified and managed CRF significantly more often than rheumatologists in RA patients (Table). Among PCPs, CRFs were identified and managed significantly more often in DM than in RA patients. Also among PCPs, CRF were independently more often managed in the GP than in RA, despite similar baseline clinical characteristics between the two groups. Subgroup analysis revealed that DM patients with abnormal CRF values had significantly increased management of these factors than in RA. Of patients with elevated LDL, PCPs managed 75% of the DM group, 60% of the GP, and 36% of the RA group ($p<0.0001$ for all groups, $p=0.01$ between RA and GP groups).

Number of patients whose CRFs were identified and managed by a rheumatologist and/or a PCP in RA, DM, and GP patients

CRF		Group A (RA) *Rheumatologist*	Group A (RA) *PCP*	Group B (DM) *PCP*	Group C (GP) *PCP*	p-all 3 *PCP*	p-A vs. C *PCP*
Smoking	Identified	52 (20.7%)	167 (66.5%)	161 (64.1%)	188 (74.9%)	0.02	0.0496
	Managed	32 (12.8%)	25 (10.0%)	28 (11.2%)	39 (15.5%)	0.1	0.08
Weight Management	Identified	67 (26.7%)	111 (44.2%)	191 (76.1%)	136 (54.2%)	<0.0001	0.03
	Managed	15 (6.0%)	72 (28.7%)	159 (63.4%)	99 (39.4%)	<0.0001	0.01
BP	Identified	233 (92.8%)	243 (96.8%)	250 (99.6%)	250 (99.6%)		0.04
	Managed	14 (5.6%)	53 (21.1%)	169 (67.3%)	80 (31.9%)	<0.0001	0.008
HDL	Identified	13 (5.2%)	109 (43.4%)	190 (75.7%)	144 (57.4%)	<0.0001	0.002
	Managed	5 (2.0%)	34 (13.5%)	137 (54.6%)	70 (27.9%)	<0.0001	0.0001
LDL	Identified	14 (5.6%)	110 (43.8%)	197 (78.5%)	146 (58.2%)	<0.0001	0.004
	Managed	4 (1.6%)	38 (15.1%)	160 (63.8%)	78 (31.1%)	<0.0001	<0.0001
Triglycerides	Identified	14 (5.6%)	109 (43.4%)	190 (75.7%)	141 (56.2%)	<0.0001	0.006
	Managed	5 (2.0%)	36 (14.3%)	142 (56.6%)	70 (27.9%)	<0.0001	0.0003
Fasting glucose	Identified	3 (1.2%)	58 (23.1%)	237 (94.4%)	68 (27.1%)	<0.0001	0.4
	Managed	0 (0%)	7 (2.8%)	232 (92.4%)	19 (7.6%)	<0.0001	0.03

Conclusion: Despite rheumatologists' awareness of increased CV risk in RA patients, they are significantly less likely to identify and manage CRFs than PCPs. Attempts at managing CRFs by PCPs are suboptimal in RA patients when compared to the GP and even more so to DM patients. Given the well-established increased CV risk associated with RA, physicians need to more aggressively identify and manage CRFs in these patients.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Novel Compounds I
Wednesday, November 9, 2011, 9:00 AM–10:30 AM

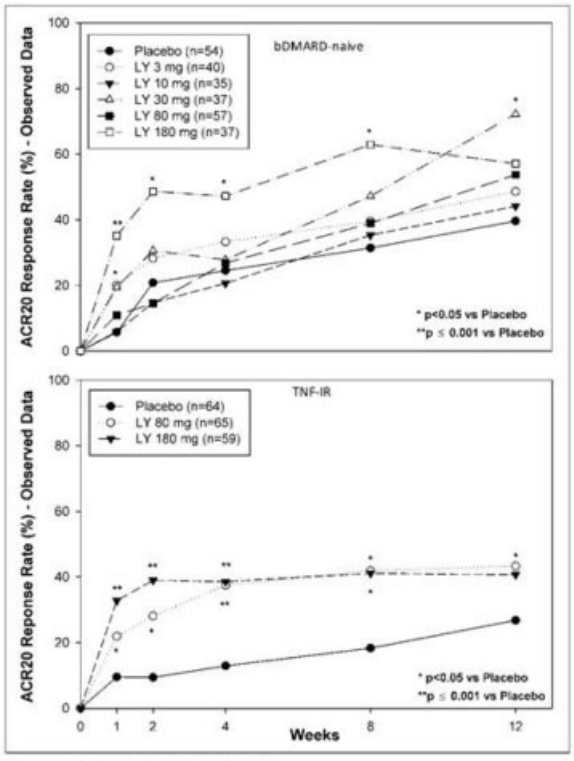
2591

A Phase 2 Study of Multiple Subcutaneous Doses of LY2439821, An Anti-IL-17 Monoclonal Antibody, in Patients with Rheumatoid Arthritis in Two Populations: Naïve to Biologic Therapy or Inadequate Responders to Tumor Necrosis Factor Alpha Inhibitors. Mark C. Genovese[1], Maria W. Greenwald[2], Chul Soo Cho[3], Alberto Berman[4], Ling Jin[5], Gregory Cameron[6], Li Xie[5], Daniel Braun[5], Subhashis Banerjee[5] and Laura Warner[7]. [1]Stanford University, Palo Alto, CA, [2]Desert Medical Advances, Palm Desert, CA, [3]St Marys Hospital, Seoul, [4]Hospital Padilla, Tucuman, Argentina, [5]Eli Lilly and Company, Indianapolis, IN, [6]Eli Lily and Company, Indianapolis, IN, [7]i3 Statprobe, Indianapolis, IN

Background/Purpose: To evaluate LY2439821 (LY), a humanized monoclonal antibody that neutralizes IL-17A, for the improvement of signs and symptoms of rheumatoid arthritis (RA) in 2 populations of patients (pts): (a) naïve to biologic therapy (bDMARD naïve) or (b) inadequate responders to tumor necrosis factor inhibitors (TNF-IR).

Methods: In this randomized, double-blind study, placebo (PB) or LY (3, 10, 30, 80, or 180 mg) was administered subcutaneously to 260 bDMARD naïve pts and 188 TNF-IR pts (LY 80 or 180 mg) at Weeks 0, 1, 2, 4, 6, 8, and 10 with concomitant conventional DMARD therapy. The primary objective was to determine the dose-response relationship of LY in bDMARD naïve pts at Week 12 based on logistic regression of the ACR20 response rate. Secondary objectives included additional safety and efficacy evaluations in the two populations at Week 12.

Results: There was a significant dose response relationship in bDMARD naive pts at Week 12 (p=0.031). Meaningful differences vs. PB were seen at Week 12 for ACR20 in bDMARD naïve pts receiving LY 30, 80 and 180 mg and in TNF-IR pts receiving LY 80 and 180 mg. (Figure, Table). There was a rapid onset of efficacy within 1 week after the first dose. CRP values showed a rapid drop with nadir values at 1 week after the first injection. Significant differences vs PB were observed for other clinical measures in both populations at Week 12. The frequency of TEAEs through Week 12 was similar across treatment arms in both populations (range: 45–64%). Infections were more frequent in LY arms compared to PB in bDMARD naïve (25 vs 19%) and TNF-IR pts (27 vs 23%). In bDMARD naive pts, SAEs occurred in 1 (1.9%) PB and 7 (3.4%) LY pts (6 were treatment emergent) with 1 serious infection-related event in a pt receiving LY 80 mg. In the TNF-IR population, SAEs occurred in 1 (1.6%) PB pt and 12 (9.7%) LY pts (10 were treatment emergent), and serious infections occurred in 4 (3.2%) pts in LY arms. There were no mycobacterial or systemic fungal infections observed in either population.



Non-responder Imputation at Week 12 in Table

Parameters at Week 12	bDMARD naïve						TNF-IR		
	PB n=54	LY 3 mg n=40	LY 10 mg n=35	LY 30 mg n=37	LY 80 mg n=57	LY 180 mg n=37	PB n=64	LY 80 mg n=65	LY 180 mg n=59
ACR20 (%, NRI) (p-value*)	35	45 (0.227)	43 (0.306)	70 (0.001)	51 (0.070)	54 (0.058)	23	40 (0.033)	39 (0.047)
ACR50 (%, NRI) (p-value*)	9	18 (0.191)	29 (0.019)	30 (0.013)	26 (0.017)	27 (0.026)	8	20 (0.039)	17 (0.102)
ACR70 (%, NRI) (p-value*)	2	5 (0.388)	14 (0.033)	14 (0.039)	7 (0.199)	14 (0.039)	3	3 (0.696)	10 (0.112)
DAS28-CRP LSMEAN Change from baseline (p-value#)	−0.8	−1.4 (0.012)	−1.5 (0.004)	−1.7 (<0.001)	−1.7 (<0.001)	−1.9 (<0.001)	−0.6	−1.3 (<0.001)	−1.6 (<0.001)
DAS28-CRP ≤3.2 (%) (p-value *)	13	23 (0.174)	29 (0.061)	22 (0.209)	18 (0.329)	30 (0.045)	11	22 (0.081)	32 (0.004)
DAS28-CRP<2.6 (%) (p-value *)	6	5 (0.712)	17 (0.081)	14 (0.173)	5 (0.678)	16 (0.095)	5	14 (0.067)	22 (0.004)
CRP (mg/L) LSMean Change from baseline (p-value^)	−0.9	−10.2 (<0.001)	−7.8 (0.012)	−11.0 (<0.001)	−10.9 (<0.001)	−10.2 (<0.001)	1.3	−5.7 (0.11)	−8.1 (0.034)

NRI=non-responder imputation.* — 1-sided Fisher's Exact test vs PB; # Last Observation Carried Forward 1-sided ANCOVA; ^ Last Observation Carried Forward 2-sided ANCOVA;

Conclusion: LY significantly improved signs and symptoms of RA compared to PB with a rapid onset of action and a safety profile comparable to other biologic therapies with no unexpected safety concerns.

2592

Tofacitinib (CP-690,550), An Oral Janus Kinase Inhibitor, in Combination with Methotrexate Reduced the Progression of Structural Damage in Patients with Rheumatoid Arthritis: a 24-Month Phase 3 Study. Désirée van der Heijde[1], Y. Tanaka[2], Roy Fleischmann[3], Edward C. Keystone[4], J. M. Kremer[5], C A. F. Zerbini[6], M. Cardiel[7], S. B. Cohen[8], P. T. Nash[9], Yeong Wook Song[10], D. Tegzova[11], B. Wyman[12], D. Gruben[12], B. Benda[13], G. Wallenstein[12], S. H. Zwillich[12], J. D. Bradley[12], C. A. Connell[12] and the ORAL Scan investigators[14]. [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]University of Occupational & Environmental Health, Kitakyushu, Fukuoka, Japan, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Mount Sinai Hospital, Toronto, ON, [5]Albany Medical College and The Center for Rheumatology, Albany, NY, [6]Centro Paulista de Investigação Clinica, Sao Paulo, Brazil, [7]Institute of Rheumatology, Prague, Czech Republic, [8]Metroplex Clinical Research Centre, Dallas, TX, [9]University of Queensland, Brisbane, Australia, [10]Seoul National University Hospital, Seoul, South Korea, [11]Institute Of Rheumatology, Prague, Czech Republic, [12]Pfizer Inc., Groton, CT, [13]Pfizer Inc., Collegeville, PA, [14]Groton

Background/Purpose: Tofacitinib (CP-690,550) is a novel, oral Janus kinase inhibitor being investigated as a targeted immunomodulator in

rheumatoid arthtitis (RA). This 24-mo study compared efficacy, including reduction of structural damage progression, and safety of tofacitinib vs placebo (PBO) in pts with active RA with inadequate response to methotrexate (MTX).

Methods: Pts on stable dose MTX were randomized 4:4:1:1 to 1 of 4 sequences in this Phase 3 study (NCT00847613): tofacitinib 5 mg twice daily (BID); 10 mg BID; PBO advanced to 5 mg BID; PBO to 10 mg BID. Pts on PBO advanced at Mo 6, or at Mo 3 if non-responsive (<20% reduction from baseline [BL] in swollen/tender joint counts). Reported data are from planned 12-mo analyses, which combined PBO into 1 group.

Results: 797 pts were randomized and treated. Pt groups were comparable for HAQ-DI, DAS28-4(ESR), disease duration, estimated structural progression, erosion score (ES), and positive RF/anti-CCP at BL. Tofacitinib 10 mg BID was efficacious compared with PBO in structure preservation measured by mean change from BL in modified Total Sharp Score (mTSS) at Mo 6 and demonstrated superior differences vs PBO for all 4 primary efficacy endpoints (Table). The 5 mg BID dose was superior to PBO for ACR20 response rates at Mo 6 but not for mTSS. Due to a step-down statistical procedure, significance was not declared for HAQ-DI and DAS28-4(ESR) <2.6 for 5 mg BID. Secondary analyses showed that the proportion of pts with no radiographic progression (mTTS change from BL ≤0.5) or no new erosions (ES change from BL ≤0.5) was superior to PBO for both doses, and evaluation of subgroups with predictors of poor prognosis showed a consistent pattern of structure preservation. Adverse events (AEs), serious AEs and serious infection events (SIEs) were distributed across groups (Table). Most frequently-reported AEs in the tofacitinib groups were infections; most were mild with similar incidence in both groups. There were 6 deaths (5 mg BID, 4; 10 mg BID, 1; PBO, 1). Decreases in neutrophils, increases in LDL and HDL, and small increases in serum creatinine were seen with tofacitinib.

Table. Primary and selected secondary efficacy endpoints and safety data

Efficacy	Tofacitinib 5 mg BID (n=321)	Tofacitinib 10 mg BID (n=316)	PBO (n=160)
ACR20[a] (%) Mo 6[e]	51.5***	61.8***	25.3
Mean change in mTSS[g] Mo 6[e]	0.12	0.06*	0.47
Mean change in ES[g] Mo 6	0.06	0.02	0.15
Mean change in JSN[g] Mo 6	0.06	0.04	0.31
Mean change in HAQ-DI[g] Mo 3[e]	-0.40[f]	-0.54***	-0.15
DAS28-4(ESR)<2.6 (%)[a] Mo 6[e]	7.2[f]	18.3***	1.6

Safety	Tofacitinib 5 mg BID (n=321)	Tofacitinib 10 mg BID (n=316)	PBO (n=160)[h]	PBO to 5 mg BID (n=81)[h]	PBO to 10 mg BID (n=79)[h]
Mo 0-3					
AEs	157 (48.9)	171 (54.1)	73 (45.6)	NA	NA
SAEs	12 (3.7)	10 (3.2)	5 (3.1)		
SIEs	5 (1.6)	3 (0.9)	0		
Mo 3-6					
AEs	145 (45.2)	111 (35.1)	21 (25.9)	18 (42.9)	15 (40.5)
SAEs	17 (5.3)	7 (2.2)	5 (6.2)	1 (2.4)	1 (2.7)
SIEs	8 (2.5)	2 (0.6)	2 (2.5)	0	0
Mo 6-12					
AEs	166 (51.7)	174 (55.1)	NA	34 (42.0)	35 (44.3)
SAEs	13 (4.0)	9 (2.8)		1 (1.2)	4 (5.1)
SIEs	3 (0.9)	2 (0.6)		0	2 (2.5)

Primary endpoints were tested by a step-down procedure; [f] p-values for HAQ-DI and DAS28-4(ESR)<2.6 for tofacitinib 5 mg BID are not significant since mTSS was not significant for 5 mg BID in the step-down procedure; *p<0.05 vs PBO, ***p<0.0001 vs PBO
[a]Primary endpoints; [e]non-responder imputation; [g]imputation using linear extrapolation then applying ANOVA; [g]mixed-effect longitudinal linear model; [h]n=81 (PBO), 42 (PBO to 5 mg BID), and 37 (PBO to 10 mg BID) at Mo 3-6; JSN, Joint Space Narrowing; NA, not applicable

Conclusion: In this P3 study, tofacitinib significantly reduced progression of structural damage vs PBO in pts with active RA on MTX. Consistent with other studies, tofacitinib demonstrated significant and clinically meaningful reductions in signs and symptoms of RA and physical function. No new safety signals were detected.

2593

The Oral S1P Lyase Inhibitor LX3305 (LX2931) Demonstrates Favorable Safety and Potential Clinical Benefit at 12-Weeks in a Phase 2 Proof-of-Concept Trial in Patients with Active Rheumatoid Arthritis on Stable Methotrexate Therapy. Roy M. Fleischmann[1], Jeffrey E. Poiley[2], Rumen Stoilov[3], Vibeke Strand[4], Joel Freiman[5], Tamas Oravecz[5], Arthur Sands[5], Brian Zambrowicz[5] and Lexicon Pharmaceuticals RA Clinical Development[6]. [1]University of Texas Southwestern Medical Center and Metroplex Clinical Research Center, Dallas, TX, [2]Arthritis Associates, Orlando, FL, [3]University Multiprofile Hospital for Active Treatment (UMHAT) St. Ivan Rilski EAD, Sofia, Bulgaria, [4]Stanford University, Palo Alto, CA, [5]Lexicon Pharmaceuticals, Inc., The Woodlands, TX, [6]The Woodlands, TX

Background/Purpose: Sphingosine-1-phosphate (S1P) is a lipid metabolite affecting lymphocyte trafficking and signal transduction pathways. S1P lyase (S1PL) catalyzed the irreversible degradation of S1P. Preclinical studies support that reduced S1PL activity reduces the inflammatory response in models of rheumatoid arthritis (RA). LX3305 (a.k.a. LX2931), a small molecule inhibitor of S1PL, is being developed as a novel, oral, disease-modifying antirheumatic drug (DMARD).

Methods: The safety, tolerability, and efficacy of LX3305 were evaluated in a multicenter, multinational, randomized, double-blind, placebo-controlled phase 2 trial in patients with active RA and an inadequate response to stable doses of methotrexate (MTX). Patients (N=208) with active RA (≥6 swollen/tender joints, C-reactive protein [CRP] >upper limits of normal [ULN]) on stable MTX therapy (10–25 mg/week) were randomly assigned with equal probability among treatments consisting of LX3305 taken orally (po) once daily (70 mg [n=55], 110 mg [n=54], 150 mg [n=50]) or placebo (n=49) in addition to their standard MTX regimen for 12 weeks. The study enrolled 177 patients in Eastern Europe and 31 patients in the United States. The primary measure of efficacy was the proportion of patients achieving an ACR20 response at Week 12. Other assessments included ACR50/70 response rates, DAS28-4, the hybrid ACR measure, individual components of the ACR and DAS28 response criteria, blood lymphocyte counts, and biomarkers of bone and cartilage turnover.

Results: ACR20 response at Week 12, the primary endpoint, was achieved by 60% of patients assigned to the 150 mg LX3305 group compared to 49% receiving placebo (not significant). The upper bound of the 95% CI computed on this difference was 29% and was consistent with a positive treatment effect. Sensitivity analyses showed that the middle and low LX3305 groups did not differ from placebo. In a post-hoc analysis, results from these groups were combined with placebo and compared against the 150 mg group in order to maximize statistical test efficiency. Sixty percent of the 150 mg LX3305 patients achieved an ACR20 response compared to 44.3% of all other patients [p = 0.038]. Overall, LX3305 was well tolerated over the 12 weeks of dosing, and adverse events were generally mild to moderate in intensity and comparable between placebo and LX3305 treatment groups. Only 2 serious adverse events were reported and these events were assessed by the Investigators as not related to study treatment.

Conclusion: LX3305, at 150 mg po QD for 12 weeks, produced a favorable safety profile and a potential clinical benefit in patients with active RA despite stable-dose MTX therapy. These results suggest that inhibition of S1PL by LX3305 represents a new mechanism for immune modulation, and supports further clinical development of LX3305 as a small molecule therapy for RA.

2594

Longer-Term Safety of Fostamatinib (R788) in Patients with Rheumatoid Arthritis—Analysis of Clinical Trial Data From up to 2 Years of Exposure. Arthur Kavanaugh[1], Michael E. Weinblatt[2], Mark C. Genovese[3], Theresa K. Musser[4], Elliott B. Grossbard[4], Daniel B. Magilavy[4], Sally Hollis[5], Eveline Wesby van-Sway[5] and David Millson[5]. [1]University of California San Diego, San Diego, CA, [2]Brigham and Women's Hospital, Boston, MA, [3]Stanford University, Palo Alto, CA, [4]Rigel Pharmaceuticals, South San Francisco, CA, [5]AstraZeneca, Macclesfield, United Kingdom

Background/Purpose: Fostamatinib, an investigational oral inhibitor of spleen tyrosine kinase has demonstrated significant outcomes in patients (pts) with rheumatoid arthritis in short-term phase II trials.[1,2] Presented here are longer-term safety and tolerability data for fostamatinib.

Methods: Data are from randomized, placebo (pbo)-controlled, fostamatinib phase II trials (TASKi1,[1] 2,[2] and 3[3]), the TASKi1 extension study and an ongoing open-label study (C-935788-012). TASKi1&2 pts were inadequate responders to methotrexate (MTX) on background MTX, and TASKi3 pts were inadequate responders to biologics on background disease-modifying antirheumatic drug (DMARD) combinations. Pts initially randomized to pbo received 100 mg bid or 150 mg qd fostamatinib in the extension study. Summaries are presented based on initial dose: fostamatinib 150 mg qd, 100 mg bid, all fostamatinib and pbo. Adverse events (AEs), serious AEs (SAEs), serious infection events (SIE), and fatal outcomes occurring from the initial treatment dose to 28 days after the last dose are presented for up to 24-mo exposure. Incidence rates (IRs) per 100 patient-years (PY) were calculated for each group.

Results: This analysis included 803 pts with 1,038 PYs of fostamatinib exposure (mean exposure 1.3 years) of which 265 PYs were contributed by 211 ex-pbo pts. Pts were well balanced across dose groups for age, gender, and ethnicity. Key findings are presented in the table. Fostamatinib IRs for SAEs, SIEs, treatment discontinuations, and dose reductions were higher in the TASKi3 (biologic refractory) group vs all other groups. The most common AEs were diarrhea (27.4%), hypertension (22.5%), and urinary tract infections (UTIs, 12.7%). Most common SAEs (IR per 100 PYs) were infective events (3.4) and gastrointestinal events (1.8). Most common SIEs (IR per 100 PYs) were pneumonia (1.0), UTIs (0.4), and cellulitis (0.3). The discontinuation rate on fostamatinib treatment was highest in the first 6 mo. Primary reasons for treatment discontinuations were lack of efficacy in TASKi3 and AEs (most commonly diarrhea, neutropenia, or increased transaminases). IRs (per 100 PYs) for blood pressure $\geq$ 160/100 mmHg and $\geq$ 180/110 mmHg for pts on fostamatinib vs pbo were (22.9 vs 24.8) and (4.9 vs 2.8), respectively. IRs (per 100 PYs) for neutrophil counts $<$ 1,500 mm^3 and $<$ 1,000 mm^3 for pts on fostamatinib vs pbo were (9.9 vs 3.7) and (2.2 vs 0), respectively.

	Inadequate responders to MTX		Inadequate responders to biologics	Inadequate response to MTX or biologics	
Dosing groups	150 mg qd + MTX	100 mg bid + MTX	100 mg bid + DMARDs	All fostamatinib* + DMARDs	Pbo** + DMARDs
	(TASKi2)	(TASKi1&2)	(TASKi3)		
	(N=218)	(N=282)	(N=204)	(N=803)	(N=273)
PY exposure	324	397	222	1038	109
Time	**Premature discontinuation rates (%)**				
6 months	13.8	15.3	34.6	20.2	26.6
24 months	35.6	35.1	59.2	42.2	–
	Incidence rates per 100 PYs (n)‡				
Any SAE	7.7 (25)	9.3 (37)	17.5 (39)	10.6 (110)	6.4 (7)
Any SIE†	3.1 (10)	3.0 (12)	6.3 (14)	3.8 (39)	4.6 (5)
Deaths††	0.6 (2)	0.5 (2)	0.4 (1)	0.5 (5)	0.9 (1)

* Includes 99 patients on other doses, mainly 50 or 150 mg fostamatinib bid in TASKi1.
** Combined pbo groups from randomized controlled trial studies. Pbo-controlled duration is 3 months for TASKi1 6 months for TASKi2.
‡ Presented for up to 24-months' exposure to a cut-off date of 7 December 2010 and excludes SAEs, SIEs, and reported fatal outcomes occurring greater than 28 days after last dose.
† There were no reported cases of tuberculosis or fungal infections.
†† A total of six deaths were reported; four occurred due to cardio- or cerebrovascular events (three were previously reported[2]) and two were due to infections (one occurred in the pbo group and was previously reported[3]).
MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; pbo, placebo; PY, patient year; SAE, serious adverse event; SIE, serious infection event.

Conclusion: No new significant safety signals were identified with longer-term dosing of fostamatinib. Biologic refractory pts on a background of mixed DMARDs had a higher incidence rate of AEs, SAEs, and SIEs compared to MTX inadequate responders on background MTX; further confounding factors may play a role.[3] This will be explored in ongoing phase III studies.

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2595

Comparative Effectiveness of Abatacept Versus Subsequent Anti-TNF Agents Among Rheumatoid Arthritis Patients with Previous Anti-TNF Exposure. Leslie R. Harrold[1], George Reed[1], Jeffrey R. Curtis[2], Daniel H. Solomon[3], Marc Hochberg[4], Alina U. Onofrei[1], Joel M. Kremer[5] and Jeffrey D. Greenberg[6]. [1]UMass Medical School, Worcester, MA, [2]Univ of Alabama-Birmingham, Birmingham, AL, [3]Brigham & Womens Hospital, Boston, MA, [4]University of Maryland School of Medicine, Baltimore, MD, [5]Albany Medical College and The Center for Rheumatology, Albany, NY, [6]New York University School of Medicine, New York, NY

Background/Purpose: There are limited data to guide a rheumatologist's selection of a biologic agent among rheumatoid arthritis (RA) patients who have failed one or more anti-TNFs. We compared the effectiveness of abatacept (ABA) versus a subsequent anti-TNF agent among RA patients with previous anti-TNF exposure using data from a multi-center observational registry within the United States (the Consortium of Rheumatology Researchers of North America: CORRONA).

Methods: We identified RA patients between 2/1/02 through 12/14/09 who had discontinued at least 1 anti-TNF and initiated either ABA or a subsequent anti-TNF, were not in remission based on the Clinical Disease Activity Index (CDAI) at the time of initiation, and had follow-up at 6 months (n=1,061) and/or 12 months (n=780). Propensity score (PS) matching (n:1 match) based on age, duration of RA, swollen joint count, patient global assessment, physician global assessment and insurance type was used to control for imbalances between treatment groups. Treatment response was measured at 6 months and 1 year after initiation based on mean change in CDAI from baseline and achievement of an American College of Rheumatology (ACR) 20 and 50 response. Last observation carried forward (LOCF) was applied to patients who discontinued treatment. Regression models accounted for PS matching, clustering by physician, as well as residual differences in baseline characteristics. As a sensitivity analysis, 1:1 PS matching was used to generate the study cohort and the analyses were repeated.

Results: Most patients were female (77–81%) with a mean age of 56 to 57 years, mean disease duration of 12–14 years and mean CDAI of 21–23. Among patients with a visit at 6 months, there were small baseline imbalances between treatment groups: ABA users had more active disease based on the patient global assessment (51 vs. 47), self-reported pain (52 vs. 48) and modified Health Assessment Questionnaire (0.66 vs. 0.58). There were no significant baseline differences between the 2 treatment groups included in the 12 month follow-up analysis. The weighted mean change in CDAI at 6 and 12 months in ABA initiators as compared to anti-TNF initiators was not significantly different in unadjusted or adjusted analyses (Table). ACR20 and ACR50 response rates were similar at 6 months and 12 (Table). Results were similar in the 1:1 PS matched analyses.

	6 months		12 months	
	335 ABA	546 anti-TNF	241 ABA	399 anti-TNF
Change in CDAI				
Weighted mean improvement	6.6	6.0	7.9	8.2
Unadjusted difference (95% CI)	0.7 (−2.1 to 3.4)		−0.5 (−3.6 to 2.6)	
Adjusted difference (95% CI)	0.3 (−1.6 to 2.3)		−0.7 (−3.0 to 1.5)	
ACR20				
Weighted response rates	29%	30%	35%	35%
Unadjusted odds ratio (95% CI)	0.97 (0.71–4.28)		1.04 (0.64–1.69)	
Adjusted odds ratio (95% CI)	0.91 (0.63–1.30)		1.01 (0.61–1.71)	
ACR50				
Weighted response rates	18%	15%	19%	19%
Unadjusted odds ratio (95% CI)	1.32 (0.93–1.86)		0.92 (0.57–1.47)	
Adjusted odds ratio (95% CI)	1.24 (0.89–1.74)		0.89 (0.54–1.47)	

Conclusion: We were unable to detect any differences in effectiveness in this US cohort over a period of 12 months after switching from a prior anti-TNF to either ABA or another anti-TNF. Analyses of adverse events and longer term outcomes will be needed in order to determine best strategies in TNF failure pts with RA in the US. Both treatments appear reasonable to use in this population.

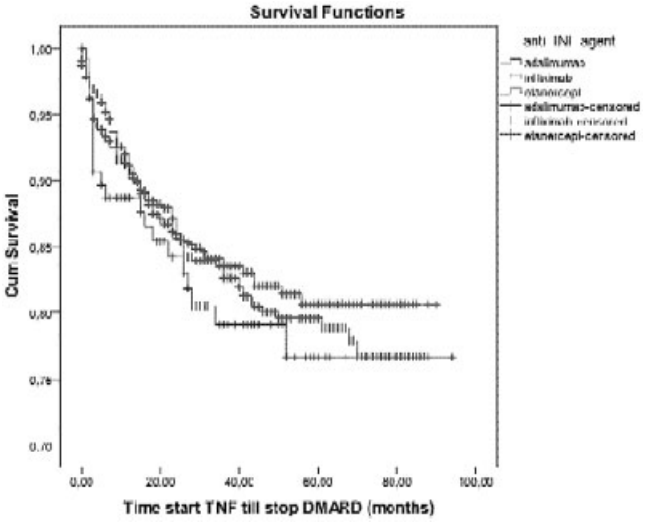
2596

Discontinuation of DMARDs in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Blocking Agents: An Analysis in the Dutch Rheumatoid Arthritis Monitoring (DREAM) Registry. Sanne van Dartel[1], Jaap Fransen[1], Wietske Kievit[1], Alfons den Broeder[2], Henk Visser[3], Andre Hartkamp[4], Mart AF van de Laar[5] and Piet Van Riel[1]. [1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Sint Maartenskliniek, Nijmegen, Netherlands, [3]Alysis Care Group, Arnhem, Netherlands, [4]Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands, [5]Medisch Spectrum Twente & Twente University, Enschede, Netherlands

Background/Purpose: The majority of rheumatoid arthritis (RA) patients currently treated with biologics combine this therapy with a disease-modifying anti-rheumatic drug (DMARD), usually methotrexate (MTX). However, DMARDS can cause considerable toxicity. Patients might prefer discontinue a DMARD when disease activity becomes low after the initiation of TNF blocking agents. Objective of the study was to analyze whether it is possible to discontinue a DMARD and especially MTX during TNF blocking therapy and keep disease activity low.

Methods: Data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) Biologic registry of 1553 RA patients using TNF blocking therapy with a DMARD as co-medication were used for the analyses. Since February 2003 the large majority of RA patients who started on one of the biologic agents for the first time in one of 13 centers in the Netherlands have been included in the DREAM register. In all analyses discontinuation of the DMARD was defined as an event on the condition that no other anti-rheumatic drugs were added within 3 months of discontinuation. Baseline differences were compared between patients in which MTX or a DMARD was discontinued and those in which MTX or a DMARD was not discontinued. The mean difference in DAS28 over 6 months after the moment of DMARD discontinuation was tested on a statistically significant difference from 0.3 (inferiority margin) by a one-sample t-test.

Results: 85% of RA patients treated with TNF inhibitors in daily clinical practice used at least one DMARD as co-medication, in 83% of the patients using a DMARD as co-medication this was MTX. Concomitant DMARDs were discontinued in only 15% of the patients (12,5% MTX). Most DMARDs were discontinued within the first three years after start of anti-TNF (13,6%), without notable differences between type of anti-TNF (p=0.71) (figure). There were no difference in characteristics between patients who discontinued a DMARD and patients who did not discontinue a concomitant DMARD. The mean (SD) DAS28 at start of the anti-TNF was 5.1 (1.1), the mean (±SD) DAS28 at discontinuation of a DMARD was 3.5 (1.4). In the patients in whom a DMARD was discontinued, there was no increase of disease activity the 6 months thereafter, (decrease −0.25 DAS28 point), significantly different from +0.3 (p=0.00).



Conclusion: Concomitant DMARDs are infrequently stopped, but in patients who stopped the disease activity did not increase.

Funding for the data collection for the DREAM cohort was obtained from the Dutch affiliations of Wyeth Pharmaceuticals, Abbott Pharmaceuticals, Schering-Plough Corporation, Roche pharmaceuticals, UCB pharma and Bristol-Myers Squibb. Funding for performing these analyses in particular was obtained from the Dutch affiliation of Wyeth Pharmaceuticals. No others than the authors were involved in the analyses, interpretation of results and writing the abstract.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects: Translational Studies
Wednesday, November 9, 2011, 9:00 AM–10:30 AM

2597

Members of the Receptor for Advanced Glycation Endproducts Axis Associate with Systemic Lupus Erythematosus, and May Serve As a Brake to Disease Activity. Manish Jain, Michael Amato, Robert M. Clancy, Peter M. Izmirly and Jill P. Buyon. New York University School of Medicine, New York, NY

Background/Purpose: The Receptor for Advanced Glycation Endproducts (RAGE) is a transmembrane cell-surface receptor found on a variety of immune and endothelial cells, which is upregulated in stress situations and mediates a pro-inflammatory response. RAGE has been implicated in the pathogenesis of diverse disease states characterized by vascular insult. Soluble forms of RAGE exist, with the total circulating pool of soluble RAGE (sRAGE) including both membrane-cleaved RAGE, as well as an alternative mRNA spliced form—endogenous soluble RAGE (esRAGE)—both with common ligand affinity. Isoforms of soluble RAGE may be protective by serving as decoy receptors. Simultaneous measurement of sRAGE and esRAGE, with attention to relative proportion, may be informative. Accordingly, RAGE axis markers in an SLE cohort with characterization of disease activity and subclinical atherosclerosis was assessed to provide insight into pathogenesis of SLE.

Methods: sRAGE and esRAGE were measured by ELISA in a cross sectional study of 99 SLE patients and 40 healthy controls in whom carotid ultrasonography was performed to evaluate for carotid plaque. SLEDAI for SLE patients was also calculated at the same visit.

Results: Median esRAGE level was higher in patients (288±262 pg/mL) than controls (171±162 pg/mL) (p=.0031), as was percent esRAGE/sRAGE (25.4±17.7 in SLE vs.14.9±11.6 in controls, p<.0001). In contrast, sRAGE levels did not differ between SLE patients and controls. A negative correlation was observed between SLEDAI score and esRAGE (rho=-.197, p=.049), and sRAGE (rho=-.303, p=.0014). SLE patients with high disease activity defined as SLEDAI >4 (23% of cohort) had lower median esRAGE levels (153±216) than patients with SLEDAI≤4 (295±269) (p=.029), with a trend for lower percent esRAGE/sRAGE in the high disease group as well (22.3±13.7 in high group vs. 27.5±18.2 in low group, p=.071). While median esRAGE in the low disease activity group was significantly different from controls (p=.0016), no significant difference in median esRAGE existed between patients with high disease activity and controls. When serologic factors (C3, C4, dsDNA) were excluded from disease activity, C3 and C4 had the strongest negative correlation with non-serologic disease activity (rho=-.294 and -.291, p=.0087 and p=.0097, respectively), followed by percent esRAGE/sRAGE (rho=-.235, p=.0438), followed by anti-dsDNA (rho=.150, p=.195). No association was noted between RAGE axis levels and the individual ACR criteria or medications. In both SLE patients and controls, no association with carotid plaque was noted with RAGE axis levels.

Conclusion: This study highlights the potential role of the RAGE axis in pathogenesis of SLE. The elevation of both esRAGE and percent esRAGE/sRAGE in SLE patients compared to controls may represent a compensatory attempt at protection. However, among SLE patients, the RAGE axis may serve as a brake to disease activity, reflected in part by inverse correlations of RAGE isoforms to disease activity, and lower esRAGE levels and percent esRAGE/sRAGE in high disease activity patients on cross-sectional analysis. Thus soluble forms of RAGE may have therapeutic value warranting further study.

2598

Regulatory Role of Umbilical Cord Mesenchymal Stem Cells on Treg and Th17 Cells in Patients with Systemic Lupus Erythematosus. Dandan Wang, Huiqing Liu, Xia Li and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background/Purpose: Mesenchymal stem cells (MSC) demonstrated multiple modulations on immune cell responses, such as effective T cells, B cells, NK cells, and dendritic cells. But its role on regulatory T cells and Th17 cells in patients with systemic lupus erythematosus (SLE) has not been well characterized. The aim of this study is to investigate the regulatory effect of umbilical cord MSC (UC-MSC) on Treg and Th17 cells in SLE patients.

Methods: Human UC-MSC were isolated, expanded and infused into 15 refractory SLE patients (ClinicalTrials.gov Identifier: NCT00698191, phase II). Clinical changes were evaluated pre and post-transplantation by SLE Disease Activity Index (SLEDAI), 24-hour urine protein, serum albumin and complement C3. The percentages of $CD4^+CD25^+Foxp3^+T$ cells and $CD3^+CD8^-IL17A^+T$ cells in peripheral blood were detected by flow cytometry. Concentrations of plasma TNF-α, TGF-β1, IL-6 and IL-17A were determined by ELISA. Gene expressions of Foxp3, RORγt, IL-6, TGF-β1 and IL23R were analyzed by real time PCR. Peripheral blood mononuclear cells (PBMC) from 11 active SLE were co-cultured with UC-MSC at different ratios (MSC: PBMC=0:1, 1:1, 1:10, 1:100) to examine the changes of $CD4^+CD25^+Foxp3^+T$ cells and $CD3^+CD8^-IL17A^+T$ cells and supernatant TNF-α, TGF-β1, IL-6 and IL-17A.

Results: SLEDAI scores decreased significantly at 3 months (7.8±1.2) and 6 months (6.9±0.9) after UC-MSC transplantation ($p<0.05$ *vs* pre-transplantation level 10.4 ± 0.9). Twenty-four-hour proteinuria decreased significantly 6 months

after MSC infusion (1489 ± 260mg vs 2454 ± 322mg, $p<0.05$). Meanwhile, serum albumin and complement C3 levels increased significantly from 1 month after transplantation ($p<0.05$). Peripheral blood $CD4^+CD25^+Foxp3^+$T cells percentage showed obvious increase at 1 week (2.32%±1.40%), 1 month (2.03%±1.30%), 3 months (2.41%±2.06%) and 6 months (2.81%±0.69%) visit (all $p<0.05$ *vs* pre-MSCT 1.58%±1.02%), in parallel with significant decline of $CD3^+CD8^-IL17A^+$T cells percentage after MSCT (1.30%±1.02% at 1 week, 0.73%±0.60% at 1 month, 0.56%±0.60% at 3 months, 0.52%±0.40% at 6 months, all $p<0.05$ *vs* pre-MSCT 1.69%±1.13%). Real time PCR showed that gene expression for RORγt decreased, while TGF-β1 increased significantly after transplantation, with no statistical change in IL-6, Foxp3 and IL23R. Plasma concentration of TNF-α decreased significantly at 1 week, 1, 3, 6 and 12 months after transplantation, with increased TGF-β1 at 1 week, 3 and 12 months ($p<0.05$ *vs* before MSCT). Plasma IL17A decreased obviously 1 month after transplantation, but no change in plasma IL-6 was found. The co-culture of UC-MSC with PBMC from active SLE patients resulted in a statistical increase of $CD4^+CD25^+Foxp3^+$T cells and reduce of $CD3^+CD8^-IL17A^+$T cells percentage in PBMC (all $p<0.05$ at UC-MSC: PBMC 1:1, 1:10, 1:100 ratio), but without a dose dependent manner. Supernatant TGF-β1 and IL-6 increased but TNF-α decreased significantly in the co-culture system. No change in IL-17A was observed.

Conclusion: UC-MSC transplantation markedly regulated Treg and Th17 cells in SLE patients, which may be one of the mechanisms for its therapeutic potential in refractory SLE.

2599

N-Acetylcysteine Improves Disease Activity by Blocking the Mammalian Target of Rapamycin in T Cells of Lupus Patients. Zhiwei Lai[1], Robert Hanczko[1], Eduardo Bonilla[1], Adam Bartos[1], Tiffany Telarico[2], Gabriella Miklossy[3], Brandon Clair[2], John Jimah[3], Edward Doherty[4], Lisa Francis[1], Hajra I. Tily[5], Ricardo Garcia[1], Maha M. Dawood[4], Jianghong Yu[1], Irene Ramos[1], Travis Boevin[1], Stephen Faraone[1], Paul E. Phillips[6] and Andras Perl[3]. [1]SUNY, Syracuse, NY, [2]SUNY Upstate Medical University, Syracuse, NY, [3]Upstate Medical University, Syracuse, NY, [4]SUNY Upstate, Syracuse, NY, [5]SUNY, NY, [6]SUNY-Upstate Medical Univ, Syracuse, NY

Background/Purpose: Systemic lupus erythematosus (SLE) patients exhibit T-cell dysfunction which is regulated through the mitochondrial transmembrane potential ($\Delta\Psi_m$) and mammalian target of rapamycin (mTOR) by glutathione. Therefore, the safety, tolerance, and efficacy of glutathione-precursor N-acetylcysteine (NAC) were examined in this double-blind placebo-controlled study (FDA approval, IND No: 101,320; clinicaltrials.gov identifier, NCT00775476).

Methods: 36 SLE patients with clinically stable disease were randomized to receive daily placebo or 1.2 g, 2.4 g or 4.8 g of NAC. Disease activity was monthly evaluated by BILAG, SLEDAI and fatigue assessment scale (FAS) before and during 3-month treatment and after 1-month washout. $\Delta\Psi_m$ and mTOR were assessed by flow cytometry. Glutathione was measured by HPLC. 42 healthy subjects matched for patients' age, gender, and ethnicity were studied as controls.

Results: NAC was tolerated by all patients up to 2.4 g/day while 33% of those receiving 4.8 g/day had reversible nausea. Initial mean disease activity scores, as measured by SLEDAI (5.5), BILAG (26.1), and FAS (28.5), were similar in patients randomized into the placebo arm or any of the 3 NAC arms. Placebo or 1.2 g/day NAC did not influence any disease activity measure. Considered together, in patients receiving daily 2.4 g and 4.8 g of NAC, 1) SLEDAI was improved from 5.8 at baseline on all follow-up visits (after 1 month: SLEDAI: 3.6, $p = 0.0007$; after 2 months: SLEDAI: 4.0, $p=0.0009$; after 3 months: SLEDAI: 4.9, $p = 0.0030$; after 4 months/1-month washout: SLEDAI: 4.4; $p = 0.0046$); BILAG was reduced from 28.0 at baseline to 24.2 after 1 month ($p = 0.029$) and to 21.8 after 3 months ($p = 0.0009$); FAS was reduced from 30.2 at baseline to 25.4 after 2 month ($p = 0.002$) and to 24.5 after 3 months ($p = 0.004$); anti-DNA was reduced from 78.9 ± 45.2 IU/ml at baseline to 19.5 ± 6.0 IU/ml ($p=0.049$) after 1 month. Glutathione was reduced in PBL, but not in whole blood, suggesting that the metabolic dysfunction in lupus is confined to the immune system. 2.4 g/day and 4.8 g/day NAC increased glutathione in lupus PBL. While NAC increased $)R_m$ ($p=0.0001$) in all T cells, it prominently reduced mTOR activity ($p=0.0001$), enhanced apoptosis ($p=0.0004$) and reversed expansion of CD4-/CD8- T cells (1.35±0.12-fold; $p=0.008$), and stimulated Foxp3 expression in $CD4^+/CD25^+$ T cells ($p=0.045$). NAC did not influence $\Delta\Psi_m$ and mTOR in B cells.

Conclusion: This dose, tolerance, and mechanism-finding double-blind placebo controlled phase I/II study provides clear evidence that NAC improves disease activity in patients with SLE primarily by uncoupling $\Delta\Psi_m$ from activation of mTOR in all T cells and promoting the apoptosis of CD4-/CD8- T cells and the expansion of $CD4^+/CD25^+/Foxp3^+$ T cells. The selectivity of NAC for mTOR activation in T cells provides a safe, inexpensive, alternative, and potentially synergistic approach to B-cell blockade in SLE. Large-scale phase II/III studies are clearly warranted to determine long-term efficacy and whether NAC could also benefit patients with unstable disease.

This work was supported by grant AT 4332 from the National Institutes of Health and the Alliance for Lupus Research.

2600

Circulating Mitochondrial DNA Copy Numbers As a Highly Sensitive Diagnostic Marker of Systemic Lupus Erythematosus and An Independent Predictor of SLE Activity. Nils Venhoff[1], Jens Thiel[1], Dirk Lebrecht[1], Chingching Foocharoen[2], Nora M. Effelsberg[1], Marten Trendelenburg[3], Paul Hasler[4], Reinhard E. Voll[1] and Ulrich A. Walker[2]. [1]Dept. of Rheumatology and Centre of Chronic Immunodeficiency, University of Freiburg, Freiburg, Germany, [2]Dept. of Rheumatology at Basel University, Felix-Platter Spital, Basel, Switzerland, [3]Dept. of Internal Medicine, University Hospital Basel, Basel, Switzerland, [4]Dept. of Rheumatology, Kantonsspital Aarau, Aarau, Switzerland

Background/Purpose: Toll-like receptor (TLR) 9 signaling is important in the pathogenesis of systemic lupus erythematosus (SLE) and its type I interferon signature. TLR9 recognizes dsDNA which may be released by neutrophil extracellular traps (NETs) upon stimulation by tissue injury. This study examines if the quantitative analysis of two dsDNA species, namely circulating mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) may contribute to the understanding of SLE, be useful in the clinical diagnosis of SLE and the monitoring of its disease activity.

Methods: 77 SLE patients (mean age 46.2 years, 65 females, median disease duration 6.1 years, 43% with a history of lupus nephritis) and 40 controls (healthy volunteers, or persons hospitalized for osteoarthritis or herniated intervertebral disks, mean age 44.2 years, range 20–95 years, 23 females) from two tertiary care centers were included in this cross-sectional study. MtDNA and nDNA copy numbers in plasma were quantified by PCR. SLE activity was determined by means of the SLEDAI. C-reactive protein (CRP), C3, C4 and C3d-levels, as well as autoantibody titers against dsDNA, phospholipids, SSA, SSB, and proteinuria were quantified at the time of blood collection.

Results: Circulating mtDNA copy numbers in the plasma of SLE patients were increased by a factor of 82 (median 1,356,667/mL; interquartile range (IQR) 844,667–2,346,667) compared to controls (median 16,500/mL; IQR 11,275–33,816) ($p<0.001$). None of the SLE patients had mtDNA copies below the highest control value (113,667/mL). Circulating mtDNA-levels were not dependent on age or gender, but correlated with anti-dsDNA titers ($R^2=0.17$, $p<0.001$), C3d ($R^2=0.21$, $p<0.001$), C4 levels ($R^2=0.06$, $p=0.05$), CRP ($R^2=0.06$, $p=0.03$), and SLEDAI ($R^2=0.31$, $p<0.001$) on univariate analysis. In multivariate analysis, only C3d ($p=0.04$), and SLEDAI ($p=0.03$) remained predictive for the mtDNA-levels.

Conversely SLEDAI was predicted on multivariate analysis by mtDNA-levels ($p=0.001$), anti-dsDNA-antibodies ($p=0.03$), and CRP ($p<0.001$). Circulating nDNA copy numbers were low in both controls (7170/mL, IQR 3203.5–18170) and SLE patients (13,607/mL, IQR 4,567–33,933, $p=0.07$) and did not correlate with any covariate in SLE.

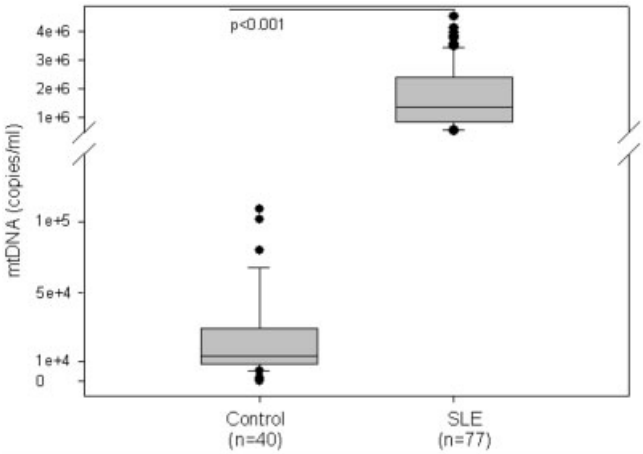


Figure 1. Circulating mtDNA copy numbers in plasma of SLE patients and control persons. Error bars represent IQR, individual points represent outliers.

Conclusion: Circulating mtDNA, unlike nDNA molecules, are markedly increased in SLE plasma. Regardless of disease activity circulating mtDNA-levels distinguish SLE patients from non-inflammatory controls with high sensitivity. In addition, circulating mtDNA copies represent an independent marker of SLE disease activity.

2601

Interferon-Alpha Activity Levels Increase Immediately Preceding Clinical Classification of Systemic Lupus. Julie M. Robertson[1], Latisha Heinlen[2], Jourdan Anderson[1], Timothy B. Niewold[3], Michael P. Keith[4], John B. Harley[5] and Judith A. James[6]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]OUHSC, Oklahoma City, OK, [3]University of Chicago, Chicago, IL, [4]National Naval Medical Center, Bethesda, MD, [5]Cincinnati Children's Hospital Medical Center and the US Department of Veterans Affairs Medical Center, Cincinnati, OH, [6]Oklahoma Medical Research Foundation and Oklahoma University Health Sciences Center, Oklahoma City, OK

Background/Purpose: Systemic lupus erythematosus (SLE) is a clinically variable disease with a complex etiology. Many lupus patients have increased interferon-inducible gene expression and elevated levels of interferon-a (IFNa) which correlate with increased disease activity. IFNa is released by plasmacytoid dendritic cells after stimulation through TLR binding by autoantigen/autoantibody complexes. However, the exact role of interferon in disease pathogenesis is still not understood. This study seeks to evaluate the temporal relationship between IFNa production and the onset of SLE characteristics.

Methods: Patient sera from 20 SLE cases with samples spanning from no ACR criteria to SLE classification were obtained from the Department of Defense Serum Repository (DODSR). Serial samples were tested for antibody isotype specificity against common lupus autoantigens (Ro, La, nRNP, Sm, Ribosomal P, dsDNA, and ANA) by ELISA and immunofluorescence. IFNa levels were examined utilizing a cell reporter assay measuring upregulation of interferon inducible genes (MX1, PKR, and IFIT1) by serum. Two sets of matched controls were also tested and results were reported as elevation of IFN levels above controls.

Results: Autoantibodies are common before diagnosis in SLE patient samples. As a patient moved toward SLE diagnosis the number of autoantibodies increased to include specificity toward multiple lupus autoantigens. Isotype class switching from IgM to IgG_1 was observed in the anti-Ro specificity. In examining dominant antibody isotypes for each lupus antigen we observed the IgG_1 isotype as dominant in nRNP, while Ro, Sm, and Ribo P had an IgG_2 isotype dominance before and at lupus classification. Interestingly, anti-La, anti-Sm, and anti-nRNP antibodies specificities showed detectable amounts of IgA and IgE antibody isotypes. Examination of IFNa levels indicated a statistically significant trend of increasing IFN levels leading up to SLE diagnosis ($p=0.0279$). There was a significant difference in IFN levels between samples prior to first criteria and at SLE diagnosis ($p<0.05$). Four individuals are shown to have autoantibody present in sera samples before the detection of serologic interferon activity.

Conclusion: Our results show IgG_2 is the dominant autoantibody specificity, class switching between IgM and IgG_1 for anti-Ro antibodies occurs leading up to diagnosis, and IFNa levels increase as the number of autoantigen specific antibodies increase leading up to SLE classification. Thus, the increase in IFN levels is more closely linked to disease onset as opposed to autoantibody production.

2602

Vascular Biomarkers and Risk of Treatment Failure in the Maintenance Phase of a Randomized Multicenter Trial Comparing Mycophenalate Mofetil and Azathioprine for Lupus Nephritis. Robert M. Clancy[1], Peter M. Izmirly[1], E.M. Ginzler[2] and On Behalf of the Investigators in the MMF/AZA Lupus Nephritis Main Trial[1]. [1]New York University School of Medicine, New York, NY, [2]SUNY-Downstate Medical Center, Brooklyn, NY

Background/Purpose: The contribution of the vascular endothelium to the pathogenesis of lupus nephritis (LN) is of central importance given the role of renal endothelial activation and recruitment of inflammatory cells, including monocytes. Biomarker studies corroborating the involvement of the endothelium in LN have included the following cytokines/cofactors: adiponectin (ADPN), endothelial protein C receptor (EPCR), monocyte chemotactic protein-1 (MCP-1), Interleukin-18 (IL-18), nitric oxide (NO) and neutrophil gelatinase-associated lipocalin (NGAL). Data regarding the utility of these biomarkers to predict stability and/or relapse in patients with LN achieving initial response to induction therapy is limited. Accordingly, samples from the maintenance phase of the Aspreva Lupus Management Study were evaluated to identify predictors of outcome following treatment with mycophenolate mofetil (MMF) or azathioprine (AZA).

Methods: The study included 52 patients in whom LN was considered responsive following 6 months of induction therapy with either cyclophosphamide or MMF. At initiation of maintenance, patients were randomized to therapy with MMF (27 pts) or AZA (25 pts). The study outcome, treatment failure during maintenance phase, was defined as death, end-stage renal disease, sustained doubling of serum creatinine, and/or renal flare (proteinuric or nephritic). This endpoint occurred in 12 pts (23%). Plasma (p) and urine (u) were analyzed using validated protocols. Measurements were done at entry and at designated study intervals until treatment failure or the end of the maintenance study after 3 years. Analyses of the urine were normalized to u-creatinine. Median values were compared using the Mann Whitney U test.

Results: At entry into the maintenance phase there were no statistical differences between patients who were treatment failures compared to responders in mean baseline glomerular filtration rates and protein/creatinine ratios. Patients considered to have failed therapy had higher median levels of the following analytes compared to those who remained responders: u-ADPN (5.9 ug/mg vs 0.1 ug/mg, $p=0.0002$), p-MCP1 (552 ng/ml vs 150 ng/ml, $p = 0.0075$), u-MCP-1 levels (64 ng/mg vs 26 ng/mg, $p=0.014$), and p-NO levels (23 uM vs 16 uM, $p=0.039$). There were no significant differences in the levels of p-ADPN, u-NO, p/u-IL-18, or p/u-NGAL between failures or sustained responders. Consistent with our previously reported observation that increased mEPCR expression in PTCs may represent a novel marker for poor response to therapy for LN, the values of EPCR rose significantly by the last visit in those who failed compared to those whose LN remained in remission (166% vs 102%, $p=0.03$). u-ADPN also increased over time in patients whose LN flared vs those who remained in remission (254 vs 122, $p=0.03$). There was no association between response and change in levels of p/u-MCP-1 and p-NO.

Conclusion: This study supports the notion that evaluation of markers reflective of endothelial activation and inflammatory cell recruitment provides important adjunct information in subsetting initial responders with regard to greater risk of relapse following induction therapy.

ACR Concurrent Abstract Session
Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics II
Wednesday, November 9, 2011, 9:00 AM–10:30 AM

2603

Intermittent Systemic VEGF Inhibition Induces Pulmonary Arterial Hypertension In a Transgenic Mouse Model of Scleroderma. Emma Derrett-Smith[1], Audrey Dooley[1], Reshma Baliga[2], Adrian Hobbs[2], David J. Abraham[3] and Christopher P. Denton[1]. [1]UCL Medical School, London, United Kingdom, [2]Centre for Cardiovascular Pharmacology, University College London, London, United Kingdom, [3]Centre for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom

Background/Purpose: Pulmonary arterial hypertension (PAH) is a major complication in ~15% of SSc cases and occurs throughout the disease suggesting that a second vascular event occurring in the context of a systemic disease may be responsible. We have previously shown that a transgenic mouse model develops many features of SSc including susceptibility to systemic vasculopathy and lung fibrosis. A role for altered VEGF signaling in PAH-SSc is supported by data that correlate circulating VEGF with mPAP at diagnosis. High circulating VEGF levels may be a marker of repair in response to vascular injury. VEGF signaling is upregulated in the TβRIIΔk-fib mouse model of SSc, which has evidence of a constitutive pulmonary vasculopathy. We have inhibited VEGF signaling using SU5416 to induce endothelial apoptosis in this model.

Methods: The transgenic mouse strain TβRIIΔk-fib expresses a kinase-deficient type II TGFβ receptor driven by a fibroblast-specific promoter leading to balanced ligand-dependent upregulation of TGFβ signalling. The constitutive pulmonary vasculopathy was confirmed by histological assessment of vessel architecture, isolated organ bath and *in vivo* haemodynamic studies. Biochemical analysis of the VEGF signaling axis by quantitative PCR and Western blotting was performed using cultured pulmonary artery smooth muscle cells, and by immunostaining of tissue sections. In vivo SU5416

administration to transgenic and wildtype animals was compared to vehicle administration alone (n=6 each group). Post mortem RV mass index measurements were taken, and histological and immunohistochemical stains (H&E, SR, CD31) were performed.

Results: Within the transgenic pulmonary arterial circulation, hypertrophy of the smooth muscle layer was increased (mean wildtype vessel thickness:circumference ratio 0.66±0.02, mean transgenic 0.88±0.04, $p<0.05$). Pulmonary arterial ring responses to direct and receptor-mediated contractile stimuli were reduced in the transgenic animals (in response to endothelin contraction at 10^{-5}M wildtype 1.10mN±0.02, transgenic 0.62±0.12, $p<0.05$) and right ventricular pressures were elevated in transgenic animals (wildtype mean 29mmHg±4 transgenic mean 37mmHg±3, $p<0.05$). Explanted transgenic PASMC showed upregulation of VEGF and VEGFR1. RV mass index in transgenic animals was increased after treatment with SU5416 (transgenic, vehicle only 0.19±0.01, SU5416 treated 0.29±0.03, $p<0.05$). Histological and immunohistochemical analysis revealed evidence of obliterative endothelial proliferation in transgenic SU5416 treated animals similar to human plexiform lesions which was not seen in any other group.

Conclusion: Treatment with SU5416 exacerbates the underlying constitutive pulmonary vascular defect of this transgenic mouse model and replicates the key histological and patho-physiological features seen in human PAH-SSc. These findings support a role for perturbed TGFβ and VEGF activity in the pulmonary circulation in SSc, supporting the concept of a second pulmonary endothelial injury leading to PAH in SSc. This model may provide a valuable platform for future therapeutic studies in vivo as well as providing insight into pathogenic mechanisms.

2604

Overexpression of $VEGF_{165}b$, An Inhibitory Splice Variant of Vascular Endothelial Growth Factor, Leads to Insufficient Angiogenesis In Patients with Systemic Sclerosis. Mirko Manetti, Serena Guiducci, Eloisa Romano, Claudia Ceccarelli, Silvia Bellando-Randone, Maria Letizia Conforti, Lidia Ibba-Manneschi and Marco Matucci-Cerinic. University of Florence, Florence, Italy

Background/Purpose: Systemic sclerosis (SSc) is a chronic connective tissue disorder characterized by widespread microangiopathy, fibrosis, and autoimmunity that affects the skin and internal organs. Although in SSc there is a lack of sufficient angiogenic response to chronic tissue ischemia culminating in the loss of capillary vessels, the expression of vascular endothelial growth factor-A (VEGF) has paradoxically been shown to be upregulated in SSc skin and circulation. However, previous studies in the field did not distinguish between the proangiogenic $VEGF_{165}$ and antiangiogenic $VEGF_{165}b$ isoforms that are generated by alternative splicing in the terminal exon of VEGF pre-RNA. In the present study, we investigated whether VEGF isoform expression could be altered in skin and circulation of SSc patients.

Methods: The expression of $VEGF_{165}b$, pan-VEGF, VEGF receptor-2 (VEGFR-2), transforming growth factor-b1 (TGF-b1) and serine/arginine protein 55 (SRp55) splicing factor were investigated in skin biopsies from patients with SSc (n=35) and healthy subjects (n=23) using RT-PCR, quantitative real-time PCR, Western blotting, immunohistochemistry and confocal microscopy. Circulating levels of $VEGF_{165}b$ and pan-VEGF were measured by ELISA in plasma samples from SSc patients (n=61) and healthy controls (n=30). VEGFR-2 phosphorylation, intracellular signaling and capillary morphogenesis on Matrigel were studied in microvascular endothelial cells (MVECs) isolated from SSc (n=6) and healthy control (n=6) skin.

Results: $VEGF_{165}b$ splice variant was selectively overexpressed at both the mRNA and protein levels in SSc skin. Elevated $VEGF_{165}b$ expression correlated with increased expression of profibrotic TGF-b1 cytokine and SRp55 splicing factor in keratinocytes, fibroblasts, endothelial cells, and perivascular inflammatory cells. Circulating levels of $VEGF_{165}b$ were significantly higher in SSc patients than in control subjects. MVECs isolated from SSc skin (SSc-MVECs) expressed and released higher levels of $VEGF_{165}b$ than healthy MVECs (H-MVECs). TGF-b1 upregulated the expression of $VEGF_{165}b$ and SRp55 in both SSc- and H-MVECs. In SSc-MVECs, VEGFR-2 was overexpressed, but its phosphorylation and ERK1/2 downstream signaling were impaired. Recombinant human $VEGF_{165}b$ and SSc-MVEC–conditioned medium inhibited $VEGF_{165}$-mediated VEGFR-2 phosphorylation, ERK1/2 activation and capillary morphogenesis in H-MVECs. The addition of anti-$VEGF_{165}b$ blocking antibodies abrogated the antiangiogenic effect of SSc-MVEC–conditioned medium. Capillary morphogenesis was severely impaired in SSc-MVECs and could be ameliorated by treatment with recombinant $VEGF_{165}$ and anti-$VEGF_{165}b$ blocking antibodies.

Conclusion: In SSc, a switch from proangiogenic to antiangiogenic VEGF isoforms may have a crucial role in the insufficient angiogenic response to chronic ischemia. The combination of proangiogenic $VEGF_{165}$ administration and $VEGF_{165}b$ neutralization might represent a potential therapeutic strategy to promote effective angiogenesis and capillary regeneration in SSc.

2605

Downregulation of Mir-193b in Systemic Sclerosis Regulates the Proliferative Vasculopathy by Urokinase-Type Plasminogen Activator Expression. Naoki Iwamoto[1], Serena Vettori[1], Britta Maurer[1], Matthias Brock[1], Maurizio Calcagni[2], Renate E. Gay[1], Steffen Gay[1] and Oliver Distler[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Division of Plastic Surgery and Hand Surgery, University Hospital Zurich, Zurich, Switzerland

Background/Purpose: We were interested in micro RNA (miR)-193b, because in silico analysis suggested that miR-193b might regulate the expression of urokinase-type plasminogen activator (uPA). uPA is a multifunctional protein that in addition to its fibrinolytic and matrix degradation capabilities also affects cytokine modulation, cell migration and proliferation. Since an association of the uPA-mediated plasminogen activation system and the pathogenesis of systemic sclerosis (SSc) have been reported, the aim of our study was to explore the expression of miR-193b in SSc and the regulation of uPA, and to investigate the functional role of uPA in SSc.

Methods: To investigate differentially expressed miRs in SSc and normal healthy (NH) skin fibroblasts, we performed micro RNA array analysis using RNA from pooled SSc and NH fibroblasts. Expression of miR-193b in SSc skin fibroblasts and paraffin embedded skin sections from SSc patients were analyzed by Real-time polymerase chain reaction (PCR). To explore factors that potentially down regulate miR-193b in SSc, skin fibroblasts were stimulated with TGF-β, PDGF-B and IL-1 β. Next, skin fibroblasts were transfected with synthetic precursor miRNA (pre-miR) / inhibitors of miRNA (anti-miR) of miR-193b using Lipofectamine and then the expression of uPA protein and mRNA were analyzed by Western blot and Real-time PCR. Basal expression of uPA in SSc and NH fibroblasts were also examined by Real-time PCR and Western blot. Furthermore, human pulmonary artery smooth muscle cells (HPASMC) were treated with human uPA and cell proliferation assay was performed using the methylthiazolyldiphenyl-tetrazolium bromide (MTT) assay.

Results: The array analysis revealed a specific expression profile of differentially expressed miRs in SSc fibroblasts. 6 miRs could be confirmed by Real-time PCR to be differentially expressed between cultured SSc and NH fibroblasts. Among them, miR-193b was further characterized, because of its consistent differential expression and its target identification by in silico analysis, which included uPA. MiR-193b was significantly down regulated in SSc fibroblasts (n=7) as compared with NH controls (n=7) (16.34 ± 10.05%, $p<0.0001$). In addition, miR-193b was also reduced in SSc skin sections (n=5) as compared with NH controls (n=5) (54.31± 16.39%, $p<0.005$). Stimulation of TGF-β, PDGF-B and IL-1β did not affect the expression of miR-193b. Induction of miR-193b in SSc and normal fibroblasts suppressed the production of uPA protein and the expression of uPA mRNA. Conversely, the knockdown of miR-193b increased the level of uPA expression. The basal expression of uPA in SSc fibroblasts was up regulated both on the protein (19.3% vs 39.6%, $p=0.29$) and mRNA levels (x-fold induction: 3.58, $p=0.43$) as compared with NH controls. Interestingly, uPA induced cell proliferation in HPASMC (121%).

Conclusion: Our results suggest that in SSc, miR-193b is down regulated independently from important cytokines. Thereby the down regulation of miR-193b induces the expression of uPA, which leads to proliferation of vascular smooth muscle cells and thereby contributes to the proliferative vasculopathy characteristic for SSc.

2606

Heart Involvement in Patients with Systemic Sclerosis Is Mimicked by Fra-2 Transgenic Mice. Paulius Venalis[1], Laszlo Cziriak[2], Alfiya Akhmetshina[3], Clara Dees[3], Pawel Zerr[3], Zygmunt Mackevic[4], Ingrid E. Lundberg[1], Oliver Distler[5], Georg Schett[3] and Jorg HW Distler[3]. [1]Karolinska Institutet, Stockholm, Sweden, [2]University of Pécs, Budapest, Hungary, [3]University of Erlangen-Nuremberg, Erlangen, Germany, [4]State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania, [5]University Hospital Zurich, Zurich, Switzerland

Background/Purpose: Systemic sclerosis (SSc) is a systemic autoimmune disease with vascular and fibrotic components. SSc-related cardio-

myopathy is increasingly recognized as a major cause of death. However, the pathogenesis of SSc-related cardiomyopathy is poorly understood. New therapies as well as platforms for testing are needed. Here, we aimed to characterize different murine models of SSc and identify the best animal model for SSc-related cardiomyopathy.

Methods: Six patients with definite systemic sclerosis were enrolled in the project. Age- and sex- matched patients autopsies served as controls. Patients with a medical record for cardiovascular disease were excluded from the study. We have chosen three systemic disease models of scleroderma: Fra-2 transgenic mice model (Fra-2), sclerodermatous chronic *Graft versus Host* disease (cGvHD) model and tight skin 1 mutation model (Tsk-1).Formalin fixed and paraffin embedded heart sections used for IHC. Heart sections from SSc patients, controls and mouse models of SSc were stained for α-SMA, CD31 and active caspase3 as well as with picrosirius and hematoxylin eosin.

Results: Significant fibrotic changes with accumulation of collagen were observed in hearts of SSc patients. The fibrotic area was increased in 8.8 ± 2.3 folds compared to controls ($P<0.001$). Same pattern was found in Fra-2 mice with 8.9 ± 2.8 fold increase ($P=0.0002$). In contrast, no significant increases in fibrotic area were observed in cGvHD mice and in Tsk-1 mice. To detect differentiation towards myofibroblasts we stained for the α-SMA. SSc samples presented with increased numbers of myofibroblasts 2.5 ± 0.6 vs. 0.5 ± 0.8 ($P=0.01$) per high power field (HPF) in controls. As expected same pattern found in all mice models of SSc, though highest mimicry to SSc hearts observed in Fra-2 model (3.0 ± 1.1 vs. 0.5 ± 0.6 $P=0.0005$). Slight increases in the numbers of myofibroblasts were also obtained in the cGvHD and in the Tsk-1 model. CD31 stainings revealed significant loss of capillaries in SSc hearts (2.16 ± 0.17 fold change vs. controls $P < 0.0001$). A prominent capillary loss was also observed in Fra-2 tg and in cGvHD models (2.0 ± 0.2 $P < 0.0001$ and 2.1 ± 0.3 $P<0.0001$ fold change, respectively). No changes were observed in Tsk-1 mice. Apoptosis of endothelial cells was increased in Fra-2 tg mice vs. controls (2.5 ± 0.9 vs. 0.17 ± 0.43 $P = 0.0001$). Apoptosis was observed in cGvHD mice though it was also elevated in controls (2.6 ± 0.7 vs. 1.2 ± 0.5 $P = 0003$). No apoptosis was detected in capillaries of Tsk-1 mice. Endothelial cell apoptosis was also elevated in SSc hearts with 1.2 ± 0.4 vs. 0.2 ± 0.4 ($P = 0.0018$) in controls. Detected higher numbers of perivascular leukocytes in SSc patients (5.8 ± 1.8 fold change, $P = 0.0001$), strengthened the hypothesis of vascular damage.

Conclusion: We demonstrate that the typical features of cardiac disease in SSc –loss of capillaries due to apoptosis of endothelial cell and fibrosis- are closely mimicked by Fra-2 tg mice. In contrast, the changes in the hearts of mice with sclerodermatous cGvHD and in Tsk-1 mice were less representative. Thus, Fra-2 tg mice are a promising preclinical model to study the mechanisms and therapeutic approaches of heart involvement in systemic sclerosis.

2607

In Vivo Delivery of Alternatively Spliced Interleukin-4 Mimics Scleroderma Lung Disease. Sergei P. Atamas and Irina G. Luzina. University of Maryland School of Medicine, Baltimore, MD

Background/Purpose: Our previous studies and works of others have suggested that scleroderma lung disease (SLD) is driven by interleukin (IL)-4 and other type 2 cytokines. However, this notion does not explain the previously reported by us predominance of CD8+ cells in the lungs of patients with SLD. It is also contradicted by the absence of the typical type 2 phenotype in SLD, e.g., by the lack of overt eosinophilia and goblet cell hyperplasia seen in such prototypic IL-4-driven disease as asthma. Based on our previous discovery of a natural splice variant of IL-4, which omits exon 2-encoded region and is called IL-4δ2, and also based on our previous observation of elevated IL-4δ2 mRNA in patients with SLD, we hypothesized that SLD may be driven mostly by IL-4δ2 rather than by IL-4. Since the *in vivo* effects of IL-4δ2 are unknown, we tested whether the effects of the *in vivo* IL-4δ2 gene delivery will differ from those of IL-4 and will mimic SLD phenotype.

Methods: Replication-deficient adenoviral constructs were created, validated, and used to deliver IL-4δ2 or IL-4 to mouse lungs *in vivo*. The effects of such gene delivery on the lungs were investigated, compared to each other and to a non-coding NULL adenoviral vehicle control.

Results: Delivery of IL-4δ2 ($2{,}150 \pm 470$ pg/ml) and IL-4 ($2{,}230 \pm 530$ pg/ml) was confirmed by ELISA assays of lung homogenates. Based on immunohistochemical analyses of lung tissue and flow cytometric analyses of BAL samples, delivery of either IL-4δ2 or IL-4 caused similar pulmonary infiltration by T and B lymphocytes; ~30 % of BAL cells were lymphocytes in either case, whereas only ~3% of lymphocytes were observed in BAL samples of NULL-challenged mice. Delivery of IL-4δ2 attracted three fold more CD8+ cells than did delivery IL-4 (15.5 ± 2.9 % *vs* 5.5 ± 1.7 % of BAL lymphocytes, respectively). Delivery of IL-4 induced eosinophilia (29 ± 8 % of total BAl cells) and goblet cell hyperplasia (25 ± 9 cells/field), whereas delivery of IL-4δ2 did not have such effects ($\sim 2 \pm 2$ % eosinophils in BAL and 4 ± 2 goblet cells/field histologically). Both variants stimulated proinflammatory cytokines; IL-4δ2 induced higher levels of TNF-α and IFN-γ, whereas IL-4 induced higher eotaxin, IL-17, and MCP-1 in the lungs. Differential effects of IL-4δ2 and IL-4 on global gene expression were observed by microarray analyses of lung tissue. Expression of 84 genes was similarly affected by either IL-4δ2 or IL-4, including genes for CTLA4, MHC II, C1q, and several chemokines. Expression of 38 genes was uniquely affected by IL-4δ2, including genes for Cyr61, CD48, Egr2, Lck, lysyl oxidase, and CXCL13. Total pulmonary hydroxyproline assays revealed that both IL-4δ2 and IL-4 tended to increase accumulation of collagen in the lungs.

Conclusion: Both complete (IL-4) and alternatively spliced (IL-4δ2) isoforms induce immune inflammation in the lungs. However, the differences in eosinophil accumulation, goblet cell hyperplasia, and relative accumulation of CD8+ cells caused by IL-4 versus IL-4δ2 resemble the differences between patients with asthma and patients with SLD, respectively. Combined with our previous observation of elevated IL-4δ2 mRNA, these findings suggest that new therapies for SLD need to focus on targeting IL-4δ2 rather than IL-4.

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Functional Inhibition of the TRPV2 Non-Selective Calcium Channel Causes a Potent Stimulation of Genes Encoding Types I and III Collagens and α-Smooth Muscle Actin in Normal Dermal Fibroblasts: A Potential Mechanism of Myofibroblast Induction in SSc. Peter J. Wermuth[1], Sankar Addya[2] and Sergio A. Jimenez[1]. [1]Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA, [2]Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background/Purpose: Transient receptor potential cation channel, subfamily V (TRPV) members are sensitive to a range of environmental stimuli, including heat, osmosensitivity and stress. Although originally described in sensory neurons, the ubiquitous expression of these non-selective calcium channels suggests a role in both sensory and nonsensory transduction. Systemic sclerosis (SSc) is a systemic disease characterized by fibrotic changes in skin and various internal organs. A comparison of global gene expression in early passage cultured dermal SSc fibroblasts to that in fibroblasts isolated from normal individuals identified the TRPV2 gene as one of the most downregulated genes in SSc versus normal dermal human fibroblasts. The role of TRPV1 and TRPV2 in regulating the expression of extracellular matrix (ECM) components was examined in this study.

Methods: Total RNA was isolated from early passage (<6) dermal fibroblasts of Caucasian subjects (3 normal, 3 diffuse SSc). RNA was labeled and hybridized to Affymetrix human U133 2.0 Plus microarrays. Volcano plots were used to identify differentially expressed genes employing the parametric testing assuming equal variances (based on the results of a Student's two-sample t-test for two groups). Comparisons were made between each normal and each SSc sample. Differential gene expression was confirmed by real-time PCR on the same RNA samples employed for the microarrays. The effect of agonists and antagonists of TRPV1 and TRPV2 on expression levels of extracellular matrix components and α-smooth muscle actin in normal human dermal fibroblasts was monitored by real-time PCR and accumulation of type I collagen in culture medium was assessed by Western blot.

Results: Microarray analyses showed that the expression of TRPV2 was downregulated 21 fold in SSc fibroblasts compared to the levels measured in normal human dermal fibroblasts whereas expression of the TRPV1 gene was unchanged. Real time-PCR analysis confirmed the dramatic decrease in TRPV2 expression. Normal dermal human fibroblasts exposed to Tranilast, a TRPV2-selective antagonist demonstrated a remarkable increase in the expression of numerous fibrosis related genes, including a 3.3-fold increase in type I collagen, a 2.8-fold increase in type III collagen and an 11.8-fold increase in α-smooth muscle actin. In contrast, the TRPV1 antagonist capsazepine, the TRPV1 agonist capsaicin, and the TRPV2 agonist probenecid did not affect the expression levels of any of these genes.

Conclusion: Expression of the TRPV2 gene was profoundly downregulated in SSc dermal fibroblasts compared to normal dermal fibroblasts by

global gene expression microarray and real time-PCR analysis. Exposure of normal human dermal fibroblasts to the TRPV2 inhibitor tranilast dramatically increased the expression of several genes encoding important ECM components and induced the expression of α-smooth muscle actin. These results suggest that downregulation of the TRPV2 receptor in SSc dermal fibroblasts may be important in the conversion of fibroblasts into activated myofibroblasts and, thus, may be involved in the dysregulated production of ECM proteins in SSc.

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ARHP Concurrent Abstract Session
ARHP Rehabilitation Science
Wednesday, November 9, 2011, 9:00 AM–10:30 AM

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A Study to Investigate the Clinical Effectiveness of a Prefabricated Foot Orthosis in Patients with Early Rheumatoid Arthritis. Vicki Cameron-Fiddes. Stirling University, Scotland, UK, Stirling, Scotland

Background/Purpose: Rheumatoid Arthritis (RA) affects the foot in up to 90% of cases (Bouysset et al. 2006). Evidence indicates that joint damage occurs early (Devlin et al. 1997) and so suggests a relatively small window of opportunity for early Podiatry intervention. Foot orthoses (FO) can be used optimally early in the disease process (Helliwell et al. 2007). There are two main approaches to supplying FO; customised foot orthoses (CFO) and prefabricated foot orthoses (PFO). CFO are made to a cast of the patient's feet while PFO are mass produced to fit a generic foot shape (Redmond et al. 2009). The effectiveness of CFO in RA is well documented (Hawke et al. 2009) however fabrication of these devices is a lengthy process, which may result in a delay of treatment for the patient (Bennett et al. 1996). Alternatively, PFO can be dispensed at the chairside on the day of diagnosis; however no evidence exists to support their use. The aim of this study was to investigate any potential effects on the foot of one commonly prescribed PFO in patients with early RA.

Methods: Ethical approval was obtained from Fife, Scotland in 2006. A total of 35 patients diagnosed with RA within the past two years were recruited from Fife. Patients were excluded if they had concomitant musculoskeletal disease, central or peripheral nervous system disease, Diabetes, a history of foot fracture, or if they were already wearing FO. The study used a repeated measures design with data collected at baseline, three months and six months. At each time point patients were randomly assessed walking barefoot, shod (with standardised footwear), and with FO. The PFO was Algeos Slimflex™ Plastic (SP) which has been shown to be the most commonly used PFO by Rheumatology Podiatrists in Scotland (Cameron et al. 2009). The SP were individually customised for each individual to reflect current clinical practice. The Foot Impact Scale (FIS) was used to investigate foot health related quality of life (QoL), and the Tekscan walkway and in-shoe systems were used to investigate pressure time integral at the forefoot (PTIft), and walking speed (WS).

Results: The SP significantly decreased the FIS between baseline and three months, and baseline and six months ($p<0.05$). The SP significantly decreased PTIft at baseline, three months and six months between barefoot and shod, barefoot and FO, and shod and FO ($p<0.05$). WS significantly increased at baseline, three months and six months between barefoot and shod, barefoot and FO, and shod and FO ($p<0.05$).

Conclusion: SP may improve foot health related QoL in patients with early RA, and an improvement may be seen by three months. PTIft and WS may be significantly improved as soon as the SP is worn in the shoe. These findings suggest that the SP is effective in the management of the foot in early RA, according to the measured variables in the study. A RCT to directly compare CFO and PFO would be a logical extension to this study.

2610

Fatigue in Rheumatoid Arthritis: What Is the Role of Lower Extremity Muscle Weakness? Patricia P. Katz[1], Mary E. Margaretten[2], Marissa San Pedro[2] and Vladimir Chernitskiy[1]. [1]University of California San Francisco, San Francisco, CA, [2]UCSF, San Francisco, CA

Background/Purpose: Fatigue is widely recognized as a problem in rheumatoid arthritis (RA), to the extent that it is now recommended as an outcome measure for clinical trials of RA treatments by both the ACR and EULAR. However, sources of RA-related fatigue are not well understood. One potential etiology is muscle weakness. Cachexia and physical inactivity, both of which are often present in RA, are each associated with muscle weakness. Yet, the role of muscle weakness in RA fatigue has received little research attention, and is the focus of this analysis.

Methods: Subjects are participants in an on-going cross-sectional study of RA fatigue. Home visits are made to individuals with documented RA to collect measurements of a number of factors, including the outcome variable, fatigue (0–10 numeric rating scale of fatigue severity in the past week), lower extremity muscle strength (knee extension, hip flexor) measured by hand-held dynamometer, and a chair stand task (time to complete 5 chair stands), which is a measure of lower extremity functional strength. Because knee extension and hip flexor strength were correlated ($r=0.6$), we also added the values of the two to create a combined lower extremity strength variable. Subjects also completed questionnaires to measure RA disease activity (RA Disease Activity Index [RADAI]), sleep quality (Pittsburgh Sleep Quality Index [PSQI]), and depression (PHQ-8), and we measured height and weight to calculate body mass index (BMI). For these analyses, we defined severe fatigue as a rating of 7 or greater. Multiple regression analyses were used to identify predictors of severe fatigue. Analyses included measured hip, knee, or combined lower extremity strength and/or score on the chair stand task, in addition to covariates (age, PSQI score, PHQ-8 score, obesity defined by BMI, and RADAI score).

Results: Data have been collected for 68 subjects. 91% are female and 74% white non-Hispanic, with mean age 59 ($\pm$11) years. 27% of respondents reported severe fatigue. In multivariate analysis, poorer performance on the chair stand was associated with greater fatigue (see Table 1); dynamometer-measured muscle weakness was associated with severe fatigue, but the confidence intervals did not exclude 1. In follow-up analyses to determine if limited functional strength (chair stand) mediated the relationship between muscle strength and fatigue, both hip flexor and knee extensor strength were significantly associated with chair stand performance ($p<.01$).

Table 1. Odds of severe fatigue conferred by measures of lower extremity strength

	Multivariate models of individual strength measures	Multivariate models of chair stand score + measured strength variable		
Strength measure	OR (95% CI)	R (95% CI)	OR (95% CI)	OR (95% CI)
Chair stand score	0.28 (0.10, 0.76)	0.32 (0.11, 0.95)	0.32 (0.12, 0.90)	0.34 (0.12, 0.99)
Knee strength (ft-lbs)	0.96 (0.96, 1.01)	0.98 (0.93, 1.04)		
Hip strength (ft-lbs)	0.89 (0.79, 1.01)		0.95 (0.84, 1.07)	
Combined lower extremity strength (ft-lbs)	0.96 (0.92, 1.01)			0.98 (0.94, 1.03)

All models included covariates: age, PSQI score, PHQ-8 score, obesity defined by BMI, and RADAI score

Conclusion: Lower extremity muscle weakness was associated with functional limitations, which were, in turn, associated with severe fatigue. Results suggest that interventions to improve muscular strength may yield improvements in severe RA fatigue.

2611

Muscle Quality Contributes More to Postural Balance Than Muscle Atrophy in People with Rheumatoid Arthritis. Samannaaz S. Khoja, Bret H. Goodpaster and Sara R. Piva. University of Pittsburgh, Pittsburgh, PA

Background/Purpose: Patients with rheumatoid arthritis (RA) experience muscle atrophy and decreased muscle quality, meaning, low lean muscle mass with increased muscle fat mass and consequent muscle weakness. Patients with RA also experience impaired balance and increased incidence of falls, putting them at risk of further disability and morbidity. While weakness of the quadriceps muscles have been related to impaired balance, evidence to support a direct relationship between muscle atrophy or muscle quality and balance in RA is limited. Determining such relationship would be important to refine the interventions to improve balance in RA. The aim of this study was to determine the association between quadriceps muscle atrophy and quality (proportion of lean and fat skeletal tissue) and postural balance in subjects with RA.

Methods: Data of 21 subjects with RA (age 60.3 $\pm$ 10.1 yrs; RA duration 15.8 $\pm$ 10.8 yrs; BMI 31.8 $\pm$ 8.1 kg/m^2; 16 female) were used for this cross-sectional study. Postural balance was assessed by single leg balance test, representing the time the subject could balance on a single leg up to 30 seconds. Subjects were asked to do three trials for each leg

and we calculated the average of the three trials. Mid-thigh cross-sectional area (CSA) for each leg was measured by computed tomography (CT). The quadriceps muscles were outlined and assessed using Slice-O-Matic software. Muscle quality was defined by Muscle Attenuation (MA) coefficient, a measure of tissue density. MA ranging from 35–100 Hounsfield units represents normal density or lean muscle (NDM), whereas 0–35 HU represent low density or fatty muscle (LDM). We calculated total muscle CSA and then divided to total muscle area into NDM CSA and LDM CSA. To account for body size, CSAs of NDM and LDM were treated as % of total muscle CSA. Bivariate correlations were calculated between single leg balance time and CSA of total muscle and % of NDM and LDM of each leg. We used Pearson's or Spearman's correlation coefficients depending on data distribution. Alpha level of significance was set at 0.05.

Results: The association between %NDM and %LDM and single let balance were higher than the associations between total muscle CSA and single leg balance test. Both %NDM and %LDM showed significant moderate associations with single leg balance time albeit in opposite directions; %NDM had a positive correlation and %LDM negative. These findings indicate that subjects with higher proportion of lean tissue within skeletal muscle could balance longer time in single leg, and consequently those with higher proportion of fat in muscle had reduced balance. Descriptives and correlation coefficients are depicted in the table.

Table. Descriptives and Correlations of Muscle Characteristics with Single Leg Balance Time

Variables	Median (IQ:25-75)		Correlation with Single Leg Balance	
	Right side	Left side	Right Side	Left Side
Total Quadriceps CSA (sq cm)	45.2 (38.4–60.8)	47.8 (41.5–51.1)	0.33‡	0.38‡
NDM CSA (sq cm)	34.6 (28.3–46.9)	38.6 (31.9–52.2)		
% NDM	82.0 (68.0–86.0)	84.6 (71.0–87.6)	0.51*†	0.43†
LDM CSA (sq cm)	8.6 (6.6–13.6)	9.0 (6.9–12.7)		
% LDM	18.0 (14.0–32.0)	15.4 (12.4–29.0)	−0.51*†	−0.43†
Single Leg Balance (sec)	15.2 (1.8–24.7)	5 (2.1–25.3)		

* $p < 0.05$
% NDM or %LDM = (NDM or LDM area/Total muscle area) *100
‡ Partial correlation controlling for BMI
† Spearman rho

Conclusion: Muscle quality seems to play a larger role in postural balance than simply total muscle quantity. Future longitudinal studies should investigate if changes in muscle quality improve balance to a larger degree than changes in muscle bulk.

2612

Improvement 3 to 12 Months Post Hip and Knee Replacement: Implications for Rehabilitation. A. M. Davis[1], A. V. Perruccio[2], S. Ibrahim[3], S. Hogg-Johnson[4], R. Wong[5], E. Schemitsch[6], N. N. Mahomed[7], J. Flannery[8] and E. M. Badley[9]. [1]Health Care and Outcomes Research, Toronto Western Research Institute; Departments of Rehabilitation Science and Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, [2]Department of Orthopedic Surgery and The Arthritis Program, Toronto Western Hospital, Toronto, ON, [3]Institute for Work and Health, Toronto, ON, [4]Institute for Work and Health, and Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [5]Health Care and Outcomes Research, Toronto Western Research Institute, Toronto, ON, [6]Division of Orthopaedics, University of Toronto and St. Michael's, Toronto, ON, [7]Division of Orthopaedics, University of Toronto and The Arthritis Program, Toronto Western Hospital, Toronto, ON, [8]Department of Physiatry, University of Toronto and Toronto Rehabilitation Institute, Toronto, ON, [9]Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON

Background/Purpose: Rehabilitation following primary hip (THR) and knee (TKR) replacement typically occurs based on care plans addressing the first 3 months following surgery. While this is the period where most recovery occurs following surgery, it is also accepted that further improvement occurs through one-year post surgery. This work evaluates the change in pain, activities of daily living (ADL) and participation in instrumental ADL (IADL) and leisure activities that occurs between 3 and 12 months post-surgery.

Methods: Participants (hip: n=437; knee: 494) completed measures pre-surgery and at 3, 6 and 12 months post-surgery. These included HOOS/KOOS pain; HOOS/KOOS activities of daily living (ADL); and, participation using the Late Life Disability Index (LLDI) limitation and frequency subscales. All measures were scored 0–10 with lower scores indicating less problems. RANOVA was used to evaluate recovery adjusting for age, sex, obesity, THR/TKR, low back pain and mood. Additionally, proportion of total change was calculated to 3 months and between 3 and 12 months post-surgery.

Results: THR: age 31–86 years with 55% female; TKR: age 35–88 years with 65% female. Significant improvements were observed for all measures over time. On average, for THR and TKR respectively from pre-surgery to 1year, pain improved 4.0 and 3.5 points; ADL improved 3.8 and 2.8 points; and, LLDI limitations improved 2.4 and 2.0 points and LLDI frequency improved 1.0 and 0.8 points. As noted in Table 1, while most change occurred up to 3 months, a large proportion of total change occurred between 3 and 12 months post surgery; 20% for pain for those with TKR and 13 and 14% for ADL for THR and TKR. For LLDI limitations in social/leisure activities, the percent of total change was 17 and 30% for those with THR and TKR respectively. Of note, frequency in IADL and social/leisure activities as measured by the LLDI while demonstrating a large proportion of change from 3 to 12 months, overall demonstrated minimal, although significant, absolute change over time.

Table 1. Proportion of total change by time interval

	Pre-surgery to 3 months post-surgery		3 to 12 months post-surgery	
	mean change	% total change	mean change	% total change
THR				
Pain	3.8	95	0.2	5
ADL	3.3	87	0.5	13
LLDI frequency	0.6	60	0.4	40
LLDI limitations	2.0	83	0.4	17
TKR				
Pain	2.8	80	0.7	20
ADL	2.4	86	0.4	14
LLDI frequency	0.4	50	0.4	50
LLDI limitations	1.4	70	0.6	30

Conclusion: A large proportion of recovery following THR and TKR occurs between 3 and 12 months post-surgery. Rehabilitation care pathways that include follow-up rehabilitation consultation during this period may improve the time to recovery and overall outcomes for people with THR and TKR, particularly related to participation in IADL and social and leisure activities.

2613

Physical Activity, Body Functions, Activity and General Health Perception in Rheumatoid Arthritis. Birgitta Nordgren[1], Patrick Bergman[2], Christina H. Opava[1], Cecilia Fridén[1] and PARA 2010 Study group[3]. [1]Karolinska Institutet, SE 14183 Huddinge, Sweden, [2]University of Gothenburg, Sahlgrenska Academy, Gothenburg, Sweden, [3]Boden, Danderyd, Eskilstuna, Linköping, Stockholm, Östersund

Background/Purpose: Reduced physical activity, substantial disability and poor general health perception have previously been described in people with rheumatoid arthritis (RA). Most studies including description of body functions in large samples were however performed more than ten years ago, before biological treatment was introduced. Therefore, the aim of our study was to describe physical activity, body functions, activity and general health perception in a sample of patients with RA.

Methods: Two hundred and forty-three patients with RA (81% female, mean age 59 years, SD 9) from six rheumatology clinics in Sweden consented to be included in a physical activity intervention and constitute our sample. Self-reported physical activity was assessed with the International Physical Activity Questionnaire (IPAQ), aerobic capacity with the Åstrand sub maximal cycle ergometer test, lower limb function with the Timed-Stands Test (TST) and grip strength with the Grippit device. Pain, fatigue and general health perception were rated on visual analog scales (VAS, 0–100) and activity limitation was assessed with the Stanford Health Assessment Questionnaire, disability index (HAQ, 0–3).

Results: Fifty seven percent (58% females and 48% males) of the sample reportedly adhered to recommendations on health-enhancing physical activity. Four percent of the total sample were classified as having low aerobic fitness, 13% as fair, 35% as average, 17% as good and 11% as high, while results could not be calculated for 20%, mainly because of use of beta-blockers. Compared to norm values 44% of our sample had reduced lower-limb muscle function and a majority had decreased (77%) grip strength compared to norm values. Median values

(ranges) for pain, fatigue and general health perception were 21 (0–88), 35 (0–93) and 25 (0–92) respectively, while median (range) for activity limitation was 0.37 (0–2.25).

Conclusion: Despite the introduction of biological treatments resulting in reduced disease activity and less symptoms on a group level, a substantial part of patients with RA still accumulate too little physical activity and have significantly reduced body functions. We suggest that these individuals should be identified and at target for appropriate rehabilitation and life style interventions.

2614

Erratic Control of Breathing During Exercise in Patients with Systemic Lupus Erythematosus. Renata Miossi[1], Danilo M. L. Prado[2], Luiz A. Perandini[2], Thalita Dassouki[2], Bruno Gualano[3], Hamilton Roschel[4], Fernanda R. Lima[2], Eduardo F. Borba[5], Eloisa Bonfa[6] and Ana Lucia S. Pinto[7]. [1]University of Sao Paulo, Rheumatology Division, Sao Paulo, Brazil, [2]University of Sao Paulo, Rheumatology Division, LACRE, Sao Paulo, Brazil, [3]University of Sao Paulo,School of Physical Education and Sport, Sao Paulo, Brazil, [4]University of Sao Paulo, School of Physical Education and Sport, Sao Paulo, Brazil, [5]University of Sao Paulo, Sao Paulo, Brazil, [6]Faculdade de Medicina da Universidade de São Paulo (FMUSP), Sao Paulo, Brazil, [7]University of Sao Paulo, School of Medicine, Rheumatology Division, LACRE, Sao Paulo, Brazil

Background/Purpose: The aim of this study was to provide a comprehensive evaluation of the pattern and timing of breathing during incremental exercise in patients with systemic lupus erythematosus (SLE).

Methods: In this cross-sectional study, 20 women with SLE without pulmonary involvement were compared with 20 gender-, BMI-, and age-matched healthy individuals. By using a cardiopulmonary incremental exercise test, the following parameters were assessed: tidal volume (VT); breathing frequency (BF); total respiratory time (TOT); inspiratory time (TI); expiratory time (TE); inspiratory time to total time (TI/TOT); mean inspiratory flow (VT/TI); ventilatory equivalent for carbon dioxide (VE/VCO_2) and end-tidal carbon dioxide pressure ($PETCO_2$).

Results: BF and BF/VT were significantly higher in patients with SLE *versus* controls, whereas VT, TE, TI and TOT were significantly lower in the former group ($p < 0.05$). Additionally, patients with SLE presented higher VE/VCO_2 and lower $PETCO_2$ than controls ($p < 0.05$), suggesting a ventilatory inefficiency.

Conclusion: We reported compelling evidence of abnormal pattern and timing of breathing during incremental exercise in SLE. Considering that an erratic control of breathing may play an important role in exercise intolerance and fatigue, respiratory exercises emerges as a potential treatment for these symptoms in patients with SLE.

ACR Concurrent Abstract Session
Infection-Related Rheumatic Disease
Wednesday, November 9, 2011, 11:00 AM–12:30 PM

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Nafamostat Mesylate, a Serine Protease Inhibitor, Demonstrates Novel Antimicrobial Properties and Anti-inflammatory Effects in Chlamydia-Induced Arthritis. Robert D. Inman[1] and Basil Chiu[2]. [1]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON, [2]Toronto Western Hospital, Toronto, ON

Background/Purpose: Effective treatment of reactive arthritis would ideally achieve both control of inflammation and eradication of persisting arthritogenic pathogens. We use a model of experimental Chlamydia-induced arthritis (CtIA) to evaluate the effectiveness of nafamostat mesylate (NM), a serine protease inhibitor with complement-modifying effects and anticoagulant properties. To date clinical use of NM has largely been in Asia and has been primarily confined to inflammatory states such as pancreatitis.

Methods: In vitro studies examined inhibition of Chlamydia proliferation using fibroblast cell lines as targets and phase contrast microscopy. In vivo studies used an established protocol, experimental CtIA, induced in LEW rats by injection of synoviocyte-packaged *C. trachomatis*. NM was dissolved in water and administered by daily ip injection at a dose of 10 mg/kg beginning the day prior to the administration of Chlamydia. Readouts in vivo included (i) joint swelling, (ii) histopathology scoring of severity of arthritis, (iii) host clearance of the pathogen (by ELISA, the IDEIA *PCE* Chlamydia).

Results: NM exerted a dose-dependent inhibition of chlamydial proliferation in vitro (Fig 1). Without NM, the mean number of inclusion bodies (IB) per well was 17886 (± 1415). At 5 μg/ mL NM, there were 8490 (± 756) IB, at 25 μg/mL NM 35 IB and at 50 μg/mL NM no IB was detectable. Chlamydial antigens in each well along the concentration gradient were assayed by ELISA, demonstrating that at 25 μg/mL NM inhibition of Chlamydia was almost complete. In the experimental arthritis model, joint swelling was significantly reduced with NM treatment: average joint width for the NM-treated animals was 8.55 mm (s.d. ± 0.6578, n=10) *vs* 11.18 mm (s.d. ± 0.5672, n=10) in controls ($p = 7.9 \times 10^{-23}$). Histopathology scoring indicated that NM resulted in a marked attenuation of the inflammatory infiltration and joint damage: mean pathology score in NM-treated animals was 10.9 (± 2.45, n = 11) *vs* 15.9 (± 1.45, n = 10) in controls ($p = 9.8 \times 10^{-6}$). With respect to persistence of chlamydia within the synovial tissues, NM treatment was accompanied by a reduction in the microbial load in the joint: mean OD for ELISA with NM treatment was 0.05 (± 0.02, n=4) *vs* 0.18 (± 0.05, n=4) in controls ($p = 0.0027$).

Conclusion: NM is a protease inhibitor not previously recognized to possess antimicrobial properties. The present study demonstrates for the first time that NM exerts significant impact on experimental Chlamydia trachomatis-induced arthritis and suggests that such approaches may prove clinically useful in chronic reactive arthritis.

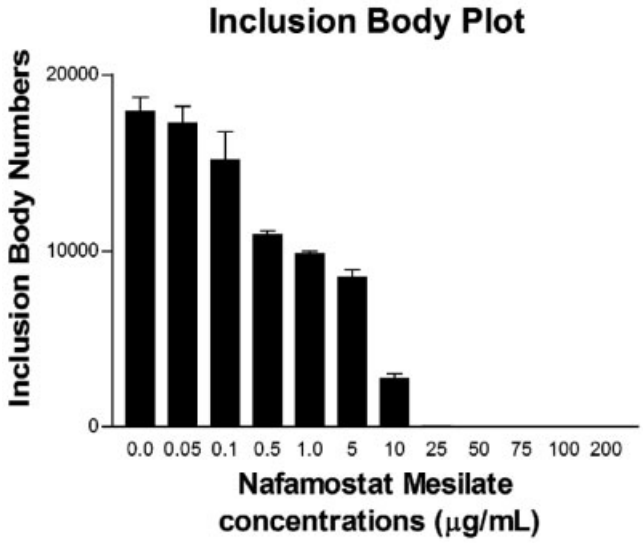

Fig 1. Number of Chlamydia inclusion bodies with increasing NM concentrations.

2616

Macrophage Polarization Plays the Defining Role in Intracellular Persistence and Clearance of *Chlamydia*. Eric Gracey[1], Basil Chiu[1] and Robert D. Inman[2]. [1]Toronto Western Hospital, Toronto, ON, [2]Toronto Western Research Institute, University Health Network and University of Toronto, Toronto, ON

Background/Purpose: The obligate intracellular pathogen, *Chlamydia*, is the commonest cause of reactive arthritis (ReA), where it can exist in the joint in a distinctive persistent phenotype. The macrophage is a central component of the innate immune response and may be important in the early host response to *Chlamydia*. The phenomenon of macrophage polarization occurs upon exposure to a Th1 or Th2 environment, resulting in the generation of inflammatory (M1) and anti-inflammatory (M2) macrophages respectively. Aberrant macrophage polarization occurs in a number of the rheumatic diseases, and in particular an excessive M2 polarization phenotype has been reported in ReA. The role of macrophage polarization in *Chlamydia* infection has not yet been defined.

Methods: Experiments were performed with bone marrow-derived macrophages (BMDM) harvested from BALB/c mice. Macrophages were untreated

(M0), or were polarized by 24 hr treatment with IFNγ 20ng/ml and LPS 100ng/ml (M1) or with IL-4 20ng/ml (M2). Polarized BMDM were subsequently infected with *Chlamydia muridarum* 1 MOI for 6–72 hr. Analyses included (i) direct immunostaining of BMDM for *Chlamydia*, (ii) enumeration of *Chlamydia* by re-infection of McCoy B fibroblasts, (iii) qPCR for bacterial and host genes.

Results: All macrophage phenotypes displayed similar rates of infection with *C. muridarum* when directly stained. Enumeration showed M0 and M2 macrophages to be permissive for *C. muridarum* proliferation (Fig 1), while M1 macrophages controlled the organism (M0: 1.9×10^6 IFU: M2: 3.4×10^6 IFU vs M1: 3.4×10^3 IFU). Further analysis by qPCR showed up to 100-fold decrease in expression of *16sRNA* in M1 macrophages indicative of effective bactericidal mechanisms in these cells. Notably, a *Chlamydia* gene expression profile characteristic of persistence was seen only in M1 macrophages, whereby *Euo* and *IncA* were up-regulated (7.6 and 6.2 fold respectively) and *Omp1* and *Tal* were down-regulated (3.6 and 5.3 fold respectively). Analysis of host gene expression by qPCR demonstrated that *C. muridarum* down-regulates the expression of *IL12B*, *NOS2* and *TLR2* in the permissive M0 and M2 macrophages up to 12 hr post infection. These altered profiles may contribute to subversion of host response by limiting ability to detect *Chlamydia* by host TLR, and by preventing an appropriate inflammatory response by iNOS and IL12p40.

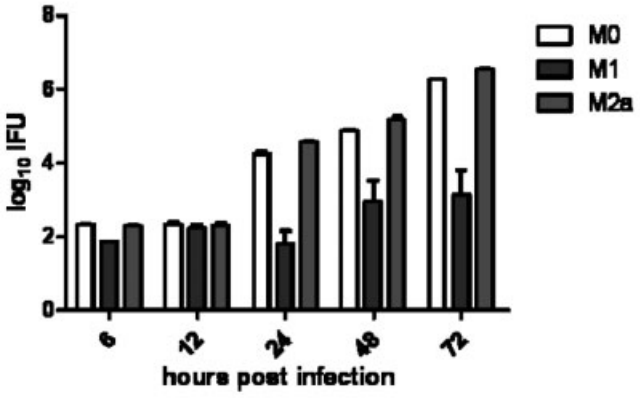

Fig 1. M0 and M2 are permissive to *Chlamydia muridarum* growth whilst M1 are controlling. Bacterial load assessed by serial dilution of infected BMDM lysate and re-infection of fibroblast monlayers.

Conclusion: These data suggest that macrophage polarization is critical in the control of *Chlamydia* infection and in the induction of persistence. These studies provide insight into the biological consequences of an M2 macrophage profile in ReA and highlight the mechanisms of ineffective host clearance of *Chlamydia.*

2617

Reduction in *Chlamydia Trachomatis*-Associated Murine Reactive Arthritis by Novel Peptide Vaccine Candidates. Ilyes Benchaala[1], Indrajit Sinha[1], Mirabela Hali[1], Balaji S. Bharatwaj[2], Herve C. Gerard[1], Alan P. Hudson[1], Sandro R.P. da Rocha[2] and Judith A. Whittum-Hudson[1]. [1]Wayne State Univ Schl of Med, Detroit, MI, [2]Wayne State University Coll of Engineering, Detroit, MI

Background/Purpose: Chlamydia-associated reactive arthritis (ReA) develops in mice after genital or ocular infection with human biovars of *Chlamydia trachomatis* because organism disseminates to joints. A genus-wide vaccine against Chlamydiae which reduces or prevents ReA would be of value. We previously showed that an anti-chlamydial vaccine could reduce pathology and chlamydial load in murine ReA. We now report on unique panel of second generation peptide vaccine candidates.

Methods: The panel of peptides was obtained by phage display with a monoclonal antibody to a chlamydial antigen (Ag; GLXA). The peptides are mimotopes of the chlamydial Ag, and represent conformational epitopes on the carbohydrate of GLXA. The peptides are unique with no homology to human, mouse or chlamydial amino acid sequences. We tested whether vaccination with several peptides in either soluble or encapsulated Peptide 4 (Pep4) would alter microbiologic, immunologic and histopathologic features of genital infection with a human biovar of *C trachomatis* (K serovar; 2000TCID50) and the subsequent ReA which develops in this model. Female BALB/c mice received three immunizations at 3 wk intervals of Pep4 (AFPQFRSATLLL) either in polylactide microparticles (MP) or in alumina as adjuvant. We tested several peptide-MP concentrations (10–40 μg) and 100 μg soluble peptide. Serologic responses were determined with sera obtained from pre-bleeds and before each boost or challenge.

Results: The peptides tested to date are immunogenic and induce immunity to whole organism as well as to the specific peptides. Both IgG1 and IgG2 responses were detected, indicating both Th1 and Th2 responses to Pep4. Antibodies recognized *C trachomatis* and *C pneumonia* organism in infected cells supporting genus-specificity. Vaginal swabs were used to monitor shedding. By day 14 post-challenge, all concentrations of Pep4-MP induced significant reductions in chlamydial shedding. Knee and paw pathology was scored on a 0–4+ scale. Pep4-MP reduced knee and paw pathology compared to unimmunized controls and the 20μg dose of Pep-MP reduced inflammation best. qPCR showed that all peptide presentations reduced chlamydial load significantly compared to unimmunized controls. In recent experiments we have shown that Pep4 induces peptide-specific spleen cell proliferation *in vitro*.

Conclusion: Our results strongly support the efficacy of at least one novel peptide as a genus-wide anti-chlamydial vaccine. The peptides alone or in combination, or in cocktails with other potential vaccine candidates, pose promising advances in anti-chlamydial vaccinology to reduce both acute infection and the damaging pro-inflammatory sequelae such as ReA.

2618

Bacterial Peptidylarginine Deiminase (PAD)-Dependent Enhancement of Collagen-Induced Arthritis in DBA/1 Mice by Radiographic and QoL Results at Week 24 *Porphyromonas Gingivalis.* Katarzyna Maresz[1], Aneta Sroka[1], Joanna Koziel[1], Sviatlana Shashkova[1], Katarzyna Marcinska[2], Marian Szczepanik[2], Piotr Mydel[3] and Jan Potempa[1]. [1]Jagiellonian University, Krakow, Poland, [2]Medical Collage of Jagiellonian University, Krakow, Poland, [3]Institute of Medicine, The Sahlgrenska Academy Gothenburg, Gothenburg, Sweden

Background/Purpose: Rheumatoid arthritis (RA) is a prevalent autoimmune disease characterized by synovial inflammation. Although, a mechanism is yet not known, periodontitis (PD) has been implicated as a risk factor for rheumatoid arthritis (RA). *Porphyromonas gingivalis* (*Pg*) is the major pathogen in periodontitis and the only prokaryote producing peptidylarginine deiminase (PAD), which catalyzes the conversion of arginine to citrulline (Cit) in proteins. Recent data has identified posttranslationally modified proteins containing Cit as specific targets of autoantibody in RA patients.

Methods: To reveal if *Pg* infection might affect collagen-induced arthritis (CIA) in DBA/1 mice, a chamber model was employed. Subcutaneously implanted titanium chambers were inoculated with *Pg* (W83) and after 2 weeks following the infection, CIA was induced.

Results: It was found that mice inoculated with *Pg* into chamber developed the onset of CIA a few days earlier than control animals inoculated with broth only. Furthermore, the disease symptoms were more severe in the *Pg* infected group. Finally, we found that only live bacteria were able to enhance arthritic symptoms in mice. This suggests enzymatic activity of live *Pg* as a trigger factor, which may contribute to the breakdown of immunotolerance.

Methods: To elucidate how PAD influence *Pg* virulence we have compared the pathogenic outcome of chamber inoculation with the wild type W83 strain and PAD-deficient *Pg* mutant in DBA/1 mice.

Results: We found that *Pg*, which produced PAD, was more immunogenic than the PAD mutant. In comparison to mice inoculated with the PPAD mutant, animals injected with the wild-type strain suffered significantly increased mortality and morbidity. The PAD mutant strain was eliminated from the chamber much faster than the parental strain. It also generated less inflammatory mediators than the wild type strain in infected animals. *In vitro* data showed that PAD mutant was engulfed and killed by macrophages as well as neutrophils more efficiently than W83. This finding correlates well with *in vivo* results.

Conclusion: To summarize, the results of our *in vivo* and *in vitro* investigation revealed that *Pg* is able to enhance CIA in DBA/1 mice, and PAD is an important virulence factor of this bacterium.

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2619

Influenza A H1N1/2009 Vaccine in Rheumatic Disease Patients Under Anti-TNF Therapy: Safety and Response. Ivan L.A. França[1], Ana C. M. Ribeiro[1], Nadia E. Aikawa[1], Carla G.S. Saad[1], Ana L. G. Calich[1], Julio C. B. Moraes[1], Ieda Laurindo[1], Joao Miraglia[2], Maria A. Ishida[3], Eloisa Bonfa[1] and Clovis Silva[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Fundação Butantan, São Paulo, Brazil, [3]Adolfo Lutz Institute, Sao Paulo, Brazil

Background/Purpose: Immunogenicity and safety of a non-adjuvanted anti-influenza A H1N1/2009 vaccine were recently reported by our group in a large population of autoimmune rheumatic diseases (ARD) (Ann Rheum Dis 2011). There are, however, few data regarding the effect of anti-TNF therapy in antibody response to such vaccine. Therefore, the objective of this study was to evaluate immunogenicity and short-term safety of anti-influenza A H1N1/2009 vaccine in rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) patients under anti-TNF therapy.

Methods: One hundred thirty-four adult patients [RA (n=45), AS (n=61), PsA (n=28)] under anti-TNF agents (62 infliximab, 43 adalimumab and 29 etanercept) regularly followed in our Rheumatology Division and 125 age-matched healthy controls were vaccinated with a non-adjuvanted preparation of influenza A/California/7/2009 (H1N1) virus-like vaccine. All participants were evaluated pre- and 21 days post-vaccination and serology for anti-H1N1 was performed by hemagglutination inhibition (HI) assay. Seroprotection (HI antibody titer≥1:40), seroconversion (percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer > 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer) rates, geometric mean titres (GMTs) and factor increase (FI) in GMT (ratio of the GMT after vaccination to the GMT before vaccination) were calculated. The effect of concomitant drugs on vaccine response was assessed and adverse events were also evaluated.

Results: Patients and controls had comparable mean current age (43.8±13.1 vs. 45.7±12.2 years, p=0.233). Three weeks after immunization, seroconversion (61.2% vs. 70.4%, p=0.119) and seroprotection rates (64.9% vs. 75.2%, p=0.072) were similar in both groups, whereas the FI in GMT was significantly lower (7.29 vs. 11.54; p=0.0089) in patients *versus* controls. The assessment of the influence of concomitant use of other drugs in patients under anti-TNF showed a trend of a higher frequency of seroconversion rate in patients under diphosphate chloroquine compared to those without it (90.9% vs. 58.5%, p=0.05), but association with other drugs, such as prednisone, methotrexate and leflunomide did not interfere in the response (p>0.05). Local and systemic vaccine adverse events were mild and with similar frequencies in patients under anti-TNF and controls (p>0.05).

Conclusion: The overall immune response to influenza A H1N1/2009 in rheumatic disease patients under TNF blockage therapy is adequate with an excellent safety profile. (ClinicalTrials.gov, #NCT01151644)

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Serum Vitamin D Status and Polymorphisms in Vitamin D Metabolism-Related Genes in Chronic Hepatitis C Virus Infection with Extra-Hepatic Manifestations. Benjamin Terrier[1], Frédéric Jehan[2], Mona Monteanu[3], Guillaume Geri[4], David Saadoun[5], Damien Sène[4], Thierry Poynard[3], Jean-Claude Souberbielle[6] and Patrice Cacoub[4]. [1]Pitié-Salpêtrière Hospital, Paris, France, [2]INSERM U561, Paris, France, [3]Hepatology, Pitié-Salpétrière, Paris, France, [4]CHU Pitié-Salpêtrière, Paris, France, [5]Department of Internal Medicine and Laboratory I3 "Immunology, Immunopathology, Immunotherapy", UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [6]Laboratoire d'Explorations Fonctionnelles, Necker, Paris, France

Background/Purpose: The critical role of vitamin D in the regulation of the immune system has been suggested, in promoting the development of regulatory T cells and decreasing pro-inflammatory cytokines and B cell differentiation. The beneficial role of vitamin D administration was also suggested in chronic HCV infection. Objective: To evaluate the association between serum 25-hydroxyvitamin D [25-OH D] levels, polymorphisms in vitamin D metabolism-related genes and the presence of HCV extra-hepatic manifestations.

Methods: 94 HCV+ untreated patients [including 48 with mixed cryoglobulinemia (MC)-vasculitis] were assessed for serum 25-OH D levels and compared for clinico-biological characteristics according to vitamin D status. We analyzed the 25-hydroxyvitamin D 1α-hydroxylase (CYP27B1) promoter region polymorphism (rs10877012 G/T) and the haplotype structure of the human vitamin D receptor (VDR) promoter region (GATA-binding site SNP rs4516035 G/A and cdx2-binding site SNP rs11568820 G/A) in 220 HCV-RNA+ patients, including 100 with chronic HCV infection without mixed cryoglobulinemia (MC), 96 with MC vasculitis and 24 with asymptomatic MC.

Results: Patients with vitamin D deficiency vs. insufficiency vs. sufficiency had more frequently vasculitis (P=0.002), neuropathy (P=0.048), purpura (P=0.004), type II MC (P=0.002) and low C4 serum levels (P<0.0001). Serum levels of 25-OH D was correlated with cryoglobulin and C4 levels, and marginal zone B cells and regulatory T cells. In multivariate analysis, type II MC and the presence of vasculitis were independently associated with low 25-OH D levels.

The CYP27B1 promoter polymorphism had an impact on the presence of MC-related systemic vasculitis (73, 38 and 44% for rs10877012 TT, GT, and GG, respectively, P=0.04). HCV-infected patients with systemic vasculitis were less frequently G allele carriers than those without systemic vasculitis (88 vs. 97%%; P=0.03).

In contrast, the analysis of the haplotype structure of the VDR promoter region revealed that the presence of Hap1 (Hap1+) was significantly associated with the presence of mixed cryoglobulinemia [62% in Hap1+ vs. 47% in Hap1- patients; OR 1.36 (1.04–1.80), P=0.03]. The absence of Hap3 (Hap3-) tended to be associated with the presence of mixed cryoglobulinemia [60% in Hap3- vs. 48% in Hap3+ patients; OR 1.28 (0.96–1.69), P=0.10].

Conclusion: In chronic HCV infection, low 25-OH D levels correlate with extra-hepatic manifestations. The CYP27B1 promoter polymorphism is associated with MC systemic vasculitis. In contrast, the Hap1 haplotype of the VDR promoter is associated with the presence of mixed cryoglobulinemia. Interestingly, previous studies have showed that the VDR promoter activity is decreased in Hap1+ patients, suggesting that the over-expressed VDR Hap1 haplotype could be considered a risk allele for mixed cryoglobulinemia in HCV-infected patients.

ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Treatment
Wednesday, November 9, 2011, 11:00 AM–12:30 PM

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Tocilizumab Is Efficacious in Patients with Systemic Juvenile Idiopathic Arthritis Across Baseline Demographic and Disease Characteristics and Prior/Baseline Treatments: 52-Week Data From a Phase 3 Clinical Trial. Fabrizio De Benedetti[1], Hermine Brunner[2], Roger Allen[3], Diane Brown[2], Jeffrey Chaitow[3], Manuela Pardeo[3], Graciela Espada[3], Berit Flatø[3], Gerd Horneff[3], Clare Devlin[4], Andrew Kenwright[4], Rayfel Schneider[2], Patricia Woo[5], Alberto Martini[3], Daniel Lovell[2] and Nicola Ruperto[3]. [1]Ospedale Pediatrico Bambino Gesù, Rome, Italy, [2]Pediatric Rheumatology Collaborative Study Group [PRCSG], Cincinnati, OH, [3]Paediatric Rheumatology International Trials Organisation—IRCCS [PRINTO], Genova, Italy, [4]Roche, Welwyn, United Kingdom, [5]University College London Medical School, London, United Kingdom

Background/Purpose: A placebo-controlled phase 3 trial (TENDER) demonstrated that the interleukin-6 (IL-6) receptor inhibitor tocilizumab (TCZ) is effective in the treatment of patients with systemic juvenile idiopathic arthritis (sJIA). The aim of this analysis was to examine whether baseline characteristics of patients with sJIA were associated with the long-term response to TCZ during the open-label (OL) extension of the TENDER trial.

Methods: Patients aged 2–17 years with active sJIA (≥6 months; inadequate response to prior nonsteroidal anti-inflammatory drugs [NSAIDs] and oral corticosteroids [CS]) who received TCZ or placebo every 2 weeks for 12 weeks in the placebo-controlled portion of the study (part 1) went on to receive OL TCZ in part 2 (extension) of the study. Stable doses of NSAIDs and methotrexate (MTX) were continued, with oral CS tapering permitted according to predefined criteria based on JIA ACR response, absence of fever, and erythrocyte sedimentation rate in part 1 and part 2. In part 1, patients qualifying for rescue therapy received standard of care and were offered OL TCZ. This post hoc analysis examines the proportion of patients with JIA ACR30 response plus absence of fever and JIA ACR70 response at week 52 by baseline demographic and disease characteristics and prior/baseline treat-

ments. Baseline for analyses was first dose of TCZ. Patients who withdrew due to insufficient therapeutic response (n=2) before week 52 were included and considered nonresponders, and patients who withdrew for non–efficacy-related reasons (safety, n=4; other, n=2) before week 52 were excluded.

Results: The intent-to-treat (ITT) population consisted of 112 patients (37 randomized to placebo and 75 randomized to TCZ in part 1). At the longer-term extension data cut, 103 patients had reached week 52 or previously withdrew due to insufficient therapeutic response. In each of the evaluated subgroups, the majority of patients achieved JIA ACR30 response plus absence of fever and/or JIA ACR70 response at week 52 (Table). No substantial differences in response were observed in patients grouped by baseline characteristics, including age, region, disease duration, number of active joints, fever status, C-reactive protein (CRP) level, oral CS dose, MTX use, and previous biologic treatment (IL-1 or TNF-α inhibitor).

Table. Efficacy End Points with TCZ Treatment at Week 52 by Selected Baseline Characteristics (ITT Population)

	n at baseline	JIA ACR30 Response + Fever Absent[a] at Week 52, % (r/n)	JIA ACR70 Response at Week 52, % (r/n)
Age, y			
2–5	27	88.5 (23/26)	88.5 (23/26)
6–12	48	88.1 (37/42)	88.1 (37/42)
13–17	37	85.7 (30/35)	85.7 (30/35)
Region			
Europe	61	83.6(46/55)	85.5 (47/55)
North America	24	86.4 (19/22)	86.4 (19/22)
South America	22	100 (21/21)	95.2 (20/21)
Other	5	80.0 (4/5)	80.0 (4/5)
CRP Level, mg/L			
<50	31	92.9 (26/28)	85.7 (24/28)
≥50	81	85.3 (64/75)	88.0 (66/75)
Disease Duration, y			
<4	56	80.8 (42/52)	90.4 (47/52)
≥4	56	94.1 (48/51)	84.3 (43/51)
Active Joints, n			
0–9	35	90.3 (28/31)	90.3 (28/31)
10–29	55	82.4 (42/51)	88.2 (45/51)
30–71	22	95.2 (20/21)	81.0 (17/21)
Fever Free[b]			
Yes	50	91.3 (42/46)	82.6 (38/46)
No	62	84.2 (48/57)	91.2 (52/57)
Oral CS Dose, mg/kg/d[c]			
<0.3	55	86.0 (43/50)	84.0 (42/50)
≥0.3	57	88.7 (47/53)	90.6 (48/53)
Background MTX Use			
Yes	78	89.0 (65/73)	90.4 (66/73)
No	34	83.3 (25/30)	80.0 (24/30)
Previous Biologic Treatment			
Yes	92	88.0 (73/83)	85.5 (71/83)
No	20	85.0 (17/20)	95.0 (19/20)
Previous IL-1 Inhibitor Treatment			
Yes	54	87.5 (42/48)	83.3 (40/48)
No	58	87.3 (48/55)	90.9 (50/55)

[a] Fever present, defined as any temperature ≥37.5°C in the 7 days preceding the week 52 visit.
[b] Fever present, defined as a temperature of ≥37.5°C in the 14 days preceding the baseline visit.
[c] Prednisone equivalent.
r/n=no. of responders/no. of patients reaching week 52 visit + no. of patients who previously withdrew due to insufficient therapeutic response.

Conclusion: TCZ was effective and provided a sustained response in patients with sJIA at 52 weeks across multiple baseline characteristics, including longer disease duration, highly active and severe disease, and previous treatment with biologic therapy.

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Phase III Study Results on the Efficacy and Safety of Canakinumab, a Long-Acting, Fully Human Anti-Interleukin-1β Antibody, in Systemic Juvenile Idiopathic Arthritis with Active Systemic Features. Hermine Brunner[1], Nicolino Ruperto[2], Gerd Horneff[2], Pierre Quartier[2], Tamás Constantin[2], Yackov Berkun[2], Tilmann Kallinich[2], Riva Brik[2], Manuel A. Ferrandiz[2], Karine Lheritier[3], Ralph Preiss[4], Lillian Tseng[4], Daniel J. Lovell[1], Alberto Martini[2], Paediatric Rheumatology International Trials Organisation[5] and Pediatric Rheumatology Collaborative Study Group [PRCSG][6]. [1]PRCSG, Cincinnati, OH, [2]PRINTO-IRCCS, Genova, Italy, [3]Novartis Pharma AG, Basel, Switzerland, [4]Novartis Pharmaceuticals Corporation, NJ, [5]Genova, Italy, [6]Cincinnati, OH

Background/Purpose: The study objective was to assess the efficacy and safety of canakinumab in systemic juvenile idiopathic arthritis (sJIA) with active systemic features at enrollment.

Methods: In this 4-week randomized, controlled, double-blind study, patients with sJIA received a single subcutaneous dose of canakinumab 4 mg/kg (maximum 300 mg) or placebo at Day 1. The primary objective was to show superior efficacy of canakinumab vs placebo in achieving an adapted ACR Ped30 (ACR criteria plus absence of fever) treatment response at Day 15.

Results: In total, 84 patients (age 2–19 yrs) received treatment (canakinumab, n=43; placebo, n=41). Baseline demographics and characteristics were comparable between groups, with the exception of age. The overall group means were: disease duration 3.4 yrs; CRP 200.6 mg/L (normal range 0–10 mg/L); number of active joints 14.1; and prednisone equivalent therapy 0.6 mg/kg/day. At Day 15, canakinumab was superior to placebo for the primary and secondary endpoints: ACR Ped30, 83.7 vs 9.8%; ACR Ped50, 67.4 vs 4.9%; ACR Ped100, 32.6% vs 0, respectively (all $p<0.0001$). ACR Ped30/50 responses with canakinumab remained significantly higher than with placebo at Day 29 (both $p<0.0001$). Six patients on canakinumab and 37 patients on placebo discontinued due to unsatisfactory therapeutic effects. Adverse events (AEs) occurred in 55.8% of canakinumab and 39.0% of placebo-treated patients. No discontinuations occurred due to AEs. Two non-fatal serious AEs were reported in each group.

Conclusion: Canakinumab has superior efficacy to placebo in patients with sJIA, providing rapid onset of action and robust response (at least ACR Ped50 with fever disappearance) in the majority of patients.

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Double Blind, Placebo-Controlled Trial with Adalimumab for Treatment of Juvenile Ankylosing Spondylitis (JAS). Gerd Horneff[1], Sigrid Fitter[1], Hans-Iko Huppertz[2], Ivan Foeldvari[3], Jasmin B. Kuemmerle-Deschner[4], Rolf M. Kuester[5], Nikolay Tzaribachev[6], Angelika Thon[7], Michael Borte[8], Gerd Ganser[9], Ralf Trauzeddel[10] and Kirsten Minden[11]. [1]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [2]Krinikum Bremen-Mitte, Bremen, Germany, [3]Hamburger Zentrum Kinder-und Jugendrheumatologie, Hamburg, Germany, [4]University Hospital Tuebingen, Tuebingen, Germany, [5]Rheumaklinik Bad Bramstedt, Bad Bramstedt, Germany, [6]Center for Rheumatic Diseases, Bad Bramstedt, Germany, [7]Kinderklinik der Medizinischen Hochschule Hannover, Hannover, Germany, [8]Sankt Georg Clinics, Leeipzig, Germany, [9]Sankt Josef Stift, Sendenhorst, Germany, [10]Helios Clinics, Berlin, Germany, [11]Charite, Berlin, Germany

Background/Purpose: While adalimumab is licensed for adult AS, open uncontrolled studies suggest therapeutic efficacy of TNF-inhibitors in jAS.

Methods: This study is to determine efficacy of adalimumab in patients with juvenile AS in a 12 weeks double blind placebo controlled trial with a 12 weeks open label extension. In total 32 subjects aged 12 to 17 years suffering from severe, active, refractory jAS were enrolled into the trial HUM06–037. All subjects were randomized and included in the Intention -to-treat (ITT) analysis, among them 2 subjects who terminated the treatment prematurely after the 3rd injection due to insufficient efficacy.

Results: 17 patients were randomized to receive adalimumab 40mg/2 weeks and 15 patients received placebo. Stable doses of NSAIDs and low dose of corticosteroids (£10 mg per day) were permitted. Two patients (one of each group) discontinued prematurely due to insufficient efficacy and were label as non-responders.

In the adalimumab group a decrease of all disease activity parameters was noted at week 12 which was even more pronounced at week 24 while in the placebo group some changes were noted at week 12 but patients significantly improved at week 24 after switching to ADA at week 12 (table).

	PLC wk 0	PLC wk 12	PLC/ADA wk 24	ADA wk 0	ADA wk 12	ADA/ADA wk 24
active joints	2.9+/−5.0	1.6+/−2.0	0.8+/−1.1***	2.2+/−2.6	1.1+/−2.1	0.2+/−0.6**
LOM	4.7+/−5.9	2.7+/−2.6	1.1+/−1.3***	2.2+/−2.6	1.4+/−2.0	0.8+/−0.8*
spinal inflammation	*5.2+/−2.3*	*3.8+/−3.0*	*2.3+/−2.9*	4.3+/−2.0	1.5+/−1.7***	1.4+/−1.3***
Back Pain	*6.1+/−1.5*	*4.2+/−2.5**	*2.2+/−1.8*	5.6+/−1.6	2.8+/−3.0**	1.9+/−2.3***
Pat. Disease Activity	*6.7+/−2.2*	*5.1+/−3.2*	*3.4+/−3.1*	5.9+/−1.9	3.1+/−3.2**	2.3+/−2.3***
BASFI	*4.2+/−2.3*	*3.3+/−2.6*	*1.8+/−2.0*	3.8+/−1.8	2.0+/−2.4*	1.1+/−1.6***
CHAQ	1.2+/−0.9	0.8+/−0.6	*0.5+/−0.6*	1.0+/−0.4	0.4+/−0.6***	0.2+/−0.3***
Physician global	5.9+/−2.4	4.3+/−3.2	*1.9+/−2.0*	5.6+/−1.8	2.4+/−2.8***	1.0+/−1.2***
ESR	17+/−6	18+/−20	*11+/−13*	22+/−27	6+/−3*	6.6+/−5.7*
ASAS 40		5 (33%)	9 (60%)		9 (53%)	12 (71%)

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ (t-test compared to baseline)

ASAS 40 response rates after 4, 8 and 12 weeks were higher in the adalimumab group (41%/53%/53%) than in the placebo (20%/20%/33%) group while significant ($p<0.05$) differences were found at week 8. Per protocol analysis excluding 3 patients with violations of the inclusion criteria at baseline (who were met at screening) also reveals significantly higher ASAS20 ($p=0.03$) and higher ASAS40 ($p=0.06$) response to adalimumab after 8 weeks. At week 24, ASAS40 was reached by 12 (71%) in the group receiving adalimumab from the beginning and 9 (60%) in the group initially treated with PLC and at wk 12 switching to adalimumab.

In the total 24 weeks 97 adverse events (AE) have been noted in 23 patients., 8 SAEs occurred in 7 patients, 7 on adalimumab (one appendicitis and one pyelonephritis leading to hospital admission). During the 12 weeks controlled phase 28 AEs occurred in 10 patients with placebo compared to 26 AEs in 11 patients on ADA. Injection site reactions were the most common adverse event. There were 17 various infections occurring in the 12 week double blind phase, 8 on placebo, 9 on adalimumab and further 19 in the 12 week open label period.

Conclusion: Adalimumab shows superiority over placebo in a double blind randomized trial in patients with juvenile ankylosing spondylitis. Treatment effects rapidly occurred and persisted at least for 24 weeks on treatment. There was no unexpected intolerance.

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Developing Consensus Treatment Plans for Proliferative Nephritis in Juvenile Systemic Lupus Erythematosus: Maintenance Therapy. Rina Mina[1], Hermine Brunner[2], B. Anne Eberhard[3], Marilynn G. Punaro[4], Stacy P. Ardoin[5], Marisa Klein-Gitelman[6], Lakshmi N. Moorthy[7], Suhas M. Radhakrishna[8], Mindy S. Lo[9], Matthew C. Hollander[10], Eyal Muscal[11], Joyce J. Hsu[12], Linda Wagner-Weiner[13], Deborah M. Levy[14], Carol Wallace[15], Norman T. Ilowite[16] and Emily von Scheven[17]. [1]Cincinnati Children's Med Ctr, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Cohen Children's Hospital Medical Center, New Hyde Park, NY, [4]Texas Scottish Rite Hospital, Dallas, TX, [5]Ohio State University, Columbus, OH, [6]Children's Memorial Hospital, Chicago, IL, [7]Robert Wood Johnson Medical School-UMDNJ, New Brunswick, NJ, [8]Children's Hosp Los Angeles, Los Angeles, CA, [9]Children's Hospital Boston, Boston, MA, [10]Seattle Children's Hospital, Seattle, WA, [11]Baylor College of Medicine, Houston, TX, [12]Stanford University, Palo Alto, CA, [13]University of Chicago Hospital, Chicago, IL, [14]The Hospital for Sick Children, Toronto, ON, [15]Childrens Hosp & Regional Med, Seattle, WA, [16]Children's Hospital Montefiore, Bronx, NY, [17]UC San Francisco, San Francisco, CA

Background/Purpose: The Childhood Arthritis and Rheumatology Research Alliance Lupus (CARRA)-Systemic Lupus Erythematosus (SLE) Committee is developing consensus treatment plans (CTPs) for proliferative lupus nephritis (LN) in juvenile SLE (jSLE) to guide therapy and to serve as the basis for future comparative effectiveness studies. The purpose of this phase of the project was to formulate CTPs for the maintenance phase (M-Rx) of proliferative LN based on medical evidence and consistent with current clinical practice.

Methods: Based on extensive literature review, an online Delphi survey addressing various aspects of M-Rx for proliferative LN was sent to 57 members of the CARRA-SLE Committee. A subsequent consensus conference held on June 1, 2011 was attended by 36 CARRA voting members who are experienced in the care of jSLE. The consensus level was set at 80%.

Results: The response rate to the Delphi survey was 86%. Consensus was reached that the duration of the CPTs for proliferative LN should be 36 months post-kidney biopsy at which time their effectiveness can be assessed (Figure 1). There was consensus that for a patient with substantial response to induction therapy (I-Rx): 1). mycophenolic acid (MMF) or cyclophosphamide (CYC) are the immunosuppressive medications to be used during M-Rx; 2). MMF and CYC dosing should be the same as specified for I-Rx; 3). MMF will be initiated within 2 weeks of the last CYC infusion given for I-Rx; 4). CYC administration, started 3 months after the last infusion of I-Rx will be continued every 3 months; and, 5). combination immunosuppressive therapy will not be used. Concerns about non-adherence, pregnancy, worsening of LN, and drug intolerance may warrant change of the immunosuppressive agent initially chosen for M-Rx; azathioprine use may be considered in these settings. There was consensus to utilize a uniform corticosteroid tapering regimen during M-Rx. Resolution of proteinuria, presence of avascular necrosis, and normalization of complement C3 and C4 levels all influence the decision to discontinue corticosteroid during M-Rx.

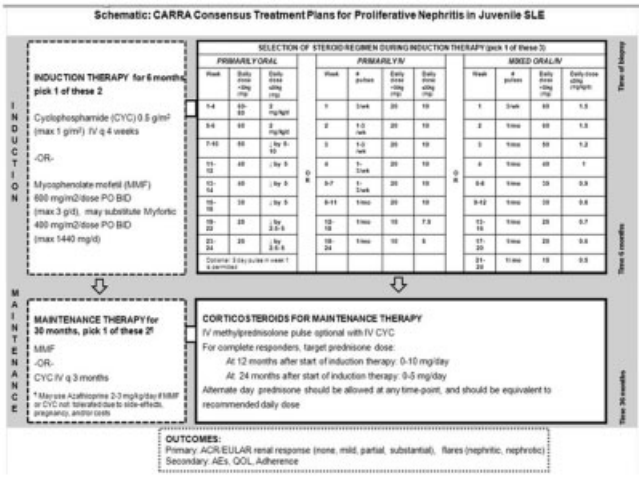

Figure 1. Consensus Treatment Plans for Proliferative LN in jSLE

Conclusion: Consensus was reached about key features of CTPs that are part of the M-Rx of proliferative LN in jSLE. Further efforts are in progress to address issues of partial response and renal flares during M-Rx for proliferative LN.

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Radiological Evaluation of Systemic Juvenile Idiopathic Arthritis Treated with Tocilizumab, An Anti-IL6 Receptor Monoclonal Antibody. Chie Aoki[1], Yutaka Inaba[1], Tomoyuki Imagawa[2], Takako Miyamae[2], Masaaki Mori[2], Tomoyuki Saito[2] and Shumpei Yokota[2]. [1]Yokohama City Unversity, Yokohama, Japan, [2]Yokohama City University, Yokohama, Japan

Background/Purpose: Recently tocilizumab (an anti-IL6 receptor monoclonal antibody) has shown clinical benefits in the treatment of systemic juvenile idiopathic arthritis (sJIA) patients. We radiologically evaluated the effects of tocilizumab on the joints by using the carpometacarpal ratio (Poznanski score) and Larsen score of sJIA patients.

Methods: Forty sJIA patients treated with 8mg/kg of tocilizumab every two weeks were enrolled in this study. We examined bilateral hand radiographs in 32 cases to assess the Poznanski score, and radiographs of the large joints, such as the shoulders, elbows, hips, knees and ankles, to assess the Larsen score in 40 cases before and during treatment. Their clinical response was assessed by active joint count and laboratory data.

Results: The mean age at the start of tocilizumab administration was 9.2 years (range: 2.0~18.6 years), and the mean follow-up period was 3.8 years (range: 0.9~8.8 years). The mean active joint count, and WBC, CRP, ESR and MMP-3 values improved significantly from 4.9 to 0.7 joints, from 15400 to 7200/μl, from 5.7 to 0mg/dl, from 40 to 2mm/h, and from 380 to 172ng/ml, respectively. The Poznanski score improved from −0.9 before tocilizumab treatment to −0.6 at the final follow-up; however, the total Larsen score increased from 10.5 to 11.7 during treatment. The Poznanski score improved in 19 cases (48%), but worsened in 12 cases (30%). The total Larsen score improved in 13 cases (33%: improved group), but worsened in 19 cases (48%: worsened group). There was a significant difference between the two groups in MMP-3 levels (53 in the improved group and 226 in the worsened group) at the final follow-up ($P<0.05$). The Larsen score in weight-bearing joints, especially the hips, increased more than in other joints in the worsened group.

Fig. 1 Improvement in damaged hip joints

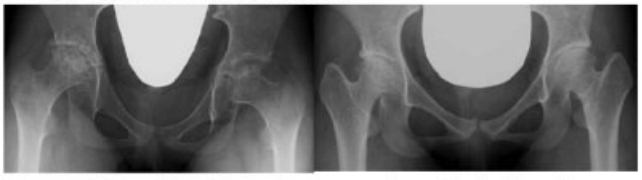
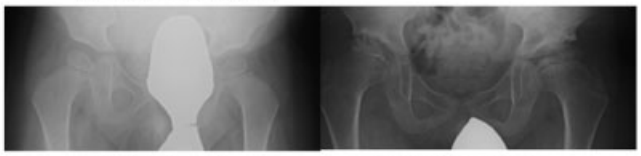


Fig. 2 Progression in hip joints



Before tocilizumab 4 years After tocilizumab

Conclusion: We evaluated radiographs of patients treated with tocilizumab and observed an improvement in Poznanski score; however, the total Larsen score worsened in patients who had high MMP-3 levels.

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Efficacy of Rituximab Retreatment in Refractory Systemic Juvenile Idiopathic Arthritis. Ekaterina Alexeeva, Saniya Valieva, Tatyana Bzarova, Rina Denisova, Kseniya Isayeva, Tatyana Sleptsova and Elena Mitenko. Scientific Center of Children's Health, Moscow, Russia

Background/Purpose: Chimeric monoclonal anti-CD20 B-cell antibody (rituximab) is promising drug for the treatment of JIA refractory to immunosuppressive drugs and TNF-α-blockers. To evaluate clinical efficacy of rituximab retreatment in patients with severe systemic juvenile idiopathic arthritis (JIA).

Methods: 75 patients were enrolled in the study, 36 boys and 39 girs with JIA. Range of age was from 2,3 to 17 years; mean disease duration was 5,32 (0.6; 7,0) years. Rituximab was administered at a mean dose of 375 mg/m^2/ administration according to the following regimen: 1 dose once a week for 4 consecutive weeks every 24 weeks. The next course of Rituximab was administrated if patients had systemic manifestations, active joints, increasing level of CRP and ESR in 24 weeks after Rituximab treatment. 75 patients have received one treatment course (24 weeks), 72 children have received 2 courses (48 weeks), 55 children have received 3 courses (72 weeks), 38–4 courses (96 weeks), 23–5 courses (120 weeks)

Results: The number of systemic manifestations was significantly reduced from 4,5±1,3 to 2,8±1,4, 1,6±0,9, 0,5±0,4, 0,7±0,5 and 0,5±0,3 at Week 24, 48, 72, 96 and 120, respectively. The ACR Pedi 30, 50, 70 were achieved by 85%,45%, 40% of patients at Week 24, and by 90%, 75%, 70% of patients at Week 48, respectively. At week 72 ACR pedi 50 and 70 were achieved by 75% and 70% of patients. The remission was achieved by 25% of patients at Week 24, by 48% of patients at Week 48, by 65% of patients at Week 72 and by 80% and 90% of patients at Week 96 and 120.

Conclusion: Rituximab is effective drug of treatment in patients with severe juvenile idiopathic arthritis. The remission was achieved by 90% of patients at Week 120.

ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Novel Compounds II
Wednesday, November 9, 2011, 11:00 AM–12:30 PM

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Tofacitinib (CP-690,550) in Combination with Traditional Disease-Modifying Anti-Rheumatic Drugs: Phase 3 Study Patient-Reported Outcomes in Patients with Active Rheumatoid Arthritis and An Inadequate Response to Disease-Modifying Anti-Rheumatic Drugs. V. Strand[1], J. M. Kremer[2], Z. G. Li[3], S. Hall[4], Roy M. Fleischmann[5], M. C. Genovese[6], E. Martin-Mola[7], J. Isaacs[8], D. Gruben[9], G. Wallenstein[9], S. Krishnaswami[9], S. H. Zwillich[9], T. Koncz[10], R. Riese[9], J. D. Bradley[9] and the ORAL Sync investigators[11]. [1]Stanford University, Palo Alto, CA, [2]Albany Medical College and The Center for Rheumatology, Albany, NY, [3]Peking University People's Hospital, Peking, China, [4]Melbourne Rheumatology, Melbourne, Australia, [5]MCRC, University of Texas, Dallas, TX, [6]Stanford University Medical Center, Palo Alto, CA, [7]Hospital Universitario La Paz, Madrid, Spain, [8]University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom, [9]Pfizer Inc., Groton, CT, [10]Pfizer Inc., New York, NY, [11]Groton

Background/Purpose: Tofacitinib (CP-690,550) is a novel, oral Janus kinase (JAK) inhibitor investigated as a targeted immunomodulator for treatment of rheumatoid arthritis (RA). The efficacy and safety of tofacitinib vs placebo (PBO) were evaluated in pts with active RA with an inadequate response to ≥1 DMARD (traditional or biologic). Primary efficacy analyses have previously been reported. Here we report patient-reported outcomes (PRO).

Methods: In this 12-month (Mo) study (NCT00856544), pts receiving traditional background DMARDs were randomized (4:4:1:1) to: tofacitinib 5 mg twice daily (BID); 10 mg BID; PBO advanced to 5 mg BID; and PBO advanced to 10 mg BID. At Mo 3 all 'non-responder' PBO pts (<20% reduction from baseline in swollen/tender joint counts) were advanced to tofacitinib 5 or 10 mg BID. At Mo 6 all remaining PBO pts were advanced to tofacitinib. Most PROs were secondary endpoints and included: patient global assessment of disease activity (PtGA), pain, physical function (HAQ-DI); health-related quality of life (Medical Outcomes Survey [MOS] Short Form 36 [SF-36]), fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]), and sleep (MOS Sleep Scale).

Results: 792 pts were treated; mean disease duration 8.1 – 10.2 years (y); mean age 50.8–53.3 y. At Mo 3 improvements from baseline in all PROs were statistically significantly greater in tofacitinib 5 and 10 mg BID groups than PBO (Table). Based on pts reporting improvements ≥ minimally clinically important differences [MCID], numbers needed to treat (NNTs) at Mo 3 for tofacitinib 5 and 10 mg BID, respectively, ranged from 4.6 – 6.0 and 3.7–8.3, respectively (full analysis set [FAS], no imputation).

Table. Patient-reported outcomes at Mo 3 (FAS, longitudinal model)

Patient-reported outcomes [MCID values]	Placebo n=159	Tofacitinib 5 mg BID n=315	Tofacitinib 10 mg BID n=318
PtGA [-10]	-12.54	-24.82*** (-16.39, -8.17)	-28.19*** (-19.76, -11.53)
NNT		5.2	4.3
Pain (VAS) [-10]	-11.38	-24.18*** (-16.90, -8.69)	-26.78*** (-19.50, -11.28)
NNT		4.6	4.2
HAQ-DI [-0.22]	-0.21	-0.46*** (-0.35, -0.16)	-0.56*** (-0.44, -0.26)
NNT		4.7	4.0
SF-36 Physical component score [-2.5]	2.40	5.92*** (2.15, 4.88)	7.54*** (3.77, 6.50)
NNT		5.8	3.7
SF-36 Mental component score [-2.5]	1.63	4.39* (1.05, 4.47)	4.40* (1.06, 4.49)
NNT		6.0	8.3
Fatigue (FACIT-F)	2.05	5.81*** (2.25, 5.28)	6.85*** (3.29, 6.33)
MOS sleep summary	-1.57	-6.19** (-7.33, -1.91)	-7.43*** (-8.58, -3.15)

*p<0.05; **p<0.001; ***p<0.0001 vs PBO

Conclusion: In this Phase 3 study of tofacitinib in combination with traditional DMARDs, treatment with 5 and 10 mg BID resulted in consistent statistically significant and clinically meaningful improvements in multiple PROs vs PBO at Mo 3.

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Double-Blind Study of Tocilizumab Plus Methotrexate Vs Tocilizumab Plus Placebo in Patients with Active Rheumatoid Arthritis Despite Prior Methotrexate: Progression of Structural Damage, Quality of Life, and Physical Function At 24 Weeks. Maxime Dougados[1], Karsten Kissel[2], Howard Amital[3], Philip G. Conaghan[4], Emilio Martin-Mola[5], Evgeny L. Nasonov[6], Georg Schett[7], Orrin M. Troum[8], Tiina Veldi[9], Corrado Bernasconi[10] and T.W.J. Huizinga[11]. [1]Paris-Descartes University, Cochin Hospital, Paris, France, [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [3]Sheba Medical Center, Tel-hashomer, Israel, [4]NIHR-Leeds Biomedical Research Unit and Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [5]Hospital Universitario La Paz, Madrid, Spain, [6]Institute of Rheumatology, Moscow, Russia, [7]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [8]USC Keck School of Medicine, Santa Monica, CA, [9]East-Tallinn Central Hospital, Tallinn, Estonia, [10]Roche, Basel, Switzerland, [11]Leiden University Medical Center, Leiden, Netherlands

Background/Purpose: To evaluate clinical efficacy (including progression of structural damage, quality of life (QoL), and physical function) and safety of adding tocilizumab (TCZ) to methotrexate (MTX) vs switching to TCZ alone in patients (pts) with moderate to severe active rheumatoid arthritis (RA) despite MTX treatment.

Methods: In the double-blind, 2-year study ACT-RAY (NCT00810199,

EudraCT No. 2008-001847-20) patients on stable doses of oral weekly MTX were randomized to continued MTX with addition of TCZ 8 mg/kg every 4 wks or oral PBO+TCZ. The study was powered to assess the primary endpoint (DAS28 remission rate [RR] at 24 wks) for superiority of the combination arm based on a 12.5% difference between groups: 42.5% on TCZ+MTX vs 30% on TCZ+PBO. Baseline and wk-24 hand and feet radiographs were scored by independent readers blinded to treatment allocation, clinical response, and sequence of X-rays.

Results: Of 556 pts randomized (TCZ+MTX=279; TCZ+PBO=277) 92% (n=512; TCZ+MTX=260; TCZ+PBO=252) completed 24 wks. Mean baseline characteristics were similar for both groups (female, 80.3%; age, 53.3 yrs; RA duration, 8.2 yrs; DAS28, 6.35) except for radiographic scores (Table). DAS28 RR was 40.4% and 34.8% in TCZ+MTX and TCZ+PBO groups, respectively (difference between groups 5.65% [95% CI: –2.41, 13.71]; P=0.19; not significant). ACR20/50/70/90 response rates were 72%/45%/25%/6% (TCZ+MTX) and 71%/41%/26%/5% (TCZ+PBO) (all P=NS). Progression of structural damage was low, as shown by change in GSS (Table) and proportion of pts showing no progression (change ≤ 0). In analyses of covariance models, taking baseline values into account, there were no significant differences between groups. HAQ-DI and RAQoL improved significantly from baseline, with no differences between groups (Table). Rates per 100 patient-yrs of SAEs and serious infections were 21 and 6 for TCZ+MTX and 18 and 6 for TCZ+PBO, respectively; infections were the most frequent AEs and SAEs. AE-related discontinuations and dose modifications occurred in 3.9% and 27.4% of TCZ+MTX and 2.9% and 18.5% of TCZ+PBO pts, respectively. ALT elevations >60 U/L were observed in 16% and 6% of TCZ+MTX and TCZ+PBO pts, respectively.

Radiographic and QoL Results at Week 24

Genant-modified Sharp Score (GSS), Mean (SD)	TCZ + MTX N = 277	TCZ + PBO N = 276	Between-group Difference (95% CI)
Total GSS	30.4 (31.8)	37.1 (40.5)	
Baseline	3.71	4.47	
Baseline annualized progression rate	0.08 (1.88)	0.22 (1.11)	−0.13 (−0.39, 0.13)
Change from baseline (wk 24)			P=0.3304*
JSN Score	14.7 (17.3)	17.7 (21.7)	
Baseline	0.08 (1.49)	0.11 (0.70)	−0.02 (−0.22, 0.17)
Change from baseline (wk 24)			P=0.8235*
Erosion Score	15.7 (15.4)	19.4 (19.8)	
Baseline	−0.01 (0.79)	0.11 (0.63)	−0.11 (−0.23, 0.02)
Change from baseline (wk 24)			P=0.0871*
No Progression in GSS (Patients with Changes ≤0), n (%)			
Total GSS	181 (65.3)	162 (58.7)	P=0.0871†
JSN Score	218 (78.7)	203 (73.6)	P=0.1319†
Erosion Score	190 (68.6)	179 (64.9)	P=0.3317†
QoL Data Change From Baseline, Mean (SD)			
HAQ-DI	−0.56 (0.67)	–0.55 (0.53)	P=0.9323‡
RAQoL	−5.97 (7.95)	–5.19 (7.06)	P=0.3080‡

* P-values are for between-group differences in adjusted means (change from baseline to wk 24) from the analysis of covariance
† P-values are for between-group differences from a two-sided Cochran-Mantel-Haenszel test stratified for region and baseline DAS28
‡ P-values are for between-group differences from a 2-sided Wilcoxon rank-sum test of no difference between the 2 treatment groups in change from baseline

Conclusion: The study did not demonstrate clinical superiority of TCZ+MTX combination therapy over TCZ monotherapy at wk 24, based on DAS28 remission rates and other efficacy endpoints. This was confirmed by near complete arrest of progression of structural damage, with no significant differences between groups, leading to significant improvement in QoL with both treatments. The safety data confirmed previous findings. TCZ combined with MTX was associated more commonly with transaminase increases. These results show that clinically meaningful responses can be obtained with TCZ monotherapy and therefore MTX may not be a required concomitant treatment with TCZ.

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Postmarketing Surveillance of Tocilizumab for Rheumatoid Arthritis In Japan—Full Analysis Report of 7,901 Patients. Hisashi Yamanaka[1], Masayoshi Harigai[2], Shigeko Inokuma[3], Naoki Ishiguro[4], Junnosuke Ryu[5], Syuji Takei[6], Tsutomu Takeuchi[7], Yoshiya Tanaka[8], Youko Sano[9] and Takao Koike[10]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Tokyo Medical and Dental Univ, Tokyo, Japan, [3]Japanese Red Cross Medical Center, Tokyo, Japan, [4]Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Aichi, Japan, [5]Nihon University School of Medicine, Tokyo, Japan, [6]Kagoshima University, Kagoshima City, Japan, [7]Keio University School of Medicine, Tokyo, Japan, [8]University of Occupational and Environmental Health, Japan, Kitakyushu, Fukuoka, Japan, [9]Chugai Pharmaceutical Co. Ltd., Tokyo, Japan, [10]Sapporo Medical Center NTT EC, Sapporo, Japan

Background/Purpose: A postmarketing surveillance (PMS) was performed for all patients with rheumatoid arthritis (RA) who were treated with tocilizumab (TCZ) in Japan to investigate the safety and effectiveness in the daily clinical setting.

Methods: This full analysis report includes 7,901 patients. They received 8 mg/kg of TCZ every 4 weeks, and were observed for 28 weeks. Baseline characteristics, effectiveness as measured by 28-joint disease activity score (DAS28-ESR) and Boolean remission criteria (tender joint count ≤ 1, swollen joint count ≤ 1, patient global assessment [on 0–10 scale] ≤ 1, and serum concentration of C-reactive protein [mg/dL] ≤ 1), and all adverse events (AEs) were assessed.

Results: Baseline patient characteristics were as follows: mean age of 58.7 years (≥70 years of age in 20.7% of patients); mean disease duration of RA of 10.4 years (≥10 years in 37.8%); respiratory comorbidities in 17.0% and cardiac comorbidities in 5.1%; previous TNF inhibitor use in 62.8%; and concomitant methotrexate (MTX) use in 55.8% and concomitant glucocorticoid use in 74.0%. Mean baseline DAS28-ESR was 5.5, which declined to 2.9 at week 28 (LOCF method); 47.6% of patients achieved DAS28 remission (DAS28-ESR < 2.6), and 15.1% of patients achieved Boolean remission. The incidences of DAS28 remission and Boolean remission in patients with disease duration <2 years were significantly better than those in patients with ≥10 years' disease duration ($p < 0.001$, χ^2 test). TNF inhibitor naïve patients showed significantly better response than the patients with prior anti-TNF use ($p < 0.001$, χ^2 test) (Table).

		Disease duration (years)			Anti-TNF naïve		Anti-TNF used	
Incidence	total	<2	2≤>10	10≤	MTX+	MTX−	MTX+	MTX−
DAS28 remission	47.6	56.1*	50.1	42.4	60.5†¶	50.6¶	45.6†	39.1
Boolean remission	15.1	22.3*	16.4	10.7	22.1¶	20.2¶	12.0	11.7
AEs	43.9	43.8	43.4	46.3	42.0	43.0	45.4	43.5
SAEs	9.6	8.5*	8.3	12.0	8.7†	10.8	8.1†	11.8
Infections	11.1	8.9*	9.4	14.0	10.0§	12.0	10.5	12.0
Serious infections	3.8	2.6*	3.3	4.9	3.6‡	4.5	3.1	4.4

* ;p<0.001 between <2years and ≤10 years, †;p<0.001, ‡;p<0.01, §;p<0.05 between MTX+ and MTX-, ¶;p<0.001 between anti-TNF naïve and anti-TNF used

The incidences of total and serious AEs (SAEs) were 43.9% and 9.6%, respectively. The incidence of SAEs was higher in the patients whose disease duration was ≥10 years ($p < 0.001$, χ^2test, vs. <10 years) or who did not use MTX concomitantly ($p < 0.001$, χ^2test, vs. concomitant MTX use) (Table). Infections and infestations were the most frequent AEs (11.1%) and the most frequent SAEs (3.8%). Although malignancies were reported as AEs in 39 patients (0.5%), no specific patterns were observed. Gastrointestinal disorders were reported in 373 patients (4.7%) including 13 (0.16%) gastrointestinal tract perforations. Thirty-five patients died within 28 weeks, and the standardized mortality ratio, with the Japanese general population in 2008 as a control, was 1.15 (95%CI: 0.83–1.61), which was numerically lower than the previous report (1.66; 95%CI: 1.12–2.46 from the interim analysis reports of 3,818 patients) and similar to the results reported in the Japanese cohort study of RA patients (Nakajima A, et al. Scand J Rheumatol. 2010; 39: 360–7)

Conclusion: The results from this study revealed that TCZ was effective and well-tolerated in Japanese RA patients in the daily clinical setting.

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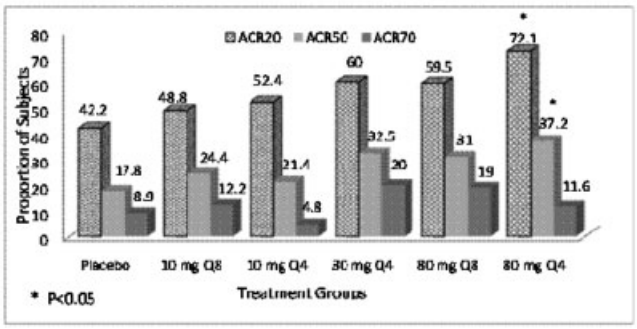
A Multiple Ascending Dose/Proof of Concept Study of ATN-103 (ozoralizumab) in Rheumatoid Arthritis Subjects on a Background of Methotrexate. Roy Fleischmann[1], Savithree Nayiager[2], Ingrid Louw[3], Bernadette Rojkovich[4], Caifeng Fu[5], Chandrasekhar Udata[6], Parvin Fardipour[7], Bonnie Marshall[7], Michelle Hinz[7], Amarnath Sharma[7], Kathy Shields[7] and Gail Comer[7]. [1]Metroplex Clinical Research Center, Dallas, TX, [2]St. Augustine Hospital, Berea, KwaZulu-Natal, South Africa, [3]Panorama Medical Centre, Panorama, Western Cape, South Africa, [4]Polyclinic of the Hospitaller Brothers of St John of God, Budapest, Hungary, [5]Pfizer, Cambridge, MA, [6]Pfizer, La Jolla, CA, [7]Pfizer, Collegeville, PA

Background/Purpose: Inhibition of tumor necrosis factor (TNF) has been shown to be an effective treatment of Rheumatoid Arthritis (RA). ATN-103 (ozoralizumab), a novel TNF inhibitor, is a humanized, trivalent, bispecific Nanobody that contains 2 human TNF-binding domains linked to a human serum albumin-binding domain. ATN-103 was evaluated in a double-blind, seamless adaptive phase 1/2, Multiple Ascending Dose (MAD)/Proof of Concept (POC) study that assessed the safety and efficacy in subjects with active RA compared to placebo (PBO).

Methods: The study started as a randomized, sequential dose escalating study, stratified by prior TNFi use, and converted to a parallel enrolling study once multiple doses of all doses levels had been evaluated to be safe by a Data Monitoring Committee. Subjects (253) received subcutaneous injections of PBO or ATN-103 doses of 10 mg, 30 mg, or 80 mg administered every 4 weeks (Q4) or 10 mg or 80 mg every 8 weeks (Q8). The primary endpoint (ACR20 at week 16) was analyzed by the Cochran-Mantel-Haenszel test stratified by prior TNFi use status using a last observation carried forward (LOCF) for the modified intent-to-treat (mITT) population (all randomized subjects receiving at least 1 dose of study drug).

Results: Statistical significance (p= 0.006) compared to PBO for the primary endpoint was achieved by the 80 mg Q4 dose regimen only. The ACR 20/50/70 response at week 16 is shown below.



Statistically significant improvements over PBO in secondary endpoints were achieved for 80 mg Q4 dose regimen in DAS28, ACR50, HAQ-DI, tender and swollen joint counts, pain and general health visual analog scales, physician and patient global assessments, CRP and EULAR response.

Exposure to ATN-103 increased in an approximately dose-proportional manner with increasing dose. The mean terminal half-life ranged from 9.5 to 13.5 days, mean apparent clearance was 0.3 to 0.5 L/day, and the area under the plasma concentration-versus-time curve ranged from 22 to 247 μg.day/mL.

ATN-103 was generally safe and well tolerated with adverse events (AEs) similar to those reported for other TNFi agents. Thirteen (5.1%) serious adverse events (SAEs) were reported with no dose-dependent increase and no dose limiting toxicity identified. No SAE was reported in more than one subject and no SAEs were reported in the 80 mg Q4 group. The most common treatment-emergent AEs were upper respiratory infections and urinary tract infections. Injection site reactions were observed in 3 subjects.

Conclusion: The 80 mg Q4wk group was significantly better than PBO at week 16 in ACR20, ACR50, DAS28, HAQ-DI and other secondary endpoints. There was no dose dependent increase in either AEs or SAEs or dose limiting toxicities. Exposure to ATN-103 increased in a dose-proportional manner.

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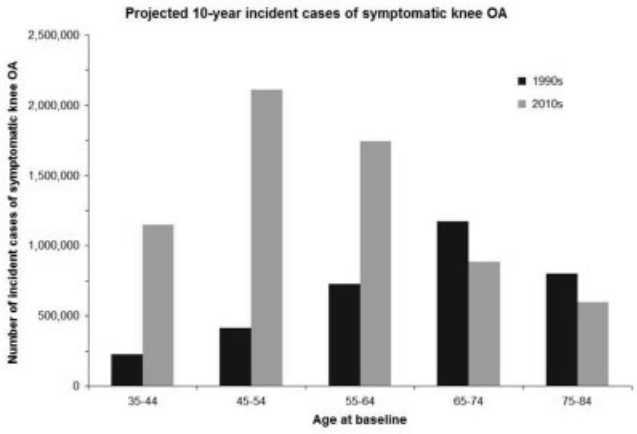
Results From a 2-Part, Proof-of-Concept, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Sirukumab, a Human Anti-Interleukin-6 Monoclonal Antibody, in Active Rheumatoid Arthritis Patients Despite Methotrexate Therapy. Benjamin Hsu[1], Shihong Sheng[2], Josef Smolen[3] and Michael Weinblatt[4]. [1]Centocor R&D, a division of J&J Pharmaceutical R& D, LLC/Univ. of Pennsylvania, Malvern/Philadelphia, PA, [2]Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [4]Brigham & Women's Hospital, Boston, MA

Background/Purpose: IL-6 overproduction is believed to be involved in RA pathogenesis. Sirukumab(formerly CNTO 136) is a human mAb that binds with high affinity to cytokine IL-6. In the proof of concept part (Part A) of a multicenter, randomized, double blind, pbo controlled, ph 2 study, 100mg sirukumab SC q2w were generally well tolerated & efficacious compared with pbo in pts with active RA despite MTX.

Methods: The ph2 dose ranging Part B was initiated to determine efficacious & safe sirukumab dose regimens and to describe SC sirukumab PK and PD in active RA pts. In Part B, pts with active RA despite MTX were randomized equally to: (1)pbo q2w at wks 0–10, then sirukumab 100mg q2w at wks12–24; (2)sirukumab 100mg q2w at wks 0–24; (3)sirukumab 100mg q4w at wks0–24; (4)sirukumab 50mg q4w at wks0–24;or (5)sirukumab 25mg q4w at wks0–24. Primary endpoint was ACR50 response at wk12, compared between each active grp vs pbo. Key secondary endpoints were change from baseline(bsl) in DAS28(CRP) at wk12, serum sirukumab PK and % change from bsl in serum CRP at wk2.

Results: In Part B, 151pts were randomized & treated(table). 85% pts were female, 60% Caucasian, 21% Japanese. At bsl, mean age: 53±11yrs, mean weight: 69±15kg, mean DAS28(CRP): 5.9±0.9, and median serum CRP: 1.7mg/dL. 26(87%) pbo pts crossed over to sirukumab 100mg q2w at wk12. At wk12, sirukumab significantly improved ACR50 response (overall p=0.010) and significantly reduced DAS28 scores (p<0.001, table). Sirukumab PK were linear over the SC dose range of 25–100mg. PK parameters were generally consistent between Caucasians& Japanese. Mean serum CRP levels decreased >80% from bsl with sirukumab at wk2 and remained suppressed thru wk24 (table). Thru wk38, AEs occurred more often with sirukumab than pbo (81 vs 67%), including mostly minor infections/infestations (31 vs 13%), GI disorders (19 vs 10%), and injection site reactions (16 vs 3%). AEs of leukopenia (9,13% [1 NCI Grade 3]), neutropenia (5,3% [3 Gr 3]), thrombocytopenia (3,2% [1 Gr 3, 1 Gr 4]), and lymphopenia (2,1%, [1 Gr 3, 1 Gr 4]) were reported with sirukumab. ALT(8 Gr 3, 7%) and AST(1 Gr 3, 1%) elevations not associated with increased bilirubin; and sustained increases from bsl starting at wk2 in total cholesterol (mean sirukumab vs pbo: 19% ± 17% vs −5% ± 12%) and LDL (20% ± 20% vs −4% ± 22%) were seen with sirukumab. These lab abnormalities occurred without dose relationship or short term clinical sequelae. SAEs were more common with pbo(4, 13%) than sirukumab(13, 9%); the majority were infections. 1 pt died of unrelated brain aneurysm. 4/136 (3%; 2 100mg q4w, 2 pbo→100mg q2w) evaluable pts had antibodies to sirukumab thru wk38; 3 of these pts were ACR50 responders at wk24, 0 had injection site reactions.

Sirukumab was efficacious & generally well tolerated in pts wi expected to incur 6,475,642 incident cases of symptomatic knee OA over the next decade, with those ages 45–64 accounting for 59% of these cases (Figure). Among Americans who were ages 45–54 at the beginning of the 1990s, an estimated 412,214 incident cases of knee OA were expected over the subsequent 10 years, resulting in a 10-year cumulative incidence of 1.5%. Among people in the same baseline age group in the 2010s, 2,108,881 incident cases of symptomatic knee OA are expected over the next 10 years, a cumulative incidence of 4.8%. The projected number of 10-year incident cases among those ages 65–74 at baseline decreased slightly between the 1990s (1,169,615 cases) and the 2010s (882,997 cases).



Conclusion: Since the early 1990s, the age of onset of physician-diagnosed symptomatic knee OA has shifted dramatically, occurring on average 16 years earlier in life. This trend may reflect temporal changes in the prevalence of OA risk factors, as well as thresholds for patient care-seeking and physician diagnosis of OA. If the current OA incidence trend continues, nearly 6.5 million Americans between the ages of 35 and 84 will be diagnosed with symptomatic knee OA in the next 10 years, with those ages 45–64 accounting for more than half of these incident cases. A resulting spike in the utilization of healthcare, specifically total knee replacements, could have a dramatic economic impact and place additional burden on the healthcare system.

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Results From a Multicenter, International, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Sirukumab, a Human Anti-IL-6 Monoclonal Antibody, in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy. Benjamin Hsu. Centocor R&D, a division of J&J Pharmaceutical R& D, LLC/Univ. of Pennsylvania, Malvern/ Philadelphia, PA, Shihong Sheng, Centocor R&D, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC, Malvern, Michael E. Weinblatt, Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA and Josef Smolen, Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Background/Purpose: To assess remission rates from a phase 2 study of sirukumab, a human monoclonal antibody against the cytokine interleukin-6 (formerly named CNTO 136), using the new provisional 2011 ACR/EULAR rheumatoid arthritis (RA) remission criteria.

Methods: In the dose-ranging part of a 2-part, multicenter, randomized, double blind, placebo controlled, phase 2 study, pts with active RA despite methotrexate (MTX) therapy were randomized equally to receive SC injections of placebo q2w at wks 0–10 and sirukumab 100 mg q2w at wks 12–24 (n=30), sirukumab 100 mg q2w at wks 0–24 (n=30), sirukumab 100 mg q4w at wks 0–24 (n=30), sirukumab 50 mg q4w at wks 0–24 (n=30), or sirukumab 25 mg q4w at wks 0–24 (n=31). RA remission rates were prospectively assessed using the DAS28 (CRP) remission criteria and retrospectively assessed using the 2011 ACR/EULAR remission criteria (Boolean- and SDAI-based) at wks 12, 24, and 38. The 2011 ACR/EULAR remission criteria used in this study were: Boolean-based (68-joint TJC ≤1, 66-joint SJC ≤1, CRP ≤1 mg/dL, PGA ≤1 on a 1–10 cm VAS), index-based (SDAI score [ie, 28-joint TJC + 28-joint SJC + PGA + physician's global assessment + CRP mg/dL] ≤3.3).

Results: At wk 12 (pre-crossover), more pts were in remission with sirukumab than with placebo according to both Boolean- and SDAI-based ACR/EULAR criteria (2% vs 0% and 6% vs 3%, Table). The percentage of pts in remission according to all 3 criteria increased to a peak at wk 24 in the sirukumab 100 mg q2w and q4w treatment groups and remained higher than wk-12 rates at wk 38, 14 wks after the last dose of sirukumab. Pts who received sirukumab 100 mg q2w throughout the study achieved the highest remission rates according to all 3 remission criteria at all time points, including a statistically significant difference compared with placebo according to DAS28 remission criteria at wk 12 (20% vs 0%, p=0.024) and Boolean-based ACR/EULAR remission in 4/30 (13%) pts and SDAI-based ACR/EULAR remission in 7/30 (23%) pts at both wk 24 and wk 38. As expected, the more stringent 2011 ACR/EULAR remission criteria resulted in generally lower remission rates than the DAS28 remission criteria at all time points. Lower remission rates were seen for all groups at all time points with the Boolean-based vs the SDAI-based definition.

Table. Patients in remission according to the 2011 ACR/EULAR RA remission criteria and the DAS28 (CRP) remission criteria at weeks 12, 24, and 38

		Placebo*	Sirukumab				
			100 mg q2w	100 mg q4w	50 mg q4w	25 mg q4w	Combined
N		30	30	30	30	31	121
Wk 12	ACR/EULAR remission: Boolean-based	0	1 (3%)	0	0	1 (3%)	2 (2%)
	ACR/EULAR remission: SDAI-based	1 (3%)	3 (10%)	1 (3%)	2 (7%)	1 (3%)	7 (6%)
	DAS28 (CRP) remission	0	6 (20%)	1 (3%)	4 (13%)	3 (10%)	14 (12%)
Wk 24	ACR/EULAR remission: Boolean-based	1 (3%)	4 (13%)	1 (3%)	0	1 (3%)	6 (5%)
	ACR/EULAR remission: SDAI-based	3 (10%)	7 (23%)	5 (17%)	1 (3%)	2 (7%)	15 (12%)
	DAS28 (CRP) remission	6 (20%)	12 (40%)	8 (27%)	4 (13%)	7 (23%)	31 (26%)
Wk 38	ACR/EULAR remission: Boolean-based	4 (13%)	4 (13%)	1 (3%)	1 (3%)	1 (3%)	7 (6%)
	ACR/EULAR remission: SDAI-based	5 (17%)	7 (23%)	2 (7%)	2 (7%)	0	11 (9%)
	DAS28 (CRP) remission	9 (30%)	11 (37%)	5 (17%)	7 (23%)	2 (7%)	25 (21%)

* Twenty-six of 30 patients in the placebo group crossed over to sirukumab 100 mg q2w at week 12.

Conclusion: Higher remission rates according to both the 2011 ACR/EULAR and the DAS28 (CRP) criteria were achieved with sirukumab at SC dose regimens ranging from 25–100 mg q2w-q4w compared with placebo. After placebo crossover to sirukumab, all groups achieved increasing remission rates over time with continued sirukumab treatment. The highest sirukumab dose regimen (100 mg q2w) achieved the highest remission rates throughout the study. The 2011 ACR/EULAR criteria were more stringent than the DAS28 (CRP) criteria; and the Boolean-based definition was more stringent than the SDAI-based definition.

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Anterior Chest Wall Inflammation by Whole Body MRI in Patients with Spondyloarthritis: Lack of Association Between Clinical and Imaging Findings. Ulrich Weber[1], Robert GW Lambert[1], Kaspar Rufibach[2], Walter P. Maksymowych[1], Juerg Hodler[3], Anna Zejden[4], Stefan Duewell[5], Rudolf O. Kissling[6], Paul L. Filipow[1] and Anne G. Jurik[4]. [1]University of Alberta, Edmonton, AB, [2]University of Zurich, Zurich, Switzerland, [3]University Hospital Zurich, Zurich, Switzerland, [4]University Hospital Aarhus, Aarhus, Denmark, [5]Hospital Thurgau AG, Frauenfeld, Frauenfeld, Switzerland, [6]Balgrist University Hospital, Zurich, Switzerland

Background/Purpose: Inflammatory involvement of the anterior chest wall (ACW) impacts the quality of life in patients with spondyloarthritis (SpA). However, ACW involvement is often neglected in clinical routine and data on ACW inflammation by clinical examination and by various imaging modalities are controversial. Whole body (WB) MRI is a promising imaging method to assess also the ACW without additional inconvenience for the patients.

Objectives: To describe the frequency and distribution of ACW inflammation by WB MRI in SpA patients; to assess the association between imaging and clinical findings; to evaluate the performance of a WB MRI scoring system for the ACW.

Methods: The ACW of 122 consecutive SpA patients (95 with ankylosing spondylitis (AS) and 27 with inflammatory back pain (IBP)) and 75 healthy controls was scanned by sagittal and coronal WB MRI. The MR images were scored independently in random order by 7 readers blinded to patient identifiers. Active and structural inflammatory lesions of the ACW were recorded on a web-based scoring form. ACW pain by patient self-report, ACW tenderness on physical examination according to the Maastricht ankylosing spondylitis enthesitis score (MASES) and MRI lesions were analyzed descriptively. Kappa statistics served to assess inter-observer reliability and the agreement between clinical and imaging findings.

Results: ACW pain or tenderness was present in 26% with little difference between AS and IBP patients. Bone marrow edema (BME), erosion and fat infiltration were recorded in 49.5%, 36.8% and 33.7% of the AS patients, in 25.9%, 25.9% and 3.7% of the IBP patients, and in 9.3%, 12.0% and 5.3% of the controls, respectively. The most frequently affected joint by MRI lesions was the manubriosternal joint. The inter-reader agreement by kappa values for 7 observers and for the 3 MRI lesions BME, erosion and fat infiltration was 0.52, 0.48 and 0.46, respectively, being highest (0.65) for BME of the manubriosternal joint. The agreement between patient self-reports of pain and ACW tenderness upon clinical examination was moderate with a kappa value of 0.5. The kappa values between clinical assessment according to MASES and MRI inflammation ranged from −0.18 to only 0.25 for all SpA patients.

Conclusion: Clinical and WB MRI signs of ACW inflammation were found in 26% and up to 44% of SpA patients, respectively. There was no agreement between clinical ACW involvement according to MASES and inflammatory MRI findings. Possible explanations are subclinical ACW inflammation captured by MRI and/or a limited construct validity of the MASES ACW section.

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Higher Frequency of Metabolic Syndrome In Psoriatic Arthritis Compared with Rheumatoid Arthritis May Be Explained by High Triglycerides and Increased Rates of Obesity and Diabetes. Asena Bahce-Altuntas[1], Julie S. Schwartzman-Morris[1], Nicole Jordan[1], Jeffrey D. Greenberg[2], Chaim Putterman[1], George Reed[3] and Anna R. Broder[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]NYU Hospital for Joint Diseases, New York, NY, [3]UMass Medical School, Worcester, MA

Background/Purpose: Our understanding of cardiovascular (CV) disease in Psoriatic Arthritis (PsA) is often extrapolated from Rheumatoid Arthritis (RA). Since PsA is characterized by inflammation of both skin and joints, we may be underestimating this CV risk in PsA. The prevalence of

Metabolic Syndrome (MetS), a clustering of classical cardiovascular risk factors, in PsA has not been well studied. Furthermore, since MetS have been shown to be highly prevalent in RA and Psoriasis (PsO) patients, we hypothesized that the prevalence of MetS and its components in PsA patients are higher than those with RA.

Methods: We conducted a cross-sectional study to compare the prevalence of MetS and its components in PsA and RA participants in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. Based on the International Diabetes Federation criteria, MetS was defined as: body mass index, BMI>30 kg/m^2, and any of the two: (1) diagnosis of diabetes, (2) diagnosis of hypertension, (3) high Triglycerides, TG>150 mg/dL (1.69 mmol/L), or (4) low High Density Lipid, HDL<40 mg/dL (1.03 mmol/L) in males, HDL<50 mg/dL (1.29 mmol/L) in females.

Results: Of the 25,976 RA and 4,015 PsA, 1956 CORRONA participants (1162 RA and 294 PsA) had all components of MetS available. The overall prevalence of MetS in PsA vs. RA patients was: 27% vs. 19%, p=0.004, with an unadjusted OR 1.5 (1.14–2.05). PsA were younger compared with RA patients, 55.7 ± 11.9 vs. 61.6 ± 12.2 years, respectively, p<0.001, and PsA patients had more men (54% vs. 23%, p<0.001) and RA patients had a higher percentage of minorities. After adjusting for age, sex, race/ethnicity in our multivariate model, the OR of MetS in PsA vs. RA decreases slightly, but remains statistically significant: OR 1.4 (1.05–1.96), p=0.02. Disease duration, history of previous cardiovascular events, and use of statins were statistically similar among the two groups. In regards to the individual components of the MetS definition, TG>150 was the only statistically significant component with a frequency of 38% in PsA compared to 28% in RA patients, p<0.001 and an unadjusted OR 1.58 (1.22–2.05). No statistically differences were observed between the two groups in frequency of low HDL and hypertension, but the difference between the two groups in prevalence of obese BMI and diabetes was nearly statistically significant (45% vs. 39%, p=0.06 and 15% vs. 11%, p=0.06, respectively). Since BMI>30 kg/m^2 was a necessary condition for MetS, we analyzed the subgroup of 133 PsA and 654 RA with obese BMI (BMI>30 kg/m^2) and found an unadjusted OR of MetS for PsA vs. RA to be 1.5 (1.04, 2.22), p=0.04. TG>150 again was more prevalent in the obese PsA group than the obese RA group (51% vs. 39%, p=0.01).

Conclusion: MetS is highly prevalent in both PsA and RA, and overall significantly higher in PsA compared to RA. Triglycerides appear to drive the estimated increase in risk of MetS in PsA vs. RA, but there is also a trend to association with obese BMI and diabetes. Thus, the difference in rates of MetS is mainly explained by potentially modifiable risk factors. More studies are needed to see if targeting these risk factors may improve cardiovascular disease related morbidity and mortality in PsA.

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The Prevalence and Risk Factors of Atlantoaxial Subluxation in Ankylosing Spondylitis. Ji-Seon Lee, Jae Hoon Kim, Jinju Kim, Joo-Hyun Lee and Tae-Hwan Kim. Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

Background/Purpose: Ankylosing spondylitis (AS) is a chronic rheumatic disorder characterized primarily by inflammation of the sacroiliac joint and spine. Cervical spine is also vulnerable the disease process, but atlantoaxial subluxation (AAS) have been considered as uncommon feature of AS, despite of several case reports, while frequent and important complication in rheumatoid arthritis (RA). This study aims at assessing the prevalence and risk factors of AAS developing in AS patients.

Methods: Total 819 patients, who fulfilled the modified New York criteria and examined with full-flexion lateral view of cervical spine x-ray, were enrolled from the outpatient clinic of Hanyang University Hospital for Rheumatic Diseases in Korea. The patients were retrospectively reviewed medical records and investigated distance between posterior aspect of atlas and anterior aspect of dens process of axis in lateral flexion view of C-spine x-ray by single subspecialty-trained radiologist with musculoskeletal experiences. In this study, we defined the AAS as an anterior atlanto-dental interval (AADI) of greater than 3 mm, and the significant progression as a progression rate of greater than 0.5mm/yr.

Results: C-spine x-ray was followed at with symptoms or routinely, a mean of 2.1 times. The AAS was revealed in 17.3% (142/819 patients) and diagnosed at mean 4.4 (± 0.4) years after diagnosis of AS, but already existed in 30.9% (44/142 patients) at diagnosis of AS. The AADI was on significant progression in 4.4% (13/297 patients) of negative AAS and in 22.1% (23/104 patients) of positive AAS (p-value=0.000), and one patient underwent operation for management of c-spinal instability with neurologic problems. As multiple logistic regression analysis, the AAS was significantly associated with AS duration (OR 1.081, 95% CI 1.036–1.128), peripheral arthritis (OR 2.030, 95% CI 1.338–3.081), uveitis (OR 1.514, 95% CI 1.022–2.394), and the usage of TNF-a antagonists (OR 2.195, 95% CI 1.447–3.330). The earlier development of AAS was associated with the younger age of diagnosis of AS (OR 1.054, 95% CI 1.005–1.106), but AS than JAS (OR 6.137, 95% CI 2.391–15.754).

Table 1. Prevalence of atlantoaxial subluxation (AAS) according to disease duration of AS

Disease duration (year)	no AAS (%)	AAS (%)
At diagnosis of AS	775 (94.6)	44 (5.4)
0–4.9*	465 (83.0)	95 (17.0)
5–9.9	133 (86.4)	21 (13.6)
10–14.9	61 (80.3)	15 (19.7)
15–19.9	16 (64.0)	9 (36.0)
>20	2 (50.0)	2 (50.0)
Total	677 (82.7)	142 (17.3)

* includng the patients with AAS at diagnosis of AS

Conclusion: AAS is more frequently complicated than we have thought during clinical course in AS. And the risk factors were revealed as the younger age at diagnosis, longer disease duration, presence of extra-axial symptoms, such as peripheral arthritis and uveitis, and severe disease activity, suggested the usage of TNF-a antagonists. So the clinician should consider the AAS during the course of AS, especially in case of having risk factors.

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Influence of Immunogenicity on the Efficacy of Long-term Treatment with Infliximab in Spondyloarthritis. Chamaida Plasencia[1], Dora Pascual-Salcedo[1], Maria Gema Bonilla[1], Laura Nuño[1], Ainhoa Ruiz[2], Emilio Martin-Mola[1] and Alejandro Balsa[1]. [1]La Paz University Hospital, Madrid, Spain, [2]PROTEOMIKA RESEARCH, Bilbao, Spain

Background/Purpose: Infliximab (IFX) is a quimeric monoclonal antibody against tumour necrosis factor (TNF) which has been shown to be very effective in the treatment of patients with Spondyloarthritis (SpA). Several studies have observed that some initially responder patients lose responsiveness or develop infusion reactions which might be related to the presence of antibodies against the drug. Our aim was to investigate the clinical relevance of the formation of anti-infliximab antibodies (anti-IFX Abs) in patients with SpA undergoing IFX treatment over a prolonged period of time

Methods: We studied 94 patients with SpA (50 Ankylosing Spondylitis, 12 Undifferenciated SpA, 22 Psoriatic Arthritis and 10 SpA associated with inflammatory bowel disease) treated with IFX from 1999–2010. Clinical characteristics, serum trough IFX levels and the presence of anti-IFX Abs were evaluated for a median of 4.45 (interval 0.4–10.2) years. Clinical activity was measured by Ankylosing Spondylitis Disease Activity Score (ASDAS) criteria: inactive <1,3; moderate ≥1,3-<2,1; high ≥2,1-≤3,5 and very high >3,5 at 3 time points (6 months, 12 months and > 4 years). We considered a clinically important improvement when ΔASDAS≥1.1.The levels of IFX and anti-IFX Abs were measured by ELISA. The survival of treatment was evaluated in relation to the presence or absence of anti-IFX Abs.

Results: Antibodies against IFX were detected in 24 (25.5%) patients. Patients with anti-IFX Abs had lower clinical improvement measured by ASDAS (0.48 ± 0.73 vs 1.4 ± 1.6 p=0.029 at 6 months; 0.81 ± 1.2 vs 1.56 ± 1.6 p=0.1 at 1 year; 0.45 ± 0.82 vs 1.43 ± 1.25 p=0.022 at > 4 years). Most patients with anti IFX Abs had high or very high activity (83% vs 30.8%; p=0.001 at 6 months, 50% vs 20%; p=0.091 at 1 year and 82% vs 24.4%; p=0.001 at > 4 years). Eleven patients (12%) developed infusion related reactions, in 8 (73%) anti-IFX Abs were present. Patients with infusion related reactions had higher titers of anti-IFX Ab (Mdn 12931, IQR 853–82437 vs Mdn 2454, IQR 449–7718 p=0,028). Patients with anti-IFX Ab had shorter survival on IFX treatment (4.25 years vs. 8.19 years, p<0.001). In 27 patients, IFX treatment was discontinued and anti-IFX Abs were present in most patients [18 (67%) vs 9 (33%), p=0.001]. In 19 patients the IFX dosing interval was reduced due to insufficient efficacy, 9/ 24 (37.5%) had anti-IFX Abs vs 10/70 (14.3%) without anti-IFX Abs, p=0.019.

Conclusion: In patients with SpA treated with IFX, the formation of anti-IFX Abs is associated with a poor clinical response, the appearance of infusion reactions and with the discontinuation of treatment. Anti-IFX Abs monitoring is useful in the assessment of the ongoing efficacy of the therapy.

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The Effect of DMARD Co-Therapy on Anti-TNF Drug Retention in 1630 Spondyloarthritis Patients. Michael J. Nissen[1], Adrian Ciurea[2], Burkhard Moller[3], Juerg Bernhard[4], Ruediger Mueller[5], Bettina Weiss[6], Giorgio Tamborrini[7], Almut Scherer[8], Cem Gabay[1] and Axel Finckh[1]. [1]Geneva University Hospital, Geneva, Switzerland, [2]Department of Rheumatology, University Hospital, Zurich, Switzerland, [3]Inselspital University Hospital, Bern, Switzerland, [4]Buergerspital, Solothurn, Switzerland, [5]Cantonal Hospital, St. Gallen, Switzerland, [6]Balgrist University Hospital, Zurich, Switzerland, [7]University Hospital, Zurich, Switzerland, [8]SCQM Foundation, Zurich, Switzerland

Background/Purpose: Current recommendations suggest little role for DMARDs as co-therapy with anti-TNF (aTNF) agents in patients with spondyloarthritis (SpA), although many physicians prescribe this combination. The benefit of co-therapy in SpA patients, related to the disease manifestations and type of aTNF is unclear. Our aim was to investigate the impact of concomitant therapy with DMARDs on aTNF drug retention (DR) in 3 prospective SpA registries.

Methods: All patients in the 'Swiss Clinical Quality Management' (SCQM) registries with suspected axial spondyloarthritis (aSpA), psoriatic arthritis (PsA) or undifferentiated SpA (uSpA) as diagnosed by board-certified Rheumatologists were included, provided that they had been treated with ≥ 1 aTNF. Sensitivity analyses with the different classification criteria were performed. Anti-TNF DR was analyzed using Cox proportional hazard regression with adjustments for potential confounders (age, sex, disease duration, education level, disease activity and concomitant medications). Andersen-Gill Cox models were utilized to account for multiple aTNF discontinuations in the same patient.

Results: 1630 patients (1060 aSpA, 535 PsA and 35 uSpA) with a mean age of 44 years (+/− 12.1) and a median follow-up of 3.2 years [IQR 1.7–4.5] were included, with a total of 2158 aTNF treatment courses. 68.9% were treated with aTNF monotherapy and 31.1% with co-therapy. 58% of patients with suspected aSpA satisfied either the "modified New York" or "ASAS axial" criteria. Adalimumab (ADA), etanercept (ETN) and infliximab (IFX) were prescribed in 37.3%, 33.7% and 29.1% of patients respectively. The DMARDs utilized were methotrexate in 72.0%, sulfasalazine in 20.9% and leflunomide in 14.0%. Co-therapy patients were older and less likely to be HLA-B27 positive or to exhibit pure axial manifestations (see table). In unadjusted analyses of the first aTNF, the median DR was 2.8 years [IQR 0.9–8.4], with no significant differences between the aTNF monotherapy group and the co-therapy group (hazard ratio (HR) 1.04, 95% CI: 0.87–1.24). Similarly, in multivariate adjusted analyses, no benefit of DMARD co-therapy on aTNF DR was demonstrated (HR 1.06, 95% CI: 0.90–1.24). Predictors for longer DR were male sex (0.79, p=0.003) and longer disease duration (0.98, p<0.001), and for shorter DR, lower BASDAI at baseline (1.20, p<0.001) and prior aTNF use (1.60, p<0.001). There was no effect modification by type of aTNF (ADA vs. ETN vs. IFX) or by clinical manifestations (axial vs. peripheral vs. mixed involvement).

Baseline characteristics	Monotherapy (n=1123)	Co-therapy (n=507)	p-value
Age (years)	43.2 (42.5-44.0)	45.9 (44.9-46.9)	<0.0001
Sex (%, male)	59.8	56.0	0.15
Weight (kg)	74.6 (73.7-75.5)	75.0 (73.5-76.4)	0.31
Disease duration (median, years) [p25, p75]	8.4 [3.5-17.0]	8.3 [3.2-14.4]	0.16
HLA-B27 (% positive)	65.9	52.4	<0.0001
University level education (%)	31.3	32.1	0.75
BASDAI	4.9 (1.9-4.8)	4.8 (1.5-4.7)	0.41
BASFI	3.7 (3.6-3.8)	3.8 (3.7-4.0)	0.17
Pure axial disease (%)	57.3	40.2	<0.0001
Pure peripheral disease (%)	5.3	12.6	<0.0001
Mixed axial and peripheral disease (%)	26.4	24.5	0.42
Axial Spondyloarthritis (%)	73.7	45.8	<0.0001
Psoriatic Arthritis (%)	24.9	50.3	<0.0001
Undifferentiated Spondyloarthritis (%)	1.4	3.9	0.001
Infliximab (%)	26.7	34.5	0.001
Adalimumab (%)	37.4	37.1	0.90
Etanercept (%)	36.1	28.4	0.002

Conclusion: This study supports current recommendations that co-therapy with DMARDs is of no additional benefit compared with aTNF monotherapy in SpA patients. Higher rates of aTNF DR were seen in males and in patients with longer disease duration and lower baseline disease activity. There were no significant differences in aTNF survival between the different aTNF agents.

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Association Between Axial Pain Site and Site of MRI Inflammatory Lesions or Structural Change in Patients with Early Inflammatory Back Pain: The DESIR Cohort Study. Bertrand Coutanceau[1], Florence canoui-Poitrine[1], Maxime Dougados[2], Martin Blachier[1], Sylvie bastuji-Garin[1], Alain Saraux[3] and Pascal Claudepierre[4]. [1]Université Paris Est, Laboratoire d'Investigation Clinique (LIC) EA 4393, AP-HP, Hôpital Henri-Mondor, Service de Santé Publique, Créteil, France, [2]Paris-Descartes University, Medicine Faculty; UPRES EA-4058; APHP, Cochin Hospital, Paris, France, [3]CHU de la Cavale Blanche, Brest Cedex, France, [4]Université Paris Est, Laboratoire d'Investigation Clinique (LIC) EA 4393, AP-HP, Hôpital Henri-Mondor, Rheumatology department, Creteil, France

Background/Purpose: Although the role of axial MRI has appeared as major in the diagnosis of recent axial spondyloarthritis, it is still unknown which MRI view (spine or sacro-iliac joints (SIJ)) is the most informative and whether it can be guided by the site of the symptoms. The objective was to assess whether site of pain (dorsal, lumbar or buttock) is associated with inflammatory or structural lesions at MRI in patients with recent inflammatory back pain (IBP).

Methods: We conducted a cross sectional analysis among patients included in the DESIR cohort study (n=708), with baseline data. Inclusion criteria were age under 50 years old and IBP for more than 3 months and less than 3 years. For each axial level (e.g. buttock, lumbar, dorsal) the following data were collected: a) pain (past or current) and site (dorsal, lumbar and/or buttock) b) any sign of damage on SIJ or lumbar X-rays ("lumbar" mSASSS>1) c) MRI structural lesions defined by at least one syndesmophyte on one disco vertebral unit at the spine level, d) MRI inflammatory lesion (scored as normal, doubtful and abnormal; doubtful being pooled with abnormal). The endpoints were presence of inflammatory lesions or structural changes at the dorsal, lumbar or SIJ MRI. For each level, an association between site of pain and the endpoints were analyzed using univariate and multivariate logistic regressions, separately in the patients with and without structural damage at X-rays (at any site). Odds Ratios (OR) were adjusted for sites of pain and significantly associated mediating or confounding factors among baseline characteristics (age, sex, HLA B27 status, hs-CRP).

Results: At baseline, among 635 patients with complete data, mean age was 34 (±9) years, 52.6% were women, 60% were B27 positive, 62.3% had dorsal pain, 91.8% lumbar pain, and 79.6% buttock pain (82% had at least two sites of pain). Among patients with SIJ or lumbar X-rays lesions (n=341, 53.7%), 26.3%, 27.6% and 64.2% had MRI inflammatory lesions located respectively in dorsal, lumbar and SIJ sites. For each level, pain was associated with inflammatory lesions only at the corresponding site (Dorsal site: adjusted Odds ratios (aOR) $_{\text{dorsal pain}}$= 2.23; 95% CI: 1.26–3.93; lumbar site: (aOR) $_{\text{lumbar pain}}$= 2.59; 95% CI:0.85–7.86; p = 0.09; SIJ site: (aOR) $_{\text{buttock pain}}$= 3.58; 95% CI:1.89–6.76; p<0.001) after full adjustment. Among patients without lesions at SIJ and lumbar X-rays (n=294; 46.3%), 11.3%, 14.6% and 25.8% had MRI inflammatory lesions located respectively in dorsal, lumbar and SI joints. No significant association was found between pain at any site and MRI inflammatory lesions. For all patients, 9%, 8% and 33% had MRI structural changes located respectively at dorsal, lumbar and SIJ sites. No association was found between axial pain and MRI structural change at any level in the entire population except between buttock pain and SIJ lesions (OR)$_{\text{buttock pain}}$= 1.89; 95% CI:1.22–2.90; p=0.004).

Conclusion: These results suggest that site of pain (dorsal, lumbar or buttock) is associated with MRI inflammatory lesion at the same level, only in patients with already X-rays structural change.

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Is Dietary Intake of Patients with Systemic Lupus Erythematosus Adequate? Ellie Aghdassi[1], Ladan Yeganeh[1], Amaris K. Balitsky[2], Stacey Morrison[3], Michael Frattasi[3], Jiandong Su[3], David WL. Ma[4] and Paul R. Fortin[5]. [1]University Health Network, Toronto, ON, [2]The University of Toronto, Toronto, ON, [3]The Toronto Western Hospital, Toronto, ON, [4]University Of Guelph, Guelph, ON, [5]Toronto Western Hospital, Toronto, ON

Background/Purpose: To compare the dietary intake of women with systemic lupus erythematosus (SLE) to the Dietary Reference Intake (DRI) established for North American women by the World Health Organization (WHO). DRI has 4 sets of nutrient standards: 1. Estimated Average Requirements (EAR) are average nutrients requirement for a population group, 2. Recommended Dietary Allowance (RDA) is based on EAR + 2 SD that would meet the needs of 97% of people in a particular population, 3. Adequate Intake (AI) is based on information about average intake of the nutrient by a healthy group of people when there is not enough information available to estimate RDA and, 4. Tolerable Upper Intake Level is the highest intake of a nutrient that does not pose a threat to health for most people. EAR is particularly appropriate for planning and assessing intakes for groups of persons while RDA and AI are both used to plan healthful diets for individuals.

Methods: Women (n=147) meeting the ACR classification criteria for SLE who attend the University of Toronto Lupus Clinic were enrolled in this study. Demographics, anthropometric measurements, SLE duration, SLE-Disease Activity Index-2000 (SLEDAI) and SLICC (Systemic Lupus International Collaboration Clinic)-Damage Index (SDI) were documented. We used a 24-hour diet recall to assess the dietary intake. Diet composition was determined using ESHA nutrient analysis software program. The adequacy of nutrients intake were determined using the EAR which is the estimated median requirement of the healthy individuals in a particular life stage and gender group.

Results: Demographic, anthropometric and disease related data for the study subjects were as following (mean (SD)): age: 47.5 (13.1) years, BMI: 25.6 (6.9) kg/m^2, waist circumference: 81.7 (14.8) cm, disease duration: 19.1 (12.0) years, SLEDAI: 2.8 (3.6), SDI: 1.9 (1.9), 55.1% were Caucasian, 32% had some post-secondary education, 60.5% were postmenopausal and 10.9% were smokers. The mean (SD) daily energy intake was 1658 (691) kcal and 10.9% of the patients had energy intake above the recommended level of 2403 kcal/day for women age 19–70 years of age. Percentage of energy from fat, saturated fat, protein and carbohydrate were 34.1% (27.0), 9.5% (7.3), 17.3% (6.1), and 54.2% (28.0), respectively. Although these mean values were close to the recommendations, 57.5% and 32.3% had fat and saturated fat intake exceeding the recommended levels (< 30% and <10% of caloric intake), 21.8% had protein intake below the EAR of 0.66 g/kg; and 32.5% of subjects had cholesterol intake more than the recommended 300 mg/d. More than 40% of the subjects had suboptimal intake of vitamins B1, B2, B3, B6, B12, C and selenium. Intakes of omega-3 fatty acids, calcium, magnesium, vitamins E and D were inadequate in more than 80% of the patients. Calcium, vitamin D, multivitamin and omega-3 supplements were used only by 68.7%, 85.7%, 42.9% and 21.8%, respectively.

Conclusion: Despite having a normal/high BMI, women with SLE do not meet the recommended levels of intake for protein and many of the micronutrients. Vitamin/mineral supplementation may be required for all SLE patients in order to meet the daily nutritional requirements of this patient population.

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Physical Activity, Body Composition, and Cognitive Impairment Among Women with Systemic Lupus Erythematosus. Patricia P. Katz[1], Laura J. Julian[1], Jinoos Yazdany[1], Holly Wing[2], Sandi Kaplan[2], Laura Trupin[3], Lindsey A. Criswell[1] and Edward Yelin[1]. [1]University of California San Francisco, San Francisco, CA, [2]University of California, San Francisco, CA, [3]UC San Francisco, San Francisco, CA

Background/Purpose: Cognitive dysfunction is frequently present in SLE. There is growing attention to the role of both obesity and physical inactivity in cognitive impairment and decline in the general population. While obesity and physical inactivity are common in SLE, neither of these factors has been examined in relation to cognitive impairment in SLE. This analysis examined the relationship of obesity and physical activity to cognitive impairment in women with SLE.

Methods: Data were collected from an in-person visit conducted at the Clinical and Translational Science Institute's Clinical Research Center (CRC). Subjects (n=138 women) were drawn from participants in the longitudinal Lupus Outcomes Study, who lived in proximity to the clinical site. Body composition was measured with dual-energy x-ray absorptiometry (DXA). Obesity was defined by DXA % body fat based on age, sex, and race criteria. Physical activity was ascertained by self-report using the International Physical Activity Questionnaire (IPAQ); inactivity was defined as expenditure of ≤600 metabolic equivalent (MET)/minutes per week. Cognitive function was measured with a 12-index neuropsychological battery modified from the ACR recommended one-hour battery for cognitive assessment in SLE. Impairment was defined as age-adjusted z-scores ≤1.5 standard deviations below mean on 1/3 of tests completed. Scores were obtained for the total battery and for memory and executive function components. Multivariate analyses examined the relationship of obesity and physical activity, individually and combined, with cognitive impairment, controlling for education, race/ethnicity, disease activity, and depression.

Results: 50% of women were obese, 28% were inactive, and 14% of subjects were cognitively impaired on the total battery. Memory impairment was present in 28%; impairment in executive function was present in 10%. Women who were cognitively impaired on the total battery were more likely to be obese (79.0% vs. 45% of not impaired, p=.01) and inactive (47 % vs. 25%, p=.05). Considering the executive function portion of the cognitive battery, differences between impaired and non-impaired women in the prevalence of obesity (92% vs. 46%, p=.002) and inactivity (69 % vs. 24%, p=.001) were greater. Memory impairment was not associated with obesity or inactivity. Controlling for covariates, both inactivity and DXA-defined obesity were significantly associated with impairment on executive function battery (Inactivity: OR=7.0 [1.5, 34.1]; Obesity: 12.6 [1.4, 115.7]).

Conclusion: Both obesity and inactivity were significantly associated with impairment in cognitive function. If longitudinal studies show that physical inactivity and obesity are precursors to cognitive impairment, these may offer potent targets for intervention.

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Objective Measurement of Levels of Physical Activity in Rheumatoid Arthritis. Marie Tierney[1], Alexander D. Fraser[2] and Norelee M. Kennedy[1]. [1]University of Limerick, Limerick, Ireland, [2]Mid Western Regional Hospital, Co. Limerick, Ireland

Background/Purpose: Regular physical activity is encouraged to allow for improvements in various dimensions of health. However, in order to assess if physical activity has positive health benefits, it is necessary to measure the quantity of physical activity occurring. To date, it has been difficult to accurately ascertain the physical activity levels of individuals with Rheumatoid Arthritis (RA) due to the use of subjective measures and measures that were not validated for the population in previously conducted studies. Sensewear Armband (SWA) is an objective outcome measure of physical activity which has been validated for use to measure energy expenditure in the RA population. The aim of this study is to assess the level of physical activity in the RA population over a one week period.

Methods: All subjects recruited had a confirmed diagnosis of RA in conjunction with American College of Rheumatology (ACR) criteria, were ambulatory independently or with assistance of one unilateral aid, were over 18 years of age and were not pregnant. Patients were recruited from the rheumatology outpatients' clinic of the Mid-Western Regional Hospitals, Limerick, Ireland. Each subject provided written informed consent and was provided with a SWA which was worn on the right upper arm for 1 week. Descriptive statistics were used to analyse the results.

Results: 29 subjects (16 female, 13 male) were included in this study. All results are defined as mean±standard deviation. The age of the recruited subjects was 59.61±9.4 years while self reported disease duration was 8.72±8.45 years.

Outcome	Energy Expenditure kJ ± SD
Average weekly energy expenditure	65098.86 ± 12095.94
Average daily energy expenditure	9301.03 ± 1727.99
Average weekday (Monday-Friday) energy expenditure	9384.71 ± 1832.59
Average weekend (Saturday and Sunday) energy expenditure	9087.65 ± 1602.47
Average male weekly energy expenditure	69027.63 ± 12907.64
Average female weekly energy expenditure	61902.28 ± 10748.70
Average weekly energy expenditure (65 years) (n = 8)	61044.56 ± 6292.74
Average weekly energy expenditure (55-65 years) (n = 13)	66002.60 ± 14556.14
Average weekly energy expenditure (<55 years) (n = 8)	67676.20 ± 12426.48
Average weekly energy expenditure (employed) (n = 7)	67454.45 ± 12459.95
Average weekly energy expenditure (not employed) (n = 22)	64345.74 ± 12175.44

Conclusion: This is the first study to assess the level of physical activity of the RA population with regard to energy expenditure using a validated objective tool. This study highlights some interesting differences between varying demographic characteristics of the RA population and provides a method by which accurate comparison between the RA and non-RA population could be applied.

2642

Influence of Lifecourse Social Position on Rheumatoid Arthritis Disease Severity in African Americans. Rebecca J. Cleveland[1], Todd A. Schwartz[1], Beth L. Jonas[1], Graciela S. Alarcon[2], Richard Brasington[3], Doyt L. Conn[4], Edwin A. Smith[5], George Howard[2], Larry W. Moreland[6], S. Louis Bridges Jr.[7] and Leigh F. Callahan[1]. [1]University of North Carolina, Chapel Hill, NC, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Washington Univ School of Med, St. Louis, MO, [4]Emory Univ School of Medicine, Atlanta, GA, [5]Med Univ of South Carolina, Charleston, SC, [6]University of Pittsburgh, Pittsburgh, PA, [7]Marguerite Jones Harbert-Gene V. Ball, MD Professor of Medicine, and Director, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

Background/Purpose: Current social position (SP), defined as individual level socioeconomic status, has been shown to be associated with poorer rheumatoid arthritis (RA) outcomes in whites, although it is less established in African Americans (AA). Associations between childhood SP and health have often been independent of adult SP, however this has not been evaluated for RA outcomes in whites or AA. We examined whether there are independent associations between SP over the lifecourse (current adult and childhood SP) with RA severity and patient reported outcomes (PROs).

Methods: We conducted a cross-sectional analysis of 371 AA individuals with RA who were part of a consortium of 5 medical centers in the southeastern US. Childhood SP was defined as the SP of their caregivers. Participants reported on their own and their childhood caregivers' SP, including educational attainment (≤ high school [HS] diploma, or >HS), occupation (OCC) (professional or non), and homeownership (yes or no). Outcomes included joint severity (tenderness, swelling and malalignment); radiographs (erosion, JSN score); laboratory measures (C-reactive protein [CRP] levels, rheumatoid factor [RF] isotype IgM [RFIgM] or RFIgA, and anti-cyclic citrullinated protein antibodies [anti-CCP]); and PROs (HAQ, pain and fatigue visual analog scales [VAS], helplessness Rheumatology Attitudes Index [RAI], and counts of poor physical, poor mental, and limited activity days). Covariates included gender, age, RA disease duration, clinical comorbidity index, current Methotrexate/Leflunomide and biologic agent use. Adjusted bivariate analyses were performed to examine mean values of RA severity markers and PROs according to measures of adult and childhood SP. Adjusted regression models were conducted on all SP measures to determine associations with RA severity and PROs.

Results: Participants' mean age was 56 years, RA duration was 137 months, and they generally had higher SP measures as adults than during childhood, where 53% of participants had >HS compared to only 16% of caregivers ($P<0.001$), and 49% had a professional OCC compared to 15% of caregivers ($P<0.01$). However, more participants' caregivers were homeowners than participants (57% vs. 46%, $P<0.05$). 11.9% had high lifecourse SP (both adult and childhood), 37.5% had current high/childhood low SP, 6.7% had childhood high/current low SP and 43.9% had low lifecourse SP. Mean fatigue VAS was significantly higher for participants' whose caregivers were non-homeowners or had ≤HS, as was physically unhealthy days. In regression models mutually adjusting for adult and childhood SP, significant associations were observed for low childhood SP for fatigue VAS (β=-1.0; 95% CI=−1.9, −0.1); however low adult SP appeared to have stronger independent associations with most measures of radiographs, lab values, HAQ, RAI and pain VAS. When compared to subjects with high lifecourse SP, those with low adult SP generally had poorer RA outcomes, regardless of childhood SP.

Conclusion: Although low childhood SP was associated with poorer values for some RA outcomes, low current adult SP appears to be a stronger independent predictor for most RA disease severity measures and PROs.

2643

Hypothyroidism and Risk of Adhesive Capsulitis in the General Population. Uyen Sa D. Nguyen[1], Hyon K. Choi[1], Christine Peloquin[1], Young Hee Rho[2], Yanyan Zhu[1], Daniel K. White[1], Jingbo Niu[1] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]Vanderbilt Medical Center, Nashville, TN

Background/Purpose: Adhesive capsulitis (AC) is a chronic shoulder condition that commonly causes pain and loss of range of motion, and can interfere with activities of daily living. Hypothyroidism is thought to be associated with AC. However, such an assumption was mainly based on case reports. One case-control study of treated hypothyroidism and idiopathic frozen shoulder had small sample size (n=224) and did not control for major potential confounders such as diabetes or cardiovascular diseases (OR=0.7 (95% CI: 0.1 to 10.1) in men; OR=1.9 (95% CI: 0.9 to 4.3) in women). We examined the association between hypothyroidism and incident AC in the general population, adjusting for key confounders.

Methods: We performed a matched case-control study nested within the Health Improvement Network (a UK general population database), an electronic medical record database of 7.3 million participants from 1990 to 2010 at 477 general practices in the UK. We defined an incident case as a person >40 years of age with first diagnosis of AC after at least one year of enrollment into the THIN database. We paired each case with a control that did not have AC at the time of the case diagnosis (i.e., index date), matching on sex, age, and year of enrollment. Hypothyroidism was present if there was a diagnosis by the general practitioner and at least one prescription for thyroid drugs prior to the index date. We used conditional logistic regression to adjust for potential confounders including diabetes, hypertension, myocardial infarction and cardiovascular disease assessed prior to hypothyroidism. We also conducted stratified analyses by sex and by age (< 65 vs. ≥ 65) to determine whether the relation between hypothyroidism and incident AC vary by these factors.

Results: There were 47,793 incident AC cases (58% women, mean age: 62 years). We found that 2.5% of cases and 2.0% of controls had hypothyroidism (crude OR=1.24, 95% CI: 1.13 to 1.35). After adjusting for potential confounders, participants with hypothyroidism had a 21% higher risk of developing incident AC than those without hypothyroidism (OR=1.21, 95% CI: 1.11 to 1.32). The magnitude of association tended to be larger among adults < 65 years old (OR=1.31, 95%CI: 1.16, 1.48) than among adults ≥ 65 years old (OR=1.11, 95%CI: 0.98 to 1.26) (p for interaction, 0.05). However, the association did not differ by gender (p for interaction, 0.66).

Conclusion: This general population study provides the first large-scale epidemiologic evidence that hypothyroidism is independently associated with the risk of incident AC. The impact may be more prominent among younger adults. Future studies should examine possible mechanisms in which hypothyroidism increased the risk for AC.

2644

Humerus Fractures In the United States: Nationwide Emergency Department Sample, 2008. Sunny Kim[1], Robert Szabo[2] and Richard A. Marder[3]. [1]University of California Davis, Sacramento, CA, [2]University of California-Davis, Sacramento, CA, [3]University of California, Davis, CA

Background/Purpose: The objective of this study was to evaluate the epidemiology of emergency department (ED) visits due to humerus fractures in the United States (U.S.). Furthermore, we provided perspectives on future demands of ED care for humerus fractures relevant to aging baby boomers. To date, there have been no published studies on humerus fractures based on a representative sample in the U.S.

Methods: We analyzed the 2008 Nationwide Emergency Department Sample, which contained approximately 28 million ED records. We identified the cases of proximal, shaft, and distal humerus fractures.

Results: In 2008, approximately 370,000 ED visits in the U.S. were due to humerus fractures. Of those, proximal humerus fractures were the most common, accounting for 50% of humerus fractures (Figure 1). The rate of proximal humerus fractures (per 100,000 people) followed the shape of an exponential function in the ages 40–84 for women (R^2=97.9%) and 60–89 for men (R^2=98.2%) (Figure 2). After the exponential increase in these age

intervals, the growth rate of proximal humerus fractures slowed and eventually decreased (Figure 2). The number of ED visits for proximal humerus fractures in women and men aged 70 years and older were 425 and 150 (per 100,000), respectively. The next most common site of fracture was the distal humerus. The peak incidence of distal humerus fractures was in children aged 5 to 9 years (Figure 1). Although distal humerus fractures were relatively uncommon among adults, elderly women were at an elevated risk (Figure 2). The risk of shaft fractures was also increasing as people got older (Figure 2). As the baby boomer generation ages, more than 477,000 ED visits are expected due to humerus fractures in 2030 when the youngest of the baby boomers turn 65 years old.

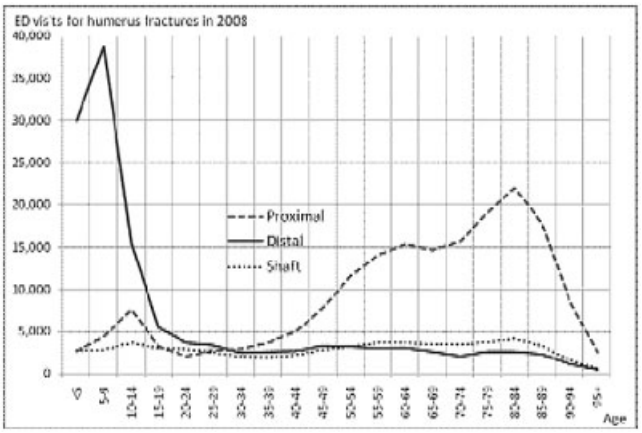

Figure 1. Number of emergency department visits due to humerus fractures in the United States.

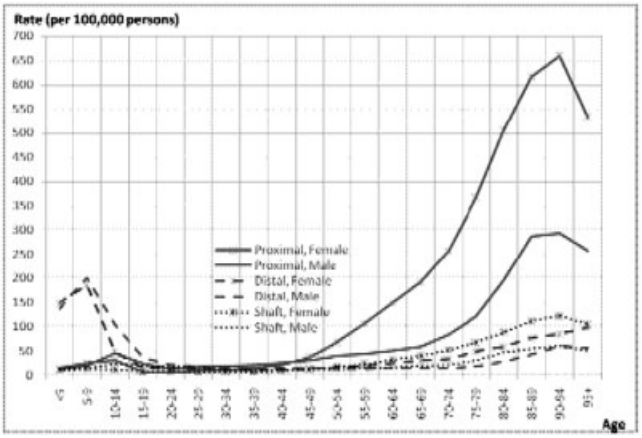

Figure 2. Rates of emergency department visits with humerus factures for every 100,000 people in each respective demographic group in the United States.

Conclusion: Compared to epidemiologic studies in other countries, the rates of proximal, distal, and shaft humerus fractures are substantially higher in the U.S. It is not clear whether Americans live in a more hazardous environment with respect to falling, or if Americans have an elevated level of osteoporosis. A recent study reported a rapid increase in total shoulder arthroplasty in the U.S. The high rate of humerus fractures in the expanding elderly population is likely to increase the demand for total shoulder arthroplasties. Rigorous safety measures to reduce falls and improved preventive treatments of osteoporosis are needed.

ACR Poster Session A

Antiphospholipid Syndrome

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

1

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ACR Poster Session A

Cell-cell Interactions and Adhesion

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

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ACR Poster Session A

Cytokines, Mediators, and Gene Regulation

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

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68

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ACR Poster Session A

Education: Medical Education

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

83

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86

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87

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88

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ACR Poster Session A

Epidemiology and Health Services Research I: Rheumatoid Arthritis

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

99

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136

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142

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146

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ACR Poster Session A

Genetics of Human Rheumatic Diseases

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

150

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158 WITHDRAWN

159

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ACR Poster Session A

Imaging of Rheumatic Disease: Ultrasound, Optical and Preclinical Imaging

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

172

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ACR Poster Session A

Metabolic and Crystal Arthropathies: Pathogenesis, Epidemiology, and Diagnosis

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

207

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ACR Poster Session A

Muscle Biology, Myositis and Myopathies: New Developments in the Clinical Evaluation, Immunology and Treatment of Myositis

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

224

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Disclosure: L. G. Rider, NIEHS, NIH and the ACR, 2; **J. A. Lee**, None; **A. V. Jansen**, None; **N. Ruperto**, None; **A. M. Huber**, None; **C. V. Oddis**, None; **B. M. Feldman**, None; **P. A. Lachenbruch**, None; **R. Aggarwal**, None; **F. W. Miller**, NIEHS, NIH and the ACR, 2.

241

Disclosure: R. C. Campbell, None; **D. L. Scott**, None; **P. D. Kiely**, None; **P. Gordon**, Bristol-Myers Squibb, 2.

242

Disclosure: R. C. Campbell, None; **G. Rafferty**, None; **D. L. Scott**, None; **C. Rielly**, None; **K. Ward**, None; **P. Gordon**, None.

243

Disclosure: R. C. Campbell, None; **D. L. Scott**, None; **P. D. Kiely**, None; **P. Gordon**, Bristol-Myers Squibb, 2.

244

Disclosure: N. Narang, None; **D. Fiorentino**, None; **E. Krishnan**, Savient, 1, Takeda Pharmceuticals International, Inc., URL Pharma, ARDEA, Metabolex, UCB, 5; **L. Chung**, Actelion Pharmaceuticals US, 5, Gilead, 2, Pfizer Inc, 2, United Therapeutics, 2, MedImmune, 2.

245

Disclosure: A. Patwardhan, None; **G. Higgins**, None; **C. H. Spencer**, None; **R. M. Rennebohm**, None.

246

Disclosure: A. Patwardhan, None; **C. H. Spencer**, None; **G. Higgins**, None; **R. M. Rennebohm**, None.

247

Disclosure: S. K. Shinjo, None, 2; **A. M. Sallum**, None; **C. A. Silva**, None, 2; **S. K. N. Marie**, None.

248

Disclosure: A. Prestridge, None; **G. Morgan**, None; **D. Wang**, None; **L. M. Pachman**, None.

249

Disclosure: E. Ghazi, None; **M. A. Kling**, None; **K. Propert**, None; **J. Okawa**, None; **V. P. Werth**, None.

250

Disclosure: F. Sandoval-Garcia, None; **M. Petri**, None; **M. A. Saavedra**, None; **C. Cruz-Reyes**, None; **L. Jara-Quezada**, None; **I. Dávalos**, None; **M. Salazar-Páramo**, None; **I. Gámez-Nava**, None; **L. Gonzalez-Lopez**, None; **T. García-Iglesias**, None; **E. Corona-Sánchez**, None; **S. Zavaleta-Muñiz**, None; **R. Vargas-Ramírez**, None; **J. Aguilar Arreola**, None; **M. Vázquez-Del Mercado**, None; **B. T. Martín-Márquez**, None.

251

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252

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253

Disclosure: F. Kreiner, None; **R. Borup**, None; **P. Schjerling**, None; **F. C. Nielsen**, None; **H. Galbo**, None.

ACR Poster Session A

Pediatric Rheumatology - Clinical and Therapeutic Aspects: Juvenile Idiopathic Arthritis

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

254

Disclosure: M. F. Parsa, None; **O. J. Rullo**, None; **J. M. P. Woo**, None; **D. Elashoff**, None; **T. Cunningham**, None; **V. K. Ranganath**, None; **K. Motamedi**, None; **D. K. McCurdy**, None; **H. E. Paulus**, None.

255

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256

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257

Disclosure: R. Carrasco, None; **J. Cobb**, None; **E. M. Baildam**, None; **H. Foster**, None; **J. Gardner-Medwin**, None; **A. Chieng**, None; **L. R. Wedderburn**, None; **J. Davidson**, None; **K. L. Hyrich**, None; **W. Thomson**, None.

258

Disclosure: M. H. Otten, Pfizer Inc, 9; **F. H. M. Prince**, None; **W. Armbrust**, None; **R. Ten Cate**, None; **E. P. A. H. Hoppenreijs**, None; **M. Twilt**, None; **Y. Koopman-Keemink**, None; **S. L. Gorter**, None; **K. M. Dolman**, None; **J. F.**

Swart, None; **J. M. Van den Berg**, None; **N. M. Wulffraat**, None; **M. A. J. Van Rossum**, None; **L. W. A. Van Suijlekom-Smit**, Pfizer Inc, 9, Abbott Immunology Pharmaceuticals, 2.

259

Disclosure: R. Rasu, None; **S. E. Kirbach**, Abbott Laboratories, 3; **O. Hayes**, Abbott Laboratories, 3; **W. A. Bawa**, None; **M. A. Cifaldi**, Abbott Laboratories, 3.

260

Disclosure: G. Horneff, Pfizer Inc, 6; **S. Bischof**, None.

261

Disclosure: C. M. Sgarlat, None; **C. F. Pelajo**, None; **J. M. Lopez-Benitez**, None; **L. C. Miller**, None.

262

Disclosure: M. O. Chan, None; **J. Guzman**, None; **R. E. Petty**, None.

263

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264

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265

Disclosure: D. J. Lovell, None; **N. Ruperto**, None; **A. Reiff**, Abbott Laboratories, 5, Amgen, 5, Genentech and Biogen IDEC Inc., 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Abbott Laboratories, 8, Amgen, 8, Genentech and Biogen IDEC Inc., 8, Merck Pharmaceuticals, 8, Pfizer Inc, 8; **L. K. Jung**, Genentech and Biogen IDEC Inc., 5; **G. Higgins**, Abbott Laboratories, 2; **I. Koné-Paut**, Roche Pharmaceuticals, 5, Pfizer Inc, 5, Genzyme Corporation, 5, Novartis Pharmaceutical Corporation, 5, UCB, 5; **O. Y. Jones**, None; **M. J. McIlraith**, Abbott Laboratories, 1, Abbott Laboratories, 3; **N. Andhivarothai**, Abbott Laboratories, 3; **H. Kupper**, Abbott Laboratories, 1, Abbott Laboratories, 3; **E. H. Giannini**, Abbott Laboratories, 2; **T. Peterson**, Abbott Laboratories, 3; **A. Martini**, None.

266

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267

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268

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269

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270

Disclosure: E. Gremese, None; **G. D'Antona**, None; **L. Messuti**, None; **L. Petricca**, None; **M. R. Gigante**, None; **G. Ferraccioli**, None.

271

Disclosure: S. Angeles-Han, None; **C. Pelajo**, None; **L. B. Vogler**, None; **C. W. Kennedy**, None; **L. Ponder**, None; **T. Leong**, None; **J. M. Lopez-Benitez**, None; **C. Drews-Botsch**, None; **S. Prahalad**, None.

272

Disclosure: E. Demirkaya, None; **R. Galasso**, None; **A. Ravelli**, None; **E. Palmisani**, None; **A. Martini**, None; **A. Pistorio**, None; **N. Ruperto**, None.

273

Disclosure: A. Naselli, None; **A. Accogli**, None; **S. Chiesa**, None; **J. Tebaldi**, None; **M. Finetti**, None; **A. Buoncompagni**, None; **S. Viola**, None; **P. Picco**, None; **A. Ravelli**, None; **A. Martini**, None; **M. Gattorno**, SOBI and Novartis, 8.

274

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275

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276

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277

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278

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279

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280

Disclosure: P. Weiss, None; **T. Beukelman**, None; **L. E. Schanberg**, None; **Y. Kimura**, Genentech and Biogen IDEC Inc., 5; **R. A. Colbert**, None.

281

Disclosure: S. Prahalad, None; **S. Angeles-Han**, None; **C. F. Pelajo**, None; **C. W. Kennedy**, None; **L. Ponder**, None; **J. M. Lopez-Benitez**, None; **L. B. Vogler**, None.

282

Disclosure: E. Morgan DeWitt, None; **T. Beukelman**, None; **P. A. Nigrovic**, None; **K. Onel**, None; **S. Prahalad**, None; **R. Schneider**, Hoffmann-La Roche, 5; **M. Stoll**, None; **N. T. Ilowite**, Abbott Immunology Pharmaceuticals, 8, Genentech and Biogen IDEC Inc, 8, Regeneron, 2, Novartis Pharmaceutical Corporation, 5, Centocor, Inc, 5; **C. A. Wallace**, Amgen, Pfizer, Centocor, Novartis, BristolMyersSquibb, 2; **Y. Kimura**, Genentech and Biogen IDEC Inc, 5.

283

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284

Disclosure: R. K. Saurenmann, Centocor, Inc., 5, Bristol-Myers Squibb, 5, Novartis Pharmaceutical Corporation, 5; **R. Hauser**, None; **S. Schroeder**, None; **E. Cannizzaro**, None; **L. Muller**, None; **C. J. Kellenberger**, None.

285

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286

Disclosure: M. H. Otten, Pfizer Inc; **F. H. M. Prince**, None; **J. Anink**, None; **M. A. J. Van Rossum**, None; **E. P. A. H. Hoppenreijs**, None; **S. L. Gorter**, None; **W. Armbrust**, None; **K. M. Dolman**, None; **Y. Koopman-Keemink**, None; **J. F. Swart**, None; **J. M. Van den Berg**, None; **N. M. Wulffraat**, None; **R. Ten Cate**, None; **L. W. A. Van Suijlekom-Smit**, Pfizer Inc, 2, 9, Abbott Immunology Pharmaceuticals, 2.

287

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288

Disclosure: G. Simonini, None; **P. Paudyal**, None; **G. T. Jones**, None; **R. Cimaz**, None; **G. J. Macfarlane**, None.

289

Disclosure: S. Prahalad, None; **S. Angeles-Han**, None; **L. Ponder**, None; **C. W. Kennedy**, None; **L. B. Vogler**, None.

290

Disclosure: D. Ghio, None; **W. Thomson**, None; **E. M. Baildam**, None; **K. Hyrich**, None; **M. W. Beresford**, None; **C. Lydon**, None; **O. Lloyd**, None; **G. Cleary**, None; **L. J. McCann**, None; **F. Ulph**, None; **L. Cordingley**, None.

291

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292

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293

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ACR Poster Session A

Pediatric Rheumatology - Pathogenesis and Genetics

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

294

Disclosure: A. Aggarwal, None; **A. Myles**, None; **A. Tuteja**, None.

295

Disclosure: M. F. Parsa, None; **D. K. McCurdy**, None; **O. J. Rullo**, None; **J. M. P. Woo**, None; **T. Cunningham**, None; **J. Thorne**, None, 2; **R. D. Levinson**, None; **R. Rajalingam**, None; **G. N. Holland**, None.

296

Disclosure: R. Karasawa, None; **M. Tamaki**, None; **K. Yudoh**, None.

297

Disclosure: Y. Yamasaki, None; **Y. Nerome**, None; **T. Kubota**, None; **Y. Nonaka**, None; **H. Akaike**, None; **T. Takezaki**, None; **H. Imanaka**, None; **Y. Kawano**, None; **S. Takei**, None.

298

Disclosure: C. E. Janssen, None; **C. D. Rose**, None; **A. Naranjo**, None; **B. Bader-Meunier**, None; **R. Cimaz**, None; **M. Harjacek**, None; **P. Quartier**, None; **R. Ten Cate**, None; **C. Thomée**, None; **I. Cleynen**, None; **T. M. Martin**, None; **G. De Hertogh**, None; **T. Roskams**, None; **V. J. Desmet**, None; **C. H. Wouters**, None.

299

Disclosure: T. Herlin, None; **M. Bjerre**, None; **B. Fiirgaard**, None; **G. Kerndrup**, None; **H. Hasle**, None; **P. J. Ferguson**, None.

300

Disclosure: B. E. Gilliam, None; **M. R. Reed**, None; **A. K. Chauhan**, ProGen Biologics, LLC, 4; **A. Dehlendorf**, None; **T. L. Moore**, None.

301

Disclosure: S. Keidel, None; **N. Wilkinson**, None.

302

Disclosure: B. E. Gilliam, None; **A. K. Ombrello**, None; **R. W. Burlingame**, Inova Diagnostics, Inc., 3; **P. H. Pepmueller**, None; **T. L. Moore**, None.

303

Disclosure: B. Liphaus, None; **M. H. B. Kiss**, None; **S. Carrasco**, None; **C. A. A. Silva**, None; **C. Goldenstein-Schainberg**, None.

304

Disclosure: A. A. Jesus, None; **E. Fujihira**, None; **M. G. Watase**, None; **M. T. Terreri**, None; **M. O. Hilario**, None; **M. Carneiro-Sampaio**, None; **C. Len**, None; **S. K. Oliveira**, None; **M. C. Rodrigues**, None; **R. M. R. Pereira**, None, 2; **B. E. Bica**, None; **N. A. Silva**, None; **A. Cavalcanti**, None; **R. Marini**, None; **F. Sztajnbok**, None; **M. V. Quintero**, None; **V. P. Ferriani**, None; **D. Moraes-Vasconcelos**, None; **J. B. Oliveira**, None; **C. A. Silva**, None, 2.

305

Disclosure: P. S. Ramos, None; **M. C. Marion**, None; **C. D. Langefeld**, None; **J. P. Buyon**, None; **R. M. Clancy**, None.

306

Disclosure: D. Holzinger, None; **J. Austermann**, None; **P. Lohse**, None; **I. Aksentijevich**, None; **S. Holland**, None; **M. Gattorno**, None; **C. Rodríguez-Gallego**, None; **S. Fessatou**, None; **B. Isidor**, None; **S. Tokio**, None; **J. Bernstein**, None; **B. Sampson**, None; **C. Sunderkoetter**, None; **D. Foell**, None; **J. Roth**, None.

307

Disclosure: S. Finnegan, None; **M. Rooney**, None; **D. S. Gibson**, None.

308

Disclosure: K. Kurzinski, None; **C. Kelsey**, None; **T. Arkachaisri**, None; **C. A. Feghali-Bostwick**, None; **K. S. Torok**, None.

309

Disclosure: B. E. Gilliam, None; **A. K. Chauhan**, ProGen Biologics, LLC, 4; **T. L. Moore**, None.

310

Disclosure: N. Habal, None; **Y. Chen**, None; **C. Jordan**, None; **Y. Liu**, None; **D. C. Chapelle Neal**, None; **D. Stone**, None; **D. Garcia**, None; **N. Plass**, None; **E. Cowen**, None; **C. C. Lee**, None; **M. Lowes**, None; **R. T. Goldbach-Mansky**, None.

ACR Poster Session A

Rheumatoid Arthritis Clinical Aspects: Rheumatoid Arthritis Classification, Disease Activity and Remission; Biomarkers and Predictors of Response

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

311

Disclosure: C. Lukas, None; **R. Knevel**, None; **A. H. M. van der Helm-van Mil**, None; **N. Rincheval**, None; **D. van der Heijde**, Abbott, Amgen, AstraZeneca, BristolMyersSquibb, Centocor, Chugai, Eli-Lilly, GlaxoSmithKline, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth, 5; **B. G. Combe**, None.

312

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313

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314

Disclosure: L. M. Kennish, None; **M. Labitigan**, None; **S. Budoff**, None; **M. T. Filopoulos**, None; **Y. Yazici**, None.

315

Disclosure: J. Nicolau Jr., None; **P. Boumier**, None; **A. Daragon**, None; **O. Mejjad**, None; **J. F. Ménard**, None; **S. Pouplin**, None; **O. Vittecoq**, None; **P. Fardellone**, None; **X. Le Loët Sr.**, None.

316

Disclosure: J. A. Gomez Puerta, None; **V. Ruiz Esquide**, None; **M. V. Hernandez**, None; **E. Graell**, None; **S. Cabrera**, None; **M. J. Gómara**, None; **J. D. Cañete**, None; **I. Haro**, None; **R. Sanmarti**, None.

317

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318

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319

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320

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321

Disclosure: P. Santos-Moreno, None; **F. Gonzalez-Malaver**, None; **L. F. Amador**, None; **C. Guzman-Saltis**, None; **M. F. Cubides**, None; **A. M. Arbelaez**, None; **R. Valle-Onate**, None.

322

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323

Disclosure: A. H. M. van der Helm-van Mil, None; **R. Knevel**, None; **F. Qureshi**, Crescendo Bioscience, Inc., 3; **W. C. Manning**, Crescendo Bioscience, Inc., 3; **G. Cavet**, Crescendo Bioscience, Inc., 3; **T. W. J. Huizinga**, Schering Plough, 5, Bristol Myers Squibb, 5, Biotest AG, 5, Wyeth Pharmaceuticals, 5, Pfizer Inc, 5, Novartis Pharmaceutical Corporation, 5, Roche Pharmaceuticals, 5, Sanofi Aventis, 5, Abbott Laboratories, 5, Axis-Shield, 5, Abbott Laboratories, 8, Schering Plough, 8, Bristol Myers Squibb, 8, Biotest AG, 8, Wyeth Pharmaceuticals, 8, Pfizer Inc, 8, Novartis Pharmaceutical Corporation, 8, Roche Pharmaceuticals, 8, Sanofi Aventis, 8, Axis-Shield, 8, Crescendo Bioscience, Inc., 5; **D. J. Haney**, Crescendo Bioscience, Inc., 3.

324

Disclosure: Y. J. Hong, None; **Y. J. Lee**, None; **K. Shin**, None; **B. Y. Choi**, None; **H. W. Kim**, None; **S. H. Chang**, None; **I. A. Choi**, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. W. Song**, None.

325

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326

Disclosure: L. R. Harrold, Corrona, 5; **G. Reed**, Corrona, 5, Corrona; **D. H. Collier**, Amgen, 3, Amgen, 1; **G. S. Park**, Amgen, 1, Amgen, 3; **H. Chang**, Corrona, 5; **A. S. Koenig**, Pfizer Inc, 1, Pfizer Inc, 3; **K. C. Saunders**, Corrona, 3; **D. J. Zack**, Amgen, 1, Amgen, 3; **J. M. Kremer**, Corrona, 1, Corrona, 3; **J. D. Greenberg**, Corrona, 1, AstraZeneca Novartis, Pfizer, Corrona, 5.

327

Disclosure: G. Westhoff, None; **G. Schett**, None; **E. Edelmann**, None; **M. Schneider**, None; **A. Zink**, None; **M. Backhaus**, Abbott Immunology Pharmaceuticals, 5.

328

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329

Disclosure: T. Dervieux, Exagen Diagnostics, 3; **C. Harris**, Exagen Diagnostics, 3; **J. M. Kremer**, Exagen Diagnostics, 2, Exagen Diagnostics, 8.

330

Disclosure: T. Ferdousi, Pfizer, Inc, 3; **A. S. Koenig**, Pfizer Inc, 1, Pfizer Inc, 3; **T. V. Jones**, Pfizer Inc., 1, Pfizer Inc., 3.

331

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332

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ACR Poster Session A

Rheumatoid Arthritis - Human Etiology and Pathogenesis

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

364

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ACR Poster Session A

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy I

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

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454

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455

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456

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457

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459

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461

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464

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ACR Poster Session A

Sjögren's Syndrome

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

465

Disclosure: S. Mathew, None; **A. N. Collamer**, None; **A. S. Papas**, EUSA, 5; **D. F. Battafarano**, None.

466

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467

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469

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470

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471

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472

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473

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474

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475

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476

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479

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481

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483

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484

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485

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489

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490

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491

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492

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493

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498

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ACR Poster Session A

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment I

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

499

Disclosure: P. Zufferey, None; **C. Mouly Jr.**, None; **H. R. Ziswiler**, None; **J. Dudler**, None.

500

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501

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502

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503

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504

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505

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506

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508

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509

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511

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512

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513

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514

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515

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516

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ACR Poster Session A

Systemic Lupus Erythematosus - Animal Models

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

553

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ACR Poster Session A

Systemic Lupus Erythematosus - Clinical Aspects I

ACR/ARHP Abstract Authors Disclosures

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

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ACR Poster Session A

Systemic Lupus Erythematosus - Human Etiology and Pathogenesis I: Susceptibility and Pathogenic Mechanisms

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

632

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ACR Poster Session A

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics

Sunday, November 6, 2011, 9:00 AM - 6:00 PM

665

Disclosure: M. P. Cruz-Dominguez, None; **M. Casarrubias-Ramirez**, None; **V. Gasca Martínez**, None; **O. L. Vera Lastra**, None; **L. J. Jara Quezada**, None; **D. H. Montes-Cortes**, None.

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696

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ACR Plenary Session

ACR Plenary Session I: Discovery 2011

Sunday, November 6, 2011, 11:00 AM - 12:30 PM

718

Disclosure: G. R. Burmester, Pfizer Inc, 2, Pfizer Inc, 5, Pfizer Inc, 8; **R. Blanco**, None; **C. Charles-Schoeman**, Pfizer Inc, 2; **J. Wollenhaupt**, Pfizer Inc, 5, Pfizer Inc, 8; **C. A. F. Zerbini**, None; **B. Benda**, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 3; **G. Wallenstein**, Pfizer Inc, 3, Pfizer Inc, 1; **S. Krishnaswami**, Pfizer Inc, 3; **S. H. Zwillich**, Pfizer Inc, 3, Pfizer Inc, 1; **T. Koncz**, Pfizer Inc, 3; **J. D. Bradley**, Pfizer Inc, 3; **C. A. Mebus**, Pfizer Inc, 3, Pfizer Inc, 1.

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ACR Concurrent Abstract Session

Antiphospholipid Syndrome

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

723

Disclosure: R. Aguilar-Valenzuela, None; **K. Nickerson**, None; **Z. Romay-Penabad**, None; **M. J. Shlomchik**, None; **G. Vargas**, None; **T. Shilagard**, None; **S. S. Pierangeli**, None.

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ACR Concurrent Abstract Session

Cell-cell Interactions and Adhesion

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

729

Disclosure: N. D. Chamberlain, None; **S. R. Pickens**, None; **R. M. Pope**, None; **M. Volin**, None; **S. Shahrara**, None.

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ACR Concurrent Abstract Session

Fibromyalgia and Soft Tissue Disorders I

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

735

Disclosure: J. B. Hargrove, Cerephex Corporation, 4; **R. M. Bennett**, None; **D. J. Clauw**, Cerephex Corporation, 5.

736

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ACR Concurrent Abstract Session

Orthopedics and Low Back Pain

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

741

Disclosure: A. Kivitz, Pfizer Inc, 1; **J. Gimbel**, Pfizer Inc, 5, Pfizer Inc, 2, Array, 5, Array, 2, QRX, 5, QRX, 2; **C. Bramson**, Pfizer Inc, 1, Pfizer Inc, 3; **M. A. Nemeth**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Keller**, Pfizer Inc, 1, Pfizer Inc, 3; **M. T. Brown**, Pfizer Inc, 3, Pfizer Inc, 1; **C. R. West**, Pfizer Inc, 3, Pfizer Inc, 1; **K. M. Verburg**, Pfizer Inc, 3, Pfizer Inc, 1.

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ACR Concurrent Abstract Session

Pediatric Rheumatology - Clinical and Therapeutic Aspects: Clinical Characteristics

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

747

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Disclosure: M. Klein-Gitelman, None; **A. Cedeno**, None; **A. Baker**, None; **F. Zelko**, None; **D. Beebe**, None; **B. Dina**, None; **A. C. P. Sagcal-Gironella**, None; **D. Gitelman**, None; **H. Brunner**, None; **M. Difrancesco**, None; **T. Beckwith**, None.

752

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ACR Concurrent Abstract Session

Quality Measures and Innovations in Practice Management and Care Delivery I

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

753

Disclosure: E. D. Newman, Pfizer Inc, 8; **V. Lerch**, None; **J. B. Jones**, None; **W. T. Ayoub**, None; **T. P. Olenginski**, None; **T. M. Harrington**, None; **A. Bili**, None; **B. DelVecchio**, None; **A. E. Denio**, None; **B. P. Oppermann**, None; **S. Dancea**, None; **J. Antohe**, None; **C. Walker**, None; **R. Bozaite-Gluosniene**, None; **W. Stewart**, None.

754

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755

Disclosure: C. P. Walker, None; **E. D. Newman**, Pfizer Inc, 8; **W. T. Ayoub**, None; **D. M. Pugliese**, None; **J. M. Barrett**, None; **S. Mealia**, None; **A. Bili**, None.

756

Disclosure: M. Kohler, None; **M. Amezega**, None; **J. Drozd**, None; **S. Crowley**, None; **B. Gulanski**, None; **D. Anderson**, None; **L. Fraenkel**, None.

757

Disclosure: P. Y. Lu, None; **J. Taylor**, None; **M. El-hallak**, None; **K. A. Sikora**, None; **D. W. Moser**, None; **T. M. Moore**, None; **J. V. Ranz**, None; **J. Thomas**, None; **G. McIntyre-Patton**, None; **J. L. Huggins**, None; **T. V. Ting**, None.

758

Disclosure: A. Patwardhan, None; **K. Kelleher**, None; **D. Cuningham**, None; **C. H. Spencer**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Clinical Aspects: Cardiovascular Disease

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

759

Disclosure: G. A. Karpouzas, None; **J. Malpeso**, None; **D. Li**, None; **P. Razaeian**, None; **M. V. Peralta**, None; **S. Munoz**, None; **M. Budoff**, None.

760

Disclosure: A. M. van Sijl, None; **K. van der Hurk**, None; **M. J. L. Peters**, None; **V. P. van Halm**, None; **G. Nijpels**, None; **C. D. A. Stehouwer**, None; **Y. M. Smulders**, None; **A. E. Voskuyl**, None; **J. M. Dekker**, None; **M. T. Nurmohamed**, None.

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Disclosure: J. M. Davis III, None; **V. L. Roger**, None; **C. S. Crowson**, None; **T. M. Therneau**, None; **E. L. Matteson**, None; **S. E. Gabriel**, None.

762

Disclosure: G. A. Karpouzas, None; **P. Razaeian**, None; **J. Malpeso**, None; **D. Li**, None; **M. V. Peralta**, None; **S. Munoz**, None; **M. Budoff**, None.

763

Disclosure: C. Charles-Schoeman, None; **D. Meriwether**, None; **Y. Y. Lee**, None; **S. T. Reddy**, None.

764

Disclosure: C. Charles-Schoeman, None; **Y. Y. Lee**, None; **V. Grijalva**, None; **J. D. FitzGerald**, None; **V. K. Ranganath**, None; **M. Taylor**, None; **M. A. McMahon**, None; **H. E. Paulus**, None; **S. T. Reddy**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis - Human Etiology and Pathogenesis I: Pathogenesis of the Earliest Stages of Rheumatoid Arthritis

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

765

Disclosure: H. S. El-Gabalawy, None; **D. B. Robinson**, None; **D. M. Hart**, None; **I. Smolik**, None; **C. N. Bernstein**, None; **M. M. Newkirk**, None; **M. J. Fritzler**, None.

766

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767

Disclosure: A. Haj Hensvold, None; **P. K. Magnusson**, None; **M. Hansson**, None; **L. Israelsson**, None; **C. Carlens**, None; **R. Holmdahl**, None; **P. J. Jakobsson**, None; **J. Askling**, None; **V. Malmström**, None; **L. Klareskog**, None; **A. I. Catrina**, None.

768

Disclosure: I. Schacter, None; **D. B. Robinson**, None; **D. M. Hart**, None; **M. Bertone**, None; **C. A. Peschken**, None; **I. Smolik**, None; **C. A. Hitchon**, None; **H. S. El-Gabalawy**, None.

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ACR Concurrent Abstract Session

Sjögren's Syndrome

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

771

Disclosure: A. Saxena, None; **E. McDonnell**, None; **P. S. Ramos**, None; **S. Sajuthi**, None; **M. C. Marion**, None; **C. D. Langefeld**, None; **J. P. Buyon**, None; **R. M. Clancy**, None.

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ACR Concurrent Abstract Session

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment I

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

777

Disclosure: D. Poddubnyy, None; **H. Haibel**, None; **J. Listing**, None; **E. Märker-Hermann**, None; **H. Zeidler**, None; **J. Braun**, None; **J. Sieper**, None; **M. Rudwaleit**, None.

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Disclosure: I. McInnes, None; **J. Sieper**, None; **J. Braun**, None; **P. Emery**, None; **D. van der Heijde**, None; **J. Isaacs**, None; **G. Dahmen**, None; **J. Wollenhaupt**, None; **H. Schulze-Koops**, None; **S. Gsteiger**, Novartis Pharma AG, 3; **A. Bertolino**, Novartis Institutes for BioMedical Research, 3; **W. Hueber**, Novartis Institutes for BioMedical Research, 3; **P. P. Tak**, None.

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Disclosure: G. A. Schett, None; **A. Hu**, Celgene, 3; **R. Stevens**, Celgene, 3.

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Disclosure: V. Chandran, None; **A. Thavaneswaran**, None; **F. Pellett**, None; **D. D. Gladman**, None.

782

Disclosure: A. Ogdie, None; **N. Seminara**, None; **S. Langan**, None; **J. Gelfand**, Abbott, Amgen, Centocor, Genentech, Novartis and Pfizer, 5.

ACR Concurrent Abstract Session

Systemic Lupus Erythematosus - Clinical Aspects: Cardiac Disease/Organ Damage

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

783

Disclosure: G. J. Pons-Estel, None; **G. S. Alarcón**, None; **D. Wojdyla**, None; **A. I. Marcos**, None; **A. J. Alvarellos**, None; **A. A. Iglesias-Gamarra**, None; **M. H. Esteva-Spinetti**, None; **L. Costallat**, None; **N. A. Silva**, None; **G. Vázquez**, None; **M. L. Massardo**, None; **M. Guibert-Toledano**, None; **G. F. Huerta-Yáñez**, None; **M. Cucho-Venegas**, None; **B. Pons-Estel**, None.

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Disclosure: A. Kiani, None; **J. Vogel-Claussen**, None; **A. Zadeh**, None; **M. Yew**, None; **L. S. Magder**, None; **J. Lima**, None; **M. Petri**, None.

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Disclosure: M. B. Urowitz, None; **D. D. Gladman**, None; **D. Ibanez**, None; **N. Anderson**, None.

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Disclosure: M. Petri, None; **K. J. Bello**, None; **H. Fang**, None; **C. D'Souza**, None; **L. S. Magder**, None.

787

Disclosure: A. Lertratanakul, NIH P60 AR30492, 2; **P. W. Wu**, Mary Kirkland Center for Lupus Research and Rheuminations, Inc, 2, NIH T32-AR07611, 2; **A. Dyer**, NIH P60-AR30692, 2, NIH P60-AR48098, 2; **W. Pearce**, NIH P60 AR30492, 2; **K. Sutton-Tyrrell**, NIH P60 AR30492, 2; **G. Kondos**, NIH P60 AR30492, 2; **D. Edmundowicz**, NIH P60 AR30492, 2; **J. Carr**, NIH P60 AR30492, 2; **R. Ramsey-Goldman**, NIH K24-AR02318, 2, NIH P60-AR30692, 2, NIH P60-AR48098, 2, NIH T32-AR07611, 2, Mary Kirkland Center for Lupus Research and Rheuminations, Inc., 2, NIH MO-1 RR00048, 2.

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Disclosure: M. A. McMahon, None; **E. Lorenco**, None; **J. M. Grossman**, None; **L. Sahakian**, None; **J. D. FitzGerald**, None; **N. Ragavendra**, None; **C. Charles-Schoeman**, None; **A. H. Gorn**, None; **M. H. Weisman**, None; **D. Wallace**, None; **B. H. Hahn**, None; **B. Skaggs**, None.

ACR Concurrent Abstract Session

Vasculitis I

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

789

Disclosure: U. Specks, Genentech and Biogen-IDEC, Inc., 2; **P. A. Merkel**, Genentech and Biogen IDEC Inc., 2; **P. Seo**, Genentech and Biogen IDEC Inc., 5; **R. Spiera**, Genentech and Biogen IDEC Inc., 2; **C. A. Langford**, Genentech and Biogen IDEC Inc., 2; **G. S. Hoffman**, Genentech and Biogen IDEC Inc., 2; **C. G. M. Kallenberg**, None; **E. W. St. Clair**, Genentech and Biogen IDEC Inc., 2; **S. Tole**, Roche Pharmaceuticals, 1, Genentech, Inc., 3; **P. Brunetta**, Genentech/, 3; **S. Shen**, Genentech/, 3; **N. Tchao**, None; **B. J. Fessler**, Genentech and Biogen IDEC Inc., 2; **L. Webber**, None; **L. Ding**, None; **L. P. Sejismundo**, None; **K. Mieras**, None; **D. J. Phippard**, None; **A. Asare**, None; **N. Lim**, None; **D. Ikle**, None; **B. Jepson**, None; **A. Lail**, None; **M. Mueller**, None**J. H. Stone**, Genentech and Biogen IDEC Inc., 5.

790

Disclosure: N. T. Baerlecken, None; **A. Linnemann**, None; **W. L. Gross**, None; **F. Moosig**, None; **T. R. Vazquez-Rodriguez**, None; **M. Gonzalez-Gay**, None; **J. Martin**, None; **I. Kötter**, None; **J. C. Henes**, None; **I. Melchers**, None; **P. Vaith**, None; **R. E. Schmidt**, None; **T. Witte**, None.

791

Disclosure: D. Saadoun, None; **B. Terrier**, None; **G. Geri**, None; **W. Chaara**, None; **M. Rosenzwajg**, None; **N. Costedoat-Chalumeau**, None; **P. Fourret**, None; **L. Musset**, None; **A. Six**, None; **D. Klatzmann**, None; **P. Cacoub**, None.

792

Disclosure: P. A. Monach, None; **R. L. Warner**, None; **G. Tomasson**, None; **U. Specks**, None; **J. H. Stone**, None; **L. Ding**, None; **F. Fervenza**, None; **B. J. Fessler**, None; **G. S. Hoffman**, None; **D. Ikle**, None; **C. G. Kallenberg**, None; **J. Krischer**, None; **C. A. Langford**, None; **M. Mueller**, None; **P. Seo**, None; **E. W. St Clair**, None; **R. Spiera**, None; **N. Tchao**, None; **S. R. Ytterberg**, None; **K. J. Johnson**, None; **P. A. Merkel**, None.

793

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794

Disclosure: W. H. Abdulahad, None; **N. Lepse**, None; **H. Tadema**, None; **M. G. Huitema**, None; **B. Doornbos-van der Meer**, None; **C. Stegeman**, None; **P. C. Limburg**, None; **P. Heeringa**, None; **C. G. Kallenberg**, None.

ARHP Concurrent Abstract Session

ARHP Epidemiology and Public Health I

Sunday, November 6, 2011, 2:30 PM - 4:00 PM

795

Disclosure: K. A. Theis, None; **C. G. Helmick**, None; **J. M. Hootman**, None.

796

Disclosure: I. N. Ackerman, None; **R. H. Osborne**, None.

797

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800

Disclosure: A. B. Dufour, None; **V. A. Casey**, None; **P. P. Katz**, None; **R. R. McLean**, None; **M. T. Hannan**, None.

ACR Concurrent Abstract Session

Epidemiology and Health Services Research V: Drugs

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

801

Disclosure: C. Grijalva, None; **L. Chen**, None; **E. S. Delzell**, Amgen, 2; **J. Baddley**, Abbott Immunology Pharmaceuticals, 5; **T. Beukelman**, None; **K. L. Winthrop**, Genentech, Abbott, and Amgen, 5; **M. Griffin**, None; **L. Herrinton**, Research grant, 2; **L. Liu**, None; **P. Nourjah**, None; **N. M. Patkar**, None; **D. H. Solomon**, Abbott Immunology Pharmaceuticals, 2, Amgen, 2, Corrona, 5, Bristol-Myers Squibb, 9; **J. Lewis**, Amgen, 5, Pfizer Inc, 5, Millenium Pharmaceuticals, 5, Allos Theraeutics, 5, Centocor, Inc., 2, Shire, 2, Takeda, 2; **F. Xie**, None; **K. G. Saag**, None; **J. R. Curtis**, Merck Pharmaceuticals, 2, Novartis Pharmaceutical Corporation, 2, Proctor & Gamble Pharmaceuticals, 2, Eli Lilly and Company, 2, Merck Pharmaceuticals, 5, Eli Lilly and Company, 5, Roche Pharmaceuticals, 5, Novartis Pharmaceutical Corporation, 5.

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805

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806

Disclosure: J. Zhang, Amgen, 2; **F. Xie**, None; **E. S. Delzell**, Amgen, 2; **L. Chen**, None; **K. G. Saag**, None; **K. L. Winthrop**, None; **J. R. Curtis**, Pfizer, BristolMyersSquibb, Crescendo, Abbott, Roche, Genentech, UCB, Centacor, Corrona, Amgen, 5.

ACR Concurrent Abstract Session

Imaging of Rheumatic Disease I: Ultrasonography and Dual-emission X-ray Absorptiometry

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

807

Disclosure: S. Finzel, None; **P. Aegerter**, None; **G. Schett**, None; **M. A. D'Agostino**, None.

808

Disclosure: Y. M. El Miedany, None; **M. El Gaafary**, None; **D. Palmer**, None; **S. Youssef**, None.

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ACR Concurrent Abstract Session

Innate Immunity and Rheumatic Disease

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

813 WITHDRAWN

814

Disclosure: U. A. Walker, Patent application, 9; **N. M. Effelsberg**, None; **N. Venhoff**, Patent application, 9; **C. Foocharoen**, None; **J. Thiel**, None; **P. Hasler**, None; **D. Lebrecht**, Patent application, 9.

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ACR Concurrent Abstract Session

Muscle Biology, Myositis and Myopathies: Insights into the Pathogenesis of Myositis

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

819

Disclosure: S. Treiger Sredni, None; **P. Hendrickson**, None; **E. Kim**, None; **G. Morgan**, None; **S. Shrestha**, None; **Y. W. Chen**, None; **C. C. Huang**, None; **L. M. Pachman**, None.

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821

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ACR Concurrent Abstract Session

Osteoarthritis - Clinical Aspects I

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

825

Disclosure: M. S. Yau, None; **L. Yerges-Armstrong**, None; **M. Doherty**, None; **M. Hochberg**, None; **J. M. Jordan**, None; **V. B. Kraus**, None; **B. Mitchell**, None; **A. G. Wilson**, None.

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Disclosure: Y. Yazici, BristolMyersSquibb, Celgene, Genentech, UCB, Merck, Pfizer, 5; **E. F. Ekman**, Novartis Pharmaceuticals Corporation, Transdel, Travanti, Bayer, 9, Pfizer Inc, 9; **H. S. Greenberg**, Pfizer Inc, 3, Pfizer Inc, 1; **M. D. Smith**, Pfizer Inc, 3, Pfizer Inc, 1; **M. T. Brown**, Pfizer Inc, 3, Pfizer Inc, 1; **C. R. West**, Pfizer Inc, 3, Pfizer Inc, 1; **K. M. Verburg**, Pfizer Inc, 3, Pfizer Inc, 1.

829

Disclosure: D. Prieto-Alhambra, None; **X. Nogués**, Eli Lilly, 5; **M. K. Javaid**, Novartis, Alliance for Better Health, Eli Lilly, 9; **N. K. Arden**, Merck, MSD, Roche, Novartis, Smith and Nephew, Q-MED, Nicox, Servier, Schering-Plough, Pfizer and Rottapharm, 9; **C. Cooper**, Alliance for Better Bone Health, Amgen, Novartis, MSD, Servier, Eli Lilly, GlaxoSmithKline, 9; **A. Wyman**, Alliance for Better Bone Health:Sanofi-Aventis, Warner Chilcott, 9; **A. Díez-Pérez**, Eli Lilly, Amgen, Procter & Gamble, Servier, and Daiichi-Sankyo, 5, Merck, Novartis, Eli Lilly, Amgen, Procter & Gamble; Novartis, Lilly, Amgen, Procter & Gamble, Roche, 9.

830

Disclosure: R. Jackson, None; **C. Lu**, None; **L. Yerges-Armstrong**, None; **D. Duggen**, None; **M. Hochberg**, None; **B. Mitchell**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis - Animal Models I

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

831

Disclosure: R. I. Scheinman, None; **R. Trivedi**, None; **U. Kompella**, None.

832

Disclosure: I. Pandis, None; **C. Ospelt**, None; **N. Karagianni**, None; **M. C. Denis**, None; **M. Reczko**, None; **A. Hatzigeorgiou**, None; **J. Ragoussis**, None; **S. Gay**, None; **G. Kollias**, None.

833

Disclosure: M. Guma, None; **D. Hammaker**, None; **M. Edgar**, None; **K. Topolewski**, None; **M. Corr**, None; **G. S. Firestein**, None.

834

Disclosure: M. Hegen, Pfizer Inc, 3; **E. Beirnaert**, Ablynx nv, 1, Ablynx nv, 3; **G. Hermans**, Ablynx nv, 1, Ablynx nv, 3; **P. Casteels**, Ablynx nv, 1, Ablynx nv, 3; **M. Shen**, Pfizer Inc, 3; **J. Lee**, Pfizer Inc, 3; **L. Fitz**, Pfizer Inc, 3; **N. Seth**, Pfizer Inc, 3; **Y. Vugmeyster**, Pfizer Inc, 3; **C. Wrocklage**, Pfizer Inc, 3; **K. Dunussi-Joannopoulos**, Pfizer Inc, 3; **C. L. Nickerson-Nutter**, Pfizer Inc, 3; **M. Collins**, Pfizer Inc, 3.

835

Disclosure: N. D. Chamberlain, None; **M. Volin**, None; **S. Shahrara**, None.

836

Disclosure: E. G. Vajda, Ligand Pharmaceuticals, 3; **T. H. Lin**, Ligand Pharmaceuticals, 3; **B. Wang**, Ligand Pharmaceuticals, 3; **K. K. Ho**, Ligand Pharmaceuticals, 3; **A. van Oeveren**, Ligand Pharmaceuticals, 3; **B. McGuinness**, Ligand Pharmaceuticals, 3; **J. Letourneau**, Ligand Pharmaceuticals, 3; **Y. H. Lee**, Ligand Pharmaceuticals, 3; **D. Rungta**, Ligand Pharmaceuticals, 3; **L. Zhi**, Ligand Pharmaceuticals, 3; **K. B. Marschke**, Ligand Pharmaceuticals, 3.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Biomarkers

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

837

Disclosure: K. Owczarczyk, Genentech, 3; **P. Lal**, Genentech, 3; **A. R. Abbas**, Genentech, 3; **K. Wolslegel**, Genentech, 3; **C. T. Holweg**, Genentech, 3; **W. Dummer**, Genentech, 3; **A. Kelman**, Genentech, 3; **P. Brunetta**, Genentech, 3; **N. Lewin-Koh**, Genentech, 3; **M. Sorani**, Genentech, 3; **D. Leong**, Genentech, 3; **P. Fielder**, Genentech, 3; **D. E. Yocum**, Roche; **C. Ho**, Genentech, 3; **W. Ortmann**, Genentech, Inc, 3; **M. J. Townsend**, Genentech, 3; **T. W. Behrens**, Genentech, Inc, 3.

838

Disclosure: A. H. M. van der Helm-van Mil, None; **R. Knevel**, None; **W. C. Manning**, Crescendo Bioscience, Inc., 3; **L. K. Hesterberg**, Crescendo Bioscience, Inc., 3; **G. Cavet**, Crescendo Bioscience, Inc., 3; **T. W. J. Huizinga**, Schering Plough, 5, Bristol Myers Squibb, 5, Biotest AG, 5, Wyeth Pharmaceuticals, 5, Pfizer Inc, 5, Novartis Pharmaceutical Corporation, 5, Roche Pharmaceuticals, 5, Sanofi Aventis, 5, Abbott Laboratories, 5, Axis-Shield, 5, Abbott Laboratories, 8, Schering Plough, 8, Bristol Myers Squibb, 8, Biotest AG, 8, Wyeth Pharmaceuticals, 8, Pfizer Inc, 8, Novartis Pharmaceutical Corporation, 8, Roche Pharmaceuticals, 8, Sanofi Aventis, 8, Axis-Shield, 8, Crescendo Bioscience, Inc., 5; **Y. Shen**, Crescendo Bioscience, Inc., 1, Geron Corp, 3.

839

Disclosure: L. Ljung, None; **K. Egerer**, None; **H. Bang**, Orgentec Diagnostics, 3, Holds a patent for application of anti-MCV in RA diagnostic, 9; **E. Feist**, Orgentec, 9; **G. R. Burmester**, Orgentec, 2; **S. Rantapää Dahlqvist**, None.

840

Disclosure: Z. Konthur, None; **K. Köpke**, None; **H. Lehrach**, None; **G. R. Burmester**, None; **K. Skriner**, None.

841

Disclosure: T. Dervieux, Exagen Diagnostics, 3; **J. Wessels**, None; **J. M. Kremer**, Exagen Diagnostics, 8; **T. W. J. Huizinga**, None; **H. J. Guchelaar**, Exagen Diagnostics, 5.

842

Disclosure: T. Dervieux, Exagen Diagnostics, 3; **J. Wessels**, None; **J. M. Kremer**, Exagen Diagnostics, 8; **L. Padyukov**, None; **M. Seddighzadeh**, None; **S. Saevarsdottir**, None; **R. F. van Vollenhoven**, None; **L. Klareskog**, None; **T. Huizinga**, None; **H. J. Guchelaar**, Exagen Diagnostics, 5.

ACR Concurrent Abstract Session

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics I

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

843

Disclosure: G. S. Ngian, None; **W. Stevens**, Actelion Pharmaceuticals US, 2, GlaxoSmithKline, 2, Pfizer Inc, 2, Bayer, 2, Pfizer Inc, 5, GlaxoSmithKline, 5; **J. Byron**, None; **A. Tran**, None; **J. E. Roddy**, None; **R. Minson**, None; **C. L. Hill**, None; **K. Chow**, None; **J. Sahhar**, None; **S. Proudman**, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 5; **M. Nikpour**, None.

844

Disclosure: M. Soejima, None; **Z. Zhijie**, None; **D. M. Jones**, None; **D. Goudeau**, None; **C. L. Amity**, None; **L. M. Frydrych**, None; **R. T. Domsic**, None; **A. M. Patel**, None; **L. W. Moreland**, None; **D. M. Lee**, None; **T. A. Medsger**, None; **M. C. Levesque**, None.

845

Disclosure: A. Ceribelli, None; **M. Satoh**, None; **E. K. L. Chan**, None.

846

Disclosure: A. Doré, None; **T. A. Medsger Jr.**, None; **M. Lucas**, None; **D. Ivanco**, None; **R. T. Domsic**, None.

847

Disclosure: E. Snell, None; **M. Lucas**, None; **D. Ivanco**, None; **T. A. Medsger**, None; **R. T. Domsic**, None.

848

Disclosure: F. A. Mendoza, None; **S. J. Nagle**, None; **J. B. Lee**, None; **S. A. Jimenez**, None.

ACR Concurrent Abstract Session

T-cell Biology and Targets in Autoimmune Disease: Lymphocyte Biology and Targets in Autoimmune Disease

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

849

Disclosure: S. G. Zheng, None; **Q. Lan**, None; **J. Wang**, None; **D. Brand**, None; **D. A. Horwitz**, Becton Dickinson, 5; **Z. M. Liu**, None; **H. Zou**, None.

850

Disclosure: J. S. Park, None; **M. L. Cho**, None; **M. A. Lim**, None; **Y. M. Moon**, None; **H. J. Oh**, None; **J. Y. Jhun**, None; **J. G. Ryu**, None; **J. K. Byun**, None; **E. J. Jeon**, None; **H. R. Jeong**, None; **S. H. Lee**, None; **H. Y. Kim**, None.

851

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852

Disclosure: N. Talaei, None; **C. Landolt-Marticorena**, None; **B. Noamani**, None; **E. Pau**, None; **N. H. Chang**, None; **J. E. Wither**, None.

853

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854

Disclosure: D. Gomez-Martin, None; **M. J., Ibarra-Sanchez**, None; **J. Cruz-Ruiz**, None; **J. Romo-Tena**, None; **J. Esparza-Lopez**, None; **M. Diaz-Zamudio**, None; **J. Alcocer-Varela**, None.

ACR Concurrent Abstract Session

Vasculitis II

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

855

Disclosure: A. Vaglio, None; **A. Palmisano**, None; **S. Ferretti**, None; **R. Cobelli**, None; **L. Boiardi**, None; **C. Buzio**, None; **C. Salvarani**, None.

856

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857

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858

Disclosure: C. Pagnoux, None; **C. Comarmond**, None; **M. Khellaf**, None; **J. F. Cordier**, None; **M. Hamidou**, None; **J. F. Viallard**, None; **F. Maurier**, None; **P. Delaval**, None; **B. Bienvenu**, None; **X. Puechal**, None; **O. Aumaître**, None; **M. Ruivard**, None; **A. Le Quellec**, None; **R. Cevallos**, None; **O. Fain**, None; **B. Godeau**, None; **R. Seror**, None; **A. Mahr**, None; **P. Cohen**, None; **L. Mouthon**, None; **L. Guillevin**, None.

859

Disclosure: D. Saadoun, None; **M. Lambert**, None; **T. Mirault**, None; **Y. Shoindre**, None; **Z. Amoura**, None; **M. Resche Rigon**, None; **P. Y. Hatron**, None; **J. Emmerich**, None; **P. P. Cacoub**, None.

860

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ACR/ARHP Combined Session

ACR/ARHP Combined Pediatrics Abstract Session

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

861

Disclosure: S. Maillard, None; **S. Bhagat**, None; **C. Bernie**, None; **A. Morgan**, None; **D. Adkins**, None; **E. Haggart**, None; **C. Pilkington**, None.

862

Disclosure: V. M. Bugni, None; **K. Y. K. Okamoto**, None; **L. S. Ozaki**, None; **F. M. Teles**, None; **J. Molina**, None; **V. C. Bueno**, None; **M. O. E. Hilário**, None; **C. A. Len**, None; **M. T. Terreri**, None.

863

Disclosure: R. A. Berard, None; **G. A. Tomlinson**, None; **X. Li**, None; **K. Oen**, None; **A. M. Rosenberg**, None; **B. M. Feldman**, None; **R. S. Yeung**, None; **C. Bombardier**, None.

864

Disclosure: L. Haverman, None; **M. A. Grootenhuis**, None; **J. M. Van den Berg**, None; **M. van Veenendaal**, None; **K. M. Dolman**, None; **J. F. Swart**, None; **T. W. Kuijpers**, None; **M. A. J. Van Rossum**, None.

865

Disclosure: N. E. Aikawa, None; **L. M. A. Campos**, None; **C. A. Silva**, None, 2; **C. G. S. Saad**, None; **J. F. Carvalho**, None, 2; **G. Trudes**, None; **A. J. S. Duarte**, None; **J. Miraglia**, None; **M. C. S. Timenetsky**, None; **V. S. T.**

Viana, None; **I. L. A. França**, None; **E. Bonfa**, None, 2; **R. M. R. Pereira**, None, 2.

866

Disclosure: N. Tzaribachev, None, 2, None, 5; **M. Horger**, None; **J. Fritz**, None.

ARHP Concurrent Abstract Session

ARHP Clinical Practice/Patient Care I

Sunday, November 6, 2011, 4:30 PM - 6:00 PM

867

Disclosure: P. G. Persad, None; **S. J. Kim**, None; **K. A. Kirou**, None; **D. Erkan**, None.

868

Disclosure: E. G. Salt, SmithKLine Beecham, 1; **S. K. Frazier**, None.

869

Disclosure: K. A. Dewing, None; **B. Belza**, None; **B. Zierler**, None; **A. LaCroix**, Scientific Advisory Committee Member/ Principal Investigator for the GLOW Study, funded through an unrestricted research grant to the University of Massachusetts, Center for Outcomes Research by sanofi-aventis and Warner-Chilcott, 2, Scientific Methodology Advisory Committee member for Amgen for postmarketing safety studies of the new drug denosumab, 5.

870

Disclosure: M. Antonelli, None; **D. Einstadter**, None; **M. N. Magrey**, None.

871

Disclosure: D. K. White, None; **Y. Zhang**, None; **J. Niu**, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **T. Neogi**, None.

872

Disclosure: G. Bukh, None; **M. S. Hansen**, Genentech and Biogen IDEC Inc., 9; **S. Larsen**, None; **S. S. Rasmussen**, None.

873 WITHDRAWN

874 WITHDRAWN

ACR/ARHP Poster Session B

Epidemiology and Health Services Research: Osteoarthritis/Osteoporosis/Gout/Cost

Monday, November 7, 2011, 9:00 AM - 6:00 PM

875

Disclosure: G. A. Hawker, None; **A. Warner**, None; **T. Simms**, None.

876

Disclosure: L. Laslett, None; **C. H. Ding**, None; **S. Quinn**, None; **J. Burgess**, None; **V. Parameswaran**, None; **T. Winzenberg**, None; **G. Jones**, None.

877

Disclosure: W. M. Reichmann, None; **J. N. Katz**, None; **S. A. Burbine**, None; **M. E. Daigle**, None; **B. N. Rome**, None; **A. M. Weinstein**, None; **E. Losina**, None.

878

Disclosure: C. A. Waimann, None; **R. J. Fernandez-Mazarambroz**, None; **S. B. Cantor**, None; **M. Lopez-Olivo**, None; **H. Zhang**, None; **G. C. Landon**, None; **S. J. Siff**, None; **M. E. Suarez-Almazor**, None.

879

Disclosure: B. T. Do, None; **L. Murphy**, None; **C. G. Helmick**, None; **K. E. Barbour**, None; **Y. J. Cheng**, None; **J. M. Jordan**, None.

880

Disclosure: G. J. Macfarlane, None; **M. Beasley**, None; **E. A. Jones**, None; **K. Lovell**, None; **G. J. Prescott**, None; **P. Keeley**, None; **J. McBeth**, None; **G. T. Jones**, None.

881

Disclosure: A. P. Goode, None; **V. B. Kraus**, None; **Y. M. Golightly**, None; **S. W. Marshall**, None; **D. E. Irwin**, None; **J. M. Jordan**, None.

882

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883

Disclosure: R. Croxford, None; **G. A. Hawker**, None.

884

Disclosure: A. M. Weinstein, None; **B. N. Rome**, None; **W. M. Reichmann**, None; **J. E. Collins**, None; **S. A. Burbine**, None; **T. S. Thornhill**, None; **J. Wright**, None; **J. N. Katz**, None; **E. Losina**, None.

885

Disclosure: C. A. Waimann, None; **R. J. Fernandez-Mazarambroz**, None; **S. B. Cantor**, None; **M. Lopez-Olivo**, None; **H. Zhang**, None; **G. C. Landon**, None; **S. J. Siff**, None; **M. E. Suarez-Almazor**, None.

886

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887

Disclosure: M. McAdams DeMarco, None; **J. W. Maynard**, None; **A. N. Baer**, None; **J. Coresh**, None.

ACR/ARHP Abstract Authors Disclosures

888

Disclosure: N. Rashid, None; **T. C. Cheetham**, Amgen, 2; **J. R. Curtis**, None; **G. D. Levy**, None; **K. G. Saag**, None; **T. R. Mikuls**, None.

889

Disclosure: K. Rascati, Takeda Pharmaceuticals America, Inc., 2; **K. Prasla**, American Regent, 2, Daiichi-Sankyo, 2, Novartis Pharmaceutical Corporation, 2, Takeda, 2; **H. Park**, Takeda Pharmaceuticals America, Inc., 2; **T. McBayne**, Takeda Pharmaceuticals America, Inc., 3.

890

Disclosure: B. W. Pinsky, None; **B. J. Pandya**, Takeda Pharmaceuticals International, Inc., 3; **G. Gomez Rey**, None; **J. A. Singh**, Takeda, Savient, 2, Takeda, Savient, Novartis, URL Pharma, 5.

891

Disclosure: B. J. Pandya, Takeda Pharmaceuticals International, Inc., 3; **B. W. Pinsky**, None; **G. Gomez Rey**, None; **J. A. Singh**, Takeda Pharmaceuticals International, Inc., Savient, 2, Takeda Pharmaceuticals International, Inc., Savient, URL Pharma, Novartis, 5.

892

Disclosure: P. Lecomte, Novartis, 3; **L. Bessette**, Novartis, 5; **A. Ferreira**, Novartis, 3; **H. P. Goertz**, Novartis, 3; **P. Jones**, Novartis, 3; **J. A. Singh**, Takeda Pharmaceuticals International, Inc, Savient, 2, Takeda Pharmaceuticals International, Inc, Savient, URL Pharma, Novartis, 5.

893

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894

Disclosure: P. Lecomte, Novartis, 3; **L. Bessette**, Novartis, 5; **A. Ferreira**, Novartis, 3; **H. P. Goertz**, Novartis, 3; **P. Jones**, Novartis, 3; **J. Singh**, Novartis, 5.

895

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896

Disclosure: C. Li, Novartis Pharmaceuticals Corporation, 2; **B. C. Martin**, EMax Health, 5, Daiichi Sankyo, 5; **D. F. Cummins**, None; **L. M. Andrews**, Novartis Pharmaceuticals Corporation, 3; **F. Frech-Tamas**, Novartis Pharmaceuticals Corporation, 3; **A. Yadao**, Novartis Pharmaceuticals Corporation, 3.

897

Disclosure: P. Navaratnam, DataMed Solutions LLC, 3; **C. deMoor**, DataMed Solutions LLC, 3; **M. Shaffer**, BioTrends Research Group LLC, 3; **P. Chakravarti**, Novartis Pharmaceuticals Corporation, 3; **L. M. Andrews**, Novartis Pharmaceuticals Corporation, 3; **A. Yadao**, Novartis Pharmaceuticals Corporation, 3.

898

Disclosure: M. McAdams DeMarco, None; **J. W. Maynard**, None; **A. N. Baer**, None; **J. Coresh**, None.

899

Disclosure: D. S. Domiciano, None; **C. Figueiredo**, None; **J. B. Lopes**, None; **V. Caparbo**, None; **L. Takayama**, None; **E. Bonfa**, None; **R. M. R. Pereira**, None, 2.

900

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901

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902

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903

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904

Disclosure: G. Cherkowski, Amgen, 1, Amgen, 3; **C. O'Malley**, Amgen, 1, Amgen, 3; **P. P. Kaur**, Amgen, 1, Amgen, 3.

905

Disclosure: K. L. Miller, None; **T. M. Frech**, None; **T. Greene**, None; **K. N. Ma**, None; **M. McFadden**, None; **L. Tom-Orme**, None; **L. J. Moyer-Mileur**, None; **M. Slattery**, None; **M. Murtaugh**, None.

906

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907

Disclosure: F. M. Constantinescu, None; **P. Bhatia**, None; **L. M. Buckley**, None; **P. Falzer**, None; **L. Fraenkel**, None.

908

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909

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910

Disclosure: E. Krishnan, None; **J. F. Fries**, None; **B. Lingala**, None.

911

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912

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913

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914

Disclosure: M. Boers, Mundipharma, 5, Horizon Pharma, 5, Merck Serono, 5; **F. Buttgereit**, Mundipharma, 5, Horizon Pharma, 5, Merck Serono, 5, Horizon Pharma, 2, Merck Serono, 2.

915

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916

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917

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918 WITHDRAWN

919

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920

Disclosure: F. Zhang, Celgene Corporation, 3; **A. Guerin**, Celgene Corporation, 5; **D. Latremouille-Viau**, Celgene Corporation, 5; **R. Day**, Celgene Corporation, 3; **Z. Khan**, Celgene Corporation, 3.

921

Disclosure: L. Alon, None; **N. Ramessar**, None; **J. Cabas-Vargas**, None; **D. Stefanov**, None; **D. M. Lazaro**, None.

922

Disclosure: A. Deodhar, Centocor R&D, a division of J&J Pharmaceutical R&D, LLC, 2; **J. Braun**, Centocor R&D, a division of J&J Pharmaceutical R&D, LLC, 2; **R. D. Inman**, Centocor R&D, a division of J&J Pharmaceutical R&D, LLC, 2; **D. van der Heijde**, Centocor R&D, a division of J&J Pharmaceutical R&D, LLC, 2; **B. Hsu**, Centocor R&D, a division of J&J Pharmaceutical R&D, LLC, 3; **N. Tandon**, Janssen Services, LLC, 3; **C. Han**, Janssen Services, LLC, 3.

923

Disclosure: K. Tascilar, None; **E. Atac**, None; **F. Esen**, None; **H. Yazici**, None.

924

Disclosure: C. H. To, None; **K. L. Yu**, None; **C. C. Mok**, None.

ACR/ARHP Poster Session B

Fibromyalgia and Soft Tissue Disorders

Monday, November 7, 2011, 9:00 AM - 6:00 PM

925

Disclosure: S. I. Blum, Forest Laboratories, 1, Forest Research Institute, 3; **S. Tourkodimitris**, Forest Research Institute, 3; **A. Spera**, Forest Research Institute, 3.

926

Disclosure: M. Okumus, None; **H. Parpucu**, None; **S. Kocaoglu**, None; **E. Ceceli**, None; **P. Borman**, None; **M. Duranay**, None.

927

Disclosure: R. S. Katz, None; **F. Leavitt**, None.

928

Disclosure: R. S. Katz, None; **B. Shahani**, None.

929

Disclosure: R. S. Katz, None; **A. Small**, None; **L. Kwan**, None; **P. Kuenzi**, None; **J. L. Polyak**, None.

930

Disclosure: I. Saral, None; **D. Sindel**, None; **O. S. Berk**, None; **S. Esmaeilzadeh**, None.

931

Disclosure: D. J. Clauw, Forest Laboratories, Inc., 5, Forest Laboratories, Inc., 2, Cypress Bioscience, Inc., 5; **P. J. Mease**,

Forest Laboratories, Inc., 2, Forest Laboratories, Inc., 5, Forest Laboratories, Inc., 8, Cypress Bioscience, Inc., 5; **Y. Ma**, Forest Research Institute, 3; **A. Baldecchi**, Forest Research Institute, 3; **R. H. Palmer**, Forest Laboratories, Inc., 1, Forest Research Institute, 3; **J. M. Trugman**, Forest Research Institute, 3.

932

Disclosure: P. A. Ste-Marie, None; **M. A. Fitzcharles**, Pfizer Inc, Valeant, Lilly, Purdue, Janssen, 8, Lilly, Janssen, 5; **P. Panopalis**, None; **J. Pereira**, Pfizer Inc, 2; **Y. Shir**, None.

933

Disclosure: P. A. Ste-Marie, None; **M. O. Martel**, None; **M. A. Fitzcharles**, Pfizer Inc, Valeant, Lilly, Purdue, Janssen, 8, Lilly, Janssen, 5; **Y. Shir**, None.

934

Disclosure: J. N. Ablin, Pfizer Inc, 2; **A. Oren**, None; **S. Cohen**, None; **V. Aloush**, None; **O. Elkayam**, None; **Y. Wolman**, None; **M. Berman**, None.

935

Disclosure: M. Antivalle, None; **M. Battellino**, None; **A. Batticciotto**, None; **M. C. Ditto**, None; **A. Mutti**, None; **G. Santalena**, None; **V. Varisco**, None; **P. Sarzi-Puttini**, None.

936

Disclosure: S. Saad, None; **A. Many**, None; **G. Jacob**, None; **J. N. Ablin**, Pfizer Inc, 2.

937

Disclosure: G. Menga, None; **B. J. Dupre**, None; **C. Gauthier**, None; **W. E. Davis**, None; **T. A. Webb-Detiege**, None; **E. Scopelitis**, None; **J. M. Zakem**, None; **R. Quinet**, None.

938

Disclosure: P. A. Ste-Marie, None; **P. Panopalis**, None; **M. A. Fitzcharles**, Pfizer Inc, Valeant, Lilly, Purdue, Janssen, 8, Lilly, Janssen, 5; **H. A. Menard**, None; **Y. Shir**, None; **F. Wolfe**, None.

939

Disclosure: C. M. Brummett, None; **A. L. Hassett**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Jazz Pharmaceuticals, 5; **K. A. Brummett**, None; **D. J. Clauw**, Pfizer Inc, 5, Forest Laboratories, 5, Johnson & Johnson, 5, Lilly, 5, Merck Pharmaceuticals, 2, Jazz, 5, Cypress Biosciences, Inc., 5, Pfizer Inc, 2, Nuvo, 5, Forest Laboratories, 2; **D. A. Williams**, Eli Lilly and Company, 5, Forest Pharmaceuticals, 5, Pfizer Inc, 5, Jazz Pharmaceuticals, 5, Bristol Meyers Squibb, 5.

940

Disclosure: T. V. Ting, None; **D. Strotman**, None; **E. Verkamp**, None; **A. Desai**, None; **A. Lynch-Jordan**, None; **L. M. Arnold**, Eli Lilly and Company, 2, Pfizer Inc, 2, Cypress Biosciences, Inc., 2, Boehringer Ingelheim, 2, Forest Laboratories, 2, Novartis Pharmaceutical Corporation, 2, Eli Lilly and Company, 5, Pfizer Inc, 5, Cypress Biosciences, Inc., 5, Forest Laboratories, 5, Takeda, 5, Astra Zeneca, 5, Sanofi-Aventis Pharmaceutical, 5, Grunenthal, 5, Johnson & Johnson, 5; **S. Kashikar-Zuck**, None.

941

Disclosure: A. Vincent, None; **D. L. Barton**, None; **D. J. Clauw**, Pfizer Inc, 5, Forest Laboratories, 5, Johnson & Johnson, 5, Lilly, 5, Merck Pharmaceuticals, 2, Jazz, 5, Cypress Biosciences, Inc., 5, Pfizer Inc, 2, Nuvo, 5, Forest Laboratories, 2; **M. Whipple**, None; **B. Lahr**, None; **E. Hawkins**, None; **T. H. Oh**, None; **C. Luedtke**, None; **J. St.Sauver**, None.

942

Disclosure: L. Bazzichi, None; **A. Rossi**, None; **C. Conversano**, None; **C. Giacomelli**, None; **C. Ferrari**, None; **F. De Feo**, None; **F. Sernissi**, None; **M. Doveri**, None; **L. Carli**, None; **S. Bombardieri**, None.

943

Disclosure: R. S. Katz, None; **V. T. Dinh**, None; **G. Stebbins**, None; **F. Leavitt**, None.

ACR/ARHP Poster Session B

Imaging of Rheumatic Disease: X-ray, Magnetic Resonance Imaging, Computed Tomography and Positron Emission Tomography

Monday, November 7, 2011, 9:00 AM - 6:00 PM

944

Disclosure: J. L. Nam, None; **E. Villeneuve**, None; **S. Das**, None; **D. McGonagle**, None; **R. Hodgson**, None; **A. Grainger**, None; **R. J. Wakefield**, None; **P. G. Conaghan**, None; **P. Emery**, Pfizer, Merck, Abbott, BristolMyersSquibb, Roche, 5.

945

Disclosure: C. Buchbender, None; **P. Sewerin**, None; **A. Scherer**, None; **F. Miese**, None; **O. Sander**, None; **K. Mattes-György**, None; **H. J. Wittsack**, None; **C. Specker**, None; **G. Antoch**, None; **M. Schneider**, None; **B. Ostendorf**, None.

946

Disclosure: M. B. Axelsen, Abbott Laboratories, 2; **B. J. Ejbjerg**, None; **M. L. Hetland**, None; **K. Hørslev-Petersen**, Abbott Immunology Pharmaceuticals, 6, UCB, Roche, 8, Danish Association agains Rheumatism, 2; **M. Boesen**, Image Analysis Ltd., 9; **O. Kubassova**, Image Analysis Ltd., 4; **U. B. Lauridsen**, None; **O. Majgaard**, None; **H. Bliddal**, None; **N. S. Krogh**, None; **M. Østergaard**, Abbott Laboratories, 2.

947

Disclosure: M. Sugihara, None; **T. Suzuki**, None; **Y. Okamoto**, None; **M. Horikoshi**, None; **M. Yokosawa**, None; **S. Hagiwara**, None; **T. Hirota**, None; **Y. Takano**, None; **N. Umeda**, None; **Y. Kondo**, None; **H. Tsuboi**, None; **H.**

Ogishima, None; **T. Hayashi**, None; **Y. Chino**, None; **D. Goto**, None; **I. Matsumoto**, None; **T. Sumida**, None.

948

Disclosure: F. Hamadeh, None; **E. Olech**, None.

949

Disclosure: A. Rastogi, None; **O. Kubassova**, Image Analysis Ltd., 4; **M. Boesen**, Image Analysis Ltd, 9; **J. V. Hajnal**, None; **P. Taylor**, None.

950

Disclosure: S. Krabbe, None; **S. J. Pedersen**, None; **P. Bøyesen**, None; **J. M. Møller**, None; **F. R. Therkildsen**, None; **O. R. Madsen**, None; **M. Østergaard**, None.

951

Disclosure: H. Kellner, None; **W. Kellner**, None.

952

Disclosure: J. C. Henes, None; **M. Horger**, None; **F. Haas**, None; **G. Zeh**, None; **D. Spira**, None; **I. Kötter**, None.

953

Disclosure: R. P. Poggenborg, None; **P. Bøyesen**, None; **C. Wiell**, None; **S. J. Pedersen**, None; **I. J. Sørensen**, None; **O. R. Madsen**, None; **O. Slot**, None; **J. M. Møller**, None; **M. Hasselquist**, None; **M. Østergaard**, None.

954 WITHDRAWN

955

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956

Disclosure: R. Hemke, None; **M. A. J. Van Rossum**, None; **M. van Veenendaal**, None; **J. M. van den Berg**, None; **K. M. Dolman**, None; **T. W. Kuijpers**, None; **M. Maas**, None.

957

Disclosure: R. Hemke, None; **T. W. Kuijpers**, None; **M. van Veenendaal**, None; **J. M. van den Berg**, None; **K. M. Dolman**, None; **M. A. J. van Rossum**, None; **M. Maas**, None.

958

Disclosure: A. G. Brown, None; **R. Hirsch**, None; **T. Laor**, None; **K. A. Francis**, None; **M. J. Hannon**, None; **C. K. Kwoh**, None.

959

Disclosure: C. K. Kwoh, None; **A. Guermazi**, Boston Imaging Core Lab, 4, Facet Solutions, Genzyme, Stryker, Merck Serono, GE, 5; **M. J. Hannon**, None; **R. M. Boudreau**, None; **S. M. Green**, None; **J. M. Jakicic**, None; **F. Roemer**, Boston Imaging Core Lab, 4.

960

Disclosure: A. Guermazi, Boston Imaging Core Lab, 4, Facet Solutions, Genzyme, Stryker, Merck Serono, GE, 5; **D. Hayashi**, None; **F. Roemer**, Boston Imaging Core Lab, 4; **D. T. Felson**, None; **K. Wang**, None; **J. Lynch**, None; **S. Amin**, Merck Pharmaceuticals, 5; **J. Torner**, None; **C. E. Lewis**, None; **M. C. Nevitt**, None.

961

Disclosure: I. Kim, None; **Y. W. Song**, None; **H. A. Kim**, None; **A. Guermazi**, Boston Imaging Core Lab, 4, Facet Solutions, Genzyme, Stryker, Merck Serono, GE, 5.

962

Disclosure: N. Mohan, None; **M. J. Hannon**, None; **C. K. Kwoh**, None.

963

Disclosure: N. Mohan, None; **M. J. Hannon**, None; **C. K. Kwoh**, None.

964

Disclosure: S. Aschenberg, None; **S. Finzel**, None; **S. Schmidt**, None; **M. Englbrecht**, None; **J. Rech**, None; **G. Schett**, None.

965

Disclosure: L. M. Feehan, None; **H. R. Buie**, None; **E. C. Sayre**, None; **S. K. Boyd**, None; **H. A. McKay**, None; **L. C. Li**, None.

966

Disclosure: A. M. Roivainen, None; **S. Hautaniemi**, None; **T. Möttönen**, None; **P. Nuutila**, None; **V. Oikonen**, None; **R. Parkkola**, None; **L. Pricop**, Hoffmann-La Roche, Inc., 1, Hoffmann-La Roche, Inc., 3; **R. Ress**, Hoffmann-La Roche, Inc., 1, Hoffmann-La Roche, Inc., 3; **N. Seneca**, Hoffmann-La Roche, Inc., 3; **M. Seppänen**, None; **T. Yli-Kerttula**, None.

967

Disclosure: T. Kameda, None; **K. Susaki**, None; **Y. Yamamoto**, None; **M. Izumikawa**, None; **J. Danjo**, None; **S. Nakashima**, None; **H. Shimada**, None; **Y. Takeuchi**, None; **Y. Nishiyama**, None; **H. Dobashi**, None; **T. Matsunaga**, None.

968

Disclosure: A. E. D. Arraes, None; **A. W. S. Souza**, None; **E. N. P. Lima**, None; **E. I. Sato**, None.

969

Disclosure: M. W. Tang, None; **D. M. Gerlag**, None; **A. E. Hak**, None; **B. L. F. van Eck-Smit**, None; **P. P. Tak**, Genentech, 5, Roche Pharmaceuticals, 5, Merck Serono S.A., 5.

970

Disclosure: B. Foerster, None; **M. Petrou**, None; **R. Edden**, None; **P. Sundgren**, None; **T. Schmidt-Wilcke**, None; **S. E. Lowe**, None; **S. Harte**, None; **D. J. Clauw**, Pfizer Inc, 5, Forest Laboratories, 5, Johnson & Johnson, 5, Lilly, 5, Merck

Pharmaceuticals, 2, Jazz, 5, Cypress Biosciences, Inc., 5, Pfizer Inc, 2, Nuvo, 5, Forest Laboratories, 2; **R. E. Harris**, Pfizer Inc, 2.

971

Disclosure: R. E. Harris, Pfizer Inc, 2; **J. P. Huggins**, Pfizer Inc, 1, Pfizer Inc., 3; **L. Pauer**, Pfizer Inc, 1, Pfizer Inc, 3; **P. Sundgren**, None; **C. Urwin**, None; **K. Scott**, None; **D. J. Clauw**, Pfizer Inc, 5, Forest Laboratories, 5, Johnson & Johnson, 5, Lilly, 5, Merck Pharmaceuticals, 2, Jazz, 5, Cypress Biosciences, Inc., 5, Pfizer Inc, 2, Nuvo, 5, Forest Laboratories, 2.

972

Disclosure: M. B. Kinds, None; **A. C. A. Marijnissen**, None; **K. L. Vincken**, None; **L. W. Bartels**, None; **M. A. Viergever**, None; **H. W. de Jong**, None; **F. P. J. G. Lafeber**, None.

973

Disclosure: X. L. Tang, None; **T. Y. Zhu**, None; **L. S. Tam**, None; **E. K. Li**, None.

974

Disclosure: X. L. Tang, None; **T. Y. Zhu**, None; **L. S. Tam**, None; **E. K. Li**, None.

ACR/ARHP Poster Session B

Innate Immunity and Rheumatic Disease

Monday, November 7, 2011, 9:00 AM - 6:00 PM

975

Disclosure: K. Strle, None; **J. J. Shin**, None; **L. Glickstein**, None; **A. C. Steere**, None.

976

Disclosure: A. Blom, None; **P. van Lent**, None; **S. Abdollahi-Roodsaz**, None; **P. M. van der Kraan**, None; **W. B. van den Berg**, None.

977

Disclosure: G. Elson, NovImmune S.A., 3; **T. Page**, None; **V. Buatois**, NovImmune S.A., 3; **B. Daubeuf**, NovImmune S.A., 3; **L. Chatel**, NovImmune S.A., 3; **L. Cons**, NovImmune S.A., 3; **C. Lippens**, NovImmune S.A., 3; **S. Salgado-Pires**, NovImmune S.A., 3; **W. Ferlin**, NovImmune S.A., 3; **M. Kosco-Vilbois**, NovImmune S.A., 3; **K. Midwood**, None; **L. Shang**, NovImmune S.A., 3.

978

Disclosure: L. Philippe, None; **G. Alsaleh**, None; **S. Pfeffer**, None; **J. E. Gottenberg**, None; **J. Sibilia**, None; **D. Wachsmann**, None; **P. Georgel**, None.

979

Disclosure: L. Harlow, None; **M. Soejima**, None; **D. P. Ascherman**, None.

980

Disclosure: L. Tourneur, None; **S. Mistou**, None; **V. Vilmont**, None; **N. Cagnard**, None; **J. E. Gottenberg**, None; **V. Devauchelle**, None; **G. Chiocchia**, None.

981

Disclosure: B. T. van Den Brand, None; **S. Abdollahi-Roodsaz**, None; **M. B. Bennink**, None; **O. J. Arntz**, None; **W. van den Berg**, None; **F. A. van de Loo**, None.

982

Disclosure: Y. Molad, None; **E. Shapira**, None; **V. Carmon**, None.

983

Disclosure: S. Herman, None; **A. Fischer**, None; **M. Hoffmann**, None; **G. Steiner**, None.

984

Disclosure: S. L. Yu, None; **C. K. Wong**, None; **D. P. Chen**, None; **C. C. Szeto**, None; **E. K. Li**, None; **L. S. Tam**, None.

985

Disclosure: G. MinNone, None; **G. Prencipe**, None; **R. Strippoli**, None; **L. De Pasquale**, None; **I. Caiello**, None; **F. De Benedetti**, None; **L. Bracci-Laudiero**, None.

986

Disclosure: H. L. Rosenzweig, None; **J. S. Clowers**, None; **J. Allensworth**, None; **E. E. Vance**, None; **S. R. Planck**, None; **M. P. Davey**, None; **J. J. Chae**, None; **D. L. Kastner**, None; **J. T. Rosenbaum**, Abbott Immunology Pharmaceuticals, 5, Regeneron, 5, Amgen, 5, Genentech and Biogen IDEC Inc., 2, Xoma Corporation, 5, Novartis Pharmaceutical Corporation, 2, Pfizer Inc, 5.

987

Disclosure: E. H. Kim, None; **J. Y. Shin**, None; **M. J. Park**, None; **S. Park**, None; **E. S. Lee**, None.

988

Disclosure: H. J. Lachmann, None; **A. Meini**, None; **I. Touitou**, None; **L. Obici**, None; **M. Finetti**, None; **K. Minden**, Abbott Immunology Pharmaceuticals, 6; **L. Cantarini**, None; **M. Desjonqueres**, None; **J. Frenkel**, None; **I. Kone-Paut**, None; **O. Vougiouka**, None; **M. J. Rua Elorduy**, None; **N. Ruperto**, None; **P. Woo**, None; **M. Gattorno**, None.

989

Disclosure: K. Yokota, None; **T. Mimura**, None; **R. E. Gay**, None; **S. Gay**, None; **C. Kolling**, None; **C. Ospelt**, None.

990

Disclosure: L. M. van Duivenvoorde, None; **G. M. Slobodin**, None; **N. Satumtira**, None; **M. L. Dorris**, None; **P. P. Tak**, None; **D. L. Baeten**, None; **J. D. Taurog**, Taconic, Inc., 7.

991

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992

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993

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994

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995

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996

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997

Disclosure: P. Ghosh, None; **A. Wiedeman**, None; **D. M. Santer**, None; **V. E. Vlamakis**, None; **K. B. Elkon**, None.

998

Disclosure: B. Rhodes, None; **B. G. Fürnrohr**, None; **T. J. Vyse**, None.

999 WITHDRAWN

1000

Disclosure: J. Imanishi, Astellas Pharma Inc, 3; **T. Ishikawa**, Astellas Pharma Inc, 3; **E. Imamura**, Astellas Pharma Inc, 3; **H. Mizuhara**, Astellas Pharma Inc, 3; **H. Iwaoka**, Astellas Pharma Inc, 3; **B. Evelyn**, Astellas Pharma Inc, 3; **H. Inami**, Astellas Pharma Inc, 3; **T. Mizutani**, Astellas Pharma Inc., 3; **J. Watanabe**, Astellas Pharma Inc, 3; **H. Usuda**, Astellas Pharma Inc, 3; **S. Nagashima**, Astellas Pharma Inc, 3; **T. Ito**, Astellas Pharma Inc, 3; **T. Kontani**, Astellas Pharma Inc, 3; **Y. Shimizu**, Astellas Pharma Inc, 3; **S. Mutoh**, Astellas Pharma Inc, 9.

1001

Disclosure: G. Alsaleh, None; **L. Philippe**, None; **A. Pichot**, None; **S. Pfeffer**, None; **J. E. Gottenberg**, None; **J. Sibilia**, None; **P. Georgel**, None; **D. Wachsmann**, None.

1002

Disclosure: U. Arad, None; **A. Angel-Korman**, None; **S. Amir**, None; **S. Tzadok**, None; **O. Seagal**, None; **O. Elkayam**, None; **D. Caspi**, None.

1003

Disclosure: N. Mor-Vaknin, None; **M. Legendre**, None; **Y. Yu**, None; **C. H. C. Serezani**, None; **S. Garg**, None; **A. Jatzek**, None; **M. D. Swanson**, None; **S. Teitz-Tennenbaum**, None; **A. Punturieri**, None; **N. C. Engleberg**, None; **R. Banerjee**, None; **M. Peters-Golden**, None; **D. Markovitz**, None.

1004

Disclosure: B. Shi, None; **Q. Q. Huang**, None; **A. Dorfleutner**, None; **C. Stehlik**, None; **P. P. Tak**, Arthrogen B.V., 3; **R. M. Pope**, None.

1005

Disclosure: M. Fangradt, None; **T. Gaber**, None; **M. Hahne**, None; **P. Hoff**, None; **M. Jakstadt**, None; **C. Strehl**, None; **G. R. Burmester**, None; **F. Buttgereit**, None.

1006

Disclosure: G. Zizzo, None; **B. A. Hilliard**, None; **M. Monestier**, None; **P. L. Cohen**, None.

1007

Disclosure: J. Presumey, None; **G. Courties**, None; **V. Escriou**, None; **D. Scherman**, None; **D. Kyburz**, None; **S. Gay**, None; **Y. M. Pers**, None; **C. Jorgensen**, None; **F. Apparailly**, None.

1008

Disclosure: J. Kurko, None; **C. Egelston**, None; **T. Besenyei**, None; **B. Tryniszewska**, None; **T. Kobezda**, None; **T. A. Rauch**, None; **T. T. Glant**, None; **K. Mikecz**, None.

1009

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1010

Disclosure: C. M. Cuda, None; **J. Chowaniec**, None; **J. Hutcheson**, None; **G. K. Haines III**, None; **C. Mohan**, None; **H. R. Perlman**, None.

1011

Disclosure: T. Matsumoto, None; **H. Hasegawa**, None; **J. Lei**, None; **K. Suemori**, None; **S. Onishi**, None; **M. Yasukawa**, None.

1012

Disclosure: P. Van Lent, None; **A. Blom**, None; **R. Schelbergen**, None; **A. Sloetjes**, None; **T. Vogl**, None; **J. Roth**, None; **W. B. Van Den Berg**, None; **A. T. NOAC study group**, None.

ACR/ARHP Poster Session B

Metabolic and Crystal Arthropathies: Anti-Gout Therapy and Outcomes

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1013

Disclosure: J. S. Sundy, Regeneron, 2; **H. R. Schumacher**, Regeneron, 5; **J. Kirstein**, None; **E. Mitha**, Regeneron, 2; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1; **J. Wang**, Regeneron, 3, Regeneron, 1; **S. King-Davis**, Regeneron, 1, Regeneron, 3; **R. R. Evans**, Regeneron, 1, Regeneron, 3.

1014

Disclosure: R. Terkeltaub, Regeneron, 5; **H. R. Schumacher**, Regeneron, 5; **A. Kivitz**, None; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1; **R. Wu**, Regeneron, 1, Regeneron, 3; **R. Gall**, Regeneron, 1, Regeneron, 3; **R. R. Evans**, Regeneron, 1, Regeneron, 3.

1015

Disclosure: R. Terkeltaub, Regeneron, 5; **H. R. Schumacher**, Regeneron, 5; **E. Mitha**, Regeneron, 2; **J. S. Sundy**, Regeneron, 2; **K. G. Saag**, None; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1; **J. Wang**, Regeneron, 3, Regeneron, 1; **R. R. Evans**, Regeneron, 1, Regeneron, 3.

1016

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1017

Disclosure: S. Wason, URL Pharma, 3; **R. D. Faulkner**, URL Pharma, 3; **D. B. Brimhall**, NOVUM PRS, 3; **M. W. Davis**, URL Pharma, 3.

1018

Disclosure: A. S. Hollister, BioCryst Pharmaceuticals, Inc, 3; **M. A. Becker**, Takeda, Savient, Regeneron, URL Mutual, Novartis, Biocryst, Menarini, 5; **R. Terkeltaub**, Takeda, 5, URL, 5, ARDEA, 5, BioCryst, 5, Regeneron, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Metabolex, 5; **A. Waugh**, BioCryst Pharmaceuticals, Inc, 3; **S. Lyman**, BioCryst Pharmaceuticals, Inc, 3; **A. Flynt**, BioCryst Pharmaceuticals, Inc, 5; **D. Fitz-Patrick**, BioCryst Pharmaceuticals, Inc, 2.

1019

Disclosure: A. So, MSD, Novartis, UCB, Pfizer Inc, 5; **R. Alten**, Novartis Pharmaceutical Corporation, 2; **H. R. Schumacher**, Takeda, Novartis, Ardea, Xoma, Regeneron, Savient, Pfizer, 5; **T. Bardin**, Novartis, Ipsen, Menarini, Savient, 5; **M. Bloch**, Funding to Holdsworth House Medical Practice, 2, 9; **D. Richard**, Novartis Pharma AG, 3; **A. Karpov**, Novartis Pharma AG, 3, Norartis Pharma AG, 1; **T. Kiechle**, Novartis Pharma AG, 3, Novartis Pharma AG, 1; **N. Schlesinger**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5, Takeda, 8.

1020

Disclosure: P. Sunkureddi, Novartis Pharmaceutical Corporation, 9; **T. Bardin**, Novartis, Ipsen, Menarini, Savient, 5; **R. Alten**, Novartis Pharmaceutical Corporation, 2; **N. Schlesinger**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5, Takeda, 8; **M. Bloch**, Funding to Holdsworth House Medical Practice, 2, 9; **T. Kiechle**, Novartis Pharma AG, 3, Novartis Pharma AG, 1; **G. Krammer**, Novartis Pharma AG, 1, Novartis Pharma AG, 3; **A. Shpilsky**, Novartis Pharmaceutical Corporation, 1, Novartis Pharmaceutical Corporation, 3; **A. So**, MSD, Novartis, UCB, Pfizer Inc, 5.

1021

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1022

Disclosure: M. A. Becker, Takeda, Savient, Regeneron, URL Mutual, Novartis, Biocryst, Menarini, 5; **P. A. MacDonald**, Takeda Global Research and Development Center, Inc., 3; **B. Hunt**, Takeda Global Research and Development Center, Inc., 3; **R. L. Jackson**, Takeda Global Research and Development Center, Inc., 3.

1023

Disclosure: J. S. Sundy, Regeneron, 2; **H. R. Schumacher**, Regeneron, 5; **R. M. Fleischmann**, Regeneron, 2; **J. M. Engelbrecht**, None; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1; **J. Wang**, Regeneron, 3, Regeneron, 1; **S. King-Davis**, Regeneron, 1, Regeneron, 3; **R. R. Evans**, Regeneron, 1, Regeneron, 3.

1024

Disclosure: H. R. Schumacher, Regeneron, 5; **R. R. Evans**, Regeneron, 1, Regeneron, 3; **C. A. Birbara**, None; **L. Fouche**, Regeneron; **S. P. Weinstein**, Regeneron, 3, Regeneron, 1; **J. Wang**, Regeneron, 3, Regeneron, 1; **R. Terkeltaub**, Regeneron, 5.

1025

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1029

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1030

Disclosure: D. Hagerty, Ardea Biosciences, 3; **B. Kerr**, Ardea Biosciences, 3; **Z. Shen**, Ardea, 3; **L. T. Yeh**, Ardea Biosciences Inc, 3; **V. Hingorani**, Ardea Biosciences, 3; **M. Cravets**, Ardea Biosciences, 3; **J. Welp**, Ardea Biosciences, 3; **J. N. Miner**, Ardea Biosciences, 3; **K. Manhard**, Ardea Biosciences, 3; **B. Quart**, Ardea Biosciences, 3.

1031

Disclosure: A. Whelton, Takeda Global Research and Development Center, Inc., 5; **P. A. MacDonald**, Takeda Global Research and Development Center, Inc., 3; **B. Hunt**, Takeda Global Research and Development Center, Inc., 3; **L. Gunawardhana**, Takeda Global Research and Development Center, Inc., 3.

1032

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1033

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1034

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1035

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1036

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ACR/ARHP Poster Session B

Miscellaneous Rheumatic and Inflammatory Diseases

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1038

Disclosure: N. Ambrose, None; **D. O. Haskard**, None.

1039

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1050

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ACR/ARHP Poster Session B

Orthopedics, Low Back Pain, and Rehabilitation

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1060

Disclosure: A. Judge, None; **N. K. Arden**, None; **C. Cooper**, None; **M. K. Javaid**, None; **A. Carr**, None; **R. E. Field**, None; **P. A. Dieppe**, None.

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1064

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1065

Disclosure: C. R. Scanzello, None; **E. F. DiCarlo**, None; **V. Kanda**, None; **A. Albert**, None; **S. R. Goldring**, Bone Therapeutics, 5, Pfizer Inc, 5, Boehringer Ingelheim, 2; **J. C. Richmond**, Carmell Therapeutics, 1, DePuy-Mitek, 1, Entopica Therapeutics, 1, Stryker, 1, Lifenet, 1, Carmell Therapeutics, 5, DePuy-Mitek, 5, Entopica Therapeutics, 5, Lifenet, 5, Stryker, 5; **B. McKeon**, Parcus, Inc., 1, Conformis, Inc, 1, Arthrex, Inc, 2.

1066

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ACR/ARHP Poster Session B

Osteoarthritis - Clinical Aspects

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1070

Disclosure: J. Samuels, None; **C. Petchprapa**, None; **E. Carpenter**, None; **M. Attur**, None; **L. Rybak**, None; **S. Krasnokutsky**, None; **C. Oh**, None; **S. B. Abramson**, None.

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1079

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1087

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ACR/ARHP Poster Session B

Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogenesis

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1097

Disclosure: A. G. S. Oldroyd, None; **J. P. Halsey**, None; **B. Evans**, None; **C. Greenbank**, None; **N. Goodson**, None; **M. Bukhari**, None.

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1099

Disclosure: T. M. Keaveny, Merck Pharmaceuticals, 2, 5, Amgen, 2, Eli Lilly and Company, 2, Johnson & Johnson, 2, Novartis, 2, O.N. Diagnostics, 4, Wright Medical, 5, O.N. Diagnostics, 6; **M. Maricic**, Eli Lilly and Company, 2, 5, 8, Novartis, 2, 5, 8, Roche, 2, 5, 8, Amgen, 2, 5, 8, Genentech, Biogen Idec, 2, Genelabs Technologies, Inc, 5, 8; **D. Kopperdahl**, O.N. Diagnostics, 3; **V. Ruff,** Eli Lilly and Company, 1, 3; **X. Wan**, Eli Lilly and Company, 3; **K. Krohn**, Eli Lilly and Company, 1, 3.

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1102

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1104

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1107

Disclosure: M. R. McClung, Amgen Inc., Merck, Novartis, Takeda, 2, Amgen Inc., Lilly, Merck, Novartis, Takeda, Warner-Chilcott, 5, Amgen Inc., Lilly, Novartis, Warner-Chilcott, 8; **E. M. Lewiecki**, Amgen Inc., Eli Lilly, Novartis, Merck, Warner Chilcott, Genentech, 2, Amgen Inc., Eli Lilly, Novartis, Genentech, Merck, 5, Amgen Inc., Eli Lilly, Novartis, Genentech, 8; **M. A. Bolognese**, Eli Lilly, Amgen Inc., Shinogi, 2, Zosano, 5, Amgen Inc., Eli Lilly, sanofi-aventis, 8; **M. Peacock**, Genzyme Corporation, 2, KAI pharmaceuticals, 5; **R. L. Weinstein**, None; **B. Ding**, Amgen Inc., 1, Amgen Inc., 3; **M. L. Geller**, Amgen Inc., 1, Amgen Inc., 3; **A. Grauer**, Amgen Inc., 1, Amgen Inc., 3; **R. B. Wagman**, Amgen Inc., 1, Amgen Inc., 3; **P. D. Miller**, Amgen Inc., Lilly, Takeda, Merck, Novartis, Procter and Gamble, Roche, 2, Amgen Inc., Novartis, Warner Chilcott, Roche, AstraZeneca, Baxter, Lilly, Merck, 5, Amgen Inc., Novartis, Warner Chilcott, Roche, 8.

1108

Disclosure: M. A. Bolognese, Eli Lilly, Amgen Inc., Shinogi, 2, Zosano, 5, Amgen Inc., Eli Lilly, sanofi-aventis, 8; **H. G. Bone**, Amgen Inc., Merck, Nordic Bioscience, Novartis, Pfizer, Takeda, and Tarsa, 2, Amgen Inc., Merck, Nordic Bioscience, Novartis, Pfizer, Takeda, and Tarsa, 5; **D. L. Kendler**, Johnson & Johnson, Amgen Inc., Novartis, Roche,

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1119

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ACR/ARHP Poster Session B

Rheumatoid Arthritis - Animal Models

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1130

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ACR/ARHP Poster Session B

Rheumatoid Arthritis Clinical Aspects: Cardiovascular Disease in Rheumatoid Arthritis; Infection and Rheumatoid Arthritis; Drug Studies and Safety; Risk Factors for Rheumatoid Arthritis

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1154

Disclosure: M. Holmqvist, None; **Ä. Mantel**, None; **T. Jernberg**, None; **L. T. Jacobsson**, None; **L. Alfredsson**, None; **S. James**, None; **J. Askling**, None.

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ACR/ARHP Poster Session B

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1207

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1244

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ACR/ARHP Poster Session B

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1284

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Disclosure: S. Tan, None; **J. Yao**, None; **J. A. Flynn**, None; **L. Yao**, None; **M. M. Ward**, None.

1299

Disclosure: E. Constant, None; **F. Chopin**, None; **B. Pallot-Prades**, None; **T. Thomas**, None; **S. Paul**, None; **H. Marotte**, None.

1300

Disclosure: I. Litinsky, None; **J. Wollman**, None; **A. Balbir-Gurman**, None; **U. Arad**, None; **D. Paran**, None; **D. Caspi**, None; **O. Elkayam**, None.

1301

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1302

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1303

Disclosure: N. Haroon, None; **H. Shen**, None; **A. Carty**, None; **A. Anton**, None; **R. J. Cook**, None; **R. D. Inman**, Sanofi-Aventis Pharmaceutical, Merck, Abbott, Amgen-Wyeth,, 5.

1304

Disclosure: I. Westhovens, None; **R. Lories**, None; **R. Westhovens**, None; **P. Verschueren**, None; **K. L. De Vlam**, None.

1305

Disclosure: M. C. Turina, None; **N. Yeremenko**, None; **J. Paramarta**, None; **B. Vandooren**, None; **P. P. Tak**, None; **L. E. De Rycke**, None; **D. L. Baeten**, None.

1306

Disclosure: A. Bahce-Altuntas, None; **J. S. Schwartzman-Morris**, None; **N. Jordan**, None; **J. D. Greenberg**, Corrona, 3; **C. Putterman**, None; **G. Reed**, Corrona, 3, Corrona, 5; **A. R. Broder**, None.

1307

Disclosure: J. Walsh, None; **D. O. Clegg**, None; **K. Callis Duffin**, None.

1308

Disclosure: S. E. Grigg, None; **B. J. Martin**, None; **R. R. Buchanan**, None; **L. Schachna**, None.

1309

Disclosure: H. Przepiera-Bedzak, None; **I. Brzosko**, None; **K. Fischer**, None; **M. Brzosko**, None.

1310

Disclosure: J. D. Greenberg, Corrona, 1, AstraZeneca Novartis, Pfizer, Corrona, 5; **R. Bolce**, Johnson & Johnson, 3, Johnson & Johnson, 1; **Y. Shan**, None; **K. C. Saunders**, Corrona, 3; **G. Reed**, Corrona, 5, Corrona, 9; **J. M. Kremer**, Corrona, 1, Corrona, 3; **D. Decktor**, Johnson & Johnson, 3.

1311

Disclosure: R. Almodovar, None; **V. Ríos**, None; **S. Ocaña**, None; **M. Gobbo**, None; **M. Casas**, None; **P. Zarco**, None; **X. Juanola-Roura**, None.

1312

Disclosure: W. P. Maksymowych, Abbott Laboratories, 2, Abbott Laboratories, 5, Abbott Laboratories, 8; **P. J. Mease**, Abbott Immunology Pharmaceuticals, 2, Amgen, 2, Bristol Myers Squibb, 2, Novartis Pharmaceutical Corporation, 2, Centocor, Inc., 2, Genentech and Biogen IDEC Inc., 2, Lilly, 2, Pfizer Inc, 2, U C B, 2, Abbott Immunology Pharmaceuticals, 5, Amgen, 5, Bristol Myers Squibb, 5, Centocor, Inc., 5, Genentech and Biogen IDEC Inc., 5, Lilly, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, U C B, 5, Abbott Immunology Pharmaceuticals, 8, Amgen, 8, Bristol Myers Squib, 8, Centocor, Inc., 8, Genentech and Biogen IDEC Inc., 8, Lilly, 8, Pfizer Inc, 8, U C B, 8; **S. Rao**, Abbott Laboratories, 1, Abbott Laboratories, 3; **A. Pangan**, Abbott Laboratories, 1, Abbott Laboratories, 3; **L. S. Brown**, Abbott Immunology Pharmaceuticals, 3; **V. Arora**, Abbott Laboratories, 1, Abbott Laboratories, 3; **M. A. Cifaldi**, Abbott Laboratories, 3.

1313

Disclosure: I. Garcia-Valladares, None; **R. Cuchacovich**, None; **A. A. Iglesias-Gamarra**, None; **L. R. Espinoza**, None.

1314

Disclosure: Z. Touma, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **D. D. Gladman**, None.

1315

Disclosure: R. M. Morlà, None; **H. Corominas**, None; **M. V. Hernandez**, None; **M. Moreno**, None; **M. Sala**, None; **V. Ortiz-Santamaria**, None; **P. Reyner**, None; **V. Torrente-Segarra Jr.**, None; **A. Sellas Fernandez**, None; **G. Salvador**, None; **E. Sirvent**, None; **C. Masuet**, None; **X. Juanola-Roura**, None.

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1317

Disclosure: F. Pimentel-Santos, None; **A. F. Mourão**, None; **C. Ribeiro**, None; **J. Costa**, None; **H. Santos**, None; **A. Barcelos**, None; **P. Pinto**, None; **F. Godinho**, None; **M. Cruz**, None; **E. Vieira-Sousa**, None; **J. Félix**, None; **J. E. Fonseca**, None; **H. Guedes-Pinto**, None; **J. C. Branco**, None.

1318

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1319

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1320

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1321

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1322

Disclosure: S. Arends, None; **E. van der Veer**, None; **P. M. Houtman**, None; **M. K. Leijsma**, None; **C. G. M. Kallenberg**, None; **E. Brouwer**, Wyeth Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2; **A. Spoorenberg**, Wyeth Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2.

1323

Disclosure: C. Magro-Checa, None; **J. L. Rosales-Alexander**, None; **J. Salvatierra Sr.**, None; **J. Cantero-Hinojosa**, None; **J. Gonzalez-Dominguez**, None; **E. Raya-Alvarez**, None.

1324

Disclosure: S. Arends, None; **M. Hofman**, None; **Y. P. T. Kamsma**, None; **E. van der Veer**, None; **M. K. Leijsma**, None; **P. M. Houtman**, None; **C. G. M. Kallenberg**, None; **A. Spoorenberg**, Wyeth Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2; **E. Brouwer**, Wyeth Pharmaceuticals, 2, Abbott Immunology Pharmaceuticals, 2.

1325

Disclosure: A. Asiri, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **G. Kalman-Lamb**, None; **D. D. Gladman**, None.

1326

Disclosure: W. P. Maksymowych, Abbott Laboratories, 5, Abbott Laboratories, 2, Abbott Laboratories, 8; **S. Rao**, Abbott Laboratories, 1, Abbott Laboratories, 3; **A. Boonen**, Abbott Laboratories, 5, Abbott Laboratories, 8, Abbott Laboratories, 2; **N. Chen**, Abbott Laboratories, 3, Abbott Laboratories, 1; **M. A. Cifaldi**, Abbott Laboratories, 3, Abbott Laboratories, 1.

1327

Disclosure: A. Haddad, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **D. D. Gladman**, None.

1328

Disclosure: Y. Yalcinkaya, None; **Ö. Pehlivan**, None; **A. Omma**, None; **B. Artim-Esen**, None; **B. Erer**, None; **N. Hüseyinsinoglu**, None; **S. Kamali**, None; **M. Inanc**, None; **O. Aral**, None; **A. Gul**, None; **L. Ocal**, None.

1329

Disclosure: A. Weiβ, None; **I. H. Song**, Pfizer Inc, Merck Sharp Dohme, Abbott, 5; **K. G. Hermann**, Johnson & Johnson, 2; **C. Althoff**, None; **B. Freundlich**, Pfizer Inc, 3; **M. Rudwaleit**, Pfizer Inc, Merck Sharp Dohme, Abbott, 5; **J. Listing**, None; **J. Sieper**, Pfizer Inc, 8, Merck Pharmaceuticals, 8, BristolMyersSquibb, 2, Roche Pharmaceuticals, 8, Abbott Immunology Pharmaceuticals, 8, UCB, 8, Lilly, 5.

1330

Disclosure: K. A. Alnaqbi, None; **N. Haroon**, None; **H. Shen**, None; **R. J. Cook**, None; **A. Carty**, None; **R. D. Inman**, None.

1331

Disclosure: A. Eissa, None; **D. D. Gladman**, None; **A. Thavaneswaran**, None; **F. Pellett**, None; **E. Diamandis**, None; **V. Chandran**, None.

1332

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1333

Disclosure: F. Zhang, Celgene Corporation, 3; **A. Guerin**, Celgene Corporation, 5; **G. Gauthier**, Celgene Corporation, 5; **R. Day**, Celgene Corporation, 3; **Z. Khan**, Celgene Corporation, 3.

1334

Disclosure: D. D. Gladman, None, 2; **R. J. Cook**, None; **L. Eder**, None; **A. Wakhlu**, None; **C. Riddell**, None; **M. Ostergaard**, None; **A. Thavaneswaran**, None; **V. Chandran**, None, 8.

1335

Disclosure: X. Baraliakos, None; **J. Listing**, None; **A. von der Recke**, None; **J. Braun**, None.

1336

Disclosure: L. C. Harty, None; **C. A. Murray**, None; **C. Fearon**, None; **M. Dockery**, None; **U. Fearon**, None; **D. J. Veale**, HRB, 2, Abbott, GlaxoSmithKline, Centocor, Wyeth,Pfizer and Schering Plough, 5, Abbott, GlaxoSmithKline, Centocor, Wyeth,Pfizer and Schering Plough, 8.

ACR/ARHP Poster Session B

Spondylarthropathies and Psoriatic Arthritis – Pathogenesis, Etiology

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1337

Disclosure: S. C. Shim, None; **D. Sheen**, None; **M. K. Lim**, None; **J. Kim**, None; **S. Lee**, None; **S. Lee**, None.

1338

Disclosure: D. Poddubnyy, None; **K. Conrad**, None; **G. Ruiz-Heiland**, None; **U. Syrbe**, None; **H. Haibel**, None; **H. Appel**, None; **M. Rudwaleit**, None; **G. Schett**, None; **J. Sieper**, None.

1339

Disclosure: M. Faham, Sequenta, Inc., 3; **V. Carlton**, Sequenta, Inc., 3; **M. Moorhead**, Sequenta, Inc., 3; **J. Zheng**, Sequenta, Inc., 3; **T. Asbury**, Sequenta, Inc., 3; **R. D. Inman**, None.

1340

Disclosure: F. Costantino, None; **B. Izac**, None; **G. Chiocchia**, None; **R. Said-Nahal**, None; **A. Leboime**, None; **E. Zinovieva**, None; **D. Zelenika**, None; **M. A. Breban**, None; **H. J. Garchon**, None.

1341

Disclosure: C. Jeanty, None; **A. Sourisce**, None; **A. Wielgosik**, None; **M. A. Breban**, None; **C. André**, None.

1342

Disclosure: H. L. Rosenzweig, None; **J. M. Kezic**, None; **M. P. Davey**, None; **S. R. Planck**, None; **T. T. Glant**, None; **J. T. Rosenbaum**, Abbott Immunology Pharmaceuticals, 5, Regeneron, 5, Amgen, 5, Genentech and Biogen IDEC Inc., 2, Xoma Corporation, 5, Novartis Pharmaceutical Corporation, 2, Pfizer Inc, 5.

1343

Disclosure: R. Misra, None; **A. Singh**, None; **A. Aggarwal**, None.

1344

Disclosure: N. Haroon, None; **A. Lin**, None; **A. Akram**, None; **R. D. Inman**, Sanofi-Aventis Pharmaceutical, Merck, Abbott, Amgen-Wyeth, 5.

1345

Disclosure: G. Slobodin, None; **A. Kessel**, None; **N. Kofman**, None; **E. Toubi**, None; **I. A. Rosner**, None; **M. Odeh**, None.

1346

Disclosure: Y. J. Kwon, None; **T. Y. Kim**, None; **S. W. Lee**, None; **Y. B. Park**, None; **S. K. Lee**, None; **M. C. Park**, None.

1347

Disclosure: R. G. Thiele, None; **B. A. Marston**, None; **D. Tabechian**, None; **A. P. Anandarajah**, None; **C. T. Ritchlin**, None.

1348

Disclosure: M. Ramez, None; **T. S. Forde**, None; **E. Kudryavtseva**, None; **V. A. Adarichev**, None.

1349

Disclosure: E. N. Blaney Davidson, None; **E. Vitters**, None; **W. B. van den Berg**, None; **P. M. van der Kraan**, None.

1350

Disclosure: L. M. van Duivenvoorde, None; **M. L. Dorris**, None; **N. Satumtira**, None; **P. P. Tak**, None; **J. D. Taurog**, Taconic, Inc., 7; **D. L. Baeten**, None.

1351

Disclosure: S. Ebihara, None; **M. Ono**, None.

1352

Disclosure: R. Winchester, None; **G. Minevich**, None; **V. Steshenko**, None; **B. Kirby**, None; **D. Kane**, None; **D. A. Greenberg**, None; **O. M. FitzGerald**, None.

1353

Disclosure: L. Eder, None; **F. Pellett**, None; **V. Chandran**, None; **S. Shanmugarajah**, None; **S. Bull**, None; **D. D. Gladman**, None.

1354

Disclosure: A. Cauli, None; **G. Dessole**, None; **G. Porru**, None; **A. Vacca**, None; **M. Piga**, None; **V. Ibba**, None; **P. Garau**, None; **S. Kollnberger**, None; **A. Mathieu**, None.

1355

Disclosure: N. Haroon, None; **R. D. Inman**, Sanofi-Aventis Pharmaceutical, Merck, Abbott, Amgen-Wyeth,, 5.

1356

Disclosure: S. Lambrecht, None; **J. Coudenys**, None; **F. De Keyser**, None; **G. Verbruggen**, None; **D. Deforce**, None; **D. Elewaut**, Merck Pharmaceuticals, 8, Abbott Immunology Pharmaceuticals, 5.

1357

Disclosure: R. Pollock, None; **F. Pellett**, None; **R. Ayearst**, None; **A. A. P. Rahman**, None; **D. D. Gladman**, None; **V. Chandran**, None.

1358

Disclosure: R. Celis, None; **R. Sanmarti**, None; **J. Ramirez**, None; **A. Palacin**, None; **J. L. Pablos**, None; **J. D. Cañete**, None.

1359

Disclosure: S. P. Raychaudhuri, None; **A. Mitra**, None; **A. Datta Mitra**, None; **S. K. Raychaudhuri**, None.

1360

Disclosure: V. Chandran, None; **F. Pellett**, None; **A. Thavaneswaran**, None; **R. Pollock**, None; **R. Ayearst**, None; **D. D. Gladman**, None.

1361

Disclosure: V. Chandran, None; **F. Pellett**, None; **R. Pollock**, None; **A. A. P. Rahman**, None; **D. D. Gladman**, None.

1362

Disclosure: V. Chandran, None; **A. Thavaneswaran**, None; **F. Pellett**, None; **D. D. Gladman**, None.

1363

Disclosure: V. Chandran, None; **A. Thavaneswaran**, None; **F. Pellett**, None; **D. D. Gladman**, None.

1364

Disclosure: V. Chandran, None; **F. Pellett**, None; **P. Rahman**, None; **D. D. Gladman**, None.

1365

Disclosure: D. Cretu, None; **D. D. Gladman**, None; **F. Pellett**, None; **E. Diamandis**, None; **V. Chandran**, None.

1366

Disclosure: D. Jadon, None; **W. Tillett**, None; **D. Wallis**, None; **C. Cavill**, None; **A. Dixon**, None; **N. Waldron**, None; **E. Korendowych**, None; **A. Barton**, None; **N. J. McHugh**, None.

ACR/ARHP Poster Session B

Systemic Lupus Erythematosus - Clinical Aspects

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1367

Disclosure: R. A. Furie, Human Genome Sciences, Inc., 2, Human Genome Sciences, GlaxoSmithKline, 5, Human Genome Sciences, GlaxoSmithKline, 8; **Z. J. Zhong**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **W. Freimuth**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **M. Petri**, Human Genome Sciences, GlaxoSmithKline, 2, Human Genome Sciences, GlaxoSmithKline, 5.

1368

Disclosure: Z. Touma, None; **D. D. Gladman**, None; **D. Ibanez**, None; **M. B. Urowitz**, None.

1369

Disclosure: V. Strand, Amgen, AstraZeneca, BristolMyersSquibb, Genentech, GlaxoSmithKline, Human Genome Sciences, Idera, Lilly, MedImmune, Merck Serono, NovoNordisk, Ono, Pfizer, Rigel, Roche, Sanofi-Aventis, Schering Plough, UCB, 5; **S. Cooper**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **Z. J. Zhong**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **G. Dennis**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3.

1370

Disclosure: J. J. Hale, None; **J. A. Kelly**, None; **C. P. Lin**, None; **S. B. Glenn**, None; **J. Anderson**, None; **P. M. Gaffney**, None; **K. L. Moser**, None; **J. B. Harley**, None; **J. A. James**, None; **C. G. Montgomery**, None.

1371

Disclosure: A. Mak, None; **T. Ren**, None; **E. H. Y. Fu**, None; **A. A. Cheak**, None; **R. C. Ho**, None.

1372

Disclosure: K. Smith, None; **S. L. Green**, None; **D. F. Brandt**, None; **B. S. Franek**, None; **T. B. Niewold**, None; **T. O. Utset**, Anthera Pharmaceutics, 5, Human Genome Sciences/GlaxoSmithKline, 8.

1373

Disclosure: Y. Schoindre, None; **M. Jallouli**, None; **B. Terrier**, None; **M. L. Tanguy**, None; **Z. Amoura**, None; **J. C. Piette**, None; **P. Cacoub**, None; **J. C. Souberbielle**, None; **N. Costedoat-Chalumeau**, None.

1374

Disclosure: Y. C. Santiago-Casas, None; **L. M. Vila**, None; **G. McGwin Jr.**, None; **M. Petri**, None; **R. Ramsey-Goldman**, None; **J. D. Reveille**, None; **R. P. Kimberly**, None; **G. S. Alarcon**, None; **E. E. Brown**, None.

1375

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1376

Disclosure: L. N. Moorthy, Arthritis Foundation, 2.

1377

Disclosure: B. M. Hoffecker, None; **L. M. Tonks**, None; **T. K. Nowling**, None; **D. L. Kamen**, None.

1378

Disclosure: M. Petri, UCB, 5; **M. C. Pike**, UCB, 5; **L. Kelley**, UCB, 3; **B. Kilgallen**, UCB, 3; **C. Gordon**, UCB, 5.

1379

Disclosure: M. Shah, Xcenda, LLC, 3; **S. Chaudhari**, Xcenda, LLC, 3; **T. McLaughlin**, Xcenda, LLC, 3; **H. Kan**, GlaxoSmithKline, 3; **B. Bechtel**, GSK, 3; 3; **C. T. Molta**, GSK, 3.

1380

Disclosure: K. J. Kim, None; **J. Y. Kim**, None; **S. J. Park**, None; **H. Yoon**, None; **Y. J. Park**, None; **C. H. Yoon**, None; **J. J. Choi**, None; **W. U. Kim**, None; **C. S. Cho**, None.

1381

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1382

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1383

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1384

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1385

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1386

Disclosure: Z. Touma, None; **D. D. Gladman**, None; **D. Ibanez**, None; **S. Taghavi-Zadeh**, None; **M. B. Urowitz**, None.

1387

Disclosure: S. T. Sridharan, Pfizer Inc, 3; **T. Zhou**, Pfizer Inc, 3; **F. Immermann**, Pfizer Inc, 3; **M. Lehmann**, Pfizer Inc, 3; **J. L. Masferrer**, Pfizer Inc, 3; **M. Honczarenko**, Pfizer Inc, 3; **J. C. Rawdon**, Pfizer Inc, 5; **J. A. James**, Pfizer Inc, 5; **J. T. Merrill**, Pfizer Inc, 5.

1388

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1389

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1390

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1392

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1393

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1394

Disclosure: R. Narwal, None, 3; **L. Roskos**, None, 3; **W. White**, AZ Stock, 1, MedImmune, 3; **W. Greth**, None, 3; **G. Robbie**, None, 3.

1395

Disclosure: D. D. Gladman, None; **M. B. Urowitz**, None; **D. Ibanez**, None; **N. Anderson**, None.

1396

Disclosure: E. Muscal, None; **E. Traipe**, None; **E. Wilde**, None; **D. R. Bloom**, None; **B. L. Myones**, None; **Z. D. Chu**, None; **R. L. Brey**, None; **J. Hunter**, None.

1397

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1398

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1399

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1400

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1401

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1402

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1403

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1404

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1405

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1406

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1408

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1410

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1411

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1412

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1413

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1414

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1415

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1416

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1417

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1418

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1419

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1420

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1421

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1422

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ACR/ARHP Poster Session B

Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: Innate Immune System and Organ Damage

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1423

Disclosure: K. Ko, None; **B. S. Franek**, None; **T. B. Niewold**, None.

1424

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1425

Disclosure: N. A. Young, None; **A. Friedman**, None; **B. Kaffenberger**, None; **W. N. Jarjour**, None.

1426

Disclosure: K. E. Sullivan, None; **L. Shi**, None; **L. Song**, None; **M. Petri**, None; **Z. Zhang**, None.

1427

Disclosure: F. Wen, None; **M. Kinter**, None; **J. Guthridge**, None; **M. B. Humphrey**, None; **P. M. Gaffney**, None.

1428

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1429

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1430

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1431

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1432

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1433

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1435

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1436

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1437

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1439

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1440

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1441

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1442

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1443

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1444

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1445

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1446

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ACR/ARHP Poster Session B

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1447

Disclosure: K. M. Walker, None; **J. E. Pope**, None; **C. S. Research Group (CSRG)**, None.

1448

Disclosure: V. Smith, None; **Y. P. Piette**, None; **S. Decuman**, None; **J. T. Van Praet**, None; **E. De Schepper**, None; **F. De Keyser**, None.

1449

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1450

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1451

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1452

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1453

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1454

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1455

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1456

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1457

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1458

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1459

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1460

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1463

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1464

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1465

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1466

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1467

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1469

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1471

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1472

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1473

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1474

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1477

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1478

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ACR/ARHP Poster Session B

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1479

Disclosure: A. Usategui, None; **M. J. Del Rey**, None; **E. Izquierdo**, None; **V. Miranda**, None; **G. Criado**, None; **J. L. Pablos**, None.

1480

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1481

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1483

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1487

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1488

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ACR/ARHP Poster Session B

Vasculitis

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1500

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1505

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1520

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1531

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1532

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ACR/ARHP Poster Session B

ARHP Epidemiology and Public Health

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1538

Disclosure: R. Wilkie, None; **A. Tajar**, None; **J. McBeth**, None.

1539

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1540

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1544

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1545

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1547

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ACR/ARHP Poster Session B

ARHP Rehabilitation Sciences

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1557

Disclosure: F. Cramp, None; **S. Hewlett**, None; **C. Almeida**, None; **J. R. Kirwan**, None; **E. Choy**, None; **T. Chalder**, None; **J. Pollock**, None; **R. Christensen**, None.

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ACR/ARHP Poster Session B

ARHP Clinical Practice/Patient Care

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1572

Disclosure: C. B. Garcia, None; **L. N. J. Matos**, None; **C. E. Negrao**, None; **H. Roschel**, None; **A. L. S. Pinto**, None; **J. F. Carvalho**, None, 2; **E. Bonfa**, None; **F. R. Lima**, None.

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ACR/ARHP Poster Session B

ARHP Education and Community Programs

Monday, November 7, 2011, 9:00 AM - 6:00 PM

1579

Disclosure: M. K. Wolrich, None; **A. Batterman**, None; **R. Horton**, None; **L. Leff**, U.S. Treat to Target Committee, 6, National Speakers Bureau for Actemra, 8; **T. R. Fields**, None; **V. Lalsa**, None.

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1585

Disclosure: J. A. Rose, None; **C. Carlstorm**, None; **R. Horton**, None; **S. Goldsmith**, None; **R. Wiesel**, None; **L. F. Imundo**, None.

1586

Disclosure: L. Bergeron, None; **D. Richards**, None; **L. Wilhelm**, None; **J. Coderre**, None; **D. Cooper**, None; **J. Gunderson**, None; **L. Crane**, None; **C. DeBow**, None; **S. Hughes**, None; **M. E. Veilleux**, None; **I. Maurstad**, None; **N. White**, None; **E. Wychreschuk**, None; **K. Miller**, None.

ACR Plenary Session

Plenary Session II: Discovery 2011

Monday, November 7, 2011, 11:00 AM - 12:30 PM

1587

Disclosure: C. Bloch-Queyrat, None; **L. Drouot**, None; **J. L. Charuel**, None; **E. Yada**, None; **D. Langui**, None; **S. Urien**, None; **S. Herson**, None; **L. Musset**, None; **G. Butler Browne**, None; **O. Boyer**, None; **O. Benveniste**, None.

1588

Disclosure: C. Beyer, None; **A. Schramm**, None; **A. Akhmetshina**, None; **T. Kireva**, None; **C. Dees**, None; **S. C. Schindler**, None; **M. M. Taketo**, None; **O. Distler**, None; **G. Schett**, None; **J. H. Distler**, None.

1589

Disclosure: A. Del Fatore, None; **M. Capannolo**, None; **B. Peruzzi**, None; **A. Cappariello**, None; **N. Rucci**, None; **F. De Benedetti**, None; **A. Teti**, None.

1590

Disclosure: J. J. Taylor, None; **L. O. Barsness**, None; **R. J. Martinez**, None; **S. R. Thomas**, None; **D. L. Mueller**, None.

1591

Disclosure: N. Yeremenko, None; **G. M. M. Rigter**, None; **I. Simon**, Agendia BV, 1, Agendia BV, 3; **J. D. Cañete**, None; **P. P. Tak**, Arthrogen b.v., 1; **D. L. Baeten**, None.

1592

Disclosure: P. K. Tan, Ardea Biosciences, 3; **D. Hyndman**, Ardea Biosciences, 3, Ardea Biosciences, 1; **J. N. Miner**, Ardea Biosciences, 3, Ardea Biosciences, 1, Scientific Advisor for Arman Tadbir Afagh - ARTA, 6.

ACR Concurrent Abstract Session

Education: Medical Education

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1593

Disclosure: J. Scheers-Masters, None; **D. R. Blumenthal**, None; **J. Macrae**, None; **M. Avitable**, None; **D. M. Lazaro**, None.

1594

Disclosure: S. Sheikh, None; **M. Smith**, None; **T. Ning**, None; **E. Shiner**, None; **D. Christianson**, None; **L. G. Criscione-Schreiber**, None; **M. B. Bolster**, None; **K. S. O'Rourke**, None; **D. MacDonald**, None; **L. F. Callahan**, None; **B. L. Jonas**, None.

1595

Disclosure: J. E. Navarro-Zarza, None; **C. Hernández-Díaz**, None; **M. A. Saavedra-Salinas**, None; **R. A. Kalish**, None; **J. J. Canoso**, None; **P. Villaseñor-Ovies**, None.

1596

Disclosure: C. E. Collins, None.

1597

Disclosure: T. P. Olenginski, Eli liily, Inc, 5, Novartis Pharmaceutical Corporation, 8, Amgen, 8; **T. M. Harrington**, None.

1598

Disclosure: E. L. M. Bezerra, None; **F. A. Bezerra Neto**, None; **M. J. Vilar**, None.

ACR Concurrent Abstract Session

Epidemiology and Health Services Research I: Gout

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1599

Disclosure: Y. Zhu, None; **Y. Zhang**, None; **J. D. Seeger**, UnitedHealth Group, 1, UnitedHealth Group, 3, UnitedHealth Group, 5; **Y. H. Rho**, None; **C. Peloquin**, None; **H. K. Choi**, Takeda, 2, Novartis Pharmaceutical Corporation, 5, URL, 2, Savient, 5, Centocor, Inc..

1600

Disclosure: M. McAdams DeMarco, None; **J. W. Maynard**, None; **A. N. Baer**, None; **A. Kottgen**, None; **L. Kao**, None; **J. Coresh**, None.

1601

Disclosure: G. G. Teng, None; **L. W. Ang**, None; **J. M. Yuan**, None; **W. P. Koh**, None.

1602

Disclosure: B. J. Pandya, Takeda Pharmaceuticals International, Inc., 3; **M. Marynchenko**, Takeda Pharmaceuticals International, Inc., 5; **H. Sharma**, Takeda Pharmaceuticals International, Inc., 5; **A. Yu**, Takeda Pharmaceuticals International, Inc., 5; **E. Wu**, Takeda Pharmaceuticals International, Inc., 5; **L. Shi**, Takeda Pharmaceuticals International, Inc., 5; **J. Liu**, None; **E. Krishnan**, Savient, 1, Takeda Pharmceuticals International, Inc., URL Pharma, ARDEA, Metabolex, UCB, 5.

1603

Disclosure: R. Akkineni, None; **A. Lee**, None; **K. L. Miller**, None; **A. N. A. Tosteson**, None; **H. K. Choi**, None; **Y. Zhu**, None; **D. A. Albert**, None.

1604

Disclosure: J. A. Singh, Takeda Pharmaceuticals International, Inc., Savient, 2, Takeda Pharmaceuticals International, Inc., Savient, URL Pharma, Novartis, 5; **B. J. Pandya**, Takeda Pharmaceuticals International, Inc., 3; **G. Gomez Rey**, None; **B. W. Pinsky**, None.

ACR Concurrent Abstract Session

Fibromyalgia and Soft Tissue Disorders II

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1605

Disclosure: P. A. Ste-Marie, None; **M. A. Fitzcharles**, Pfizer Inc, Valeant, Lilly, Purdue, Janssen, 8, Lilly, Janssen, 5; **M. O. Martel**, None; **A. Gamsa**, None; **P. Panopalis**, None; **Y. Shir**, None.

1606

Disclosure: S. Ogino, Astellas Pharma, Inc, 3; **M. Tsukamoto**, Astellas Pharma, Inc, 3; **Y. Nagakura**, Astellas Pharma, Inc, 3; **T. Watabiki**, Astellas Pharma, Inc, 3; **Y. Shimizu**, Astellas Pharma, Inc, 3; **H. Ito**, Astellas Pharma, Inc, 3.

1607

Disclosure: S. A. Mazzuca, None; **A. Kaleth**, None; **C. Saha**, None; **J. Slaven**, None; **D. C. Ang**, None.

1608

Disclosure: S. Martin, Pfizer Inc, 9; **C. Coon**, Pfizer, 9; **L. McLeod**, Pfizer Inc, 3; **A. Chandran**, Pfizer Inc, 3; **L. M. Arnold**, Eli Lilly and Company, 2, Pfizer Inc, 2, Cypress Biosciences, Inc., 2, Boehringer Ingelheim, 2, Forest Laboratories, 2, Novartis Pharmaceutical Corporation, 2, Eli Lilly and Company, 5, Pfizer Inc, 5, Cypress Biosciences, Inc., 5, Forest Laboratories, 5, Takeda, 5, Astra Zeneca, 5, Sanofi-Aventis Pharmaceutical, 5, Grunenthal, 5, Johnson & Johnson, 5.

1609

Disclosure: L. Bateman, Forest Laboratories, 5, Forest Laboratories, 8; **A. Spera**, Forest Research Institute, 3; **R. H. Palmer**, Forest Research Institute, 3, Forest Laboratories, Inc., 1; **J. M. Trugman**, Forest Laboratories, 3; **J. Lin**, Forest Research Institute, 3.

1610

Disclosure: F. Wolfe, None; **B. T. Walitt**, Jazz Pharmaceuticals, 5; **R. S. Katz**, Forrest Pharmaceuticals, 8; **Y. C. Lee**, Merck, Novartis, Elan, 1, Forrest Research Institute, 2; **K. D. Michaud**, None; **W. Häuser**, Dr. Häuser has received honoraria for educational lectures from Eli-Lilly & Company, Janssen-Cilag and Pfizer, and congress travel support from Eli Lilly & Company in the previous 3 years, 8.

ACR Concurrent Abstract Session

Imaging of Rheumatic Disease II: X-ray, Computed Tomography and Magnetic Resonance Imaging

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1611

Disclosure: S. Finzel, None; **C. Ernet**, None; **J. Rech Sr.**, None; **C. M. Stach**, None; **K. Engelke**, None; **M. Englbrecht**, None; **J. Zwerina**, None; **G. Schett**, None.

1612

Disclosure: C. G. Peterfy, Spire Sciences, LLC, 1, Synarc, Inc., 1, Astellas, Akros, AstraZeneca, Biogen-Idec, Bristol-Myers Squibb, Celegene, Centocor, Genentech, Lilly, Merck, Novartis, Pfizer, Rigel, Roche, UCB, 5; **B. Haraoui**, Abbott, Amgen, BristolMyersSquibb, Merck, Pfizer, Roche, UCB, 5, Abbott, Amgen, BristolMyersSquibb, Merck, Pfizer, Roche, UCB, 2, Abbott, Amgen, BristolMyersSquibb, Merck, Pfizer, Roche, UCB, 8; **A. Kavanaugh**, Abbott, 5; **J. S. Smolen**, Abbott, BristolMyersSquibb, Centocor-Schering-Plough(MSD), Roche, UCB, Wyeth (Pfizer), 2, Abbott, BristolMyersSquibb, Centocor-Schering-Plough(MSD), Roche, UCB, Wyeth (Pfizer), 5; **S. Santra**, Abbott Laboratories, 1, Abbott Laboratories, 3; **H. Kupper**, Abbott Laboratories, 1, Abbott Laboratories, 3; **T. F. Nicholson**, Abbott, 3; **P. Emery**, Pfizer, Merck, Abbott, BristolMyersSquibb, Roche, 5.

1613

Disclosure: C. F. Allaart, Centocor, Inc., 2, Schering-Plough, 2, Dutch College of Health Insurances, 2; **L. Dirven**, Centocor, Inc., 2, Schering-Plough, 2, Dutch College of Health Insurances, 2; **S. Hirata**, None; **P. J. S. M. Kerstens**, None; **B. A. C. Dijkmans**, None; **D. Chernoff**, Crescendo Bioscience, Inc., 5; **G. Cavet**, Crescendo Bioscience, Inc., 3; **M. Centola**, Crescendo Bioscience, Inc., 5, Oklahoma Medical Research Foundation, 3; **L. K. Hesterberg**, Crescendo Bioscience, Inc., 3; **Y. Tanaka**, Abbott Japan, Astellas Pharma, Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma, Merck & Co. Inc, Pfizer Japan Inc., and Takeda Pharmaceutical Co. Ltd., 2, Abbott Japan, Astellas Pharma, Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma, Merck & Co. Inc, Pfizer Japan Inc., and Takeda Pharmaceutical Co. Ltd., 5, Abbott Japan, Astellas Pharma, Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma, Merck & Co. Inc, Pfizer Japan Inc., and Takeda Pharmaceutical Co. Ltd., 8; **T. W. J. Huizinga**, Schering Plough, 5, Bristol Myers Squibb, 5, Biotest AG, 5, Wyeth Pharmaceuticals, 5, Pfizer Inc, 5, Novartis Pharmaceutical Corporation, 5, Roche Pharmaceuticals, 5, Sanofi Aventis, 5, Abbott Laboratories, 5, Axis-Shield, 5, Abbott Laboratories, 8, Schering Plough, 8, Bristol Myers Squibb, 8, Biotest AG, 8, Wyeth Pharmaceuticals, 8, Pfizer Inc, 8, Novartis Pharmaceutical Corporation, 8, Roche Pharmaceuticals, 8, Sanofi Aventis, 8, Axis-Shield, 8, Crescendo Bioscience, Inc., 5; **Y. Shen**, Crescendo Bioscience, Inc., 1, Geron Corporation, 3.

1614

Disclosure: J. Smolen, Roche Pharmaceuticals, 5; **J. Martinez-Avila**, None; **D. Aletaha**, Roche Pharmaceuticals, 5.

1615

Disclosure: S. Finzel, None; **J. Rech Sr.**, None; **S. Schmidt**, None; **K. Engelke**, None; **M. Englbrecht**, None; **C. M. Stach**, None; **G. Schett**, None.

1616

Disclosure: F. Roemer, Boston Imaging Core Lab, 4; **D. T. Felson**, None; **K. Wang**, None; **M. Crema**, Boston Imaging Core Lab, 4; **M. D. Marra**, Boston Imaging Corea Lab, 4; **Y.**

Zhang, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **A. Guermazi**, Boston Imaging Core Lab, 4, Facet Solutions, Genzyme, Stryker, Merck Serono, GE, 5.

ACR Concurrent Abstract Session

Metabolic and Crystal Arthropathies I: Concurrent Session on Pathogenesis of Gout, a Potential Novel Therapy, and Validity of Dual Energy Computed Tomography

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1617

Disclosure: T. Bongartz, None; **K. N. Glazebrook**, None; **S. J. Kavros**, None; **C. J. Michet**, None; **S. P. Merry**, None; **N. S. Murthy**, None; **B. M. Akkara Veetil**, None; **J. M. Davis III**, None; **T. G. Mason II**, None; **K. J. Warrington**, None; **N. J. Manek**, None; **T. A. Kermani**, None; **D. D. Hoganson**, None; **A. K. Bacani**, None; **H. Wang**, None; **C. H. McCollough**, Siemens, 2.

1618

Disclosure: N. Dalbeth, None; **O. Aati**, None; **A. Gao**, None; **M. House**, None; **Q. Liu**, None; **A. Horne**, None; **A. Doyle**, None; **F. M. McQueen**, None.

1619

Disclosure: M. A. Amin, Takeda Pharmaceuticals, 2; **Q. Shu**, Takeda Pharmaceuticals, 2; **J. W. Vargo**, Takeda Pharmaceuticals, 2; **J. H. Ruth**, Takeda Pharmaceuticals, 2; **T. Isozaki**, Takeda Pharmaceuticals, 2; **S. Lee**, Takeda Pharmaceuticals, 2; **A. E. Koch**, Takeda Pharmaceuticals, 2.

1620

Disclosure: S. J. Lee, None; **H. M. Jin**, None; **Y. N. Cho**, None; **S. C. Park**, None; **D. J. Park**, None; **T. J. Kim**, None; **S. S. Lee**, None; **S. J. Kee**, None; **Y. W. Park**, None.

1621

Disclosure: A. Bree, Pfizer Inc, 3; **K. Phillips**, Pfizer Inc, 3; **M. Benson**, Pfizer Inc, 3; **K. Dower**, Pfizer Inc, 3; **M. Shen**, Pfizer Inc, 3; **K. Lee**, Pfizer Inc, 3; **V. Rao**, Pfizer Inc, 3; **C. L. Nickerson-Nutter**, Pfizer Inc, 3; **M. Ruzek**, Pfizer Inc, 3.

1622

Disclosure: T. R. Merriman, None; **N. Dalbeth**, None; **L. K. Stamp**, None; **M. E. Merriman**, None; **R. Topless**, None; **P. J. Gow**, None; **A. Harrison**, None; **J. Highton**, None; **P. B. B. Jones**, None; **C. Glue**, None.

ACR Concurrent Abstract Session

Osteoarthritis - Clinical Aspects II

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1623

Disclosure: I. K. Haugen, None; **P. Bøyesen**, None; **B. Slatkowsky-Christensen**, None; **S. Sesseng**, None; **D. van der Heijde**, None; **T. K. Kvien**, None.

1624

Disclosure: K. D. Gross, None; **J. Niu**, None; **J. J. Stefanik**, None; **A. Guermazi**, Boston Imaging Core Lab, 4, Facet Solutions, Genzyme, Stryker, Merck Serono, GE, 5; **F. Roemer**, Boston Imaging Core Lab, 4; **L. Sharma**, None; **M. C. Nevitt**, None; **N. Segal**, None; **C. E. Lewis**, None; **D. T. Felson**, None.

1625

Disclosure: J. Hall, None; **L. Laslett**, None; **J. M. Pelletier**, ArthroLab Inc. and ArthroVision Inc., 1, ArthroLab Inc. and ArthroVision Inc., 5; **J. P. Pelletier**, ArthroLab Inc., 1, ArthroLab Inc., 5; **F. Abram**, ArthroVision Inc., 3; **C. H. Ding**, None; **F. Cicuttini**, None; **G. Jones**, None.

1626

Disclosure: C. R. Chu, None; **A. A. Williams**, None; **Y. Qian**, None.

1627

Disclosure: T. Neogi, None; **J. Niu**, None; **L. Arendt-Nielsen**, None; **J. Scholz**, None; **L. Frey-Law**, None; **C. Woolf**, None; **Y. Zhang**, None; **L. Bradley**, None; **M. C. Nevitt**, None; **D. T. Felson**, None.

1628

Disclosure: T. Neogi, None; **J. Niu**, None; **D. T. Felson**, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **M. French**, None; **G. A. Hawker**, None.

ACR Concurrent Abstract Session

Osteoporosis and Metabolic Bone Disease: Clinical Aspects and Pathogenesis

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1629

Disclosure: T. Furuya, None; **E. Inoue**, None; **T. Hosoi**, None; **A. Taniguchi**, None; **S. Momohara**, None; **H. Yamanaka**, Abbott Japan Co. Ltd., 5, Pfizer Japan Inc., 5, Teijin Pharma Limited, 5, Chugai Pharmaceutical Co. Ltd., 5, Daiichi Sankyo Co. Ltd., 5, Eisai Co. Ltd., 5, Takeda Pharmaceutical Company Limited, 5, Mitsubishi Tanabe Pharma Corporation, 5.

1630

Disclosure: J. P. David, None; **M. Edgar**, None; **D. L. Boyle**, None; **G. Schett**, None; **G. S. Firestein**, None.

1631

Disclosure: C. Libanati, Amgen Inc., 3, Amgen Inc., 1; **S. K. Boyd**, Amgen, Servier, 2, Merck Pharmaceuticals, 5; **K. K. Nishiyama**, None; **R. M. Zebaze**, Amgen, 2, Servier, 5; **D. A. Hanley**, Amgen, Merck, Pfizer, NPS Pharmaceuticals, Eli

Lilly, Novartis, Warner-Chilcott, 2, Amgen, Merck, Eli Lilly, Novartis, Warner-Chilcott, 5; **J. R. Zanchetta**, Amgen, Eli Lilly, Merck, Pfizer, 2, Amgen, Eli Lilly, GlaxoSmithKline, Merck, Pfizer, Servier, 5; **T. Thomas**, Amgen, Chugai, Lilly, Merck, Pfizer, Roche, Servier, Warner Chilcott, 2, Amgen, Daiichi-Sankyo, BristolMyersSquibb, GlaxoSmithKline, Lilly, Merck, Novartis, Roche, Servier, Warner Chilcott, 5; **S. Boutroy**, None; **C. E. Bogado**, GlaxoSmithKline, 5; **M. Austin**, Amgen Inc., 1, Amgen Inc., 3; **E. Seeman**, MSD, Amgen, Servier, Novartis, Warner Chilcott, 5, MSD, Amgen, Servier, Novartis, Warner Chilcott, 8.

1632

Disclosure: S. Amin, Merck Pharmaceuticals, 5; **S. E. Gabriel**, None; **S. J. Achenbach**, None; **E. J. Atkinson**, None; **L. J. Melton III**, None.

1633

Disclosure: B. A. Lang, None; **C. Rodd**, None; **D. A. Cabral**, None; **P. B. Dent**, None; **J. E. Ellsworth**, None; **A. M. Huber**, None; **K. M. Houghton**, None; **R. Jurencak**, None; **M. Larché**, None; **C. M. LeBlanc**, None; **B. Lentle**, None; **M. Matzinger**, None; **P. M. Miettunen**, None; **K. Oen**, None; **J. Roth**, None; **C. Saint-Cyr**, None; **R. Scuccimarri**, None; **N. Shenouda**, None; **L. M. Ward**, None.

1634

Disclosure: J. T. Schousboe, Merck Pharmaceuticals, 5.

ACR Concurrent Abstract Session

Rheumatoid Arthritis - Animal Models II

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1635

Disclosure: Q. Liang, None; **R. Wood**, None; **B. Boyce**, None; **E. M. Schwarz**, None; **L. Xing**, None.

1636

Disclosure: M. J. Park, None; **K. S. Park**, None; **M. L. Cho**, None; **J. M. Kim**, None; **S. H. Lee**, None; **H. Y. Kim**, None.

1637

Disclosure: M. T. Shekhani, None; **T. S. Forde**, None; **A. S. Cuttler**, None; **V. Lindner**, None; **V. A. Adarichev**, None.

1638

Disclosure: S. Min, None; **M. Yan**, None; **Y. Du**, None; **C. Arriens**, None; **T. Wu**, None; **C. Mohan**, None.

1639

Disclosure: R. Stevens, None; **R. Adachi**, None; **P. A. Nigrovic**, None; **M. J. Hamilton**, None; **S. Krilis**, None.

1640

Disclosure: M. Armaka, None; **M. Pasparakis**, None; **G. Mosialos**, None; **G. Kollias**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Existing Biologics

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1641

Disclosure: J. E. Gottenberg, None; **P. Ravaud**, None; **T. Bardin**, Savient Pharmaceutiicals, Inc., 5; **P. Cacoub**, None; **A. G. Cantagrel**, None; **B. G. Combe**, None; **M. Dougados**, Abbott Immunology Pharmaceuticals, 5, Pfizer Inc, 5, sanofi aventis, 2, Abbott Immunology Pharmaceuticals, 2, Pfizer Inc, 2; **R. M. Flipo**, None; **B. Godeau**, None; **L. Guillevin**, None; **X. X. Le Loet**, None; **E. Hachulla**, None; **T. Schaeverbeke**, Pfizer, Roche, Abbott, 5; **J. Sibilia**, None; **I. Pane**, None; **A. Abbe**, None; **G. Baron**, None; **X. Mariette**, Pfizer Inc, 2, Roche Pharmaceuticals, 2, GlaxoSmithKline, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, UCB, 5.

1642

Disclosure: V. Rao, Genentech, Inc., 3; **A. Pavlov**, Everest, 3; **M. Klearman**, Genentech, Inc., 3; **D. Musselman**, F. Hoffmann-La Roche Ltd, 3; **J. T. Giles**, Fa Hoffmann-La Roche Ltd, 5, Genentech, Inc., 5, IDEC, 5; **J. M. Bathon**, None; **N. Sattar**, F. Hoffmann-La Roche Ltd, 5, F. Hoffmann-La Roche Ltd, 8; **J. S. Lee**, F. Hoffmann-La Roche, 3.

1643

Disclosure: E. M. Vital, Roche Pharmaceuticals, 8; **S. Das**, None; **S. Dass**, Roche Pharmaceuticals, 8; **M. H. Buch**, Abbott Immunology Pharmaceuticals, 5, UCB, 8, Roche Pharmaceuticals, 5, Pfizer Inc, 8; **F. Ponchel**, None; **A. Rawstron**, None; **P. Emery**, None.

1644

Disclosure: J. Verheyen, Roche Pharmaceuticals, 8; **E. Feist**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 8, Roche Pharmaceuticals, 9; **K. Maizus**, None; **Z. Tolman**, None; **E. Knops**, None; **T. Waterboer**, None; **G. R. Burmester**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 8, Roche Pharmaceuticals, 9; **M. Pawlita**, None; **H. Pfister**, None; **A. Rubbert**, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 8, Roche Pharmaceuticals, 9.

1645

Disclosure: K. Chatzidionysiou, Roche Pharmaceuticals, 5; **E. Lie**, Roche Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 7, BristolMyersSquibb, 8; **E. L. Nasonov**, Roche Pharmaceuticals, 5; **G. Lukina**, Roche Pharmaceuticals, 5; **M. L. Hetland**, Roche Diagnostics, 2; **U. Tarp**, Roche Pharmaceuticals, 5; **I. Ancuta**, Roche Pharmaceuticals, 5; **K. Pavelka**, Roche Pharmaceuticals, 5; **D. C. Nordström**, Roche Pharmaceuticals, 5; **C. Gabay**, Roche Pharmaceuticals, 5; **H. Canhao**, None; **M. Tomsic**, Roche Pharmaceuticals, 5; **P. L. van Riel**, Roche Pharmaceuticals, 5; **J. J. Gomez-Reino**, Roche Pharmaceuticals, 5; **T. K. Kvien**, Abbott Immunology Pharmaceuticals, 5, BristolMyersSquibb, 5, Merck ering Plough, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, UCB, 5,

Wyeth Pharmaceuticals, 5; **R. F. van Vollenhoven**, Roche Pharmaceuticals, 5.

1646

Disclosure: K. Chatzidionysiou, Roche Pharmaceuticals, 5; **E. Lie**, Roche Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 7, BristolMyersSquibb, 8; **E. L. Nasonov**, Roche Pharmaceuticals, 5; **G. Lukina**, Roche Pharmaceuticals, 5; **M. L. Hetland**, Roche Pharmaceuticals, 5; **U. Tarp**, Roche Pharmaceuticals, 5; **I. Ancuta**, Roche Pharmaceuticals, 5; **K. Pavelka**, Roche Pharmaceuticals, 5; **D. C. Nordström**, Roche Pharmaceuticals, 5; **C. Gabay**, Roche Pharmaceuticals, 5; **H. Canhao**, None; **M. Tomsic**, Roche Pharmaceuticals, 5; **P. L. Van Riel**, Roche Pharmaceuticals, 5; **J. J. Gomez-Reino**, Roche Pharmaceuticals, 5; **T. K. Kvien**, Roche Pharmaceuticals, 5; **R. F. van Vollenhoven**, Roche Pharmaceuticals, 5.

ACR Concurrent Abstract Session

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment II

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1647

Disclosure: C. G. S. Saad, None, 2; **A. C. M. Ribeiro**, None; **J. C. B. Moraes**, None; **L. Takayama**, None; **C. Goncalves**, None; **R. M. Oliveira**, None; **C. A. A. Silva**, None, 2; **E. Bonfa**, None, 2; **R. M. R. Pereira**, None, 2.

1648

Disclosure: K. J. Kim, None; **J. Y. Kim**, None; **S. J. Park**, None; **H. Yoon**, None; **C. H. Yoon**, None; **J. J. Choi**, None; **W. U. Kim**, None; **C. S. Cho**, None.

1649

Disclosure: W. P. Maksymowych, None; **N. Haroon**, None; **N. Morency**, None; **R. J. Cook**, None; **K. A. Lee**, None; **S. Wichuk**, None; **P. Rahman**, None; **D. D. Gladman**, None; **R. D. Inman**, Sanofi-Aventis Pharmaceutical, Merck, Abbott, Amgen-Wyeth,, 5.

1650

Disclosure: P. Machado, None; **H. Y. Chung**, None; **D. van der Heijde**, None; **M. A. D'Agostino**, None; **M. Dougados**, None.

1651

Disclosure: A. Haddad, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **D. D. Gladman**, None.

1652

Disclosure: E. Pathan, None; **S. M. Abraham**, None; **L. Van-Rossen**, None; **R. Withrington**, None; **A. Keat**, None; **P. J. Charles**, None; **E. Paterson**, None; **M. Chowdhury**, None; **L. Hastings**, None; **A. Fox**, None; **C. McClinton**, None; **P. Taylor**, Celgene, 2.

ACR Concurrent Abstract Session

Systemic Lupus Erythematosus - Clinical Aspects: Renal

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1653

Disclosure: A. M. Orbai, None; **L. S. Magder**, None; **M. Petri**, None.

1654

Disclosure: B. Abujam, None; **S. Swamy**, None; **A. Aggarwal**, None.

1655

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1656

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ACR Concurrent Abstract Session

Systemic Lupus Erythematosus - Human Etiology and Pathogenesis I

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1659

Disclosure: D. A. Abdulahad, None; **J. Westra**, None; **G. Horst**, None; **P. C. Limburg**, None; **C. G. Kallenberg**, None; **M. Bijl**, None.

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ARHP Concurrent Abstract Session

ARHP Education and Community Programs

Monday, November 7, 2011, 2:30 PM - 4:00 PM

1665

Disclosure: T. M. Kristiansen, None; **J. Primdahl**, None; **R. Antoft**, None; **K. Hørslev-Petersen**, None.

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ACR Concurrent Abstract Session

Cytokines, Mediators, and Gene Regulation I

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1671

Disclosure: M. Trenkmann, None; **M. Brock**, None; **R. E. Gay**, None; **C. Kolling**, None; **R. Speich**, None; **B. A. Michel**, None; **S. Gay**, None; **L. C. Huber**, None.

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ACR Concurrent Abstract Session

Genetics, Genomics, and Proteomics

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1677

Disclosure: S. Eyre, None; **J. Bowes**, None; **A. Barton**, None; **S. Raychaudhuri**, None; **C. Amos**, None; **D. Diogo**, None; **A. T. Lee**, None; **L. Klareskog**, None; **L. Padyukov**, None; **E. A. Stahl**, None; **P. K. Gregersen**, None; **R. M. Plenge**, None; **J. Worthington**, None.

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ACR Concurrent Abstract Session

Pediatric Rheumatology - Pathogenesis

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1683

Disclosure: S. W. Canna, None; **M. E. Paessler**, None; **P. Kreiger**, None; **K. Slade**, None; **S. Rao**, None; **E. M. Behrens**, None.

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ACR Concurrent Abstract Session

Rheumatoid Arthritis Clinical Aspects: Clinical Features

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1689

Disclosure: M. Witt, None; **F. Mueller**, None; **A. Nigg**, None; **C. Reindl**, None; **N. Stein**, None; **S. Mayer**, None; **C. Gebhardt**, None; **A. Hammitzsch**, None; **C. Dechant**, None; **H. Schulze-Koops**, Abbott Laboratories, 5; **M. Grunke**, None.

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ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Existing Disease-modifying Antirheumatic Drugs: Tight Control, Induction and Drug Withdrawal Trials

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1695

Disclosure: M. F. Bakker, None; **J. W. G. Jacobs**, None; **P. M. J. Welsing**, None; **S. M. M. Verstappen**, None; **J.**

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ACR Concurrent Abstract Session

Spondylarthropathies and Psoriatic Arthritis – Pathogenesis, Etiology

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1701

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ACR Concurrent Abstract Session

Systemic Lupus Erythematosus - Clinical Aspects: General

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1707

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ACR Concurrent Abstract Session

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics II

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1713

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ACR/ARHP Combined Abstract Session

ACR/ARHP Combined Rehabilitation Abstract Session

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1719

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Disclosure: H. P. French, None; **T. Cusack**, None; **A. Brennan**, None; **A. Caffrey**, None; **V. Cuddy**, None; **M. Fitzpatrick**, None; **O. M. FitzGerald**, None; **C. Gilsenan**, None; **D. Kane**, None; **P. G. O'Connell**, None; **B. White**, None; **G. M. McCarthy**, None.

1723

Disclosure: D. M. L. Prado, None; **R. Miossi**, None; **T. Dassouki**, None; **L. A. Perandini**, None; **F. R. Lima**, None; **B. Gualano**, None; **A. L. S. Pinto**, None; **E. Bonfa**, None; **H. Roschel**, None.

1724

Disclosure: D. K. White, None; **D. T. Felson**, None; **Y. Zhang**, None; **K. D. Gross**, None; **J. Niu**, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **T. Neogi**, None.

ACR REF Special Session

ACR REF Marshall J. Schiff, MD, Memorial Lectureship: Multicenter Orthopaedic Outcomes Network - A Prospective Longitudinal Cohort of Anterior Cruciate Ligament Reconstruction Outcomes

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1725

Disclosure: G. Valverde-Franco, None; **M. Kapoor**, None; **D. Hum**, None; **K. Matsuo**, None; **B. Lussier**, None; **J. P. Pelletier**, None; **J. M. Pelletier**, None.

1726

Disclosure: D. F. G. Remst, None; **E. N. Blaney Davidson**, None; **E. L. Vitters**, None; **R. A. Bank**, None; **W. B. van den Berg**, None; **P. M. van der Kraan**, None.

ARHP Concurrent Abstract Session

ARHP Health Services Research

Monday, November 7, 2011, 4:30 PM - 6:00 PM

1727

Disclosure: A. M. Davis, None; **C. Cott**, None; **L. Li**, None; **M. Landry**, None; **A. Jones**, None; **R. Wong**, None; **C. Frank**, None; **L. Bergeron**, None; **R. Birtwhistle**, None; **E. M. Badley**, None.

1728

Disclosure: L. Wright, None; **J. O'Toole**, None.

1729

Disclosure: C. Kennedy, None; **K. Warmington**, None; **L. J. Soever**, None; **L. A. Passalent**, None; **S. C. Lineker**, The Arthritis Society, 3; **K. Lundon**, None; **R. Shupak**, None; **R. Schneider**, None.

1730

Disclosure: K. Warmington, None; **C. Kennedy**, None; **S. C. Lineker**, The Arthritis Society, 3; **L. J. Soever**, None; **L. A. Passalent**, None; **K. Lundon**, None; **R. Shupak**, None; **R. Schneider**, None.

1731

Disclosure: K. Lundon, None; **C. Kennedy**, None; **K. Warmington**, None; **L. Rozmovits**, None; **L. J. Soever**, None; **L. A. Passalent**, None; **S. C. Lineker**, The Arthritis Society, 3; **R. Shupak**, None; **R. Schneider**, Hoffmann-La Roche, 5; **L. Sinclair**, None.

1732

Disclosure: L. A. Passalent, None; **C. Kennedy**, None; **L. J. Soever**, None; **K. Warmington**, None; **S. C. Lineker**, Part time employee of The Arthritis Society whose therapists participated in this study., 3; **K. Lundon**, None; **R. Shupak**, None; **R. Schneider**, None.

ACR/ARHP Poster Session C

B-cell Biology and Targets in Autoimmune Disease

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1733

Disclosure: K. Muhammad, None; **A. Palanichamy**, None; **P. Roll**, None; **S. Kleinert**, None; **T. Dörner**, None; **H. P. Tony**, None.

1734

Disclosure: G. Arumugakani, None; **A. Rawstron**, None; **R. Tooze**, None; **P. Emery**, UCB Inc, 2, UCB Inc, 5; **D. McGonagle**, None.

1735

Disclosure: G. Cambridge, None; **M. J. Leandro**, None; **J. C. Edwards**, None; **H. M. Parsons**, None; **M. C. Dickson**, None; **H. Perry**, None.

1736

Disclosure: H. P. Tony, None; **P. Roll**, None; **H. Mei**, None; **L. Gnuegge**, Roche Pharma AG, 3; **M. Kobialko**, Roche Pharma AG, 3; **T. Dörner**, None.

1737

Disclosure: E. Becerra-Fernandez, None; **I. de la Torre**, None; **L. Valor**, None; **M. J. Leandro**, Roche, GlaxoSmithKline, 5; **G. Cambridge**, None.

1738

Disclosure: M. Deschamp, None; **B. Gaugler**, None; **P. Saas**, None; **C. Ferrand**, None; **E. Toussirot**, None.

1739

Disclosure: A. Palanichamy, None; **J. Roger**, None; **W. Wang**, None; **J. Barnard**, None; **J. Biear**, None; **C. Wei**, None; **I. Sanz**, Bristol-Myers Squibb, 5, GlaxoSmithKline, 5, Medimmune, 5, Pfizer Inc, 5; **J. H. Anolik**, MedImmune, 5, UCB, 5.

1740

Disclosure: A. Khosroshahi, None; **M. Carruthers**, None; **V. Deshpande**, None; **S. Unizony**, None; **D. B. Bloch**, None; **J. H. Stone**, Genentech and Biogen IDEC Inc., 2, Genentech and Biogen IDEC Inc., 5.

1741

Disclosure: K. Smith, None; **J. Muther**, None; **A. Duke**, None; **E. McKee**, None; **P. C. Wilson**, None; **J. A. James**, None.

1742

Disclosure: N. Sieger, UCB, 2; **K. Reiter**, UCB, 2; **H. E. Mei**, UCB, 2; **T. Shock**, UCB, 3; **C. Daridon**, UCB, 2; **T. Dörner**, UCB, Roche/Chugai, 2, UCB, Roche/Chugai, MSD, 5, Roche/Chugai, 8.

1743

Disclosure: D. Saadoun, None; **L. Menard**, None; **I. Isnardi**, None; **Y. S. Ng**, None; **G. Meyers**, None; **C. Abraham**, None; **R. Moyaghedi**, None; **J. Buckner**, None; **P. K. Gregersen**, None; **E. Meffre**, None.

1744

Disclosure: C. Wei, None; **P. M. Barr**, None; **J. Schaefer-Cutillo**, None; **J. Jung**, None; **J. Roger**, None; **J. L. Kelly**, None; **A. Rosenberg**, None; **J. W. Friedberg**, None; **I. Sanz**, None.

1745

Disclosure: H. Bang, Orgentec Diagnostics, 3, 9; **K. Egerer**, None; **A. Krämer**, Orgentec Diagnostics, 3; **E. Feist**, Orgentec, 5; **G. R. Burmester**, Orgentec, 2.

1746

Disclosure: A. L. Fedele, None; **B. Tolusso**, None; **S. L. Bosello**, None; **S. Canestri**, None; **E. Gremese**, None; **G. Ferraccioli**, None.

1747

Disclosure: J. J. B. C. Van Beers, None; **A. M. C. Segbers-Lokate**, None; **W. T. M. Vree Egberts**, None; **R. B. M. Schasfoort**, CSO IBIS Technologies BV, 3; **G. J. M. Pruijn**, None.

1748

Disclosure: X. Zhao, Crescendo Bioscience, Inc., 3; **P. S. Eastman**, Crescendo Bioscience, 3; **F. Qureshi**, Crescendo Bioscience, Inc., 3; **W. C. Manning**, Crescendo Bioscience, Inc., 3; **W. Robinson**, Patents, 7; **L. K. Hesterberg**, Crescendo Bioscience, Inc., 3.

1749

Disclosure: B. Marklein, None; **Z. Konthur**, None; **G. R. Burmester**, None; **K. Skriner**, None.

1750

Disclosure: P. Roll, None; **K. Muhammad**, None; **M. Schumann**, None; **S. Kleinert**, None; **H. P. Tony**, None.

1751

Disclosure: R. Lindop, None; **G. Arentz**, None; **T. K. Chataway**, None; **L. A. Thurgood**, None; **M. W. Jackson**, None; **T. P. Gordon**, None.

1752

Disclosure: R. Pollard, None; **W. H. Abdulahad**, None; **M. G. Huitema**, None; **A. Visser**, None; **J. Meijer**, None; **H. Burgerhof**, None; **F. Spijkervet**, None; **C. G. Kallenberg**, None; **A. Vissink**, None; **F. Kroese**, None; **H. Bootsma**, None.

1753

Disclosure: B. Terrier, None; **F. Joly**, None; **P. Benech**, None; **M. Rosenzwajg**, None; **W. Carpentier**, None; **P. Ghillani-Dalbin**, None; **D. Klatzmann**, None; **P. Cacoub**, None; **D. Saadoun**, None.

1754

Disclosure: G. Pongratz, None; **J. Anthofer**, None; **M. Melzer**, None; **R. H. Straub**, None.

1755

Disclosure: K. Kis-Toth, None; **M. Radacs**, None; **T. Kobezda**, None; **W. van Eden**, None; **K. Mikecz**, None; **T. T. Glant**, None.

1756

Disclosure: M. W. Klinker, None; **B. Alzua**, None; **T. Reed**, None; **C. Shaw**, None; **D. A. Fox**, None; **S. K. Lundy**, None.

1757

Disclosure: E. Evans, Avila Therapeutics, 3; **R. Tester**, Avila Therapeutics, 3; **S. Aslanian**, Avila Therapeutics, 3; **P. Chaturvedi**, Avila Therapeutics, 3; **R. Karp**, Avila Therapeutics, 3; **M. Labenski**, Avila Therapeutics, 3; **H. Mazdiyasni**, Avila Therapeutics, 3; **M. Nacht**, Avila Therapeutics, 3; **M. Sheets**, Avila Therapeutics, 3; **K. Stiede**, AVila Therapeutics, 3; **S. Witowski**, Avila Therapeutics, 3; **H. Lounsbury**, Avila Therapeutics, 3; **R. Petter**, Avila Therapeutics, 3; **J. Singh**, Avila Therapeutics, 3; **W. Westlin**, Avila Therapeutics, 3.

1758

Disclosure: M. Benson, Pfizer, Inc, 3; **V. A. Rodriguez**, Pfizer Inc, 3; **T. Andreyeva**, Pfizer Inc, 3; **S. Keegan**, Pfizer Inc, 3; **J. R. Springer**, Pfizer Inc, 3; **M. E. Schnute**, Pfizer Inc, 3; **K. Dunussi-Joannopoulos**, Pfizer Inc, 3; **C. L. Nickerson-Nutter**, Pfizer Inc, 3; **A. L. Rankin**, Pfizer Inc, 3; **M. Ruzek**, Pfizer Inc, 3; **J. Douhan III**, Pfizer, 3.

1759

Disclosure: K. Yanaba, None; **S. Sato**, None.

1760

Disclosure: S. Ashaye, None; **K. Hamel**, None; **Y. Cao**, None; **Y. Wang**, None; **T. T. Glant**, None; **A. Finnegan**, None.

1761

Disclosure: C. M. Starke, None; **V. Urbonaviciute**, None; **S. Frey**, None; **G. Schett**, None; **R. E. Voll**, None.

1762

Disclosure: A. Wiedeman, None; **K. B. Elkon**, None.

1763

Disclosure: A. Silva-Sanchez, None; **C. Liu**, None; **P. Kapoor**, None; **Y. Zhuang**, None; **T. R. Schoeb**, None; **H. W. Schroeder Jr.**, None.

1764

Disclosure: E. Marasco, None; **N. Manjarrez Orduño**, None; **P. K. Gregersen**, None; **B. Diamond**, None.

1765

Disclosure: T. Matsutani, None; **M. Murakami**, None; **H. M. Lee**, None; **H. Sugino**, None; **N. Nishimoto**, None.

1766

Disclosure: S. I. Ota, None; **H. Niiro**, None; **N. Ueki**, None; **H. Tsuzuki**, None; **S. Jabbarzadeh-Tabrizi**, None; **Y. Inoue**, None; **Y. Arinobu**, None; **K. Akashi**, None.

1767

Disclosure: J. Jung, None; **J. Biear**, None; **Y. Huang**, None; **B. Neary**, None; **E. Marin**, None; **J. Hossler**, None; **E. Palmer**, None; **S. Smith**, None; **E. Akhter**, None; **T. Sanford**, None; **J. Xu**, None; **M. Petri**, None; **A. Rosenberg**, None; **J. H. Anolik**, None; **C. Wei**, None; **I. Sanz**, Bristol-Myers Squibb, 5, GlaxoSmithKline, 5, Medimmune, 5, Pfizer Inc, 5.

1768

Disclosure: E. S. Sobel, None; **E. Butfiloski**, None; **J. Hunt**, None; **M. Segal**, None; **L. Morel**, None; **W. H. Reeves**, None; **M. Satoh**, None.

1769

Disclosure: S. Eickenberg, None; **E. Jung**, None; **E. Mickholz**, None; **A. M. Jacobi**, None.

ACR/ARHP Poster Session C

Biology and Pathology of Bone and Joint: Inflammation and Osteoarthritis

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1770

Disclosure: R. Kamath, Abbott, 1.

1771

Disclosure: S. Hirohata, None; **T. Yanagida**, None; **T. Tomita**, None; **H. Yoshikawa**, None.

1772

Disclosure: M. J. Del Rey, None; **A. Usategui**, None; **E. Izquierdo**, None; **V. Miranda**, None; **J. D. Cañete**, None; **F. J. Blanco Sr.**, None; **G. Criado**, None; **J. L. Pablos**, None.

1773

Disclosure: R. E. Miller, None; **P. Tran**, None; **N. Ghoreishi-Haack**, None; **R. Das**, None; **A. M. Malfait**, Pfizer Inc, 1, Pfizer Inc, 5.

1774

Disclosure: B. P. Harvey, Abbott Laboratories, 3, Abbott Laboratories, 1; **F. A. Syed**, Abbott Laboratories, 3, Abbott Laboratories, 1; **Z. Kaymakcalan**, Abbott Laboratories, 3, Abbott Laboratories, 1.

1775

Disclosure: Z. Jenei-Lanzl, None; **P. Angele**, None; **R. H. Straub**, None.

1776

Disclosure: A. Koskinen, None; **S. Juslin**, None; **K. Vuolteenaho**, None; **R. Nieminen**, None; **T. Moilanen**, None; **E. Moilanen**, None.

1777

Disclosure: N. Magarinos, None; **K. J. Bryant**, None; **A. J. Fosang**, None; **R. L. Stevens**, None; **H. P. McNeil**, None.

1778

Disclosure: Y. Sun, None; **D. Mauerhan**, None; **A. Franklin**, None; **A. Sun**, None; **N. Zinchenko**, None; **H. Norton**, None; **E. Hanley Jr.**, None; **H. Gruber**, None.

1779

Disclosure: M. Seitz, None; **D. Aeberli**, None; **R. K. Kamgang**, None; **W. Hofstetter**, None; **D. Balani**, None; **P. M. Villiger**, None.

1780

Disclosure: F. Oprenyeszk, None; **C. Sanchez**, None; **J. E. Dubuc**, None; **V. Maquet**, None; **Y. Henrotin**, None.

1781

Disclosure: A. Mediero, None; **S. Frenkel**, None; **T. Wilder**, None; **B. N. Cronstein**, Bristol-Myers Squibb; Novartis; Canfite Piophamaceuticals; Cypress Laboratories; Regeneron; Endocyte; Protalex; Allos Inc; Gismo Therapeutics; CanFite Biopharmaceuticals; NIH; Vilcek Foundation; OSI Pharmaceuticals; URL Pharmaceuticals, Inc; Gilead Pharmaceuticals; Eli Lilly & Co; UCB; Pfizer; Merck; Amgen; Tap Pharmaceuticals; Prometheus Laboratories; Endocyte; Savient.

1782

Disclosure: M. I. Guillen, None; **V. Clerigues**, None; **M. A. Castejon**, None; **F. Gomar**, None; **M. J. Alcaraz**, None.

1783

Disclosure: A. P. M. van Caam, None; **E. N. Blaney Davidson**, None; **E. L. Vitters**, None; **W. B. van den Berg**, None; **P. M. van der Kraan**, None.

1784

Disclosure: M. C. ter Huurne, None; **P. L. E. M. van Lent**, None; **A. B. Blom**, None; **R. Blattes**, None; **Y. Jeanson**, None; **L. Casteilla**, None; **C. Jorgensen**, None; **W. B. van den Berg**, None.

1785

Disclosure: O. J. Arntz, None; **E. A. Vermeij**, None; **E. N. Blaney Davidson**, None; **S. Abdollahi-Roodsaz**, None; **M. B. Bennink**, None; **P. M. van der Kraan**, None; **W. B. van den Berg**, None; **F. Van De Loo**, None.

1786

Disclosure: K. Vuolteenaho, None; **A. Koskinen**, None; **S. Juslin**, None; **R. Nieminen**, None; **T. Moilanen**, None; **E. Moilanen**, None.

1787

Disclosure: W. He, None; **B. N. Cronstein**, Bristol-Myers Squibb; Novartis; Canfite Piophamaceuticals; Cypress Laboratories; Regeneron; Endocyte; Protalex; Allos Inc; Gismo Therapeutics; CanFite Biopharmaceuticals; NIH; Vilcek Foundation; OSI Pharmaceuticals; URL Pharmaceuticals, Inc; Gilead Pharmaceuticals; Eli Lilly & Co; UCB; Pfizer; Merck; Amgen; Tap Pharmaceuticals; Prometheus Laboratories; Endocyte; Savient.

1788

Disclosure: T. Braun, None; **J. Lepper**, None; **G. Ruiz Heiland**, None; **G. Schett**, None; **J. Zwerina**, None.

1789

Disclosure: J. M. Whitbred, None; **R. M. Lowe**, None; **D. P. Lennon**, None; **J. Molter**, None; **C. A. Flask**, None; **T. L. Bonfield**, None; **A. I. Caplan**, Case Western Reserve University, 7; **N. G. Singer**, None.

1790

Disclosure: D. Guerit, None; **D. Philipot**, None; **P. Chuchana**, None; **J. Brondello**, None; **C. Jorgensen**, None; **D. Noel**, None.

1791

Disclosure: F. Petursson, None; **X. Zhao**, None; **R. Terkeltaub**, None; **R. L. Bryan**, None.

1792

Disclosure: A. M. Rodrigues, None; **J. Caetano-Lopes**, None; **A. Lopes**, None; **A. C. Vale**, None; **I. Aleixo**, None; **I. P. Perpétuo**, None; **A. S. Pena**, None; **A. Faustino**, None; **A. Sepriano**, None; **J. Polido-Pereira**, None; **E. Vieira-Sousa**, None; **B. Vidal**, None; **J. Romeu**, None; **P. Amaral**, None; **L. G. Rosa**, None; **J. A. Pereira da Silva**, None; **J. Monteiro**, None; **M. F. Vaz**, None; **J. E. Fonseca**, None; **H. Canhão**, None.

1793

Disclosure: R. Schelbergen, None; **A. B. Blom**, None; **M. H. J. van den Bosch**, None; **A. Sloetjes**, None; **T. Vogl**, None; **J. Roth**, None; **W. B. van den Berg**, None; **P. L. E. M. van Lent**, None.

1794

Disclosure: M. Attur, None; **G. Palmer**, None; **Y. Tachida**, Daiichi Sankyo, 3; **S. Kumakura**, Daiichi Sankyo, 3; **K. Shimada**, Daiicho Sankyo, 3; **S. B. Abramson**, None.

1795

Disclosure: O. H. Gabay Engel, None; **C. Sanchez**, None; **M. dvir-Ginzberg**, None; **V. Gagarina**, None; **E. J. Lee**, None; **K. J. Zaal**, None; **M. McBurney**, None; **D. J. Hall**, None.

1796

Disclosure: R. F. Loeser, None; **E. A. Erickson**, None; **D. A. Long**, None.

1797

Disclosure: C. Wunrau, None; **M. Heitzmann**, None; **C. Wehmeyer**, None; **G. Kollias**, None; **T. Pap**, None; **B. Dankbar**, None.

1798

Disclosure: K. A. Hasty, None; **H. Cho**, None; **E. Pinkhassik**, None; **J. M. Stuart**, None.

1799

Disclosure: M. Vis, None; **K. Britsemmer**, None; **A. C. Heijboer**, None; **N. Bravenboer**, None; **D. van Schaardenburg**, None; **W. F. Lems**, None.

1800

Disclosure: J. Kushi, None; **C. Gohr**, None; **B. Jubeck**, None; **P. A. Simkin**, Takeda, 2, Ardea, 5; **A. K. Rosenthal**, None.

1801

Disclosure: C. Nguyen, None; **F. Lioté**, None; **D. Hannouche**, None; **V. Bousson**, None; **F. Velard**, None; **M. Daudon**, None; **D. Bazin**, None; **H. K. Ea**, None.

1802

Disclosure: K. Braem, None; **F. P. Luyten**, None; **R. Lories**, None.

1803

Disclosure: V. Martelli, None; **J. A. Di Battista**, None; **P. Panopalis**, None; **J. Antoniou**, None; **M. Sebag**, None; **B. Gilfix**, None; **H. A. Ménard**, None.

1804

Disclosure: C. Sekine, None; **A. Koyanagi**, None; **N. Koyama**, None; **K. Hozumi**, None; **S. Chiba**, None; **H. Yagita**, None.

ACR/ARHP Poster Session C

Cytokines, Mediators, and Gene Regulation

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1805

Disclosure: S. Capellino, None; **Z. Jenei-Lanzl**, None; **R. H. Straub**, None.

1806

Disclosure: J. D. Canete, None; **R. Celis**, None; **J. Ramirez**, None; **S. Marsal**, None; **G. Avila**, None; **R. Sanmarti**, None; **J. L. Pablos**, None.

1807

Disclosure: E. E. Jacek, None; **M. Olferiev**, None; **V. Domingues**, None; **R. Duculan**, None; **N. Pan**, None; **M. K. Crow**, Astra Zeneca, 6, Bristol Meyers Squibb, 6, Centocor/ Johnson and Johnson, 8, Eisai, Inc, 5, EMD Merck Serono, 5, GlaxoSmithKline, 5, Idera Pharmaceuticals, 5, Medimmune, 5, Novartis Pharmaceutical Corporation, 8, Novo Nordisk, 5, Regeneron, 8, Vertex Pharmaceuticals, 6; **K. A. Kirou**, None.

1808

Disclosure: A. B. Reiss, None; **I. Voloshyna**, None; **M. J. Littlefield**, None; **E. Belilos**, None; **K. B. BeloStocki**, None; **L. A. Bonetti**, None; **G. C. Rosenblum**, None; **S. E. Carsons**, None.

1809

Disclosure: S. Rosengren, None; **G. S. Firestein**, None, 5; **D. L. Boyle**, Pfizer Inc, 2.

1810

Disclosure: T. Okuyama, None; **Y. Kosugi**, None; **K. Komai**, None; **A. Hashiramoto**, None; **K. Shiozawa**, None; **S. Shiozawa**, None.

1811

Disclosure: H. Endo, None; **M. Kabraki**, None; **Y. Kusunoki**, None; **N. Kusunoki**, None; **S. Kawai**, None.

1812

Disclosure: A. A. Welihinda, None; **E. P. Amento**, None.

1813

Disclosure: B. Jones, None; **M. Beamer**, None; **A. Rahman**, None; **W. A. Aboualaiwi**, None; **S. Ahmed**, None.

1814

Disclosure: S. Shaw, UCB, 3; **D. Marshall**, UCB, 3; **H. Neale**, UCB, 3; **K. Kretsos**, UCB, 3; **T. Bourne**, UCB, 3; **A. Lawson**, UCB, 3.

1815

Disclosure: B. Le Goff, None; **B. A. Tonkin**, None; **S. Singbrant**, None; **T. J. Martin**, None; **E. Romas**, None; **N. A. Sims**, None; **N. C. Walsh**, None.

1816

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1817

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1818

Disclosure: M. T. Arce-Franco, None; **M. J. Dominguez-Luis**, None; **A. Diaz-Martin**, None; **A. Herrera-Garcia**, None; **M. E. Miranda-Carus**, None; **S. Bustabad-Reyes**, None; **A. Castrillo**, None; **F. Diaz-Gonzalez**, None.

1819

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1820

Disclosure: H. Hulejová, None; **O. Kryštufková**, None; **K. Kuncová**, None; **J. Zámecník**, None; **H. F. Mann**, None; **L. Senolt**, None; **J. Vencovsky**, None.

1821

Disclosure: M. I. Martins Ramos, None; **S. Aarrass**, None; **L. G. M. van Baarsen**, None; **D. M. Gerlag**, None; **P. Tak**, None; **M. C. Lebre**, None.

1822

Disclosure: A. Chioato, Novartis, 3.

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1823

Disclosure: K. Frommer, None; **R. Engel**, None; **A. Schäffler**, None; **C. Büchler**, None; **J. Steinmeyer**, None; **M. Rickert**, None; **S. Rehart**, None; **F. Brentano**, None; **S. Gay**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

1824

Disclosure: J. Liu, None; **G. Palmer**, None; **Y. Qing**, None; **D. Rifkin**, None; **M. Attur**, None; **S. B. Abramson**, None.

1825

Disclosure: S. Junker, None; **K. Frommer**, None; **G. Krumbholz**, None; **A. Lehr**, None; **S. Rehart**, None; **M. Rickert**, None; **J. Steinmeyer**, None; **G. Schett**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

1826

Disclosure: K. S. Torok, None; **K. Kurzinski**, None; **C. Kelsey**, None; **C. A. Feghali-Bostwick**, None.

1827

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1828

Disclosure: K. Kayakabe, None; **T. Kuroiwa**, Chugai Pharmaceutical Co., Eizai Co., 2; **N. Sakurai**, None; **H. Ikeuchi**, Chugai Pharmaceutical Co., Ltd, 6, Takeda Pharmaceutical Company Limited, 6, Mitsubishi Tanabe Pharma Corporation, 6, Eisai Co., Ltd, 6; **A. K.T.**, None; **T. Sakairi**, None; **A. Maeshima**, None; **K. Hiromura**, None; **Y. Nojima**, Astellas Pharma Inc, Mitsubishi Tanabe Pharm, MSD, Takeda Pharmaceutical Company Limited, Kyowa Hakko Kirin Co., Chugai Pharmaceutical Co., Teijin Pharma Limited, Daiichi Sankyo Co., Eizai Co., Torii Pharmaceutical Co., Asahi Kasei Co., 2.

1829

Disclosure: L. C. Harty, None; **M. Biniecka**, None; **E. Fox**, None; **J. N. O'Sullivan**, None; **U. Fearon**, None; **D. J. Veale**, HRB, 2, Abbott, GlaxoSmithKline, Centocor, Wyeth,Pfizer and Schering Plough, 5, Abbott, GlaxoSmithKline, Centocor, Wyeth, Pfizer and Schering Plough, 8.

1830

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1831

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1832

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1833

Disclosure: B. S. Koo, None; **Y. G. Kim**, None; **M. W. So**, None; **C. K. Lee**, None; **B. Yoo**, None.

1834

Disclosure: B. W. Higgs, AZStock, 1, MedImmune, 3; **W. Zhu**, AZ Stock, 1, MedImmune, 3; **L. Richman**, AZ Stock, 1, MedImmune, 3; **D. Fiorentino**, None; **S. A. Greenberg**, Greenberg has a Sponsored Research Agreement with MedImmune, 2; **B. Jallal**, AZ Stock, 1, MedImmune, 3; **Y. Yao**, AZ Stock, 1, MedImmune, 3.

1835

Disclosure: B. W. Higgs, AZStock, 1, MedImmune, 3; **Z. Liu**, AZ Stock, 1, MedImmune, 3; **B. White**, None; **W. Zhu**, AZ Stock, 1, MedImmune, 3; **W. White**, AZ Stock, 1, MedImmune, 3; **C. Morehouse**, AZ Stock, 1, MedImmune, 3; **P. Brohawn**, AZ Stock, 1, MedImmune, 3; **P. Kiener**, None; **L. Richman**, AZ Stock, 1, MedImmune, 3; **D. Fiorentino**, None; **S. A. Greenberg**, MedImmune, 2; **B. Jallal**, AZ Stock, 1, MedImmune, 3; **Y. Yao**, AZ Stock, 1, MedImmune, 3.

1836

Disclosure: A. Marotta, Augurex Life Sciences Corp, 4; **Y. Gui**, None; **A. Ghahary**, Augurex Life Sciences Corp, 9; **R. Kilani**, Augurex Life Sciences Corp, 9; **W. P. Maksymowych**, Abbott Laboratories, 5, Amgen, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Bristol-Myers Squibb, 5, Augurex Life Sciences Corp, 5.

1837

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1838

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1839

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1840

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1843

Disclosure: M. I. Martins Ramos, None; **S. Aarrass**, None; **D. M. Gerlag**, None; **P. Tak**, None; **M. C. Lebre**, None.

1844

Disclosure: L. Capone, Celgene, 3; **A. Rogovitz**, Celgene, 3; **A. Gandhi**, Celgene, 3; **P. Schafer**, Celgene, 3.

1845

Disclosure: S. Khetan, None; **M. Muthana**, None; **A. G. Wilson**, None.

ACR/ARHP Poster Session C

Epidemiology and Health Services Research: Connective Tissue Diseases/Vasculitis/ Inflammatory Arthritis

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1846

Disclosure: J. A. Avina-Zubieta, None; **E. C. Sayre**, None; **S. Bernatsky**, None; **A. J. Lehman**, None; **K. Shojania**, None; **J. Esdaile**, None; **D. Lacaille**, None.

1847

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1848

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1849

Disclosure: E. C. Somers, None; **W. Marder**, None; **P. C. Cagnoli**, None; **E. E. Lewis**, None; **P. DeGuire**, None; **C. Gordon**, None; **C. G. Helmick**, None; **L. Wang**, None; **J. J. Wing**, None; **J. P. Dhar**, None; **J. C. Leisen**, None; **W. J. McCune**, None.

1850

Disclosure: P. S. Poynter, None; **K. S. Lee**, None; **H. Bush**, None; **L. J. Crofford**, None.

1851

Disclosure: E. R. Vina, None; **C. M. Masi**, None; **S. L. Green**, None; **T. O. Utset**, None.

1852

Disclosure: J. G. Richter, None; **T. Muth**, None; **B. Koerbl**, None; **N. Hoffmann**, None; **T. Koch**, None; **J. Siegrist**, None; **M. Schneider**, None.

1853

Disclosure: J. Xu, None; **H. Fang**, None; **M. Petri**, MedImmune, 2, 5.

1854

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1855

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1856

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1857

Disclosure: A. Eudy, GlaxoSmithKline, 3; **A. I. Vines**, None; **C. Poole**, GlaxoSmithKline, 2; **C. G. Parks**, None.

1858

Disclosure: C. G. Parks, None; **A. I. Vines**, None; **A. Eudy**, GlaxoSmithKline, 3.

1859

Disclosure: S. Navarra, None; **R. A. Mikolaitis**, None; **J. A. Block**, None; **M. Jolly**, None.

1860

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1862

Disclosure: C. C. Barnabe, None; **L. Joseph**, None; **P. Belisle**, None; **J. Labrecque**, None; **L. W. Svenson**, None; **S. M. Edworthy**, None; **S. G. Barr**, None; **M. J. Fritzler**, None; **C. A. Peschken**, None; **B. Hemmelgarn**, None; **S. Bernatsky**, None.

1863

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1864

Disclosure: D. E. Furst, Abbott, Actelion, Amgen, BristolMyersSquibb, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 2, Corrona, 3, Abbott, Actelion, Amgen, BristolMyersSquibb, BiogenIdec, Centocor, Gilead, GlaxoSmithKline, NIH, Nitec, Novartis, Pfizer, Roche/Genentech, UCB, 5, Abbott, Actelion, UCB, 8, Abbott, Actelion, Amgen, BristolMyersSquibb, BiogenIdec, Centocor, Gilead, NIH, Roche/Genentech, 9; **A. A. Amato**, MedImmune, 5; **S. R. Iorga**, None; **K. Gajria**, MedImmune LLC, 3; **A. Fernandes**, MedImmune LLC, 3.

1865

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1866

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1869

Disclosure: D. Dalal, None; **Y. C. Lin**, None; **D. Brennan**, None; **K. Wolski**, None; **N. Borkar**, None; **N. J. Korman**, None; **D. Dylinski**, None; **M. E. Husni**, National Psoriasis Foundation, Arthritis National Research Foundation, 2, Centers for Disease Control, 5, PASE questionnaire- co developer, 4, PASE questionnaire- co developer, 7, Pfizer, Amgen, and UCB, 5.

1870

Disclosure: B. M. Akkara Veetil, Pfizer Inc, 2; **E. L. Matteson**, Pfizer Inc, 2; **H. Maradit-Kremers**, Amgen, 2; **M. T. McEvoy**, Amgen, 2; **C. S. Crowson**, Pfizer Inc, 2, Amgen, 2.

1871

Disclosure: B. M. Akkara Veetil, Pfizer Inc, 2; **E. L. Matteson**, Pfizer Inc, 2; **H. Maradit-Kremers**, Amgen, 2; **M. T. McEvoy**, Amgen, 2; **C. S. Crowson**, Pfizer Inc, 2, Amgen, 2.

1872

Disclosure: E. M. Camacho, None; **S. Verstappen**, None; **D. K. Bunn**, None; **D. D. Symmons**, None.

1873

Disclosure: E. M. Camacho, None; **S. Verstappen**, None; **M. Lunt**, None; **D. K. Bunn**, None; **D. P. M. Symmons**, None.

1874

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1875

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1878

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1879

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1880

Disclosure: C. Barber, None; **D. V. Lacaille**, None; **J. E. Wither**, None; **P. R. Fortin**, None.

1881

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1885

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1886

Disclosure: M. Cinar, None; **S. Yilmaz**, None; **S. S. Koca**, None; **H. Erdem**, None; **S. Pay**, None; **Y. Yazici**, BristolMyersSquibb, Celgene, Centocor, Genentech, UCB, Pfizer, Merck, 5, Centocor,Genentech, BristolMyersSquibb, 2; **I. Simsek**, None.

1887

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1888

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1890

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1891

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1892

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1893

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1894

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1895

Disclosure: M. Lahiri, None; **C. Morgan**, None; **R. N. Luben**, None; **M. Lentjes**, None; **D. K. Bunn**, None; **M. Lunt**, None; **N. Wareham**, None; **S. M. M. Verstappen**, None; **D. P. M. Symmons**, None; **K. T. Khaw**, None; **I. N. Bruce**, None.

ACR/ARHP Poster Session C

Fibromyalgia and Soft-Tissue Disorders

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1896

Disclosure: D. Ly-Pen, None; **J. L. Andreu**, None; **I. Millán**, None; **G. de Blas**, None; **A. Sánchez-Olaso**, None.

1897

Disclosure: A. Torrent, BIOIBERICA S.A., 3; **R. Ruhí**, BIOIBERICA S.A., 3; **C. Martínez**, BIOIBERICA S.A., 3; **M. Cid**, BIOIBERICA S.A., 3; **C. Buhrmann**, None; **M. Shakibaei**, None.

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1899

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Disclosure: R. S. Katz, None; **B. J. Small**, None; **S. M. Ferbert**, None; **P. Kuenzi**, None; **S. Shott**, None.

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1902

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Disclosure: P. J. Mease, Forest Laboratories, Inc., 2, Forest Laboratories, Inc., 5, Forest Laboratories, Inc., 8, Cypress Bioscience, Inc., 5; **D. J. Clauw**, Forest Laboratories, Inc., 5, Cypress Bioscience, Inc., 5, Forest Laboratories, 2; **Y. Ma**, Forest Research Institute, 3; **A. Baldecchi**, Forest Research Institute, 3; **J. M. Trugman**, Forest Research Instiute, 3; **R. H. Palmer**, Forest Research Institute, 3, Forest Laboratories, Inc., 1.

1905

Disclosure: L. M. Arnold, Eli Lilly and Company, 2, Pfizer Inc, 2, Cypress Biosciences, Inc., 2, Boehringer Ingelheim, 2, Forest Laboratories, 2, Novartis Pharmaceutical Corporation, 2, Eli Lilly and Company, 5, Pfizer Inc, 5, Cypress Biosciences, Inc., 5, Forest Laboratories, 5, Takeda, 5, Astra Zeneca, 5, Sanofi-Aventis Pharmaceutical, 5, Grunenthal, 5, Johnson & Johnson, 5; **Y. Ma**, Forest Research Institute, 3; **R. H. Palmer**, Forest Research Institute, 3, Forest Laboratories, Inc., 1; **A. Spera**, Forest Research Institute, 3; **A. Baldecchi**, Forest Research Institute, 3.

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1908

Disclosure: P. J. Mease, Forest Laboratories, Inc., 2, Forest Laboratories, Inc., 5, Forest Laboratires, Inc., 8, Cypress Bioscience, Inc., 5; **R. H. Palmer**, Forest Research Institute, 3, Forest Laboratories, Inc., 1; **Y. Wang**, Forest Research Institute, 3; **R. M. Gendreau**, Cypress Bioscience, Inc., 3, Cypress Bioscience, Inc., 1.

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Disclosure: A. L. Hassett, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Jazz Pharmaceuticals, 5; **C. M. Brummett**, None; **J. Goesling**, None; **K. Rakovitis**, None; **D. J. Clauw**, Pfizer Inc, 5, Forest Laboratories, 5, Johnson & Johnson, 5, Lilly, 5, Merck Pharmaceuticals, 2, Jazz, 5, Cypress Biosciences, Inc., 5, Pfizer Inc, 2, Nuvo, 5, Forest Laboratories, 2; **D. A. Williams**, Eli Lilly and Company, 5, Forest Pharmaceuticals, 5, Pfizer Inc, 5, Jazz Pharmaceuticals, 5, Bristol Meyers Squibb, 5.

1912

Disclosure: J. Goesling, None; **C. M. Brummett**, None; **K. Rakovitis**, None; **D. J. Clauw**, Pfizer Inc, 5, Forest Laboratories, 5, Johnson & Johnson, 5, Lilly, 5, Merck Pharmaceuticals, 2, Jazz, 5, Cypress Biosciences, Inc., 5, Pfizer Inc, 2, Nuvo, 5, Forest Laboratories, 2; **A. L. Hassett**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Jazz Pharmaceuticals, 5.

1913

Disclosure: J. Lobert, None; **X. Morgan**, None; **L. M. Arnold**, Eli Lilly and Company, 2, Pfizer Inc, 2, Cypress Biosciences, Inc., 2, Boehringer Ingelheim, 2, Forest Laboratories, 2, Novartis Pharmaceutical Corporation, 2, Eli Lilly and Company, 5, Pfizer Inc, 5, Cypress Biosciences, Inc., 5, Forest Laboratories, 5, Takeda, 5, Astra Zeneca, 5, Sanofi-Aventis Pharmaceutical, 5, Grunenthal, 5, Johnson & Johnson, 5.

1914

Disclosure: R. E. Heymann, Pfizer Inc, Lilly, 8; **E. S. Paiva**, Pfizer Inc, Lilly, 8; **M. C. Rezende**, None; **D. Feldman**, Pfizer Inc, 8; **M. Helfenstein Jr.**, Pfizer Inc, 8; **J. E. Martinez**, Pfizer Inc, 8; **J. R. Provenza**, Pfizer Inc, 8; **A. Ranzolin**, None; **L. S. Ribeiro**, None; **E. J. R. Souza**, None.

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1916

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ACR/ARHP Poster Session C

Genomics, Proteomics, and Genetics

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1918

Disclosure: C. Charles-Schoeman, None; **Y. Miao**, None; **J. Watanabe**, None; **Y. Y. Lee**, None; **G. Katselis**, None; **T. D. Lee**, None; **S. T. Reddy**, None.

1919

Disclosure: M. Petri, Biogen Idec Inc, 2, 5; **H. Fang**, None; **W. Hu**, None; **J. Bienkowska**, Biogen Idec Inc, 1, 3; **N. Allaire**, Biogen Idec Inc, 1, 3; **J. Carulli**, Biogen Idec Inc, 1, 3; **M. D. Linnik**, Biogen Idec, 1, 3.

1920

Disclosure: M. Petri, Biogen Idec Inc, 2, 5; **H. Fang**, None; **J. Xu**, None; **W. Hu**, None; **E. Akhter**, None; **J. Bienkowska**, Biogen Idec, Inc, 1, 3; **N. Allaire**, Biogen Idec Inc, 1, 3; **J. Carulli**, Biogen Idec Inc, 1, 3; **L. S. Magder**, None; **M. D. Linnik**, Biogen Idec Inc, 1, 3.

1921

Disclosure: T. Besenyei, None; **A. Kadar**, None; **B. Tryniszewska**, None; **V. A. Adarichev**, None; **K. Mikecz**, None; **T. T. Glant**, None.

1922

Disclosure: W. Fan, None; **Y. Tang**, None; **B. Qu**, None; **H. Cui**, None; **X. Huang**, None; **B. W. Higgs**, AZStock, 1, MedImmune, 3; **Y. Yao**, AZ Stock, 1, MedImmune, 3; **B. Jallal**, AZ Stock, 1, MedImmune, 3; **N. Shen**, MedImmune, 2.

1923

Disclosure: F. Niederer, None; **C. Ospelt**, None; **J. Stanczyk**, None; **M. Trenkmann**, None; **E. Karouzakis**, None; **M. Dahlhaus**, None; **B. A. Michel**, University Hospital Zurich, 3; **C. Kolling**, None; **R. E. Gay**, None; **S. Gay**, Unitersity Hospital Zurich, 3; **A. Juengel**, None; **D. Kyburz**, None.

1924

Disclosure: Q. Lan, None; **W. Xu**, None; **J. Wang**, None; **H. M. Fan**, None; **B. Ryffel**, None; **W. Shi**, None; **S. G. Zheng**, None.

1925

Disclosure: H. M. Lee, None; **H. Sugino**, None; **C. Aoki**, None; **M. Murakami**, None; **T. Matsutani**, None; **T. Ochi**, None; **N. Nishimoto**, None.

1926

Disclosure: C. T. Nielsen, None; **O. Østergaard**, None; **L. V. Iversen**, None; **S. Jacobsen**, None; **N. H. H. Heegaard**, None.

1927

Disclosure: I. Focant, None; **D. Hernandez-Lobato**, None; **J. Ducreux**, None; **P. Durez**, None; **A. Nzeusseu Toukap**, None; **D. Elewaut**, None; **F. A. Houssiau**, None; **P. Dupont**, None; **B. Lauwerys**, None.

1928

Disclosure: T. Besenyei, None; **J. Kurkó**, None; **K. Mikecz**, None; **T. T. Glant**, None; **T. A. Rauch**, None.

1929

Disclosure: T. Kobezda, None; **K. Olasz**, None; **K. Mikecz**, None; **T. T. Glant**, None; **T. A. Rauch**, None.

1930

Disclosure: K. Uto, None; **K. Tsumiyama**, None; **S. Shiozawa**, None.

1931

Disclosure: R. Normand, None; **O. Vittecoq**, None; **M. Hiron**, None; **C. Derambure**, None; **X. Le Loët**, None; **T. Lequerré**, None.

1932

Disclosure: A. Obry, None; **P. Cosette**, None; **P. Chan Tchi Tsong**, None; **J. Siemowski**, None; **P. Morel**, None; **O. Boyer**, None; **P. Fardellone**, None; **R. M. Flipo**, None; **C. Marcelli**, None; **X. Le Loët**, None; **T. Lequerré**, None; **O. Vittecoq**, None.

1933

Disclosure: C. Baldini, None; **D. Martini**, None; **S. Grossi**, None; **N. Luciano**, None; **F. Ferro**, None; **S. Bombardieri**, None.

1934

Disclosure: R. A. Moura, None; **H. Canhão**, None; **J. Polido-Pereira**, None; **A. M. Rodrigues**, None; **M. Navalho**, None; **A. F. Mourão**, None; **C. M. Rosa**, None; **C. Resende**, None; **R. Campanilho-Marques**, None; **J. Madruga Dias**, None; **J. R. da Silva**, None; **M. Bexiga**, None; **J. A. Pereira da Silva**, None; **L. Graca**, None; **J. E. Fonseca**, None.

1935

Disclosure: P. L. Riches, None; **S. Gray**, None; **O. Albagha**, None; **S. H. Ralston**, None.

1936

Disclosure: M. Attur, None; **J. D. Greenberg**, None; **J. Todd**, shareholder, 3; **Q. A. Lu**, shareholder, 3; **R. Ramirez**, Sharehold, 1; **C. Oh**, None; **J. Samuels**, None; **S. Krasnokutsky**, None; **S. B. Abramson**, None.

1937

Disclosure: A. Rowzee, None; **M. Tandon**, None; **A. Gallo**, None; **J. Routsias**, None; **A. G. Tzioufas**, None; **I. Alevizos**, None.

1938

Disclosure: S. Frank, None; **S. Strietholt**, None; **C. Seyfert**, None; **M. A. Peters**, None; **T. Pauly**, None; **G. Kollias**, None; **T. Pap**, None.

ACR/ARHP Poster Session C

Infection-Related Rheumatic Disease

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1939

Disclosure: N. K. Vudattu, None; **E. E. Drouin**, None; **A. C. Steere**, None.

1940

Disclosure: J. D. Carter, None; **H. C. Gerard**, None; **A. P. Hudson**, None.

1941

Disclosure: M. Martínez-Morillo, None; **S. Mínguez**, None; **L. Mateo-Soria**, None; **I. Latorre**, None; **J. Domínguez**, None; **D. Grados**, None; **B. Tejera**, None; **S. Holgado**, None; **A. Olivé**, None; **X. Tena**, None.

1942

Disclosure: L. Bazzichi, None; **F. Maggi**, None; **F. Sernissi**, None; **P. Scarpellini**, None; **C. Giacomelli**, None; **A. Consensi**, None; **M. L. Vatteroni**, None; **M. Pistello**, None; **S. Bombardieri**, None.

1943

Disclosure: F. Hanses, None; **I. Fink**, None; **S. Graessel**, None; **B. Salzberger**, None; **M. Fleck**, Roche Pharmaceuticals, 8, Chugai, 8.

1944

Disclosure: O. Elkayam, None; **S. Amir**, None; **U. Arad**, None; **J. Wollman**, None; **A. Brill**, None; **D. Paran**, None; **D. Levartovsky**, None; **I. Wigler**, None; **D. Caspi**, None.

1945

Disclosure: A. Spanò, None; **L. Postiglione**, None; **P. Sabatini**, None; **I. Soriente**, None; **M. G. Sangiolo**, None; **V. Bruner**, None; **R. Scarpa**, None; **A. Riccio**, None.

1946

Disclosure: R. Kalagate, None; **S. T. McCollum**, None; **C. H. Pritchard**, None; **L. H. Brent**, None.

1947

Disclosure: G. Ozgon, None; **A. Engin**, None; **G. Hatemi**, None; **S. Ugurlu**, None; **E. Akyayla**, None; **M. Bakir**, None; **H. Ozdogan**, None.

1948

Disclosure: J. P. Guthrie, None; **A. Rehman**, None; **H. C. Gerard**, None; **J. Stanich**, None; **A. P. Hudson**, None; **J. D. Carter**, None.

1949

Disclosure: N. J. Patel, None; **R. Rajan**, None; **R. Clark**, None; **L. R. Espinoza**, None.

1950

Disclosure: I. Pérez-Martín, None; **D. de la Hera**, None; **R. Blanco**, None; **J. Rueda**, None; **C. Bejerano**, None; **O. Pompei**, None; **J. Cañal**, None; **J. Ventosa**, None; **M. Gutiérrez-Cuadra**, None; **V. Calvo**, None; **J. Loricera**, None; **M. A. González-Gay**, None.

1951

Disclosure: B. Kisacik, None; **M. Aydinli**, None; **Y. Pehlivan**, None; **M. S. Dag**, None; **M. Sayarlioglu**, None; **A. M. Onat**, None.

1952

Disclosure: R. V. Juarez, None.

ACR/ARHP Poster Session C

Miscellaneous Rheumatic and Inflammatory Diseases

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1953

Disclosure: V. K. Shanmugam, Spouse is an attorney with Williams and Connolly LLP and represents various pharmaceutical companies., 9, NIH, 2; **A. Schilling**, None; **A. Germinario**, None; **M. Mete**, None; **C. Attinger**, None.

1954

Disclosure: V. Ramoni, None; **R. Caporali**, None; **A. Spinillo**, None; **F. Beneventi**, None; **M. Simonetta**, None; **E. Locatelli**, None; **C. Cavagnoli**, None; **C. Alpini**, None; **G. Albonico**, None; **E. Prisco**, None; **C. M. Montecucco**, None.

1955

Disclosure: D. Lebeaux, None; **C. Frances**, None; **S. Barete**, None; **B. Wechsler**, None; **O. Dubourg**, None; **J. Renoux**, None; **T. Maisonobe**, None; **O. Benveniste**, None; **M. Gatfossé**, None; **P. Bourgeois**, None; **Z. Amoura**, None; **J. C. Piette**, None; **P. Cacoub**, None; **D. Sène**, None.

1956

Disclosure: Y. Koyama, None; **C. Era**, None; **M. Tanino**, None; **D. Hidaka**, None; **T. Ota**, None; **A. Uchino**, None.

1957

Disclosure: F. Kemta Lekpa, None; **V. B. Kraus**, None; **X. Chevalier**, None.

1958

Disclosure: Y. Cai, Hutchison Medipharma Limited, 3; **W. Shen**, Hutchison Medipharma Limited, 3; **Q. Dong**, Hutchison Medipharma Limited, 3; **Z. Wu**, Hutchison Medipharma Limited, 3; **X. Yang**, Hutchison Medipharma Limited, 3; **P. Ren**, Hutchison Medipharma Limited, 3; **Y. Yu**, Hutchison Medipharma Limited, 3; **H. Shen**, Hutchison Medipharma Limited, 3; **J. Li**, Hutchison Medipharma Limited, 3; **J. Wang**, Hutchison Medipharma Limited, 3; **Y. Sai**, Hutchison Medipharma Limited, 3; **J. Yan**, Hutchison Medipharma Limited, 3; **W. Deng**, Hutchison Medipharma Limited, 3; **J. Ji**, Hutchison Medipharma Limited, 9; **W. Su**, Hutchison Medipharma Limited, 3; **H. Zhao**, Hutchison Medipharma Limited, 3.

1959

Disclosure: R. Rokutanda, None; **M. Kishimoto**, None; **H. Shimizu**, None; **A. Nomura**, None; **Y. Suyama**, None; **Y. Ohara**, None; **A. Takeda**, None; **K. I. Yamaguchi**, None; **M. Okada**, None.

1960

Disclosure: E. Becerra-Fernandez, None; **P. Panopalis**, None; **H. A. Menard**, None.

1961

Disclosure: Q. Yao, None.

1962

Disclosure: A. Muthalaly, None; **D. C. Ang**, None; **S. T. Hugenberg**, None; **R. Sampson**, None; **A. Muthalaly**, None.

1963

Disclosure: C. Vergara, None; **A. Borzutzky**, None; **M. A. Gutierrez**, None; **S. Iacobelli**, None; **E. Talesnik**, None; **M. E. Martinez**, None; **L. Stange**, None; **J. Basualdo**, None; **V. Maluje**, None; **R. Jimenez**, None; **E. Jarpa**, None; **R. Wiener**, None; **J. Tinoco**, None; **J. I. Arostegui**, FIS PS09/01182 Grant, 2; **J. Yague**, FIS PS09/01182 Grant, 2; **M. Alvarez-Lobos**, FONDECYT Grant 1100971, 2.

1964

Disclosure: R. Caorsi, None; **L. Lepore**, None; **F. Zulian**, None; **M. Alessio**, None; **A. Stabile**, None; **M. Finetti**, None; **A. Martini**, Novartis Pharmaceutical Corporation, 8; **M. Gattorno**, SOBI and Novartis, 8.

1965

Disclosure: H. Ichida, None; **Y. Kawaguchi**, None; **T. Sugiura**, None; **T. Gono**, None; **K. Takagi**, None; **Y. Ota**, None; **I. Masuda**, None; **H. Yamanaka**, Chugai Pharmaceutical Co. Ltd., Astellas Pharma Inc., Wyeth K.K., Daiichi Sankyo Co. Ltd., Banyu Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Abbott Japan Co. Ltd., Eisai Co. Ltd., Santen Pharmaceutical Co. Ltd., Taishotoyama Pharmaceuti, 2, Abbott, Eisai Co. Ltd., Takeda Pharmaceutical Company Limited, Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceutical K.K., Hoffmann-La Roche, Chugai Pharmaceutical Co. Ltd, Pfizer Inc., 5.

1966

Disclosure: K. H. Jung, None; **J. H. Lee**, None; **J. Kim**, None; **J. S. Lee**, None; **W. Park**, None; **T. H. Kim**, None; **D. H. Yoo**, None.

1967

Disclosure: H. M. Hoffman, Novartis Pharmaceutical Corporation, Regeneron, and Sobi Pharmaceuticals, 5; **U. A. Walker**, Novartis Pharmaceutical Corporation, 9; **H. Tilson**, Novartis Pharmaceutical Corporation, 9; **J. B. Kuemmerle-Deschner**, Novartis Pharmaceutical Corporation, 9; **P. Hawkins**, Novartis Pharmaceutical Corporation, 9.

1968

Disclosure: I. Pérez-Martín, None; **R. Blanco**, None; **J. Rueda**, None; **C. Bejerano**, None; **O. Pompei**, None; **M. C. González-Vela**, None; **M. A. González-López**, None; **H. Fernández-Llaca**, None; **A. Oterino**, None; **M. J. Sedano**, None; **M. Agudo**, None; **V. M. Martínez-Taboada**, None; **M. A. González-Gay**, None.

1969

Disclosure: F. Luk, None; **C. R. O'Connor**, None; **H. Hussain**, None; **V. Zarro**, None; **A. E. Checa**, None.

1970

Disclosure: Y. J. Kim, None; **B. S. Koo**, None; **M. W. So**, None; **W. J. Seo**, None; **J. S. Oh**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

1971

Disclosure: A. C. Araújo, None; **C. Noronha**, None; **A. Grilo**, None; **M. F. Moraes-Fontes**, None; **N. Riso**, None; **M. V. Riscado**, None.

1972

Disclosure: J. Ramirez, None; **I. Pomés**, None; **J. Pomés**, None; **J. D. Cañete**, None.

1973

Disclosure: C. Malattia, None; **M. Finetti**, None; **M. B. Damasio**, None; **C. Mattiuz**, None; **G. Chiusano**, None; **C. Basso**, None; **A. Naselli**, None; **A. Martini**, None; **M. Gattorno**, None.

1974

Disclosure: S. Akar, None; **D. Solmaz**, None; **F. Onen**, None; **V. Gerdan**, None; **O. Soysal**, None; **N. Akkoc**, None.

1975

Disclosure: E. Russell, None; **C. R. O'Connor**, None; **H. Hussain**, None.

1976

Disclosure: J. B. Kuemmerle-Deschner, None; **A. Koitschev**, None; **P. N. Tyrrell**, None; **K. Ummenhofer**, None; **P. Lohse**, None; **S. Hansmann**, None; **S. Plontke**, None; **C. Koitschev**, None; **S. M. Benseler**, None.

ACR/ARHP Poster Session C

Osteoarthritis - Clinical Aspects

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

1977

Disclosure: J. B. Driban, None; **J. M. Hootman**, None; **M. R. Sitler**, None; **K. P. Harris**, None; **N. M. Cattano**, None.

1978

Disclosure: K. E. Barbour, None; **J. M. Hootman**, None; **C. G. Helmick**, None; **L. Murphy**, None; **Y. Cheng**, None; **K. A. Theis**, None; **B. Do**, None; **J. M. Jordan**, None.

1979

Disclosure: Y. Zhang, None; **D. Wheaton**, None; **J. Niu**, None; **B. Wise**, None; **W. Havey**, None; **J. Goggins**, None; **D. J. Hunter**, None.

1980

Disclosure: J. Lee, None; **R. W. Chang**, None; **L. Manheim**, None; **P. A. Semanik**, None; **J. Song**, None; **D. D. Dunlop**, None.

1981

Disclosure: S. Perrot, None; **P. Bertin**, None; **P. Ravaud**, None.

ACR/ARHP Abstract Authors Disclosures

1982

Disclosure: S. Cahue, None; **J. Chmiel**, None; **K. W. Hayes**, None; **O. Almagor**, None; **K. Moisio**, None; **C. J. Colbert**, None; **C. Saurel**, None; **Y. Zhang**, None; **L. Sharma**, None.

1983

Disclosure: N. Shah, None; **M. J. Hannon**, None; **W. Zhijie**, None; **C. K. Kwoh**, None.

1984

Disclosure: B. Wise, Pfizer Inc, 2; **J. Niu**, Pfizer Inc, 5; **N. E. Lane**, None; **M. C. Nevitt**, None; **D. K. White**, None; **J. Torner**, None; **C. E. Lewis**, None; **Y. Zhang**, Pfizer Inc, 5.

1985

Disclosure: C. J. Colbert, None; **K. W. Hayes**, None; **O. Almagor**, None; **J. S. Chmiel**, None; **A. H. Chang**, None; **K. Moisio**, None; **S. Cahue**, None; **Y. Zhang**, None; **C. Saurel**, None; **L. Sharma**, None.

1986

Disclosure: B. Wise, Pfizer Inc, 2; **J. Niu**, Pfizer Inc, 5; **N. E. Lane**, None; **M. C. Nevitt**, None; **D. T. Felson**, None; **J. Hietpas**, None; **A. Sadosky**, Pfizer Inc, 3; **J. Torner**, None; **C. E. Lewis**, None; **Y. Zhang**, Pfizer Inc, 5.

1987

Disclosure: T. N. de Boer, Pfizer Inc, 2; **M. J. P. M. Stukstette**, None; **P. M. J. Welsing**, None; **A. M. Huisman**, None; **A. A. Polak**, None; **J. W. J. Bijlsma**, Pfizer Inc, 2; **S. C. Mastbergen**, Pfizer Inc, 2; **F. P. J. G. Lafeber**, Pfizer Inc, 2.

1988

Disclosure: C. M. Brummett, None; **B. Hallstrom**, None; **A. Urquhart**, None; **M. Morris**, None; **D. J. Clauw**, Pfizer Inc, 5, Forest Laboratories, 5, Johnson & Johnson, 5, Lilly, 5, Merck Pharmaceuticals, 2, Jazz, 5, Cypress Biosciences, Inc., 5, Pfizer Inc, 2, Nuvo, 5, Forest Laboratories, 2; **D. A. Williams**, Eli Lilly and Company, 5, Forest Pharmaceuticals, 5, Pfizer Inc, 5, Jazz Pharmaceuticals, 5, Bristol Meyers Squibb, 5.

1989

Disclosure: J. Niu, None; **M. C. Nevitt**, None; **C. E. McCulloch**, None; **J. Torner**, None; **C. E. Lewis**, None; **D. T. Felson**, None.

1990

Disclosure: K. C. Foucher, None; **B. R. Schlink**, None; **N. Shakoor**, None; **M. A. Wimmer**, None.

1991

Disclosure: K. D. Gross, None; **H. J. Hillstrom**, None; **J. Niu**, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **D. T. Felson**, None.

1992

Disclosure: P. Ornetti, None; **C. Fortunet**, None; **D. LaRoche**, None; **C. Morisset**, None; **J. M. Casillas**, None; **J. F. Maillefert**, None.

1993

Disclosure: U. S. D. Nguyen, None; **D. T. Felson**, None; **J. Niu**, None; **Y. Zhu**, None; **D. K. White**, None; **N. Segal**, None; **C. E. Lewis**, None; **M. Rasmussen**, None; **M. C. Nevitt**, None.

1994

Disclosure: B. Goker, None; **A. Tufan**, None; **R. H. Lidtke**, None; **J. A. Block**, None.

1995

Disclosure: N. Shakoor, None; **H. J. Hillstrom**, None; **K. D. Gross**, None; **K. Wang**, None; **D. T. Felson**, None; **N. Segal**, None; **C. E. Lewis**, None; **M. C. Nevitt**, None.

1996

Disclosure: R. Hilfiker, None; **P. Juni**, None; **E. Nüesch**, None; **P. A. Dieppe**, None; **S. Reichenbach**, None.

1997

Disclosure: T. N. de Boer, Pfizer Inc, 2; **S. C. Mastbergen**, Pfizer Inc, 2; **A. M. Huisman**, None; **J. W. J. Bijlsma**, Pfizer Inc, 2; **F. P. J. G. Lafeber**, Pfizer Inc, 2.

1998

Disclosure: J. B. Driban, None; **L. L. Price**, None; **A. M. Tassinari**, None; **G. H. Lo**, None; **T. E. McAlindon**, Flexion, Novartis, EMD Merck Serono, 5, Novartis Pharmaceutical Corporation, 2, Online clinical trials, 7.

1999

Disclosure: S. H. Roth, Transdel Pharmaceuticals, 1, self-employed, 3, Covidien, 8, Covidien, 5; **P. Fuller**, Covidien, 1, Covidien, 3.

2000

Disclosure: M. Hasegawa, None; **K. Tanaka**, None; **N. Horiki**, None; **H. Wakabayashi**, None; **Y. Takei**, None; **A. Uchida**, None; **A. Sudo**, None.

2001

Disclosure: B. Cryer, Pfizer Inc, 2, Pfizer Inc, 5; **C. Li**, Pfizer Inc, 1, Pfizer Inc, 3; **L. S. Simon**, Pfizer Inc, 5; **G. Singh**, Pfizer Inc, 2; **M. Stillman**, Pfizer Inc, 5; **M. Berger**, Pfizer Inc, 1, Pfizer Inc, 3.

2002

Disclosure: I. L. Meek, None; **J. Kasemier**, None; **H. E. Vonkeman**, None; **K. Movig**, None; **M. A. van de Laar**, None.

2003

Disclosure: H. E. Krug, None; **C. W. Dorman**, None; **S. Frizelle**, None; **M. L. Mahowald**, None.

2004

Disclosure: B. Goker, None; **T. Akalin**, None; **J. A. Block**, None.

2005

Disclosure: F. Roemer, Boston Imaging Core Lab, 4; **M. C. Nevitt**, None; **D. T. Felson**, None; **J. Niu**, None; **J. Lynch**, None; **M. Crema**, Boston Imaging Core Lab, 4; **C. E. Lewis**, None; **J. Torner**, None; **A. Guermazi**, Boston Imaging Core Lab, 4, Facet Solutions, Genzyme, Stryker, Merck Serono, GE, 5.

2006

Disclosure: J. P. Raynauld, ArthroVision Inc., 5; **L. M. Wildi**, None; **F. Abram**, ArthroVision Inc., 3; **T. Moser**, ArthroVision, 5; **M. Girard**, ArthroVision, 5; **J. Martel-Pelletier**, ArthroVision, 1, ArthroVisoin, 5; **J. P. Pelletier**, ArthroVision, 1, ArthroVision, 5.

ACR/ARHP Poster Session C

Pediatric Rheumatology - Clinical and Therapeutic Aspects: Pediatric Rheumatology Systemic Lupus Erythematosus, Juvenile Dermatomyositis, Vasculitis and Other

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2007

Disclosure: R. QuiNones, None; **G. Morgan**, None; **M. Amoruso**, None; **D. Wang**, None; **L. M. Pachman**, None.

2008

Disclosure: H. Brunner, None; **A. Baker**, None; **A. Cedeno**, None; **J. L. Huggins**, None; **A. C. P. Sagcal-Gironella**, None; **J. Ying**, None; **M. Klein-Gitelman**, None; **T. Roebuck-Spencer**, None.

2009

Disclosure: P. Miettunen, None; **A. Pistorio**, None; **A. Ravelli**, None; **S. Oliveira**, None; **M. Alessio**, None; **R. Cuttica**, None; **D. Mihaylova**, None; **G. Espada**, None; **S. Pasic**, None; **E. Cortis**, None; **S. Ozen**, None; **O. Porras**, None; **F. Sztajnbok**, None; **A. Martini**, None; **N. Ruperto**, None.

2010

Disclosure: O. J. Rullo, None; **D. K. McCurdy**, None; **O. Yadin**, None; **A. D. Hoftman**, None; **J. M. P. Woo**, None; **E. von Scheven**, None.

2011

Disclosure: A. Cedeno, None; **A. Baker**, None; **M. Klein-Gitelman**, None; **A. C. P. Sagcal-Gironella**, None; **A. German**, None; **C. Scharf**, None; **J. Ying**, None; **H. Brunner**, None; **D. Beebe**, None; **F. Zelko**, None.

2012

Disclosure: D. Lazarevic, None; **A. Pistorio**, None; **P. Miettunen**, None; **A. Ravelli**, None; **C. Malattia**, None; **C. Pilkington**, None; **N. Wulffraat**, None; **S. M. Garay**, None; **M. Hofer**, None; **P. Quartier**, None; **P. Dolezalova**, None; **I. Calvo Penades**, None; **V. P. L. Ferriani**, None; **G. Ganser**, None; **O. Kasapcopur**, None; **J. A. Melo-Gomes**, None; **M. Wierzbowska**, None; **A. Martini**, None; **N. Ruperto**, None.

2013

Disclosure: Y. Berkun, URL Pharma, 2; **E. Ben-Chetrit**, URL Pharma, 2; **S. Wason**, URL Pharma, 3; **R. Faulkner**, URL Pharma, 3; **S. Levenstein**, URL Pharma, 5.

2014

Disclosure: R. Mina, None; **M. Klein-Gitelman**, None; **S. L. Nelson**, None; **B. A. Eberhard**, None; **G. C. Higgins**, None; **N. G. Singer**, None; **D. M. Levy**, None; **K. Onel**, None; **J. C. Olson**, None; **J. D. Pendl**, None; **A. Baker**, None; **L. F. Imundo**, None; **L. B. Tucker**, None; **L. E. Schanberg**, Pfizer Inc, 2; **M. G. Punaro**, None; **K. M. O'Neil**, None; **N. Ruperto**, None; **D. J. Lovell**, None; **H. Brunner**, None.

2015

Disclosure: S. P. Ardoin, None; **L. E. Schanberg**, Pfizer Inc, 9; **C. I. Sandborg**, None; **H. Barnhart**, None; **E. Yow**, None; **G. Evans**, None; **K. Mieszkalski**, None; **N. T. Ilowite**, Abbott Immunology Pharmaceuticals, 8, Genentech and Biogen IDEC Inc., 8, Regeneron, 2, Novartis Pharmaceutical Corporation, 5, Centocor, Inc., 5; **E. von Scheven**, None; **B. A. Eberhard**, None; **L. F. Imundo**, None; **D. M. Levy**, None; **Y. Kimura**, None; **E. D. Silverman**, None; **S. L. Bowyer**, None; **M. G. Punaro**, None; **N. G. Singer**, None; **D. D. Sherry**, None; **D. K. McCurdy**, None; **M. Klein-Gitelman**, None; **C. A. Wallace**, Amgen,Pfier, Centocor, Novartis, BristolMyersSquibb, 2; **R. M. Silver**, None; **L. Wagner-Weiner**, None; **G. Higgins**, None.

2016

Disclosure: N. E. Aikawa, None; **A. M. Sallum**, None; **R. M. R. Pereira**, None, 2; **E. Bonfa**, None, 2; **L. Suzuki**, None; **V. S. T. Viana**, None; **C. A. Silva**, None, 2.

2017

Disclosure: J. D. Frankovich, None; **P. D. Barnes**, None; **C. I. Sandborg**, None; **E. F. Chakravarty**, None.

2018

Disclosure: F. Zulian, None; **C. Vallongo**, None; **F. Vittadello**, None; **A. Patrizi**, None; **M. Alessio**, None; **A. Belloni Fortina**, None; **S. Martino**, None; **G. Martini**, None.

2019

Disclosure: A. B. Robinson, None; **M. F. Hoeltzel**, None; **M. Becker**, None; **D. M. Wahezi**, None; **A. M. Huber**, None; **B. M. Feldman**, Novartis Pharmaceutical Corporation, 9; **A. M. Reed**, None.

2020

Disclosure: V. R. Guissa, None; **N. E. Aikawa**, None; **A. M. Sallum**, None; **L. M. A. Campos**, None; **R. M. R. Pereira**, None, 2; **E. Bonfa**, None, 2; **C. A. Silva**, CNPQ #300248/2008-3 and Federico Foundation, 2.

2021

Disclosure: J. Wipff, None; **M. -. A. Dumitrescu**, None; **M. Lorrot**, None; **A. Faye**, None; **S. lacassagne-Compeyrot**,

None; **B. Bader Meunier**, None; **R. Mouy**, None; **C. H. Wouters**, None; **M. Desjonqueres**, None; **S. Jean**, None; **V. Despert**, None; **A. Duquesne**, None; **I. Lemelle**, None; **P. Pillet**, None; **M. Grall-Lerosey**, None; **P. Quartier**, None; **C. Job-Deslandre**, None.

2022

Disclosure: G. Vigo, None; **G. Martini**, None; **F. Vittadello**, None; **I. Ceccherini**, None; **L. Obici**, None; **F. Zulian**, None.

2023

Disclosure: E. Y. Wu, None; **E. C. Rabinovich**, None; **K. S. Torok**, None; **S. C. Li**, None; **R. C. Fuhlbrigge**, None.

2024

Disclosure: A. Uribe, None; **L. B. Tucker**, None; **L. Masse**, None; **J. Guzman**, None; **D. A. Cabral**, None.

2025

Disclosure: E. F. Lawson, None; **A. O. Hersh**, None; **L. J. Julian**, None; **L. Trupin**, None; **E. von Scheven**, None; **P. P. Katz**, None; **E. Yelin**, None.

2026

Disclosure: A. Nascif, None; **V. Valim**, None; **M. Dorio**, None; **J. Gomes**, None; **A. Pereira**, None; **E. Zandonade**, None; **C. Len**, None.

2027

Disclosure: M. F. Hoeltzel, None; **M. Becker**, None; **A. B. Robinson**, None; **A. M. Huber**, None; **B. M. Feldman**, Novartis Pharmaceutical Corporation; **A. M. Reed**, None.

2028

Disclosure: D. P. Goldsmith, None; **K. S. Barron**, None; **A. K. Ombrello**, None; **R. Lembo**, None; **D. Stone**, None; **A. Jones**, None; **D. C. Chapelle Neal**, None; **D. L. Kastner**, None.

2029

Disclosure: B. Bader-Meunier, None; **C. Jurado**, None; **B. Ranchin**, None; **S. Decramer**, None; **M. Fischbach**, None; **E. Berard**, None; **F. Saint Marcoux**, None.

2030

Disclosure: J. Duncan, None; **J. Heath**, None; **E. M. Baildam**, None; **G. Cleary**, None; **M. W. Beresford**, None; **L. J. McCann**, None.

2031

Disclosure: L. Trupin, None; **A. O. Hersh**, None; **J. Yazdany**, None; **E. F. Lawson**, None; **E. von Scheven**, None.

2032

Disclosure: S. Vora, None; **E. L. Roth-Wojcicki**, None.

2033

Disclosure: J. M. P. Woo, None; **P. Liu**, None; **M. F. Parsa**, None; **G. Amarilyo**, None; **A. D. Hoftman**, None; **D. K. McCurdy**, None; **O. J. Rullo**, None.

2034

Disclosure: M. F. Hoeltzel, None; **M. Becker**, None; **A. B. Robinson**, None; **A. M. Huber**, None; **B. M. Feldman**, Novartis Pharmaceutical Corporation; **A. M. Reed**, None.

2035

Disclosure: N. Abisror, None; **A. Mekinian**, None; **E. Lachassinne**, None; **P. nicaise-Roland**, None; **J. Stirnemann**, None; **L. de Pontual,** None; **L. Carbillon**, None; **O. Fain**, None.

2036

Disclosure: J. G. Ovalles, None; **J. Martínez-Barrio**, None; **F. J. López-Longo**, None; **I. de la Torre**, None; **L. Martínez-Estupiñán**, None; **J. C. Nieto**, None; **L. Carreño**, None.

2037

Disclosure: L. P. C. Seguro, None; **C. B. Casella**, None; **L. Takayama**, None; **E. Bonfa**, None, 2; **R. M. R. Pereira**, None, 2.

2038

Disclosure: S. L. Nelson, None; **R. Mina**, None; **L. Romick-Rosendale**, None; **H. Brunner**, None; **M. Bennett**, None; **J. D. Pendl**, None; **M. Petri**, Human Genome Sciences, Inc., 2, HGS, 5, GlaxoSmithKline, 2, GlaxoSmithKline, 5; **A. Kiani**, None; **P. Devarajan**, None; **M. Kennedy**, None.

2039

Disclosure: E. L. Boulter, None; **L. Beard**, None; **C. Ryder**, None; **C. Pilkington**, None.

2040

Disclosure: N. Luca, None; **J. C. Y. Ching**, None; **C. Manlhiot**, None; **B. W. McCrindle**, None; **R. S. Yeung**, None.

2041

Disclosure: P. H. White, None; **P. McManus**, None; **J. McAllister**, None; **C. Cooley**, None.

2042

Disclosure: T. Kizawa, None; **T. Imagawa**, None; **T. Nozawa**, None; **M. Kikuchi**, None; **T. Harada**, None; **T. Miyamae**, None; **S. Yokota**, None.

2043

Disclosure: C. Hoffart, None; **P. Weiss**, None; **A. J. Klink**, None; **D. D. Sherry**, None; **C. Feudtner**, None.

2044

Disclosure: S. J. Khiani, None; **S. Lowe**, None; **M. Zacharisen**, None; **S. Vora**, None.

2045

Disclosure: E. V. Rozenblyum, None; **D. M. Levy**, None; **E. Harvey**, None; **D. Hebert**, None; **E. D. Silverman**, None.

2046

Disclosure: D. B. Araujo, None; **E. F. Borba Neto**, None, 2; **C. A. Silva**, None, 2; **L. M. A. Campos**, None; **R. M. R. Pereira**, None, 2; **E. Bonfa**, None, 2; **S. K. Shinjo**, None, 2.

2047

Disclosure: S. P. Ardoin, None; **T. Povsic**, None; **L. E. Schanberg**, Pfizer Inc, 9; **C. I. Sandborg**, None; **H. Barnhart**, None; **E. Yow**, None; **G. Evans**, None; **K. L. Mieszkalski**, None; **N. T. Ilowite**, Abbott Immunology Pharmaceuticals, 8, Genentech and Biogen IDEC Inc., 8, Regeneron, 2, Novartis Pharmaceutical Corporation, 5, Centocor, Inc., 5; **E. von Scheven**, None; **B. A. Eberhard**, None; **L. F. Imundo**, None; **Y. Kimura**, None; **E. D. Silverman**, None; **S. L. Bowyer**, None; **M. G. Punaro**, None; **N. G. Singer**, None; **D. D. Sherry**, None; **D. K. McCurdy**, None; **M. Klein-Gitelman**, None; **C. Wallace**, Amgen, 2, Pfizer Inc, 2, Bristol myers Squibb, 5; **R. M. Silver**, None; **L. Wagner-Weiner**, None; **G. C. Higgins**, None; **H. Brunner**, None.

ACR/ARHP Poster Session C

Quality Measures and Innovations in Practice Management and Care Delivery

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2048

Disclosure: M. A. Becker, Takeda, Savient, Regeneron, URL Mutual, Novartis, Biocryst, Menarini, 5; **B. J. Pandya**, Takeda Pharmaceuticals International, Inc., 3; **J. R. Young**, Takeda Pharmaceuticals International, Inc., 2; **X. Ye**, None; **S. Unni**, None; **S. Yu**, Takeda Pharmaceuticals International, Inc., 3; **C. V. Asche**, Takeda Pharmaceuticals International, Inc., 2.

2049

Disclosure: M. K. Pemberton, None; **G. Runde**, None; **W. D. Bronson**, None.

2050

Disclosure: P. Cheung, None; **V. Andre**, None; **N. Balandraud**, None; **G. H. Chales**, None; **I. Chary-Valckaneare**, None; **E. Chatelus**, None; **E. Dernis**, None; **G. Gill**, None; **M. Gilson**, None; **S. Guis**, None; **T. Marhadour**, None; **G. Mouterde**, None; **S. Pavy**, None; **F. Pouyol**, None; **P. Richette**, None; **A. Ruyssen-Witrand**, None; **M. Soubrier**, None; **M. Dougados**, None; **L. Gossec**, None.

2051

Disclosure: N. B. Riblet, None; **A. J. Zbehlik**, None; **Y. Y. Cheung**, None; **D. A. Albert**, None.

2052

Disclosure: I. Castrejón, None; **Y. Yazici**, None; **T. Pincus**, None.

2053

Disclosure: I. Castrejón, None; **Y. Yazici**, None; **T. Pincus**, None.

2054

Disclosure: T. Ronis, None; **J. D. Frankovich**, None; **C. I. Sandborg**, None; **P. Chira**, None.

2055

Disclosure: R. W. Martin, None; **N. Lajevardi**, None; **S. Sevak**, None; **A. J. Head**, None; **A. T. Eggebeen**, None; **D. J. Tellinghuisen**, None.

2056

Disclosure: S. R. Pittman-Hobbs, None; **A. M. Reimold**, None.

2057

Disclosure: G. Wilson, None; **C. Siva**, None; **C. Velazquez**, None; **K. L. Smarr**, None; **J. Fresen**, None; **M. Petruc**, None.

2058

Disclosure: I. Castrejón, Bristol-Myers Squibb, 2; **M. J. Bergman**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5; **Y. Yazici**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5; **T. Pincus**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5.

2059

Disclosure: C. R. MacKenzie, None; **M. Meltzer**, None; **E. A. Kitsis**, None.

2060

Disclosure: J. L. Rosales-Alexander, None; **C. Magro-Checa**, None; **J. Salvatierra**, None; **J. Cantero-Hinojosa**, None; **E. Raya-Alvarez**, None.

2061

Disclosure: E. Morgan DeWitt, None; **T. Beukelman**, None; **B. S. Gottlieb**, None; **N. Griffin**, None; **Y. Kimura**, None; **I. Barnes**, None; **M. H. Passo**, None.

2062

Disclosure: Z. Rosales, None; **A. B. Rodríguez-Cambrón**, None; **L. Abásolo**, None; **L. León**, None; **O. Fontsere**, None; **C. Vadillo**, None; **J. L. Fernández Rueda**, None; **J. A. Jover**, None.

2063

Disclosure: Y. Suyama, None; **M. Kishimoto**, None; **Y. Ohara**, None; **R. Rokutanda**, None; **A. Nomura**, None; **H. Shimizu**, None; **K. I. Yamaguchi**, None; **Y. Matsui**, None; **M. Okada**, None.

2064

Disclosure: P. R. Fortin, The Arthritis Society, 2, GlaxoSmithKline, 5, Lupus Foundation of America, Inc, 6; **E. Aghdassi**, None; **A. Cymet**, None; **S. Morrison**, None; **J. Su**, None; **W. Wynant**, None; **J. E. Pope**, Canadian Institute of Health Research, 2; **S. Hewitt**, None; **C. A. Pineau**, None; **C.**

Neville, None; **P. Harvey**, None; **J. C. Tardif**, None; **M. Abrahamowicz**, None; **D. DaCosta**, None.

2065

Disclosure: L. Tarter, None; **L. Trupin**, None; **G. Schmajuk**, None; **M. Margaretten**, None; **E. Yelin**, None; **J. Yazdany**, None.

2066

Disclosure: M. Jolly, None; **J. Cornejo**, None; **R. A. Mikoliatis**, None; **J. A. Block**, None.

2067

Disclosure: M. Osman, None; **H. Burnett**, None; **A. Kydd**, None; **P. Davis**, None; **C. Rudnisky**, None; **M. Tennant**, None; **E. Yacyshyn**, None.

2068

Disclosure: J. D. Frankovich, None; **C. Longhurst**, None; **S. Sutherland**, None; **C. I. Sandborg**, None.

2069

Disclosure: M. M. Katsicas, None; **E. Hammermuller**, None; **B. Cervini**, None; **R. A. Russo**, None.

2070

Disclosure: C. M. Bartels, None; **A. J. Kind**, None; **C. Thorpe**, None; **C. Everett**, None; **M. Smith**, None.

2071

Disclosure: J. Parrino, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1; **F. Marquez**, Merck Pharmaceuticals, 2; **C. L. Fisher Jr.**, Merck Pharmaceuticals, 2; **W. Spieler**, Merck Pharmaceuticals, 2; **T. Tomala**, Merck Pharmaceuticals, 2; **J. E. Stek**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1; **A. F. Russell**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1; **K. E. Coll**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1; **S. C. Su**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1; **J. Xu**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1; **X. Li**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1; **K. Schlienger**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1; **J. L. Silber**, Merck Pharmaceuticals, 3, Merck Pharmaceuticals, 1.

2072

Disclosure: A. Finckh, None; **M. Escher**, None; **M. H. Liang**, None; **N. Bansback**, None.

2073

Disclosure: E. Yelin, None; **J. Yazdany**, None; **L. Trupin**, None; **C. Tonner**, None; **P. P. Katz**, None; **G. Schmajuk**, None; **J. Zell**, None; **P. Panopalis**, None; **L. A. Criswell**, None; **L. J. Julian**, None.

2074

Disclosure: R. Conway, None; **R. J. Coughlan**, None; **J. J. Carey**, None.

2075

Disclosure: G. R. Burmester, MSD, 5, MSD, 8; **T. Lupton**, Merck Pharmaceuticals, 5, Merck Pharmaceuticals, 8; **J. Alvaro-Gracia**, MSD, 5, MSD, 9, MSD, 8; **B. Haraoui**, Merck Pharmaceuticals, 5.

2076

Disclosure: J. M. P. Woo, None; **M. F. Parsa**, None; **G. Amarilyo**, None; **N. Afsar-manesh**, None; **O. J. Rullo**, None; **D. K. McCurdy**, None.

2077

Disclosure: M. QuiNones, None; **S. Dowell**, None; **A. Sharma**, None; **R. Flores**, None; **M. Hochberg**, None; **J. Mikdashi**, None; **V. Rus**, None.

2078

Disclosure: K. Martell, None; **M. S. McMurtry**, None; **F. McAlister**, None; **G. Gyenes**, CME talks for AZ, 5; **S. O. Keeling**, Unrestricted Educational grants for CV clinic establishment, 9, CME talk sponsored by Roche, 5, Peer reviewed Canadian Initiative For IMproved Outcomes in Rheumatology Care Grant, 2.

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Disclosure: C. K. Kwoh, None; **M. J. Hannon**, None; **S. M. Green**, None; **A. Guermazi**, Boston Imaging Core Lab, 4, Facet Solutions, Genzyme, Stryker, Merck Serono, GE, 5; **R. M. Boudreau**, None.

ACR/ARHP Poster Session C

Rheumatoid Arthritis - Animal Models

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2080

Disclosure: N. Yagishita, None; **D. Hasegawa**, None; **S. Aratani**, None; **Y. Yamano**, None; **T. Nakajima**, None.

2081

Disclosure: M. Ozgen, None; **S. S. Koca**, None; **A. Karatas**, None; **A. F. Dagli**, None; **F. Erman**, None; **N. Sahin**, None; **K. Sahin**, None; **A. Isik**, None.

2082

Disclosure: C. Wolff, None; **L. Rauch**, None; **T. Lowin**, None; **S. Klatt**, None; **R. H. Straub**, None.

2083

Disclosure: M. Ozgen, None; **S. S. Koca**, None; **A. F. Dagli**, None; **A. Karatas**, None; **C. Orhan**, None; **M. Tuzcu**, None; **N. Sahin**, None; **K. Sahin**, None; **A. Isik**, None.

2084

Disclosure: Z. C. Sun, Huthison medipharma Limited, 3; **Y. Cai**, Hutchison Medipharma Limited, 3; **Y. Qiu**, Hutchison Medipharma Limited, 3; **L. Fang**, Hutchison Medipharma Limited, 3; **X. Dai**, Hutchison Medipharma Limited, 3; **Z. Wu**, Hutchison MediPharma Ltd, 3; **P. Ren**, Hutchison MediPharma Ltd, 3; **J. He**, Hutchison MediPharma Ltd, 3; **C.**

Lu, Hutchison MediPharma Ltd, 3; **Y. Yu**, Hutchison MediPharma Ltd, 3; **J. Wang**, Hutchison MediPharma Ltd, 3; **Y. Sai**, Hutchison MediPharma Ltd, 3; **J. Yan**, Hutchison MediPharma Ltd, 3; **J. Li**, Hutchison MediPharma Ltd, 3; **W. Deng**, Hutchison MediPharma Ltd, 3; **W. Zhang**, Hutchison MediPharma Ltd, 3; **J. Ji**, Hutchison MediPharma Ltd, 9; **W. Su**, Hutchison MediPharma Ltd, 3; **H. Zhao**, Hutchison MediPharma Ltd, 3.

2085

Disclosure: M. M. Hossain, None; **Q. Q. Huang**, None; **L. D. Hazlet**, None; **S. A. McClellan**, None; **R. M. Pope**, None; **J. -. P. Jin**, None.

2086

Disclosure: Q. Q. Huang, None; **A. Misharin**, None; **R. Birtett**, None; **C. M. Cuda**, None; **C. V. Nicchitta**, None; **H. R. Perlman**, None; **R. M. Pope**, None.

2087

Disclosure: S. I. Choi, None; **L. D. Klaman**, Transition Therapeutics, 3; **W. Chen**, None; **E. Brahn**, Research Grant, 2.

2088

Disclosure: Y. J. Kwon, None; **T. Y. Kim**, None; **S. W. Lee**, None; **Y. B. Park**, None; **S. K. Lee**, None; **M. C. Park**, None.

2089

Disclosure: E. M. Bouta, None; **R. Wood**, R. Wood is an inventor of University of Rochester Medical Center intellectual property licensed to Novadaq., 9, R. Wood is a partner in Meliora Devices LLC, a medical device company, 4; **C. T. Ritchlin**, None; **E. M. Schwarz**, None.

2090

Disclosure: H. Yoshida, None; **M. Hashizume**, None; **K. Tanaka**, None; **M. Suzuki**, None; **T. Sumida**, None; **I. Matsumoto**, None; **M. Mihara**, None.

2091

Disclosure: J. F. Kaye, Teva Pharmaceuticals, 3; **E. Blaugrund**, Teva Pharmaceuticals, 3.

2092

Disclosure: J. P. Hatcher, MedImmune Ltd, 3; **J. Whitworth**, MedImmune Ltd, 3; **I. K. Anderson**, MedImmune Ltd, 3; **I. P. Chessell**, MedImmune Ltd, 3; **M. A. Sleeman**, MedImmune Ltd, 3.

2093

Disclosure: C. Guillou, None; **G. Avenel**, None; **C. Derambure**, None; **M. Verdet**, None; **M. Hiron**, None; **M. Maho**, None; **X. Le Loët**, None; **S. Adriouch**, None; **O. Boyer**, None; **T. Lequerré**, None; **O. Vittecoq**, None.

2094

Disclosure: M. Ozgen, None; **S. S. Koca**, None; **A. F. Dagli**, None; **A. Karatas**, None; **C. Orhan**, None; **H. Gencoglu**, None; **N. Sahin**, None; **K. Sahin**, None; **A. Isik**, None.

2095

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2096

Disclosure: E. T. Lyons, None; **D. Magnani**, None; **T. S. Forde**, None; **G. Splitter**, None; **V. A. Adarichev**, None.

2097

Disclosure: H. Li, None; **H. C. Hsu**, None; **J. Li**, None; **Q. Wu**, None; **P. Yang**, None; **D. Cua**, None; **J. D. Mountz**, None.

2098

Disclosure: K. Y. Kang, None; **I. Kim**, None; **J. H. Ju**, None.

2099

Disclosure: T. Mukai, None; **T. Yoshitaka**, None; **K. Nishida**, None; **Y. Ueki**, None.

2100

Disclosure: C. Bouffi, None; **C. Bony**, None; **C. Jorgensen**, None; **D. Noel**, None.

2101

Disclosure: K. H. Park, None; **J. H. Kim**, None; **S. W. Lee**, None; **S. K. Lee**, None; **Y. B. Park**, None.

2102

Disclosure: S. M. Rose, None; **H. R. Perlman**, None.

2103

Disclosure: S. M. Rose, None; **H. R. Perlman**, None.

ACR/ARHP Poster Session C

Rheumatoid Arthritis Clinical Aspects: Clinical Features of Rheumatoid Arthritis; Disease Severity; Outcomes Research and Metrology

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2104

Disclosure: C. S. Crowson, None; **L. Hickson**, None; **S. E. Gabriel**, None; **J. T. McCarthy**, None; **E. L. Matteson**, None.

2105

Disclosure: P. A. MacMullan, None; **E. Dunne**, None; **A. M. Madigan**, None; **M. C. Berndt**, None; **R. K. Andrews**, None; **E. E. Gardiner**, None; **D. Kenny**, None; **G. M. McCarthy**, None.

2106

Disclosure: S. M. Verstappen, None; **M. Lunt**, None; **R. N. Luben**, None; **J. Chipping**, None; **N. Wareham**, None; **K. T. Khaw**, None; **I. N. Bruce**, None; **D. P. Symmons**, None.

2107

Disclosure: M. E. Margaretten, None; **L. J. Julian**, None; **V. Chernitskiy**, None; **J. D. Graf**, None; **P. P. Katz**, None; **J. B. Imboden**, None; **E. H. Yelin**, None.

2108

Disclosure: T. Nakamura, None; **S. Koyano**, None; **K. Funahashi**, None; **T. Hagiwara**, None; **T. Miura**, None; **K. Okuda**, None; **A. Sagawa**, None; **T. Sakurai**, None; **H. Matsuno**, None; **T. Izumihara**, None; **E. Shono**, None; **T. Matsubara**, None.

2109

Disclosure: M. E. B. Clowse, None; **E. F. Chakravarty**, Exagen Diagnostics, 2; **K. H. Costenbader**, None; **C. Chambers**, Abbott Laboratories, 2; **F. Wolfe**, None; **K. Michaud**, None.

2110

Disclosure: G. S. Kerr, Genentech and Biogen IDEC Inc., 2; **Y. R. S. Sherrer**, AstraZeneca, Mercke, UCB, Sanofi adventis, Celgene, Lily, Roche, 2, Amgen, wyeth, Pfizer, Novartis, GHS, Astra Zeneca, 8; **R. G. Nair**, None; **E. L. Treadwell**, None; **A. D. Mosley-Williams**, None; **A. M. Mubashir**, None; **L. R. Espinoza**, None; **J. Huang**, None; **C. Swearingen**, None; **Y. Yazici**, BristolMyersSquibb, Celgene, Centocor, Genentech, UCB, Pfizer, Merck, 5, Centocor,Genentech, BristolMyersSquibb, 2.

2111

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2112

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ACR/ARHP Poster Session C

Rheumatoid Arthritis - Human Etiology and Pathogenesis

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2155

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ACR/ARHP Poster Session C

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy

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2241

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2242

Disclosure: E. Lie, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 8, Abbott Immunology Pharmaceuticals, 5, Abbott Immunology Pharmaceuticals, 8, Bristol-Myers Squibb, 8; **K. Chatzidionysiou**, Roche Pharmaceuticals, 5; **E. L. Nasonov**, Roche Pharmaceuticals, 5; **G. Lukina**, Roche Pharmaceuticals, 5; **K. Pavelka**, Roche Pharmaceuticals, 5; **D. C. Nordström**, Roche Pharmaceuticals, 5; **M. Tomsic**, Roche Pharmaceuticals, 5; **C. Gabay**, Roche Pharmaceuticals, 5; **I. Ancuta**, Roche Pharmaceuticals, 5; **P. L. van Riel**, Roche Pharmaceuticals, 5; **J. J. Gomez-Reino**, Roche Pharmaceuticals, 5; **J. E. Fonseca**, Roche Pharmaceuticals, 5, Roche Pharmaceuticals, 8, Roche Pharmaceuticals, 2; **M. L. Hetland**, Roche Pharmaceuticals, 5; **U. Tarp**, Roche Pharmaceuticals, 5; **T. K. Kvien**, Roche Pharmaceuticals, 5; **R. F. van Vollenhoven**, Roche Pharmaceuticals, 5.

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2244

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2245

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2246

Disclosure: J. Li, None; **H. C. Hsu**, None; **P. Yang**, None; **Q. Wu**, None; **H. Li**, None; **J. D. Mountz**, None.

2247

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2248

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2249

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2251

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2253

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ACR/ARHP Poster Session C

Systemic Lupus Erythematosus - Clinical Aspects

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2254

Disclosure: J. Bourré-Tessier, None; **M. B. Urowitz**, None; **M. J. Krantz**, None; **L. Joseph**, None; **C. A. Pineau**, None.

2255

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2256

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2257

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2258

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2259

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2260

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2261

Disclosure: T. Costello, Exagen Diagnostics, 3; **C. Harris**, Exagen Diagnostics, 3, Exagen Diagnostics, 1.

2262

Disclosure: M. B. Urowitz, None; **D. Ibanez**, None; **D. D. Gladman**, None.

2263

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2264

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2265

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2266

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2267

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2268

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2269

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2270

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2271

Disclosure: S. Bernatsky, None; **A. E. Clarke**, None; **C. Gordon**, None; **J. Labrecque**, None; **R. Ramsey-Goldman**, None.

2272

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2274

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2275

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2276

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2277

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2278

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2279

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2280

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2281

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2282

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2283

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2284

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2285

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2290

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2291

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2292

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2293

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2294

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2296

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2297

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2298

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2299

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2300

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2301

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2302

Disclosure: Z. Touma, None; **D. D. Gladman**, None; **D. Ibanez**, None; **S. Taghavi-Zadeh**, None; **M. B. Urowitz**, None.

2303

Disclosure: N. Al Ghanim, None; **J. Su**, None; **E. Aghdassi**, None; **W. Lou**, None; **P. R. Fortin**, The Arthritis Society, 2, GlaxoSmithKline, 5, Lupus Foundation of America, Inc, 6.

2304

Disclosure: S. Malani, None.

2305

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2306

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2307

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2308

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ACR/ARHP Poster Session C

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2309

Disclosure: E. J. Bernstein, None; **T. Isakova**, None; **M. E. Sullivan**, None; **L. B. Chibnik**, None; **H. Bazari**, None; **M. Wolf**, Abbott, Genzyme, 5, Shire, Amgen, 2; **J. Kay**, None.

2310

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2312

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2314

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2315

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2316

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2317

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2318

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2320

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2321

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2322

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2323

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2324

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2325

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2326

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2327

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ACR/ARHP Poster Session C

T-cell Biology and Targets in Autoimmune Disease: Lymphocyte Biology and Targets in Autoimmune Disease

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2331

Disclosure: T. E. Davis, None; **K. Kis-Toth**, None; **A. Szanto**, None; **L. C. Miller**, None; **G. C. Tsokos**, None.

2332

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2333

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2334

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2337

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2338

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2339

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2340

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2343

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2344

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2345

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2346

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2347

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2348

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2351

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2352

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2353

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2354

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2355

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2356

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2362

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2363

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ACR/ARHP Poster Session C

Vasculitis

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2365

Disclosure: Y. H. Lee, None; **S. J. Choi**, None; **J. D. Ji**, None; **G. G. Song**, None.

2366

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2367

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2368

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2369

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2370

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2372

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2373

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2374

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2375

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2376

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2393

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2394

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ACR/ARHP Poster Session C

ARHP Pediatrics

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2403

Disclosure: M. Fraga, None; **C. A. Len**, None; **R. Azevedo**, None; **M. I. Yoguim**, None; **M. T. Terreri**, None; **M. O. E. Hilário**, None.

ACR/ARHP Poster Session C

ARHP Psychology/Social Sciences

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2404

Disclosure: E. G. Salt, None; **L. J. Crofford**, None; **J. L. Studts**, None; **R. W. Lightfoot**, None; **L. Hall**, None.

2405

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2407

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2408

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2409

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2410

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2412

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ACR/ARHP Poster Session C

ARHP Health Services Research

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2413

Disclosure: S. P. Lee, None; **D. Kane**, None.

2414

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2415

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2416

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ACR/ARHP Poster Session C

ARHP Research Methodology

Tuesday, November 8, 2011, 9:00 AM - 6:00 PM

2417

Disclosure: L. Kwakkenbos, None; **F. H. J. van den Hoogen**, None; **J. Custers**, None; **J. Prins**, None; **M. C. Vonk**, None; **W. G. J. M. van Lankveld**, None; **E. S. Becker**, None; **C. H. M. van den Ende**, None.

2418

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2419

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2420

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2421

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ACR Plenary Session

Plenary Session III: Discovery 2011

Tuesday, November 8, 2011, 11:00 AM - 12:30 PM

2427

Disclosure: C. Dees, None; **M. Tomcik**, None; **K. Palumbo**, None; **A. Akhmetshina**, None; **A. Horn**, None; **P. Zerr**, None; **O. Distler**, Actelion Pharmaceuticals US, 5, Bristol-Myers Squibb, 5, Fibrogen, 5, Ergonex, 5, Pfizer Inc, 9, Sanofi Aventis, 9, Genentech and Biogen IDEC Inc., 5, Active Biotech, 5, Novartis Pharmaceutical Corporation, 5, UBC, 5, 4 D Science, 9; **G. Schett**, None; **J. H. Distler**, Actelion Pharmaceuticals US, 5, Array Biopharma, 9, Bayer Schering Plough, 9, Bristol-Myers Squibb, 9, Celgne, 9, Ergonex, 9, NiCox, S.A., 9, Novartis Pharmaceutical Corporation, 9, Pfizer Inc, 5, Sanofi Aventis, 9, 4 D Science, 1.

2428

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2429

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2430

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2432

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ACR Concurrent Abstract Session

Biology and Pathology of Bone and Joint: Molecular Targets for an Effective Therapy

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2433

Disclosure: V. Paringe, None; **A. C. Bloom**, None; **E. Choy**, None; **B. P. Morgan**, None; **A. S. Williams**, None.

2434

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2437

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2438

Disclosure: M. R. Husa, None; **F. Petturson**, None; **R. June**, None; **S. Grogan**, None; **D. D'Lima**, None; **M. K. Lotz**, None; **R. Liu-Bryan**, None; **R. Terkeltaub**, Regeneron, 5.

ACR Concurrent Abstract Session

Epidemiology and Health Services Research VI: Lupus/Vasculitis

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2439

Disclosure: G. Tomasson, None; **J. Bjornsson**, None; **M. P. LaValley**, None; **Y. Zhang**, None; **V. Gudnason**, None; **P. A. Merkel**, None.

2440

Disclosure: A. Mohammad, None; **J. Mohammad**, None; **J. Å. Nilsson**, None; **L. T. Jacobsson**, None; **P. A. Merkel**, None; **C. Turesson**, None.

2441

Disclosure: C. H. Feldman, None; **L. T. Hiraki**, None; **D. H. Solomon**, Amgen, 2, Abbott Immunology Pharmaceuticals, 2, Bristol-Myers Squibb, 9, Corrona, 5; **T. Shaykevich**, None; **M. A. Fischer**, None; **W. C. Winkelmayer**, None; **K. H. Costenbader**, None.

2442

Disclosure: S. M. Barnhart, None; **W. J. McCune**, None; **W. Marder**, None; **P. C. Cagnoli**, None; **E. E. Lewis**, None; **P. DeGuire**, None; **C. Gordon**, None; **C. G. Helmick**, None; **J. P. Dhar**, None; **J. C. Leisen**, None; **E. C. Somers**, None.

2443

Disclosure: P. Watson, None; **A. Brennan**, GlaxoSmithKline, 5; **H. Birch**, GlaxoSmithKline, 3; **H. Fang**, None; **M. Petri**, GlaxoSmithKline, 5, Human Genome Sciences, Inc., 5.

2444

Disclosure: S. S. Lim, None; **R. Bayakly**, None; **C. Gordon**, None; **C. G. Helmick**, None; **K. Easley**, None; **G. Bao**, None; **N. Shenvi**, None; **C. M. Drenkard**, None.

ACR Concurrent Abstract Session

Miscellaneous Rheumatic and Inflammatory Diseases

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2445

Disclosure: P. J. Hashkes, Novartis Pharmaceutical Corporation, 8, Regeneron, 9; **S. J. Spalding**, None; **E. H. Giannini**, None; **B. Huang**, None; **G. Park**, None; **K. S. Barron**, None; **M. H. Weisman**, None; **N. Pashinian**, None; **A. Reiff**, Abbott Immunology Pharmaceuticals, 8, Abbott Immunology Pharmaceuticals, 5, Amgen, 5, Amgen, 8, Genentech and Biogen IDEC Inc., 5, Genentech and Biogen IDEC Inc., 8, Pfizer Inc, 5, Pfizer Inc, 8; **J. Samuels**, None; **D. A. Wright**, None; **D. L. Kastner**, None; **D. J. Lovell**, Novartis Pharmaceutical Corporation, 5, Regeneron, 5.

2446

Disclosure: H. D. de Koning, Novartis Pharmaceutical Corporation, 2; **J. Schalkwijk**, None; **J. van der Ven-Jongekrijg**, None; **M. Stoffels**, None; **J. W. M. van der Meer**, Novartis Pharmaceutical Corporation, 5; **A. Simon**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5.

2447

Disclosure: H. Ida, None; **K. Arima**, None; **N. Kanazawa**, None; **K. I. Yoshiura**, None.

2448

Disclosure: E. S. Molloy, Bristol-Myers Squibb, 8, MSD, 8, Abbott Laboratories, 8, GlaxoSmithKline, 5, Roche, 8; **L. H. Calabrese**, Genentech and Biogen IDEC Inc., 5, Roche Pharmaceuticals, 5, Pfizer Inc, 5, Bristol-Myers Squibb, 5, Centocor, Inc., 5, Amgen, 5.

2449

Disclosure: F. Kausar, None; **T. K. Takagishi**, None; **R. A. Ostrowski**, None; **R. Tehrani**, None.

2450

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ACR Concurrent Abstract Session

Pediatric Rheumatology - Clinical and Therapeutic Aspects: Predictors and Outcomes

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2451

Disclosure: C. H. Sibley, None; **N. Plass**, None; **C. Brewer**, None; **K. King**, None; **C. Zalewski**, None; **H. J. Kim**, None; **R. Bishop**, None; **P. Kicker**, None; **Z. Phillips**, None; **J. G. Dolan**, None; **D. Stone**, None; **D. C. Chapelle Neal**, None; **C. Snyder**, None; **J. Butman**, None; **R. Wesley**, None; **R. T. Goldbach-Mansky**, None.

2452

Disclosure: S. Federici, None; **G. Calcagno**, None; **M. Finetti**, None; **R. Gallizzi**, None; **A. Meini**, None; **A. Vitale**, None; **F. Caroli**, None; **M. Cattalini**, None; **R. Caorsi**, None; **F. Zulian**, None; **A. Tommasini**, None; **A. Insalaco**, None; **M. P. Sormani**, None; **M. Baldi**, None; **I. Ceccherini**, None; **A. Martini**, None; **M. Gattorno**, None.

2453

Disclosure: S. C. Li, None; **K. S. Torok**, None; **E. Pope**, None; **K. G. Stewart**, None; **G. C. Higgins**, None; **E. C. Rabinovich**, None; **K. M. O'Neil**, None; **I. Foeldvari**, Actelion, 2, Chugai, Abbott, 5; **K. A. Haines**, None; **H. Jacobe**, None; **M. G. Punaro**, None; **R. M. Laxer**, None; **T. Nyirenda**, None; **K. M. Wittkowski**, None.

2454

Disclosure: R. Mina, None; **L. E. Schanberg**, Pfizer Inc, 2; **M. Klein-Gitelman**, None; **B. A. Eberhard**, None; **G. Higgins**, None; **K. Onel**, None; **N. G. Singer**, None; **K. M. O'Neil**, None; **D. M. Levy**, None; **S. L. Nelson**, None; **W. Yousaf**, None; **R. J. Cuttica**, None; **L. B. Tucker**, None; **M. W. Beresford**, None; **G. Espada**, None; **A. Ravelli**, None; **A. Martini**, None; **E. H. Giannini**, None; **H. Brunner**, None.

2455

Disclosure: S. Bernatsky, None; **R. Ramsey-Goldman**, None; **E. D. Silverman**, None; **C. M. Duffy**, None; **K. Oen**, None; **A. M. Rosenberg**, None; **L. E. Schanberg**, None; **K. M. O'Neil**, None; **E. von Scheven**, None; **J. Labrecque**, None; **E. M. Turnbull**, None; **A. E. Clarke**, None.

2456

Disclosure: M. Klein-Gitelman, None; **A. Cedeno**, None; **A. Baker**, None; **F. Zelko**, None; **D. Beebe**, None; **B. Dina**, None; **A. C. P. Sagcal-Gironella**, None; **D. Gitelman**, None; **H. Brunner**, None; **M. Difrancesco**, None; **B. Zappia**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Clinical Aspects: Diagnostic and Remission Criteria

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2457

Disclosure: Y. Sun, None; **C. Lim**, None; **G. Boire**, None; **B. Haraoui**, None; **C. A. Hitchon**, None; **E. C. Keystone**, None; **J. E. Pope**, None; **J. C. Thorne**, None; **D. S. Ferland**, None; **V. P. Bykerk**, Amgen, Abbott, BristolMyersSquibb, Pfizer, Roche, UCB, 2.

2458

Disclosure: R. Knevel, None; **D. van der Heijde**, Abbott, Amgen, AstraZeneca, BristolMyersSquibb, Centocor, Chugai, Eli-Lilly, GlaxoSmithKline, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth, 5, UCB, 8; **T. W. J. Huizinga**, None; **C. Lukas**, None; **B. G. Combe**, None; **A. H. M. van der Helm-van Mil**, None.

2459

Disclosure: M. Vermeer, None; **I. H. Kuper**, None; **A. E. van der Bijl**, None; **H. Baan**, None; **M. D. Posthumus**, None; **H. L. M. Brus**, None; **P. L. C. M. van Riel**, None; **M. A. F. J. van de Laar**, None.

2460

Disclosure: D. Huscher, None; **K. Thiele**, None; **S. Bischoff**, None; **M. Backhaus**, None; **M. Aringer**, None; **I. Kötter**, None; **A. Zink**, None.

2461

Disclosure: Y. Yazici, BristolMyersSquibb, Celgene, Centocor, Genentech, UCB, Pfizer, Merck, 5, Centocor,Genentech, BristolMyersSquibb, 2; **M. T. Filopoulos**, None; **C. J. Swearingen**, None.

2462

Disclosure: N. A. Khan, None; **T. Sokka**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Existing Disease-modifying Antirheumatic Drugs and Corticosteroids

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2463

Disclosure: W. G. Dixon, None; **M. Abrahamowicz**, None; **M. E. Beauchamp**, None; **D. W. Ray**, None; **S. Bernatsky**, None; **S. Suissa**, None; **M. P. Sylvestre**, None.

2464

Disclosure: T. G. Woodworth, None; **E. Thomas**, None; **J. D. Greenberg**, Corrona, 5, Corrona, 1; **D. E. Furst**, Abbott, Actelion, Amgen, BristolMyersSquibb, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 2, Corrona, 3, Abbott, Actelion, Amgen, BristolMyersSquibb, BiogenIdec, Centocor, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 5, Abbott, Actelion, UCB, 8.

2465

Disclosure: E. Villeneuve, None; **J. L. Nam**, None; **E. Hensor**, None; **R. J. Wakefield**, None; **P. G. Conaghan**, Centocor, Inc., 2, F. Hoffmann-La Roche Ltd, 2, AstraZeneca, 8, Bioberica, 8, Bristol-Myers Squibb, 8, Centocor, Inc., 8, Merck Pharmaceuticals, 8, Novartis Pharmaceutical Corporation, 8, Pfizer Inc, 8, F. Hoffmann-La Roche Ltd, 8; **M. J. Green**, None; **A. K. Gough**, None; **M. Quinn**, None; **R. J. Reece**, None; **S. R. Cox**, None; **P. Emery**, Pfizer, Merck, Abbott, BristolMyersSquibb, Roche, 5.

2466

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2467

Disclosure: L. K. Stamp, None; **P. T. Chapman**, None; **M. Barclay**, None; **J. M. Kremer**, Exagen DIagnostics, 2; **T. Dervieux**, Exagen Diagnositics, 3.

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ACR Concurrent Abstract Session

Systemic Lupus Erythematosus - Clinical Aspects: New Therapies

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2469

Disclosure: R. Furie, Bristol-Myers Squibb, 9; **K. Nicholls**, None; **T. T. Cheng**, None; **F. Houssiau**, Aspreva, BristolMyersSquibb, GlaxoSmithKline, Human Genome Sciences, Inc., Roche, Serono, UCB, Inc, 5; **R. Burgos-Vargas**, Abbott Laboratories, BristolMyersSquibb, Merck Pharmaceuticals, MSD, Pfizer Inc, Roche, Schering-Plough, Wyeth Pharmaceuticals, 5, Abbott Laboratories, BristolMyersSquibb, Merck Pharmaceuticals, MSD, Pfizer Inc, Roche, Schering-Plough, Wyeth Pharmaceuticals, 8; **S. L. Chen**, None; **R. Aranda**, Bristol-Myers Squibb [at time of study], 3, Bristol-Myers Squibb [at time of study], 1; **S. Meadows-Shropshire**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **M. Kinaszczuk**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **J. T. Merrill**, Human Genome Sciences/ GlaxoSmithKline, Pfizer, Lilly, EMD Serono, MedImmune/ Astra Zeneka, Genentech/Roche, UCB, Astellas, Amgen, Ono, Questcor, Cephalon, Bristol Myers-Squibb, Eisai, Abbott, 5, Pfizer, Genentech/Roche, UCB, 2.

2470

Disclosure: F. A. Houssiau, None; **R. Rashkov**, None; **E. Hachulla**, None; **E. Lazaro**, None; **C. Jorgensen**, None; **F. Spertini**, None; **X. Mariette**, None; **G. Grouard-Vogel**, Neovacs, 3; **B. Fanget**, Neovacs, 3; **O. Dhellin**, Neovacs, 3; **B. Lauwerys**, None; **P. Vandepapelière**, Neovacs, 3.

2471

Disclosure: K. J. Bello, None; **H. Fang**, None; **L. S. Magder**, None; **M. Petri**, None.

2472

Disclosure: M. A. Dooley, Human Genome Sciences, UCB, Genentech, Cephalon, Bristol-Myers Squibb, Eli Lilly, 2, Human Genome Sciences, GlaxoSmithKline, Vifor Pharma, Lupus Foundation of America Medical Scientific and Advisory Board, 5; **F. Houssiau**, Human Genome Sciences/ GlaxoSmithKline, 5; **C. Aranow**, GlaxoSmithKline, 5; **D. P. D'Cruz**, GlaxoSmithKline, 5, GlaxoSmithKline, 8; **A. D. Askanase**, None; **D. Roth**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **Z. J. Zhong**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **W. Freimuth**, Human Genome Sciences, Inc., 1, Human Genome Sciences, Inc., 3; **E. M. Ginzler**, Human Genome Sciences, Inc., 2, Human Genome Sciences, Inc., 5.

2473

Disclosure: L. Sun, None; **D. Wang**, None; **H. Zhang**, None; **X. Li**, None; **X. Feng**, None.

2474

Disclosure: D. Wofsy, Bristol-Myers Squibb, 5; **S. Meadows Shropshire**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **J. L. Hillson**, Bristol-Myers Squibb, 3; **B. Diamond**, None.

ACR Concurrent Abstract Session

Systemic Lupus Erythematosus - Human Etiology and Pathogenesis II: Genetics

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2475

Disclosure: C. J. Lessard, None; **I. Adrianto**, None; **J. A. Ice**, None; **J. A. Kelly**, None; **H. Li**, None; **G. B. Wiley**, None; **A. Rasmussen**, None; **M. E. Alarcon-Riquelme**, None; **J. M. Anaya**, None; **S. C. Bae**, None; **E. E. Brown for PROFILE**, None; **C. O. Jacob**, None; **J. A. James**, None; **J. Martin**, None; **T. B. Niewold**, None; **B. Pons-Estel**, None; **B. P. Tsao**, None; **T. J. Vyse**, None; **J. B. Harley**, None; **E. Wakeland**, None; **K. M. Kaufman**, None; **C. Montgomery**, None; **C. D. Langefeld**, None; **P. M. Gaffney**, None; **K. L. Moser**, None.

2476

Disclosure: E. Sanchez, None; **M. E. Comeau**, None; **B. I. Freedman**, None; **J. A. Kelly**, None; **K. Kaufman**, None; **C. D. Langefeld**, None; **E. E. Brown for PROFILE**, None; **J. T. Merrill**, None; **B. P. Tsao**, None; **D. L. Kamen**, None; **G. S. Gilkeson**, None; **J. A. James**, None; **T. J. Vyse**, None; **P. M. Gaffney**, None; **C. O. Jacob**, None; **T. B. Niewold**, None; **B. C. Richardson**, None; **J. B. Harley**, None; **M. E. Alarcon-Riquelme**, None; **A. H. Sawalha**, None.

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Disclosure: D. Sakurai, None; **J. Zhao**, None; **Y. Deng**, None; **K. Kaufman**, None; **J. A. Kelly**, None; **R. P. Kimberly on behalf of PROFILE investigators**, None; **M. E. Alarcón-Riquelme on behalf of the BIOLUPUS and GENLES networ**, None; **J. B. Harley**, None; **S. C. Bae**, None; **C. O. Jacob**, None; **T. J. Vyse**, None; **T. B. Niewold**, None; **P. M. Gaffney**, None; **K. L. Moser**, None; **J. A. James**, None; **G. S. Gilkeson**, None; **D. L. Kamen**, None; **C. D. Langefeld**, None; **D. M. Chang**, None; **Y. W. Song**, None; **C. Y. Yu**, None; **J. M. Grossman**, None; **R. M. Cantor**, None; **B. H. Hahn**, None; **B. P. Tsao**, None.

2478

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2479

Disclosure: S. A. Chung, None; **E. E. Brown**, None; **A. H. Williams**, None; **T. Bhangale**, Genentech, Inc., 3; **P. S. Ramos**, None; **J. T. Ziegler**, None; **B. I. Freedman**, None;

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2480

Disclosure: K. G. Eriksson, None; **A. Zickert**, None; **J. K. Sandling**, None; **A. Jönsen**, None; **E. Svenungsson**, None; **L. Rönnblom**, None; **T. W. Behrens**, Genentech, Inc., 3; **R. R. Graham**, Genentech, Inc., 3; **W. Ortmann**, Genentech, Inc., 3; **A. C. Syvänen**, None; **I. Gunnarsson**, None; **G. Nordmark**, None.

ACR Concurrent Abstract Session

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics III

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2481

Disclosure: S. R. Johnson, None; **J. T. Granton**, None; **G. A. Tomlinson**, None; **H. Grosbein**, None; **T. Le**, None; **P. Lee**, None; **M. E. Seary**, None; **G. A. Hawker**, None; **B. M. Feldman**, None.

2482

Disclosure: B. E. Schreiber, Actelion Pharmaceuticals US, 8, GlaxoSmithKline, 8; **C. Valerio**, Actelion, 9, Pfizer Inc, 9; **G. Keir**, None; **C. Handler**, None; **A. U. Wells**, Actelion, 5; **C. P. Denton**, Actelion Pharmaceuticals US, 5; **J. G. Coghlan**, Actelion Pharmaceuticals US, 2, Pfizer Inc, 2, GlaxoSmithKline, 2, Bayer, 5, Ely Lilly, 5.

2483

Disclosure: J. R. Seibold, Actelion Pharmaceuticals US, 2, United Therapeutics, 2, Celgene, 5, Sanofi-Aventis Pharmaceutical, 5, Genentech and Biogen IDEC Inc., 5, Fibrogen, 5, Apricus, 5; **F. M. Wigley**, United Therapeutics, 2; **E. Schiopu**, United Therapeutics, 2, United Therapeutics, 8; **C. D. Denton**, None; **R. M. Silver**, None; **V. D. Steen**, Gilead, 2, United Therapeutics, 2, Pfizer Inc, 2, Actelion Pharmaceuticals US, 2, Genentech and Biogen IDEC Inc., 5, Gilead, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Gilead, 8, Actelion Pharmaceuticals US, 8; **T. A. Medsger Jr.**, None; **M. D. Mayes**, United Therapeutics, 2, Actelion Pharmaceuticals US, Gilead, 8, Novartis Pharmaceutical Corporation, Actelion Pharmaceuticals US; **S. Chatterjee**, None; **L. Chung**, Actelion Pharmaceuticals US, 5, Gilead, 2, Pfizer Inc, 2, United Therapeutics, 2, MedImmune, 2; **M. E. Csuka**, Actelion Pharmaceuticals US, 2, United Therapeutics, 2; **D. Khanna**, Actelion Pharmaceuticals US, 5, United Therapeutics, 5, Pfizer Inc, 5, Novartis Pharmaceutical Corporation, 5, Actelion Pharmaceuticals US, 8, United Therapeutics, 8, Gilead, 8; **T. M. Frech**, None; **J. A. Molitor**, Actelion Pharmaceuticals US, 5; **N. F. Rothfield**, United Therapeutics, 2; **A. L. Herrick**, Actelion Pharmaceuticals US, 5, Pfizer Inc, 5, Actelion Pharmaceuticals US, 2, United Therapeutics, 2, Orion, 2; **R. W. Simms**, None; **J. E. Pope**, United Therapeutics, 2; **K. D. Rollins**, United Therapeutics, 1, United Therapeutics, 3; **C. Arneson**, United Therapeutics, 1, United Therapeutics, 3; **M. Wade**, United Therapeutics, 1, United Therapeutics, 3.

2484

Disclosure: T. S. Rodriguez-Reyna, None; **M. Morelos-Guzman**, None; **P. Hernandez-Reyes**, None; **J. Morales-Blanhir**, None; **K. Montero-Duarte**, None; **C. Martinez-Reyes**, None; **C. Reyes-Utrera**, None; **J. Vazquez-Lamadrid**, None.

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ACR Concurrent Abstract Session

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2486A

Disclosure: J. Sieper, Abbott, Merck, Pfizer, UCB, 2, Abbott, Merck, Pfizer, UCB, 5, Abbott, Merck, Pfizer, UCB, 8 ; **D. van der Heijde**, Abbott, Amgen, AstraZeneca, BristolMyersSquibb, Centocor, Chugai, Eli-Lilly, GlaxoSmithKline, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth, 5; **M. Dougados**, Abbott, Pfizer, Roche, UCB, BristolMyersSquibb, Merck, 2, Abbott, Pfizer, Roche, UCB, BristolMyersSquibb, Merck, 5; **P. J. Mease,** Abbott Immunology Pharmaceuticals, 2, Amgen, 2, Bristol Myers Squibb, 2, Novartis Pharmaceutical Corporation, 2, Centocor, Inc., 2, Genentech and Biogen IDEC Inc, 2, Lilly , 2, Pfizer Inc, 2, U C B, 2, Abbott Immunology Pharmaceuticals, 5, Amgen, 5, Bristol Myers Squibb, 5, Centocor, Inc., 5, Genentech and Biogen IDEC Inc., 5, Lilly, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, ucb, 5, Abbott Immunology Pharmaceuticals, 8, Amgen, 8, Bristol Myers Squib, 8, Centocor, Inc., 8, Genentech and Biogen IDEC Inc., 8, Lilly, 8, Pfizer Inc, 8, U C B, 8 ; **L. S. Brown,** Abbott , 3, Abbott , 1; **T. F. Nicholson**, Abbott, 3; **A. Pangan**, Abbott Laboratories, 1, Abbott Laboratories, 3.

2486B

Disclosure: D. Poddubnyy, None; **H. Haibel**, None; **J. Listing**, None; **E. Märker-Hermann**, None; **H. Zeidler**, None; **J. Braun**, None; **M. Rudwaleit**, None; **J. Sieper**, None.

2486C

Disclosure: L. Eder, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **D. D. Gladman**, None.

2486D

Disclosure: X. Baraliakos, None; **J. Braun**, None; **D. D. Laurent**, Novartis Institutes for BioMedical Research, 3; **D. Baeten**, None; **D. van der Heijde**, None; **J. Sieper**, None; **P. Emery**, None; **I. McInnes**, None; **J. van Laar**, None; **R. Landewe**, None; **P. Wordsworth**, None; **J. Wollenhaupt**, None; **H. Kellner**, None; **A. M. Wright**, Novartis Pharma AG, 3; **S. Gsteiger**, Novartis Pharma AG, 3; **W. Hueber**, Novartis Institutes for BioMedical Research, 3.

2486E

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2486F

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ACR Concurrent Abstract Session

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics III

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2486

Disclosure: A. C. Gelber, None; **R. L. Manno**, None; **A. Woods**, None; **A. A. Shah**, Actelion Pharmaceuticals US, 2; **F. Boin**, None; **L. K. Hummers**, None; **F. M. Wigley**, MedImmune, 2, United Therapeutics, 2.

ARHP Concurrent Abstract Session

ARHP Psychology/Social Sciences

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2487

Disclosure: L. Kwakkenbos, None; **W. G. J. M. van Lankveld**, None; **M. C. Vonk**, None; **E. S. Becker**, None; **F. H. J. van den Hoogen**, None; **C. H. M. van den Ende**, None.

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ACR Concurrent Abstract Session

B-cell Biology and Targets in Autoimmune Disease

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2493

Disclosure: J. Li, None; **C. T. Ritchlin**, None; **I. Sanz**, None; **A. Bottaro**, None; **R. Wood**, None; **L. Xing**, None; **E. M. Schwarz**, None.

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2497

Disclosure: L. Chen, None.

2498

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ACR Concurrent Abstract Session

Cytokines, Mediators, and Gene Regulation II

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2499

Disclosure: O. B. J. Corneth, None; **A. M. Mus**, None; **P. S. Asmawidjaja**, None; **R. W. Hendriks**, None; **E. Lubberts**, None.

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ACR Concurrent Abstract Session

Epidemiology and Health Services Research II: Osteoarthritis

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2505

Disclosure: J. Song, None; **M. Hochberg**, Theralogix LLC, 1, U.S. Bone and Joint Initiative, 6, Abbott Laboratories, Amgen, Astra-Zeneca Pharmaceuticals, Bioiberica S.A., Bristol Myers Squibb, Covidien, Eli Lilly, Genentech/Roche, Iroko Pharmaceuticals, Merck, EMD Serono, NiCox S.A., Novartis Pharma AG, Pfizer, Pozen, Smith and Nephew, Stryker LLC,, 5; **R. W. Chang**, None; **L. Manheim**, None; **J. Lee**, None; **P. A. Semanik**, None; **L. Sharma**, None; **D. D. Dunlop**, None.

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ACR Concurrent Abstract Session

Rheumatoid Arthritis Clinical Aspects: Predictors of Outcome

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2511

Disclosure: J. Kay, None; **S. P. Messing**, Corrona, 5; **J. M. Kremer**, Corrona, 1, Corrona, 3; **J. D. Greenberg**, Corrona, 5, Corrona, 1; **D. E. Furst**, Corrona, 5.

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ACR Concurrent Abstract Session

Rheumatoid Arthritis - Human Etiology and Pathogenesis II: Pathogenesis of Rheumatoid Arthritis - What's New?

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2517

Disclosure: K. Nakano, None; **J. Whitaker**, None; **W. Wang**, None; **D. L. Boyle**, None; **G. S. Firestein**, None.

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ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Further Insights into Efficacy and Safety of TNF-Inhibitors

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2523

Disclosure: P. Raaschou, None; **J. F. Simard**, None; **M. Neovius**, None; **M. Holmqvist**, None; **J. Eriksson**, None; **J. Askling**, Pfizer Inc, Bristol Meyer Squibb, 5.

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ACR Concurrent Abstract Session

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment III

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2529

Disclosure: N. T. Baerlecken, None; **G. H. Stummvoll**, None; **R. E. Schmidt**, None; **T. Witte**, None.

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ACR Concurrent Abstract Session

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics I

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2535

Disclosure: A. Akhmetshina, None; **K. Palumbo**, None; **C. Bergmann**, None; **P. Venalis**, None; **C. Dees**, None; **P. Zerr**, None; **A. Horn**, None; **C. Beyer**, None; **J. Zwerina**, None; **O. A. MacDougald**, None; **O. Distler**, None; **G. Schett**, None; **J. H. Distler**, None.

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ACR/ARHP Combined Abstract Session

ACR/ARHP Combined Epidemiology Abstract Session

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2541

Disclosure: J. R. Curtis, Pfizer, BristolMyersSquibb, Crescendo, Abbott, Roche, Genentech, UCB, Centacor, Corrona, Amgen, 5; **J. Lange**, Proctor and Gamble, 3; **H. Yun**, None; **E. S. Delzell**, Amgen, 2.

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ACR REF Special Session

ACR REF Edmond L. Dubois, MD, Memorial Lectureship: Interfering with Vascular Health: How Innate Immunity Promotes Premature Organ Damage in Systemic Lupus Erythematosus

Tuesday, November 8, 2011, 2:30 PM - 4:00 PM

2547

Disclosure: S. G. Thacker, None; **W. Zhao**, None; **W. Luo**, None; **A. Vivekanandan-Giri**, None; **B. J. Rabquer**, None; **A. E. Koch**, None; **S. Pennathur**, None; **A. Davidson**, None; **D. T. Eitzman**, None; **M. J. Kaplan**, None.

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ARHP Concurrent Abstract Session

ARHP Research Methodology

Tuesday, November 8, 2011, 4:30 PM - 6:00 PM

2553

Disclosure: B. Zhang, None; **U. S. D. Nguyen**, None; **J. Niu**, None; **Y. Zhang**, None.

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ARHP Concurrent Abstract Session

ARHP Clinical Practice/Patient Care III

Wednesday, November 9, 2011, 9:00 AM - 10:00 AM

2559A

Disclosure: M. F. Marengo, None; **R. L. Street Jr.**, None; **S. De Achaval**, None; **H. Zhang**, None; **M. Richardson**, None; **M. E. Suarez-Almazor**, None.

2559C

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2559B

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ARHP Concurrent Abstract Session

ARHP Clinical Practice/Patient Care II

Wednesday, November 9, 2011, 7:30 AM - 8:30 AM

2561

Disclosure: P. J. Cornell, Abbott Immunology Pharmaceuticals, UCB, Roche, 5; **S. Richards**, None; **S. Westlake**, None.

2562

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ACR Concurrent Abstract Session

Cytokines, Mediators, and Gene Regulation III

Wednesday, November 9, 2011, 9:00 AM - 10:30 AM

2567

Disclosure: M. Feng, None; **Y. P. Han**, None; **S. G. Zheng**, None.

2568

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ACR Concurrent Abstract Session

Epidemiology and Health Services Research III: Rheumatoid Arthritis

Wednesday, November 9, 2011, 9:00 AM - 10:30 AM

2573

Disclosure: C. A. Peschken, None; **C. A. Hitchon**, None; **H. Chen**, None; **A. Garland**, None; **H. S. El-Gabalawy**, None; **C. N. Bernstein**, None; **R. A. Marrie**, None.

2574

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2575

Disclosure: S. Lillegraven, None; **F. H. M. Prince**, None; **N. A. Shadick**, Amgen Abbott, genentech, crescendo biosciences, Biogen Idec, 2; **E. A. Haavardsholm**, None; **M. A. Frits**, None; **C. K. Iannaccone**, Biogen Idec, 9, Crescendo Biosciences, 9; **T. K. Kvien**, None; **M. E. Weinblatt**, BiogenIdec, 2, Crescendo Bioscience, Inc, 2, BiogenIdec, 5, Crescendo Bioscience, Inc., 5; **D. H. Solomon**, Abbott Immunology Pharmaceuticals, 2, Corrona, 5, Bristol Myers Squibb, 9, Amgen, 2.

2576

Disclosure: H. Jalal, None; **K. Michaud**, None; **H. K. Choi**, Takeda, 2, Novartis Pharmaceutical Corporation, 5, URL, 2, Savient, 5, Centocor, Inc.; **Y. H. Rho**, None; **K. Kuntz**, None.

2577

Disclosure: M. De Vera, None; **D. Lacaille**, None; **M. Abrahamowicz**, None; **J. A. Kopec**, None; **H. K. Choi**, Takeda, 2, Novartis Pharmaceutical Corporation, 5, URL, 2, Savient, 5, Centocor, Inc..

2578

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ACR Concurrent Abstract Session

Metabolic and Crystal Arthropathies II: Concurrent Session on the Anti-Gout Medications – Dosing, Adverse Effects, and Economic Burden

Wednesday, November 9, 2011, 9:00 AM - 10:30 AM

2579

Disclosure: L. K. Stamp, None; **W. Taylor**, None; **P. B. B. Jones**, None; **J. L. Dockerty**, None; **J. Drake**, None; **C. Frampton**, None; **N. Dalbeth**, Fonterra NZ, 2, Abbott Laboratories, Roche, Takeda, Novartis, Fonterra, 5, Abbott Laboratories, Novartis, 8, Named on patent on milk products in gout, 9.

2580

Disclosure: S. Y. Kim, Takeda Pharmaceuticals, 2; **C. Newcomb**, None; **D. Margolis**, None; **J. Roy**, Roche Pharmaceuticals, 2, Amgen, 2; **S. Hennessy**, Takeda, 5, Millenium Pharmaceuticals, 5, Teva Pharmaceuticals, 5, Pfizer Inc, 5, Endo Pharmaceuticals Inc., 5, Takeda, 2.

2581

Disclosure: S. Wason, URL Pharma, 3; **R. D. Faulkner**, URL Pharma, 3; **M. W. Davis**, URL Pharma, 3.

2582

Disclosure: H. Baraf, Savient Pharmaceuticals, Inc, 5, Savient Pharmaceuticals. Inc, 8; **R. A. Yood**, Savient Pharmaceuticals, Inc, 9; **J. S. Sundy**, Savient Pharmaceuticals, Inc., 5; **F. D. Ottery**, Savient Pharmaceuticals, Inc, 9, Savient Pharmaceuticals, Inc., 1; **Z. D. Horowitz**, Savient Pharmaceuticals, Inc., 9; **M. A. Becker**, Savient Pharmaceuticals, Inc, 5.

2583

Disclosure: A. Forsythe, Savient Pharmaceticals, Inc., 3; **H. K. Choi**, Takeda, 2, Novartis Pharmaceutical Corporation, 5, URL, 2, Savient, 5, Centocor, Inc., 9.

2584

Disclosure: G. C. Saha, Metabolex, Inc, 1, Metabolex, Inc, 3; **D. B. Karpf**, Metabolex, Inc, 5; **Y. J. Choi**, Metabolex, Inc, 1, Metabolex, Inc, 3; **B. K. Roberts**, Metabolex, Inc, 1, Metabolex, Inc, 3.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Clinical Aspects: Risk of Cardiovascular Disease

Wednesday, November 9, 2011, 9:00 AM - 10:30 AM

2585

Disclosure: E. E. A. Arts, None; **J. Fransen**, None; **A. den Broeder**, None; **C. Popa**, None; **P. L. C. M. Van Riel**, None.

2586

Disclosure: F. Wolfe, None; **K. Michaud**, None.

2587

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2588

Disclosure: H. Mirjafari, None; **S. Verstappen**, None; **M. Lahiri**, None; **P. Welsh**, None; **D. K. Bunn**, None; **T. Marshall**, None; **M. Lunt**, None; **N. Sattar**, F. Hoffmann-La Roche Ltd, 5, F. Hoffmann-La Roche Ltd, 8; **D. P. M. Symmons**, None; **I. N. Bruce**, None.

2589

Disclosure: F. Wolfe, None; **M. B. Bolster**, Novartis, Amgen, Eli Lilly, 8; **C. Colon-Emeric**, Novartis, Amgen, Smithklin Beecham; Research: Novartis, Wyeth, 5, Bisphosphonate Cardiovascular Effects, 9; **C. M. O'Connor**, Johnson and Johnson, 5, 9, Co-founder Cardiobis, 9, Methods for preventing or reducing secondary fractures after hip fracture", Number 20050272707, 9; **K. Michaud**, None; **K. W. Lyles**, Novartis, Alliance for Better Bone Health, Amgen, 2, Novartis, Procter & Gamble, Merck, Amgen, Kirin Pharmaceutical, GTx, Lilly, GlaxoSmithKline, Bone Medical Ltd., Wyeth, Osteologix, 5, Patent, 9.

2590

Disclosure: S. S. Desai, None; **J. D. Myles**, None; **M. J. Kaplan**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Novel Compounds I

Wednesday, November 9, 2011, 9:00 AM - 10:30 AM

2591

Disclosure: M. C. Genovese, Eli Lilly and Company, 2, Eli Lilly and Company, 5; **M. W. Greenwald**, Eli Lilly and Company, 2; **C. S. Cho**, None; **A. Berman**, None; **L. Jin**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **G. Cameron**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **L. Xie**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **D. Braun**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **S. Banerjee**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **L. Warner**, Eli Lilly and Company, 9.

2592

Disclosure: D. van der Heijde, Abbott, Amgen, AstraZeneca, BristolMyersSquibb, Centocor, Chugai, Eli-Lilly, GlaxoSmithKline, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth, 5; **Y. Tanaka**, Pfizer Inc, 5; **R. Fleischmann**, Pfizer Inc, 2, Pfizer Inc, 5; **E. C. Keystone**, Pfizer Inc, 2, Pfizer Inc, 5; **J. M. Kremer**, Pfizer Inc, 2, Pfizer Inc, 5; **C. A. F. Zerbini**, None; **M. Cardiel**, None; **S. B. Cohen**, Genentech and Biogen IDEC Inc., 5, Merck Pharmaceuticals, 5, Sanofi-Aventis Pharmaceutical, 5, Proctor & Gamble Pharmaceuticals, 5, Pfizer Inc, 5, Centocor, Inc., 3, Amgen, 5, Scios, Inc., 5, Bristol-Myers Squibb, 5, Wyeth Pharmaceuticals, 5; **P. T. Nash**, Pfizer Inc, Wyeth, 5, Pfizer Inc, Wyeth, 5; **Y. W. Song**, Pfizer Inc, 2; **D. Tegzova**, None; **B. Wyman**, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 3; **B. Benda**, Pfizer Inc, 3; **G. Wallenstein**, Pfizer Inc, 1, Pfizer Inc, 3; **S. H. Zwillich**, Pfizer Inc, 3, Pfizer Inc, 1; **J. D. Bradley**, Pfizer Inc, 3; **C. A. Connell**, Pfizer Inc, 3.

2593

Disclosure: R. M. Fleischmann, None; **J. E. Poiley**, None; **R. Stoilov**, None; **V. Strand**, Lexicon Pharmaceuticals, Inc., 5; **J. Freiman**, Lexicon Pharmaceuticals, Inc., 1, Lexicon Pharmaceuticals, Inc., 3; **T. Oravecz**, Lexicon Pharmaceuticals, Inc., 1, Lexicon Pharmaceuticals, Inc., 3; **A. Sands**, Lexicon Pharmaceuticals, Inc., 1, Lexicon

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2594

Disclosure: A. Kavanaugh, Rigel Pharma, 5; **M. E. Weinblatt**, Rigel Pharmaceuticals, 5, AstraZeneca, 5; **M. C. Genovese**, Rigel Pharma, 2, Rigel Pharma, 5, AstraZeneca, 2, AstraZeneca, 5; **T. K. Musser**, Rigel Pharma, 3; **E. B. Grossbard**, Rigel Pharma, 1, Rigel Pharma, 3; **D. B. Magilavy**, Rigel Pharma, 3; **S. Hollis**, AstraZeneca, 1, AstraZeneca, 3; **E. Wesby van-Sway**, AstraZeneca, 1, AstraZeneca, 3; **D. Millson**, AstraZeneca, 1, AstraZeneca, 3.

2595

Disclosure: L. R. Harrold, Corrona, 5; **G. Reed**, Corrona, 5, Corrona, 9; **J. R. Curtis**, Pfizer, BristolMyersSquibb, Crescendo, Abbott, Roche, Genentech, UCB, Centacor, Corrona, Amgen, 5; **D. H. Solomon**, Amgen, Abbott, 2, Corrona, 5, Bristol-Myers Squibb, 9; **M. Hochberg**, Theralogix LLC, 1, U.S. Bone and Joint Initiative, 6, Abbott Laboratories, Amgen, Astra-Zeneca Pharmaceuticals, Bioiberica S.A., Bristol Myers Squibb, Covidien, Eli Lilly, Genentech/Roche, Iroko Pharmaceuticals, Merck, EMD Serono, NiCox S.A., Novartis Pharma AG, Pfizer, Pozen, Smith and Nephew, Stryker LLC,, 5; **A. U. Onofrei**, None; **J. M. Kremer**, Corrona, 1, Corrona, 3; **J. D. Greenberg**, Corrona, 1, AstraZeneca Novartis, Pfizer, Corrona, 5.

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ACR Concurrent Abstract Session

Systemic Lupus Erythematosus - Clinical Aspects: Translational Studies

Wednesday, November 9, 2011, 9:00 AM - 10:30 AM

2597

Disclosure: M. Jain, Arthritis Foundation, 2; **M. Amato**, None; **R. M. Clancy**, None; **P. M. Izmirly**, None; **J. P. Buyon**, None.

2598

Disclosure: D. Wang, None; **H. Liu**, None; **X. Li**, None; **L. Sun**, None.

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2602

Disclosure: R. M. Clancy, NIH R01 AR055088-01, 2; **P. M. Izmirly**, None; **E. M. Ginzler**, Human Genome Sciences, Inc., 2, Human Genome Sciences, Inc., 5; **O. B. O. T. I. I. T. MMF/AZA Lupus Nephritis Main Trial**, None.

ACR Concurrent Abstract Session

Systemic Sclerosis Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics II

Wednesday, November 9, 2011, 9:00 AM - 10:30 AM

2603

Disclosure: E. Derrett-Smith, None; **A. Dooley**, None; **R. Baliga**, None; **A. Hobbs**, None; **D. J. Abraham**, None; **C. P. Denton**, Actelion Pharmaceuticals US, 5.

2604

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2605

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2606

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2608

Disclosure: P. J. Wermuth, None; **S. Addya**, None; **S. A. Jimenez**, None.

ARHP Concurrent Abstract Session

ARHP Rehabilitation Sciences

Wednesday, November 9, 2011, 9:00 AM - 10:30 AM

2609

Disclosure: V. Cameron-Fiddes, None.

2610

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2611

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2613

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2614

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ACR Concurrent Abstract Session

Infection-Related Rheumatic Disease

Wednesday, November 9, 2011, 11:00 AM - 12:30 PM

2615

Disclosure: R. D. Inman, None; **B. Chiu**, None.

2616

Disclosure: E. Gracey, None; **B. Chiu**, None; **R. D. Inman**, None.

2617

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ACR Concurrent Abstract Session

Pediatric Rheumatology - Clinical and Therapeutic Aspects: Treatment

Wednesday, November 9, 2011, 11:00 AM - 12:30 PM

2621

Disclosure: F. De Benedetti, F Hoffman-La Roche, 2, F Hoffman-La Roche, 5, Pfizer Inc, 5, Bristol-Myers Squibb, 5; **H. Brunner**, None; **R. Allen**, Roche Pharmaceuticals, 2; **D. Brown**, None; **J. Chaitow**, None; **M. Pardeo**, None; **G. Espada**, None; **B. Flatø**, None; **G. Horneff**, None; **C. Devlin**, Roche Pharmaceuticals, 3; **A. Kenwright**, Roche Pharmaceuticals, 3; **R. Schneider**, Hoffmann-La Roche, Inc., 5; **P. Woo**, None; **A. Martini**, None; **D. Lovell**, Roche Pharmaceuticals, 5; **N. Ruperto**, None.

2622

Disclosure: H. Brunner, None; **N. Ruperto**, Novartis Pharmaceutical Corporation, 2, Bristol Myers Squibb, 2, Roche Pharmaceuticals, 2, Pfizer Inc, 2; **G. Horneff**, Abbott Laboratories, 5, Pfizer Inc, 5, Chugai, 5, Novartis Pharmaceutical Corporation, 5; **P. Quartier**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5; **T. Constantin**, None; **Y. Berkun**, None; **T. Kallinich**, None; **R. Brik**, None; **M. A. Ferrandiz**, None; **K. Lheritier**, Novartis Pharmaceutical Corporation, 3; **R. Preiss**, Novartis Pharmaceutical Corporation, 3; **L. Tseng**, Novartis Pharmaceutical Corporation, 3; **D. J. Lovell**, Abbott Laboratories, 5, Amgen, 5, Astra Zeneca Pharmaceutical, 5, Bristol-Myers Squibb, 5, Hoffmann-La Roche, Inc., 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Regeneron, 5, UBC, 5, Wyeth Pharmaceuticals, 5, Xoma Corporation, 5; **A. Martini**, Novartis Pharmaceutical Corporation, 2, Novartis Pharmaceutical Corporation, 5.

2623

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ACR Concurrent Abstract Session

Rheumatoid Arthritis Treatment - Small Molecules, Biologics, Therapy: Novel Compounds II

Wednesday, November 9, 2011, 11:00 AM - 12:30 PM

2627

Disclosure: V. Strand, Amgen, AstraZeneca, BristolMyersSquibb, Genentech, GlaxoSmithKline, Human Genome Sciences, Idera, Lilly, MedImmune, Merck Serono, NovoNordisk, Ono, Pfizer, Rigel, Roche, Sanofi-Aventis, Schering Plough, UCB, 5; **J. M. Kremer**, Pfizer Inc, 2, Pfizer Inc, 5; **Z. G. Li**, Pfizer Inc, 5; **S. Hall**, Pfizer Inc, 5; **R. M. Fleischmann**, Pfizer Inc, 2, Pfizer Inc, 5; **M. C. Genovese**, Pfizer Inc., 2, Pfizer Inc., 5; **E. Martin-Mola**, Pfizer Inc, 9; **J. Isaacs**, Pfizer Inc., 5; **D. Gruben**, Pfizer Inc, 3; **G. Wallenstein**, Pfizer Inc, 3, Pfizer Inc, 1; **S. Krishnaswami**, Pfizer Inc, 3; **S. H. Zwillich**, Pfizer Inc, 3, Pfizer Inc, 1; **T. Koncz**, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 3; **J. D. Bradley**, Pfizer Inc, 3.

2628

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2629

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2631

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ACR Concurrent Abstract Session

Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment IV

Wednesday, November 9, 2011, 11:00 AM - 12:30 PM

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Disclosure: U. Weber, None; **R. G. Lambert**, None; **K. Rufibach**, None; **W. P. Maksymowych**, None; **J. Hodler**, None; **A. Zejden**, None; **S. Duewell**, None; **R. O. Kissling**, None; **P. L. Filipow**, None; **A. G. Jurik**, None.

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2635

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2636

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ARHP Concurrent Abstract Session

ARHP Epidemioloogy and Public Health II

Wednesday, November 9, 2011, 11:00 AM - 12:30 PM

2639

Disclosure: E. Aghdassi, None; **L. Yeganeh**, None; **A. K. Balitsky**, None; **S. Morrison**, None; **M. Frattasi**, None; **J. Su**, None; **D. W. Ma**, None; **P. R. Fortin**, The Arthritis Society, 2, GlaxoSmithKline, 5, Lupus Foundation of America, Inc., 6.

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